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# Use of herbal and food galactagogues to support breastfeeding in Aotearoa New Zealand

A thesis presented in partial fulfilment of the requirements for the degree of

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To  
my loving husband  
Kai  
and our beautiful children  
Avon  
Bruce  
&  
Cooper

## Abstract

**Background:** Galactagogues are substances used to increase breast milk production and support breastfeeding. Women in many countries used herbal and food galactagogues to address perceived insufficient milk production (PIM), but little is known about how they are used in Aotearoa New Zealand (Aotearoa NZ). This thesis aimed to explore galactagogue use in Aotearoa NZ, to explore the relationship between mothers' perception of milk supply and galactagogue use, and to investigate the influence of a *Saccharomyces cerevisiae* yeast-based supplement (SCYS) on breast milk and breastfeeding.

**Method:** A mixed-methods approach was used, consisting of a qualitative study followed by a cross-sectional survey and a randomised placebo-controlled trial (RCT) on the effects of SCYS on breast milk and breastfeeding. The qualitative study conducted in-depth interviews with mothers (n = 22) and postnatal healthcare professionals (n = 16) to explore experiences of and attitudes to herbal and food galactagogue use. The qualitative study informed the development of the questionnaire used in the cross-sectional survey (at baseline for the RCT) as well as the weekly and follow-up surveys. Seventy-two women responded to the baseline survey and 68 completed the RCT. Galactagogue use and PIM before the RCT were investigated at the baseline. Breast milk samples were collected to compare human milk oligosaccharide (HMO) concentration change from baseline to the endpoint. Participants' perceptions of milk supply, feeding status and infant anthropometry were measured before and after the intervention.

**Results:** Women in Aotearoa NZ not only used herbal and food galactagogues to increase breast milk production, but also used them to maintain milk supply and/or quality and to support breastfeeding generally. Galactagogue use was not associated with PIM among the cross-sectional survey respondents, who mostly had solid and positive perceptions of their milk supply. Although significantly more women in the SCYS group perceived the intervention as increasing their milk supply compared

with the placebo group, SCYS had limited effect on mothers' perceptions of milk quantity and quality or infant behaviours and no effect on HMO concentration change. There were significantly smaller numbers of women in the SCYS used formula at six months postpartum compared with the placebo group.

**Conclusion:** A wide range of herbal and food galactagogues were used in Aotearoa NZ to support breastfeeding. The prevalence of galactagogue use among women who experienced PIM or if galactagogue use prevents PIM needs to be evaluated further in a large representative sample. The SCYS may positively influence breast milk supply other than the placebo effect and therefore supports breastfeeding. An RCT in a bigger sample investigating the effect of SCYS on breast milk production and another RCT at the initiation stage of lactation are required in the future.

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# Table of Contents

Abstract.....	ii
Acknowledgements.....	iv
Table of Contents.....	vii
List of Figures.....	xi
List of Tables.....	xii
List of Abbreviations.....	xiv
List of Articles and Conference Presentations.....	xvi
List of Appendices.....	xvii
Chapter 1 Introduction.....	1
1.1 Background.....	1
1.2 Research question and aims of the thesis.....	5
1.3 Structure of the thesis.....	5
1.4 References.....	7
Chapter 2 Literature review.....	12
2.1 Introduction.....	12
2.2 Physiology of human lactation.....	12
2.2.1 Anatomy and physiology stages of human lactation.....	12
2.2.2 Endocrine, autocrine, and paracrine control of breast milk production.....	14
2.3 Perceived insufficient breast milk production.....	15
2.3.1 Actual insufficient milk production.....	16
2.3.2 Factors that can cause insufficient milk production.....	17
2.3.3 Factors influencing perceived insufficient milk production.....	19
2.3.5 Galactagogues and perceived insufficient milk.....	20
2.4 Galactagogues.....	21
2.4.1 Use of galactagogues among breastfeeding women.....	21
2.4.2 Recommendation of galactagogues by postnatal healthcare professionals.....	22
2.4.3 Efficacy and safety of galactagogues.....	23
2.5 Scoping review of human studies of galactagogues to identify outcome measures.....	24
2.5.1 Description of the reviewed studies.....	25
2.5.2 Various measurements of breast milk volume.....	28
2.5.3 Indirect measures of breast milk production.....	32
2.5.4 The proportions of women breastfeeding at different stages of lactation.....	37
2.5.5 Safety of galactagogues.....	38

2.6 Conclusions .....	39
2.7 References .....	40
Chapter 3 Methodology .....	50
3.1 Introduction .....	50
3.2 Research methodology .....	50
3.3 Qualitative study design and its contribution to the randomised placebo-controlled trial design .....	51
3.4 Randomised placebo-controlled trial design and changes .....	52
3.5 References .....	54
Chapter 4 The experience of and attitudes to galactagogue use among Aotearoa New Zealand breastfeeding women and postnatal healthcare professionals: a qualitative study .....	56
4.1 Abstract .....	57
4.2 Background .....	58
4.3 Methods .....	60
4.3.1 Design .....	60
4.3.2 Participants .....	60
4.3.3 Data collection .....	61
4.3.4 Definition of infant feeding status .....	62
4.3.5 Data analysis .....	63
4.4 Results .....	63
4.4.1 Galactagogues mentioned by participants .....	64
4.4.2 The reasons for galactagogue use .....	66
4.4.3 Perceived effectiveness of galactagogues .....	68
4.4.4 The overall safety concerns of galactagogues use .....	70
4.5 Discussion .....	73
4.5.1 Strength and Limitations .....	76
4.6 Conclusion .....	77
4.7 References .....	77
Chapter 5 Use of galactagogues in Aotearoa New Zealand women and its relationship to perceived insufficient milk supply: a cross-sectional survey .....	80
5.1 Abstract .....	81
5.2 Introduction .....	82
5.2 Materials and Methods .....	83
5.2.1 Participants and settings .....	83
5.2.2 Data collection .....	84
5.2.3 Statistical analysis .....	87
5.3 Results .....	87

5.4 Discussion.....	91
5.5 Conclusions .....	94
5.6 References .....	95
Chapter 6 <i>Saccharomyces cerevisiae</i> Yeast-Based Supplementation as a Galactagogue in Breastfeeding Women? A Review of Evidence from Animal and Human Studies .....	97
6.1 Abstract.....	98
6.2 Introduction .....	99
6.3 An overview of information of <i>Saccharomyces cerevisiae</i> yeast-based supplement on the internet .....	102
6.4 Using <i>Saccharomyces cerevisiae</i> yeast as a galactagogue in ruminants and non-ruminants... 107	
6.5 Hypotheses of the mechanism of <i>Saccharomyces cerevisiae</i> yeast-based supplement on breast milk production.....	110
6.6 Safety considerations of taking <i>Saccharomyces cerevisiae</i> yeast-based supplement during lactation .....	114
6.7 Conclusions .....	116
6.8 References .....	117
Chapter 7 Effect of <i>Saccharomyces cerevisiae</i> yeast-based supplement on human milk oligosaccharide concentration and other indicators of breast milk supply: a randomised placebo-controlled trial .. 124	
7.1 Abstract.....	125
7.2 Introduction .....	126
7.3 Method .....	129
7.3.1 Study design.....	129
7.3.2 Setting .....	129
7.3.3 Participants .....	129
7.3.4 Intervention .....	130
7.3.5 Compliance .....	130
7.3.6 Data collection .....	130
7.3.7 Data analysis .....	135
7.4 Results.....	137
7.4.1 The effect on human milk oligosaccharide concentration .....	139
7.4.2 Other indicators of breast milk production .....	141
7.4.3 Breastfeeding status and participants' perceptions at six months postpartum.....	145
7.5 Discussion.....	146
7.6 Conclusion.....	150
7.7 References .....	150
Chapter 8 Reflections on the use of an adapted protocol of hourly expression in a sample of breastfeeding women in Aotearoa New Zealand .....	155
8.1 Abstract.....	156

8.2 Introduction .....	157
8.3 Materials and Methods.....	158
8.3.1 Study design and participants.....	158
8.3.2 Study procedure.....	158
8.3.3 Statistics .....	160
8.4 Results .....	161
8.5 Discussion.....	167
8.6 Conclusion.....	169
8.7 References .....	169
Chapter 9 Discussion and conclusion.....	171
9.1 Introduction .....	171
9.2 Increased amount of herbal and food galactagogue research .....	171
9.3 The role of herbal and food galactagogues in breastfeeding and addressing perceived insufficient milk supply .....	173
9.4 Use of <i>Saccharomyces cerevisiae</i> yeast-based supplement as a galactagogue.....	175
9.5 Outcome measurements of the efficacy of galactagogues .....	177
9.6 Strengths and limitations.....	178
9.7 Final conclusions .....	179
9.8 Implications for postnatal healthcare practice .....	180
9.9 References .....	180
Appendices.....	183

## List of Figures

Figure 1-1 An illustration of the research methodology and the relationship between the chapters of this thesis. ....	7
Figure 6-1 The potential mechanism of <i>Saccharomyces cerevisiae</i> yeast-based supplements (SCYS) on breast milk production and composition.....	111
Figure 7-1 Flowchart of participant recruitment. ....	138
Figure 7-2 Summary of multivariate linear regression of the intervention (group) and confounders (secretor status, maternal age, and breastfeeding status) and HMO concentration change among 67 participants. ....	141
Figure 8-1 The amount of milk from hourly expressions. Box plots with different letters indicate significant differences. ....	165
Figure 8-2 Examples of the amount of milk from each expression in three visits for three participants. ....	166
Figure 9-1 The relationship between galactagogue use and perceived insufficient milk supply. ....	174

## List of Tables

Table 2-1 Effects of galactagogues evaluated in the reviewed studies .....	27
Table 4-1 Characteristics of interviewed breastfeeding women and postnatal healthcare professionals. .....	64
Table 4-2 Galactagogues reportedly used by breastfeeding women in New Zealand .....	65
Table 5-1 Statement of women’s perception of breast milk production. ....	86
Table 5-2 Demographics and characteristics of 72 breastfeeding mothers and their infants. ....	88
Table 5-3 Galactagogue used by participants who experienced or did not experienced PIM. ....	89
Table 5-4 Multiple logistic regression model for factors associated with the galactagogue use in New Zealand breastfeeding women. ....	91
Table 6-1 A selection of information on <i>Saccharomyces cerevisiae</i> yeast-based supplements (SCYS) available on the internet* . ....	102
Table 6-2 Description of B vitamin and mineral concentrations in a selection of commercially available <i>Saccharomyces cerevisiae</i> yeast-based supplements (SCYS).....	104
Table 6-3 A selection of information found on the internet about taking <i>Saccharomyces cerevisiae</i> yeast-based supplements (SCYS) to increase breast milk production* . ....	105
Table 7-1 Human milk oligosaccharides included in the analysis.....	131
Table 7-2 Demographic and infant and breastfeeding information .....	138
Table 7-3 Human milk oligosaccharide concentrations at the baseline and endpoint .....	140
Table 7-4 Participants’ perceptions of milk supply at baseline, each week, and at endpoint, and perceived effectiveness of the intervention at endpoint (n = 68).....	142
Table 7-5 Other adverse events reported by study participants.....	145

Table 7-6 Participants' perceptions of milk supply at endpoint and at follow-up at six months postpartum (n = 44) .....	146
Table 8-1 Demographics and other characteristics of participants (n = 24).....	161
Table 8-2 Description of the sessions and expressions .....	163

## List of Abbreviations

2'-FL	2-fucosyllactose
3-FL	3-fucosyllactose
3'-SL	3-sialyllactose
6'-SL	6-sialyllactose
AIC	Akaike's information criterion
AIM	Actual insufficient milk production
ANOVA	Analysis of Variance
Aotearoa NZ	Aotearoa New Zealand
ART	Aligned Rank Transform
A-Tet	A-tetrasaccharide
CI	Confidence interval
COR	Crude odds ratio
DASS	Depression Anxiety Stress Scales
EBF	Exclusive breastfeeding
FIB	Feedback inhibitor of lactation
HCAZ	Head circumference-for-age Z-score
HMO	Human milk oligosaccharides
LAZ	Length-for-age Z-score
LLL	La Leche League
LNFP-I	Lacto-N-fucosylpentaose-I
LNFP-II	Lacto-N-fucosylpentaose-II
LNFP-III	Lacto-N-fucosylpentaose-III
LNFP-V	Lacto-N-fucosylpentaose-V
LNNFP	Lacto-N-neofucosylpentaose
LNT	Lacto-N-neotetraose
LNT	Lacto-N-tetraose
LS	Lactation specialist
MMR	Mixed-methods research
MOS	Mannan oligosaccharides
MPR	Milk production rate
NZMoH	New Zealand Mistry of Health
OR	Odds ratio
ORS	Oral rehydration solutions

OTA	Ochratoxin A
PCOS	Polycystic ovary syndrome
PEI	Perceived effectiveness of the intervention
PHP	Postnatal healthcare professional
PIM	Perceived insufficient milk production
PIB	Perceived infant behaviour
PMQ	Perceived milk quantity and quality
PSA	Perceived significant others' attitudes
Q1	The first quartile
Q3	The third quartile
RCT	Randomised controlled trial
SCY	<i>Saccharomyces cerevisiae</i> yeast
SCYS	<i>Saccharomyces cerevisiae</i> yeast-based supplement
SD	Standard deviation
SPSS	Statistical Package for the Social Sciences
UL	Upper level
UK	United Kingdom
US	United States of America
USDA	US Food and Drug Administration
WAZ	Weight-for-age Z-score
WLZ	Weight-for-length Z-score
WHO	World Health Organization
YCWP	Yeast cell wall products

## List of Articles and Conference Presentations

### Published article

1. Jia, L. L., Brough, L., & Weber, J. L. (2021). *Saccharomyces cerevisiae* Yeast-Based Supplementation as a Galactagogue in Breastfeeding Women? A Review of Evidence from Animal and Human Studies. *Nutrients*, 13(3), 727. DOI: 10.3390/nu13030727

### Conference papers and presentation

1. Jia, L. L., Brough, L., & Weber, J. L. (2015). How Healthcare Professionals and Breastfeeding Women in New Zealand Use Food and Herbal Galactagogues: a Pilot Study. *Proceedings of the Nutrition Society of Australia*. 39, 96
2. Jia, L. L., Brough, L., & Weber, J. L. (2022, May). Use of Galactagogues and Perceptions of Breast Milk Supply among Breastfeeding Women. In *Medical Sciences Forum* (Vol. 9, No. 1, p. 46). MDPI.
3. Jia, L. L., Brough, L., & Weber, J. L. Effect of *Saccharomyces cerevisiae* yeast-based supplement on human milk oligosaccharides concentration and mothers' perception of breast milk supply: a randomised placebo-controlled trial. Abstract presented at the "MORE THAN MILK" Lactation Science Symposium 2022 (November 25, 2022) at Perth, Australia.
4. Jia, L. L., Brough, L., & Weber, J. L. Concentration of 12 Oligosaccharides in the Milk of New Zealand Breastfeeding Women. Abstract presented at the Nutrition Society New Zealand Conference 2022 (December 1-2, 2022), poster presentation.

## List of Appendices

Appendix 1 Literature search strategy.....	183
Appendix 2 Summary of studies on galactagogues (by postpartum days at the baseline) that included in the literature review (Chapter 2).....	185
Appendix 3 Sample size calculation based on human milk oligosaccharides concentration change (Chapter 3).....	214
Appendix 4 Timeline of changes in study design and recruitment procedures of the randomised placebo-controlled trial (Chapter 3).....	216
Appendix 5 Ethics approval for the qualitative study (Chapter 4).....	217
Appendix 6 Interview guides for postnatal healthcare professionals and breastfeeding mothers in the qualitative study (Chapter 4).....	218
Appendix 7 Ethics approval letter for the randomised placebo-controlled trial (Chapter 7).....	220
Appendix 8 Questionnaire of the baseline survey of the randomised placebo-controlled trial (Chapter 5 and Chapter 7).....	221
Appendix 9 Supplementary Table: Effectiveness of <i>Saccharomyces cerevisiae</i> yeast-based supplement (SCYS) on milk production in animals (Chapter 6).....	234
Appendix 10 The calculation of nicotinic acid and folic acid intake from <i>Saccharomyces cerevisiae</i> yeast-based supplement and risk of approaching upper level, and estimation of Ochratoxin A intake for New Zealand women (Chapter 6).....	242
Appendix 11 Questionnaire of the eligibility screening survey of the randomised placebo-controlled trial (Chapter 7).....	244
Appendix 12 Questionnaires of the weekly survey, the endpoint survey, and the follow-up survey of the randomised placebo-controlled trial (Chapter 7).....	246
Appendix 13 Twenty-four hour feeding and nappy change record (Chapter 7).....	269
Appendix 14 Infant anthropometric measurements for the randomised placebo-controlled trial (Chapter 7).....	272

Appendix 15 Multivariate linear regression of the intervention (group) and confounders (secretor status, maternal age, and breastfeeding status) and HMO concentration change from baseline to the endpoint of individual and total HMO among 67 participants (Chapter 7).....	273
Appendix 16 Participants' scores on the DASS-21 and subscales at baseline and endpoint (n = 68) (Chapter 7) .....	275
Appendix 17 Infant anthropometry measurements and Z-scores at the baseline and the endpoint (n = 67) (Chapter 7) .....	276
Appendix 18 Infant breastfeeding frequency and duration over 24 hours at baseline and the endpoint (n = 68) (Chapter 7) .....	277
Appendix 20 Participants' self-reported adverse effects at baseline and the endpoint (n = 66) (Chapter 7) .....	279
Appendix 21 Hourly expression record (Chapter 8) .....	280
Appendix 22 Summary of studies on galactagogues published in 2022 and 2023 (Chapter 9) .....	281
Appendix 23 DRC 16 forms for Chapter 4, 5, 6, 7, and 8 .....	290
Appendix 24 Researchers' contributions .....	295

# Chapter 1 Introduction

## 1.1 Background

Breastfeeding not only provides optimal nutrition for infants but is also recommended for many short-term and long-term benefits for both infants and mothers. Breastfeeding can enhance immunity, reduce the risk of sudden infant death syndrome, protect from asthma, eczema and infections, and promote neurodevelopment for infants, especially preterm and low birth weight [1-6]. Breastfeeding also decreases the risk of postpartum depression and breast and ovarian cancers in mothers [7-9].

It is recommended that infants should be exclusively breastfed in the first six months of life and continue to be breastfed for at least two years [10, 11]. However, the breastfeeding rate in Aotearoa New Zealand (Aotearoa NZ) drops sharply from approximately 80% exclusive breastfeeding (EBF) at discharge to 16% EBF at six months of age and 13% breastfeeding to two years [12, 13].

Mothers reported perceived insufficient breast milk production (PIM) as one of the main causes of breastfeeding cessation or early introduction of formula. One integrative review published in 2008 suggested that globally 35% of women with early cessation of breastfeeding reported PIM as the primary reason [14].

Studies published after 2007 found that PIM was the first [15-26] or the second highest [27-30] self-reported reason for breastfeeding or EBF discontinuation. The rate of PIM ranges from 14% to 93% in these studies. Further, PIM was reported as the main reason for breastfeeding cessation in infants over six months [23, 28], suggesting that PIM is a common problem at all stages of breastfeeding.

Women in Aotearoa NZ commonly reported PIM as causing breastfeeding cessation. In the recent large longitudinal study "Growing up in New Zealand" (GUINZ), of 52% women (n = 3221) who were no longer breastfeeding their infant at nine months postpartum, 38% (n=1246) reported PIM as the primary reason for discontinuation [31]. In a large longitudinal study of 1085 Pacific mothers in Auckland reporting reasons for EBF cessation, PIM was ranked as the top reason by 56% (n=604) of

respondents [32]. In a longitudinal study in Manawatū, 44% (n = 61) of participants reported PIM as the main reason for introducing infant formula [33]. In a small qualitative study, Māori women also reported PIM as a reason for breastfeeding cessation [34].

PIM may be caused by the actual inadequate breast milk production or mothers' misperceptions of infant behaviours or other signs as meaning their milk supply is insufficient. Actual insufficient milk production may result from physiological issues that influence hormone related to breast milk production, affect milk composition or reduce milk removal, thus adversely influencing milk production [35, 36]. Breast hypoplasia or breast reduction surgery can lead to inability to produce sufficient milk [37, 38]. Additionally, inappropriate breastfeeding management and infant problems may result in insufficient milk removal causing downregulation of milk production [39, 40]. At times milk supply may be adequate, but women may misperceive it to be insufficient due to unsatisfied, unsettled or crying behaviour of infants or the watery appearance of breast milk, soft breasts, or small volume from expression may be taken as signs of the lack of quality or quantity of milk [41, 42]. Thus, women's perceptions of milk supply do not define adequacy of milk production.

Breastfeeding women and healthcare professionals sometimes use oral galactagogues with appropriate breastfeeding management to address PIM. Galactagogues are substances that may help to initiate, maintain or increase breast milk production and support breastfeeding [43, 44]. These substances are either pharmacological or natural products.

Pharmacological galactagogues are medications that can increase prolactin or oxytocin levels [45, 46]. To date, there are no medication approved as galactagogues in Aotearoa NZ [47]. However, domperidone is used "off-label" as a galactagogue [46]. Domperidone is a dopamine antagonist that can increase plasma prolactin levels [45, 48], thus it can address actual insufficient milk production for some women. A meta-analysis of five randomised placebo-controlled trials (RCTs) assessing the efficacy of domperidone found a small (93.97 ml/day) but significant increase in the amount of milk expressed [49], although one RCT found no significant differences in the mean volume of daily

expressed milk between the domperidone and placebo groups [50]. Studies in populations of healthy lactating women suggest that domperidone is safe and has a low risk of adverse effects on both term and preterm infants [51-53].

Compared with the requirement for a prescription for pharmacological galactagogues, herbal and food galactagogues such as herbal products and lactogenic foods are more easily available from community pharmacies, health food stores, supermarkets, and the internet [43, 54, 55].

Importantly, herbal and food galactagogues are associated with specific cultures and traditions. In Asian countries, local plants that have been used traditionally with the intent to improve breast milk quality and quantity are commonly added to maternal diets or made into special remedies as galactagogues [56-60]. In Western countries, commercial products containing herbs with reputations for increasing breast milk production are widely available as galactagogues [55, 61, 62]. However, galactagogues commonly used and studied in one country are not always widely used in others [63, 64]. Thus, galactagogue use in other countries provides a limited understanding of galactagogue use in Aotearoa NZ.

Surveys and qualitative studies have found that women used herbal and food galactagogues without PIM [54, 65, 66]. Apart from addressing PIM, women also reported using herbal and food galactagogues for other reasons such as to “support” breastfeeding [23] or use herbal galactagogues prophylactically before being concerned about their milk supply [26, 29]. These studies only provide limited information how and why women use galactagogues. More research is needed to explore the relationship between mothers’ perceptions of their breast milk supply and their galactagogue use.

Although breastfeeding mothers use galactagogues, there is limited scientific evidence of their efficacy and safety, especially for herbal and food galactagogues. A recent Cochrane review of 23 herbal and food galactagogues suggests they may increase breast milk volume and benefit infant weight but the authors were uncertain about the effect magnitude due to the insufficient evidence

[43]. The adverse effects of any particular galactagogues included in this review was unknown due to the limited data [43].

Interestingly, studies in this review not only evaluated the effectiveness of herbal and food galactagogues in increasing breast milk volume but also evaluated their effects on addressing PIM and supporting breastfeeding [43]. Measurements of mothers' perceptions of milk quantity and quality, infant behaviours, and breastfeeding self-efficacy were used to evaluate the effects of galactagogues. The proportions of breastfeeding (exclusive or any) at two, three, or six months postpartum were highlighted as the most important primary outcomes for trials, because improving exclusivity and duration of breastfeeding are the eventual goals of galactagogue use. Thus, herbal and food galactagogues are expected to increase breast milk volume, address PIM, and/or support breastfeeding.

To date, little is known about what galactagogues are used in Aotearoa NZ, how they are used, and the relationship between galactagogue use and mothers' perceptions of milk supply.

Women in Aotearoa NZ are reported to frequently source information about breastfeeding support from the internet [67]. *Saccharomyces cerevisiae* yeast-based supplement (SCYS) such as brewer's yeast is promoted online as the effective ingredient in lactation cookies to increase breast milk production. SCYS is also reported as a galactagogue used by breastfeeding women in the US [62], South Africa [68], and Australia [65]. However, no scientific evidence supports the effect of SCYS on increasing breast milk production. Animal studies suggest that SCYS can increase milk yield in ruminants and possibly affect milk composition [69-71]. The interspecies differences in digestion systems and the physiology of lactation make it inappropriate to extrapolate the outcomes from animal studies to human lactation [72, 73]. Thus, human studies are required to investigate if and how SCYS influences breast milk production, milk composition and PIM.

One potential mechanism by which SCYS could reduce PIM is by altering milk composition (e.g., human milk oligosaccharides), which may benefit infant growth, development, and gut immunity and consequently reduce infant unsettled or crying behaviour. These infant behaviours are commonly recognised by breastfeeding women as signs of inadequate milk supply [41, 74, 75]. Human milk oligosaccharides (HMOs) are the third most abundant component in human milk and as prebiotics benefit infants' gut health and modulate infant immune responses [76, 77]. A recent study found a maternal diet high in prebiotic fibre affected oligosaccharide content of rat milk and consequently influenced the gut microbiota in offspring [78]. Human studies have also found maternal diet can influence HMOs abundance and profile [79, 80]. SCYS can act as a prebiotic [81, 82], but to date there is no research in human or animal models investigating the effect of maternal supplementation with SCYS on milk oligosaccharides.

## 1.2 Research question and aims of the thesis

The research questions for this thesis are: How are herbal and food galactagogues used in Aotearoa NZ, and what are their potential effects?

The aims of this thesis are:

1. To explore galactagogue use in a sample of women in Aotearoa NZ.
2. To explore the relationship between mothers' perceptions of milk supply and galactagogue use.
3. To investigate the influence of a *Saccharomyces cerevisiae* yeast-based supplement (SCYS) on breast milk and breastfeeding.

## 1.3 Structure of the thesis

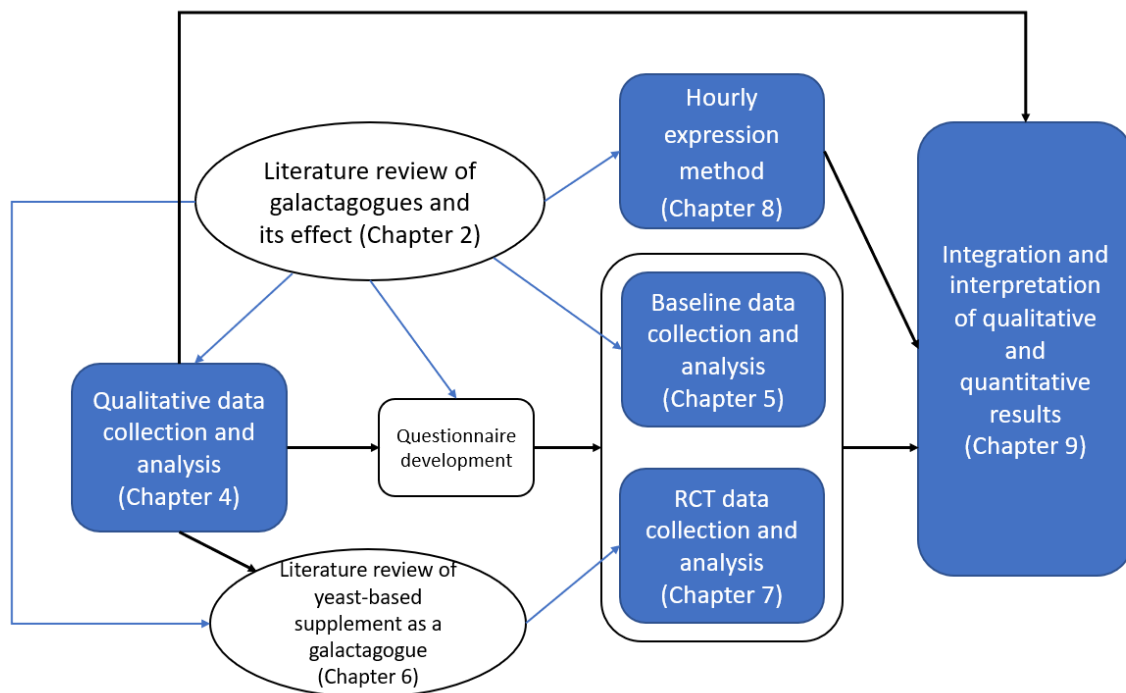
This thesis consists of nine chapters, which can be divided into three main sections. The first three chapters form the first section to introduce the background knowledge, research gaps, the research

questions and aims, and the objectives of this study. Chapter 1 is an introduction which provides a general background on herbal and food galactagogue use among breastfeeding women, as well as a description of the aims and objectives of the thesis. This is followed by a literature review (Chapter 2) covering the physiology of human lactation, factors influencing breast milk production and mothers' perceptions of breast milk production, as well as an overview of galactagogue use in other countries. A scoping review is also included in Chapter 2 to overview the effects of galactagogues investigated in the literature and how these effects have been measured. Chapter 3 describes the overarching methods for this thesis and the connections between the two studies conducted (a qualitative study and an RCT on the effect of SCYS). Chapter 3 also briefly describes changes made to the study design for the RCT.

This is followed by the second section, comprised of the five chapters about the two studies carried out. These are written in manuscripts format for journal publication. Chapter 4 describes the findings from the qualitative study about the experiences of and attitudes to galactagogue use among breastfeeding women and postnatal healthcare professionals in Aotearoa NZ. Chapter 5 investigates the relationship between galactagogue use and PIM using data from the baseline survey of the RCT. Chapter 6 is a literature review about SCYS and the supplement's role as a galactagogue. Chapter 7 describes the main findings from the RCT that investigated the effect of a SCYS on the concentrations of human milk oligosaccharides and on mothers' perceptions of milk supply. Chapter 8 focuses on the hourly expression method used to estimate breast milk production. Data collected from a subgroup of participants in the RCT is used to highlight issues that arose using the hourly expression protocols.

The last section, Chapter 9, is the final discussion and conclusion of the thesis. This chapter includes a summary of the main findings, considerations of the contributions this work has made to the research field, priorities for future research, and the study's strengths and limitations, as well as recommendations for public health practice.

The links between the chapters for this thesis is illustrated in **Figure 1-1**.



**Figure 1-1 An illustration of the research methodology and the relationship between the chapters of this thesis.** This thesis includes two literature reviews (Chapter 2 and Chapter 6) and two studies (a qualitative study reported on in Chapter 4 and a randomised placebo-controlled trial (RCT) reported on in Chapter 5, 7 and 8). Chapter 2 provides background knowledge about human lactation and galactagogues. This knowledge builds to the study aims and design for the above two studies, as well as the literature review of the effect of *Saccharomyces cerevisiae* yeast-based supplementation on breast milk production, composition and mothers’ perceptions of milk supply in Chapter 6. Chapter 6 builds to the study aims and design for the randomised placebo-controlled trial in Chapter 7. The qualitative study in Chapter 4 supports the questionnaire developed for the RCT. The results from both studies are integrated and interpreted in Chapter 9.

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## Chapter 2 Literature review

### 2.1 Introduction

This chapter introduces several topics relevant to breast milk production and galactagogue use. The physiology of human lactation, which provides the knowledge to understand the mechanisms by which galactagogues may increase breast milk volume, is explored first. It is followed by the definition and signs of perceived insufficient breast milk production (PIM) and factors influencing mothers' perceptions of breast milk production. This knowledge is required to understand the potential relationship between galactagogue use and PIM. Following is a wider discussion on galactagogue use among breastfeeding women and postnatal healthcare professionals (PHPs) and the efficacy and safety of galactagogues. This section highlights the lack of understanding behind the reasons for galactagogue use among breastfeeding women. Furthermore, it illustrates breastfeeding women's and PHPs' expectations of galactagogues' effects on addressing PIM and breastfeeding support. A scoping review of studies on galactagogue is presented, reporting on the outcomes evaluated, and the measures used to assess these outcomes. In summary it is concluded that galactagogues may be used to support breastfeeding in many ways, and PIM can be addressed in ways other than by increasing breast milk volume.

### 2.2 Physiology of human lactation

#### 2.2.1 Anatomy and physiology stages of human lactation

The basic units of a mature mammary gland are the alveoli which are constituted of mammary epithelial cells capable of milk synthesis [1, 2]. Each alveolus is surrounded by a contractile unit of myoepithelial cells responsible for ejecting milk into the ducts [2]. About 10 – 100 alveoli compose a lobule, and 20 - 40 lobules are connected to a lactiferous duct that drains milk into nipple openings [2]. The lobules and draining ducts related to each lactiferous duct constitute a lobe of the mammary gland, and one breast consists of 15 – 20 lobes [2].

The physiology of human lactation is commonly described in five stages. The first stage is mammogenesis, or proliferative phase, which involves mammary gland development from early pregnancy to mid-pregnancy. The amount of adipose tissue decreases to half that of glandular tissue, and the breast size and weight increase [1-4].

The second stage, secretory differentiation or lactogenesis I, starts from mid-pregnancy to late pregnancy. Mammary epithelial cells differentiate into secretory cells, and colostrum is synthesised and accumulated in secretory lobular alveoli [2, 4, 5].

The third stage is secretory activation or lactogenesis II, commonly known as “milk coming in”. Secretory activation happens around 3 - 8 days postpartum when copious milk is produced. Mother's self-reported sudden breast fullness correlates with the actual timing of the onset of copious milk [6, 7]. Frequent and effective milk removal and the rapid and irregular infant sucking patterns after birth play critical roles in the consequent milk production. The frequency of milk removal in the first 24 hours is associated with the milk intake of a healthy term infant in the first week [8]. It is also reported that for exclusive pumping mothers of preterm infants a higher number of expressions during the first day postpartum resulted in a greater amount of expressed milk during the first 14 days [9]. A study using a breast pump that mimics the suction patterns of healthy term infants found that the infant suckling pattern before the onset of secretory activation may significantly impact the transition from the initiation to the maintenance of lactation [10].

From the copious secretion of milk (around 9 – 15 days postpartum) to the beginning of involution, milk secretion is regulated locally by the mammary gland and the supply is maintained according to infant demand. This maintenance stage is also known as galactopoiesis or lactogenesis III [11]. At this stage, the infant's effective and frequent milk removal continues to play a significant role in regulating breast milk production, as shown in observation of healthy full-term dyads as well as mothers exclusively expressing [12-14].

At the end of lactation, mammary glands gradually remodel and return to pre-pregnancy sizes under regulation by hormones and proapoptotic factors [4]. This involution stage lasts an average of 40 days after breastfeeding has ceased [2, 3].

### 2.2.2 Endocrine, autocrine, and paracrine control of breast milk production

Oestrogen and progesterone mainly control the development and proliferation of mammary cells during pregnancy [3]. Prolactin also regulates mammary gland development during pregnancy and stimulates milk (and colostrum) secretion after mid-pregnancy [4]. Plasma oestrogen and progesterone concentrations increase during pregnancy, and the high oestrogen and progesterone concentrations inhibit milk synthesis. After the delivery of the placenta, the progesterone concentration decreases, which triggers secretory activation [15, 16].

Prolactin and oxytocin are two essential hormones for breast milk production. Prolactin is secreted by the anterior pituitary gland, and its secretion is inhibited by dopamine from the hypothalamus. During pregnancy, prolactin serum concentration increases dramatically from 10 ng/ml at pre-pregnancy to 200 ng/ml at 40 weeks gestation [17]. The baseline prolactin concentration remains high after delivery and gradually decreases and returns to pre-pregnancy concentration around six months postpartum [18]. During lactation, prolactin secretion responds to infant suckling episodically, and the basal prolactin concentration (blood prolactin concentration  $\geq$  90 minutes after a breastfeed) is associated with the intensity of breast stimulation [18, 19]. Thus, breastfeeding on demand is important to stimulate and maintain prolactin concentration. However, blood prolactin concentration does not correlate with milk synthesis rate from one to six months postpartum [18], which suggests that prolactin has a permissive function in milk synthesis after lactation is established.

Oxytocin is a peptide hormone secreted by the posterior pituitary gland. Oxytocin stimulates milk ejection by signalling the contraction of myoepithelial cells surrounding the alveoli and by relaxing the milk duct sphincters. The release of oxytocin occurs immediately in response to infant suckling and

lasts about 20 minutes on average [20]. The pulsatile release of oxytocin causes several milk ejections during a feed [21, 22]. Infant milk intake from one feed correlates with the number of pulses of oxytocin [23] and the number of milk ejections [22]. However, only some studies investigating the relationship between maternal blood oxytocin concentration and milk production found a correlation between oxytocin concentration and infant milk intake in one feed (or volume from one expression) [20].

Besides prolactin and oxytocin, other hormones also influence milk production indirectly. These hormones include hypothalamic peptide hormones, thyrotropin-releasing hormone, prolactin-releasing peptide, growth hormone, glucocorticoids, cortisol and insulin [15, 24-26].

In addition, a few autocrine-paracrine factors have been proposed for the mechanisms of the emptying of the breast in regulating breast milk production. Serotonin, parathyroid hormone-related protein and insulin-like growth factors are suggested to increase milk secretion. In contrast, transforming growth factor  $\beta$ ,  $\alpha$ -lactalbumin, and casein-derived phosphopeptides are down-regulators of milk secretion [27]. Serotonin is also proposed as a feedback inhibitor of lactation that reduces milk synthesis [28]. Serotonin is reported to modestly delay the onset of copious milk production in breastfeeding women but does not impact breastfeeding success [29]. The knowledge of local regulation of human lactation is still growing.

### **2.3 Perceived insufficient breast milk production**

Perceived insufficient breast milk production (PIM) is reported as an important reason women give up breastfeeding or discontinue exclusive breastfeeding before the infant is six months of age [30]. PIM is defined by some researchers as breastfeeding women's perception of inadequate milk production to meet the infants' needs [30, 31]. Perceptions of milk supply can include perceptions regarding both the quantity and quality of milk [32-34]. The definition of PIM implies that PIM may result from actual insufficient milk production (AIM) or misperceptions of of milk supply, e.g. interpreting unsettled

infants or frequent breastfeeding as due to the infant receiving insufficient milk [35, 36]. In this thesis, the term PIM refers to women's perception of insufficient quantity and/or quality of milk to meet infant needs, regardless of the actual adequacy of her milk supply.

There are many reasons why a woman may perceive her milk to be insufficient. Furthermore, psychological conditions and the attitudes of significant others may affect her perception of her breast milk supply. These signs and factors are described in the following sections.

### 2.3.1 Actual insufficient milk production

Milk production measures the infant's breast milk intake instead of the mother's capacity for milk synthesis [16]. Studies reported a relatively stable mean milk production (i.e., 750 – 800 mL/24 hours) up to six months after lactation is established, however, a large variation between women was found (480 mL to 1,200 mL/24 hours) [37-40].

Many terms are documented in the literature to describe the problem of actual low milk production, such as “insufficient lactation”, “lactation failure”, or “failed lactogenesis II”. The definition of these terms varies from study to study. Some researchers defined the problem as low milk volume compared with “normal” or “peak volume” [41].

Some signs are commonly used to identify actual insufficient milk production, including infant weight gain, milk transfer, audible swallowing from the infant and the number of soiled nappies [42]. The American Academy of Paediatrics (AAP) recommended in 2005 that a healthy term infant should pass “3–5 urines and 3–4 stools per day by 3–5 days of age; 4–6 urines and 3–6 stools per day by 5–7 days of age” and weight loss should not exceed 7% of birth weight [43]. In practice, these indicators are commonly used to identify delayed secretory activation, a later-than-usual onset of copious milk production [42, 44]. Infant weight crossing the WHO growth chart centiles downward is suggested as a critical indicator for actual insufficient milk production in the first three months [42].

### 2.3.2 Factors that can cause insufficient milk production

Many factors can lead to AIM and, therefore, influence PIM. Some factors are modifiable, and milk production may increase once the problem is addressed. However, the mother may have physiological problems that impair her milk production capacity, leading to long-term lactation insufficiency.

Anatomical breast problems, including glandular and nipple problems, may result in AIM. Insufficient glandular tissue can prevent women from producing copious milk (i.e., failed secretory activation) due to inadequate glandular development [45, 46]. This problem is referred to as primary lactation insufficiency by researchers and PHPs, and the prevalence is reported as less than 5% of breastfeeding women based on limited scientific evidence [45, 47]. Breast surgery may also cause damage to breast tissue, ducts, nerves, or blood supply and impair milk synthesis and milk ejection [48]. Nipple abnormalities such as inverted or flat nipples can cause difficulty for infant suckling and consequently decrease milk removal and thus reduce milk production [49]. Some treatments and techniques can address the nipple abnormality and enable those women to breastfeed their infants successfully [49, 50].

Some other health problems and conditions can result in hormone or metabolism disorders, leading to AIM, although the mechanisms are unclear [51]. Maternal diabetes and obesity are risk factors for delayed secretory activation, low milk production and early cessation of breastfeeding [52, 53]. Diabetes and obesity are associated with insulin resistance and consequently influence milk synthesis [54]. Thyroid dysfunction may adversely affect milk synthesis and the milk ejection reflex, causing ongoing issues of maintenance of lactation [55]. Polycystic ovary syndrome (PCOS) may adversely influence mammary gland development and milk synthesis, potentially due to the high levels of androgen, the elevated oestrogen concentrations in obese women with PCOS, insulin resistance which is common to PCOS, or the low progesterone concentrations in some cases [56, 57].

Many drugs can adversely influence prolactin or oxytocin concentrations and cause AIM. Dopamine agonists such as ergot alkaloid drugs can decrease prolactin secretion and significantly affect milk production [58]. Oestrogen-containing contraceptives increase dopamine which inhibits prolactin release and also interferes with the initiation of lactation, so it is recommended to delay use until four weeks postpartum [51]. Nicotine consumption interferes with prolactin secretion and the milk ejection reflex [59]. Daily breast milk production at two weeks postpartum was about 100 ml lower among women smoking tobacco than in a non-smoking control group [59]. Alcohol consumption can increase prolactin concentrations but decrease oxytocin concentrations, which results in a significantly lower amount of expressed milk [60-62]. The suppressive effect of alcohol on serum oxytocin concentrations is dose-related [62].

Mild maternal malnutrition does not appear to result in AIM. Lactating women have higher energy and nutrient intake requirements than in pre-pregnancy to support their health and that of their infant [63-65]. Observational studies suggest malnutrition does not affect breast milk protein concentration [66]. In another study, decreasing maternal fat and energy intake by 25% (compared to the pre-study fat and energy intake) did not impair breast milk volume and composition [67]. However, maternal nutrient deficiencies such as protein, vitamin A, D and B12, and iron and zinc are reported to affect mammary gland development and function in rats or mice [26].

Infant health issues can result in infrequent or ineffective milk removal and cause short- or long-term AIM. Infants with oral problems such as cleft palate, tongue-tie or lip-tie can have difficulty latching onto the breast [68]. Neurological issues, low motor tone, sedation caused by drugs used during labour, preterm delivery, infant hypoglycaemia, Down's syndrome, and heart defects result in low demand, weak suckling or indirect lactation [69, 70]. These problems cause low prolactin concentrations as a consequence of insufficient stimulation of the breast at the early stages [15]. If the infants are admitted to the neonatal care unit and supplementary fed with formula, it can further increase the mothers' risk of insufficient milk production [52]. Moreover, it may lead to reduced ongoing milk

production if the infant issue continues because less frequent milk removal leads to the downregulation of milk synthesis [27].

Additionally, inappropriate breastfeeding management may lead to infrequent and/or ineffective breast milk removal and consequently cause AIM at different stages of lactation. Mother-infant separation, lack of skin-to-skin contact, delayed first feed, and formula feeds at the early stages may cause delayed secretory activation [51]. Inappropriate breastfeeding management at later stages, such as not feeding on demand, formula feeds and indirect lactation, may decrease breast stimulation and reduce milk removal, leading to milk synthesis downregulation and gradually decreasing milk production [27].

Problems such as inappropriate breastfeeding management and temporary conditions of the mother or infant are preventable or treatable. Once the problem is solved, the milk supply can increase. However, it is common in practice that the mother of an infant with oral problems (e.g., tongue-tie) or nipple problems herself may have to express breast milk temporarily. Indirect latching in these cases may lead to supplementary feeding and further reduction in milk production [69].

### 2.3.3 Factors influencing perceived insufficient milk production

Psychological and social factors may not directly influence milk production but impact women's perceptions of their milk supply and lead to PIM. However, the adverse perceptions may result in feeding the infant formula, which leads to reduced breast stimulation and less milk removal and eventually causes AIM.

Women's personalities, attitudes and knowledge of breastfeeding are psychological factors influencing PIM. Women who are motivated and determined to breastfeed exclusively and have adequate knowledge of breastfeeding management techniques usually strongly believe in their milk supply [31]. Postnatal distress (i.e., anxiety, stress and depression) may inversely correlate with endogenous oxytocin [71] and decreases breastfeeding self-efficacy [72], and potentially leads to PIM

[73]. Women who stopped breastfeeding because of PIM for their first child are also at higher risk of early cessation of breastfeeding due to PIM for subsequent children [74].

Significant others include health professionals, women's partners, family members and friends [34, 75, 76]. When these people doubt the mother's milk supply, she may consequently believe her milk is insufficient.

### 2.3.5 Galactagogues and perceived insufficient milk

Galactagogues are substances used by PHPs and breastfeeding women to address insufficient milk production and support breastfeeding [77, 78]. PHPs suggest women take galactagogues along with implementing methods of lactation management, especially when lactation management methods are not effective alone [44, 79, 80]. However, breastfeeding women often self-evaluate insufficient milk (i.e., PIM) with observation of infant behaviours and feeding practices as described previously. Thus, their milk production may be adequate or even excessive. Hence for breastfeeding women to assess galactagogues as effective, it may be unnecessary or even insufficient to measure breast milk volume. However, milk volume is often the primary focus for research investigating the efficacy of galactagogues [81, 82].

Existing research finds that most herbal and food galactagogues have limited influence on breast milk volume [77]. However, herbal and food galactagogues may have other mechanisms of action for the mother and/or the infant, impacting mothers' perception of breast milk production. These assumptions can be categorised as 1) improving mothers' physical and/or mental health status, which improves prolactin and/or oxytocin concentrations; 2) substance transferring into breast milk or altering milk composition, therefore altering infant behaviour; and 3) altering energy and fat content in breast milk to increase infant satisfaction. There has been limited research into these potential impacts of galactagogues. However, some studies have investigated the influence of herbal

galactagogues on mothers' perceptions of breast fullness, maternal satisfaction, and perceived infant satisfaction [83-86]. A scoping review in section 2.5 will further discuss the effects of galactagogues.

## 2.4 Galactagogues

### 2.4.1 Use of galactagogues among breastfeeding women

Although the prevalence of herbal and food galactagogues in the populations is not reported, results from non-probabilistic sampling surveys suggest that they are widely used among breastfeeding women in Western countries. At the beginning of the 21st century, approximately 15% of US breastfeeding women used herbal galactagogues [81]. In 2004, a Norwegian survey of 400 women using herbs in pregnancy found that 43% had used herbal galactagogues during previous breastfeeding [87]. In 2013, a survey of 304 Australian breastfeeding women reported 24% of women used at least one herbal galactagogue [88]. However, one Italian survey (n=244) published in 2014 suggested that only 2.8% of women used herbs to stimulate or maintain breast milk production [89]. More recent surveys in the US and Australia reported higher proportions of herbal and food galactagogue use among breastfeeding women. An online survey of 188 women from 27 states in the US found that 46% of women used at least one herbal galactagogue [90]. An Australian online survey of 1876 breastfeeding women reported 60% of women using one or more galactagogues, with the top three most used being lactation cookies (47%), brewer's yeast (32%), and fenugreek (22%) [91].

The use of domperidone as a galactagogue also shows an increasing trend. Investigations of prescription and dispensing records from Australia, Canada, and the UK suggested that the overall prevalence of use increased from 2.7% to 20% from 2000 to 2015 [92-95], with up to 30% prevalence of domperidone use as a galactagogue in preterm birth [92, 93]. The above Australian online survey of 1876 breastfeeding women found 19% of women (n = 355) using domperidone to increase breast milk production, making it the fourth most used galactagogue [91].

Qualitative studies exploring women's experiences and perspectives of galactagogue use suggest that women may use herbal and food galactagogues to support breastfeeding. First, women not only use galactagogues to increase milk production when they perceive or are diagnosed with insufficient milk supply, but they also use galactagogues prophylactically [96, 97]. Second, women were found to use herbal and food galactagogues to build milk supply and to support post-birth recovery as part of cultural traditions [98-100].

Many factors may impact women's decisions to take galactagogues, according to the findings from the qualitative research. These factors include perceived effectiveness [96, 97, 99], concerns about safety [97, 99, 101], as well as the influence of significant others such as partners, family members, friends, and other breastfeeding women [96, 97, 102, 103]. Further, the internet has become an important information source regarding breastfeeding support and galactagogue use and contributes to how breastfeeding women choose herbal and food galactagogues [97, 104].

#### **2.4.2 Recommendation of galactagogues by postnatal healthcare professionals**

Although women reported PHPs as an important source of information regarding galactagogue use [90, 91, 97, 103, 105, 106], only a few studies are available to provide a limited understanding of how PHPs recommend galactagogues in practice. A survey of a convenience sample of midwives in Switzerland (n = 351) and Canada (n = 80) found that most of the midwives surveyed (93% in Switzerland and 100% in Canada) discussed galactagogue use with their patients. However, only a small percentage of respondents (14% in Switzerland and 26% in Canada) reported using an official protocol or national guideline [107]. The authors did not detail that "official protocol or national guideline". The midwives in both countries believed in the effectiveness of natural and pharmaceutical galactagogues based on their experiences and observations in practice [107]. A survey in the US (n = 71) reported that 70% of a convenience sample of PHPs recommended galactagogues, including obstetricians/gynaecologists, paediatricians, nurses, midwives, lactation consultants and breastfeeding peer support providers (i.e., counsellors and Le Leche League leaders). In this survey,

82% of PHPs perceived that galactagogues were useful and 24% expressed their concerns about the lack of evidence regarding the efficacy and safety of galactagogues [108]. It is important to note that all these studies were conducted in convenience samples that may overestimate or underestimate herbal and food galactagogue use by PHPs.

#### 2.4.3 Efficacy and safety of galactagogues

Although galactagogues are commonly used by breastfeeding mothers and recommended by some PHPs, there is limited scientific evidence of efficacy and safety for galactagogues, except for domperidone. The mechanism of how domperidone increases breast milk volume is based on the stimulation of maternal prolactin concentrations [109]. A recent meta-analysis on the efficacy of domperidone combined results from five randomised placebo-controlled trials (RCT) involving 239 patients. The effect size showed a mean increase of expressed breast milk volume of 93.97 ml/day in women receiving domperidone [110]. A few adverse effects were reported by women using domperidone, such as headache, dry mouth, and gastrointestinal problems [111-113]. However, a review on RCTs of domperidone use suggested no increased risk of adverse effects compared to placebo (risk ratio 1.05, 95% CI 0.65–1.71) [109].

A recent Cochrane systematic review suggested little evidence to support the effect of herbal and food galactagogues on infant weight, milk volume or support breastfeeding, as well as no apparent adverse effect for the mother or the infant, based on limited research of 23 herbal and food galactagogues in women with term infants [77].

However, many of the galactagogues included in this Cochrane review were herbal remedies that consisted of multi-ingredients of herbs and foods. Thus, the effect of these galactagogues on breast milk production cannot speak to the effect of individual herbs or food ingredients in a remedy. The only two herbs evaluated in more than one intervention study are moringa [77, 114, 115] and fenugreek [83, 116-119]. However, these studies evaluated different outcomes, such as infant weight

and volume of breast milk. They used different participant groups, e.g., women with or without AIM in different stages of lactation. The diverse study design makes it impossible to conclude the galactagogue efficacy of fenugreek or moringa.

Despite differing methods and outcome measures between the studies, this Cochrane review compared three primary outcomes across studies, i.e. the proportion of breastfeeding women (exclusive or any) at different infant ages, the weight of the infants receiving only their own mothers' milk, and the volume of breast milk [77]. The authors criticised the heterogeneity in the outcome measures, making it difficult to compare the results between studies for the same galactagogue. Therefore, consistency in outcomes and their measures is needed in future studies to reduce heterogeneity across studies.

## 2.5 Scoping review of human studies of galactagogues to identify outcome measures

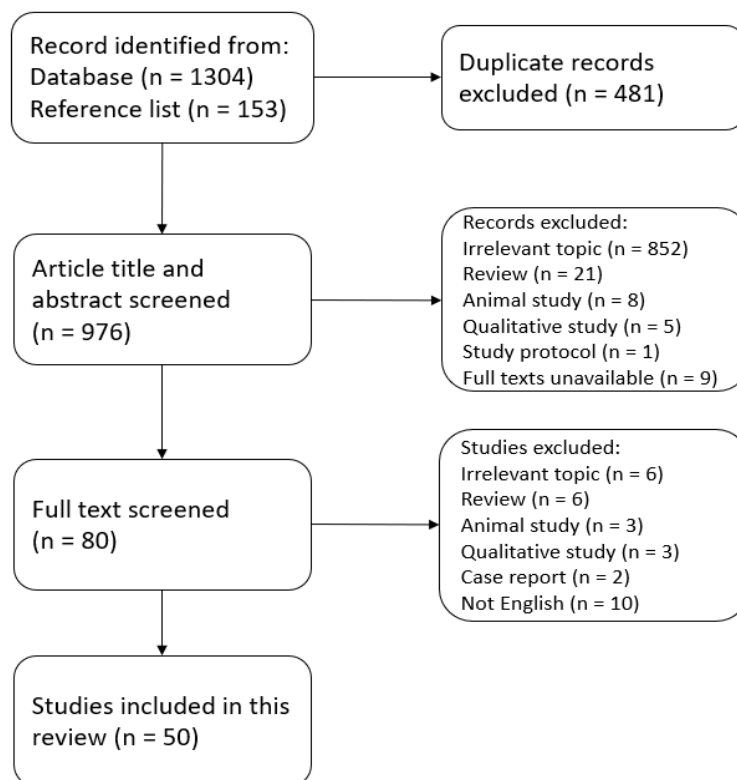
This section aims to review which effects of galactagogues are evaluated in human studies and how these effects (i.e., the outcomes) are measured. Since the recent systematic review and meta-analysis of research assessing the efficacy and safety of galactagogues in human studies have discussed their results [77, 109], this review only focuses on discussing methods.

The databases screened included PubMed, Scopus, and Web of Science, with publishing dates from 1 January 2000 to 31 December 2021. The search terms included “galactagogue” or “galactogogue” and the (scientific or common) names of specific galactagogues combined with “breast milk” or “human milk” or “human lactation” (e.g., “Foeniculum vulgare” or “fennel” AND “breast milk” or “human milk” or “human lactation”). A complete list of the search terms is in **Appendix 1**. A preliminary screening of article titles and abstracts was conducted to exclude duplicate records and irrelevant results, and then the remaining articles were screened by reading full texts. The reference lists of identified articles and review articles of galactagogues were further screened for additional relevant articles. Only articles published in the English language were included. Articles with human participants with

prospective or retrospective designs were chosen, whereas animal studies and *in vitro* studies were excluded. Studies involving galactagogues through injection or other non-oral delivery methods were also excluded.

### 2.5.1 Description of the reviewed studies

A total of 50 articles were identified, which studied 29 types of galactagogues. Of these 50 articles, 34 studies are randomised controlled trials (RCTs) with a control and/or placebo group, three studies had quasi-experimental designs with control groups, one trial was a case-control study, three studies had two or three randomised treatment groups without a control group, four studies had a one group pre-test post-test design, and one pilot was a randomised feasibility study. In addition, there was one post-marketing surveillance study and two retrospective studies (**Figure 2-1**). These studies not only have diverse study designs but also have a wide range of participants, study durations, as well as outcomes reported. An overview of the study designs, participants, and outcomes of the included studies by postpartum days is in **Appendix 2**.



**Figure 2-1 Study flowchart.**

## Participants' characteristics

The recruitment criteria differed among studies; therefore, participants' demographic and clinical characteristics varied considerably. Thirteen studies (14 articles) enrolled women with preterm infants, 17 included mothers with infants aged 0 – 7 days at baseline, and ten enrolled women whose infants aged over seven days at baseline or ranged from newborn to six months of age. Furthermore, three studies did not report infant age at baseline, and another study recruited women during the third trimester of pregnancy. Fourteen studies recruited women experiencing insufficient milk supply or lactation failure with inconsistent definitions, and none of these studies reported if the infant was receiving other sources of nutrition (e.g., wet nurse, donor breast milk, or formula). In addition, five studies only recruited mothers who were exclusively breastfeeding, three studies recruited mothers of infants who were mixed-fed with formula, and the other studies did not describe if they recruited any women who were using formula.

## Study aims and outcomes

The main aim of most of the reviewed studies was to investigate the effect of galactagogues on breast milk production (n = 48); two studies had other aims. Of these two studies, one study aimed to investigate the safety of a galactagogue tea among breastfeeding women but also included outcomes on milk production and mothers' perceptions. The other study aimed to evaluate the influence of one galactagogue tea on the antioxidant capacity of participants' milk and only included relevant outcomes.

Although the volume of milk was the most frequently measured outcome of breast milk production, various outcomes were reported across the reviewed studies (**Table 2-1**). Some studies indicated a primary outcome, whereas others had a few outcomes without indicating the primary one. Further, the methods used to measure the outcomes differed between studies. The outcomes and the methods used to measure these outcomes are discussed in section 2.5.2 to section 2.5.4.

**Table 2-1 Effects of galactagogues evaluated in the reviewed studies**

Effect	Number of articles		
	Preterm N = 14	≤7 days postpartum at baseline N = 17	> 7 days postpartum at baseline or not provided N = 19
Breast milk volume	13	11	10
Breast milk production score			1
Formula volume		2	1
Hormones related to breast milk production			
Blood prolactin concentrations	7	4	3
Blood oxytocin concentrations		1	
Breast milk composition	1	1	3
Maternal perceptions			
Perceived effectiveness	1	1	3
Perceived breast fullness		1	2
Perceived milk ejection			1
Perceived insufficient milk			1
Perceived infant satisfaction			2
Maternal satisfaction		1	2
Postnatal distress	1		1
Infant			
Infant weight	1	5	8
Weight loss after birth		2	
Time to regain birth weight		1	
Infant growth		1	4
Breastfeeding frequency in 24 hrs		2	3
Breastfeeding duration in 24 hrs		1	
Urination frequency in 24 hrs		1	2
Defecation frequency in 24 hrs			2
Infant sleep duration		1	
The proportion of women who were breastfeeding	1	3	2
Safety			
Adverse effects	12	6	9
Transfer into milk	3		
Other effects			
Total antioxidant capacity of milk		1	
Maternal weight			1
Maternal food consumption		1	

### Limitations in RCT design

In this review, 68% of the studies were RCTs, considered the gold standard to evaluate the effectiveness of an intervention or treatment [120]. However, these RCTs had many limitations, such

as small sample size, lack of statistical power, insufficient randomisation and blinding, short duration, lack of compliance data and absence of a placebo group.

Moreover, only a few RCTs controlled potential confounders of galactagogue efficacy. Psychological, nutritional, and environmental factors such as lactation management, breastfeeding education and access to breastfeeding support can influence breastfeeding and PIM [121-123]. Although it is difficult to control the impact of these factors adequately, researchers need to minimise the influences of these factors in a small trial by appropriate randomisation and control the factors as confounders in data analysis. However, only five trials provided standard procedure of breastfeeding education and support during their hospital stay [112, 117, 124-126]. Two trials that evaluated the effect of food groups or a food programme provided standard diets to participants, which would improve homogeneity between groups [127, 128]. The mental and emotional status of the mother was evaluated in three trials [86, 129, 130]. Further, studies targeting women with lactation inadequacy and providing explicit criteria for lactation inadequacy had limited the study population to a small and homogeneous group (as shown in **Appendix 2**) [84, 131, 132].

## 2.5.2 Various measurements of breast milk volume

### Studies used diverse outcomes after measuring breast milk volume

Breast milk volume was measured in 32 studies, but some reported milk volume as outcomes, and others used outcomes created/calculated from the breast milk volume. Twenty studies reported 24-hour milk volume as the outcome, either from the amount of milk produced in 24 hours [111, 112, 114, 118, 125-127, 130, 132-139], or an average 24-hour milk volume of a few consecutive days [140-143]. One study reported the total milk volume from the whole study period as the outcome (14 days) [144]. Three studies used the within-participant milk volume change from baseline to the time point of evaluation as the outcome, including two studies of preterm infants that measured 24-hour milk volume [145, 146] and the other study that measured volume from one expression at 48 hours and

72 hours postpartum [128]. Calculating within-participant milk volume change can control the intra-individual variation, so it is appropriate in a small sample.

Another six studies also evaluated the amount of milk from one expression [117, 124, 131, 147], two expressions in one day [113], or from one breastfeed [148]. Five of these studies reported the volume of milk as the outcome, but the other study used the number of participants with adequate improvement of milk as the outcome. The adequate improvement of milk production was defined as the volume at the endpoint being 50 mL more than the volume at baseline [131].

The 24-hour milk volume measurement is more reliable than milk volume from a few expressions/breastfeeds for representing breast milk production. The milk volume from a single expression (breastfeed) or two expressions can be influenced by the time of a previous feed or expression and introduce bias to the study. Two studies reported the timing of expression since the previous expression/breastfeed [113, 147], but only one study suggested that participants emptied both breasts in the previous expression [147].

The average amount of 24-hour milk volume from a few consecutive days may be more reliable than a single 24-hour evaluation due to the approximate 10% daily variation within an individual in milk production [39, 149]. However, it is a burden for mothers to measure breast milk production for a few days. Researchers may consequently face poor compliance during the study or many withdrawals. Unfortunately, the above studies did not report the compliance and withdrawal rate.

In addition, two studies evaluated the amount of milk but did not use the amount of milk as the outcome. One study transformed milk volume to lactation level and compared pre-test and post-test lactation levels in each group. However, the authors neither reported whether the milk volume was from one breastfeed or a total amount over 24 hours nor described how to transform milk volume to lactation level [150]. The other reported the number of women with reference to different milk volume categories (<200mL/day, 200 – 400 mL/day and >400 mL/day) and the milk volume was not

reported [151]. None of these two studies justified why they transformed the volume of milk into other outcomes, so it is unknown if these outcomes are more appropriate than the volume of milk.

#### Various methods of measuring breast milk volume

Notably, five methods were used for measuring the amount of milk across these studies. The most frequently used method was milk expression by hand, manual breast pump or electric breast pump in 21 studies [111-114, 117, 124-126, 128, 130-133, 137, 138, 140-145]. The separation of mother and infant and the fragility of preterm infants make it challenging to establish breastfeeding and effective breast milk expression in neonatal units for breastfeeding promotion [152]. Thus, all 14 studies, including women with preterm infants, measured breast milk volume by exclusively expressing/pumping [112, 125, 126, 130, 133, 137, 138, 142-145]. However, exclusive pumping on schedule can interfere with normal breastfeeding patterns for term infants with demand feeding and may not denote milk production.

Seven studies in the current review used 24-hour weighing of the infant before and after feeds to estimate breastmilk volume [118, 134, 135, 139, 147, 148, 150]. One study used test weighing of the mother, accounting for evaporative water loss, before and after feeds to determine the total infant milk intake in 24 hours [136]. Twenty-four-hour test weighing has been established as the standard to assess milk production [153].

Importantly, a few issues need to be considered and managed when using 24-hour test weighing to evaluate the effect of galactagogue on increasing breast milk volume. The volume of vomiting and spilling could influence the total breast milk intake in 24 hours if the infant vomits/spills frequently. One study investigating the accuracy and precision of test weighing reported that vomiting happened in 15% of infants and spilling happened in 20% of infants [154]. These percentages cannot necessarily be applied to breastfeeding on demand since infants in this study were fed by bottle, cup, or nasogastric tube in the hospital. The percentage of vomiting/spilling in studies using 24-hour test

weighing to evaluate breast milk intake of infants fed on demand has not been reported in the literature. Researchers have also questioned that 24-hour test weighing may “disturb infant feeding pattern” [155]. For example, an infant may fall asleep after a breastfeed. If the infant woke up during weighing, the mother might give the infant another feed. It is unknown how often this subsequent feed happens during 24-hour test weighing and if the infant would be weighed again after this subsequent feed. When evaluating the effect of a galactagogue on increasing breast milk production, these issues may introduce bias as they may happen randomly during the 24-hour test weighing, at the baseline or the endpoint. Researchers should consider the above potential bias during sample size calculation and eliminate them from data analysis if necessary.

Further, 24-hour test weighing indicates infant intake but not the mothers’ capacity for breast milk production. The infant may or may not drink the milk if more milk is available. If the excessive milk was not removed (either by the infant or the breast pump), the stored milk would induce the local downregulation of milk synthesis and consequently lead to milk production reducing back to the infant’s need. Thus, it may be difficult to use the 24-hour test weighing method to evaluate the increase milk volume due to galactagogues.

Another study used the hourly expression method, as described by Lai et al. [149], with adaptation by having the participants empty their breasts then express for 15 minutes one hour later (i.e., the second expression) and multiplying the amount by 24 to estimate 24-hour milk volume [147]. However, the authors did not report if they had experiments to validate the adapted method. In the original hourly expression method, Lai et al. suggested that the average amount of milk from at least two consecutive expressions after two hours can be used to calculate the 24-hour milk volume [149].

Further, one study used 24-hour weighing of the infant before and after feeds, then adding the residual milk expressed after each feed to estimate mothers’ total milk produced in 24 hours [127]. This method evaluates the mothers’ capacity for milk production. However, it may not work for

everyone because women reported negative experiences with breast pumps, such as expressing a small amount of milk or being unable to express any milk, especially after a feed [156-158].

To summarise, breast milk volume is the most frequently used outcome across these studies, and 24-hour milk volume is the direct indicator of milk production. When infants cannot feed on breasts, exclusive expressing is valid to evaluate the volume of milk. However, measuring 24-hour milk volume may be difficult to manage if the infant is breastfeeding on demand. Cases of vomiting, spilling, and subsequent feed that are caused by disturbed sleep during test weighing need to be recorded and managed for evaluating the efficacy of galactagogues.

### 2.5.3 Indirect measures of breast milk production

Many outcomes in studies included in this review used measures that are not direct indicators of breast milk production. These factors are supplementary feeds of formula, maternal prolactin and oxytocin concentrations, infant weight and growth, breastfeeding frequency, infant urination and defecation frequency, as well as maternal perceptions other than PIM.

#### Supplementary feeds of formula

Three studies reported the volume of supplementary feeds given to the infant before and after the intervention. Two studies compared the mean volume of infant formula consumed between the galactagogue and the control group and reported the volume of formula as a secondary outcome [85, 159]. However, Manjula et al. used the reduction in formula intake as the primary outcome and compared the volume of formula between the galactagogue and the placebo group [84]. This study recruited mothers of infants aged 10 – 180 days with lactation failure, defined as failure to regain birth weight at 15 days postpartum or supplementing formula in volumes of more than 250 mL/day.

Importantly, reduction of formula use could result from interventions such addressing breastfeeding management, additional expressing or taking galactagogues. Manjula et al. did not report if they controlled breastfeeding management, expressing, or other galactagogue use in their study, so these

factors could be confounding the reduction of infant formula and making it inappropriate to be used as the primary outcome.

Further, women with AIM may need to use other methods (i.e., addressing breastfeeding management, additional expressing or taking other galactagogues) if the studied galactagogue failed to increase her milk supply. If the researchers accepted interventions other than the studied galactagogue during the study, they would need a bigger sample size and ensure the randomisation worked effectively to control these confounders. Compliance and withdrawal rates should also be included as secondary outcomes to evaluate the success of the studied galactagogue.

#### **Hormones related to breast milk production**

Fourteen studies evaluated maternal blood hormone concentrations related to breast milk production, including 13 studies evaluating prolactin concentrations [86, 111, 125, 126, 130, 132, 133, 143, 146, 147, 160-162], and one evaluated both prolactin and oxytocin concentrations [139]. Most of these studies reported the hormone concentrations as secondary outcomes, except for one study that aimed to evaluate the effect of papaya leaf on increasing prolactin concentrations [162].

Of note, three of these studies used prolactin concentrations as the primary outcomes to evaluate the effect of galactagogues on breast milk production [86, 160, 161]. Concrete changes in prolactin concentrations may provide evidence of pathways to milk supply increase. However, insufficient evidence supports the determination of a prolactin concentration threshold that may be associated with milk supply sufficiency [18, 163]. Thus, maternal prolactin concentrations should not be used as the primary outcome to evaluate breast milk production [86, 160].

#### **Breast milk composition**

Breast milk composition was used as an outcome in some studies. Five studies described breast milk composition with reference to protein and carbohydrates [111, 118, 127, 140, 164]; fats [111, 127, 140, 164]; vitamin A [140, 164]; calcium [111, 118, 140]; iron [118, 140]; zinc, potassium, and

magnesium [118]; and sodium and phosphate [111]. All these studies indicated that the aim of testing milk composition was to evaluate the effect of galactagogue use on milk quality or nutrient contents.

A change in milk composition may be a mechanism by which galactagogue can address PIM or support breastfeeding. A change in milk composition could possibly promote infant growth and development or improve infant comfort and consequently reduce infant crying behaviour, finally improving mothers' perception of milk production. To test this hypothesis, researchers need to evaluate the relationship between the targeted component in breast milk and infant growth, infant behaviour, and PIM.

### Maternal perceptions

Nine studies evaluated maternal perceptions of the effectiveness of galactagogue use, milk supply, infant satisfaction, and other maternal perceptions relevant to the mothers' psychological status [84-86, 129, 130, 145, 148, 165, 166].

Four studies evaluated the perceived effectiveness of the galactagogues. Two RCTs reported perceived effectiveness as a secondary outcome by recording the mother's guess if she received milk thistle or placebo [145] or by a 5-point Likert scale on perceived effectiveness [84]. In a retrospective survey, Kim et al. used the percentage of women who perceived pigs' feet as effective in increasing their milk supply as the primary outcome [165]. In a post-marketing surveillance study, participants' perceived lactation improvement and perceived supply increase were reported as primary outcomes, although no description of the measurements was provided [166].

Women may guess if they consumed the galactagogue or placebo by other signs than the effectiveness on milk supply. For example, some women reported having sweet smelling urine or sweat after taking fenugreek [140, 148]. This side effect may be an obvious sign for women to guess they were taking fenugreek. Thus, guessing the consumption of galactagogue/placebo could be inappropriate to evaluate mothers' perception of effectiveness.

Furthermore, mothers may use several signs to judge the effectiveness of galactagogues, such as the volume of milk they express, their breast fullness, frequency of milk ejection or breastfeeding patterns [99]. Comparing women's perceptions of these signs between the galactagogue group and the placebo and/or the control groups may provide more objective measures of mothers' perceptions of their milk supply.

Four studies evaluated the participants' perceptions of milk supply, including one study that evaluated PIM using a 7-point Likert scale [148], while the other three assessed perceptions of breast fullness [84, 85, 129]. Two studies evaluated perceptions of breast fullness using a 5-point Likert scale (infants aged 10 – 180 days) [84] or a 10-point Likert scale (infants aged 0 – 2 months) [129]. A third study used the number of women perceiving breast fullness within 48 hours postpartum as the primary outcome of the galactagogue's efficacy on breast milk production [85]. The sudden feeling of breast fullness within 72 hours postpartum is suggested to be an indicator of the onset of secretory activation [42, 69]. However, after the milk supply is established, the feeling of breast fullness could be less frequent or disappear when the infant is 2 – 4 months of age [69]. Thus, researchers can only use perceptions of breast fullness as a secondary outcome once at the stage of galactopoiesis.

Maternal perceptions of infant satisfaction were evaluated as a secondary outcome in two studies using 5-point Likert scales, but infant satisfaction could have different meanings in these two studies. One study evaluated perceived infant satisfaction regarding the amount of milk received [129]. The other study evaluated participants' perceptions regarding infant happiness and wellbeing [84].

Further, other maternal perceptions relevant to the mothers' psychological status, such as maternal satisfaction, breastfeeding self-efficacy and postnatal distress, were reported in three studies as secondary outcomes [86, 129, 130].

PIM could be the primary outcome for studies on the efficacy of galactagogues when the efficacy of galactagogues is defined as addressing PIM and supporting breastfeeding. Hill and Humenick's

Lactation Scale [167] and the Perception of Insufficient Milk questionnaire [32] are two established scales used to evaluate PIM. However, neither of them was used in the studies included in this literature review. Breast fullness and perception of infant satisfaction may both be indicators of PIM. Mothers' psychological status can influence breastfeeding self-efficacy which is associated with PIM [168, 169]. However, more factors may influence mothers' perception of milk supply, as described in the section 2.3.2. A measurement tool that can capture all aspects of mothers' perceptions of milk supply (i.e., evaluating all these factors) may provide a more thorough evaluation of PIM.

### Infant measurements

The effects of galactagogues on infant growth and behaviours were evaluated in terms of a few factors, such as infant weight, infant growth, infant sleep, 24-hour breastfeeding frequency and duration, and 24-hour waste elimination frequency.

Fifteen studies evaluated infant weight, including 13 studies using infant weight as the outcome [83, 84, 86, 117, 133-135, 150, 160-162, 166, 170, 171], one study using numbers of infants with excessive weight loss after birth (defined as > 7% of birth weight) as the outcome [85], and the other study using maximum infant weight loss and time to regain birth weight as the outcomes [124]. Five studies also used other outcomes of infant growth, including head circumference (four studies) [83, 134, 160, 170] and head circumference-for-age-z-score (one study) [134], chest and mid-arm circumference (one study) [160], length and length-for-age-z-score (one study) [134], weight-for-age-z-score (one study) [134], and infant BMI (one study) [141].

In practice, excessive infant weight loss after birth and not regaining birth weight by 14 days postpartum are indicators of delayed or failed secretory activation [42, 69]. Thus, measuring infant weight can indicate milk production for exclusively breastfeeding women at the initiation stage of lactation. However, infant weight does not accurately measure breast milk production once the milk supply is established. When using infant weight as an outcome, researchers assumed that an infant

would drink more milk after the mother used galactagogues. However, infants fed on demand may or may not drink more. If the galactagogue increased milk synthesis, but the infant did not drink that excess milk, the local control of milk synthesis would adjust it to meet the infant's needs [27-29]. Thus, infant weight is an insufficient outcome to evaluate the efficacy of galactagogues on breast milk production.

Infant weight and growth can be affected by many factors, such as heredity, infant sex, gestational age and maternal BMI [172]. Although random allocation may help achieve an even distribution of these factors in the galactagogue and the placebo groups, power analysis is necessary to estimate the sample size and compare these variables at baseline to check if randomisation is effective.

Six studies evaluated the effect of galactagogues on infant behaviour changes as outcomes, describing this as breastfeeding frequency in 24 hours (five studies) [83, 85, 136, 170, 173], mean breastfeeding duration per feed (one study) [136], infant morning and evening sleep duration (one study) [161], defecation and/or urination frequency in 24 hours (three studies) [83, 170, 171]. Breastfeeding frequency, urination and defecation frequency can be impacted by many factors, such as infant appetite, digestion and health conditions, so they are inappropriate to be used as primary outcomes to evaluate the efficacy of galactagogues on breast milk production.

#### **2.5.4 The proportions of women breastfeeding at different stages of lactation**

Six studies reported the proportions of breastfeeding women in the total number of study participants at different stages of lactation. Three studies reported the proportion of women exclusively breastfeeding at three months postpartum (two studies) [134, 174] or at six months postpartum (one study) [175]. Another three studies reported the proportion of women breastfeeding (exclusive or any) at day one, day three and day seven postpartum (one study) [159], at one week, one month, four months, six months and 12 months postpartum (one study) [176], or at three, six, nine and twelve months after 4-week intervention (one study with infants aged 0 – 2 months) [129].

Promoting breastfeeding rate and duration is the ultimate goal for galactagogue use; thus, the proportion of breastfeeding women is an appropriate primary outcome for RCTs investigating the effect of galactagogues on supporting breastfeeding. However, breastfeeding duration is associated with many demographic factors, physical factors of the mother and the infant, social support and maternal psychological factors such as intention in breastfeeding and breastfeeding self-efficacy [177, 178]. These factors need to be controlled in the study using the proportion of breastfeeding women (exclusive or any) at different stages of lactation, especially for the studies that follow up in the long term.

### 2.5.5 Safety of galactagogues

Twenty-seven studies evaluated the safety of taking galactagogues [84, 86, 111-113, 124, 126, 129-134, 137-140, 142-145, 148, 159, 165, 171, 173]. All studies reported evaluating adverse effects on the mother; six also reported evaluating adverse effects on the infant [129, 132, 140, 148, 159, 173]; and three reported on the transfer of the galactagogue into the breast milk [126, 143, 145]. One study reported the toxicity of shatavari in mice [86].

Most of these studies used self-reported adverse effects by reporting the number of cases. However, one study that aimed to evaluate the safety of a commercial breastfeeding tea evaluated the self-reported adverse effects on the mothers themselves and their infants [129]. The authors recorded the number of days without any symptoms and the number of days with digestive symptoms, respiratory symptoms, dermatological symptoms, or other symptoms. This method provides more objective measures on the adverse effect than asking the mother to report adverse effects because one may forget to report a minor symptom.

Monitoring the side effects for the mother and infant is essential for all intervention studies. Comparing the symptoms between the galactagogue and the placebo groups is necessary since the mothers usually self-reported adverse effects. Comparing the compliance and withdrawal rates

between the galactagogue and the placebo groups may also help evaluate the potential influence of side effects. Unfortunately, none of the above studies reported compliance and withdrawal rates.

## 2.6 Conclusions

Galactagogues are substances suggested to increase breast milk production. Breastfeeding women in Western countries used a wide range of herbal and food galactagogues. Surveys and qualitative studies of breastfeeding women and PHPs suggest that galactagogues are used not only among women with milk supply issues but also among women without milk supply concerns. However, future research needs to provide an in-depth understanding of the roles of galactagogues in breastfeeding, particularly in Aotearoa NZ since research has yet to investigate galactagogue use here.

There is limited scientific evidence to support the efficacy of most herbal and food galactagogues in breast milk production and their safety during lactation. Many studies of galactagogues' efficacy and safety had limitations in study design, including non-homogeneous participant selection, biased measures of breast milk volume or insufficient measure of breast milk production, or limited understanding of the mechanisms behind a galactagogue's use.

A scoping review of human studies on galactagogue efficacy and safety found that various outcomes were evaluated, and the measurements for the same outcome differed from one study to the other. Breast milk volume was the most frequently evaluated primary outcome in studies investigating the effect of galactagogues on breast milk production and was evaluated by different methods. When the mother is exclusively pumping/expressing, 24-hour expressed milk volume is valid to estimate her milk production. However, when the infant is breastfeeding on demand, 24-hour test weighing of the infant/mother provides the infant's milk intake but not the mothers' milk production capacity. These studies also included many indirect outcome measures of breast milk production, such as maternal prolactin concentrations, breast milk composition, maternal perceptions, and infant weight. There is a lack of measurement tools that may capture all aspects of mothers' perceptions of milk supply.

Further, the proportion of women breastfeeding at different stages of lactation was used to evaluate the effect of galactagogues to support breastfeeding. Thus, researchers need to choose appropriate outcome measures according to their interest in the effect of galactagogues. Breast milk volume and mothers' perceptions of milk supply are appropriate if a study aims to investigate a galactagogue's effect on addressing PIM. In contrast, the proportion of women breastfeeding at different infant ages is appropriate for evaluating the effect of a galactagogue on supporting breastfeeding.

Self-reported adverse effects of the mother and infant were commonly reported as the outcome measure for the safety of galactagogues. However, most studies only reported the number of cases of adverse effects without reporting compliance or withdrawal of the study.

Future research needs to investigate potential mechanisms and make reasonable hypotheses before designing RCTs of galactagogue effects on breast milk volume. Researchers also need to choose appropriate measurements for outcomes, recruit participants at the same stage of lactation, monitor compliance and withdrawal of the study, and control for psychological, nutritional, and environmental factors that influence breast milk production in an RCT.

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## Chapter 3 Methodology

### 3.1 Introduction

This PhD project answers its broad research question through two related but independent research questions: 1) how are galactagogues being used in Aotearoa New Zealand (Aotearoa NZ) to support breastfeeding; and 2) what are the effects of these galactagogues? A mixed-methods research design was developed, which resulted in one qualitative study and one randomised placebo-controlled trial (RCT). This chapter describes the methodology of the project and briefly introduces the study design of the two studies. It also explains the changes made to the aims and objectives, study design and primary outcomes of the RCT as a result of problems in the method evaluating breast milk volume and the adverse impact of COVID-19. More details of the study design, sample size estimation, participant recruitment criteria, recruitment procedures, and outcome measures are described in the following chapters, which are written in the format of manuscripts for publication in scientific journals.

### 3.2 Research methodology

Mixed-methods research (MMR) has gained attention in social science and health science because it integrates quantitative and qualitative data through the study design, methods, interpretation, and reporting [1-3]. The exploratory sequential design is one type of MMR. It starts with qualitative data collection and analysis phases, which inform the instrument design, and it is followed by a quantitative phase of either an observation/survey or an intervention [4]. The exploratory sequential design has been widely used in health and nutrition studies to develop questionnaires or assessment tools [5-8]. These studies include three steps: first, the qualitative data are collected to understand individual experiences deeply; second, an instrument is established based on the literature and the findings from the qualitative approach; last, quantitative data are collected for a bigger sample using the newly developed instrument.

To achieve the aims of this thesis, the exploratory sequential design was used. In the first phase, qualitative methods were applied to collect and analyse data from purposive samples of breastfeeding women and postnatal healthcare professionals (PHPs). Qualitative findings informed the consideration of outcomes and questionnaire design for a randomised placebo-controlled trial (RCT), the second phase of this PhD project.

### 3.3 Qualitative study design and its contribution to the randomised placebo-controlled trial design

The first phase was a qualitative descriptive study that investigated how galactagogues are used in Aotearoa NZ, and explored the attitudes of breastfeeding women and PHPs to galactagogues. Qualitative description is a method used to understand and describe phenomena without theoretical construction and with low-inference interpretations of data [9-11]. Using qualitative description in research is appropriate to gain knowledge from original sources [9].

Semi-structured interviews were conducted with a sample (n = 22) of breastfeeding women and women who had breastfed in the past year and with a sample (n = 16) of PHPs who were involved in breastfeeding support in Aotearoa NZ. Inductive thematic analysis was used to identify and analyse the themes within the data. The details of the study design and results from the first phase of the qualitative study are described in Chapter 4.

The results from the qualitative study led to the choice of the galactagogue for further investigation, i.e., *Saccharomyces cerevisiae* yeast-based supplement, SCYS, which was frequently mentioned as a galactagogue among study participants. The results of the qualitative study also informed the outcomes to be measured in the RCT to evaluate SCYS. The main concern related to milk supply among participants in the qualitative study was the quantity of milk. Participants in the qualitative study also reported concerns about milk quality and infant behaviour as signs of PIM. Further, participants suggested that when significant others questioned their milk supply, they would perceive their supply

was insufficient. These findings informed the development of a questionnaire used for data collection in the second phase. More details of the survey design and results are reported in Chapter 5 and Chapter 7.

### 3.4 Randomised placebo-controlled trial design and changes

We designed a double-blind, randomised, placebo-controlled trial to assess the efficacy of a SCYS to address PIM and support breastfeeding.

We proposed that SCYS may address PIM by 1) increasing the volume of breast milk, 2) improving postnatal distress that may impact oxytocin release and enhance breastfeeding self-efficacy, and 3) altering breast milk composition (i.e., human milk oligosaccharides [HMO]) which may consequently change mothers' perception of milk supply or perception of infant behaviour. More details of these hypotheses for mechanisms are discussed in Chapter 6.

In the originally designed RCT, breast milk volume was the primary outcome. The sample size was estimated as 40 in each group, with the assumption of a 10% increase in milk production in the SCYS group and no increase in the placebo group at a power of 80% and a significance level of 0.05. The target sample size was 120, considering the high drop-off rate in studies on breast milk production [12].

We evaluated breast milk volume using the 'hourly expression' method [13]. In this method, the mother expressed one breast for ten minutes by an electric pump every hour, and the volume of milk obtained after two hours is defined as the "milk synthesis rate", which can be used to estimate 24-hour milk volume [14]. The hourly expression method suggests that the volume of milk obtained from the third hour (fourth expression) represents the individual milk synthesis rate. However, in our RCT, we found that consistent amounts of milk from the third and fourth expressions using mini-electric pumps were only achieved by some participants. We also observed increases and decreases in the amount of milk expressed during the 3-hour expression sessions. For this reason, we were uncertain

about using this measure of milk synthesis as an outcome measure for our RCT. Our experience with the hourly expression method is discussed in Chapter 8.

In addition to the questions about the accuracy of the milk production estimate, we had difficulties conducting the hourly expression protocol during the COVID-19 pandemic, especially during Level 3 and Level 4 lockdowns, where all research at the University was suspended. Participants had to store the milk from each of the four expressions separately in their home freezer until the researcher could meet them in person. This procedure differed from pre-pandemic, where the researcher evaluated the volume of milk immediately after each milk expression session. This difference introduced error with respect to the volume of milk. It also increased the risk of missing data if the participant was unable to follow the updated procedure or if the participant was isolated at the time of the study visit, which meant the milk sample could not be collected.

Considering the above issues, we decided to abandon evaluating the quantity of milk as the primary outcome. Instead, we used HMO concentration change as the primary outcome of the RCT. Accordingly, the sample size was estimated as 32 in each group, with the calculation based on the assumption that the change of total HMO concentration in the SCYS group was 80% of that in the placebo group (**Appendix 3**).

The decision about the change in study design assumed that randomisation would result in participants' secretor status being evenly distributed between the SCYS and placebo groups. The most abundant HMO, 2-fucosyllactose (2'-FL), is only present in approximately 70% of women's milk [15, 16]. These women (secretors) have an active secretor gene to encode the enzyme responsible for 2'-FL synthesis [17]. The secretor status is associated with the concentration of many individual HMOs [18], making it the biggest confounder in our RCT to evaluate the effect of the SCYS on HMO concentration. Unfortunately, there were significantly more secretors in the placebo group than in the SCYS group. Therefore, it was inappropriate to compare the concentration change of total HMO between the two groups without adjusting for secretor status. Thus, multivariate linear regression

with the bootstrap method [19, 20] was used to address potential confounders. In addition to the intervention as the main factor to be investigated, the confounders included in the regression model were secretor status, maternal age, and breastfeeding status [18, 21, 22]. Thus, four predictors were included in each model to evaluate individual and total HMO concentration change from baseline to the endpoint of the RCT. The final estimated sample size was 53, with the assumption of the effect size of the model of total HMO concentration change as 0.25, at a power of 80% and a significance level of 0.05 [23].

The details of the study design and recruitment for the final method are reported in Chapter 8. The timeline of changes in study design and recruitment procedures is described in **Appendix 4**.

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## Chapter 4 The experience of and attitudes to galactagogue use among Aotearoa New Zealand breastfeeding women and postnatal healthcare professionals: a qualitative study

Herbal and food galactagogues are used in many Western countries. However, galactagogue use is related to culture and galactagogues widely used in one country may not be popular to the same degree in another country. Little is known about how galactagogues are used in Aotearoa New Zealand (Aotearoa NZ). The qualitative study presented in this chapter aimed to understand the experiences of and attitudes to galactagogue use among breastfeeding women and postnatal healthcare professionals in Aotearoa NZ.

The results from this study informed the choice of galactagogue (i.e., *Saccharomyces cerevisiae* yeast-based supplement) investigated in the randomised placebo-controlled trial in Chapter 8 as well as the questionnaire design described in Chapter 7 and Chapter 8.

This chapter has been prepared for submission to the *International Journal of Environmental Research and Public Health*.

## 4.1 Abstract

**Background:** Herbal and food galactagogues are used in many Western countries. A few studies suggest that women may use herbal and food galactagogues for reasons other than increasing breast milk production. To date, no research has investigated galactagogue use in Aotearoa New Zealand (Aotearoa NZ). This study aims to explore the role of galactagogues in breastfeeding in Aotearoa NZ, and to understand breastfeeding women's and postnatal healthcare professionals' (PHPs) attitudes to galactagogue use.

**Methods:** Semi-structured in-depth interviews with two groups of participants (22 breastfeeding women and 16 PHPs) were conducted from October 2014 to October 2015. Qualitative descriptive and thematic analysis were applied with an inductive approach.

**Results:** Many foods, herbs, and other products were used as galactagogues, such as lactation cookies, lactation tea, fenugreek, naturopath and homeopath remedies, and brewer's yeast. Domperidone was the only pharmacological galactagogue used by the participants. Apart from increasing breast milk supply, women used herbal and food galactagogues to maintain milk supply and milk quality or prophylactically to support breastfeeding. Women's desires to breastfeed and beliefs in natural products facilitated the use of herbal and food galactagogues. Interviewed PHPs were cautious about galactagogue use and suggested the implementation of breastfeeding management techniques prior to discussing galactagogue use.

**Conclusion:** Galactagogues are used by Aotearoa NZ women to address breast milk supply problems and support breastfeeding generally. Future studies should evaluate efficacy and safety of herbal and food galactagogues to provide evidence-based information to mothers and PHPs.

## 4.2 Background

The benefits of breastfeeding for both child and maternal health are well established [1, 2]. However, the exclusive breastfeeding rate drops sharply in developed countries from around 80% at the initiation stage of lactation [2, 3] to 29% in Australia [4], 25.8% in the US [5], 17% in Aotearoa NZ [6], and 1% in the UK [5], respectively, at six months postpartum. Insufficient milk production is the most common cause of early cessation of breastfeeding both globally [7] and in Aotearoa NZ [8]. However, actual milk production is often not evaluated in the literature or in practice; instead, maternal perceptions of milk supply are used [7]. Perceived insufficient milk production (PIM) was defined in the literature as the statement by the mother that she thought her milk supply was inadequate to meet her infant's needs [7, 9]. To address the problem, breastfeeding women and postnatal healthcare professionals (PHPs) sometimes use galactagogues, which are medications, herbs, foods and supplements that are proposed to enhance milk production [10, 11].

There is no existing evidence of how galactagogues are used in Aotearoa NZ. However, international surveys suggest a wide range of herbal and food galactagogues are used in Western countries. A recent Australian survey (n = 1876) reported that 60% of respondents are using one or more galactagogues, and the most used galactagogues are lactation cookies (47%), brewer's yeast (32%) and fenugreek (22%) [12]. Another Australian study investigating breastfeeding-related phone call queries to a medical service (n = 2034) found that approximately 3% were on galactagogue use [13]. Although discussion of domperidone accounts for most of these phone calls, queries related to herbal galactagogues increased from 0% in 2001 to 23% in 2014 [13]. One recent online survey of a convenience sample of US breastfeeding women (n = 188) found that fenugreek and fennel were used as galactagogues by 45.7% and 30% of respondents, respectively, but less than 3% of respondents used medications such as domperidone and metoclopramide to increase breast milk production [14]. Another US survey reported that 70.4% of 71 PHPs recommended galactagogues in their practice [15].

A survey of midwives in Switzerland (n = 351) and Canada (n = 80) found that 93% of midwives in Switzerland and 100% of midwives in Canada discussed galactagogue use with their patients [16].

The use of galactagogues is associated with cultural traditions, especially for herbal and food galactagogues. Special foods and herbs (e.g., fermented rice chicken soup, ginger, banana flower, and fenugreek) traditionally recognised as galactagogues are added to the postpartum diet to increase milk production in many Asian countries [17-20]. However, in Europe, the US and South Africa, commercial herbal products and supplements are commonly used as galactagogues whether or not these products are recommended by PHPs [14, 16, 21-25].

Interestingly, survey and qualitative studies investigating galactagogue use among breastfeeding women suggest that women may use herbal and food galactagogues for reasons other than increasing breast milk production. A small Malaysian survey (n = 83) found that 53% of respondents reported PIM as the reason for using herbal galactagogues [26]. Also, in the survey, however, 23% of women reported the reason for galactagogue use was to provide good supplements for breastfeeding, and 12% used herbal galactagogues as part of postnatal treatments [24]. Qualitative studies suggest that some Australian women used herbal galactagogues prophylactically [27, 28], which could contribute to the increased use of herbal galactagogues in Australia.

However, there is a lack of understanding of herbal and food galactagogues' other roles, i.e., in addition to increasing breast milk production, in the current literature. Most surveys focused solely on the percentage of respondents using galactagogues [12, 14, 23, 29] and/or the perceived effectiveness and safety of galactagogues [12, 14, 29, 30] without directly examining the specific reasons behind galactagogue use. Whereas the qualitative studies only illustrated the decision-making process that women went through surrounding the use of herbal galactagogues, they have yet to examine the different purposes for which breastfeeding women use galactagogues aside from increasing the amount of breast milk they produce [25, 27, 28, 31, 32].

Furthermore, it remains unknown how the widespread use of herbal and food galactagogues influences breastfeeding practice. In practice, postnatal healthcare professionals usually introduce appropriate breastfeeding management, such as correcting latching and positioning, breast compression, and extra expressing, prior to galactagogue use [33, 34]. This is because of limited scientific evidence relating to the efficacy of most herbal and food galactagogues and their possible side effects [10]. More importantly, breast milk synthesis mainly depends on frequent milk removal on infant demand after the milk supply is established at secretory activation [35]. It is important to investigate if breastfeeding women would perceive galactagogue use as an appropriate replacement for other methods that address PIM.

Only one qualitative study investigated breastfeeding women's perspectives and attitudes to herbal galactagogue use, which focused on the reasons for using herbal galactagogues [27]. There is a lack of understanding of PHPs' attitudes to galactagogue use.

Therefore, this qualitative study aims: 1) to explore the roles and purposes of using galactagogues during breastfeeding in Aotearoa NZ and 2) to understand breastfeeding women and PHPs' attitudes to galactagogue use.

## 4.3 Methods

### 4.3.1 Design

We designed a qualitative descriptive study using semi-structured interviews to explore galactagogue use among breastfeeding women and PHPs in Aotearoa NZ [36]. This study was approved by the Massey University Human Ethics Committee: Southern A (14/68) (**Appendix 5**).

### 4.3.2 Participants

Participants were recruited nationwide in Aotearoa NZ. Interviews were completed in Palmerston North or via telephone based on the participants' locations and preferences, except for one

breastfeeding woman and two PHPs interviewed during the La Leche League (LLL) Conference 2014 in Auckland.

Two participant groups were targeted: 1) breastfeeding women and women who had breastfed their infants in the previous year and 2) PHPs involved in breastfeeding support, including midwives, lactation consultants (LCs), nurses working in maternity healthcare, Whānau Āwhina Plunket nurses<sup>1</sup>, LLL leaders and naturopath/homeopath practitioners. These two groups of participants were selected purposively to provide a well-rounded perspective on galactagogue use. Participants included women who reported being concerned or never being concerned about their milk supply and women who used or had never used galactagogues. Further, the participants included PHPs who might not use galactagogues themselves and/or in their practices, and they were able to provide different views on galactagogue use from a health professional vantage point.

Convenience sampling and snowball sampling were used for recruitment. Many organisations were contacted to recruit breastfeeding women and PHPs, such as Playcentres, local childcare centres, LLL New Zealand, the Plunket Society, Manawatū College of Midwives, and Palmerston North Hospital. Information sheets were distributed to potential participants through these organisations. Recruitment was ceased once saturation had been achieved [36-38]. A previous qualitative study exploring Australian breastfeeding women's experience using herbal galactagogues suggested that a sample size of 20 participants may achieve theoretical saturation [25, 27].

#### 4.3.3 Data collection

Participants were recruited between October 2014 and October 2015. The primary researcher (LJ) conducted one semi-structured in-depth interview with each participant after securing their consent. Oral consent was recorded separately from interviews when conducted by telephone calls. The

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<sup>1</sup> Whānau Āwhina Plunket is a non-profit organisation in Aotearoa NZ and the largest Well Child services provider to support the development, health, and wellbeing of children under five. Usually, Plunket nurses start to visit the mother and infant from 6 weeks of age.

average length of the interviews was 25 minutes (range 12 – 70). All interviews were audio-recorded via a digital recorder (during face-to-face interviews) or via Microsoft Lync (for telephone interviews). Two sets of interview guides were developed for the two participant groups (**Appendix 6**). The interview questions for breastfeeding women included how they dealt with concerns about milk supply and how they used galactagogues, their attitudes, information sources and understanding of galactagogue use. As for PHPs, the interview questions included how they managed insufficient milk production in practice, how they recommended galactagogues, and their personal experience and information sources about galactagogues. Interview probes were used to explore additional individual experiences and attitudes that arose from the interview process organically. Previous breastfeeding experiences were also explored for women who had more than one child. Demographic data was extracted retrospectively from the interview manuscripts.

#### 4.3.4 Definition of infant feeding status

This study used the World Health Organization (WHO) definition of exclusive breastfeeding. This means the infant was fed with breast milk only (including feeding on breasts, milk expressed or donor milk) without having water or any other food or drink for the first six months of life. However, the infant may have received rehydration solution, drops and syrups (vitamins, minerals and medicines) [39].

We used the term “predominant breastfeeding” with adaptation from the WHO definition [39], which means breast milk (including feeding on breasts, milk expressed or donor milk) was the main source of nutrition for the infant. In addition, the infant may also have received water and water-based drinks, fruit juice, ritual fluids, rehydration solution, drops and syrups (vitamins, minerals and medicines), and a small amount of formula (i.e., less than 100 mL) on occasion.

Mixed feeding is defined as the infant receiving both breast milk (including feeding on breasts, milk expressed or donor milk) and formula as the sources of nutrition, and the infant has received formula regularly.

#### 4.3.5 Data analysis

Demographic data were analysed using descriptive statistics and were described as frequencies (%). All the interviews were manually transcribed, and another researcher outside the research team reviewed the transcripts for accuracy. To protect participants' privacy, a pseudonym or study ID was provided based on their preference.

Inductive thematic analysis was used for data analysis [40, 41]. Briefly, LJ first read the transcripts multiple times to understand the data thoroughly. Trial coding was conducted using the first five interviews of breastfeeding women and the first four interviews of PHPs. Codes were discussed in multiple meetings with the other two authors (LB and JLW), and final codes were generated and applied to all transcripts. LJ iterated the new coding through all transcripts whenever a new code was identified. In the final stages of thematic analysis, LJ, LB and JLW reviewed and discussed the codes again and organised themes and categories. Data analysis was based on key questions providing fundamental description of galactagogue use in Aotearoa NZ. Qualitative description was used in this study. Sandelowski described this method as producing research findings closer to the data with lower-inference interpretation than phenomenological or theoretical descriptions [38, 42]. Since this is the first study to describe women's experiences of galactagogue use in Aotearoa NZ, qualitative description is considered appropriate. Coding and analysis were conducted using NVivo 12 software.

#### 4.4 Results

Twenty-two breastfeeding women and 16 PHPs were interviewed (**Table 4-1**). Most women experienced PIM and used galactagogues; one woman without concerns about her breast milk supply also reported the use of galactagogues. The PHPs interviewed include various occupations; seven had

more than one role (e.g., one midwife was also an IBCLC and a homeopath practitioner). Twelve PHPs reported discussing galactagogues with breastfeeding women in their practice, including midwives, IBCLC, LLL leaders and peer counsellors.

**Table 4-1 Characteristics of interviewed breastfeeding women and postnatal healthcare professionals.**

<b>Characteristics</b>	<b>n</b>	<b>%</b>
<i>Breastfeeding women (n=22)</i>		
Only one child	4	18
<b>Exclusive breastfeeding *</b>	11	50
<b>Predominant breastfeeding *</b>	4	18
<b>Mixed feeding *</b>	7	32
Concern of milk supply – Yes	20	91
Experienced PIM – Yes (n = 20)	18	90
Use of galactagogues – Yes	19	86
<i>Postnatal healthcare professionals (n=16)</i>		
Occupation (self-identified main practice area)		
IBCLC	4	25
Midwife	3	19
LLL leaders and breastfeeding counsellors	3	19
Whānau Āwhina Plunket nurse	3	19
Community nurse	1	6
Naturopath practitioner	1	6
Homeopath practitioner	1	6
Discussion of galactagogue use with breastfeeding women – Yes	12	75

PIM, perceived insufficient milk production; IBCLC, International Board Certified Lactation Consultant; LLL, La Leche League.

\* World Health Organization definition of exclusive breastfeeding was used[39]. Predominant breastfeeding was defined as the infant taking breast milk as the main source of nutrition but also receiving water and water-based drinks, fruit juice, ritual fluids, rehydration solution, drops and syrups (vitamins, minerals and medicines), and a small amount of formula (i.e., less than 100 mL) on occasion. Mixed feeding was defined as the infant being given some breast milk (including breast feed, milk expressed or milk from a wet nurse) and formula.

#### 4.4.1 Galactagogues mentioned by participants

Women were asked if they used any special food and herbs during breastfeeding in relation to their milk supply concerns. Participants mentioned a wide range of products as galactagogues, such as foods, supplements, breastfeeding teas, homeopathic, naturopathic and herbal medicines, domperidone and the mother’s placenta (**Table 4-2**).

**Table 4-2 Galactagogues reportedly used by breastfeeding women in New Zealand**

<b>Category</b>	<b>Galactagogues mentioned by participants</b>
Food	Oat, almonds, flaxseed, avocado, seaweed, molasses, pig trotter soup, chicken soup, garlic, fish, milo, hops, beer Lactation cookies*, wonder fudge, smoothie*
Supplements	Complan, Blackthorn Elixir, fish oil, brewer's yeast, spirulina, evening primrose oil, multi-vitamins and minerals
Homeopath, naturopath, and herbal products	Lactation AOK, Milk flow, homeo-botanical lacta, Tonic, breastfeeding tea**, fenugreek, blessed thistle, milk thistle, fennel, moringa, stinging nettles in capsule/tablet format
Medication	Domperidone
Other	Dried placenta from the mother

\* The potential lactogenic food, supplements and herbs mentioned in the lactation cookie and smoothie recipes include oat, flaxseed, brewer's yeast, spirulina, fennel, fenugreek, and blessed thistle.

\*\* Breastfeeding tea includes commercial products with different brands as well as homemade breastfeeding tea made of fenugreek or fennel.

Popular galactagogues that were used by most breastfeeding women (n = 19) were breastfeeding tea (n = 15), lactation cookie (n = 11), oat (n = 9), domperidone (n = 8), fenugreek (n = 8) and blessed thistle (n = 7). Breastfeeding teas were commercial or homemade using herbs such as fenugreek and fennel. Fenugreek and blessed thistle were commercial tablets or capsules recognised by the women interviewed as herbal medicine. The women mentioned various lactation cookies recipes, identifying oats, brewer's yeast, fenugreek, fennel, and flaxseeds as lactogenic ingredients.

Importantly, participants expressed different attitudes to the above categories of galactagogues. For example, most participants expressed less concern about food galactagogues than herbal medicines and domperidone. The participants' attitudes will be discussed in more detail in the following sections.

Three main themes were developed from the interviews of breastfeeding women and PHPs, including the reasons behind galactagogue use, the perceived effectiveness of galactagogues, and the overall safety of galactagogue use. The similarities or differences in women's and PHPs' experiences of and attitudes to galactagogue use are described further below with respect to these three themes.

#### 4.4.2 The reasons for galactagogue use

Breastfeeding women and PHPs reported three main reasons for galactagogue use: to address milk supply problems, to maintain milk supply or milk quality, and prophylactic use.

##### The use of galactagogues to address actual milk supply problems

Women reported concerns about actual milk supply problems, such as delayed milk coming in or insufficient milk supply for the first few months or even longer term.

The delayed milk coming in was identified by insufficient infant weight gain. Women took galactagogues such as food, supplements, herbal products, and naturopathic and homeopathic products in “a week or two” postpartum to encourage milk coming in. A few of them stopped taking galactagogues after their supply was established. However, the others had persistent problems of insufficient milk supply. They used domperidone along with other galactagogues.

*“I felt like I was thinking about my supply all day and everything I did, like take my natural supplements (fenugreek and blessed thistle), I had domperidone as well. And I'd be pumping, and I'd take my protein shakes. .... he was fully breastfed with no bottles by about 10 weeks. I felt so proud of myself eventually when I came through the fog of it.” (M13)*

This woman (M13) faced a complicated situation leading to a poorly established milk supply and resorted to using formula for the first few weeks. After establishing a solid milk supply, she stopped taking domperidone but continued taking fenugreek until her baby started solids.

There is an underlying theme of trying everything to build up the milk supply. Women expressed their strong desire to breastfeed their infant, which encouraged them to try anything that might increase their milk supply, including breastfeeding management techniques as well as taking galactagogues. This can be further supported by the following quote from another woman whose milk did not come in until ten days postpartum:

*“I thought even if it was just like a placebo effect that I am taking this [herbal tea] so my milk will come in, I was willing to try anything. I would have eaten dirt if I had been told to eat dirt you know.” (Jane)*

The other women with milk supply issues that continued for weeks or months stated that they had to take herbal and food galactagogues as well as domperidone long-term to increase their supply. Interestingly, they all tried to wean off domperidone and herbal medicines (such as fenugreek and blessed thistle capsules/tablets), but some could not because their milk supply decreased after stopping these galactagogues.

PHPs mentioned being “*cautious*” about galactagogue use, and all of them suggested firstly identifying if actual problems were causing insufficient milk supply and addressing breastfeeding management techniques for feeding the infant. For the 12 PHPs who discussed or recommended galactagogues, it usually happened in the first few months postpartum. All these PHPs reported to follow the above procedures prior to introducing galactagogues. They considered breastfeeding management as the “*foundation*” and that a galactagogue did “*not work on its own*” (L2).

*“If you have got everything OK with the baby’s feeding but there is still a problem with the mother’s milk production, then I would be looking at medicine or natural supplements to increase milk production.” (L3)*

Like L3, some PHPs reported that they recommended food, herbal products and/or domperidone after confirming breastfeeding management techniques had been tried. The other PHPs who reported discussing galactagogues with women declared that they did not recommend galactagogues but shared information about what other breastfeeding women used to increase their milk supply.

#### Use galactagogue to maintain milk supply or milk quality

Interviewed breastfeeding women reported two ways of using galactagogues to maintain milk supply. Some women reported using oats, lactation cookies, or breastfeeding tea “*all the time*” to keep their milk supply up after having their supply established or during exclusive pumping. Others occasionally used breastfeeding tea, naturopathic remedies, fenugreek plus blessed thistle, or domperidone to

maintain their milk supply when their infant had “*growth spurts*” (M14 and Susan) or if they felt “*very tired and very, very run down and need[ed] a good back up supply*” (Rouge).

Further, a woman who was exclusively expressing mentioned taking lactation cookies not only to support and maintain her milk supply but also to maintain her milk quality.

*“It (lactation cookies) increases the quality of the milk as well. So, in case if there was anything missing from my diet, and I knew that I was giving her good milk.”* (M16)

#### Use galactagogue prophylactically

Two women used the same herbal galactagogues that they had used during the initiation of lactation whenever they anticipated an increase in their infants’ demand.

*“I tried to sort of pre-empt when I thought he was going to need more supply if that makes sense and start[ed] taking them [fenugreek and blessed thistle] before it happened”* (M14).

Interestingly, one woman reported another type of prophylactic use of a herbal galactagogue when she had no concern about milk supply.

*“Before I had had my son, I was drinking herbal tea. But it was supposed to help your milk supply... I didn't look for, I sort of just came across it one day and thought might as well give it a try.”* (M7)

This woman (M7) used this breastfeeding tea to prepare herself to have enough breast milk. It is important to note that she found this product by chance when she visited a health food shop on a holiday. She stated that she believed in that product because it was manufactured by a brand that she was familiar.

#### 4.4.3 Perceived effectiveness of galactagogues

Perceived effectiveness was the main consideration for the choice of galactagogues, for both the initial choice of a specific galactagogue and continued use. Importantly, none of the galactagogues used by breastfeeding women in this study were perceived to be effective for all these women. This was also

reported by some PHPs in this study, i.e., that, in practice, the same galactagogue worked for some women but did not work for others. These PHPs perceived the effectiveness of galactagogues based on the feedback from the women they looked after in practice, but the others suggested they were *“not effective enough to overcome the real low milk supply”* (PM1).

Breastfeeding women assessed if a specific galactagogue was effective by their observations and perceptions of the amount of milk and/or infant behaviour. Some of them thought they might experience a placebo effect. However, others were unable to evaluate the effect of the galactagogues they used.

#### Perceived supply increase from observations

Women perceived their milk supply increased after taking galactagogues by observing their infants' behaviours, such as satisfaction after feeds, length of sleep, and length and frequency of crying.

*“They were both more settled after they had a feed, like they weren't um, they seemed satisfied when they finished a feed, when my supply sorted itself out [after taking Lactation AOK].”* (M14)

Although changes in infant behaviour can be subjective based on individual feeding practices and personal perceptions, these women all felt motivated to continue breastfeeding after observing behavioural changes in their infant.

In addition, five women perceived an increase in their milk supply with measurable signs such as infant weight gain and an increased amount of expressed milk.

*“And they [milk thistle and breastfeeding tea] were effective because if you don't use them, you did notice quite a drop in supply. I can even quantify it, it was probably something like 50-70 ml, if I wasn't taking it, you know, if I skipped taking it. Instead of expressing like 200 ml I would get maybe 150 ml.”*  
(Rouge)

## Placebo effect

Women mentioned that taking galactagogues helped them psychologically to relax, which may help their milk supply.

*“I have no idea if lactation cookies helped or not, it's very subjective isn't it. But I think in my mind, mentally, that placebos help enormously. I think I was doing something to increase my milk supply and I relaxed; and the moment I relaxed, my milk supply came in better. I think there's a huge psychological battle.”* (MM1)

PHPs also mentioned this placebo effect as a reason for advocating for herbal and food galactagogues because they may help women to *“feel better for doing something that may help”*.

## Unsure of the effect of galactagogues

Some women who had milk supply concerns took more than one galactagogue before or at the same time as correcting breastfeeding management. They commented that it was impossible to evaluate the effect of galactagogues.

*“Because I was doing everything at the same time. So, I don't know what was doing better. I used everything.”* (Katy)

Interestingly, this mother (Katy) also proposed that a *“right study”*, which had enough groups with *“treatment A taking herbs, treatment B having special food, and treatment C having acupuncture”*, would provide a clear idea of which *“treatment”* worked. She reported that she did not see any study to compare the effectiveness of galactagogues and breastfeeding management.

### 4.4.4 The overall safety concerns of galactagogues use

Women were asked if they had any safety concerns about the galactagogues they had used. Both breastfeeding women and PHPs had different attitudes to the safety of different groups of galactagogues. They tended to contrast the herbal and food galactagogues with domperidone when it came down to the safety of consuming them.

## Belief in natural products

The majority of breastfeeding women and some PHPs in this study highlighted “natural” as a preferred quality of galactagogues. Although these study participants referred to both herbal and food products as natural, some of them stated that food was the *“number one medicine”* and would consider food galactagogues before herbs. Others specifically compared herbs with domperidone and expressed no safety concerns when taking special foods as galactagogues.

*“I was trying to decide really whether I would rather take a drug or have my baby have formula. And I did not really know which one was better. Formula or drugs. And I am really grateful that there are other natural options out there.”* (M16)

This woman (M16) used a breastfeeding tea and an herbal tincture to support her milk supply during exclusive expressing. The drug in her quote was referred to as domperidone.

*“A lot of mums I see would like to do natural things, so it's something we can try. I had some amazing things happen with herbs myself that work really well but didn't work with medicines. I think it is worth it.”* (L2)

This lactation consultant (L2) recommended herbal galactagogues such as fenugreek and blessed thistle in her practice and explained to women that the herbs *“don't work instantly”* and women *“have to use them consistently”*. Although she also discussed the safety concerns of domperidone with women, she informed that only doctors and midwives could prescribe it.

Some women and PHPs also mentioned confidence in using natural galactagogues because of their historical use. They suggested that the extended historical use of herbs when it came to lactation was well-documented before the introduction of domperidone or even longer than *“the breastfeeding consultants were trained”* (Rouge).

## Trusted source

Women stated that they trusted the safety of specific galactagogues such as special foods, herbal products, homeopathic products, or dietary supplements, especially when they were introduced to them by trusted sources.

*“Obviously, I wouldn't take anything unsafe. But I trusted the advice I was being given, that they were safe and may help.”* (Wendy)

The trusted sources included midwives, female family members such as the mother, mother-in-law and sisters, and the local health food shop. Further, some women mentioned that they would trust a specific brand if they considered it to be *“well-established”*, which referred to brands with a long history and multiple products on the market.

## Concern about the dose

A woman and two PHPs thought to consume in moderation when it came to galactagogues. One woman said, “I think do not take too much of something, you know, that may have a bad effect. But a little of something is not going to hurt.” (M7)

One healthcare professional mentioned an extreme case when a woman had been eating whole bulbs of garlic to support her milk supply, which upset the infant and made him *“smell like a garlic clove”* (Kelly).

They all suggested that the appropriate dose of galactagogues was the one that would maximise the effect of increasing the milk supply and minimise the adverse effects or any safety risks.

Some breastfeeding women and PHPs expressed concerns about the lack of evidence to support an appropriate dose of herbal galactagogues. They pointed out that there may be *“something”* in a tablet or a capsule of the herbal product, but there was insufficient evidence to quantify the appropriate dose.

*“With the medication like the domperidone, you knew there was an amount that had been proven by studies and trials to be effective, whereas with the herbs, you could take this little amount and it could have a really good effect or you could take so much and have only a tiny effect, but it can have all these other side effects. But it’s kind of like there was no scientific dosage to back it up.” (Nicky)*

#### Adverse effects

Women mentioned concerns about adverse effects of fenugreek and domperidone, but no concerns were raised about food galactagogues or supplements. Two women complained about the “*maple syrup*” body odour after taking fenugreek for a few days and stopped taking it. One woman mentioned adverse effects after taking domperidone.

*“From domperidone I’ve been gaining a lot of weight. Maybe 10 kg. And digestive issues.” (M5)*

However, she decided to continue because it was the most efficient way to increase and maintain her milk supply. She stated, “*It’s sort of sacrificing my own health for him*”. Her statement underlines the benefit-risk considerations for taking galactagogues.

#### 4.5 Discussion

This is the first study to describe the use of galactagogues in Aotearoa NZ, from both breastfeeding women and PHPs’ perspectives. It shows that various products were used as galactagogues, including food, commercial herbal products, dietary supplements, homeopathic products, naturopathic remedies and domperidone. Women used these galactagogues concurrently with breastfeeding management techniques when their milk did not come in or had long-term milk supply problems. Breastfeeding women also used herbal and food galactagogues to maintain their milk supply and milk quality or used them prophylactically to support breastfeeding. All PHPs were cautious about galactagogue use, and only midwives, IBCLC, La Leche League leaders and peer counsellors discussed or recommended galactagogues but only after addressing the breastfeeding management techniques. Participants’ attitudes and reasons for using certain galactagogues contributed to their choice of galactagogues. Some preferred natural products, whereas others used both herbs and domperidone.

Women used herbal and food galactagogues at different stages of breastfeeding. In some cases, women started using herbal and food galactagogues right after birth to support secretory activation but stopped using them after their supply was established. Others continued to use oats, lactation cookies and breastfeeding tea to maintain their milk supply.

Most women considered herbal and food galactagogues to be natural and safe. These findings are similar to an Australian study which found that breastfeeding women perceived herbal galactagogues as being “natural”, which equated to being “safe”, and they used them with or without milk supply concerns [25]. Research has shown that herbal and food products labelled as “natural” are perceived by consumers as providing health advantages, a lack of contamination and improved safety. Hence, consumers in general populations consider these “natural” products as better alternatives to medication [43-45]. This study did not investigate whether breastfeeding women’s beliefs in the term “natural” resulted from marketing and promoting “natural” products.

In contrast, domperidone was the last choice for most women in this study who used it, and they perceived domperidone as more risky than taking herbal galactagogues. Some of these women showed more careful attitudes to considering the use of domperidone than considering the use of herbal and food galactagogues. They highlighted the collation process of the relevant safety information and evaluation of the associated benefits and risks of taking domperidone. If the benefit of increasing their milk supply outweighed the risks of adverse effects to both their infant and themselves, they would use domperidone. Zirro et al. also observed this decision-making process for domperidone use among Australian breastfeeding women, and they named it a “risk-risk trade-off” [28].

Furthermore, women used other galactagogues such as dietary supplements and naturopathic and homeopathic products. Midwives in Aotearoa NZ frequently use complementary and alternative medicines, such as naturopathic and homeopathic products, to treat breastfeeding problems [46, 47].

Homeopathic and naturopathic products were also used in Switzerland, Canada, South Africa, and Australia as galactagogues [16, 23, 29].

Importantly, women who used herbal and homeopathic products first introduced to them by trusted sources (midwives, family members, friends, health food shops, or an established brand) did not express any safety concerns. Trust in sources has also been reported as important for Australian pregnant and breastfeeding women to decide whether to use naturopathic and homeopathic products [31, 32]. However, some women in our study accepted the product and/or information from a trusted source and skipped the complicated information collection and assessment processes reported in previous research [32]. This study aimed to examine galactagogue use among breastfeeding women in Aotearoa NZ. The nuances surrounding how breastfeeding women decide to use a specific galactagogue were not explored. Thus, more research is required to understand whether breastfeeding women have different decision-making processes when evaluating the efficacy and safety of different types of galactagogues.

In this study, many women reported using herbal and food galactagogues concurrently with corrective breastfeeding management or using multiple galactagogues concomitantly. This resulted in them being unable to evaluate the effectiveness of galactagogues. These findings were also observed in qualitative studies in Australian women, which suggested that the desire for breastfeeding led to the use of herbal galactagogues [25, 27]. Moreover, some women in the current study used herbal galactagogues prophylactically. Despite the possible placebo effect, women's desire for successful exclusive breastfeeding drove them to use herbal and food galactagogues. This has also been reported among Australian women [27, 28]. These findings imply that the purpose of using herbal and food galactagogues is not only to conquer milk supply problems but also to support breastfeeding more generally.

Although 12 PHPs did discuss galactagogue use with breastfeeding women in their practice, they described a different approach to galactagogue use compared to breastfeeding women. These PHPs

only reported discussing galactagogue use with women who consulted with them about breast milk supply during the first few months postpartum. They usually started by distinguishing the misperception of insufficient milk supply from an actual supply problem. They considered breastfeeding management the fundamental, first-line approach, while galactagogue use was the last. This approach of recommending galactagogues as a last resort suggests that the PHPs considered galactagogues as a supplemental or complementary treatment for actual milk supply problems.

Interestingly, five of these PHPs who discussed galactagogue use with women stated that they did not believe in the effects of galactagogues on breast milk supply and did not make recommendations. However, they shared information about what other breastfeeding women used when the mothers consulted with them regarding galactagogue use. Breastfeeding women value the information they get from their PHPs more than any other sources [31]. Our study also reported this: women trusted the information and/or specific galactagogues raised by PHPs and skipped their own evaluation of risks in these cases. Thus, PHPs should be aware that all information they provided is potentially considered by breastfeeding women as a recommendation.

Although this study did not ask specific questions about how participants evaluated the evidence on the efficacy and safety of galactagogues, some women and PHPs mentioned their concerns about the lack of scientific evidence to support the effectiveness and safety of herbal and food galactagogues, especially those herbs that had been reported to have multiple health effects in humans.

#### 4.5.1 Strength and Limitations

This is the first study investigating galactagogue use in Aotearoa NZ. The qualitative design provides an in-depth understanding of the reasons behind galactagogue use among breastfeeding women and PHPs. However, this study has several limitations. First, the qualitative study only revealed the range of use among the respondents rather than the prevalence of galactagogue use in the population. Second, this study sample may be more likely to use galactagogues than the general population. This

is because the study aim, to understand how women used herbs and foods to help them deal with insufficient milk supply, was shared with potential participants during recruitment. Furthermore, in this study, we were unable to recruit Māori women or PHPs, making it impossible to explore the use of galactagogues in Māori communities.

#### 4.6 Conclusion

Many products were used in Aotearoa NZ as galactagogues, including foods, herbs, dietary supplements, homeopathic products, naturopathic remedies, and domperidone. Breastfeeding women use galactagogues not only in response to milk supply problems but also to maintain milk supply and to support breastfeeding. Women's desire to breastfeed, their innate belief in natural products, and perceived effectiveness of the products facilitated galactagogue use, especially the herbal and food galactagogues. Some women expressed major concerns about safety regarding domperidone use and the lack of evidence on the effectiveness of galactagogues. A follow-up survey with a large representative sample is needed to investigate further galactagogue use in Aotearoa NZ and its relationship with PIM and breastfeeding. Future research is also needed to explore galactagogue use in Māori populations in Aotearoa NZ.

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## Chapter 5 Use of galactagogues in Aotearoa New Zealand women and its relationship to perceived insufficient milk supply: a cross-sectional survey

In the qualitative study described in Chapter 4, many foods and herbal products were reported to be used for the initiation and maintenance of breast milk supply among breastfeeding women in Aotearoa New Zealand (Aotearoa NZ). Some participants in the qualitative study used galactagogues when they had perceived their milk supply to be insufficient (PIM), but some also reported using herbal and food galactagogues prophylactically to prevent milk supply drop or to use them to support milk quality. We used a cross-sectional survey to explore further what galactagogues are used in Aotearoa NZ, and to investigate the relationship between galactagogue use and PIM.

This cross-sectional survey was part of the second phase of this PhD project. Participants (n = 72) in a randomised placebo-controlled trial (RCT) on a *Saccharomyces cerevisiae* yeast-based supplement completed this survey at baseline. Thus, this survey is a pilot study.

This chapter had been submitted to, and was under review at, *Nutrients* (Manuscript ID: nutrients-2006281) by the time of submission. It was rejected before the oral examination. I will make minor changes on the format and language of the manuscript aiming to submit to the *Journal of Human Lactation*. However, the format and language of this chapter are not changed.

## 5.1 Abstract

Galactagogues are substances suggested to increase breast milk supply, and their use is increasing, especially for herbal and food galactagogues. However, little is known about galactagogue use in Aotearoa New Zealand (Aotearoa NZ). This study investigates women's intentional use of galactagogues in Aotearoa NZ, and its relationship with perceived insufficient milk production (PIM). Seventy-two women (mean age 32 years, 75% Caucasian) who volunteered for a trial of galactagogue efficacy completed this preliminary online survey investigating PIM and self-reported use of galactagogues. The participants named 19 galactagogues that they had used, and frequently used galactagogues were lactation cookies, brewer's yeast, lactation teas, fenugreek, and lactation blends. Galactagogue use was not associated with PIM or other perceptions of milk supply. Interestingly, of the women who thought they had sufficient milk (n = 59), 54% used a galactagogue, compared to 78% of women with PIM (n = 13). Galactagogues were used by women in this study sample regardless of women's perception of milk supply. Further research with a large representative sample is required to estimate the prevalence of galactagogue use in Aotearoa NZ, and to fully evaluate the relationship between galactagogue use, PIM and breastfeeding success.

**Keywords:** breastfeeding; breast milk; human milk; milk production; lactation; galactagogue; women's health

## 5.2 Introduction

Breastfeeding provides optimal nutrition and health benefits to mothers and their infants [1-3]. Both international and Aotearoa New Zealand (Aotearoa NZ) recommendations suggest that infants should be exclusively breastfed to six months of age and continue to be breastfed with complementary feeding to at least two years [3, 4]. Global research shows that approximately 35% of women who stopped breastfeeding by four months postpartum reported perceived insufficient milk (PIM) as the main reason for cessation [5]. The nationally representative Growing Up in New Zealand cohort study recruited 6822 pregnant women with an estimated delivery date between 25 April 2009 and 25 March 2010 [6]. This study found that only 16% of Aotearoa NZ infants were exclusively breastfed to age six months, and 13% were breastfed to two years [7]. From the same cohort, PIM was reported as the primary reason for cessation of breastfeeding by 38% of the women who stopped breastfeeding by eight months postpartum (52%, n = 3221) [8].

Galactagogues are foods, herbs, medications, and other substances used to induce, maintain, or enhance the amount of breast milk produced [9, 10]. Cross-sectional surveys suggested that herbal and food galactagogues are widely used among breastfeeding women globally [11-17]. Evidence suggests that their use may be increasing. An Australian study examining queries relating to galactagogue use at a medicine information centre reported that phone calls regarding herbal galactagogues increased from 0% in 2001 to 23% in 2014, whereas the percentage of queries about domperidone (the medication commonly used off-label to increase breast milk supply) use was consistent (between 80% and 95% of annual queries) [18]. In a recent survey of Australian breastfeeding women (n = 2055), the top three named galactagogues were lactation cookies (89%), brewer's yeast (79%) and fenugreek (74%) [16]. However, little is known about how galactagogues are used in Aotearoa NZ.

It is assumed that women who experience PIM would be more likely to consume galactagogues, considering the main effect of galactagogues is reported to increase breast milk production [9].

However, a recent cross-sectional survey in Australia found that among 1120 women who reported using galactagogues, 32% of them did not report experiencing PIM [17]. A small Malaysian study (n = 83) found that 53% of women used herbal galactagogues because of PIM, and 23% chose to use herbal galactagogues because they believed those herbs were a good supplement for breastfeeding mothers [15]. These findings suggest women may use galactagogues, especially herbal and food galactagogues, for reasons other than PIM.

There is limited evidence for the efficacy of herbal and food galactagogues, and most of these studies had a high risk of bias due to lack of statistical power, insufficient randomisation and blinding, short duration, and lack of compliance data [10]. Thus, herbal and food galactagogues are not officially recommended by the New Zealand Ministry of Health (NZMoH) or postnatal healthcare professionals (PHPs) such as midwives and lactation consultants.

However, women frequently search for information about breastfeeding online, where anecdotal information on herbal and food galactagogues is widely available [19, 20]. The effectiveness of these herbal and food galactagogues is usually reported in relation to breastfeeding women's perceptions of their milk supply [21].

This pilot study aims to investigate which galactagogues are used in Aotearoa NZ, and explore the relationship between women's galactagogue use and their perceptions of breast milk supply.

## 5.2 Materials and Methods

### 5.2.1 Participants and settings

This was a cross-sectional study using an online questionnaire. The targeted respondents were breastfeeding women living in Manawatū, Whanganui and Wellington regions, in the North Island of Aotearoa NZ, with term singleton infants (gestational age at birth  $\geq$  37 weeks) aged one to seven months.

Respondents of the current survey were volunteers for a randomised placebo-controlled trial (RCT). The RCT aimed to evaluate the effect of a *Saccharomyces cerevisiae* yeast-based supplement on breast milk composition and PIM (trial registration number: ACTRN12619000704190). Women with the following problems were excluded from the RCT and, therefore, excluded from the current survey:

- Allergy to yeasts.
- Taking medicines such as Phenelzine (Nardil), Tranylcypromine (Parnate), Selegiline (Ensam, Eldepryl), Isocarboxazid (Marplan) and Meperidine (Demerol) or any other medications containing Monoamine Oxidase Inhibitors.
- Having health conditions or taking medications that could influence milk secretion-related hormones, or milk supply.
- Crohn's disease.
- Compromised immunity.
- Treatment for fungal infections.

The recruiting procedures were: women first expressed their interest after seeing the study advertisements displayed at places pregnant and breastfeeding women may visit, posted in parenting magazines or on Facebook. An information sheet was then provided, and the mothers who expressed interest completed the eligibility screening. Women who passed the screening survey were invited to complete the baseline survey, which comprises the data for this study. Online consent was obtained prior to answering the survey. This study was approved by Massey University Human Ethics Committee: Southern A (SOA 18/80) (**Appendix 7**).

### 5.2.2 Data collection

The survey was conducted between May 2019 and June 2021. The questionnaire included 30 questions (**Appendix 8**), both closed and open-ended. Some closed questions also included the "other" option so the respondents could describe their experience if not included in the answers. Questions were categorised as demographics (six questions), infant and birth (nine questions), feeding practice (six questions), galactagogue use (six questions), and PIM and other perceptions (three questions). Participants were not obliged to answer every question.

Feeding practice questions asked about women's feeding experiences from birth to the date of taking the survey. Two categorical variables were created: history of breastfeeding the current baby (always breastfed, or ever fed with formula, donor's milk and/or other food) and current feeding status (breast milk only, mixed feeding with formula, or started solids). Breastfeeding history could be different from current feeding status. The category "always breastfeeding" refers to always feeding on breasts and/or feeding with expressed milk and colostrum since the infant was born. However, if the woman fed formula at some time but returned to exclusive breast milk before completing the survey, her current feeding status would be fully breastfeeding.

Two closed questions with yes/no answers were applied to ask if the women had taken any medications, supplements, or herbs to influence milk supply and if they had taken any foods for that purpose. Women who answered yes to either of these questions were considered to have used galactagogues. Another two questions with yes/no answers asked if they had taken any other medications or supplements since the infant was born. If they answered yes to any of the above four questions, they were asked to list the product name, dose and/or recipes, date of commencing/finishing, and the reasons for taking the medication, herbs and/or supplements. If a participant did not report anything to influence milk supply but listed the reason of taking a specific product as boosting milk quality or milk supply, she was also considered to have used galactagogues. Two tables were provided for listing the products, one for medications, supplements, and herbs, and the other for "special foods". The galactagogues were categorised as medications, supplements and herbs or as special foods according to the product name and the table in which the product was listed.

To investigate if the participant had ever experienced PIM, one question asked in general if she believed her breasts made the right amount of milk to satisfy her infant. Women who thought they made too much milk or just the right amount of milk were considered to have "never experienced PIM", and women who sometimes or often felt they did not have enough milk were considered to have "experienced PIM". Women who chose "not sure" were asked to explain the reasons. Based on

their explanation, they were categorised as never experienced PIM or experienced PIM. Further, participants were asked to respond to ten statements using a five-point Likert scale ranging from one = strongly agree to five = strongly disagree. These statements include perceived milk quantity and quality (three statements), perceived infant behaviours (three statements), and significant others' attitudes to their milk supply (four statements) (**Table 5-1**). The questions were derived from the literature [22-25] and consultation with PHPs. The survey questionnaire was reviewed by independent expert and was pretested with breastfeeding women.

**Table 5-1 Statement of women's perception of breast milk production.**

<b>Category</b>	<b>Statement</b>
Perceived milk quantity and quality	My milk is of good quality
	My milk is nutritious enough to nourish my baby
	My baby generally appears satisfied with the amount of breast milk received
Perceived infant behaviours	Most of the time my baby seems settled
	My baby is crying a lot because of not getting enough milk
	My baby sleeps well during the night even if he/she wakes up for breastfeeding
Significant others' attitude to women's milk supply	My partner/husband never questions my milk supply
	My important family members never question my milk supply
	My friends never question my milk supply
	The health professionals never question my milk supply

Variables of perceived milk quantity and quality (PMQ) and perceived infant behaviours (PIB) were created by adding the total score for each relevant statement, with a maximum score of 15 for both PMQ and PIB. One statement of PIB was worded in a negative direction, and the scale was reversed to calculate PIB points. A binominal variable of "perceived attitude of significant others" (PSA) was created by combining Likert scale ratings regarding a mother's belief that her partner, family, friends, or health professionals believed her milk supply to be sufficient. Responses of "strongly agree" or "agree" to all these statements were recorded as "positive attitude", responses of "strongly disagree" or "disagree" to one or more statements were recorded as "negative attitude", and responses of "neither agree nor disagree" to all these statements were recorded as "neutral".

### 5.2.3 Statistical analysis

All data were analysed using SPSS version 25.0 (IBM, Armonk, NY, US). Continuous data were expressed as mean and standard deviation (SD) or median (Q1, Q3) for non-normally distributed data, and categorical data were expressed as frequencies (%). Bivariate and multiple logistic regression analyses were performed to examine if demographics and mothers' perceptions were associated with galactagogue use. Odds ratios (OR) for the bivariate models and the full model and 95% confidence intervals (CI) were determined, and independent variables with  $p < 0.05$  were considered significant predictors.

### 5.3 Results

A total of 72 women completed the survey. The demographics and characteristics of women and infants are in **Table 5-2**. The caesarean section rate was 29%, the same as the national caesarean section rate in 2019 [26]. Most of the participants could follow recommended breastfeeding practices at the initiation stage. For example, 94% of mothers and infants stayed in the same room after birth, and 82% of mother and infant dyads had skin-to-skin contact within 30 minutes of birth and first breastfeeding within one hour after birth.

Fifty-three percent of infants ( $n = 38$ ) had at some time been given formula, donor's milk and/or other food after birth, but 50% of them ( $n = 19$ ) were fully breastfeeding at the time of taking the survey and, 37% of them ( $n = 14$ ) were fed with breast milk and solids. Only 13% ( $n = 5$ ) of the women fed the infant formula when completing this survey. Thirteen participants (18%) had experienced PIM. Most participants had a strong positive belief in their milk quantity and quality.

**Table 5-2 Demographics and characteristics of 72 breastfeeding mothers and their infants.**

<b>Characteristics (n = 72)</b>	<b>N (%), Mean (SD) or Median (Q1, Q3)</b>
Maternal age, years, mean (SD)	32.1 (4.9)
Tertiary Education	56 (78)
Ethnicity (Caucasian)	54 (75)
Ethnicity (Māori) *	6 (8)
Ethnicity (Asian)	9 (13)
Ethnicity (Other)	3 (4)
Annual household income (n = 68), above median <sup>#</sup>	43 (63)
Live with partner and child(ren)	68 (94)
Number of children (1)	33 (46)
Number of children (2)	22 (31)
Number of children (≥3)	17 (23)
Caesarean birth	21 (29)
Infant age, days, median (Q1, Q3)	107.5 (70, 166)
Infants birth weight, grams, median (Q1, Q3)	3678 (3335, 3975)
Male infant	40 (56)
Mother and infant stay in the same room	68 (94)
Skin-to-skin within 30 minutes after birth	59 (82)
First time on breasts ≤ 1 hour	59 (82)
Breastfeeding history (always breastfeeding)	34 (47)
Breastfeeding status (breast milk only)	48 (67)
Breastfeeding status (mixed feeding)	5 (7)
Breastfeeding status (started solids) †	22 (30)
Experienced PIM	13 (18)
PMQ, median (Q1, Q3)	15 (13, 15)
PIB, median (Q1, Q3)	13 (12, 15)
PSA, positive	62 (86)
PSA, neutral	0 (0)
PSA, negative	10 (14)

PIM, perceived insufficient milk supply; PMQ, Perceived milk quantity and quality; PIB, perceived infant behaviours; PSA, perceived significant other's attitude; Q1, Q3, the first quartile, the third quartile.

\* Five also identified themselves as New Zealand European but they were only categorized to Māori ethnicity group according to the prioritization of ethnicity [27].

<sup>#</sup> Median annual household income based on Statistics New Zealand is 87,607 New Zealand dollars for the year ended June 2020 [28].

† The frequencies of breastfeeding status do not add up to 100% because three mixed feeding infants had started solid.

Forty-two participants (58%) reported using galactagogues, and half of these women (n = 21) reported using more than one galactagogue. In total, 19 galactagogues were reported by participants, including nine "special foods", eight supplements and herbs, and two medications (**Table 5-3**). "Special foods" were more commonly mentioned as galactagogues than were supplements and herbs. Only three

women used domperidone, a medication with off-label use to increase breast milk, and one woman reported using Paracetamol 1000 mg every 4-6 hours for five weeks to “help boost supply”. These four women also used herbs and/or special foods as galactagogues.

**Table 5-3 Galactagogue used by participants who experienced or did not experienced PIM.**

Galactagogue type	N (%)	Experienced PIM, n (%) #	
		Yes (n = 13)	No (n = 59)
Total galactagogue use	42	10 (78)	32 (54)
Special foods <sup>1</sup>	38 (90)	10 (77)	28 (47)
Lactation cookies	30 (71)	5 (38)	25 (42)
Lactation blends *	7 (17)		
Oats	4 (10)		
Supplements and herbal products <sup>2</sup>	22 (52)	6 (46)	16 (27)
Lactation tea	8 (19)		
Fenugreek	7 (17)		
Multi-vitamin and/or iodine supplements	5 (12)		
Medications	4 (10)	2 (15)	2 (3)
Domperidone	3 (7)		
Paracetamol	1 (2)		

PIM, perceived insufficient milk supply.

<sup>1</sup> Other special food include brewer’s yeast, flaxseeds, blackseed oil, fish soup, fermented rice porridge and Tigers Milk (a milkshake with brewer’s yeast, banana, and milk as main ingredients).

<sup>2</sup> Other supplements and herbs include milk thistle, blessed thistle, and moringa.

\* Lactation blends are powdered products with oats, brewer’s yeast as common ingredients, as well as fennel seeds, flaxseeds, or other foods with reputation to increase breast milk supply.

# Percentage of galactagogue use in women who experienced or did not experienced PIM.

Although most women reported the reason for using galactagogues was to increase milk supply, one mother who used lactation tea as a galactagogue reported the reason was to “support my body for breastfeeding”. Interestingly, five women listed taking multi-vitamins or iodine supplements for their milk supply or milk quality.

The four most frequently mentioned substances used as galactagogues were lactation cookies (n = 30, 71%), lactation tea (n = 8, 19%), lactation blends and fenugreek (n = 7, 17% each; see **Table 5-3**). Lactation cookies and lactation blends were listed as “special foods”, and lactation tea and fenugreek were listed as the supplements/herbs to increase milk production. Lactation blends are powders added to other foods and drinks, containing oats, brewer’s yeast with fennel seeds, flaxseeds, or other

suggested ingredients to increase breast milk supply. Oats and brewer's yeast were listed as the common ingredients perceived to increase breast milk supply in all lactation cookies and lactation blends. Some participants also mentioned flaxseeds, fenugreek, and fennel as effective ingredients in lactation cookies and lactation blends to increase milk supply.

Other galactagogues used by the respondents include milk thistle, blessed thistle, moringa, oats, brewer's yeast, flaxseeds, blackseed oil, fish soup, fermented rice porridge and Tigers Milk (a milkshake with brewer's yeast, banana, and milk as main ingredients). Besides women who reported brewer's yeast as the effective ingredient in lactation cookies and lactation blends, three participants took brewer's yeast supplements to increase their milk supply. This made brewer's yeast another commonly mentioned galactagogue in this study.

Women who experienced PIM and women who did not experience PIM reported the use of all types of galactagogues, such as special foods, supplements, herbal products, and medications (**Table 5-3**). There were 12% of women ( $n = 3$ ) who experienced PIM reported not using any galactagogues. Although there was a higher percentage of galactagogue use in women who experienced PIM than in women who did not experience PIM (78% vs. 54%, respectively, **Table 5-3**), results from logistic regression analysis found that PIM, PMQ, and PSA were not associated with galactagogue use (**Table 5-4**). Age was associated with an increased likelihood of galactagogue use ( $OR = 1.16$ ,  $p = 0.022$ ). Increasing PIB score was associated with a reduction in the likelihood of galactagogue use ( $OR = 0.33$ ,  $p = 0.041$ ), suggesting that women with a positive perception of their infants' behaviour, such as settled and less crying, were less likely to use galactagogues.

**Table 5-4 Multiple logistic regression model for factors associated with the galactagogue use in New Zealand breastfeeding women.**

<b>Variables<sup>1</sup></b>	<b>COR (95% CI)</b>	<b>P-value</b>	<b>OR (95% CI)</b>	<b>P-value</b>
Maternal age	1.10 (0.99, 1.22)	0.064	1.16 (1.02, 1.33)	0.022
Ethnicity		0.409		0.080
Other	1		1	
Caucasian	1.57 (0.54, 4.60)		3.84 (0.85, 17.26)	
Maternal education level		0.341		0.119
Non-Tertiary	1		1	
Tertiary and above	0.56 (0.17, 1.84)		3.26 (0.74, 14.38)	
Annual household income		0.968		0.512
Below median	1		1	
Above median	0.98 (0.38, 2.55)		0.66 (0.19, 2.30)	
Number of children		0.549		0.668
Only one	1		1	
More than one	1.33 (0.52, 3.42)		1.31 (0.38, 4.45)	
Experienced PIM		0.144		0.371
Yes	1		1	
No	0.36 (0.09, 1.43)		0.44 (0.07, 2.69)	
PMQ	0.85 (0.61, 1.19)	0.350	1.30 (0.79, 2.13)	0.298
PIB	0.75 (0.56, 0.99)	0.043	0.61 (0.38, 0.96)	0.033
PSA		0.151		0.332
Negative	1		1	
Positive	0.30 (0.06, 1.55)		0.38 (0.05, 2.68)	

COR, crude odds ratio; OR, odds ratio; CI, confidence interval; PIM, perceived insufficient milk supply; PMQ, perceived milk quantity and quality; PIB, perceived infant behaviours; PSA, perceived significant other's attitude.

<sup>1</sup> Reference level with minimum sample size was set for each categorical variable, to allow adequate statistical power.

## 5.4 Discussion

Little is known about the use of galactagogues by women in Aotearoa NZ women. In this online survey of women who volunteered to participate in a trial of galactagogue efficacy, we found that 67% of participants had chosen to use galactagogues. They reported 19 foods, herbs, supplements, and medications intentionally used as galactagogues. Galactagogue use was not associated with PIM. However, a significant association between galactagogue use and maternal age was found in the adjusted model, and PIB score was inversely associated with galactagogue use.

This survey reported a higher proportion of galactagogue users than reported in surveys in other Western countries with convenience samples such as Norway (43%, n = 400), the US (46%, n = 188),

and Australia (60%, n = 1876) [12, 13, 17]. However, this is not surprising given that the women were volunteers to participate in a study about the effectiveness of a galactagogue.

The respondents had used various products as galactagogues, including special foods, herbs, supplements, and medications. Lactation cookie was the most commonly reported galactagogue, similar to the findings in the survey of breastfeeding women in Australia [17]. The other frequently used galactagogues reported in this study included lactation tea (n =10, 22%), fenugreek and lactation blends (n = 7, 15% for both). Fenugreek is the most popular herbal galactagogue in many countries [13, 16, 29], and it is also a main ingredient of lactation teas [10]. However, lactation tea was not reported as a frequently used galactagogue in the US or Australia [13, 17]. Lactation blends are new commercial products. Some manufacturers recommend on their websites that lactation blends can be used “1 – 4 tablespoons per day, adding to smoothies, juices, and cereals” to boost women’s milk supply [30]. It has been suggested that the availability and accessibility of recipes and commercial products and high levels of marketing contribute to the wide use of lactation cookies in Australia [16]. Little is known about the availability and accessibility of lactation cookies in Aotearoa NZ.

Brewer’s yeast was recognised as the effective ingredient to increase milk supply by most participants who reported using lactation cookies, lactation blends and Tigers Milk. Brewer’s yeast is widely available via local or online health food shops in Aotearoa NZ, and manufacturers promote the effect on increasing breast milk based on anecdotal evidence of efficacy [19]. Marketing the effect of increasing milk supply for commercial products may lead breastfeeding women to believe that these products effectively support their milk supply and that they need something “extra” to be able to breastfeed their infants. Thus, PHPs should be aware of the influence of marketing these products and inform breastfeeding women of the lack of scientific evidence to support the benefits of most herbal and food galactagogues.

In the current study, 54% of women who had not experienced PIM used galactagogues (n = 32). The use of galactagogues was not associated with women’s experience of PIM or their perception of milk

quantity and quality. This was different from the findings in a recent Australian online survey of 1876 women that the proportion of women who experienced PIM was significantly higher among galactagogue users than among women who never used galactagogue (68% and 22%, respectively,  $p < 0.001$ ) [17]. These results from the current study may be caused by inadequate evaluation of women's experiences of PIM. The question about PIM asked if, in general, the mother believed her breasts made the right amount of milk to satisfy her infant without an explicit statement of the timeframe from birth to the completion date of this survey. This is inconsistent with the timeframe of the questions about galactagogue use (i.e., since birth). Thus, it is possible that women experienced PIM during galactagogue use but did not experience PIM when they completed the survey.

In this study, galactagogue use was inversely associated with women's perception of infant behaviour (PIB). This finding reveals that women who perceived their infants unsatisfied, unsettled and crying were more likely to take galactagogue. These infant behaviours are commonly perceived by women as signs of insufficient milk supply [22, 31, 32]. Thus, this finding partially suggests that women with PIM are more likely to use galactagogues. The relationship between PIM and galactagogue use needs to be further investigated.

Maternal age was positively associated with galactagogue use in the adjusted regression model. This finding conflicts with the above Australian survey that women who use galactagogues were significantly younger than those who did not, although the difference in the mean age between the two groups was only 0.8 years [17]. In this study, the number of children had no relationship with galactagogue use, suggesting that primiparous is irrelevant to galactagogue use. This finding also differs from the above Australian survey, which found that first-time mothers were more likely to use galactagogues [17]. There needs to be more research comparing the maternal characteristics of women who use and do not use galactagogues.

In the current study, women reported prolonged use of special foods and supplements for good milk supply and quality. This seemed to be a "just-in-case" approach and may contribute to a positive

perception of their milk supply. Prophylactic use of herbal galactagogues was also reported in Australian breastfeeding women [33]. The prophylactic use of galactagogues highlights that women generally take galactagogues to support breastfeeding.

It is worth noting that some of the women who have experienced PIM may choose not to use galactagogues, which is in line with the lack of official recommendations from NZMoH and PHPs.

This survey is the first to explore galactagogue use and its relationship with experiencing PIM in Aotearoa NZ. Although the participants were asked to recall their experiences in the past few months (maximum seven months after birth), recall bias is a limitation of this study. Importantly, the participants were recruited for an RCT on the effect of a yeast-based galactagogue. Thus, the advertising of this study might attract women who had used galactagogues, which may bias the sample and limit the generalisation of the findings. Furthermore, the unclear timeframe of PIM in the survey may have resulted in an underestimate of the number of women who experienced PIM when taking galactagogues. Thus, a study with a bigger sample size and random sample selection is needed to estimate the prevalence of galactagogue use in Aotearoa NZ, and to fully evaluate the relationship between galactagogue use, PIM and breastfeeding practice.

## 5.5 Conclusions

More than half of the respondents of this survey reported galactagogue use, both women who had and had not experienced PIM. This suggests that PIM is not the only motivator for using galactagogues. Various supplements, herbs and foods were used to improve milk supply and support breastfeeding more generally. Lactation cookies were the most commonly reported galactagogue in this survey. This small survey highlights the need for more research to fully understand how galactagogues are used in Aotearoa NZ to support breastfeeding and its relationship with PIM in a random, representative sample.

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## Chapter 6 *Saccharomyces cerevisiae* Yeast-Based Supplementation as a Galactagogue in Breastfeeding Women? A Review of Evidence from Animal and Human Studies

In the qualitative study described in Chapter 4, brewer's yeast was frequently mentioned as a galactagogue. Although use of brewer's yeast as a galactagogue in breastfeeding was only reported in surveys and/or qualitative studies until recently, anecdotal information that brewer's yeast and nutritional yeast (both are *Saccharomyces cerevisiae* yeast-based supplements, SCYS) may increase breast milk production was widely available on the internet within the last decade. Considering the absence of knowledge on SCYS and the lack of research on its use in human lactation, this chapter aimed to review the evidence of the effects of SCYS on milk production in mammals, to propose possible mechanisms and to review the safety of taking SCYS during lactation.

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## 6.1 Abstract

Perceived insufficient milk production (PIM) adversely affects breastfeeding duration. Women sometimes use galactagogues with the intent to increase breast milk production and support lactation. *Saccharomyces cerevisiae* yeast-based supplement (SCYS) is an inactive form of *Saccharomyces cerevisiae* yeast (SCY) either obtained from the fermentation process or grown on molasses. Anecdotal evidence suggests SCYS is a galactagogue. SCYS is promoted on the internet as a galactagogue in various forms and doses. Dietary supplementation with SCYS during gestation and lactation significantly increases milk yield in ruminants. No human study has evaluated efficacy of SCYS as a galactagogue. SCYS is rich in B vitamins, beta-glucan, mannan oligosaccharides and bioavailable chromium; these may impact breast milk production or composition, thus may alleviate PIM. The safety of taking SCYS during lactation is not well studied. Studies have reported contamination of SCYS with ochratoxin A (OTA) as well as minor side effects from SCYS. Studies are needed to evaluate the efficacy of SCYS on breast milk production and composition and to assess the safety of taking SCYS during lactation in humans.

**Key words:** *Saccharomyces cerevisiae*; brewer's yeast; nutritional yeast; supplement; breastfeeding; breast milk; human milk; milk production; galactagogue

## 6.2 Introduction

Perceived insufficient milk production (PIM) is a worldwide problem affecting breastfeeding duration [1-6]. Globally, approximately 35% of women who stopped breastfeeding before four months postpartum reported PIM as the primary reason for discontinuation [5].

Many factors can affect women's perceptions of milk production. For example milk production may actually be low due to some physical problems or medications which can suppress hormone release related to milk production [7]. In addition, lactation problems or difficulties with positioning and latching may decrease stimulation of the breast or decrease milk removal, which adversely influences milk production [8]. Furthermore, postnatal distress (depression, anxiety and stress) which influence oxytocin secretion can also result in decreased milk production [8]. Maternal diet has limited impact on breast milk production. Maternal nutrition status, maternal body composition and maternal energy intake are not associated with breast milk volume [9]. Food supplementation to address malnutrition or maternal energy restriction have little effect on milk volume [10, 11]. Maternal intake of some nutrients influence their respective concentration in breast milk [12, 13].

Women may also incorrectly perceive their milk supply to be insufficient. For instance, some women may interpret their infants' unsatisfied, unsettled or crying behaviour as meaning inadequate milk [5, 14-16]. Whereas others may perceive that their milk looks watery, or that they have empty/soft breasts, or that the infant has frequent or long feeds, and they mistake these as signs of the lack of quality or quantity of milk [15, 17]. Good lactation management and support can enable women to overcome these situations and continue to breastfeed successfully. However, if PIM results in the introduction of supplementary feeding, this can reduce milk production and may ultimately result in the cessation of breastfeeding [17].

Women's perception of milk supply may be influenced by health professionals, family, and friends. If these people questioned the mother's milk supply, the mother would perceive her milk supply as inadequate [18].

To address PIM, women sometimes use galactagogues, which are medications, herbs, supplements and foods, to increase breast milk production and support lactation [19, 20]. *Saccharomyces cerevisiae* yeast-based supplement (SCYS) is one galactagogue used by breastfeeding women [21, 22], and some lactation specialists recommend SCYS based on anecdotal evidence of efficacy [19, 23]. To date, no professional body has endorsed the use of SCYS as a galactagogue and there are no recommendations or guidelines for use during lactation.

*Saccharomyces cerevisiae* yeast (SCY) includes thousands of strains that have a long history of use in brewing and baking [24]. Strains used for brewing ale are named brewer's yeast<sup>2</sup> [25], whereas baker's yeast strains provide the leavening to make bread [25]. SCYS, the inactive form of SCY (dead yeast cells without the fermentation or leavening property), is popular as a dietary supplement for humans. It is promoted as containing high concentrations of protein, some B vitamins and minerals, as well as beta-glucan and mannan oligosaccharides (MOS) from yeast cell walls [24, 26]. Research investigating health benefits of SCYS for human participants mainly focuses on two areas. First, SCYS (i.e. brewer's yeast) contains organic chromium with better absorption compared to inorganic chromium [27]. Thus, brewer's yeast has been used for decades in research evaluating the effect of chromium supplementation on fasting plasma glucose, lipid metabolism and blood pressure in diabetic patients [28-30]. Second, beta-glucan derived from SCY cell walls modulate the innate immune system, and the effects of yeast beta-glucan supplementation on upper respiratory tract infection and allergy

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<sup>2</sup> In the brewing industry, "brewer's yeast" is the common name for all types of yeast used for brewing beer. Beer can be categorised as lager or ale according to the yeast used. Lager yeast (*Saccharomyces pastorianus* or *Saccharomyces carlsbergensis*) produces so called bottom fermenting beer or lager. *Saccharomyces cerevisiae* is used to produce top fermenting beer, that is, ale [12]. In this review, brewer's yeast only refers to *Saccharomyces cerevisiae*.

symptoms have been evaluated in a few trials [31, 32]. The influence of SCYS on human lactation has not yet been investigated.

SCYS products are widely available as tablets, powders, flakes and in liquid form [26, 33]. These products are from three different processes: spent yeast from brewing, yeast from fermentation with malted barley, and yeast grown on molasses. Yeast cultivated on malted barley is the same as brewing with the difference that the yeast is the product, not beer. Thus, products from the first two sources usually have a bitter taste from the fermentation [33, 34], and they must be debittered and washed prior to drying [34]. The third source, SCY is grown on molasses enriched by additional nutrients such as minerals and B vitamins under aerobic conditions; the nutrients in the resultant SCYS depends on the composition of molasses [33].

SCYS is approved as a food additive for human consumption by the US Food and Drug Administration (USDA) [35]. However, there is no standard or regulation regarding the product names, sources, or dosage of SCYS.

In the literature, SCYS used for diabetic participants is commonly named “brewer’s yeast”, but information of the strain and product source or process is generally absent [28, 29, 36]. However, in marketing material, SCYS are defined by their method of production: SCYS from the fermentation processes are commonly named as “brewer’s yeast” or “nutritional brewer’s yeast”; and SCYS grown on molasses are named as “nutritional yeast” or “brewer’s type yeast” [26, 33, 37]. However, it is not reported in the literature if the different designations imply variation of the nutrition composition of SCYS.

Although used by breastfeeding women, it is unknown how or if SCYS influences breast milk production. This review aims to evaluate evidence of the effect of SCYS on milk production in other mammals, to propose possible mechanisms that human milk production could be influenced, and to review the safety of using SCYS during lactation. In addition to reviewing the literature, we used Google

search engine to obtain an overview of SCYS on the market and the anecdotal recommendations posted for breastfeeding women.

### 6.3 An overview of information of *Saccharomyces cerevisiae* yeast-based supplement on the internet

Alianmoghaddam et al suggested Google is breastfeeding women’s main source of information for lactation problems [38]. A Google search of advertisements for SCYS products sold online highlighted that product designation was confusing within the SCYS market, especially the term “brewer’s yeast”. We used “brewer’s yeast” or “nutritional yeast” as keywords for searching. We chose first ten products without duplicates to show the variation of product name, source, and daily dose (**Table 6-1**). Some of the products named “brewer’s yeast” were reported to be grown on molasses. Some of the products explicitly indicated the medium or the production process but others provided no information. Furthermore, some products provided information of yeast species, but the information of strains was missing from all products. Although it is assumed that products from fermentation processes use brewer’s yeast strains, there is no denying the possibility that the products grown on molasses may use baker’s yeast strains. The information presented in **Table 6-1** suggests a range of “brewer’s yeast” products aimed at breastfeeding women are available for purchase online.

**Table 6-1 A selection of information on *Saccharomyces cerevisiae* yeast-based supplements (SCYS) available on the internet\*.**

Product name	Production information	Dose (g/day) **
Product 1: Brewer’s yeast powder <sup>1</sup>	Species and strains: <i>Saccharomyces cerevisiae</i> Medium: unclear	30
	Other ***: “brewer’s yeast is generally from the fermentation of beer, adding grains (such as rice or wheat), malt, dried flowers of hops to the medium for cultivation”	
Product 2: Brewer’s yeast powder <sup>2</sup>	Species and strains: select strains of <i>Saccharomyces cerevisiae</i> Medium: sugar beet molasses	30
	Species and strains: <i>Saccharomyces cerevisiae</i> Medium: malted barley in the production of beer	
	Other ***: “dehbittered”	15

Product 3: Brewer's yeast powder <sup>3</sup>	Species and strains: select strains of <i>Saccharomyces cerevisiae</i>	
Product 4: Nutritional yeast flakes <sup>4</sup>	Medium: enriched purified cane and beet molasses Other <sup>***</sup> : "added niacin, pyridoxine hydrochloride, riboflavin, thiamin hydrochloride, folic acid and vitamin B12/ not from brewing process"	9
Product 5: Nutritional yeast flakes <sup>5</sup>	Species and strains: <i>Saccharomyces cerevisiae</i> Medium: a mixture of sugar cane and beet molasses Other <sup>***</sup> : "NOT brewer's yeast, baker's yeast or torula yeast"	15
Product 6: Nutritional yeast flakes <sup>6</sup>	Species and strains: <i>Saccharomyces cerevisiae</i> Medium: molasses Other <sup>***</sup> : "added niacin, pyridoxine HCl, riboflavin, thiamine HCl, folic acid and vitamin B12; gluten free"	20
Product 7: Brewer's yeast powder <sup>7</sup>	Species and strains: no information Medium: no information Other <sup>***</sup> : "from brewing process"	11.5
Product 8: Brewer's yeast powder <sup>8</sup>	Species and strains: <i>Saccharomyces cerevisiae</i> Medium: no information Other <sup>***</sup> : "from production of beer"	16
Product 9: Brewer's yeast tablet <sup>9</sup>	Species and strains: <i>Saccharomyces cerevisiae</i> Medium: no information Other <sup>***</sup> : "manufactured using non-debittered brewer's yeast powder"	1.8 – 3.6 (300 mg/tablet; 6 – 12 tablets/day)
Product 10: Brewer's Yeast tablet <sup>10</sup>	Species and strains: no information Medium: no information	0.5 – 2 (500 mg/tablet; 1 – 4 tablets/day)

\* Information accessed on 4 June 2020, from the advertisements of Google search of "brewer's yeast".

\*\* Doses were provided on the product package.

\*\*\* Information quoted from the websites.

<sup>1</sup> <https://www.solgar.com/products/brewers-yeast-powder/>, accessed on 4 June 2020.

<sup>2</sup> <https://www.bluebonnetnutrition.com/product/bluebonnet-nutrition-super-earth-brewers-yeast-powder-1-lb/>, accessed on 4 June 2020.

<sup>3</sup> <https://nz.pipingrock.com/brewers-yeast/brewers-yeast-powder-debittered-100-pure-1-lb-454-g-9260>, accessed on 4 June 2020.

<sup>4</sup> <https://www.nowfoods.com/supplements/nutritional-yeast-flakes>, accessed on 4 June 2020.

<sup>5</sup> <https://foodsalive.com/products/nutritional-yeast-vegan-non-gmo>, accessed on 4 June 2020.

<sup>6</sup> <https://www.luckyvitamin.com/p-1756-kal-nutritional-yeast-flakes-22-oz>, accessed on 4 June 2020.

<sup>7</sup> <https://www.luckyvitamin.com/p-3420807-kal-brewer-s-yeast-powder-100-natural-unfortified-unsweetened-7-4-oz>, accessed on 4 June 2020.

<sup>8</sup> <https://www.nowfoods.com/supplements/brewers-yeast-powder>, accessed on 4 June 2020.

<sup>9</sup> <https://www.naturesaid.co.uk/brewers-yeast-300-mg.html>, accessed on 4 June 2020.

<sup>10</sup> <https://www.thompsons.co.nz/products/general-wellbeing/brewers-yeast-tablets/>, accessed on 4 June 2020.

Furthermore, the reported nutrient concentrations varied among products. Only five of the products from **Table 6-1** had nutrition information available online. **Table 6-2** shows the concentrations of B vitamins and minerals of these products. Vitamin concentrations in SCYS vary by over 100-fold. Nutrient concentrations of products with the same name (e.g., brewer’s yeast) may also differ from each other.

**Table 6-2 Description of B vitamin and mineral concentrations in a selection of commercially available *Saccharomyces cerevisiae* yeast-based supplements (SCYS).**

Nutrients	Content *				
	Product 1*	Product 2*	Product 3*	Product 4*	Product 5*
	Brewer’s yeast powder	Brewer’s yeast powder	Brewer’s yeast powder	Nutritional yeast flakes	Nutritional yeast flakes
Thiamin	10	30	20	666.7	1600
Riboflavin	30	60	60	666.7	5
Niacin	190	333.3	380	3555.6	1000
Vitamin B6	5	30	10	666.7	666.7
Vitamin B12	-	-	-	1.6	-
Folate (DFE)	11.4**	14.2	13.3	75**	-
Pantothenic acid	-	100	-	-	2333.3
Biotin	-	0.3	0.3	-	1
Calcium	-	1500	733.3	666.7	1733.3
Iron	20	40	40	55.6	466.7
Zinc	-	166.7	-	-	2000
Selenium	-	2.2	-	-	1.4
Chromium	-	0.43	-	-	0.3

DFE, dietary folate equivalent.

\* Product numbers match the numbers in Table 1. Nutrition information was accessed on 4 June 2020.

\*\* On websites the values were provided as folic acid, we calculated DFE as 1 µg DFE = 0.6 µg folic acid [39].

The difference in nutrient content between different SCYS products is caused by several factors. First, different strains grown in the same medium have different growth patterns and biomass [40]. For example, brewer’s yeast strains contain higher concentrations of chromium compared to baker’s yeast strains [24]. Second, the composition of spent yeast varies between different fermentation processes due to the growth conditions, material of the brewing plant and yeast recycling [24, 34]. Third, the growing medium has significant influence. For example, yeast grown on enriched molasses has higher

concentrations of some B vitamins and minerals [37], and cultures enriched with chromium salts or selenium salts are used to produce chromium yeast or selenium yeast [41-43]. Lastly, as shown in **Table 5-1**, extra B vitamins may be added to the final product, which leads to a much higher B vitamin concentration than unfortified products grown on unenriched medium (**Table 6-2**).

Although SCYS is not endorsed as a galactagogue by any professional organization there are many references to this use of it on the internet. We searched “brewer’s yeast”, “nutritional yeast” or “*Saccharomyces cerevisiae*” with “breast milk”, “milk production” or “milk supply” on Google and reviewed the first 50 results of each combination. After removing duplicates, we chose the articles and recipes which either indicated the author’s qualification in health or breastfeeding or was provided by breastfeeding advocates (i.e., doula and breast pump manufacturer) as shown in **Table 6-3**. The daily dose of SCYS recommended in these articles and recipes is below 5 g if suggested in tablet form but is as high as 30 g in the suggestion of adding three tablespoons of powder to a drink. It is more difficult to evaluate the daily intake if SCYS is added to lactation cookies, because most recipes only provide the amount to add to a batch, but the daily dose depends on the cookie size and numbers of cookies eaten per day. Furthermore, one online article insisted that brewer’s yeast was the only effective yeast to increase breast milk production [44], whereas another stated that both brewer’s yeast and nutritional yeast were *Saccharomyces cerevisiae* yeast, and that both provided B vitamins and so were interchangeable [45]. The lack of consistent advice and the variable nutrient composition of the commercial products has efficacy and safety implications.

**Table 6-3 A selection of information found on the internet about taking *Saccharomyces cerevisiae* yeast-based supplements (SCYS) to increase breast milk production\*.**

Author or source	Product information	Dose (g/day)	Format of the supplement	Ingestion method	Claimed benefits
Anne Smith, IBCLC <sup>1</sup>	Brewer’s yeast	2.7 (300 mg tablet) or 4.5 (500 mg tablet) <sup>**</sup>	Tablets	3 tablets taken with meals, 3 times per day	Increase milk production, contains B vitamins
Donna Murray, RN.	Brewer’s yeast	No information	Tablets or powder	No information	Increase milk supply,

Reviewed by Meredith Shur, MD <sup>2</sup>					improve mood and baby blues
Rohit Garoo, BSc. Reviewed by Briana Violand, IBCLC <sup>3</sup>	Brewer's yeast (used in brewing and making bread, but different from baker's yeast)	30 g <sup>***</sup>	Recommend using powder because the dose of tablets varies between manufacturers	Add to cookies or water, 3 tablespoons per day, can increase the quantity by half-a-teaspoon a day if not seeing any improvement	Anecdotally increases milk supply, improves acne, improves glucose tolerance in diabetes, considered as a nutritional supplement for B vitamins and selenium Boost breast milk supply
Kelly Winder, doula <sup>4</sup>	Brewer's yeast (not substitutable with baker's yeast or nutritional yeast)	Unclear <sup>****</sup>	Powder or flakes	As an ingredient in lactation cookie recipe, 1 to 2 tablespoons per recipe, 2-5 cookies per day	Increase breast milk supply
Medela, breast pump manufacturer <sup>5</sup>	Brewer's yeast	Unclear <sup>****</sup>	Powder	As an ingredient in lactation cookie recipe, 5 tablespoons per recipe, no information of how many cookies to take per day	Naturally help support milk supply, offer a boost of B vitamins, iron and other minerals
Crystal Karges, RDN, IBCLC <sup>6</sup>	Brewer's yeast (can be substituted by nutritional yeast)	Unclear <sup>****</sup>	Powder	As an ingredient in lactation cookie, 4 tablespoons per recipe, 2 cookies per day	

IBCLC, international board-certified lactation consultant. RN, registered nurse. MD, doctor in medicine. RDN, registered dietitian nutritionist. \* Information accessed on 4 June 2020. \*\* Determined from 9 x 300 mg or 500 mg brewer's yeast tablets in the Table 1, as no indication of brand or dose of brewer's yeast tablets in this article. \*\*\* Determined by measuring 1 tablespoon (15 mL) brewer's yeast powder, which weighs 10 g. \*\*\*\* Lactation cookie recipes without information on the cookie size or how many cookies per batch.

<sup>1</sup> <https://www.breastfeedingbasics.com/articles/increasing-your-milk-supply>, accessed on 4 June 2020.

<sup>2</sup> <https://www.verywellfamily.com/foods-that-increase-breast-milk-supply-431598>, accessed on 4 June 2020.

<sup>3</sup> [https://www.momjunction.com/articles/brewers-yeast-when-breastfeeding\\_00456918/](https://www.momjunction.com/articles/brewers-yeast-when-breastfeeding_00456918/), accessed on 4 June 2020.

<sup>4</sup> <https://www.bellybelly.com.au/breastfeeding/lactation-cookies/>, accessed on 4 June 2020.

<sup>5</sup> <https://www.medelabreastfeedingus.com/article/298/oatmeal-chocolate-chip-lactation-cookies>, accessed on 4 June 2020.

<sup>6</sup> <https://www.crystalkarges.com/blog/family-friendly-lactation-oat-cookie-recipe>, accessed on 4 June 2020.

## 6.4 Using *Saccharomyces cerevisiae* yeast as a galactagogue in ruminants and non-ruminants

SCY products are widely used as dietary supplements to increase milk yield in ruminants [46-58] and to improve the reproductive performance of sows and growth of offspring [59-65]. These products include active SCY, inactive SCY (SCYS) and yeast cell wall products (YCWP), such as beta-glucan, MOS or combined products. The benefit of active SCY on milk production is attributed mainly to probiotic properties, which improve nutrient digestibility and metabolism [46, 59-61]. However, use of live yeast is irrelevant in humans because dietary supplements are in the form of SCYS (i.e., inactive cells) [43], so the effect of active SCY will not be further discussed in this review.

We reviewed studies on supplementation of lactating animals using SCYS and YCWP produced from SCY that were published from January 2000 to December 2019 in peer reviewed journals in English with full texts accessible. We searched three databases: Web of Science, PubMed and Scopus. The terms used for searching are "*Saccharomyces cerevisiae*", "brewer's yeast", "baker's yeast", "yeast cell wall products", "beta-glucan" or "mannan oligosaccharides", with "milk production", "milk yield" or "lactation". Fifteen studies were identified with ten studies on ruminants, four studies on sows and one study on rabbit does. Information on the study design and results are provided in the Supplementary table (**Appendix 9**).

In ten studies on ruminants, eight studies are supplementation studies using SCYS and/or YCWP in addition to the feed and concentrate [48, 50, 52-57], including two studies using both SCYS and YCWP [53, 57]; and a further two studies using SCYS as protein sources to replace soybeans [51, 58]. Four of

five studies supplementing with SCYS in ruminants found positive results on milk yields [48, 50, 52, 57]. Studies using YCWP also had positive results. One study using MOS [54], two studies using beta-glucan [56, 57] and another study using YCWP (containing MOS and beta-glucan) [52] found significant higher milk yields in supplementing groups compared to control groups. However, one study using YCWP (without information of composition of MOS and beta-glucan) found a nonsignificant increase in milk yield at an early lactation stage (day in milk < 120) [55].

The effect of SCYS on milk production was attributed to improving microflora metabolic activity [52], digestibility of feed and energy metabolism [48, 55], improving mammary gland health shown as lower somatic cell count in milk [50, 52, 56, 66], as well as improving immunity shown as increasing maternal blood gamma-globulin concentrations and other immunological parameters [48, 50, 57]. The researchers suggested that beta-glucan and MOS from SCYS were mainly responsible for improving maternal immunity and health status [48, 52]. Beta-glucan is a natural immunomodulator influencing both humoral and cellular immunity in ruminants [56, 67]. MOS can bind selected pathogenic microbes and prevent pathogen colonisation in the host's gastrointestinal tract [48].

However, in studies that tested both SCYS and YCWP, the milk yield was higher in the SCYS groups than in the YCWP groups [52, 57], which suggests that the benefit of yeast supplementation is not limited to the effect from beta-glucan and MOS.

The significant effect of SCYS on milk yield in ruminants may have been partly due to improving nutrition compared to the control group. Although the composition of feeds administered to study groups was identical, the supplementing studies provided limited information about the nutritional value of the SCYS used. Only one study reported the composition of the SCYS, which added an extra 4.3% crude protein into the diet of SCYS group [52]. Furthermore, there was limited information of how the feed and SCYS were consumed by the animals. Only one study reported to feed the SCYS "by hands" [53]. Thus, it is possible that ruminants in the supplement groups had better nutritional status compared with the animals in the control groups, if they consumed the same amount of feed in

addition to the SCYS which provided significantly extra nutrition. The results from studies assessing the replacement of protein source with SCYS also support the above presumption. When SCYS replaced soybean meal as the protein source, providing similar nutrient concentration in both diets, no difference in milk yield or milk composition was observed in dairy goats [51, 58].

In the literature, YCWP, but not SCYS has been used to supplement lactating non-ruminants. Four studies that evaluate the effect of YCWP supplementation on sows and one study on rabbit does yield inconsistent results [62-65, 68]. Litter weight was used as the outcome in these studies. Only two out of five studies found the litter weight of piglets and rabbits pups in the MOS group to be significantly higher at day 14 and day 18 of lactation [62] or at weaning [65]; another study found that the piglets body weight in beta-glucan groups was significantly higher at day 45 postpartum after weaning [63]. However, the piglets were also supplemented with beta-glucan from day ten postpartum in this study, which may contribute to the significant weight gain after weaning [63]. The variation in doses and YCWP composition may have led to the inconsistent results among these studies. Moreover, the offspring usually started to consume feed in addition to milk a few days after birth, so the litter weight gain at weaning is a reflection of both milk consumption and feed utilization. Since none of these studies evaluated the volume of milk yield, the results are weak and insufficient to indicate the effectiveness of supplementation on milk production in pigs and rabbits.

In addition to some evidence of a positive effect on milk production, there is also some evidence of SCYS impacting the milk composition in ruminants and non-ruminants. Supplementing with SCYS significantly increased milk fat in ruminants [53, 57, 58]. YCWP supplementation also significantly increased total protein in ewe milk [56] and sow milk [64]. SCYS also affected milk protein composition. The  $\beta$ -casein concentrations had a significant reduction and k-casein had a significant increase in ewe milk after 70 days supplementation with SCYS with a daily dose of 30 g/animal during lactation [69], and whey  $\gamma$ -globulin in sow milk significantly increased with supplementation of  $\beta$ -glucan from gestation to lactation at the 200–300 ppm level [63]. Significant increases in milk IgG was also

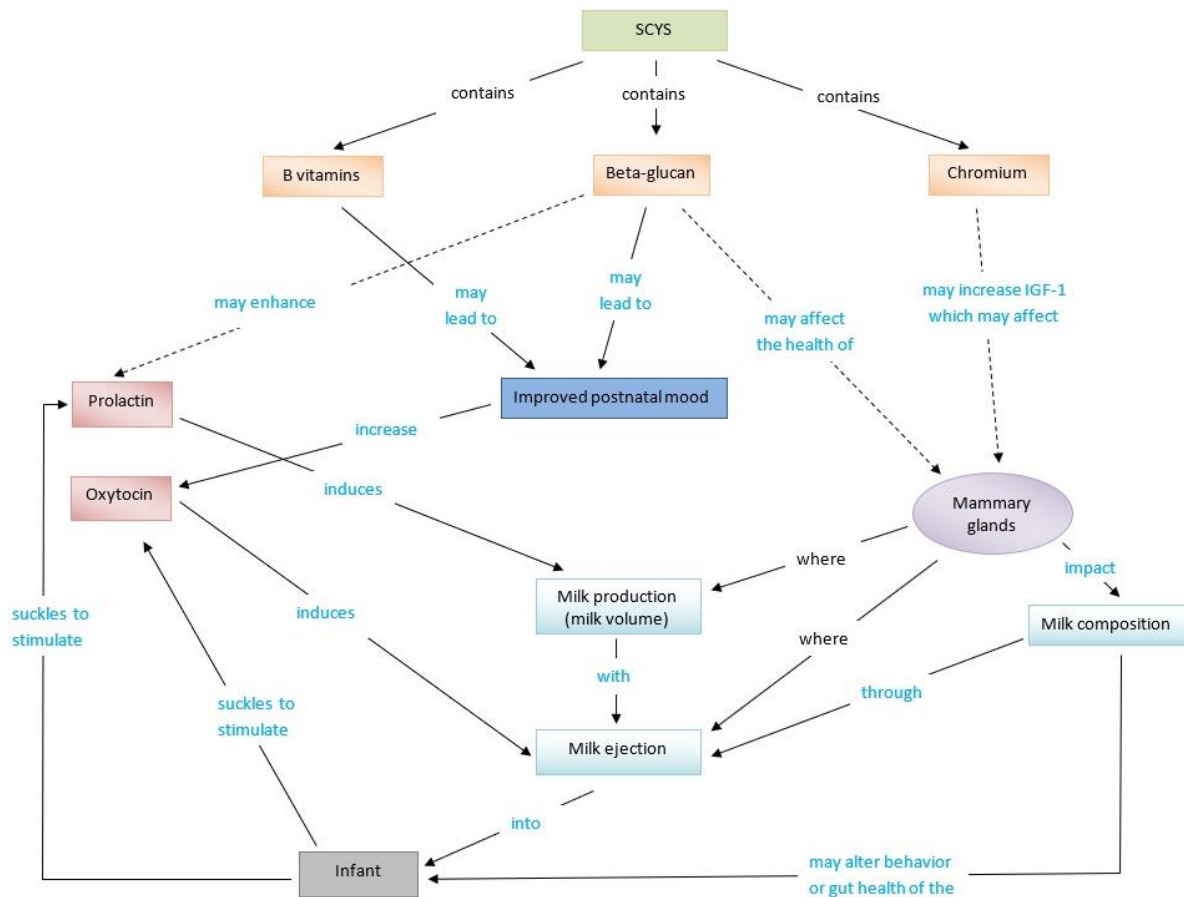
observed in two studies on sows supplemented with MOS with a daily dose of 8 g/animal at day 21 of lactation in one study [62] and a daily dose of 900 mg/feed at day 23 of lactation in another study [64].

The results from animal studies suggest that supplementation with SCYS has a strong positive effect on milk yield in ruminants, limited improvement on weight gain in suckling piglets and a possible effect on milk composition. Extrapolation of these results to humans are inappropriate because the proposed mechanism in animals may not be effective due to interspecies differences in digestion systems and physiology of lactation [70-72]. It is important to note that SCYS is commonly taken in the first few months of lactation in humans, but animal supplementation is usually conducted long-term, starting in gestation and continuing through the whole lactation period. Furthermore, the positive effect of SCYS on milk production in animals may come from the higher nutrition requirements required by multiple births, whereas humans predominantly have single births. Thus, the results from the animal studies only partially support the potential effectiveness of SCYS supplementation on increase of human milk production.

## 6.5 Hypotheses of the mechanism of *Saccharomyces cerevisiae* yeast-based supplement on breast milk production

Although no scientific evidence directly supports the effectiveness of SCYS to influence breast milk production, hypotheses of the mechanism can be made based on the composition of SCYS, knowledge of physiology of human lactation and SCYS studies in lactating animals (**Figure 6-1**). We assume that SCYS may either increase the breast milk volume or improve women's perception of milk production by changing milk composition and consequently influencing infant behaviour.

A literature review of Web of Science, PubMed and Scopus was conducted regarding each proposed mechanism. Studies in humans were primarily reviewed, but studies in animals and *in vitro* are also included when evidence from human studies were not found. The pathways of proposed mechanisms are described in the following sections.



**Figure 6-1 The potential mechanism of *Saccharomyces cerevisiae* yeast-based supplements (SCYS) on breast milk production and composition.** The dashed arrow means there is a lack of evidence in humans to support the proposed effect.

First, high B vitamin content from SCYS supplementation may improve postnatal mood, leading to increased oxytocin release and milk ejection. SCYS is rich in B vitamins and minerals [73, 74]. B vitamin deficiency is associated with negative mood changes, and B1, B6, folate, B12 or multi-nutrient supplementation is reported to improve symptoms in the general population [75, 76]. Although there is limited data regarding B vitamin status and postnatal mood symptoms [77, 78], one study showed that multi-nutrient supplementation containing several B vitamins and minerals had a better protective effect on postnatal depression than only calcium and vitamin D3 supplementation [79]. Consumption of yeast-based spreads such as marmite and vegemite produced from SCY extract have been reported to improve anxiety and stress symptoms but not depressive symptoms in the general population [80]. Supplementing with SCY derived beta-glucan significantly reduced Profile of Mood States scores compared to placebo in non-lactating women with moderate stress [81]. Thus, taking

SCYS during breastfeeding may improve postnatal mood symptoms such as stress, anxiety and depression.

Studies on postnatal distress and breast milk production suggested that the postnatal mood may be indirectly related to milk secretion by influencing oxytocin release [82, 83]. Postnatal depression was associated with reduced length of exclusively breastfeeding period [84] and women with postnatal distress had higher risks of PIM [18, 84]. However, no difference of breast milk volume was observed between women with and without perinatal depression [84]. A lower postnatal plasma oxytocin concentration was associated with greater postnatal mood symptoms [82, 83], and psychological stress was reported to decrease suckling-induced pulsatile oxytocin release during one breastfeeding session [85-87]. A lower postnatal plasma oxytocin concentration was also inversely correlated to the baseline oxytocin before a breast feed in breastfeeding women [87]. Thus, improved postnatal mood may enhance oxytocin release and hence milk ejection. Improved milk ejection leads to better milk removal and may increase milk production. Improved milk ejection may also reduce infant frustration and allow infant to feed to demand. Therefore, increased oxytocin may reduce PIM.

Second, SCYS contains bioavailable chromium which may increase breast milk production by influencing insulin-like growth factor 1 (IGF-1). Chromium was reported to upregulate IGF-1 mRNA and IGF-1 receptor concentrations in rat skeletal muscle cells with presence of insulin [88]. However, the form of chromium supplemented in the cell culture in this study was different from the bioavailable chromium in SCYS. IGF-1 is a hormone found in both maternal blood and breast milk [89], which may benefit milk production in different ways. For example, higher concentrations of maternal blood IGF-1 can enhance mammary gland growth, improve blood flow and milk secretion [90], and breast milk IGF-1 can promote neonatal growth and nutrient absorption [90, 91], and may optimise weight gain in exclusively breastfeeding infants [92, 93].

Third, the large amount of beta-glucan and MOS in SCYS [43, 94] may benefit milk quantity and quality through several pathways. Beta-glucan was reported to have a dose-related stimulation on the

secretion of prolactin from GH3/B6 rat pituitary tumour cells [95]. SCY derived beta-glucan has been reported to stimulate the innate immune system, for example, suppressing production of interferon- $\gamma$  (IFN- $\gamma$ ) *in vitro* [96] and activating IL-1 $\beta$  transcription and secretion in human macrophages [97]. Supplementation of beta-glucan and MOS from SCYS or YCWP improve mammary gland health in lactating animals [50, 52, 56, 66]. Moreover, orally taking SCY derived beta-glucan has been reported to influence the synthesis and release of interleukins IL-6 and IL-10 *in vivo* [98-100] and reduce blood IL-6 and increase blood IL-10 in overweight and obese people [101]. These cytokines were also detected in breast milk and may potentially regulate infant gut immunity [102], although no maternal supplementation studies have evaluated human milk cytokines.

The other potential pathway through which SCYS could impact lactation is to affect infant demand by alteration in milk composition such as milk hormones and human milk oligosaccharides (HMOs). Researchers have suggested that SCY derived beta-glucan supplementation could increase blood ghrelin in weanling piglets [103] and could lower blood leptin concentrations in patients with diabetic retinopathy [104], but there is no published information about the effect on milk composition. Human milk leptin and ghrelin could regulate infant breast milk intake by stimulating infant appetite [89]. However, the findings of studies on the relationship of human milk hormones and infant weight gain are inconsistent [105]. There is also a lack of studies that examine the relationship of milk hormones and milk intake [93].

Human milk oligosaccharides (HMOs) are the third most abundant component in human milk and benefits to infants are thought to include prebiotic effects, prevention of pathogen adhesion, modulation of intestinal epithelial cell responses and direct modulation on immune responses [106, 107]. Very limited evidence suggests that maternal diet has an influence on milk HMOs abundance and profile [108, 109]. This effect has been seen in rats, where high prebiotic fibre diets modified the amount of some milk oligosaccharides in rat and consequently influenced the establishment of gut microbiota in offspring [110].

Milk composition changes such as milk cytokines, milk hormones and HMOs may benefit infant growth and development as well as gut immunity and result in the improvement of colic, unsatisfied, unsettled or crying behaviour, which is commonly perceived by the mother as signs of insufficient milk production (PIM) [5, 14-16]. Thus, although not directly influencing milk volume, SCYS could reduce PIM by influencing milk composition.

## 6.6 Safety considerations of taking *Saccharomyces cerevisiae* yeast-based supplement during lactation

SCYS is approved as a food additive by the USDA with total folic acid not exceeding 0.04 mg/g [35]. However, there is no regulation or recommendation on the safe dosage of SCYS in lactation. We searched Web of Science, PubMed and Scopus using “contamination”, “food-drug interaction” or “side effect” with “brewer’s yeast”, “nutritional yeast” or “*Saccharomyces cerevisiae*” to review the safety risks. Possible safety concerns from taking SCYS during breastfeeding are described as follows.

First, the nutrient contents vary in strains of SCY and batches of SCYS products [43]. This could increase the risk of nicotinic acid and folic acid intake approaching the upper level (UL) if women regularly consume a high dose of SCYS (i.e. 30 g/day as the highest dose recommended in Table 3) and take multivitamins or B vitamins supplements at the same time. The calculation of nicotinic acid and folic acid intake from SCYS and risk of approaching UL can be found in **Appendix 10**.

Second, SCYS has been found to be contaminated with ochratoxin A (OTA) in Germany [111, 112]. OTA is a type of mycotoxin [111] which can cause nephrotoxicity, immunotoxicity and carcinogenicity [113]. It can bind to yeast cell walls [114] and cause contamination of SCYS. OTA contamination is frequently reported in breast milk samples worldwide [115, 116]. Consumption of breast milk contaminated with OTA may increase risks of renal injury in exclusively breastfeeding infants [117]. OTA is also a contaminant in many other foods including cereals, coffee, wine, grapes, meat and dairy foods [115, 118]. Maternal blood OTA levels will increase if the mother habitually consumes contaminated foods,

as the half-life in human blood is 35-36 days [115, 116]. The OTA concentration in mature breast milk is about 8% to 44% of that in maternal blood [117, 119]. A daily dose of 30 g of SCYS (the highest dose recommended in **Table 5-3**), along with dietary exposure, could result in an estimated OTA intake of 27.4% of Provisional Tolerable Weekly Intake for Aotearoa New Zealand lactating women. The estimation of OTA intake is described in **Appendix 10**.

Third, SCYS may contain large amounts of tyramine that can interact with monoamine oxidase inhibitors. This interaction may cause a significant rise in blood pressure and increase the risk of heart attack or stroke [120, 121]. As such, SCYS should be avoided when taking medications containing monoamine oxidase inhibitors.

Fourth, SCYS may aggravate inflammatory bowel diseases such as Crohn's disease. Anti-*Saccharomyces cerevisiae* antibodies are suggested as biomarkers of Crohn's disease [122]. One study found patients had significantly higher Crohn's disease activity during time of exposure to baker's yeast [123]. However, the authors did not say if the baker's yeast was active or inactive, and not all patients had symptoms associated with yeast exposure. None the less, patients with Crohn's disease need to be aware if taking SCYS.

Finally, minor adverse effects of taking SCYS were recorded in two [124, 125] of seven [28, 29, 36, 124-127] human studies, although none of these studies were conducted in lactating women. In one randomised placebo-controlled study on type 2 diabetes, one case of nausea was reported in the intervention group (n = 29) [125]. In another placebo-controlled crossover study on type 2 diabetes, one case of skin rash, one case of constipation, and one case of decreased appetite was documented in the intervention group (n = 14) [124]. In both studies, participants in the intervention group received chromium enriched brewer's yeast supplements.

There are four studies in which lactating women have been given SCYS (selenium enriched), for the purpose of evaluating maternal selenium supplementation on selenium concentration in breast milk

[128-131]. Unfortunately, these studies did not report either the number of participants not completing the trial nor adverse effects from supplementation. Thus, the likelihood of adverse effects due to taking SCYS during lactation remains unknown.

## 6.7 Conclusions

SCYS is used as a galactagogue by breastfeeding women, but there is no peer review evidence of its effectiveness and no recommendation or guideline of its use from any professional organisations. SCYS is available online with product names “brewer’s yeast” or “nutritional yeast”. The production process and nutrient composition vary between products. SCYS, in a range of doses, is recommended on the internet as a galactagogue to increase breast milk production. The inconsistent information may be misleading and cause confusion about use of SCYS as a galactagogue.

SCYS has been shown as a dietary supplement to increase milk production in ruminant animals. However, the influence of SCYS on breast milk production in humans has not yet been established. There are potential mechanisms through which postnatal supplementation of SCYS could increase breast milk volume or change milk composition, thus affecting infant behaviour and hence address PIM.

The safety of taking SCYS during lactation is unknown. It is approved by the USDA as a food additive and widely consumed as a supplement. However, minor adverse effects were reported in human supplementation studies with diabetics and OTA contamination has been found in SCYS.

Further research is required to investigate the efficacy and safety of SCYS consumption as a galactagogue in breastfeeding women. Researchers should be aware that addressing milk volume as the endpoint is ethically difficult because women with true insufficient milk production need to increase milk production or supplement breastfeeding, i.e., they cannot rely on a randomised placebo-controlled trial. Researchers can test the mechanisms proposed in this review by investigating changes of milk composition, mothers’ perception of milk production and maternal blood prolactin and

oxytocin levels. The B vitamin concentrations and OTA concentration of SCYS should be determined before the trial to ensure intake is under the tolerable intake. Adverse effects should be monitored and recorded.

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## Chapter 7 Effect of *Saccharomyces cerevisiae* yeast-based supplement on human milk oligosaccharide concentration and other indicators of breast milk supply: a randomised placebo-controlled trial

In Chapter 6, the mechanisms of how *Saccharomyces cerevisiae* yeast-based supplements (SCYS) could influence breast milk production and mothers' perception of their milk supply were proposed based on the current evidence in the literature. This chapter reports on an RCT which investigated the effect of SCYS on human milk oligosaccharide (HMO) concentration and other outcomes that could be impacted by SCYS supplementation and may influence mothers' perceptions or breastfeeding status. These outcomes are PIM, mothers' perceptions of milk quantity and quality, infant behaviours, attitudes of significant others to mothers' milk supply, postnatal distress, infant growth, and breastfeeding patterns.

The original study aim was to investigate the effect of SCYS on the volume of breast milk using an adapted hourly expression method. However, the problem with the method evaluating breast milk production and the adverse impact of COVID restrictions on human studies visiting participants led to the difficulty to obtain the required sample size for assessing change in breast milk volume. An adapted hourly expression method was used to evaluate milk production for the first 24 participants. Some participants expressed small amounts (i.e., < 10 g) at the second and/or following expressions, leading to 21% invalid sessions (n = 15). Analysis of the valid sessions found the volume of milk from the third and fourth expressions were inconsistent (see Chapter 8). The adapted method did not seem to be valid. Therefore, the aims and primary outcomes for the RCT were changed to the above to ensure this study could continue during the pandemic.

This chapter has been prepared for submission to the *International Breastfeeding Journal*.

## 7.1 Abstract

**Background:** Perceived insufficient milk (PIM) is commonly reported as the primary reason for discontinuation of breastfeeding or introducing formula before six months of age. *Saccharomyces cerevisiae* yeast-based supplements (SCYS) such as brewer's yeast are frequently used by breastfeeding women as galactagogues, substances used to increase breast milk supply and support breastfeeding. However, their efficacy has only been evaluated in lactating ruminants and sows. This study aims to investigate the effect of SCYS on human milk oligosaccharide (HMO) concentration and indicators of PIM, as well as to assess the safety of taking SCYS during lactation.

**Method:** A randomised, double-blind, placebo-controlled trial was conducted in Palmerston North, Aotearoa New Zealand, from May 2019 – July 2021. Breastfeeding women with a term infant aged 1 – 7 months were enrolled and randomly assigned to consume SCYS (5 g/day) or a placebo for four weeks. Breast milk samples were collected at baseline and the endpoint of the study for analysis of the concentration of 11 HMOs (by UHPLC with fluorescence detection). Online questionnaires were used to evaluate PIM, postnatal distress (DASS-21 scale), infant feeding status, and self-reported symptoms that might be side effects of taking SCYS. Questionnaires were administered at baseline, weekly during the four-week intervention and at six months postpartum where applicable. In addition, infant anthropometry and feeding pattern (24-hour feeding record) were measured at baseline and at the end of the intervention. Intention-to-treat analysis was performed.

**Results:** Seventy-two women were recruited, and 68 participants (34 in each group) completed the study and were included in the data analysis. The SCYS had no effect on individual or total HMO concentration. There were no significant differences in PIM, postnatal distress, infant weight, length, head circumference or feeding pattern between the SCYS and placebo groups. More participants in the SCYS group than in the placebo group perceived that the intervention increased their milk production (65% vs. 35%,  $p < 0.05$ ). Women reported a few side effects from taking the SCYS, but none withdrew from this study.

**Conclusion:** The SCYS has no effect on HMO concentration or other outcomes, except for mother's perceived effectiveness of the intervention on milk supply.

**Trial registration:** This trial was registered at Australian New Zealand Clinical Trials Registry (ACTRN12619000704190).

## 7.2 Introduction

Breastfeeding not only promotes the growth and development of infants but also benefits mothers' physical and mental health in both the short and long-term [1, 2]. Despite World Health Organization (WHO) and Aotearoa New Zealand (Aotearoa NZ) recommendations of exclusive breastfeeding to six months of age and prolonged breastfeeding to at least two years [3, 4], a nationally representative cohort study of infants born between 2009 and 2010 in Aotearoa NZ found only 16% were exclusively breastfeeding at six months postpartum and 13% were breastfed to two years [5].

Perceived insufficient milk (PIM) is frequently reported by breastfeeding women as the primary reason to stop breastfeeding or to introduce infant formula [6, 7]. Many factors may influence women's perceptions of their milk supply. For example, women may construe infants' unsettled or crying behaviour as meaning there is insufficient breast milk [8, 9]. Some women interpret watery milk, empty/soft breasts, frequent feeds, or long feeds as signs of low quality or quantity of breast milk [10]. Further, women may report PIM in response to health professionals, family members, or friends questioning their milk supply [11].

Breastfeeding women sometimes use galactagogues when they experience PIM or have concerns about their milk supply. Galactagogues are foods, herbs, supplements and medications that are suggested to increase breast milk production [12]. Although women expect that galactagogues will increase their milk supply, it is possible that galactagogues address PIM by influencing signs mothers interpret as suggesting their milk supply is inadequate, rather than influence actual volume of milk.

*Saccharomyces cerevisiae* yeast-based supplements (SCYS) such as brewer's yeast are popular galactagogues among breastfeeding women [13-15]. However, their efficacy has only been demonstrated in lactating ruminants and sows [16]. We recently proposed that SCYS could affect mothers' perception of their milk supply by influencing human milk oligosaccharides (HMOs) or by altering maternal perceptions of infant growth, infant feeding and behaviour, and postnatal distress [16].

Human milk oligosaccharides (HMOs) are the third most abundant component in human milk; they benefit infant gut health, modulate immune responses, and promote brain development [17, 18]. More than 200 HMOs have been identified to date, although about 20 of them account for over 90% of total HMO content [19, 20]. Neutral fucosylated HMOs account for 35% - 50% of the total HMO content, neutral nonfucosylated HMOs account for 42% - 55% of the total HMO content, and sialylated HMOs represent 12% - 14% of the total HMO content [19].

The profile and concentration of HMOs vary considerably among breastfeeding women. The main reason for the variation in HMO composition is the presence of certain glycosyltransferase enzymes, which are determined by the Secretor (Se) and Lewis (Le) genes. For example, the most abundant HMO, 2'-FL, is present in about 70% - 80% of women's breast milk [19, 21]. These women have an active Secretor gene locus that encodes  $\alpha$ 1-2-fucosyltransferase, the enzyme responsible for the synthesis of 2'-FL and LNFP-I [20].

The concentration of most HMOs shows a decreasing trend from one to nine months postpartum except for 3-FL and LNFP-III [22-28]. The actual concentration of HMOs in breast milk is difficult to compare between studies due to the different HMOs measured, inconsistent time points for milk sampling, and different analytical methods. HMOs that were measured in all these studies include 2'-FL, 3-FL, LNFP-I, LNFP-II, LNFP-III, 3'-SL, 6'-SL, LNT and LNnT [22-28].

Maternal diet may affect HMO concentrations and, consequently, influence infant health. A recent study found that having a high prebiotic fibre diet affected oligosaccharides in rat milk, influencing the gut microbiota in offspring [29]. Results in human studies also suggest that maternal diet influences HMOs abundance and profile [30, 31]. However, no study in humans or animal models has evaluated whether SCYS affects milk oligosaccharides.

Additionally, SCYS supplementation may improve postnatal distress and, accordingly, address PIM. Symptoms of postnatal distress such as stress, anxiety and depression are reported to adversely influence milk ejection reflex [32] and decrease breastfeeding self-efficacy [33], which can result in PIM. Consumption of spreads produced from *Saccharomyces cerevisiae* yeast extract has been reported to improve stress and anxiety [34]. Supplementing with *Saccharomyces cerevisiae* yeast derived beta-glucan has also significantly reduced Profile of Mood States scores in women with moderate stress [35]. No studies on how SCYS supplementation influences postnatal distress in lactating women have yet been conducted.

Adverse effects of taking brewer's yeast supplements, including constipation, nausea, decreased appetite, and skin rash, were reported in two human studies investigating the health benefits of chromium enriched yeast supplementation on type 2 diabetes [36, 37]. Studies on selenium-enriched yeast supplementation during lactation did not report any adverse effects [38-41]. Thus, it remains unknown if taking yeast-based supplements during lactation causes any adverse effects for women or infants.

The aims of this study are to evaluate the effect of maternal supplementation with SCYS on HMO concentration and indicators of PIM and to assess some safety aspects of taking SCYS during lactation. We hypothesise that SCYS affects HMO concentration and, consequently, results in more settled infant behaviour, which may alter mother's perceptions of her milk supply and so reduce PIM. We also propose that SCYS addresses postnatal distress, leading to improved breast milk outputs and altering the mother's perception of the inadequacy of her milk supply.

## 7.3 Method

### 7.3.1 Study design

This was a randomised, double-blind, placebo-controlled trial with a two-arm, parallel design. The participants were randomly assigned to a placebo group or a SCYS group with an allocation ratio of 1:1. This trial was registered at Australian New Zealand Clinical Trials Registry (trial registration number: ACTRN12619000704190). Massey University Human Ethics Committee approved this study (SOA 18/80) (**Appendix 7**).

### 7.3.2 Setting

This trial was conducted in Palmerston North, Aotearoa NZ, between May 2019 and July 2021. Participants were recruited from Manawatū-Wanganui and Wellington regions in the North Island of Aotearoa NZ.

### 7.3.3 Participants

Participants first contacted the researcher after seeing the advertisement online or at local sites where pregnant and breastfeeding women commonly visited. The study information sheet was then sent to the potential participants, and an online screening questionnaire (**Appendix 11**) was completed to check eligibility. Inclusion criteria included: women aged over 16 years with a healthy, singleton infant 1 – 7 months of age; currently breastfeeding, including feeding directly from the breast, feeding with expressed milk or mixed feeding with formula. Mothers with the following problems were excluded: allergy to yeasts; taking medicines such as Phenelzine (Nardil), Tranylcypromine (Parnate), Selegiline (Ensam, Eldepryl), Isocarboxazid (Marplan) and Meperidine (Demerol) or any other medications containing Monoamine Oxidase Inhibitors; having health conditions or taking medications that could influence milk secretion-related hormones or milk supply; Crohn's disease; compromised immunity; or treatment for fungal infections.

The estimated sample size was 32 in each group. This calculation was based on an assumption to capture a 20% difference in total HMO concentrations between the SCYS group and the placebo group at a significance level of 0.05 and a power of 80% (**Appendix 3**).

#### 7.3.4 Intervention

Eligible participants were randomly assigned to take either the yeast-based supplement or placebo. Randomisation schedules were conducted by an independent research technician using the toss-of-coin method for a block of four. The participants received nine capsules per day of either yeast (5 g, powdered brewer's yeast that was grown on molasses, purchased at a local market) or a placebo (corn starch, Novation 4600, Ingredion, NZ) for four weeks. The capsules were filled manually at the Food Product Development Laboratory at Massey University. The empty capsules (Capsuline, US) were orange in colour and flavour to mask the colour and flavour of the yeast. Both the researcher and the participants were blind to the intervention during recruitment and data analysis.

#### 7.3.5 Compliance

Capsules were in containers labelled with the week and day of the study. Participants took capsules following the labels and left the capsules in the container if they missed doses. A photo of the containers was taken weekly to count the number of capsules consumed. Consumption more than 80% of capsules in total was considered good compliance.

#### 7.3.6 Data collection

Data were collected at baseline, every week during the study period, and at follow-up at six months postpartum for the subgroup of infants aged <5 months at baseline. At baseline and week four of the study (the endpoint), participants visited the Human Nutrition Research Unit at Massey University or met the researcher at their home as per their preference. Milk sample collection and anthropometric measurements for infants were conducted during these visits. A record of 24-hour breastfeeding and nappy change were completed one day before the baseline visit and the endpoint visit. Questionnaires

regarding mothers' perceptions of milk production, infant behaviours, attitudes of significant others, postnatal distress and experiences reported as side effects were completed at baseline, every week during the intervention, and during follow-up at six months postpartum if applicable (**Appendix 7** and **Appendix 12**). The recording forms for 24-hour breastfeeding, nappy change and infant anthropometric measurement visits are shown in **Appendix 13** and **Appendix 14**, respectively.

### Milk sampling and HMO analysis

Approximately 50 ml of breast milk was collected at the baseline and the endpoint. Milk samples were collected from one breast or both breasts with one or two morning expressions between 9:30 am and 11:00 am to avoid variations in milk composition caused by circadian rhythm [42]. The milk samples were kept at 4°C during transfer to the lab and then separated into 5 mL tubes and stored at – 80 °C until analysis.

HMOs were analysed by UHPLC with fluorescence detection after labelling with 2-aminobenzamide as described by Austin and colleagues [43], with online solid phase extraction clean-up [44]. Twelve HMOs were quantified, including nine HMOs quantified directly with available standards (2'-FL, 3-FL, A-Tet, LNFP-I, LNFP-V, 3'-SL, 6'-SL, LNT, and LNnT) and three HMOs (LNFP-II, LNFP-III and LNnFP) quantified indirectly against LNFP-I assuming a similar detector response (**Table 7-1**). The presence of 2'-FL was used to define Secretor status.

**Table 7-1 Human milk oligosaccharides included in the analysis.**

<b>Name</b>	<b>Abbreviation</b>
<i>Fucosylated HMOs</i>	
2-fucosyllactose	2'-FL
3-fucosyllactose	3-FL
A-tetrasaccharide	A-Tet
Lacto-N-fucosylpentaose-I	LNFP-I
Lacto-N-fucosylpentaose-II	LNFP-II
Lacto-N-fucosylpentaose-III	LNFP-III
Lacto-N-fucosylpentaose-V	LNFP-V
Lacto-N-neofucosylpentaose	LNnFP
<i>Sialylated HMOs</i>	
3-sialyllactose	3'-SL

6-sialyllactose	6'-SL
<i>Non-fucosylated, non-sialylated HMOs</i>	
Lacto-N-tetraose	LNT
Lacto-N-neotetraose	LNTnT

## Mothers' perceptions

Women were asked about their perceptions at baseline, every week during the study, and at follow-up at six months if the infant was < 5 months at baseline. PIM was evaluated by a single question asking if the participant believed she was producing the right amount of milk to satisfy her baby with five options: make too much, just right, sometimes not enough, often not enough, and not sure. Participants who selected "not sure" were asked to explain the reasons, and their responses were then coded to the above options according to their answers.

Mothers' perceptions investigated include perceived milk quantity and quality (PMQ), perceived infant behaviour (PIB), and perceived significant others' attitudes (PSA). These perceptions were measured by five-point Likert scale from five (strongly agree) to one (strongly disagree), with reverse scoring for one negative item of perceived infant behaviour. Scores of three items on perceived milk quantity and quality were summed to create the variable of perceived milk quantity and quality (PMQ); similarly three items were combined for the variable of perceived infant behaviour (PIB). The variable of perceived significant others' attitude (PSA) was created from the four relevant items; if "strongly disagree" or "disagree" was chosen for one or more items PSA was coded as PSA-negative (i.e., significant others questioned the participant's milk supply). In contrast, the other choices were coded as PSA-positive. These questions were developed by consulting previous research [8, 45-47] and from the results of our unpublished qualitative study (i.e., Chapter 4).

An open-ended question at the endpoint visit evaluated the perceived effectiveness of the intervention. Participants were asked how they thought the intervention influenced their milk supply and the reasons. The answers were coded to "no influence", "no idea", and "effective". A binominal

variable of perceived effectiveness of the intervention (PEI) was created with “effective” coded as positive and “no influence”/ “no idea” coded as neutral.

### **Postnatal distress**

Postnatal distress was assessed by the DASS-21 scale [48]. This scale has 21 Likert scale (0-3) items, including three subscales of depression, anxiety, and stress. Each subscale contains seven items. Scores for each subscale were calculated by summing up the points for relevant items, and then multiplying by two; the total score was calculated by summing up the scores of the three subscales and higher scores indicated more severe symptoms [49]. The DASS-21 scale has been used to evaluate psychological distress, depression, anxiety, stress in pregnant women and mothers of young children in the Aotearoa NZ [50, 51].

### **Infant breastfeeding patterns**

Infant feeding practices were recorded in the questionnaire at baseline, every week during the study and at follow-up after six months. A binominal variable of breastfeeding status (exclusive breastfeeding vs other) was created at baseline, endpoint, and follow-up to compare the proportion of women exclusively breastfeeding. A variable of predominant breastfeeding was also created.

The WHO definition of exclusive breastfeeding was used in this study [52]. This means that from birth to each time point of the survey, the infant only received breast milk as their primary source of nutrition (including feeding on breasts, expressed milk and donor milk) but also that they could have received oral rehydration solution (ORS), drops and syrups (vitamins, minerals and medicines). Predominant breastfeeding in this study means that from birth to each time point of the survey, the infant mostly received breast milk (including feeding on breasts, expressed milk and donor milk). In addition, the infant might also have received liquids (water and water-based drinks, fruit juice), ritual fluids and ORS, drops or syrups (vitamins, minerals and medicines), as well as a small amount of formula (< 100 mL) occasionally.

The participants recorded breastfeeding timing and duration for each feed over 24 hours at baseline and the study endpoint. Participants were asked to record one feed beyond 24 hours to ensure the record covered 24 hours. Both feeding on the breasts and feeding with expressed milk were recorded to calculate breastfeeding frequency in 24 hours. Breastfeeding duration over 24 hours was only calculated from feeds on the breast. The definition of one feed (on breast) was completion of latching on, swallowing and latching off, regardless of the time between latching on and off. For example, if the infant latched on one side and fed for one minute, then switched to the other side and fed for another two minutes, this was counted as two feeds. This definition of one feed differs from previous research, which limited the feeding time to at least one minute [53-55] or two minutes [56], without involving the time between the latches. This study focused on the effect of the intervention on infant feeding behaviour; therefore, even short feeds were recorded.

#### **Infant urination and defecation frequency**

Infant urination and defecation frequency were estimated by recording all nappy changes in the same 24-hour period. The numbers of wet nappies were calculated by adding up the number of wet nappies as well as the number of both wet and soiled nappies over 24 hours. The number of soiled nappies was calculated by summing up the number of soiled nappies as well as the number of both wet and soiled nappies over 24 hours.

#### **Infant anthropometry**

The researcher measured the infant's weight, length and head circumference at baseline and the study endpoint. Infants were weighed using a baby weighing scale (Nagata Scale Co Ltd), and the weight was recorded to the nearest 5 g. Infant length was measured from heel to crown using an infant length board and recorded to the nearest millimetre. Infant head circumference was measured using a flexible, non-stretch tape [56] and recorded to the nearest millimetre.

### Side effects

Self-reported frequency of symptoms related to potential side effects from SCYS, including constipation, decreased appetite, nausea, and skin rash, were collected at the baseline and weekly during the study by using a five-point Likert scale for each symptom ranking from five (always) to one (never). Participants were also asked to record any other issues they perceived related to taking the study capsules.

### Socio-demographic and maternal factors

Socio-demographic information was collected at baseline, including maternal age and education level, ethnicity, number of children, living status (e.g., with partner and child), and family income. This information was used to describe the study sample. Birth and infant information: infant age, infant sex, delivery mode and birth weight were also collected at baseline.

### 7.3.7 Data analysis

Data analyses were performed using SPSS version 25.0 (IBM, Armonk, NY, US). Intention-to-treat analysis was used. All continuous variables were tested for normality using a combination of methods, including stem-and-leaf plot of residuals, normality plot, and Shapiro–Wilk test. Descriptive analysis was conducted for all the data. Data were summarised using mean  $\pm$  standard deviation (SD) for normally distributed variables or median (Q1, Q3) for non-normally distributed variables. Categorical variables were summarised using frequencies (%).

The total concentration of fucosylated HMOs was calculated by summing the concentrations of 2'-FL, 3-FL, LNFP-I, LNFP-II, LNFP-III, LNFP-V and LNnFP. The concentration of sialylated HMOs was calculated by summing of the concentrations of 3'-SL and 6'-SL. The total concentration of non-fucosylated, non-sialylated HMOs was calculated by summing the concentrations of LNT and LNnT. The total HMO concentration was calculated by summing the concentration of all 11 of these HMOs. A-Tet was present in only 26% of milk samples (n = 18), and the concentration of A-Tet was only 1 – 3 % of the

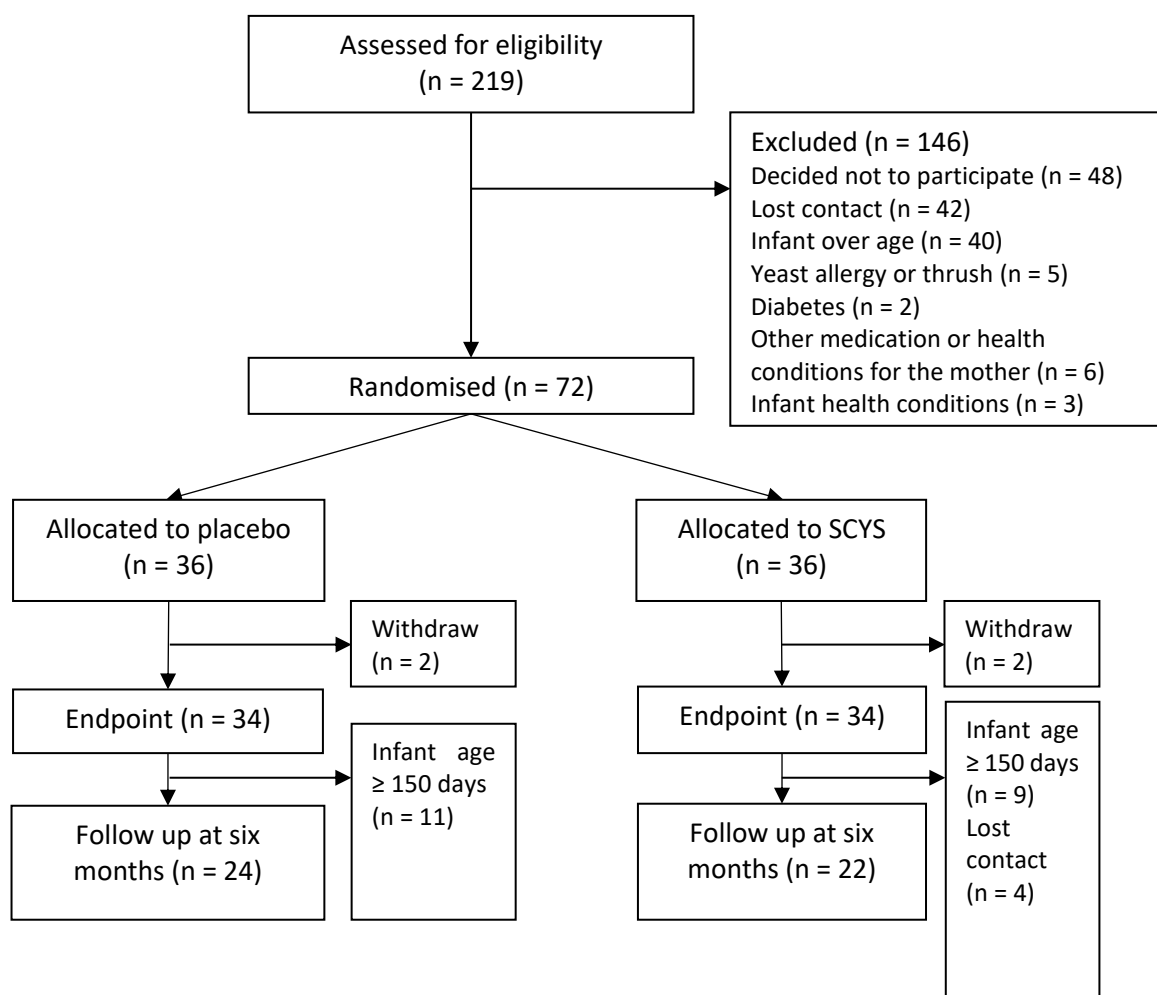
total HMO concentration in most milk samples. Thus, A-Tet concentration was excluded from the data analysis. Multivariate linear regression with the bootstrap method [58, 59] was used to address potential confounders and to examine the relationship between the effect of intervention and HMO concentration changes from baseline to endpoint. The potential confounders included: secretor status, maternal age, and breastfeeding status [23, 60, 61]. Thus, four predictors were included in the model to evaluate individual and total HMO concentration change from baseline to the endpoint. The estimated sample size required for this analysis was 53, with the assumption of an effect size of the model of total HMO concentration change as 0.25, at a power of 80% and significance level of 0.05 [62].

A comparison of mothers' perceptions (PIM, PMQ and PIB) between the two groups was made using the Mann-Whitney U test at baseline, each week of the study and at follow-up. Friedman's ANOVA was used to compare the changes in mothers' perceptions over time within each group. The difference in PSA and PEI between the two groups at the endpoint was assessed using the Chi-square test. Postnatal distress (scores of DASS-21 scale and subscales), breastfeeding frequency, breastfeeding duration, numbers of nappy changes over 24 hours, and infant growth were analysed by mixed ANOVA or nonparametric factorial ANOVA. Variables of breastfeeding duration and frequency were created by summing up breastfeeding time and number of feeds for the day (6 am – 6 pm), night (6 pm – 6 am the next day), and over 24 hours. Variables related to infant growth were infant weight, length and head circumference, as well as weight-for-age Z-score (WAZ), length-for-age Z-score (LAZ), head circumference-for-age Z-score (HCAZ) and weight-for-length Z-score (WLZ), which were calculated using WHO Anthro software version 3.2.2 [63]. The Aligned Rank Transform (ART) method was used for non-normally distributed variables during nonparametric factorial ANOVA [64, 65]. Perceived side effects were evaluated by Friedman's ANOVA and a post hoc test with a Bonferroni correction where applicable.

In the subgroup of women who completed the follow-up survey when the infant was six months of age, the proportions of predominant breastfeeding, exclusive breastfeeding, and formula use between the two groups were compared by Fisher's Exact test. The change of mothers' perceptions (PIM, PMQ and PIB) from baseline, endpoint to follow-up after six months was evaluated by Friedman's ANOVA. PIM, PMQ, PIB and PSA between the two groups were tested by Mann-Whitney U test or Fisher's Exact test.

## 7.4 Results

In total, 72 women were recruited in this study and were randomly allocated to either the yeast or the placebo group. Two participants in the SCYS group withdrew after the completion of the baseline survey. One participant in the placebo group withdrew in the first week of intervention due to increased infant crying, and another participant in the placebo group lost contact after the first week of intervention. These four participants were excluded from the data analysis (**Figure 7-1**). Most participants had good compliance during the intervention: 57 participants consumed  $\geq 90\%$  of capsules, 10 participants consumed 80% – 89% of capsules (five in each group), and only one participant in the placebo group consumed  $< 80\%$  of capsules.



**Figure 7-1 Flowchart of participant recruitment.**

Demographics and baseline characteristics were similar in the two groups (**Table 7-2**). The mean age of participants was 32.1 years, similar to the median age of women having an infant in Aotearoa NZ (31.2 years) [66]. Compared to the census data in 2018 [67], there was a much higher proportion of participants who were Caucasian and had received tertiary education. About 60% of participants had an annual family income above the median income of Aotearoa NZ in 2020 [68]. Fewer women had a caesarean delivery than nationally (21% vs 29%) [69].

**Table 7-2 Demographic and infant and breastfeeding information**

Characteristics	Total (n = 72)	Placebo (n = 36)	Yeast (n = 36)	<i>p</i> value
Maternal age, years (mean ± SD)	32.1 ± 4.9	31.9 ± 5.4	32.4 ± 4.3	0.682

Tertiary Education (n, %)	56 (78)	28 (78)	28 (78)	0.659
Ethnicity – Caucasian (n, %) *	59 (82)	31 (86)	28 (78)	0.677
Ethnicity – Māori (n, %)	6 (8)	5 (14)	1 (3)	0.200
Ethnicity – Asian (n, %)	9 (13)	4 (11)	5 (14)	0.732
Ethnicity – Other (n, %)	3 (4)	1 (3)	2 (6)	
Annual household income, n = 68 (Above median, n, %) #	43 (63)	23 (64)	20 (56)	0.664
Live with partner and child(ren) (n, %)	68 (94)	35 (97)	33 (92)	0.350
Number of children – 1 (n, %)	33 (46)	17 (47)	16 (45)	0.709
Number of children – 2 (n, %)	22 (31)	9 (25)	13 (36)	
Number of children – ≥3 (n, %)	17 (23)	10 (28)	7 (19)	
Smoking (n, %)	2 (3)	1 (3)	1 (3)	1.000
Drinking alcohol (n, %)	43 (60)	20 (56)	23 (64)	0.313
Drinking <1 standard drink each time (n, % in drinking alcohol)	32 (74)	13 (65)	19 (83)	0.187
Caesarean delivery (n, %)	21 (29)	11 (30)	10 (28)	0.914
Gestation age, week (median [Q1, Q3])	40 (39, 40.8)	40 (38.9, 40.9)	39.8 (39.4, 40.7)	0.996
Infant age, days (median [Q1, Q3]) at the first visit	108 (70, 166)	108 (66, 170)	105 (76, 157)	0.752
Infants birth weight, grams (median [Q1, Q3])	3678 (3335, 3975)	3740 (3465, 3975)	3575 (3255, 4005)	0.401
Male infant (n, %)	40 (56)	23 (64)	17 (47)	0.102
Breastfeeding status – predominant breastfeeding (n, %) †	64 (89)	33 (92)	31 (86)	0.785
Breastfeeding status – exclusive breastfeeding (n, %)	34 (47)	18 (50)	16 (44)	0.803
Breastfeeding status – currently formula (n, %)	5 (7)	2 (5)	3 (8)	0.505
Breastfeeding status – started solids (n, %)	22 (30)	10 (28)	12 (33)	0.504

\* The frequencies of ethnicity do not add up to 100% as some participants selected more than one ethnicity group.

# Median annual household income based on Statistics New Zealand is 87,607 New Zealand Dollars for the year ended June 2020 [68].

† The frequencies of breastfeeding status do not add up to 100% as three infants who were mixed-fed with breast milk and formula had started consuming solids.

Predominant breastfeeding means from birth to each time point of survey, the infant majorly received breast milk (including feeding on breasts, expressed milk and donor milk), and may also have received liquids (water and water-based drinks, fruit juice) ritual fluids and oral hydrate solutions (ORS), drops or syrups (vitamins, minerals and medicines), as well as a small amount of formula (<100 mL) occasionally.

Exclusive breastfeeding means from birth to each time point of survey, the infant received breast milk as the only source of nutrition (including feeding on breasts, expressed milk and donor milk), but may receive ORS, drops or syrups (vitamins, minerals and medicines) [52].

#### 7.4.1 The effect on human milk oligosaccharide concentration

The change of HMO concentration from baseline to endpoint was evaluated in 67 participants (**Table**

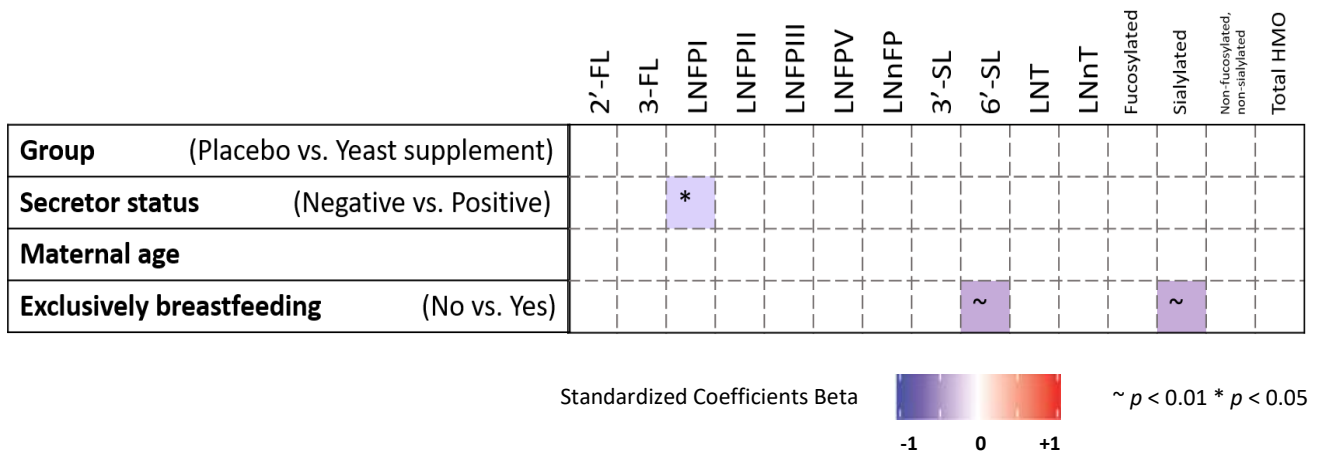
**7-3**). There were significantly more secretors in the placebo group (n = 26, 72%) than in the SCYS group

(n =19, 53%,  $p = 0.046$ ). Multivariate linear regression analysis was used to adjust the potential influences of secretor status and the other cofounders [60, 61] (the regression models are shown in **Appendix 15**). The SCYS had no significant influence on the change in concentration of total HMOs or any individual HMO during the 4-week intervention (**Figure 7-2**). However, exclusive breastfeeding significantly impacted the concentration change of 6'-SL and the concentration change of non-fucosylated, non-sialylated HMOs (i.e., LNT and LNnT).

**Table 7-3 Human milk oligosaccharide concentrations at the baseline and endpoint**

HMO Concentration, mg/L (Median [Q1, Q3])	Baseline		Endpoint	
	Placebo (n = 33)	Yeast (n = 34)	Placebo (n = 33)	Yeast (n = 34)
2'-FL	1639 (1021, 2215)	1475 (0, 2744)	1490 (1000, 2163)	1461 (0, 2550)
3-FL	1747 (1022, 2655)	2034 (1099, 3313)	1936 (1218, 2491)	2405 (1094, 3769)
LNFP-I	330 (107, 550)	204 (2, 700)	269 (140, 482)	128 (2, 595)
LNFP-II	559 (291, 994)	611 (326, 1175)	511 (304, 942)	571 (296, 1085)
LNFP-III	502 (365, 676)	523 (411, 639)	527 (408, 643)	492 (408, 667)
LNFP-V	67 (41, 111)	74 (45, 139)	58 (35, 111)	57 (40, 134)
LNnFP	21 (11, 41)	16 (10, 28)	17 (11, 34)	12 (6, 27)
Total Fucosylated	5286 (4814, 6082)	5502 (4951, 6444)	5250 (4818, 6141)	5524 (4897, 6809)
3'-SL	179 (149, 206)	171 (145, 209)	181 (163, 236)	169 (145, 206)
6'-SL	116 (70, 241)	181 (75, 257)	98 (66, 160)	113 (56, 177)
Total Sialylated	311 (241, 466)	365 (237, 419)	288 (241, 466)	294 (217, 357)
LNT	1088 (714, 1423)	984 (689, 1534)	917 (672, 1272)	841 (606, 1159)
LNnT	145 (67, 216)	113 (40, 212)	123 (60, 194)	101 (29, 189)
Total Non-fucosylated, non-sialylated	1175 (965, 1552)	1106 (833, 1707)	984 (805, 1462)	980 (714, 1303)
Total	6682 (6135, 8156)	7128 (6340, 8266)	6870 (5979, 7494)	6849 (5947, 8366)

HMO, human milk oligosaccharides; 2'-FL, 2-fucosyllactose; 3-FL, 3-fucosyllactose; LNFP-I, Lacto-N-fucosylpentaose-I; LNFP-II, Lacto-N-fucosylpentaose-II; LNFP-III, Lacto-N-fucosylpentaose-III; LNFP-V, Lacto-N-fucosylpentaose-V; LNnFP, Lacto-N-neofucosylpentaose; 3'-SL, 3-sialyllactose; 6'-SL, 6-sialyllactose; LNT, Lacto-N-tetraose; LNnT, Lacto-N-neotetraose.



**Figure 7-2 Summary of multivariate linear regression of the intervention (group) and confounders (secretor status, maternal age, and breastfeeding status) and HMO concentration change among 67 participants.** Beta estimates are from multivariate linear regression models with bootstrap method for the concentration of each HMO at the endpoint. Colouring reflects direction and magnitude of the coefficient beta. ~  $p < 0.01$ , \*  $p < 0.05$ . The first category of each factor is the reference category. HMO, human milk oligosaccharides; 2'-FL, 2-fucosyllactose; 3-FL, 3-fucosyllactose; LNFP-I, Lacto-N-fucosylpentaose-I; LNFP-II, Lacto-N-fucosylpentaose-II; LNFP-III, Lacto-N-fucosylpentaose-III; LNFP-V, Lacto-N-fucosylpentaose-V; LNnFP, Lacto-N-neofucosylpentaose; 3'-SL, 3-sialyllactose; 6'-SL, 6-sialyllactose; LNT, Lacto-N-tetraose; LNnT, Lacto-N-neotetraose.

#### 7.4.2 Other indicators of breast milk production

##### Participants' perceptions

Most of the participants had positive perceptions of their milk supply (PIM), milk quantity and quality (PMQ) and infant behaviour (PIB) at baseline. There was no difference between mothers' perceptions in the placebo group and the SCYS group at baseline, each week, or at the study's endpoint (**Table 7-4**); however, PMQ in the SCYS group significantly changed over the four-week study ( $\chi^2(4) = 11.88, p = 0.018$ ). *Post hoc* analysis of the effect at a  $0.05/4 = 0.0125$  level of significance suggested that total scores of PMQ in the SCYS group significantly increased from baseline to endpoint ( $T = 7, r = -0.31$ ). However, no significant changes for individual items of PMQ in the SCYS group were found. Thus, taking SCYS appears to be associated with some aspects of mothers' perceptions.

There were also significantly more participants in the SCYS group than in the placebo group who perceived that the intervention effectively increased their milk supply ( $n = 22, 65\%$  and  $n = 12, 35\%$ ,

respectively,  $p = 0.043$ ). Participants self-reported the signs and reasons for the effectiveness of the intervention, which included (in order of frequency of mention) breast fullness and/or leaking, faster and stronger milk ejection, more settled infant or improved infant sleep, increased amount of expressed milk, and more efficient or shorter time at each feeding (only reported in the SCYS group). While individual participants mentioned more than one sign/reason for the effectiveness of the intervention, the limited number of women perceiving the intervention to be effective made it impossible to conduct further quantitative analyses.

**Table 7-4 Participants' perceptions of milk supply at baseline, each week, and at endpoint, and perceived effectiveness of the intervention at endpoint (n = 68).**

Perceptions	Baseline		Week 1		Week 2		Week 3		Endpoint	
	Placebo (n = 34)	Yeast (n = 34)	Placebo (n = 34)	Yeast (n = 34)	Placebo (n = 34)	Yeast (n = 34)	Placebo (n = 34)	Yeast (n = 34)	Placebo (n = 34)	Yeast (n = 34)
PIM (Median [Q1, Q3])	4 (3.75, 4)	4 (4, 4)	4 (4, 4)	4 (4, 4)	4 (4, 4)	4 (4, 4)	4 (4, 4)	4 (4, 4)	4 (4, 4)	4 (4, 4)
PMQ (Median [Q1, Q3])	14.5 (13, 15)	15 (13, 15)*	15 (13, 15)	15 (13, 15)	15 (13, 15)	15 (13, 15)	15 (13, 15)	15 (14.75, 15)	15 (13, 15)	15 (14, 15)*
PIB (Median [Q1, Q3])	13 (12, 14)	14 (12, 15)	13 (12, 15)	14 (12, 15)	14 (13, 15)	13.5 (12.75, 14)	14 (12, 15)	14.5 (13, 15)	14 (13, 14)	15 (13, 15)
PSA, positive (n [%])	25 (74)	27 (79)	29 (85)	30 (88)	29 (85)	32 (94)	30 (88)	33 (97)	30 (88)	33 (97)
PEI (n [%])	—	—	—	—	—	—	—	—	12 (35)	22 (65) <sup>§</sup>

PIM, perceived insufficient milk supply; PMQ, perceived milk quantity and quality; PIB, perceived infant behaviour; PSA, perceived significant others' attitude to mothers' milk supply; PEI, Perceived effectiveness of the intervention. Mann-Whitney U test for PIM, PMQ and PIB scores found no significant differences between two groups at each time point. Friedman's ANOVA for PIM, PMQ and PIB scores within each group. Chi-square test for PSA between two groups at each time point and for PEI at the endpoint. \* Friedman's ANOVA and *post hoc* test using Wilcoxon signed ranks test with a Bonferroni correction, compared with SCYS group at the baseline,  $p = 0.011$ . <sup>§</sup> Chi-square test, ( $\chi^2 = 4.099$ ,  $p = 0.043$ ).

#### Postnatal distress

DASS-21 score significantly decreased from baseline to the study endpoint, suggesting that postnatal distress improved over time. However, there was no interaction between time and the intervention.

Compared to the placebo, taking the yeast supplement did not significantly relate to the DASS-21 score or score of depression, anxiety, or stress (data shown in **Appendix 16**).

#### Infant anthropometry measurements

Infant weight, length and head circumference increased significantly from baseline to endpoint; however, there was no interaction between time and the intervention. There were no differences in WAZ, LAZ, HAZ or WLZ between the SCYS and placebo groups. Taking SCYS was not associated with infant growth (data shown in **Appendix 17**).

#### Breastfeeding pattern, urination frequency, and defecation frequency

After the four-week intervention, the proportion of predominant breastfeeding (n = 27, 79% in the placebo group and n = 26, 77% in the SCYS group) and the proportion of exclusive breastfeeding (n = 20, 59% in the placebo group and n = 19, 56% in the SCYS group) were similar in the two groups.

The total breastfeeding time and the number of breastfeeds over 24 hours (6 am – 6 am the next day) significantly decreased from baseline to endpoint (data shown in **Appendix 18**). There were no differences in total breastfeeding time and number of feeds during the day (6 am – 6 pm), night (6 pm – 6 am the next day) or over 24 hours between the SCYS group and the placebo group. Taking SCYS had no significant influence on infant breastfeeding patterns (data shown in **Appendix 18**).

There was no significant difference in the number of wet or soiled nappies produced over 24 hours between the SCYS group and the placebo group at baseline or endpoint. Taking SCYS had no effect on infant urination frequency or defecation frequency (data shown in **Appendix 19**).

#### The adverse effects

There were no significant differences between the placebo and the SCYS group in the self-reported frequency of constipation, nausea, decreased appetite or skin rash at baseline, each week during the intervention, or at the endpoint (data shown in **Appendix 20**).

There was no significant change in frequency of nausea and skin rash over the four weeks of intervention in both the placebo group and the SCYS group (data shown in **Appendix 20**; however, there was a significant change over time in constipation in both the placebo group ( $\chi^2 (4) = 16.78, p = 0.002$ ) and the SCYS group ( $\chi^2 (4) = 37.89, p < 0.001$ ), and a significant change over time in decreased appetite in the SCYS group ( $\chi^2 (4) = 11.69, p = 0.020$ ).

The *post hoc* Wilcoxon tests with a Bonferroni correction (0.0125 [0.05/4] level of significance) were used to follow up the findings on constipation and decreased appetite by comparing the change from baseline to week one, from week one to week two, from week two to week three and from week three to endpoint. Participants in both groups appeared to be significantly less constipated from baseline to the end of week one ( $Z = -3.50, p < 0.001$  in the placebo group and  $Z = -3.39, p = 0.001$  in the SCYS group). However, there was no significant change between each week of the study or between baseline and endpoint. There were no significant changes in the frequency of decreased appetite between baseline and week one or between each week of the study. Thus, the intervention did not influence participants' constipation status or appetite.

Twenty-two women (32%) reported adverse effects, other than the four listed in the survey, either for themselves or for their infants, including eight (24%) in the placebo group and 14 (41%) in the SCYS group. Four women in the placebo group and seven in the SCYS group reported adverse effects in only one out of four weekly surveys, whereas the others reported the same problem in two or more weekly surveys. However, all these participants continued taking the capsules and completed the study. These adverse events reported by participants are summarised in **Table 7-5**.

**Table 7-5 Other adverse events reported by study participants.**

Adverse events	Placebo group (n = 34)	SCYS group (n = 34)
<i>Adverse events from the mother</i>		
Upper back pain	1	
Headache		1
Abdominal pain	1	
Thrush		2
Itchy/dry skin		3
Orange aftertaste	1	1
Dry mouth	1	
Increased appetite		1
Thirsty		1
Heart burn	1	1
Reflux	1	2
Gassiness/bloating and flatulence	2	3
Decreased frequency of bowel movements	1	
Change smell of urine		1
<i>Adverse events from the infant</i>		
Choke/cough during milk ejection		2
Increased spill after feedings		1
Nappy rash		1
Change smell of faeces	1	
Decreased frequency of bowel movements	1	1

### 7.4.3 Breastfeeding status and participants' perceptions at six months postpartum

Forty-six women completed the follow-up survey at six months postpartum. Two participants in the placebo group had ceased breastfeeding, and the other 44 women were breastfeeding their infants. In this subgroup, there was no difference in maternal age, education level or family income between the placebo and SCYS groups. There was also no difference in mean infant age at baseline ( $88 \pm 33.3$  days in the placebo group vs.  $96 \pm 30.8$  days in the SCYS group).

The proportion of predominant breastfeeding (n = 11, 50% in the placebo group and n = 13, 59% in the SCYS group) and the proportion of exclusive breastfeeding (n = 8, 36% in the placebo group and n = 10, 45% in the SCYS group) were similar in the two groups. No difference was observed in the proportion of infants who started complementary feeding (n = 5, 23% in the placebo group and n = 7, 32% in the SCYS group). However, formula use in the SCYS group was significantly lower than in the placebo group (n = 1, 4% and n = 6, 27% respectively,  $p = 0.047$ ).

Participants in both groups had positive perceptions of their milk supply and milk quality at six months postpartum, these were the same as their perceptions at the endpoint. There were no significant differences in PIM, PMQ or PSA between the two groups at six months postpartum. However, women in the SCYS group had significantly higher PIB scores than women in the placebo group at the baseline and six months (**Table 7-6**), suggesting a failure in randomisation in this small subgroup.

**Table 7-6 Participants' perceptions of milk supply at endpoint and at follow-up at six months postpartum (n = 44).**

Perceptions	Baseline		Endpoint		Follow up	
	Placebo (n = 22)	Yeast (n = 22)	Placebo (n = 22)	Yeast (n = 22)	Placebo (n = 22)	Yeast (n = 22)
PIM (Median [Q1, Q3])	4 (4, 4)	4 (4, 4)	4 (4, 4)	4 (4, 4)	4 (3.75, 4)	4 (4, 4)
PMQ (Median [Q1, Q3])	14.5 (13, 15)	15 (14, 15)	15 (14, 15)	15 (15, 15)	15 (13.5, 15)	15 (14.75, 15)
PIB (Median [Q1, Q3])	13 (11.75, 15) *	15 (13.75, 15) *	14 (13, 15)	15 (13.75, 15)	13 (11.5, 15) *	14.5 (13, 15) *
PSA, positive (n [%])	14 (64) <sup>§</sup>	20 (91) <sup>§</sup>	19 (86)	22 (100)	18 (86)	22 (100)

PIM, perceived insufficient milk supply; PMQ, perceived milk quantity and quality; PIB, perceived infant behaviour; PSA, perceived significant others' attitude to mothers' milk supply. Friedman's ANOVA for PIM, PMQ and PIB within each group. Mann-Whitney U test for PIM, PMQ and PIB between two groups at each timepoint. Fisher's Exact test for PSA between two groups at each timepoint. \* Mann-Whitney U test,  $p < 0.05$ . <sup>§</sup> Chi-square test, ( $\chi^2 = 4.659$ ,  $p = 0.031$ ).

## 7.5 Discussion

This is the first RCT to test the effect of maternal supplementation of SCYS on the concentration of HMOs, on indicators of PIM, and on potential adverse effects of both the mothers and infants. Compared to the placebo, SCYS did not affect the concentration of individual HMOs or total HMOs. There was no significant difference in PIM, PMQ, PIB, PSA, postnatal distress, infant feeding pattern, infant anthropometry measurements or adverse events between the SCYS and placebo groups at the endpoint. However, the endpoint PMQ score in the SCYS group was significantly increased compared to the baseline. Furthermore, compared to women who received the placebo, women who consumed SCYS were significantly more likely to report that the intervention was effective after the intervention (35% in the placebo group vs. 65% in the SCYS group,  $p < 0.05$ ). Compared to the placebo group, women in the SCYS group had significantly lower formula use at six months postpartum.

In this study, SCYS supplementation did not affect total HMO concentration or concentration of any single HMO. Notably, only 11 HMOs were tested in this study accounting for approximately 80% of the concentration of total HMOs [20]. This study did not measure a few neutral HMOs, reported to be at higher concentrations than 3-FL, such as TF-LNH, DF-LNH II and LNDFH-I [20]. These HMOs may impact the total HMO concentration of non-secretor's milk more than that of secretor's milk. Future research with a larger sample size should include these HMOs and compare the individual and total HMO concentrations of secretor's and non-secretor's milk separately.

Further, the significant interindividual variation in HMO concentration suggest a need of a larger sample size. In this study, the concentration of some HMOs decreased for some women but increased for others. This has also been observed in previous research [28]. This interindividual variation may result from day-to-day variation of HMO concentration, which is poorly documented in the literature. Furthermore, HMO concentration is affected by fixed factors such as genetic secretor status and maternal age, as well as modifiable and environmental factors, including diet, season and geography [30, 60, 61]. Although the influence of secretor status and maternal age were controlled for during regression analysis, the influence of diet, season and geography could be confounding. Future studies need to collect these data to check for the effectiveness of randomisation and/or replicate in a bigger sample, making it more likely that randomisation was effective.

There was a significant inverse association between the exclusivity of breastfeeding and the concentration change of 6'-SL. It was also reported in the literature that 6'-SL was enriched in the milk of women feeding formula to their infants [60]. However, the reasons for this change and the influence on infant growth and development are unknown.

Participants in the SCYS group were more likely to report the intervention as impacting their milk supply positively than participants in the placebo group. However, there was no difference in PIM between the two groups after the intervention. This may be because most of the participants in both groups already had strong beliefs in their breast milk supply at baseline, so most participants were not

likely to experience PIM regardless of intervention. In the SCYS group, the scores of PMQ were significantly higher at the study's endpoint than at baseline. This finding suggests that the women perceived their milk quality was improved after taking SCYS, which aligned with the perceived effectiveness of SCYS. However, no differences between the two groups were found; this suggests there was a small, insignificant increase in the placebo group. Replication in a larger sample would show if there is a difference in mothers' perceptions between the two groups.

At six months postpartum, significantly less formula use was found in the SCYS group than in the placebo group, but no differences in exclusive breastfeeding or complementary feeding were observed. Women in the SCYS group also had significantly higher PIB scores than women in the placebo group. It is possible that women in the SCYS group perceived their infants to be more satisfied and settled, and, therefore, they decided not to feed formula at six months. However, in this subgroup of women, the baseline PIB score in the SCYS group was significantly higher than that in the placebo group, and no difference was found at the endpoint. Similar results were also observed for PSA at the baseline and endpoint. These results indicated that the women's perceptions were unrelated to the intervention, and differences were seen due to the ineffective randomisation. All women reported improved infant behaviour at the endpoint, regardless of group. The small sample size in this subgroup provided insufficient power to state if SCYS has any effect.

There were no differences between the two groups for postnatal distress, infant anthropometry measurements, breastfeeding pattern, urination frequency, and defecation frequency in this study. The sample size was estimated based on the total HMO concentration changes, however, and, as such, the sample was too small to identify any differences in these indicators between the two groups.

This study found no evidence of major adverse effects of SCYS supplementation on women and/or their infants. Both groups suggested significant improvements in constipation at the end of the first week to baseline. Constipation is a common problem during pregnancy and the first few weeks postpartum, and the prevalence is much higher in early-stage postpartum than in the general

population [70]. Since participants were asked to rate the severity of constipation since birth at the baseline, the higher scores in the first week of this study may then reflect the improvement of the problem over time (i.e., from birth to the time of the survey) rather than the effect of the intervention. Women in the SCYS group reported some possible adverse effects not recorded in previous trials with yeast supplements, such as thrush, itchy/dry skin, increased appetite, thirst, and change in the smell of urine for the mother, as well as choke/cough upon milk ejection, increased spill after feedings and nappy rash for infants. Although these symptoms were only reported in the SCYS group, they are common problems and might be due to causes unrelated to supplementation. Moreover, all these adverse effects were rarely reported (less than three), and all the participants completed the study. Thus, SCYS supplementation had limited adverse effects on mothers and their infants.

This is the first study that aimed to evaluate the effect of SCYS on breastfeeding. Randomisation with a double-blind design controlled for selection, performance and detection bias [71]. The low number of participants that withdrew from the study and the intention-to-treat analysis controlled for attrition bias [71]. However, there are a few limitations to this study. First, the failure of randomisation regarding secretor status made it impossible to compare individual and total HMO concentrations between the two groups. Currently, the practical method for identifying secretor status is based on the presence of 2'-FL in breast milk samples [21]. This was done retrospectively, after data collection. Future research could include 2'-FL concentration tests during recruitment and use the block randomisation method to ensure that participants are evenly allocated across intervention and placebo groups. Second, the lack of women with PIM was a limitation. A bigger sample with recruiting a sufficient number of women experienced PIM and not experienced PIM would solve this limitation. However, if recruiting women with PIM, it is more likely they will introduce or increase formula use during the study, which may consequently decrease breast milk production [72, 73]. This will introduce formula use as a confounder in the study and may increase the proportion of women who withdraw from the study. Third, the survey questions did not capture some aspects of the perceived effectiveness of the intervention that were reported qualitatively by the participants. Therefore, the

instrument of PIM and perceptions on milk supply need to be amended and validated for future research. Finally, women's milk production was not evaluated in this study. It would be necessary to include the volume of milk as an outcome to investigate the effect of SCYS on breast milk production as opposed to the current study, which only examined indicators of milk supply and women's perceptions.

## 7.6 Conclusion

This is the first RCT that examines the effect of a SCYS grown on molasses on HMO concentration and indicators of milk supply. Participants had good compliance and no strong adverse effects. No difference was observed in changes in the concentration of HMOs measured or in measured indicators of milk supply between the two groups. However, participants who received the SCYS were more likely to notice a change in their milk supply than those receiving the placebo. The low prevalence of PIM in both groups at baseline and endpoint may have contributed to this lack of difference in PIM between the SCYS and placebo groups. An RCT in a bigger sample with concurrent measures of milk production, milk composition, women's breastfeeding knowledge and perceptions of their milk supply is needed to investigate the effect of SCYS on breast milk production, milk composition and the effect on addressing PIM.

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## Chapter 8 Reflections on the use of an adapted protocol of hourly expression in a sample of breastfeeding women in Aotearoa New Zealand

As discussed in the literature review (Chapter 2), the volume of breast milk is a key variable used to evaluate the efficacy of galactagogues on breast milk production. A validated method to evaluate the 24-hour milk volume of individual women is necessary to measure the change in milk volume in response to interventions evaluating galactagogue use.

An adaptation of a validated hourly expression protocol to estimate 24-hour milk production was used for the first 33% of participants (n = 24) to measure milk volume in the randomised placebo-controlled trial on the effect of SCYS. However, the method did not work as expected, with some participants expressing very small amounts for some expressions. These variations made us question the validity of hourly expression for estimating participants' breast milk production using mini-electric pumps. This chapter aims to discuss our experience with and identify the problems of this adapted hourly expression protocol to evaluate breast milk production for a group of exclusively breastfeeding women.

This chapter has been prepared for submission to Breastfeeding Medicine.

## 8.1 Abstract

**Introduction:** Hourly expression using hospital-grade pumps has been shown to yield consistent amount of milk at the third and fourth expressions. This hourly expression method over three hours is suggested to be as valid as the test weighing method to estimate 24-hour milk production. This study aims to investigate if consistent amounts of milk from the third and fourth expressions can be collected using mini-electric breast pumps within a group of exclusively breastfeeding women.

**Methods:** Mothers (n=24) used a mini-electric breast pump to express one breast every hour over three consecutive hours at three fortnightly sessions. Milk yield at each expression was weighed using an electric balance sensitive to  $\pm 0.01$  g. When  $< 10$  g milk was expressed at the second or subsequent expressions, it was termed an “incomplete expression”. Linear mixed models were used to compare the amount of milk obtained from each expression at all sessions and for the subset of valid sessions without incomplete expressions.

**Results:** Of 70 sessions 79% (n = 55) sessions were valid (subset). Ten participants (42%) experienced incomplete expressions. The median amount of milk from the third expression was not statistically different from the fourth for the whole dataset. However, for the subset the amount of milk from the third expression was significantly more than the fourth ( $p < 0.05$ ).

**Conclusion:** Using mini-electric pumps obtained inconsistent volume from the third and fourth expressions. Incomplete expressions experienced by some participants suggested that the method may not be suitable for estimating milk volume for individual women.

**Key words:** woman; breastfeeding; human lactation; breast milk production; insufficient breast milk; low milk supply; hourly expression

## 8.2 Introduction

Measuring the amount of breast milk produced in 24 hours can provide objective information on women's milk production, help health professionals identify insufficient milk production, and improve breastfeeding confidence in women with term infants [1, 2]. Measuring the amount of milk is also relevant in interventions aiming to influence breast milk production [3, 4].

Test weighing of the infant before and after each breastfeed over 24 hours is a standard method for evaluating breast milk production [1, 2, 5-7]. However, 24-hour test weighing is time-consuming and may disturb infant feeding and sleeping patterns, especially for those infants who have several night feeds.

In 2010, Lai and colleagues proposed an hourly expression method to estimate milk synthesis rate and calculate 24-hour milk production [8]. Lai et al. asked breastfeeding women to express ten minutes every hour for seven hours. The amount of milk from the first two expressions varied widely, but the amount from the third to eighth expression was consistent. Furthermore, the amount of milk from the third and subsequent expressions was not statistically different from the hourly rate of milk synthesis calculated from the 24-hour test weighing of the infants. Lai et al. suggested using the average amount of milk expressed at two to seven hours to estimate hourly milk production [8].

Subsequently, Kent et al. used the same protocol over three hours (four expressions) and found that the mean volumes from the third and fourth expressions were similar. In addition, the amount of milk from the fourth expression was not significantly different from the hourly rate calculated from the 24-hour test weighing of the infants. Therefore, hourly expression over three hours is proposed as an alternative method to the 24-hour test weighing of infants, with the milk yield from the fourth expression used to estimate milk production [9].

In a recent study, Roznowski et al. used a similar protocol to estimate the hourly milk production rate (MPR). Roznowski et al. also found that the amount of milk from the third and fourth expressions was

consistent and proposed using the mean volume of the third and fourth expressions to estimate MPR. However, 24-hour milk output ( $\text{MPR} \times 24$ ), as estimated by Roznowski et al., was 1.5 fold of the amount obtained from the 24-hour test weighing of the infants [10]. The differences in study protocol from that used by Lai et al. and Kent et al. may cause this variation. In Lai et al. and Kent et al.'s studies, participants started expression 60 minutes after the starting time of the previous expression. However, Roznowski et al. allowed 60 minutes between the end of one expression and the start of the following, thus, in effect, adding the milk produced during the time taken for each expression without counting that time when calculating hourly rate.

All previous research used hospital-grade pumps. However, in low-resource settings, hospital-grade pumps may not be accessible. This study aims to investigate if consistent amounts of milk from the third and fourth expressions can be collected using a mini-electric breast pump within a group of women who are exclusively breastfeeding.

## 8.3 Materials and Methods

### 8.3.1 Study design and participants

Exclusively breastfeeding women with a healthy, term, singleton infant aged one to five months participated in a study with a repeated measurement design involving three sessions of hourly expression (for three hours) at two-week intervals. Women were recruited via advertisements displayed at Palmerston North Hospital, local GP clinics, pharmacies, libraries, and childcare centres, as well as posted online on local breastfeeding and/or parenting Facebook Pages and Groups. Written consent was obtained from all participants. The study was approved by Massey University Human Ethics Committee: Southern A (SOA 18/80) (**Appendix 7**).

### 8.3.2 Study procedure

An hourly expression protocol was developed based on Lai et al. and Kent et al. [8, 9]. The researcher met with participants three times at fortnightly intervals in the same setting, i.e., at their home or the

Human Nutrition Research Unit at Massey University, Manawatū campus. Participants used a mini-electric pump (Philips Avent single electric breast pump provided by the researcher or the participant's electric pump, maximum vacuum 245 – 300 mmHg) to express milk from one breast. The same pump was used at each visit unless there were unavoidable reasons (e.g., the pump was broken). The participant used the same vacuum level for all the expressions in each visit. The vacuum level was determined at the first expression using the highest vacuum setting of the pump, then adjusting to a lower level until the participant felt comfortable. Once milk ejection was observed (by an increase in milk flow), the participants continued to pump for ten minutes. This procedure was repeated hourly for three hours. The first expression started between 8:30 and 10:00 am, and the second expression started one hour after observing the first milk ejection. For example, if the first milk ejection was at 9:10 am, the second expression would start at 10:10 am, the third at 11:10 am and the fourth at 12:10 pm. Breastfeeding was not restricted before the first expression. However, once the mother started expressing, the infant could only feed from the other breast. The amount of milk from each expression was determined by weighing the collection bottle twice before and after expression using an electric balance (Entris®, Sartorius, Germany, capacity 1200 g,  $\pm 0.01$  g). The mean value was recorded as the amount of milk obtained (the record template is shown in **Appendix 21**). This expression protocol was repeated using the same breast at each visit.

If required, techniques were used to stimulate milk ejection, such as the application of a warm cloth before and/or during expressing, breast compression, covering the bottle to avoid attention to the amount of milk expressed, soft music and other techniques to help the mother to relax, showing a photo of the infant (if the infant was sleeping), and latching the infant on the other breast whilst expressing [11-15]. If there was no increase in milk flow (i.e., the expressed milk dripped into the bottle at a slow, steady rate or stopped dripping) after 20 minutes, expressing was stopped and the amount obtained was recorded.

Demographic information was collected (the questionnaire is shown in **Appendix 8**). Participants completed weekly surveys during the 4-week study, including reporting if they expressed breastmilk in the previous week and the reasons for expressing (questionnaires are shown in **Appendix 12**). A categorical variable of expression practice was created based on the weekly reporting of expressing in one week or less and expressing in two or more weeks. The expressing frequency in each week was not recorded.

### 8.3.3 Statistics

A preliminary review of the data showed that for 21% of the sessions ( $n = 15$  visits)  $< 10$  g breastmilk was obtained from the second or subsequent expressions. Women who are exclusively breastfeeding a singleton infant produce 480 to 1200 g/day of breast milk at one to five months postpartum [16-18], which means at least 10 g/hour produced from one breast, assuming both breasts produce the same amount of milk (i.e., 480 g/d). Therefore,  $< 10$  g from the second or the subsequent expressions was defined as incomplete expression. Data analysis was conducted on the whole dataset and on the subset of valid sessions, which excluded incomplete expressions.

Data were tested for normality using the Shapiro-Wilk test. Normally distributed data are presented as mean  $\pm$  SD, and non-normally distributed data are presented as median (Q1, Q3). Categorical variables are presented as frequencies (%). SPSS version 25.0 (IBM, Armonk, NY, US) was used for descriptive data analysis. A linear mixed model was established to compare the amount of milk from each hourly expression for both the whole dataset and subset, using the R statistical programme (Vienna, Austria. <https://www.R-project.org/>) [19]. The amount of milk was log-transformed to achieve a normal distribution. The expression number (1, 2, 3, or 4) was the fixed effect, and potential random effects included the participant, the visit number (1, 2, or 3), and the pump. Selection of the best fitted model was conducted due to the possibility that the visit number and the pump had little effect because most participants used the same pump to express from the same breast for three visits. The best-fitted model was chosen by comparing three models with the same fixed effect but different

random effects (the participant, the participant + the pump, the participant + the pump + the visit number) using Akaike’s information criterion (AIC). The smallest AIC value indicates the best-fitted model. After selecting the best-fitted model, a t-test was completed to compare the amount of milk from the first expression with the amounts from the other three expressions using the Satterthwaite method for approximating degrees of freedom. Then, the simultaneous test with Tukey Contrasts was used to compare differences between the second and third, the third and fourth, and the second and fourth expressions. The association between the occurrence of incomplete expression and the variable “expression practice” was assessed by Fisher's Exact test.

Results of hourly expression milk yield for individual women were illustrated with graphs made using individual value plots in Minitab Statistical Software version 19.1 (Minitab Inc., US).

## 8.4 Results

Data were collected from 24 participants. The demographics and maternal characteristics are presented in **Table 8-1**. About half of the participants expressed breast milk in two or more weeks outside the study. The main reasons women expressed during the four weeks were to allow others to feed the infant, remove excess milk, store milk or donate milk.

**Table 8-1 Demographics and other characteristics of participants (n = 24).**

<b>Variable description</b>	<b>Mean ± SD or n (%)</b>
Maternal age, years	31 ± 5
Maternal ethnicity	
Caucasian	18 (75)
European + Māori	1
European + Dutch	2
European Canadian	1
Brazilian	1 (4)
Chinese	3 (13)
Indian	1 (4)
Other Asian	1 (4)
Maternal education	
Secondary school	2 (8)
Diploma	3 (13)
Bachelor’s degree	12 (50)

Postgraduates	7 (29)
Family income (before tax)	
≤ \$34,100	1 (4)
\$34,101-\$60,299	2 (8)
\$60,300-\$89,799	5 (21)
\$89,800-\$135,099	9 (38)
\$135,100+	5 (21)
Prefer not to say	2 (8)
Living status	
With a partner and children	23 (96)
With children and parents	1 (4)
Number of children	
1	10 (42)
2	10 (42)
3	4 (16)
Delivery mode	
Vaginal	16 (67)
Caesarean	8 (33)
Recent expression outside of the study *	
Expressed in two or more weeks	13 (54)
Expressed in one week	5 (21)
Never expressed	6 (25)
Reasons for expression (n = 18) *	
Allow others to feed the infant	9 (50)
Store milk for the future	7 (39)
Have too much milk	6 (33)
Donate milk	5 (28)
Will be away from the baby	4 (22)
Relieve engorgement	3 (17)
Increase milk supply	2 (9)
Other problem affected latching directly	2 (9)
Infant sex	
Male	16 (67)
Female	8 (33)
Infant birth weight, g	3653 ± 465
Infant age at the time of the first visit, days	89 ± 33

\* Information regarding expressing and reasons for expressing was collected by weekly survey during the four-week study. Participants might express for multiple reasons, so the percentages do not add up to 100%. The same reason reported by the same participant in different weeks was recorded once.

Twenty-two participants completed three visits, and two completed two visits, providing data for 70 occasions of the completed three-hourly expression protocol (i.e., 70 sessions and 280 expressions).

Seven different brands or models of mini-electric pumps were used in this study. Twenty-one participants used the same pump for the three visits. Three participants changed the pump across visits, but the same pump was used in each visit. In 10% of visits (n = 7), the mother fed the infant an hour or less prior to the visit, resulting in < 10 g of milk from the first expression (**Table 8-2**).

Sixteen incomplete expressions were recorded at 15 sessions. Less than 10 g of milk was obtained from the second expression at eight sessions, the third expression at four sessions and the fourth expression at four sessions. Incomplete expression occurred for ten women (42%). Six of these ten women had incomplete expressions at only one visit, including one who obtained < 10 g from both the second and the third expressions at the same visit. The other four women obtained < 10 g of milk at more than one visit, including one woman with an incomplete expression at all three visits. Seven of the participants who had at least one incomplete expression expressed in one week or less outside of this study. However, there were no significant differences in the occurrence of incomplete expression between the women who reported expressing in one week or less compared to the women who reported expressing in two or more weeks ( $p = 0.95$ ).

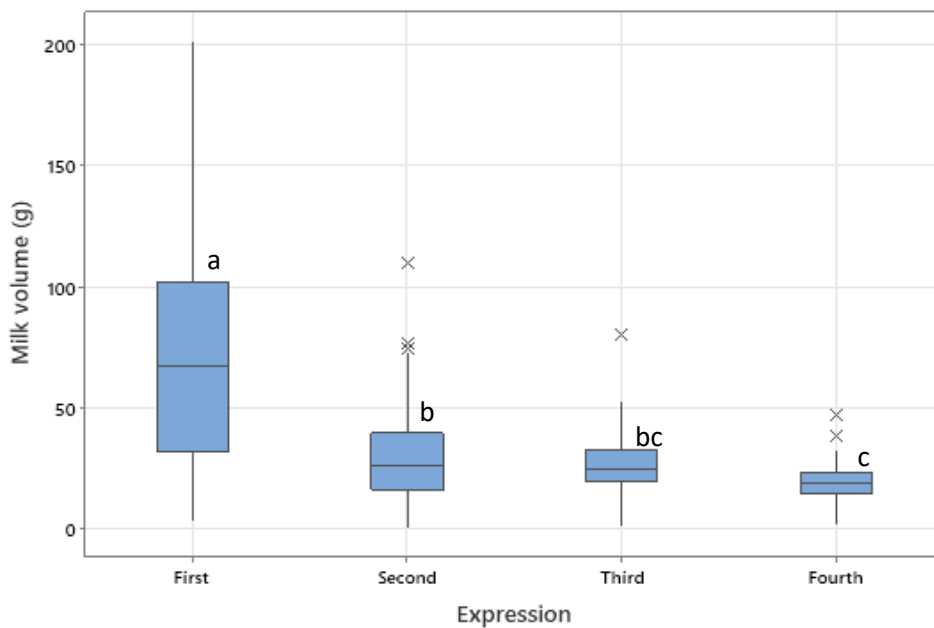
**Table 8-2 Description of the sessions and expressions**

Variable description	N (%)	
	Whole dataset	Subset
Number of sessions	70	55
Breast expressed		
Left	44 (63)	37 (67)
Right	26 (37)	18 (33)
Fed the infant $\leq 1$ hour before the visit		
Yes	7 (10)	6 (11)
No	63 (90)	49 (89)
< 10 g milk obtained at the second, third, or fourth expression		
Yes	15 (21)	–
No	55 (79)	–
Pump used *		
Pump provided by the researcher	36 (51)	30 (55)
Own pump	34 (49)	25 (45)
Number of expressions	280	210
The infant latched on the other breast during the expression		
Yes	19 (7)	11 (5)
No	261 (93)	99 (95)

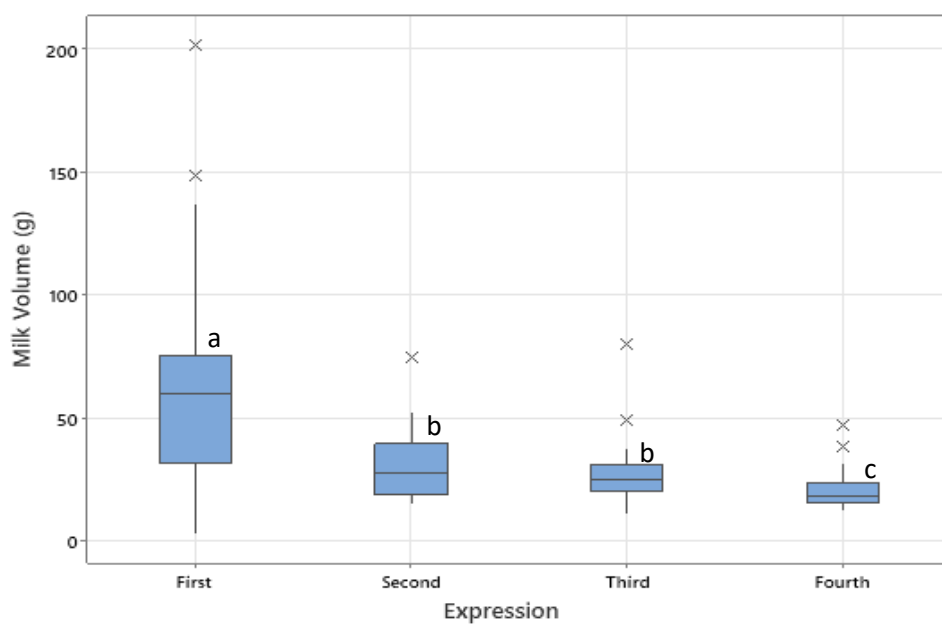
\* The researcher provided a Phillip Avent electric pump. The others were mini-electric pumps, except that one mother used a manual pump at one visit.

In the whole dataset of 70 sessions, the median (Q1, Q3) amount of milk obtained from the first to fourth expressions was 67.51 (31.78, 101.90) g, 26.28 (16.08, 39.54) g, 24.50 (19.66, 32.84) g, and 18.64 (14.21, 23.10) g, respectively (**Figure 8-1, A**). In the subset of 55 sessions (23 women) excluding

the incomplete expressions, the median (Q1, Q3) amount of milk obtained from the first to fourth expressions was 68.06 (40.11, 101.81) g, 27.41 (18.91, 39.99) g, 24.32 (20.39, 32.73) g, and 18.72 (15.30, 23.38) g, respectively (**Figure 8-1, B**). After model comparison, the best-fitted LMM for both datasets only included the participant as the random effect (AIC = 555.11, df = 6 for the whole dataset; AIC = 346.60, df = 6 for the subset). This means no significant difference in the volume of expressed milk between the mini-electric pumps used by participants.



**(A, whole dataset, n = 70 at each expression time point)**



**(B, subset, n = 55 at each expression time point)**

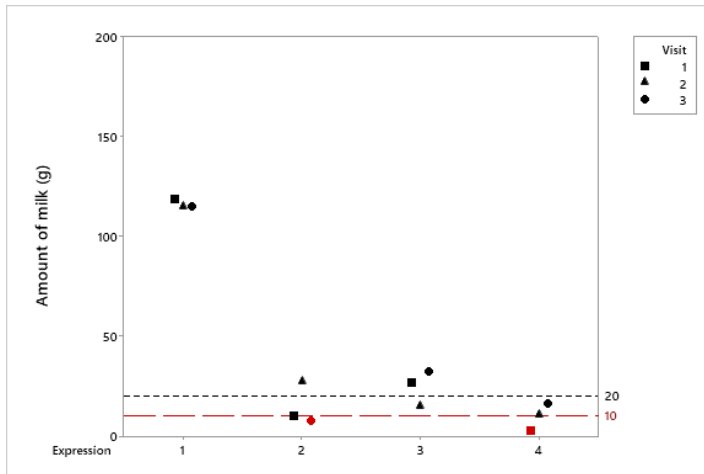
**Figure 8-1 The amount of milk from hourly expressions.** Box plots with different letters indicate significant differences. For the whole dataset,  $p < 0.001$  for the difference between the first and all the other expressions, and  $p < 0.05$  for the difference between the second and fourth expressions. For the subset,  $p < 0.001$  for the difference between the first and all the other expressions,  $p < 0.001$  for the difference between the second and fourth expressions, and  $p < 0.05$  for the difference between the third and fourth expressions.

Models for both groups showed a similar trend of the median milk output over time (**Figure 8-1**). In both models, the amount of milk obtained from the first expression was significantly more than the other three expressions ( $p < 0.001$ ). The milk yield from the second expression was significantly larger than the fourth expression ( $p < 0.05$  in the whole dataset and  $p < 0.001$  in the subset) but the same as that from the third expression. In the whole dataset, there was no significant difference between the amount from the third and fourth expressions, whereas, in the subset, the amount from the third expression was significantly more than the fourth expression ( $p < 0.05$ ).

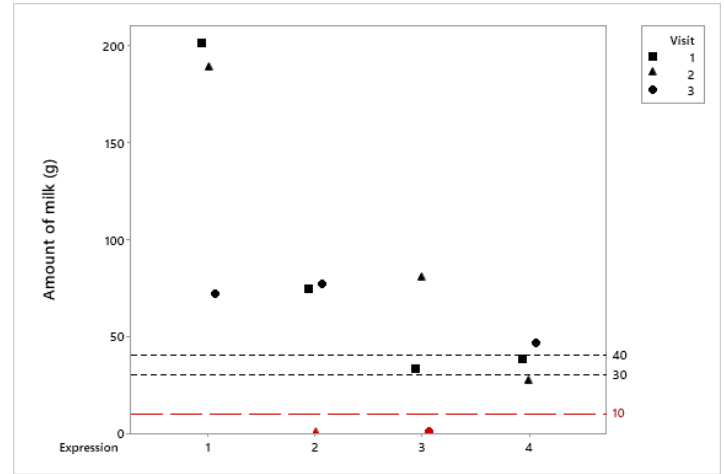
The amount of milk obtained from each expression over three visits for two participants who had incomplete expressions on different occasions and one participant who had valid sessions in all visits is shown in **Figure 8-2**. Example A shows a participant who used her own electric pump at all three visits. She expressed  $< 10$  g of milk from the fourth expression in the first session. Similar amounts were obtained from the third and fourth expressions in the second session (15.10 g and 10.65 g, respectively). In the third session,  $< 10$  g milk was obtained from the second expression, followed by 32.15 g from the third expression and 16.53 g from the fourth expression. Participants in examples B and C used the pump provided by the researcher in all three visits. Example B shows a participant who obtained similar amounts from the third and fourth expressions at the first session (33.11 g and 38.37 g, respectively). In the second session,  $< 10$  g milk was obtained from the second expression, and the amount from the third expression jumped to 80.14 g and then fell to 26.81 g from the fourth expression. In the third session,  $< 10$  g of milk was obtained from the third expression, and 46.68 g from the fourth expression. Example C shows one of the 13 participants without incomplete expressions, i.e., obtained  $> 10$  g from the second to the fourth expressions in all sessions. The

amounts from the third and fourth expressions were similar across the three sessions, and the amount from the fourth expression in three sessions was similar (15 – 20 g).

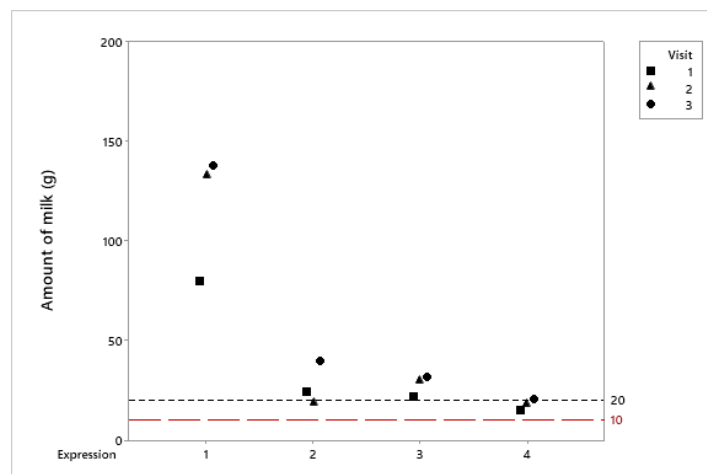
**Example A**



**Example B**



**Example C**



**Figure 8-2 Examples of the amount of milk from each expression in three visits for three participants.** The amount of milk was Y variable, the expression number (1, 2, 3, 4) was the graph variable, and the visit number (1, 2, 3) was the categorical variable for grouping. Symbols in red indicate incomplete expressions (i.e., expressed < 10 g milk). Example A shows a participant who had < 10 g milk from the fourth expression in the first visit. Example B shows a participant who had < 10 g milk from the second expression in the second visit. Example C shows a participant who had > 10 g from second and consequent expressions in all visits.

## 8.5 Discussion

This study found that using mini-electric breast pumps for an hourly milk expression protocol was unable to replicate the results found using hospital-grade pumps. Although the results from the whole group were similar to studies using hospital-grade pumps [8-10], the volume from the fourth expression was significantly smaller than the third in the subset of valid sessions. The results for the whole group can be attributed to the inclusion of the incomplete expression data which increased the interquartile range and led to a failure to find a significant difference between third and fourth expression.

The significant difference in the volume of milk from the third and fourth expressions in the subset may be caused by less efficient and less effective milk removal by the mini-electric pumps compared to the hospital-grade pumps which were used in the previous research [8-10]. Hospital-grade pumps provide standard suction strength and maximum milk removal effectiveness and efficiency compared to mini-electric pumps [20]. The effectiveness of milk removal can be accurately evaluated by the percentage of available milk removal [21, 22]. The efficiency of milk removal is measured by the volume of milk removed per unit of time spent expressing [20]. More research could investigate if specific mini-electric pumps, especially the ones advertised as hospital-grade, can replicate the results from the hourly expression protocol in three hours using a hospital-grade pump.

Notably, 42% of participants (n = 10) had incomplete expression in at least one session; this has not been reported in previous research [8]. No obvious pattern was seen for when incomplete expression occurred, and it was not associated with the practice of expressing milk outside this study. It is possible that the incomplete expression was due to the use of mini-electric pumps, but a few other issues may contribute to incomplete expressions in hourly expression.

Failure to stimulate a milk ejection might be a problem when the breast is close to empty, as reported in the literature that some women failed to have further milk ejections after ten minutes of continuous

pumping [23-25]. In this study, for some participants the absence of milk ejection only happened at the second to fourth expressions, i.e., once the breast had been “emptied” in the previous hour.

Additionally, stress and anxiety can adversely impact endogenous oxytocin [26, 27], and stress was reported to impair milk ejection [28]. Although the women’s preferred venue and pump setting were used to provide maximum comfort during this study, the participants might be stressed and exhausted by the hourly pumping and by the pressure of completion of the study protocol. A recent study using the hourly expression method to investigate the effect of lactation cookies on breast milk production reported 50% of missing data due to the stress and burdens from the protocol [29].

Moreover, negative experiences of expressing and pumping could be related to incomplete expression. Although women who never expressed outside of this study were no more likely to have incomplete expressions, six out of ten women who had incomplete expression reported anecdotally that they had similar negative experiences with expressing in the past. This negative experience of only being able to express a small amount of milk has been reported as one of the reasons women give up using a breast pump during breastfeeding or even switch to formula feeding in the first few weeks postpartum [30-32]. It is not clear from the literature whether women experienced this failure when using hospital-grade pumps [30, 33].

This is the first study describing the individual experiences of hourly expression protocol using the mini-electric pumps. The study involved repeated measures and most women completed the protocol three times. One limitation of this study is the small number of participants using some pumps, making it impossible to compare the difference between pumps, or to assess if incomplete expression was related to a specific pump. Furthermore, participants’ 24-hour milk production was not evaluated in this study, making it impossible to conclude if the mean volume of the third and fourth expression could be used to estimate 24-hour milk production.

## 8.6 Conclusion

This study found that for a group of women using mini-electric pumps, the amount of breast milk obtained from the third expression is significantly different from the fourth expression. Further study should investigate specific mini-electric pumps. Incomplete expressions (i.e., < 10 g milk expressed from the second, third or fourth expression) were observed in 42% of women (n = 10). Incomplete expressions experienced by some participants suggested that the method may not be suitable for estimating milk volume for individual women. Further research also needs to investigate whether incomplete expression influences the results of hourly expression using hospital-grade pumps.

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## Chapter 9 Discussion and conclusion

### 9.1 Introduction

This chapter provides an update on the literature of the effects on galactagogues (published in 2022 and 2023) and an overview of the key findings from the two studies reported on in this thesis: the qualitative study and the randomised placebo-controlled trial (RCT). The qualitative study investigated the experiences of and attitudes toward galactagogue use among breastfeeding women and postnatal healthcare professionals (PHPs) in Aotearoa New Zealand (Aotearoa NZ). The RCT evaluated the effect of a *Saccharomyces cerevisiae* yeast-based supplement (SCYS) on human milk oligosaccharide (HMO) concentration and indicators of perceived insufficient milk production (PIM). With close consideration of the overarching aims of this thesis and the objectives of each study, the findings can be summarised into three main aspects: 1) the role of herbal and food galactagogues in breastfeeding and PIM; 2) the use of SCYS as a galactagogue; and 3) outcome measurements to indicate the efficacy of galactagogues. The strengths and limitations of this thesis are acknowledged after discussing the above aspects. The contribution of this research to the literature is also described, and priorities for future research on the efficacy and safety of galactagogues are outlined.

### 9.2 Increased amount of herbal and food galactagogue research

There has been a recent increase of research on herbal and food galactagogues. From January 2022 to September 2023, 14 studies were published, including one secondary data analysis on a previously published RCT on domperidone [1], eight studies on herbal galactagogues [2-9] and five studies on food galactagogues [10-14]. Of these 14 studies, ten were RCTs with a control and/or placebo group [1-6, 8, 11-13], one had a quasi-experimental non-equivalent control group pretest-posttest design [7], one had a single group pre-test pro-test design [14], and the other two were questionnaire surveys with repeated measures [9, 10]. An overview of the study designs, participants and outcomes is in the **Appendix 22**.

All studies aimed to evaluate the effect of galactagogues on breast milk production, and the majority (n = 10) used the volume of milk as the primary outcome [1-6, 8, 11, 12, 14]. Milk volume from 24 hours were measured by exclusively expressing in three studies [1, 4, 14] and by 24-hour test weighing in two studies [3, 11]. Evaluating milk volume from one expression instead of 24-hour milk volume remains the method for many studies [2, 5, 6, 8].

Two studies reported using an hourly expression method to evaluate breast milk production [5, 12]. Palacios et al. had high proportions of sessions with missing data at the baseline and endpoint (38% and 49%, respectively) [12]. The authors suggested that fully remote study and burdens of hourly expression protocol contributed to the large amount of missing data. Reasons for missing individual expressions within a session were not reported, and participants' experience with expressing breast milk was not reported. It is unknown whether women's negative experiences of expressing outside of their study contributed to the high amount of missing data. Although Maenpuen et al. referred to the hourly expression method in their study design, the authors did not follow the protocol. Participants expressed both breasts for 15 minutes after a two-hour interval from the previous feeding their infants at breast [5]. The volume from this measurement could not be used to estimate hourly milk production rate or 24-hour milk production.

In addition to measuring breastmilk volume, indirect measures of breast milk production were also used in some studies. PIM was measured in three studies. One study evaluated PIM as the primary outcome using the Hill and Humenick Lactation Scale [10], the other two assessed PIM as the secondary outcome using the Perception of Insufficient Milk questionnaire [12], or a self-designed questionnaire [7]. Infant weight was used as a secondary outcome in two studies [4, 5].

The proportion of participants who continued breastfeeding at one week, one, two, three, four, six and 12 months postpartum was used as the primary outcome in one study [9], and the proportion of participants who were exclusive breastfeeding was used as the secondary outcome in three studies, at the endpoint (the seventh day postpartum) [7], at one, two, three and four months postpartum [10]

and at six months postpartum respectively [3]. Furthermore, one study investigated the effect of a mixture of honey and fenugreek on “breastfeeding success”, which was measured by a self-designed questionnaire consisted of similar questions from Hill and Humenick Lactation Scale and Breastfeeding Self-efficacy Scale [13].

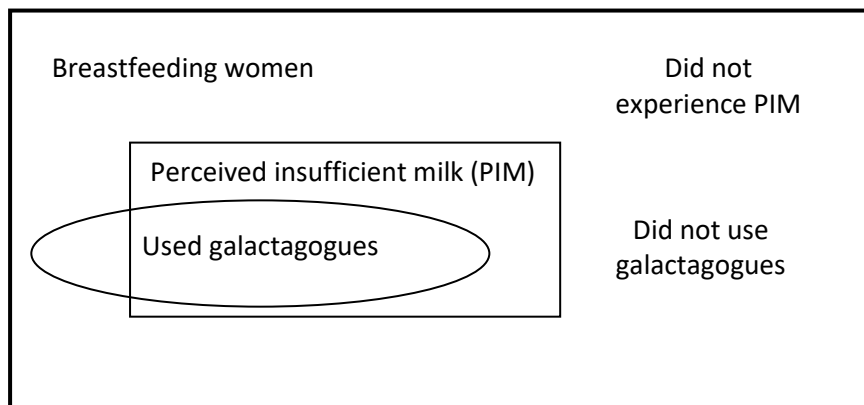
All the recent 14 studies described the study aims clearly and described the rationale of choosing the primary and secondary outcomes. There were also improvements in study design, such as controlling the daily total energy intake for the trials on food galactagogues and monitoring compliance. However, the recently published studies still used various measures of breast milk volume and PIM. The diverse study methodology and outcomes remain the central problems in evaluating the effect of herbal and food galactagogues or conducting a meta-analysis for RCTs investigating the same galactagogues.

### 9.3 The role of herbal and food galactagogues in breastfeeding and addressing perceived insufficient milk supply

Galactagogues have been used in both animal dairy industry and human clinic conditions to induce, maintain and increase milk production [15, 16]. However, the findings of this thesis suggest that women also use herbal and food galactagogues for other reasons to improve breast milk production. In our qualitative study, galactagogues were reportedly used to address PIM with or without actual insufficient breast milk production and prophylactically to prevent insufficient milk supply and support breastfeeding. Our participants also took herbal and food galactagogues to maintain milk supply and/or milk quality. Their motivation for taking galactagogues was their desire to breastfeed their infants. Further, PHPs provided information about herbal and food galactagogues at times, but only after addressing breastfeeding management, such as appropriate position and latching, breast compression and expressing. Thus, our findings suggest that herbal and food galactagogues are used in Aotearoa NZ to increase breast milk production and support breastfeeding generally.

This was further demonstrated in the cross-sectional survey (i.e., the baseline survey of the RCT). We found that PIM was not associated with galactagogue use among the participants. In other words, some women who did not experience PIM used galactagogues, and some who reported PIM did not use galactagogues. Similar findings were reported in a recent Australian online survey that 32% of women who used a galactagogue (n = 1120) did not report PIM, and 22% of women who did not use galactagogue (n = 756) reported PIM [17].

Based on the results in this thesis, the relationship between galactagogue use and PIM is proposed in **Figure 9-1**. Women who experience PIM may not use galactagogues, and women who use galactagogues may not experience PIM.



**Figure 9-1 The relationship between galactagogue use and perceived insufficient milk supply.**

However, a study with a big, representative sample is needed to explore the proportion of women who experience PIM but do not use galactagogues and women who used galactagogues but do not experience PIM and to test if galactagogue use is associated with PIM. A qualitative study may also be required to provide an in-depth understanding of why women who experience PIM do not use galactagogues and why women who do not experience PIM do use galactagogues.

#### 9.4 Use of *Saccharomyces cerevisiae* yeast-based supplement as a galactagogue

SCYS was commonly used as a galactagogue by the qualitative study participants and our RCT participants before enrolling. The widely available information online that promotes the benefit of SCYS in boosting breast milk supply (discussed in Chapter 6) may contribute to the popularity of SCYS among breastfeeding women in Aotearoa NZ. Furthermore, the increased commercial availability of lactation cookies and lactation blends containing SCYS as a “key” ingredient is a good reason to investigate the effect of SCYS as a galactagogue more thoroughly.

Although this RCT found no effect of SCYS on PIM, a significantly higher proportion of women in the SCYS group compared to the placebo group perceived the intervention to influence milk supply positively. Participants reported breast fullness and/or leaking, faster and stronger milk ejection, more settled infant or improved infant sleep, increased amount of expressed milk, and more efficient or shorter time at each feeding as the signs and reasons for the perceived effectiveness of the intervention. However, further comparison of these signs/reasons between the SCYS and placebo groups could not be conducted due to the small sample size. These findings suggest the possibility that the SCYS impacts breast milk supply other than the placebo effect, albeit the mechanism remains unknown.

The mechanisms by which SCYS may increase breast milk quantity and addressing PIM are proposed in Chapter 6. This RCT found no effect on the concentration of measured HMO or on the other possible indicators of breast milk production. The influence of SCYS supplementation on maternal blood prolactin concentration, oxytocin concentration, IGF-1 concentration, the volume of breast milk, or milk composition (i.e., IgA, appetite hormones and cytokines) could be tested in future studies.

This RCT also found a significantly greater number of women in the placebo group than in the SCYS group fed formula at six months postpartum. Women in the SCYS group also had significantly better perceptions of their infant behaviours than women in the placebo group. However, the two groups

had no difference in the proportion of exclusive breastfeeding. These findings suggest that the SCYS positively support breastfeeding. However, an estimated sample of 225 in each group is required to detect a 10% higher proportion of exclusive breastfeeding in the SCYS group than in the placebo group at a power of 80% and a significance level of 0.05 [18]. This sample estimation assumes that women in the placebo have a similar percentage of exclusive breastfeeding as the national exclusive breastfeeding rate at six months postpartum (i.e., 16%) [19].

Before this study, there were only studies on ruminants and non-ruminant animals that showed the effect of SCYS on milk production but no evidence for breast milk. It is worthy of note that SCYS is used in ruminants from pregnancy to early lactation [20], which suggests that the SCYS may impact secretory differentiation and secretory activation. The current RCT only tested the effect of SCYS at galactopoiesis (i.e., after the copious milk is produced). Thus, future research could also investigate the effect of SCYS on the initiation of human lactation.

The SCYS used in this RCT was inactive *Saccharomyces cerevisiae* yeast grown on molasses. This SCYS varies in nutritional composition compared with SCYS produced from a brewing process [20]. Nutrition composition may influence the mechanism of action in milk synthesis. As such, the results from this study may not be generalised to the SCYS produced from the brewing process.

This RCT is the first to report on the adverse effects of SCYS supplementation on breastfeeding mothers and their infants. In evaluating the participants' experiences of adverse effects documented in the literature of yeast supplementation trials, no difference in severity was found between the two groups. Although participants in the SCYS group but not in the placebo group reported a few cases of itchy/dry skin, thrush, increased appetite, thirst, and changed smell of urine for the mother, all these participants continued taking the SCYS and completed the RCT. There was no difference in compliance with taking the study capsules between the SCYS and placebo groups. Thus, the SCYS appears to have minor, if any, adverse effects on breastfeeding mothers and their infants.

Overall, this research is a starting point to investigate the effect of SCYS on addressing PIM and supporting breastfeeding. More research is needed to investigate the effect of SCYS on breast milk production, mothers' perceptions of milk supply and to test the other proposed mechanisms of SCYS on breast milk production and/or milk composition at different stages of lactation.

## 9.5 Outcome measurements of the efficacy of galactagogues

As stated in section 9.3, researchers have measured milk production as an outcome when studying efficacy of galactagogues in dairy animals and humans. However, the scoping review in Chapter 2 found that apart from the volume of breast milk, many other outcomes were used in the human studies assessing the efficacy of galactagogues. These outcomes include milk composition, mothers' perceptions of milk supply, and the proportion of exclusive breastfeeding at different infant ages. The changes in breast milk volume, milk composition and mothers' perception of milk supply are immediate/short-term outcomes of taking galactagogues. In contrast, the proportion of exclusive breastfeeding is the long-term outcome reflecting the eventual goal of using galactagogues.

Importantly, the appropriate measurement of these outcomes could influence the results of an RCT on efficacy of galactagogues. For example, our original design on RCT of the effect of SCYS was to measure 24-hour milk volume and the hourly expression method was used. This hourly expression protocol over three hours has been shown to provide an equivalent estimation of the 24-hour milk volume as the 24-hour test weighing of the infant before and after each breastfeeding [21].

However, we found this method did not work well for some participants. When milk yield was less than 10 g at the second, third or fourth expression in one session, it is unlikely that the amount from the fourth expression was the actual milk production rate. Therefore, using the volume from the fourth expression in these cases may underestimate or overestimate the 24-hour milk volume. One limitation was the mini-electric pumps used in this study. However, it is also likely that this method

does not work for everyone since it is reported that some women can only express a small amount of milk using breast pump [22-24].

Moreover, the 24-hour test weighing of infants before and after each feed measures the volume of infant intake rather than the mothers' capacity for milk synthesis. If the supply is increased because of galactagogue use, the infant might or might not consume the extra amount of milk. The local downregulation of milk synthesis could lead to the milk supply returning to the baseline level. Thus, more research is needed to develop a valid method to evaluate mothers' milk synthesis capacity if that is the outcome of interest.

Measuring mothers' perceptions of breast milk supply is more practical than measuring breast milk volume for studies evaluating the efficacy of galactagogues when participants are breastfeeding their infants on demand. However, measuring mothers' perceptions of breast milk supply could be less objective than measuring breast milk volume. We developed questionnaires to evaluate mothers' perceptions of milk quantity and milk quality (PMQ), infant behaviours (PIB) as well as attitudes of significant others (PSA) since these are factors/reasons that are relevant to mothers' perception in her milk supply identified in the qualitative study as well as in the literature [25-29]. However, we found that the mothers who perceived the intervention (either the SCYS or the placebo) as effective reported other signs/reasons than the above factors/reasons used in the questionnaire. This might also explain why a significantly higher proportion of women in the SCYS group than the placebo group perceived the intervention was effective, but no differences in PMQ, PIB or PSA between the two groups were found at the endpoint. Future research may need to explore all the signs/reasons relevant to mothers' perceptions of milk supply and develop a better measuring tool to capture all the above aspects.

## 9.6 Strengths and limitations

This thesis is the first study to investigate herbal and food galactagogue use in Aotearoa NZ, including the perspectives of both breastfeeding women and PHPs. This is also the first study to evaluate the

effect of SCYS on milk composition and mothers' perceptions of milk supply and infant behaviour, including possible adverse effects. One limitation of the qualitative study was the limited number of women who used galactagogues but did not experience PIM and the limited number who experienced PIM but did not use galactagogues, leading to less understanding of these two groups of women's experiences. Thus, future research needs to recruit women in these situations to understand why they use or do not use galactagogues. One limitation of the RCT was that the randomisation was unfortunately ineffective to achieve even numbers of secretors in the two groups. The secretor status not only determines the presence of 2'-FL in mothers' milk but also associates with concentration of many other HMOs [30, 31]. A bigger sample would be helpful to control for secretor status and allow for analysis of change in HMO concentration among secretors and non-secretors separately. The small sample also makes it impossible to investigate further the reasons for the women's perceived effectiveness of SCYS on milk supply. Moreover, the volume of milk was not measured. Lastly, the women enrolled in the RCT had all already established their breast milk supply, so we cannot make statements about the effect of SCYS on initiation of human lactation.

## 9.7 Final conclusions

Herbal and food galactagogues are used by breastfeeding women and PHPs in Aotearoa NZ, not only for increasing breast milk production but also for maintaining milk supply and milk quality, as well as for generally supporting breastfeeding. PHPS only recommend galactagogues in conjunction with breastfeeding management. Both breastfeeding women and PHPs expressed some concerns about the safety and efficacy of herbal and food galactagogues. SCYS supplementation of breastfeeding women with infants aged one to seven months for four weeks did not affect HMO concentrations, but women receiving SCYS perceived a positive influence on their milk supply. There is no evidence of severe adverse effects in either breastfeeding women or their infants.

More research is needed to investigate herbal and food galactagogue use and whether it can support women to meet their breastfeeding goals and improve breastfeeding rates in the population.

Additional studies are also needed to evaluate the effectiveness of SCYS on breastfeeding support, mothers' perceptions of milk supply and infant behaviours, and potential mechanisms for addressing PIM. Researchers need to choose appropriate outcomes and measures that address the goal of using galactagogues, e.g., increase milk production, address PIM, or support breastfeeding.

## 9.8 Implications for postnatal healthcare practice

The qualitative study of this thesis found PHPs were reported to be the main, trusted source of information for breastfeeding women about herbal and food galactagogue use. This is also reported in previous research [32, 33]. A recent review of 46 studies about the use of complementary medicine products during pregnancy and lactation also suggested that the information provided by PHPs plays a significant role in women's decision-making surrounding the use of herbal and food products [34].

The current study provides evidence that PHPs agree to prioritise breastfeeding managements before introducing galactagogues. This procedure should be continued in practice. When discussing herbal and food galactagogues with breastfeeding women, PHPs should highlight the lack of strong scientific evidence that any herbal and food galactagogues increase milk volume. This will consequently help women to have realistic expectations of the efficacy of herbal and food galactagogues.

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# Appendices

## Appendix 1 Literature search strategy

Three databases were searched: Web Of Science, Scopes and PubMed. The search strategy was to combine searches of “galactagogue” related terms and “human milk” related terms such as “human milk”, “breast milk”, “breast milk production”, “breast milk supply” and “human lactation”. Each specific galactagogue was identified from the literature then was added to the galactagogue related terms. For the food and herbal ones, both the common names and the scientific names were included.

Galactagogue terms are:

1. Galactagogue / galactagogue
2. Domperidone
3. Karpasa Beeja / *Gossypium herbacum* Linn.
4. Mahua / *Madhuca longifolia*
5. Caraway / *carum carvi*
6. *Biancaea sappan* / sappanwood / Indian redwood
7. *Ochna integerrima* / yellow Mai
8. *Salacia chinensis* / Chinese salacia / lolly berry / saptachakra
9. *Asparagus gonoclados* Baker
10. *Launaea taraxacifolia* / African Lettuc
11. Resveratrol
12. Chamomile
13. Fenugreek / *Trigonella foenum-graecum*
14. *Achyranthes aspera* / chaff-flower / prickly chaff flower / devil's horsewhip
15. *Saponaria officinalis* L / fuller's herb / soapwort
16. Jamu
17. *Ajuga laxmannii*
18. Garden cress / *Lepidium sativum*
19. *Reichardia picroide*
20. *Galega officinalis* / galega / goat's rue / French lilac / Italian fitch / professor weed
21. *Brassica nigra* / black mustard
22. *Momordica charantia* / bitter melon / bitter gourd / bitter squash
23. *Linum usitatissimum* / flaxseed / linseed
24. *Musa x paradisiaca* flower / banana flower
25. *Asparagus racemosus* / shatavari
26. *Hygroryza aristate* / Asian watergrass
27. *Solanecio biafrae*
28. *Eremurus himalaicus* / Foxtail Lily
29. *Ficus racemose* / cluster fig
30. *Holostemma ada-kodien*
31. *Cuminum cyminum* / cumin
32. *Nigella glandulifera*
33. *Foeniculum vulgare* / fennel
34. *Coleus amboinicus* / *Plectranthus amboinicus* / Indian Borage / torbangun
35. *Sauropus androgynus* / katuk / star gooseberry / sweet leaf
36. *Moringa oleifera* / moringa / drumstick
37. *Carica papaya* / papaya / pawpaw
38. *Nigella Sativa* / black seed / black caraway / black cumin / nigella / kalojeera / kalonji / kalanji

39. *Alternanthera bettzickiana* / calico plant
40. *Lllicium griffithii* / star anise
41. *Pimpinella anisum* / anise / aniseed
42. *Gliricidia maculate*
43. *Mondia whitei* / white's ginger
44. *Himatanthus obovatus*
45. *Smithia sensitive*
46. *Trachyspermum ammi* / ajwain / ajowan
47. *Wrightia tinctoria* / pala indigo plant / dyer's oleander
48. *Actaea racemose* / black cohosh / black bugbane / black snakeroot / fairy candle
49. Ginseng
50. Alfalfa / lucerne / *Medicago sativa*
51. *Astragalus* / *Astragalus membranaceus*
52. Barley / *Hordeum vulgare*
53. Basil / *Ocimum basilicum* / Saint Joseph's wort
54. Betony / *stachys* / common hedgenettle / *Betonica officinalis*
55. Blessed thistle / *Cnicus benedictus* / *Cardui benedicti* / St. Benedict's thistle / holy thistle / spotted thistle
56. Borage / *Borago officinalis* / starflower
57. Castor / *Ricinus communis*
58. Chasteberry / *Vitex agnus-castus* / chaste tree
59. Coriander / *Coriandrum sativum* / cilantro / Chinese parsley / dhania
60. Dandelion / *Taraxacum officinale*
61. Dill / *Anethum graveolens*
62. Euphorbia
63. Garlic / *Allium sativum*
64. Ginger / *Zingiber officinale*
65. *Crataegus* / hawthorn / quickthorn / thornapple / may-tree / whitethorn / hawberry
66. Hibiscus / *Hibiscus sabdariffa*
67. Hops / *Humulus lupulus*
68. Licorice / liquorice / *Glycyrrhiza glabra*
69. Marshmallow / *Althaea officinalis*
70. Milk thistle / St. Mary's thistle / silymarin / *Silybum marianum*
71. Parsley / *Carum Petroselinum*
72. Peanut / *Arachis hypogaea*
73. *Pulsatilla* / pasque flower / *Anemone pulsatilla* / meadow anemone
74. Raspberry / *Rubus idaeus*
75. Brown seaweed / *Ascophyllum nodosum* / *undaria pinnatifida*
76. Stinging nettle / nettle / *urtica dioica*
77. Turmeric / *Curcuma longa*
78. Vervain / *Verbena officinalis* / verbena
79. Withania / *Withania somnifera* / ashwagandha
80. Gourd
81. Jackfruit / *Artocarpus heterophyllus*
82. Chives / *Allium schoenoprasum*
83. Giant Cane / *Arundo donax*
84. Abuta / Laghu Patha / *Cissampelos pareira*
85. Bhringraj / false daisy / *Eclipta alba*
86. Black Nightshade / *Solanum nigrum*
87. Jivanti / *Leptadenia reticulata*
88. Red clover / *Trifolium pratense*

## Appendix 2 Summary of studies on galactagogues (by postpartum days at the baseline) that included in the literature review (Chapter 2).

Study design	Galactagogue and study aims	Dosage and timeframe	study Subjects and recruiting criteria	Effect on milk volume	Other effects on milk production	Reported side effects
<b>Preterm</b>						
Abdou and Fathey 2018 [1] Case-control study Egypt	Fenugreek Aim: To evaluate the efficacy of fenugreek in increasing milk volume and prolactin level in mothers of preterm newborns.	200 ml tea contain 50g fenugreek seeds, 3x day 15-day duration Infant mean age 22.7 days at the baseline.	Fenugreek (n = 30) Control (n = 30) Inclusion criteria: Mother age > 18 years, preterm infant (<32 weeks' gestation), admitted to NICU > 2 weeks, stated pumping within 24 hrs after birth and used manual pump to express milk prior to study entry. Exclusion criteria: Contraindication to fenugreek; history of infertility or induction pregnancy; abnormalities in the breast growth or surgery; hypertension, diabetes or thyroid dysfunction or any endocrinal disease; severe nutrition deficiencies or anaemia; history of allergy to fenugreek or other food allergies.	<b>Mean milk volume</b> (SD) (mL/day) by manually pumping 8 times and self-recorded in 24 hours. Day 3: Fenugreek 274.60 (46.97) Control 246.37 (46.62) P = 0.023 Day 8: Fenugreek 485.27 (58.84) Control 474.83 (59.11) P = 0.496 Day 15: Fenugreek 771.33 (90.43) Control 772.50 (89.58) P = 0.96	Mean serum prolactin levels (SD) (ng/L) Day 3: Fenugreek 152.77 (18.46) Control 134.53 (17.35) P = 0.000 Day 15: Day 3: Fenugreek 73.53 (8.29) Control 76.10 (8.56) P = 0.243	Not reported.
Asztalos et al. (2017) [2] Multicentre, double-masked RCT, intention-to-treat analysis Canada	Domperidone Aim: To determine if taking domperidone results in higher proportion of mothers having a 50% increase in milk volume than taking placebo.	10 mg, 3x day Group A: 28 days Group B: placebo for 14 days then domperidone for 14 days Infant aged 8 to 21 days at the baseline.	Domperidone (n = 45) Placebo (n = 45) Inclusion criteria: Preterm (<29 weeks' gestation), pumping ≥ 6x/day in the 4 days prior to study entry. Lactation inadequacy with the 72 hrs prior to study entry: 1) ≤ 150 ml/kg/d (based on infant's birthweight); or 2) milk volume reduction ≥ peak volume. Exclusion criteria: Cardiac dysrhythmias or receiving an anti-arrhythmic medication; mastitis; previous breast surgery; any illness; receiving medications alter the metabolism and pharmacokinetics of domperidone or medications affect prolactin levels; triplet or higher; and cigarette smoking.	Mean milk volume (SD) (mL/day) by exclusively pumping and self-recorded in 24 hours. Days 14: Domperidone: 267 (189) Placebo: 217 (168) Day 28: Domperidone: 290 (211) Placebo: 302 (230) No significant differences	More <b>mothers achieved a 50% increase in milk volume after 14 days</b> in domperidone group (77.8%) compared with placebo (57.8%), odds ratio = 2.56, 95% confidence interval [1.02, 6.25] (p = 0.04) No difference in the proportion of women achieved a 50% increase in milk volume after 28 days.	Cardiac, gastro, obstetrical, central nervous system, respiratory, infection Group A: 31 events Group B: 23 events

Study and design	Galactagogue and study aims	Dosage and timeframe	study	Subjects and recruiting criteria	Effect on milk volume	Other effects on milk production	Reported side effects
Campbell-Yeo et al. (2010) [3] Blinded RCT Canada	Domperidone Aim: To examine the effect of domperidone on the nutrient composition of breast milk.	10 mg, 3× day 14-day duration Unclear infant age at the baseline		Domperidone (n = 19) Placebo (n = 19) Inclusion criteria: Preterm (<31 weeks' gestation), double pumping, experienced lactation failure ≥ 3 weeks, which defined as 1) milk supply decrease >30% peak volume; or 2) breast milk failed to meet infant daily nutritional requirement. Exclusion criteria: Taking medicine affect or interact with domperidone; mastitis; chronic illness; history of breast surgery; lactose intolerance; or already taking domperidone.	Mean milk volume (SD) (mL/day) by exclusively double pumping and self-recorded in 24 hours. Day 0: Domperidone: 184.4 (167.0) Placebo: 217.7 (154.5) Day 14: Domperidone: 380.2 (201.6) Placebo: 250.8 (171.6) Milk volume increase: Domperidone: 267% Placebo: 18.5% (p = 0.005)	<b>Within participants milk protein concentration change</b> Domperidone: -9.6% Placebo: 3.6% (p = 0.16) Serum prolactin increase: Domperidone: 97% Placebo: 17% (p = 0.07) Milk carbohydrate: Domperidone: 2.7% Placebo: -2.7% (p = 0.05) Milk calcium: Domperidone: 61.8% Placebo: -4.4% (p = 0.001) No significant differences in mean within participants concentration changes of milk energy or milk fat, sodium or phosphate.	No severe side effects observed, one case of mild abdominal cramps in placebo group.
da Silva et al. (2001) [4] Double-blind RCT Canada	Domperidone Aims: To assess the efficacy in augmenting lactation; to determine the prolactin level and the domperidone levels in serum and breast milk.	10 mg, 3× day 7-day duration Infant mean age 31.9 days in domperidone group and 33.1 days in placebo group at the baseline.		Domperidone (n = 19) Placebo (n = 19) Inclusion criteria: Preterm (mean 29.1 weeks' gestation), double pumping, milk production failed to meet infant daily oral feeding requirement after extensively counselling with lactation experts. Exclusion criteria: Taking medicine affect serum prolactin levels; chronic illness.	<b>Mean milk volume</b> (mL/day) by exclusively double pumping and self-recorded in 24 hours. Domperidone: 130.4 on Day 2 to 183.5 on Day 7 (44.5% increase) Placebo: 54.7 on Day 2 to 66.1 on Day 7 (16.6% increase) Significantly higher mean increases of milk volume in domperidone group compared to placebo group (p < 0.05)	Mean serum prolactin levels (SD) (µg/L) at day 5: Domperidone: 119.3 (97.3) Placebo: 18.1 (14.7) (p = 0.008) Mean domperidone concentration (SD) (ng/mL) (as measured in randomly selected samples) at day 5: Serum (n = 6): 6.6 (5.7) Breast milk (n = 6): 1.2 (0.6)	No obvious side effects observed.
Estrella et al. (2000) [5] Double-blind RCT	Moringa ( <i>moringa oleifera</i> ) Aim:	Moringa leaves in capsules, 250 mg, 2x day 3-day duration		Moringa (n = 31); Placebo (n = 37) Inclusion criteria: Preterm infant (<37 weeks' gestation), admitted to the	<b>Mean milk volume</b> (SD) (mL/day) by exclusively double pumping every 4 hrs	Not evaluated.	No obvious side effects observed.

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Philippines	To determine if there is a significant difference in milk volume at day 3 and 5 postpartum between moringa and placebo groups.	Infant aged 3 days at the baseline.		NICU for tube feedings. Exclusion criteria: mothers with hypertension post-delivery; diabetes mellitus; chorioamnionitis; chronic illness; taking any medication on a regular basis; breast anomalies; infants with congenital anomalies.	and self-recorded by participants. Day 3 (the baseline) Moringa: 114.1 (62.9) Placebo: 87.2 (49.1) (p = 0.052) Day 5 Moringa: 319.7 (154.1) Placebo: 120.2 (54.7) (p = 0.052)		
Fazilla et al. (2017) [6] Double blind RCT Indonesia	Domperidone Aims: To evaluate milk production in Mothers of preterm infants; to assess relationships between milk production and maternal age, gestational age, parity, method of delivery, and educational level.	10 mg, 3× day 7-day duration + 3-day follow-up. Infant mean age 5.6 days in domperidone group and 4.8 days in placebo group at the baseline		Domperidone (n = 25) Placebo (n = 25) Inclusion criteria: Mothers aged 20 - 30 years, preterm (<37 weeks' gestation), failure to lactate and with little or no improvement in milk production after 7-day lactation counselling, infant receiving feeding through a nasogastric tube. Failure to lactate was defined as 1) milk supply decrease >30% peak volume; or 2) breast milk failed to meet infant daily nutritional requirement. Exclusion criteria: Taking medicine affect or interact with domperidone; mastitis; history of breast surgery; heart problems; obesity; diabetes; twins.	<b>Mean milk volume</b> (SD) (mL/day) by exclusively double pumping and self-recorded in 24 hours Day 0 Domperidone: 83.3 (42.99) Placebo: 66.6 (49.84) No report of significance. Days 7 Domperidone: 181.6 (80.26) Placebo: 72.46 (57.84) (p = 0.001) Day 10 Domperidone: 179.12 (82.4) Placebo: 69.32 (51.74) (p = 0.001)	No significant differences in mean breast milk volume (P>0.05) between day 7 and day 10 in domperidone group. No significant differences in mean breast milk volume between day 0, day 7, and day 10 in placebo group (P >0.05) The intervention type was the only predictor in linear regression model for milk production on day 7.	No obvious side effects observed.
Knoppert et. al. (2013) [7] RCT Canada	Domperidone Aim: To determine an optimal dosage of domperidone as a galactagogue	Low dosage group (L): 10 mg, 3× day High dosage group (H): 20 mg, 3× day 28-day duration		L (n = 8) H (n = 7) Inclusion criteria: Women aged 18-45 years, with a singleton or multiples (twins, triplets) born at < 33 weeks' gestation, and daily milk volume < 500 mL at postpartum day 14-21.	Milk volume by exclusively pumping and self-recorded 8-10x day. Mean volume of milk not provided.	A significant increase in daily milk volumes within each group (p < 0.01). No significant difference between groups over 4-week period (p = 0.46), no	One case of nausea, relieved by taking domperidone with food.

Study design	and Galactagogue and study aims	Dosage and study timeframe	Subjects and recruiting criteria	Effect on milk volume	Other effects on milk production	Reported side effects
		Infant aged 14-21 days at the baseline.	Exclusion criteria: Breast expressing < 8x in 24 hours; history of breast surgery, breast cancer, chronic debilitating disease or endocrine disorder; history of a clinically recognised arrhythmia; taking an antiarrhythmic drug, a quinolone antibiotic, or a drug metabolized by CYP 3A4 (eg, ketoconazole, macrolide antibiotic); infants developed necrotizing enterocolitis.		significant between groups in weeks 1 (p = 0.70), 2 (p = 0.49), 3 (p = 0.33), or 4 (p = 0.41). Data only shown in the figure. Median serum prolactin level (IQR) (mcg/L), baseline: L 20.5 (10.5) H 15.5 (40.8); day 28: L 114.0 (89.0) H 167.0 (65.0); both non-significant. Median serum domperidone level (IQR) (mcg/L) at day 10-15: L 14.2 (15.3) H 12.6(37.9). Median milk domperidone level (IQR) (mcg/L) at day 10-15: L 3.4 (2.1) H 6.9 (11).	
Ozalkaya et al. (2018) [8] RCT Turkey	Commercial herbal mixture tea contains 1.0% of stinging nettle and six other herbs (melissa, caraway, anise, fennel, goat's rue, and lemon grass) Aims: To evaluate the effects on milk production and serum prolactin levels of mothers, and weight gain of preterm infants.	8 g granules, 2x day 7-day duration Infant aged 3-39 days in placebo group (P), 4-40 days in control group (C) and 4-47 days in treatment group (T).	P (n = 32) C (n = 21) T (n = 32) Inclusion criteria: Preterm infants (<37 weeks' gestation), birth weight <2000 g, admitted to the NICU for orogastric tube feedings and having no contraindication. Exclusion criteria: Infant with congenital anomaly and acute problems such as pneumonia, sepsis, necrotizing enterocolitis; mothers with chronic disease, cigarette smoking, consuming alcohol, and any galactagogue drug or herb.	<b>Mean milk volume</b> (range) (mL/day) by exclusively pumping and self-recorded 8x day. Day 1 P: 355.6 (50-1010) C: 323.8 (50-890) T: 320.2 (10-1025) P = 0.81 Day 7 P: 477.7 (140-1200) C: 422.6 (40-1305) T: 577.5 (60-1250) P = 0.22	Difference of milk volume between day 1 and day 7 P: 122.1 (100-520) C: 100.2 (-60-415) T: 261.0 (10-954) P = 0.003 (P/T) P = 0.002 (C/T) Difference of infant weight between day 1 and day 7: P: 183.3 (67-690) C: 181.0 (40-395) T: 161.0 (10-305) (p=0.63) Difference of blood prolactin level between day 1 and day 7: P: -2.7(-200-146) C: 0.77(-58-66) T: -9.2(-151-332) (p=0.86)	No obvious side effects observed.
Peila et al. (2015) [9] RCT Italy	Milk thistle ( <i>Cardus Marianus L.</i> ) and micronized silymarin Aims:	1 sachet 2x day, providing daily dose of <i>Cardus Marianus L.</i> dry extract 420 mg and micronized silymarin 252 mg.	Silymarin (n = 25) Placebo (n = 25) Inclusion criteria: Preterm infants (<32 weeks' gestation). Exclusion criteria: History of smoke; not able to breastfeed because of their clinical conditions, such as HIV infection.	<b>Mean milk production</b> (g/day) evaluated by sequential pumping at least 6 times/day or 24 hr test weighing	Perception of substance efficacy was evaluated by participant's guess of substance she was taking. Milk production in two guess groups (g/day):	No obvious side effects observed.

Study and design	Galactagogue and study aims	Dosage and study timeframe	Subjects and recruiting criteria	Effect on milk volume	Other effects on milk production	Reported side effects
	To assess galactagogue effect, tolerability and pharmacodynamics in mothers of preterm infants.	Infant aged 10±1 days at the baseline.		after the infant can latch on the breast. No significant difference in milk production between the baseline and the endpoint (day 26, 27 and 28). Differences in milk production variation (g/day) between the baseline and the endpoint: Sylimarin: 24.9±38.1 Placebo: 77.3±24.9 Difference sylimarin-placebo: -52.4±45.5, P=0.872	Silymarin-guess: 61.6±35.7 Placebo-guess: 30.9±19.6 Difference silymarin-guess – placebo-guess: +30.7±48.4 P=0.529 Silymarin was not detectable (<0.3 mg/kg) in human milk collected at day 14.	
Rai et al. (2016) [10] RCT India	Domperidone Aim: To evaluate the effect of early use of domperidone (7–14 day postpartum) on the milk volume in mothers of preterm infants.	Dosage not reported. 7-day duration Infant aged 7 – 14 days at the baseline.	Domperidone (n = 16) Placebo (n = 16) Inclusion criteria: Preterm and sick infant, with insufficient milk production (no definition). Exclusion criteria: Not reported.	No report of milk volume or the evaluation method of milk volume.	<b>Within participants milk volume change</b> , median (IQR) (mL/day) Domperidone: 186.0 (126.5 – 240) Placebo: 70 (49.5 – 97) (p = 0.004) Within participants serum prolactin levels change from Day 1 to Day 8, median (IQR) (µg/L) Domperidone: 18.7 (–39.5 – 55.6) Placebo: 11.9 (–8.3 – 37.5) Not significant.	Not reported.
Reeder et al. (2013) [11] RCT US	Fenugreek ( <i>Trigonella foenum-graecum</i> ) Aim: To determine if fenugreek	3 capsules (575 mg) 3x day. 21-day duration. Started from the 5 <sup>th</sup> day postpartum.	Fenugreek (n = 14) Placebo (n = 12) Inclusion criteria: Preterm infants (<31 weeks' gestation). Mother age > 18 years, able to speak and write English, had access to a telephone, started pumping within 12 hours of delivery, able to visit their hospitalized infant daily.	<b>Mean milk volume</b> (SD) (mL) by pumping both breasts 8 – 12 times daily. Day 5: Fenugreek: 345 (198)	Mean serum prolactin level (SD) (ng/ml): Day 5: Fenugreek: 131.0 (128) Placebo: 108.9 (43.8) Day 10: Fenugreek: 97.5 (93.4)	No side effects observed.

Study design	and Galactagogue and study aims	Dosage and timeframe	study	Subjects and recruiting criteria	Effect on milk volume	Other effects on milk production	Reported side effects
	increases breast milk volumes and prolactin levels in mothers of preterm infants.			Exclusion criteria: history of infertility; lack of prenatal breast growth; breast surgery (excluding breast augmentation); smoking; allergy to chickpeas or peanuts; endocrine problems including diabetes or thyroid disorders; taking steroids for any diagnosis other than preterm labour.	Placebo: 391 (282) Day 10: Fenugreek: 514 (351) Placebo: 577 (400) Day 15: Fenugreek: 568 (419) Placebo: 622 (400) No significant differences.	Placebo: 118.5 (75.1) Day 15: Fenugreek: 65.2 (67.5) Placebo: 84.9 (86.1) No significant differences. Postnatal distress was evaluated daily using Perceived Stress/Sleep/Energy/Calmness Scale, which had non-significant relationship with milk volume (data not provided).	
Wesolowska et al. (2021) [12] Double-blind RCT Poland	Femaltiker®, a commercial product containing powdered lemon balm leaves ( <i>Melissa officinalis L.</i> ), barley malt ( <i>Hordeum vulgare Linn</i> ), enriched with 70% barley-glucan, exact composition is protected by patent (229569). Aims: To investigate efficacy in increasing milk production and safety.	1 package 2x day. 14-day duration. Started from the first day after delivery.		Femaltiker (n = 40) Placebo (n = 40) Inclusion criteria: Women aged ≥ 18 years with preterm infants (< 37 weeks' gestation), declared electric breast pump use and agreed on filling up the lactation diary. Exclusion criteria: Hypothyroidism; either type 1 or 2 diabetes before pregnancy and receiving treatment; already participating in another clinical trial.	<b>Mean total milk volume (SE)</b> (mL) for 14 days by expressing breasts every four hours (six times per day for 10–15 minutes per breast) using a standardized electric breast pump. Femaltiker (F): 6036 (498) Placebo (P): 4209 (335) P = 0.003.	Records in expression log: Total expression time, mean (SE): F 2280 (123) P 2211 (114), p = 0.68 Numbers of expression sessions, mean (SE): F 85 (2) P 82 (2), p = 0.27 Mean daily milk volume (SE) (mL), day 4: F 203.4 (26.7) P 149.3 (23.5), p = 0.13 Day 5: F 333.3 (35.9) P 233.4 (23.5), p = 0.02 Day 6: F 424.6 (41.8) P 325.9 (28.8), p = 0.05 Day 7: F 508.6 (48.2) P 359.5 (29.7), p = 0.01 Day 8: F 556.4 (50.6) P 398.9 (32.0), p = 0.01 Day 9: F 94.3 (54.0) P 421.4 (34.1), p = 0.008 Day 10: F 579.5 (48.0) P 449.7 (34.4), p = 0.03 Day 11: F 605.8 (52.4) P 469.2 (37.9), p = 0.03	Adverse effect evaluated by a health professional and self-report at each visit including skin examination and collecting information of digestive symptoms such as nausea, a bad taste in the mouth, and pain. No adverse event in Femaltiker group. In Placebo group, one case of serious side effect, one case of skin dryness both not related to the product taken; one case of perceived bad taste.
Zecca et al. (2016) [13] RCT Italy	Silymarin-phosphatidylserine and galega Aim:	5 g 1x day. 26-day duration. Started from day 3 postpartum.	3	Treatment (n = 50) Placebo (n = 50) Inclusion criteria: Women aimed to breastfeed, preterm infants (<33 weeks' gestation). Exclusion criteria:	Median milk volume (IQR) (mL) postpartum by pumping each breast for 15 mins every 2-3	Total milk volume (SD) (mL) in the study period: Treatment: 6523 (5298) Placebo: 4136 ± 4093 P < 0.02	No side effects observed.

Study design	Galactagogue and study aims	Dosage and timeframe	study	Subjects and recruiting criteria	Effect on milk volume	Other effects on milk production	Reported side effects
	To evaluate the galactagogue efficacy in mothers of preterm infants.			Women with contraindication to breastfeeding; lactose (placebo) intolerance.	hrs daily was significantly higher in the treatment group at day 7 and day 30 (P<0.05). Milk volume only shown in figure. <b>Individual average daily milk volume</b> (IQR) (mL) from day 7 to day 30: Treatment: 200 (110–380) Placebo: 115 (60–245) P < 0.0001	Numbers of mothers achieved production higher than 200 ml/day: At day 7: Treatment 29 Placebo 15 P < 0.05 At the end of the study: Treatment 45 Placebo 25 P < 0.0001	
Serrao et al. (2018) [14] RCT Italy (a follow up of the study Zucca 2016)	Silymarin-phosphatidylserine and galega Aim: To investigate the influence on the duration of breastfeeding.	5 g 1x day. Treatment duration: 26 days started from day 3 postpartum. Follow up at 3 months and 6 months postpartum.		Treatment (n =45) Placebo (n = 44) Inclusion criteria: Women completed previous study (Zucca 2016) who responded comprehensively to the questions at 3 months and 6 months postpartum.	Not evaluated.	At 3 months postpartum: Numbers of exclusively breastfeeding mothers: Treatment 22 Placebo 12 P < 0.05 Numbers of mothers feed more than 50% breast milk: Treatment 29 Placebo 18 P < 0.05 At 3 months postpartum: Numbers of mothers feed more than 50% breast milk: Treatment 22 Placebo 12 P < 0.05	Not reported
<b>Term infant, ≤ 7 days postpartum at the baseline</b>							
Achalapong (2016) [15] Thailand RCT	Egg and milk supplements Aim: To determine if egg and milk supplement can increase breast milk volume at 48	C: control group with control diet M: 200ml milk, 3x day with meals E: 1 medium boiled egg, 3x day with meals M+E: 200ml milk + 1 medium boiled egg, 3x day with meals		C (n = 30) M (n = 30) E (n = 30) M+E (n = 30) Inclusion criteria: Term infant, singleton, birth weight > 2500 g, Mother without complication and with spontaneous vaginal delivery. No exclusion criteria reported.	Mean milk volume (SD) (mL) by pumping both breasts for 15 mins at 48 hrs and 72 hrs postpartum: At 48 hrs: C 5.2 (6.7) At 72 hrs: C 19.6 (18.7)	<b>Mean differences in milk volume</b> (95% CI) compared to control group at 48 hrs and 72 hrs postpartum: At 48 hrs: M: +3.8 (-6.8, 14.5), p = 0.477 E: +7.5 (-3.1, 18.1), p = 0.163 M+E: +14.6 (3.8, 25.4), p = 0.008 At 72 hrs: M: +4.1 (-17.9, 26.0), p = 0.715	Not reported.

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	and 72 hours postpartum.	All intervention groups having same diet as control group 3-day duration, started from day 1 postpartum		No report of volumes in other groups.	E: +19.6 (-2.5, 41.7), p = 0.082 M+E: +41.1 (18.8, 63.5), p < 0.001	
Damanik et al. (2006) [16] RCT Indonesia	Torbangun ( <i>Coleus amboinicus Lour</i> ) Aim: To evaluate the effect on the quantity and quality of breast milk.	Torbangun (T): 150 g of leaves in soup, 6 days/week; Fenugreek (F): capsule 600mg, 3x day; Moloco + B12 (M): 920 µg VB12 and 15 mg placental extract) 3x day; 30-day duration + 30-day follow-up. Infant aged 2 days at start point.	Torbangun (n = 23) Fenugreek (n = 22) Moloco + B12 (n = 22) Inclusion criteria: Women aged 20-40 years; healthy, intend to breastfeed their infants exclusively for at least 4 months; term, healthy infant, birth weight >2.5 kg. Exclusion criteria: Malnutrition; chronic diseases; taking any medication; any medical conditions; complications during previous pregnancies or deliveries; smoking or alcohol.	Mean milk volume (SD) (mL/day) by 24-hr test weighing Day 14 (the baseline) T 361.1 (201.1); F 466.9 (253.0); M 453.8 (192.6) Day 28 T 478.7 (157.0); F 400.3 (215.1); M 385.1 (201.9) Day 42 T 439.8 (196.7); F 456.6 (247.1); M 387.4 (188.3) Day 56 T 478.3 (265.0); F 358.5 (135.2); M 385.5 (170.5) No statistically difference	Milk composition (g/100g), Mean (SD): From day 8 to day 33: Protein: 1.3 (0.1) to 1.2 (0.0), p < 0.0001 % Change in % milk composition (g/100g) T vs. M: From day 8 to day 33: Protein, -1.2 (5.3) vs. 3.4 (3.3), p < 0.001 Ash, 0.5 (3.7) vs. 3.1 (3.9) p < 0.05 From day 8 to day 60: Ash, -2.6 (3.5) vs. 1.8 (2.1) p < 0.0001 No significant changes in micronutrients (iron, zinc, calcium, potassium, and magnesium).	Not reported.
Espinosa-Kuo (2005) [17] RCT Philippines	Moringa ( <i>moringa oleifera</i> ) Aims: To determine the breast milk volume after the intervention and to record the adverse effect of taking moringa.	Moringa leaves in capsules (250 mg/capsule), 2 capsules, 1x day 8-day duration Started from 3 <sup>rd</sup> day postpartum.	Moringa (n = 41); Placebo (n = 47) Inclusion criteria: Mothers aged 18 – 38 years with term infants (37-42 weeks' gestation) via non-spontaneous delivery, mother willing to breastfeed. Exclusion criteria: Mothers with hypertension; diabetes mellitus; chorioamnionitis; chronic illness; acute illnesses such as acute upper respiratory tract infection, urinary tract infection; taking any medication on a regular basis; breast anomalies; infants with neonatal illness and congenital anomalies.	Mean milk volume (SD) (mL/day) by manually pumping every 4 hrs and self-recorded by participants, no reporting of breastfeeding status. Day 3 (the baseline) Moringa: 96.35 (14.3) Placebo: 78.56 (9.81) No significant difference.	Not evaluated.	No obvious side effects observed.

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				Day 10 Moringa: 395.9 (36.33) Placebo: 150.8 (16.5) No significant difference.		
Inam et al. (2013) [18] RCT Pakistan	Domperidone Aim: To compare the efficacy of domperidone and placebo among women with insufficient milk production.	10 mg, 3× day 7-day duration. Infant aged 6 days at the baseline.	Domperidone (n = 50) Placebo (n = 50) Inclusion criteria: Term infant at 6 days postpartum with inadequate breast milk production, which defined as < 10ml breast milk per single expression from both breasts. Exclusion criteria: Chronic renal diseases or tuberculosis possibly decreasing milk output; malnutrition with BMI <18kg/m; breast abscess; mastitis; history of allergy; prior reaction to domperidone.	Milk volume evaluated by single expression from both breasts. No report of milk volume.	Significant increase of adequate improvement in domperidone group compared to placebo group: 36 mothers (72%) vs. 11 mothers (22%), p = 0.002. <b>Adequate improvement</b> defined as >50 mL milk expressed per single expression.	No obvious side effects observed.
Karapati et al. (2021) [19] Retrospective cohort Greece	Silitidil (silymarin from thistle with incorporated phospholipids). Aim: To assess the influence on the duration of breastfeeding.	5 g per day. 14-day duration. First prescription during the mother's hospital staying after birth.	N = 161 Inclusion criteria: Women needing additional lactation support, or with low milk supply; mothers of twins or premature infants, or those whose neonates had (a) weight loss ≥10% of birthweight, (b) needed phototherapy, (c) required transport to a tertiary NICU, and who unable to breastfeed due to any other reason.	Not evaluated	The proportion of breastfeeding (recorded by telephone interviews of breastfeeding status), at 1 week: 161 (100%); 1 <sup>st</sup> month: 159 (98.8%); 4 <sup>th</sup> month: 140 (87%); 6 <sup>th</sup> month: 91 (56.5%); 12 <sup>th</sup> month 66 (41%).	Not reported.
Kavurt et al. (2013) [20] RCT Turkey	Fenugreek Aims: To compare total antioxidant capacity (TAC), total oxidant status (TOS) and the oxidative stress index (OSI) of breast milk among women drinking galactagogue tea or not.	200 mL commercial herbal tea containing fenugreek (the amount not provided) or water as placebo, 3× day. 10-day duration. The baseline milk sample was collected in day 1 after birth and started intervention at day 2. The second milk sample was collected at day 7-10.	Herbal tea (n = 40) Placebo (n = 40) Inclusion criteria: Exclusively breastfeeding women aged 18–35 years, without any known antenatal or perinatal risk factors, with healthy, vaginally born, term infants, birth weight ≥ 2500 g. Exclusion criteria: Women having chronic disorders like diabetes mellitus, hypertension, bronchial asthma, allergic problems and mastitis; smokers, alcohol and drug users.	Not evaluated	Mean TAC level (SD) measured by Erel's TAC method, Baseline: Tea: 4.21 (1.79), Placebo: 3.93 (1.65), p = 0.465 Endpoint: Tea: 3.76 (1.16), Placebo: 3.36 (0.82), p = 0.08 Mean TOS level (SD) measured by Erel's TOS method, Baseline: Tea: 26.62 (21.53), Placebo: 24.20 (32.42), p = 0.111 Endpoint: Tea: 29.84 (18.06), Placebo: 27.16 (19.69), p = 0.439	Not reported.

Study and design	Galactagogue and study aims	Dosage and timeframe	study Subjects and recruiting criteria	Effect on milk volume	Other effects on milk production	Reported side effects
Jantarsaengaram and Sreewapa (2012) [21] Double blind RCT Thailand	Domperidone Aims: To evaluate the efficacy and adverse effects of domperidone for women had caesarean delivery of full-term infants.	10 mg, 4× day 4-day duration. Infant aged 1 day at the baseline.	Domperidone (n = 22) Placebo (n = 23) Inclusion criteria: Women aged 18–35 years, term infants via caesarean delivery, singleton. Exclusion criteria: Women BMI >24; postpartum bleeding > 1L; chronic medical disease; history of allergies to domperidone; history of smoking or substance abuse; gross breast or nipple abnormalities; other conditions contraindicate breastfeeding.	<b>Mean milk volume</b> (SD) (mL) by pumping both breasts for 15 mins, 2 hr after breastfeeding, collected twice daily. Day 0 Domperidone: 3.9 (4.6) Placebo: 3.4 (9.3) (p = 0.007) Days 7 Domperidone: 191.3 (136.1) Placebo: 91.4 (60.3) (p = 0.003)	OSI calculated as TAC/TOS, Baseline: Tea: 0.058 (0.033), Placebo: 0.051 (0.057), p = 0.057 Endpoint: Tea: 0.083 (0.054), Placebo: 0.077 (0.054), p = 0.507 Mean increases within participant in milk volume (data not reported) collected on days 1, 2, 3, and 4 were significantly higher in the domperidone group than in the placebo group, compared to day 0.	Dry mouth: domperidone group: 7 cases (31.8%).
Ngadiarti et al. (2021) [22] quasi-experimental design with two randomised groups Indonesia	Mixed galactagogue drink (Sweet leaf [ <i>Sauropus androgynus</i> ], papaya leaves, and mung beans) Aim: To compare breast milk volume, breastfeeding frequency, and duration after the administration of mixed	Mixed galactagogue drink group (G): 400 ml (2 bottles) per day within the interval of the main meal and at night before sleep. Ingredients per serving: 50 g sweet leaf, 25 g papaya leaves, 15 g mung beans, 15 g sugar, 25 g tomatoes and 12 g tamarind. Control group (C): 30-45 minutes counselling 3 times (at birth, 7–14, and 35 days old). 4-week duration.	G (n = 30) C (n = 30) Inclusion criteria: Healthy pregnant women in the third trimester, aged 20–35 years, with a single pregnancy, routinely attended antenatal care. Exclusion criteria: Smoking; with serious medical conditions, food allergy; had other galactagogue supplements besides what was administered.	<b>Mean milk volume</b> (SD) (mL/day) by 24-hr weighing the participants with evaporative water loss method, Week 1: G 622.9 (289.2), C 507.7 (231.3), p = 0.094. Week 2: G 683.0 (252.4), C 582.6 (225.4), p = 0.110 Week 3: G 801.4 (273.3), C 656.2 (214.4), p = 0.026	Mean breastfeeding frequency (SD) by interview of numbers of feedings per day, Week 1: G 14.2 (2.7), C 15.1 (2.3), p = 0.145 Week 2: G 14.2 (3.1), C 16.2 (2.8), p = 0.130 Week 3: G 13.8 (2.8), C 14.2 (2.5), p = 0.534 Week 4: G 13.0 (2.6), C 13.8 (2.8), p = 0.273 Mean breastfeeding duration (SD) by recall in the interviews of duration per breastfeeding, Week 1:	Not reported.

Study design	and	Galactagogue and study aims	Dosage and timeframe	study	Subjects and recruiting criteria	Effect on milk volume	Other effects on milk production	Reported side effects
		galactagogue drink and receiving counselling only.	Started immediately after delivery.			Week 4: G 908.5 (271.3), C 756.7 (196.3), p = 0.016	G 18.5 (13.0), C 14.7 (12.0), p = 0.241 Week 2: G 18.1 (12.8), C 14.7 (6.8), p = 0.200 Week 3: G 25.5 (14.8), C 19.8 (9.7), p = 0.084 Week 4: G 23.2 (12.1), C 22.3 (9.4), p = 0.767	
Paritakul et al. (2016) [23] RCT Thailand		Ginger (the root of <i>Zingiber officinale</i> ) Aim: To compare the breast milk volume during the early postpartum period between women taking ginger and women taking placebo.	500 mg, 2x day 7-day duration. Started 2hrs after delivery.		Ginger (n = 30) Placebo (n = 33) Inclusion criteria: Healthy pregnant women aged ≥ 18 years, term infant (≥ 37 weeks' gestation), aim to exclusively breastfeeding for at least 6 months. Exclusion criteria: Serious medical conditions presumed to result in mother–infant separation (e.g. postpartum haemorrhage, postpartum sepsis); allergic to ginger; contraindication to breastfeeding (e.g. HIV infection).	<b>Mean milk volume (SD)</b> (mL/day) by 24-hr test weighing at day 3: Ginger (n=30): 191.0 (71.2) Placebo (n=33): 135.0 (61.5) (p < 0.01) <b>Mean milk volume (SD)</b> (mL/hr) by expression for 15 mins at 1 hr after empty both breasts by pumping at day 7: Ginger (n=15): 80.0 (58.5) Placebo (n=21): 112.1 (91.6) (p = 0.24)	Mean serum prolactin level (SD) (ng/mL) at day 3: Ginger (n=30): 321.5 (131.8) Placebo (n=33): 331.4 (100.7) (p = 0.74)	Not reported.
Ravi and Joseph (2020) [24] RCT India		Fenugreek Aims: To determine the effect of fenugreek on breast milk production; to determine the effect of fenugreek on	Fenugreek water 1x day in the morning (7.5 g of fenugreek soaked overnight, volume of water not provided). 7-day duration. Infant aged 0 – 1 week.		Fenugreek (n = 30) Placebo (n = 30) Inclusion criteria: Term healthy infants aged 0 – 1 week, with poor milk supply as reported to the health professionals. Exclusion criteria: Documented mastitis; breast engorgement; inverted nipples; currently consuming any other herbals used to induce milk production; clinically ill; history of breast surgery.	Not evaluated.	<b>Frequency of Urination</b> , Mean (SD) at day 7: Fenugreek: 6.1 (0.9) Placebo: 4.4 (1.1) P = 0.001 Mean Infant weight (SD) (kg) over days (day 1 to 7) was significantly increased in fenugreek group (from 2.2 (0.4) to 2.8 (0.5), p = 0.001) but not in placebo group.	No side effects observed.

Study design	and Galactagogue and study aims	Dosage and study timeframe	study Subjects and recruiting criteria	Effect on milk volume	Other effects on milk production	Reported side effects
	infant weight gain.					
Sakka et al. (2014) [25] RCT Egypt	Fenugreek ( <i>Trigonella foenumgraecum</i> ) Palm dates Aims: To assess the effects of palm dates and fenugreek on breast milk production and infant weight gain within the first two postpartum weeks.	1 cup fenugreek herbal tea (2 g/cup), 3x day. 10 palm dates (100g), 3x day. 14-day duration. Started from day 1 postpartum.	Fenugreek (n = 25) Palm date (n = 25) Control (n = 25) Inclusion criteria: mothers who were willing to breastfeeding and pump for the study period. Exclusion criteria: high-risk pregnancy as diabetes or hypertension; inverted nipple; history of asthma or allergy to peanuts; and infants with cleft lip or palate or gross congenital malformations or genetic syndromes.	<b>Mean milk volume</b> (SD) (mL) by pumping both breasts before the first feed in the morning at day 3: Fenugreek 51 (19) Palm dates 68 (19) Control 36 (7) (F = 25.59, p < 0.001)	Mean % increase in infant weight (SD) at day 3: Fenugreek -5.5 (0.9) Palm dates -6.5 (5.1) Control -9.3 (2.9) (p < 0.01) Day 7 Fenugreek -0.5 (5.1) Palm dates 2.9 (4.5) Control -3.3 (5.2) (p < 0.01)	Not reported.
Srinivas et al. (2014) [26] RCT India	Galactagogue mixes containing fenugreek or garlic Aims: To evaluate the effects on breast milk production and on the pattern of infant weight gain in early postnatal period.	Fenugreek: 20g /day. Garlic: 30 g/day. Duration and start time not reported, completed in the first week postpartum.	Fenugreek (n = 10) Garlic (n = 10) Control (n = 10) Inclusion criteria: mothers with full term healthy infants, willing to exclusively breastfeed, with insufficient breast milk production. Exclusion criteria: Infants with low birth weight, low APGAR scores and intrauterine growth retardation; infants with any illnesses or congenital abnormalities; mothers with chronic illness such as diabetes, hypertension, bronchial asthma, and any allergies; mothers with any breast problems such as inverted nipples, mastitis, engorgement, cracks etc.; history of smoking, alcohol, or any drug use meant for improving breast milk production.	Not evaluated.	Mean prolactin level (SD) (ng / ml) at the endpoint: Fenugreek 236.98 (59.36) Garlic 226.74 (100.98) Control 142.49 (48.69) p = 0.013 No significant difference between fenugreek and garlic groups, both were significantly higher than control. Mean infant weight (SD) at the endpoint: Fenugreek 3.284 (0.46812) Garlic 3.319 (0.37355) Control 2.836 (0.38103) P = 0.024 No significant difference in mean chest, head and mid arm circumference of the infants.	Not reported.

Study and design	Galactagogue and study aims	Dosage and study timeframe	Subjects and recruiting criteria	Effect on milk volume	Other effects on milk production	Reported side effects
Sulistiawati et al. (2017) [27] Quasi-Experimental pre-post design Indonesia	Moringa Oliefera Aims: To examine the effect on breast milk production and prolactin level.	Moringa Oliefera: 250 mg, 2x day. 14-day duration. Started from day 1 postpartum.	Moringa (n = 15) Control (n = 15) Inclusion criteria: women willing to breastfeed exclusively, not taking herbs or any breastfeeding supplements, aged 20-35 years old, and infant weight 2500-4000 g. Exclusion criteria: mother with abnormal breast nipple, chronic energy deficiency (upper arm circumference <23.5 cm); complications (bleeding, infection); infant with cleft lip.	Not evaluated.	Mean differences in prolactin level (SD) (ng / ml): Moringa: 231.72 (60.45) Control: 152.75 (66.99) P = 0.002 Mean differences in infant weight (SD) (g): Moringa: 3783.33 (460.07) Control: 3599.00 (520.19) P = 0.313 Mean differences in infants' morning and evening sleep duration (SD) (minutes), no information about how to record infant sleep: Moringa: 128.20 (5.47) Control: 108.80 (6.74) P = 0.000	Not recorded.
Thaweekul et al. (2014) [28] Quasi-experimental design Thailand	Hospital-based food programme contain galactagogue foods. such as hot basil, lemon basil, sweet basil, banana flower, garlic, garlic chives, ginger and pepper. Aim: To evaluate the hospital-based food programme as galactagogues at the initiation stage of lactation.	Food program provided 2500 kcal and 70g protein per 'day. No information of specific galactagogue foods. From day 1 postpartum to discharge from the hospital.	Intervention (n = 106) Control (n = 127) Inclusion criteria: Normal delivery, singleton, birth weight 2500 - 4000 g. Exclusion criteria: Women with serious medical conditions affecting lactation; receiving breastfeeding contraindicated medications; infants admitted to NICU.	Not evaluated.	Number of cases <b>perceived breast fullness</b> within 48 hrs postpartum (%): Intervention 76 (71.7) Control 72 (56.7) (p < 0.001) Number of <b>infants with excessive weight loss</b> defined as >7% birth weight (%) At 24 hrs: Intervention 0 (0) Control 7 (5.5) (p = 0.012) At 48 hrs: Intervention 16 (15.1) Control 31 (24.4) (p = 0.043) No difference in 24-hr breastfeeding frequency (8±2.5 in intervention group and 8±2.1 in the control group, p = 0.902) or formula intake in the first 24	Not reported.

Study design	and Galactagogue and study aims	Dosage and timeframe	study Subjects and recruiting criteria	Effect on milk volume	Other effects on milk production	Reported side effects
Turkylmaz et al. (2011) [29] RCT Turkey	Fenugreek ( <i>Trigonella foenumgraecum</i> ) Aims: To evaluate the effects on breast milk production and on the recovery of pattern of infant weight gain during early postpartum days.	3 cups (200 ml/cup) daily commercial tea containing 100 mg fenugreek or apple tea as placebo, from birth to recovery of birth weight	Fenugreek (n = 22) Placebo (n = 22) Control (n = 22) Inclusion criteria: term, healthy baby; mothers 1) have been willing to exclusively breastfeed; 2) have consented to follow-up visits until infant catch up birth weight; and 3) have agreed to pump the breast by electrical pump on the third day following delivery. Exclusion criteria: infants with low birth weight, low Apgar scores, intrauterine growth retardation, and any illnesses or congenital abnormalities; mothers with diabetes, hypertension, bronchial asthma, any allergies, and any breast problems such as inverted nipples, mastitis, and a history of smoking, alcohol, or any drug use	<b>Mean milk volume (SD)</b> (mL) by pumping both breasts for 15 mins on day 3 postpartum, no info of timing: Fenugreek (F) 73.2 (53.5) Placebo (P) 38.8 (16.3) Control (C) 31.1 (12.9) Kruskal-Wallis test for 3 groups, p= 0.004 Mann-Whitney U test for F vs P, p=0.003; F vs C, p= 0.05.	hrs (0 [IQR 0-30] in the intervention group and 0 [0-30] in the control group, p = 0.198). Women in the intervention group were more frequent to consume all food served as compared to controls (75.8% and 63.3% respectively, p = 0.032). Maximum weight loss as % of birth weight (SD) F 5.7 (2.6); P 6.6 (2.2); C 8.3 (2.2) Kruskal-Wallis test for 3 groups, p= 0.003 Mann-Whitney U test for F vs P, p=0.001; F vs C, p= 0.02 Time to regain birth weight (SD) (day) F 6.7 (3.2); P 7.3 (2.7); C 9.9 (3.5) Kruskal-Wallis test for 3 groups, p= 0.007 Mann-Whitney U test for F vs P, p=0.004; F vs C, p= 0.01	No obvious side effects reported by participants.
Ushiroyama et al. (2007) [30] RCT Japan	Xiong-gui-tiao-xue-yin Aims: To evaluate the efficacy by assessing enhancement of lactation and changes in the plasma prolactin and oxytocin levels.	6 g/day treatment drug or 0.375 mg/day ergometrine Started right after delivery to Day 6	Treatment (n = 41) Ergometrine (n = 41) Inclusion criteria: had spontaneous labour pain followed by a normal delivery Exclusion criteria: breech presentation; gestational toxico-sis; diabetes mellitus; multiple conception; or premature rupture of membranes during pregnancy	Breast milk volume (SD) (g) by 24hr test weighing: Day 4: Treatment 277 (21) Ergometrine 155 (61) p = 0.042 Day 5: Treatment 342.6 (43.6) Ergometrine 245.5 (59.4) p = 0.038 Day 6: Treatment 414 (68)	Plasma prolactin level (SD) (ng/mL), Day 1: Treatment (T) 158 (78) Ergometrine (E) 129 (65) p = 0.037 Day 6: T 168(95), E 117 (54) p = 0.0024 Plasma oxytocin level was significantly higher in Ergometrine group at day 1 (p = 0.024) but no differences at day 6 (results only shown in figure).	No obvious adverse effect.

Study design	and Galactagogue and study aims	Dosage and timeframe	study	Subjects and recruiting criteria	Effect on milk volume	Other effects on milk production	Reported side effects
Wang et al. (2018) [31] RCT China	Zengru Gao (An OTC mixed herbal product of eight herbs: Semen Vaccariae, Medulla Tetrapanacis, Radix Rehmanniae Praeparata, Radix Angelicae Sinensis, Radix Paeoniae Alba, Rhizoma Chuanxiong, Herba Leonuri, Radix Trichosantheri) Aims: To evaluate the breast milk enhancing effects and to record any maternal side effects.	Zengru Gao (Z): 30 g, 3x day. Control (C): no administration. All participants received similar level of breastfeeding education and health professional consultation. From day 1 to day 7 postpartum.		Z (n = 256) C (n = 271) Inclusion criteria: Women aged 20-35 years, willing to breastfeed at the time in the hospital, no illnesses to contraindicate breastfeeding or severely compromise its success, with one healthy singleton newborn, ≥ 37 weeks' gestation, ≥2500 birth weight, Apgar score ≥ 8. Exclusion criteria: Women with history of adverse reaction to either drug; women taking other medication that might be contraindicated; not contactable by telephone after discharge.	Ergometrine 293 (98.5) p = 0.0046 Not evaluated.	Breastfeeding was defined as mother's milk given by direct breast feeding. Full breastfeeding: no other types of milk or solids. Partially breastfeeding, sustained latch with deep rhythmic sucking through the length of the feed, with some pause, on either/or both breasts. Number (%) of fully/partially breastfeeding, at day 1: Z 15 (5.86)/41 (16.02), C 23 (8.49)/54 (19.93), p = 0.078 Day 3: Z 70 (27.34)/126(49.22), C 62 (22.88)/122(45.02), p = 0.037 Day 7: Z 183(71.48)/53 (20.7), C 159 (58.67)/82 (30.26), p = 0.003 Mean volume (SD) of infant formula intake (mL), day 1: Z 134.24 (105.76), C 133.14 (105.5), p = 0.885 Day 3: Z 107.09 (123.85), C 121.33 (124.57), p = 0.146 Day 7: Z 55.46 (115.39), C 90.66 (153.89), p = 0.005	Fifteen other/newborns (5.42%) reported adverse effect: 4 cases of infant diarrhea, 3 cases of infant allergies; 4 cases of cough, 2 case of upper respiratory tract infections, 1 case of dry pharynx, and 1 case of neonatal hyperbilirubinemia. Six blind investigators independently assessed side effect of the medication and suggested all the adverse effects were irrelevant to the medication.
<b>Term infant, &gt; 7 days postpartum at the baseline or unclear</b>							
Bumrungpert et al. (2018) [32] Double-blinded RCT	Commercial herbal mixture of fenugreek, ginger, turmeric Aims:	3 capsule 3x day containing 200 mg fenugreek seed, 120 mg ginger,		Herb (n = 25) Placebo (n = 25) Inclusion criteria: Women aged 20 to 40 years, 1 month postpartum with exclusive breastfeeding, willing to participate.	<b>Mean milk volume (SD)</b> (mL/day) by manually pumping for 2 days at the baseline:	No significant differences of milk composition between the baseline and Week 4. % Change: Energy (kcal/100 mL):	The liver function and kidney function tested by blood test, no significant difference between two groups before and after the intervention (data not reported).

Study and design	Galactagogue and study aims	Dosage and study timeframe	Subjects and recruiting criteria	Effect on milk volume	Other effects on milk production	Reported side effects
Thailand	To examine the effects on human milk volume, nutrient content, and adverse effects.	and 100 mg turmeric per capsule. 4-week duration Infant aged 1 month at the baseline.	Exclusion criteria: having chronic disease; using a galactagogue herb or medicine; smoking; drinking; twins, separated from their infants.	Herb 710 (216) Placebo 736 (179) P = 0.425 Week 2: Herb 1030 (264) Placebo 805 (181) P = 0.003 Week 4: Herb 1399 (312) Placebo 896 (185) P < 0.001	Herb -1.59 (19.68) Placebo -0.95 (9.48), p=0.979 Carbohydrate (g/100 mL): Herb 1.64 (5.94) Placebo 1.18 (3.63), p = 0.673 Protein (g/100 mL): Herb 1.43 (9.47) Placebo -1.13 (9.04), p=0.791 Fat (g/100 mL): Herb 0.3 (15.35) Placebo -1.47 (11.1), p=0.5 Vitamin A (µg/100 mL): Herb 1.52 (9.16) Placebo -3.46 (8.59), p=0.06 Calcium (mg/100 mL): Herb: 3.15 (9.46) Placebo 2.37 (3.41), p=0.801 Iron (mg/100 mL): Herb: 3.5 (8.72) Placebo 3.11 (6.71), p=0.25	Other effects evaluated by interview of individual participant. Excessive rectal gas: 2 cases in each group. Maple syrup smelling urine: 2 cases in herb group. No adverse effect in infants.
Demirci et al. (2016) [33] Pilot randomised feasibility study US	Commercial herb mixture containing fenugreek ( <i>Trigonella foenum-graecum</i> ), blessed thistle ( <i>Cnicus benedictus</i> ), nettle ( <i>Urtica dioica</i> ), and fennel ( <i>Foeniculum vulgare</i> ). Aims: To compare the feasibility and acceptability of two CAM	1 capsule 4x day or 2 capsules 3x day for women over 79 kg, talking with ≤ 30 ml water. 9-day duration Infant aged 1 – 3 weeks postpartum at the baseline.	Herb (n = 6) Meditation (n = 4) Inclusion criteria: Currently providing any breast milk, intention to provide breast milk exclusively for at least 2 months, breastfeeding or pumping at least 6 times per day and perception of low or insufficient milk supply. Exclusion criteria: Conditions with potential to affect milk supply (e.g., hypothyroidism, polycystic ovarian syndrome).	Median volume (range) (mL) by test weighing for 1 feed: The baseline H: 32 (20 - 81); M: 23 (9 - 43) Day 9 H: 60 (-1 - 100); M: 33 (8 - 163) Median volume (range) (mL) by 1 expression: The baseline H: 55.5 (12 - 114); M: 78 (43 - 110) Day 9 H: 77.5 (15 - 131); M: 68 (31 - 78) Data was presented for individual	Self-reported % feed of breast milk, median (range): The baseline H: 59 (8-100); M: 100 (38-100) Day 9 H: 65 (8-100); M: 95 (0-100) Mothers' perception of insufficient milk (average of 1–7 Likert scale): The baseline: H: 4.5; M: 5 Day 9: H: 3; M: 4 Number of exclusively breastfeeding Day 9: H: 2; M: 1 Follow up to 2 months postpartum H: 1; M: 0	Adverse effect evaluated by interviews. Perceived infant side-effects (n=1); headache (n=1), nausea (n=1), maple-syrup smell sweat (n= 2), and increased perspiration (n=1)

Study design	Galactagogue and study aims	Dosage and timeframe	study	Subjects and recruiting criteria	Effect on milk volume	Other effects on milk production	Reported side effects
	interventions for treatment of PIM.				participant, without statistical analysis.		
Di Pierro et al. (2008) [34] RCT Peru	Milk thistle ( <i>Silybum Marianum</i> ) Aim: To demonstrate the galactagogue effect of micronized silymarin in healthy lactating women.	420 mg/d micronized silymarin (a standardized extract) 63-day duration No report of standardised start time point		Milk thistle (n = 25) Placebo (n = 25) Inclusion criteria: no anomalies or diseases found by psychological, medical, pharmacological and objective examination; borderline in terms of normal daily milk production (around 700 mL/day)	<b>Mean milk volume</b> (SD) by 24-hr test weighing plus pumping after each feed (g): Day 0 Milk thistle 601.92 (65.12) Placebo 503.36 (69.37) No significant difference. Day 30 Milk thistle 989.76 (102.33) Placebo 649.76 (78.35) p< 0.01 Day 63 Milk thistle 1119.24 (115.89) Placebo 700.56 (95.66) p< 0.01	Milk composition (no report of analysis method), mean (SD): Water: day 0 Milk thistle 86.8 (0.2) Placebo 86.8 (0.4) Day 30 Milk thistle 87.9 (0.6) Placebo 87.2 (0.8) Day 63 Milk thistle 87.5 (0.6) Placebo 86.9 (0.5) Fat: day 0 Milk thistle 3.7 (0.3) Placebo 3.4 (0.3) Day 30 Milk thistle 2.6 (0.1) Placebo 2.7 (0.2) Day 63 Milk thistle 2.9 (0.1) Placebo 3.1 (0.2) Protein: day 0 Milk thistle 1.2 (0.02) Placebo 1.2 (0.02) Day 30 Milk thistle 1.1 (0.09) Placebo 1.2 (0.1) Day 63 Milk thistle 1.1 (0.1) Placebo 1.2 (0.09) Carbohydrates: day 0 Milk thistle 7.1 (0.09) Placebo 7.2 (0.1) Day 30 Milk thistle 7.4 (0.004) Placebo 7.4 (0.04)	Not reported.

Study and design	Galactagogue and study aims	Dosage and timeframe	study Subjects and recruiting criteria	Effect on milk volume	Other effects on milk production	Reported side effects
					Day 63 Milk thistle 7.8 (0.3) Placebo 7.6 (0.4)	
Ghasemi et al. (2014) [35] RCT Iran	Fennel Aim: To determine the effect of herbal tea containing Fennel seed on breast milk sufficiency signs and growth parameters of Iranian infants.	7.5g 3x day 4-week duration Infant aged 0-4 months	Fennel (n = 39) Placebo (n = 39) Inclusion criteria: Term girl infant, birth weight 2500 - 4000 g, normal ability of sucking, non-initiation of complementary feeding Exclusion criteria: Using any galactagogues or infant formula during the study; mother and infant with diseases contradiction with breastfeeding such as infection with HIV; addiction to narcotic substances and alcohol; untreated active tuberculosis using special medicines such as phenobarbital and ergotamine etc.; women under breast cancer treatment; breast problems such as breast nipple indentation, abscess, mastitis; asthma; cardiac diseases; blood clotting diseases and diabetes.	Not evaluated.	Significant increases of following factors were found in the fennel group (p < 0.001): mean <b>infant weight</b> (SD) (g) from 5261.0 (1167.7) to 6393.3 (1083.4); mean infant head circumferences (SD) (cm) from 38.6 (2.2) to 40.2 (2.0); the number of wet diapers (SD) from 5.5 (1.1) to 8.5 (1.2), the frequency of defecation (SD) 1.8 (1.0) to 2.6 (1.1); and the number of breastfeeding in 24 hrs (SD) from 9.9 (1.9) to 16.7 (1.6); but no significant increase in placebo group. No significant increase in infant height in both groups.	Not reported.
Ghasemi et al. (2015) [36] RCT Iran	Fenugreek Aim: To determine the effect of herbal tea containing fenugreek seed on the signs of breast milk sufficiency in Iranian girl infants.	7.5g 3x day 4-week duration Infant aged 0-4 months, mean (SD) age (day) at the baseline: Fenugreek: 71.02 ± 33.78 Placebo: 61.82 ± 32.76 No differences.	Fenugreek (n = 39) Placebo (n = 39) Inclusion criteria: Term girl infant, birth weight 2500 - 4000 g, normal ability of sucking, non-initiation of complementary feeding Exclusion criteria: Using any galactagogues or infant formula during the study; mother and infant with diseases contradiction with breastfeeding such as infection with HIV; addiction to narcotic substances and alcohol; untreated active tuberculosis using special medicines such as phenobarbital and ergotamine etc.; women under breast cancer treatment; breast problems such as breast nipple indentation, abscess,	Not evaluated.	Significant increases of following factors were found in the fenugreek group (p < 0.001): mean <b>infant weight</b> (SD) (g) from 5282 (1021) to 6383 (952); head circumference from 38.3 (1.6) to 39.9 (1.5); number of wet nappies from 5.3 (0.9) to 8.2 (1.2); frequency of defecation from 1.9 (1.1) to 2.7 (0.9) and the number of feeds from 9.2 (1.4) to 16.0 (1.5). No significant effect on infant length variation (P = 0.078). No significant difference of the above factors in the control	Not reported.

Study design	and Galactagogue and study aims	Dosage and timeframe	and study	Subjects and recruiting criteria	Effect on milk volume	Other effects on milk production	Reported side effects
				mastitis; asthma; cardiac diseases; blood clotting diseases and diabetes.		group before and after the intervention.	
Gupta et al. (2011) [37] RCT India	Shatavari ( <i>Asparagus racemosus</i> ) Aims: To evaluate the galactagogue efficacy by direct measurement of the prolactin hormone level and assessment of the secondary outcome measures.	1 capsule containing shatavari root powder 60 mg/kg of body weight 30-day duration Infant aged up to 6 months (average 2.8 months)	3x day	Shatavari (n = 30) Placebo (n = 30) Inclusion criteria: mother aged 20-40 yrs; infant up to 6 months; having one or more of the following symptoms: deficient lactation, infant's crying just after feeding, painful sensation in breasts during the time of feeding, loss of appetite in mother or the manifestation of any anxiety disorder which could affect the lactation	Not evaluated.	<b>Mean % increase in prolactin level</b> (SD): S 32.9 (6.5), P 9.6 (4.6), $p < 0.05$ Mean % increase in infant weight (SD): S 16.13 (3.65), P 5.68 (2.57), $p < 0.05$ Mean % increase in mothers' weight (SD): S 3.78 (0.68), P 1.37 (0.44), $p < 0.05$ Mean increase in scores of satisfaction in lactation, measured by graded scale (1-5, 1=unsatisfied and 5 = highly satisfied) (SD): S 1.54 (0.28), P 0.48 (0.33), $p < 0.05$ Mean increase in scores of overall well-being & happiness of infants, measured by graded scale (1-5, 1=unsatisfied and 5 = highly satisfied) (SD): S 1.27 (0.45), P 0.29 (0.23), $p < 0.05$	No acute oral toxicity in mice, but long-term study in mice found mortality at the dose of 5000 mg/kg. Not reported in human trial.
Huynh et al. (2018) [38] Multicentre RCT Vietnam	Maternal nutritional supplementation (MNS) providing 252 kcal, 16.8 g protein, 1.4 g fat and 39.2 g carbohydrate. Aims: To determine the effects on the proportion of	2 servings MNS per day + breastfeeding support From third trimester in pregnancy to 12 weeks postpartum		MNS (n = 104) Control (n = 100) Inclusion criteria: Healthy pregnant women aged 20 - 35 years, first-time mother with a singleton pregnancy (gestation 26 - 29 weeks), pre-pregnancy BMI $< 25.0 \text{ kg/m}^2$ Exclusion criteria: Smoke; Allergy or intolerance to any ingredient in the supplement; gestational diabetes; pre-eclampsia, adverse maternal or fetal conditions that could have potential effects on child's growth and/or development; preterm ( $< 37$	Infant breast milk intake (g) measured by 24-h test weighing the infants with the baseline mid-upper arm circumference (MUAC) $< 50^{\text{th}}$ percentile at 12 weeks postpartum: MNS (n = 54) 695.1 (209.1)	<b>The proportion of breastfeeding at 12 weeks postpartum</b> , evaluated by daily record of infant feeding: The intervention was 2.09 times more likely to exclusively breastfeed over the 12 weeks than the control (95% CI: 1.05–4.13, $p = 0.0358$ ) after controlling for mother's age and MUAC at the baseline, infant	Case (%) of adverse effect: MNS 17 (15.0%) Control 11 (9.7%). Majority was gastrointestinal disorders: MNS 7 cases Control 6 cases.

Study design	Galactagogue and study aims	Dosage and timeframe	study	Subjects and recruiting criteria	Effect on milk volume	Other effects on milk production	Reported side effects
	exclusively breastfeeding, birth, and growth outcomes of the offspring.			weeks' gestation); birth weight <2500 g; mother or infant required intensive care admission >24 hrs after delivery	Control (n = 47) 646.5 (234.6) No significant difference. After controlling for mother's age, MUAC, wealth index score, infant sex, study site, and visit, infants in MNS group consumed 64.2 g more milk than control group over 12 weeks postpartum (p = 0.0251)	sex, delivery mode, and study sites. Longitudinal growth from birth to 12 weeks (95% CI), intervention compared to control (as reference) after controlling for mother's age, mother's MUAC at baseline, wealth index score, gestational age, infant's sex, and visit: Weight (g): 68.7 (-34.2, 171.7), p = 0.1922 Length (cm): 0.27 (-0.1, 0.6), p = 0.1419 Head circ (cm): 0.26 (0.005, 0.52), p = 0.0473 After controlling for mother's age, wealth index score, infant sex, visit, and study site: Weight-for-age z-score: 0.16 (-0.03, 0.36), p = 0.0636 Length-for-age z-score: 0.19 (-0.01, 0.39), p = 0.0690 Head-for-age z-score: 0.28 (0.05, 0.51), p = 0.0183	
Ikhlasiah et al. (2020) [39] One group pre-test post-test design Indonesia	Papaya leaf ( <i>Carica papaya</i> ) Aims: To determine the effect on increasing prolactin level and infant weight.	Moderate papaya leaf (the amount not provided), 80 mL boiled water, 20 mL star fruit water, and two tablespoons of honey: 2x day. 7-day duration Infant aged 0 – 6 months.	N = 10	Inclusion criteria: working mother (before and after having infants), with problem of the insufficient amount of breastfeed (no definition).	Not evaluated.	Mean prolactin level (ng/ml): Pretest: 89.12 Protest: 108.71 Mean infant weight (g): Pretest: 4800 Protest: 4965 No statistical analysis. Average increase in prolactin level: 19.59 ng/ml. Average increase in infant weight: 165 g.	Not reported.
Kim et al. (2013) [40] Retrospective survey	Pig's feet Aims: To retrospectively evaluate the	No information of dose and recipe.		Total respondents: n = 516. Women consumed pig's feet: n = 188.	Not evaluated.	Number of women perceived /not perceived effectiveness: 120 (65%) vs. 65 (35%).	Four cases of adverse effect with one reported cessation of consuming pig's feet due to moderate diarrhoea, no

Study design	and Galactagogue and study aims	Dosage and timeframe	study Subjects and recruiting criteria	Effect on milk volume	Other effects on milk production	Reported side effects
Korea	effects of pigs' feet consumption by Korean women.		Recruiting method: women were recruited at drug stores, shopping malls, and street corners in urban and rural areas in South Korea.		Number of only breastfeeding women who perceived /not perceived effectiveness: 73 (61%) vs. 16 (25%), p<0.001 Number of women would recommend pig's feet who perceived /not perceived effectiveness: 98 (82%) vs. 3 (4.6%), p<0.001. The proportion of women who perceived effectiveness significantly increased with advanced age (p = 0.001, data not provided).	detailed information provided for the other three cases.
Manjula et al. (2014) [41] RCT India	Pambadana ( <i>Gossypiumherba ceum Linn</i> ) Aim: To evaluate the Effectiveness in augmenting breast milk production.	10 g powder of seed divided in the same dose, 3x day. 4-week duration Infant aged 10-180 days	Pambadana (n = 30) Placebo (n = 15) Inclusion criteria: term baby without birth complication; birth weight > 2 kg; failure to regain birth weight at 15 days or supplementing feed $\geq$ 250 ml/day after 4 weeks Exclusion criteria: mothers with breast abscess, cracked nipples, epilepsy, psychosis, alcohol addiction, mastitis, previous breast surgery, tuberculosis, malignancy, and acquired immune deficiency syndrome and infants with prematurity and inborn errors.	Not evaluated.	<b>Supplementary feed (mL/day) (SD):</b> No significant differences between groups in each measurement before treatment. After treatment: Treatment (T) 40 (75.88) Placebo (P) 226.66 (149.84) P = 0.008 Infant weight, mean (SD): T 5790.66 (1121.4), P 5940 (885.44), p = 0.65 Mothers' perceptions after treatment measured by 5 points Likert scale (1=unsatisfied to 5=highly satisfied), mean (SD): Breast fullness: T 3.46 (0.94), P 1.93 (0.79) P = 0.001 Contralateral milk ejection: T 3.19 (1.14), P 1.93 (0.79) P = 0.001 Perceived supply increase: T 3.42 (0.92), P 1.93 (0.79) P = 0.001	No obvious side effects reported by participants.

Study and design	Galactagogue and study aims	Dosage and study timeframe	Subjects and recruiting criteria	Effect on milk volume	Other effects on milk production	Reported side effects
Mathew et al. (2018) [42] Randomised trial with two parallel groups India	Fenugreek vs. fennel Aims: To assess the effect of fenugreek and fennel on human lactation; to compare the effects of fenugreek and fennel on human lactation; to find an association between selected variables and lactation.	Fenugreek tea or fennel tea 300mL per day. Fenugreek/fennel seeds (14g), added with 2L boiled water and boiling for 10 minutes, added with honey or sugar as sweetener. 7-day duration. Infant aged 10 days up to 3 months.	Fenugreek (n = 15) Fennel (n = 15) Inclusion criteria: breastfeeding women aged 20-35 years with infant aged 10 days to 3 months.	Milk production evaluated by test weighing the infant before and after breastfeeding for seven days, milk volume not provided.	Mother's satisfaction regarding infant happiness and wellbeing T 3.52 (1.07), P 1.93 (0.79) P = 0.001  Mean pre-test vs. post-test lactational levels (no description of the measurement): Fenugreek: 4.584 vs. 4.75, p < 0.05 Fennel: 4.566 vs. 4.729, p < 0.05 Comparison of fenugreek and fennel at the endpoint, p = 0.96 Comparison of true weight gain with the average (approximate) ideal weight gain, t = 4.55, p < 0.05.	Not reported.
Mehta (2014) [43] Post marketing surveillance study India	Lactancia Powder, a commercial product containing multivitamin, minerals, amino acid, DHA along with herbal blend of Shatavari Powder ( <i>Asparagus Racemosus</i> ), and Jivanti ( <i>Leptandenia Reticulata</i> ). Aim: To evaluate the effect on quantitative	30 g Lactancia Powder, 2x day 30-day duration. No report of infant age.	N = 1132 Inclusion criteria: women with insufficient/no breast milk at the time of delivery and women with preterm infant associated with insufficient milk production.	Not evaluated.	Reported lactation improvement (no description of measurement) in 1049 participants within a week: 492 reported increased supply in 3 days of treatment, 334 in 5 days and 223 in 7 days, (p < 0.001). 49% participants reported excellent improvement and 49% reported good improvement. 90% good compliance (no description of measurement). Infant weight (kg) pretest vs. posttest: 2.69 vs. 3.4.	Not reported.

Study design	and Galactagogue and study aims	Dosage and timeframe	study Subjects and recruiting criteria	Effect on milk volume	Other effects on milk production	Reported side effects
	improvement of breast milk, patient satisfaction, compliance and infant weight gain.					
Modepeng et al. (2021) [44] RCT Thailand	Date fruits Aims: To assess the effect of date fruits on breast milk quantity and infant nutritional status in 1-3 months postpartum.	Intervention group: 10 date fruits per day or 100 g/day. The intervention group and control group consumed their habitual dietary intake. 4-week duration. Infant aged 1-3 months.	Intervention (I) (n = 25) Control (C) (n = 23) Inclusion criteria: women aged 20–35 years, 1–3 months postpartum, infant only consuming breast milk indirectly. Exclusion criteria: smoking tobacco, drinking alcohol, having twin infants, and having breast problems during the week before the study enrolment.	Median milk volume (range) (mL/day) evaluated by exclusively expressing for 24 hours, at the baseline: I 580 (120-1110) C 545 (225-1080) No significant difference. Week 4: I 750 (400-1310) C 555 (335-1055) No statistical comparison.	Median change of milk volume (Q1, Q3), Week 0-2: I 45.0 (32.5, 95.0) C 5 (-7.50, 40.00), p = 0.002 Week 2-4: I 75.0 (-2.5, 161.3) C 5 (-25.00, 43.5), p = 0.017 Week 0-4: I 135.0 (60.0, 206.3) C 10 (-5.0, 40.00), p = 0.001. Median change of infant weight-for-age percentile (Q1, Q3), Week 0-4: I 0.90 (-4.80, 7.85) C -0.40 (-7.60, 2.7), p = 0.358.	Not reported.
Nordin et al. (2020) [45] RCT Malaysia	Banana flower (Musa x paradisiaca) Aim: To test the effectiveness in lactating women.	2 cookies per day (3.24 g/day banana flower extract) 1-month duration Infant aged 2 – 6 months	Banana flower (n = 29) Placebo (n = 29) Inclusion criteria: exclusively breastfeeding women aged 18 to 40 years, working < 9 hrs/day, healthy full-term infant aged 2 - 6 months, without complementary feeds. Exclusion criteria: history of smoking, alcohol, or any drug or herbs being used to improve breast milk production; low birth weight infant; low APGAR scores; intrauterine growth retardation; with any illnesses or congenital abnormalities.	<b>Mean expressed milk volume (SD)</b> (mL/day) by average of expressed milk in 5 working days, without indication of numbers of breastfeeding on the breasts: The baseline: Banana flower 380.02 (183.12) Placebo 344.38 (95.36) P = 0.36 Endpoint:	Infant BMI for age was 0.47 points higher than before the intervention in banana flower group (p = 0.001).	Not reported

Study and design	Galactagogue and study aims	Dosage and timeframe	study Subjects and recruiting criteria	Effect on milk volume	Other effects on milk production	Reported side effects
				Banana flower 454.34 (182.94) Placebo 360.56 (119.39) P = 0.002		
Pesak et al. (2021) [46] One group pre-test post-test design Indonesia	Papaya fruit Aim: To determine the effect on breast milk production.	Papaya fruit 200 g, 3x day. 7-day duration. Infant aged 0 – 6 months	N = 14. Inclusion criteria: breastfeeding women aged 20–35 years, with a gestation interval of 2 years, infant aged 0 – 6 months. Exclusion criteria: high blood pressure; heart disease; diabetes; history of labour by action experience of postpartum infection; history of breast cancer.	Not evaluated.	Number (%) of women in each group of breast milk production score, pretest: <3 (Low) 10 (71), 4-5 (Adequate) 4(29) >6 (high) 0. Posttest: Low 0, Adequate 2 (13), High 12 (87). Mean milk production score (SD) pretest vs. posttest: 2.21 (0.80) vs. 6.36(0.75), p=0.001. No description of the measurement of milk production score.	Not reported.
Renityas (2018) [47] One group pre-test post-test design Indonesia	Moringa leaf extract and acupressure point cancong. Aims: To evaluate the effectiveness of moringa leaf extract and cancong point massage in increase of breast milk volume.	2 capsules per day, containing moringa leaf extract 320 mg. Participants also received 2x acupressure treatment. 1-month duration Infant age at the baseline was not reported.	N = 20. No information of inclusion criteria and exclusion criteria.	No information of how milk volume was evaluated.	Number of women in each group before and after the treatment, before: <200 ml/day: 8, 200-400ml/day: 7, >400 ml/day: 5. After: <200 ml/day: 0, 200-400 ml/day: 3, >400 ml/day: 17.	Not reported.
Sumarni et al. (2020) [48] Experimental study with pre and post control group design Indonesia	Moringa oleifera Aims: To analyse the effect in increasing breast milk production and nutrient content in breast milk.	Moringa oleifera cookies 50 g/day, no information of content of moringa in the cookies. Duration: 1 month. Infant age 0 – 4 months.	Moringa (n = 10) Control (n = 7) Inclusion criteria: Breastfeeding women with infants aged 0-4 months selected by purposive sampling technique. Exclusion criteria: Not reported.	Not evaluated.	Mean fat content (SD) in intervention group, analysed by liquid extraction method: Pretest: 2.86 (0.11) Posttest: 2.87 (0.11), p = 0.145 Mean protein content (SD) in intervention group, analysed by spectrophotometric method: Pretest: 1.51 (0.16)	Not reported.

Study design	and Galactagogue and study aims	Dosage and timeframe	and study	Subjects and recruiting criteria	Effect on milk volume	Other effects on milk production	Reported side effects
						<p>Posttest: 1.57 (0.13), p = 0.029 Mean carbohydrate content (SD) in intervention group, analysed by Luffschool method: Pretest: 7.17 (0.52) Posttest: 7.23 (0.68), p = 0.565 Mean Vit A content (SD) in intervention group, analysed by spectrophotometric method: Pretest: 0.0067 (0.0008) Posttest: 0.0067 (0.0072), p = 1 No significant differences in milk composition between groups at the endpoint.</p>	
Wada et al. (2019) [49] One group pilot pre-test post-test design Japan	Domperidone Aim: To evaluate the effects of domperidone for Japanese mothers with insufficient lactation.	10 mg, 3x day. 14-day duration. Started after 2 weeks postpartum, without accurate starting time.		N = 10. Inclusion criteria: Women with insufficient lactation and adequate breastfeeding support and effort, infants hospitalized in the neonatal intensive care unit. Insufficient lactation was defined as expressed <300 mL/day or provide <160 mL/kg per day to the infant. Adequate breastfeeding support and effort was confirmed by expressing ≥ 6x day. Exclusion criteria: Allergy to domperidone; already taking domperidone; a history of breast surgery.	Median milk volume (range) (mL/day) by expression diary: Pretest: 60 (2–310) Posttest: 176 (11–400).	70% participants had >1.5 times increase in milk volume, median 2.8 times (range 1.8–5.4). Median serum prolactin level (range) (ng/mL): Pretest: 46 (4–128) Posttest: 167 (59–356) No correlation between blood prolactin level and expressed milk volume (data not provided).	Two mild adverse events: headache in one case and abdominal pain in another case. No adverse events were observed in infants.
Wagner et al. (2019) [50] Double-blind RCT US	Mother's milk tea, a commercial tea, each teabag containing: 560 mg bitter fennel fruit, 350 mg anise fruit, 210 mg coriander fruit, 35 mg fenugreek seed, 35 mg blessed thistle herb Aim:	3–5 cups/day Mother's milk tea (MMT) or placebo tea (PT). 4-week duration. Infant age 0 – 2 months.		MMT (n = 31) PT (n = 29) Inclusion criteria: exclusively breastfeeding or fully breastfeeding mothers with no milk production issues, agreed to continue to breastfeed their infants exclusively or fully during the study, maternal age 18 - 45 years, BMI <50 or without morbid obesity, with a singleton infant age 2 – 3 weeks, ≥37 weeks' gestation. Exclusion criteria: allergic reactions or sensitivity to any of the component herbs in MMT or cross-reactive plant species; specific chronic illnesses (diabetes, hypertension, bronchial asthma, Gastroesophageal Reflux Disease, atopic	Not evaluated.	Perceived infant satisfaction with volume of milk, rating, 5-points scale, Mean (SE): Baseline: MMT 4.27 (0.11) PT 4.32 (0.1), p = 0.588 2 weeks: MMT 4.35 (0.11) PT 4.21 (0.11), p = 0.567 4 weeks: MMT 4.24 (0.09) PT 4.29 (0.11), p = 0.64 Perceived milk volume evaluated by a scale from 0 to 10, with 0 being no milk to 10 being engorged. No significant	Mean number days (SD) without symptoms, mothers: MMT 24.9 (5.09) PT 20.14 (5.44), p = 0.58 Infants: MMT 17.55 (8.75) PT 19.69 (7.58), p = 0.32 Mean number days (SD) of digestive symptoms, mothers: MMT 1.71 (2.38) PT 2.62 (5.19), p = 0.39 Infants:

Study design	and Galactagogue and study aims	Dosage and timeframe	study Subjects and recruiting criteria	Effect on milk volume	Other effects on milk production	Reported side effects
	To evaluate the safety among exclusively (no other liquids or foods) or fully (water and breast milk) breastfeeding women and their infants.		dermatitis, celiac disease or gluten sensitivity, Crohn's disease, ulcerative colitis, eating disorders, breast cancer, blood disorder, mental health disorders); pre-pregnancy BMI >50 consistent with morbid obesity; history of alcohol, drug abuse, or cigarette smoking; and reported intake of diuretics, pseudoephedrine, anticholinergics, warfarin (or any anticoagulant agent), estrogen-containing birth control pill or estrogen-containing device, selective serotonin reuptake inhibitor (SSRI), or drugs/herbals used to induce milk production.		differences between two groups at each visit, no data provided. Breastfeeding Self-Efficacy Scale, Mean (SE): Baseline: MMT 60.7 (0.97) PT 62.56 (1.0), p = 0.189 Week 2: MMT 61.35 (0.97) PT 62.87 (1.0), p = 0.281 Week 4: MMT 61.96 (0.97) PT 63.7 (1.0), p = 0.219 No differences between MMT and PT at each visit in psychological measurements such as World Health Organization Quality of Life Scale, Satisfaction With Life Scale, State/Trait Anxiety Inventory or Edinburgh Postnatal Depression Scale. All analysis adjusted for maternal age, infant age, and maternal parity. Follow up to 3, 6, 9 and 12 months found no difference in the proportion of breastfeeding between two groups.	MMT 5.19 (5.58) PT 4.86 (7.51), p = 0.85 Mean number days (SD) of respiratory symptoms, mothers: MMT 1.68 (3.0) PT 1.72 (3.17), p = 0.95 Infants: MMT 2.35 (5.26) PT 0.66 (1.54), p = 0.09 Mean number days (SD) of dermatological symptoms, mothers: MMT 0.06 (0.25) PT 0.03 (0.19), p = 0.60 Infants: MMT 1.97 (5.22) PT 1.83 (4.42), p = 0.91 Mean number days (SD) of breast symptoms: MMT 1.68 (2.52) PT 1.31 (1.83), p = 0.52 Mean number days (SD) of other symptoms, mothers: MMT 0.74 (1.48) PT 0.55 (1.4), p = 0.61 Infants: MMT 1.55 (5.48) PT 0.55 (1.57), p = 0.34

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### Appendix 3 Sample size calculation based on human milk oligosaccharides concentration change (Chapter 3)

It is assumed that the total human milk oligosaccharides (HMO) concentration change in the yeast supplement group is 80% of that in the placebo group. It is further assumed that the total HMO concentration change is skewed distributed, and the variance is equal to 0.3-fold of the median of the total HMO concentration in both groups. These assumptions were based on findings from longitudinal studies on HMO concentration at 1 – 9 months postpartum [1-7].

The following equation was used to calculate the sample size [8]. Where:  $m_1 = 1$  (median in the placebo group at the endpoint);  $m_2 = 0.8$  (median in the yeast supplement group at the endpoint);  $\phi_1 = \phi_2 = 0.3$  (variances);  $z_{\alpha/2} = 1.96$  (5% significance level); and  $z_{\beta} = 0.84$  (80% power). The number of participants required in each group was 32.

$$n = \frac{(\sigma_1^2 + \sigma_2^2) (z_{\frac{\alpha}{2}} + z_{\beta})^2}{(\log(m_1) - \log(m_2))^2} = \frac{\left[ \log\left(\frac{1}{2} + \sqrt{\frac{1}{4} + \frac{\phi_1^2}{m_1^2}}\right) + \log\left(\frac{1}{2} + \sqrt{\frac{1}{4} + \frac{\phi_2^2}{m_2^2}}\right) \right] (z_{\frac{\alpha}{2}} + z_{\beta})^2}{(\log(m_1) - \log(m_2))^2}$$

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**Appendix 4 Timeline of changes in study design and recruitment procedures of the randomised placebo-controlled trial (Chapter 3)**

<b>Time</b>	<b>Activities</b>	<b>Outcomes and changes in study design</b>
October 2018 – May 2019	Ethics approval, trial registration and preparation of recruitment	Primary outcome: volume of breast milk evaluated by hourly expression. Secondary outcomes: milk composition, women’s perception of breast milk supply, postnatal distress, infant feeding patterns, Infant anthropometric measurements, adverse effects.
May 2019 – February 2020	Recruitment Ethics approval for changes in study settings	Extended recruitment area so that it covered from Palmerston North (PN) to Wellington City along the west coast.
March 2020 – October 2020	Suspended recruitment for 3 months due to COVID-19 pandemic Ethics approval for changes in study design	Changed the primary outcome from milk volume to measuring the change of total HMO concentration and consequently changed sample size. Changed inclusion criteria from exclusively breastfeeding infant aged 1 – 4 months to all types of breastfeeding infant aged 1 – 7 months. Reduced the number of visits from three to two, shorter visit time (less than one hour) and reduced pumping/expressing to once per visit.
October 2020 – July 2021	Recruitment	Primary outcome: HMO concentration. Secondary outcomes: women’s perception of breast milk supply, postnatal distress, infant feeding patterns, Infant anthropometric measurements, adverse effects.

**Appendix 5 Ethics approval for the qualitative study (Chapter 4)**



**MASSEY UNIVERSITY**  
TE KUNENGA KI PŪREHUROA

25 September 2014

Lili Jia  
6/513 Church Street  
**PALMERSTON NORTH 4410**

Dear Lili

**Re: HEC: Southern A Application – 14/68**  
**How health professionals and breastfeeding women in New Zealand use food and herbs to support breastfeeding women: A pilot study**

Thank you for your letter dated 24 September 2014.

On behalf of the Massey University Human Ethics Committee: Southern A I am pleased to advise you that the ethics of your application are now approved. Approval is for three years. If this project has not been completed within three years from the date of this letter, reapproval must be requested.

If the nature, content, location, procedures or personnel of your approved application change, please advise the Secretary of the Committee.

Yours sincerely

A handwritten signature in black ink, appearing to read "B Finch".

Dr Brian Finch, Chair  
**Massey University Human Ethics Committee: Southern A**

cc Dr Janet Weber  
IFNHH  
PN452

Dr Louise Brough  
IFNHH  
PN452

A/Prof Rachel Page, Acting HoI  
IFNHH  
**WELLINGTON**

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**Massey University Human Ethics Committee**  
**Accredited by the Health Research Council**  
Research Ethics Office, Research and Enterprise

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## **Appendix 6 Interview guides for postnatal healthcare professionals and breastfeeding mothers in the qualitative study (Chapter 4)**

### **Interview guide (for professionals)**

1. New moms often worry about if they have enough milk. According to the literature, lack of milk is a most common reason to stop breastfeeding at an early stage. You may also have similar cases in your practice. Would you please talk about how you deal with mothers' concerns about insufficient milk production?

*Probes: Is there any order when using different therapies (methods of management)? Is there any difference in management during different stages of breastfeeding? How to tell the difference between perceived lack of milk and actual lack of milk? Are there any changes after addressing perceived insufficient milk production?*

2. Many herbs and foods are suggested to increase breast milk, these are called galactagogues. People may have different opinions on the use of galactagogues. Some people believe they are effective while others may worry about the safety. How do you usually recommend galactagogues in practice?

*Probes: In what situation do you prescribe galactagogues? Have you ever prescribe any medicine to increase breast milk production? What specific herbs or foods do you recommend? Do your patients ask for directions about using galactagogues? What kind of information do they usually ask for? (Efficacy, safety, dosage, duration, what time to take, etc.) If you don't use galactagogues, why?*

3. Any policy or guidelines influence your recommendation of galactagogues?
4. Did you use any herbs or foods to increase your own milk supply when you were breastfeeding?
5. How do you find out information about galactagogues?

*Probes: Do you attend courses, meetings and workshops about galactagogues? Do you communicate with other professionals about galactagogues? Do you read books and other publications about galactagogues?*

## Interview guide (for breastfeeding women)

1. New moms often worry about if they have enough milk. According to the literature, lack of milk is a most common reason to stop breastfeeding at early stage. Some working moms also complain about milk supply drops when they came back work. Based on your experience, would you please talk about how you deal with concerns about milk supply?

*Probes: What methods did you use? How effective are they? Have you been to consult any professionals?*

2. Many herbs and foods are suggested to increase breast milk. Have you ever used them? Have they been suggested to you?

*Probes: By who are you suggested? What is your response to suggestion?*

3. People may have different opinions on the use of special foods or herbs to increase milk supply. Some of them believe they are effective while others may worry about the safety. What are your thoughts?

*Probes: In what situation do you use special foods or herbs? Why do you consider using special foods or herbs? What specific herbs or foods do you use? Do you ask for directions about using special foods or herbs from the professionals? Do they prescribe any medicine to increase breast milk? What kind of information do you care about? (Efficacy, safety, dosage, duration, what time to take, transfer into milk, harm to the baby etc.) If you don't use any special foods or herbs, why?*

4. Have you heard of any *special foods or herbs to increase milk supply* based on your culture?

5. How do you find out information about *special foods or herbs to increase milk supply*?

## Appendix 7 Ethics approval letter for the randomised placebo-controlled trial (Chapter 7)



Date: 26 February 2019

Dear Lili Jia

Re: Ethics Notification - SOA 18/80 - Randomised controlled study of the effects of brewer's yeast on milk production in breastfeeding women - the Breastfeeding and Brewer's Yeast (BaBY) Study

Thank you for the above application that was considered by the Massey University Human Ethics

Approval is for three years. If this project has not been completed within three years from the date of this letter, reapproval must be requested.

If the nature, content, location, procedures or personnel of your approved application change, please advise the Secretary of the Committee.

Yours sincerely



Professor Craig Johnson  
Chair, Human Ethics Chairs' Committee and Director (Research Ethics)

## BaBY Study - baseline

---

**Please tick to indicate you consent to the following:**

I have read, or have had read to me in my first language, and I understand the Participant Information Sheet.

I have been given sufficient time to consider whether or not to participate in this study.

I am satisfied with the answers I have been given regarding the study and I understand that I may ask further questions at any time.

I understand that taking part in this study is voluntary (my choice) and that I may withdraw from the study at any time.

I consent to the research staff collecting and processing my information, including information about my health.

If I decide to withdraw from the study, I agree that the information collected about me up to the point when I withdraw may continue to be processed.

I understand that my participation in this study is confidential and that no material, which could identify me personally, will be used in any reports on this study.

I know who to contact if I have any questions about the study in general.

I will receive a summary of the results from the study.

By clicking the button below, you acknowledge that your participation in the study is voluntary, you are 18 years of age, and that you are aware that you may choose to terminate your participation in the study at any time and for any reason.

- I consent, I want to participate
- I do not consent, I do not wish to participate

*Skip To: End of Survey If Please tick to indicate you consent to the following: I have read, or have had r... = I do not consent, I do not wish to participate*

---

### Start of Block: Default Question Block

*Thank you so much for giving your precious time to participate in "BaBY" study. It will take 15-20 minutes to answer all the questions. Be assured that all answers you provide will be confidential. If you are not able to answer all the questions at once, please feel free to come back later. Your answers will be auto saved by the system.*

*Now I would like to ask you some questions about your feeding experience since your baby was born, what was working well and if there were any concerns, problems or difficulties. Some of the questions are open ended. You are welcome to give more details if all the options provided do NOT describe your situation.*

*Please note that this survey will be best displayed on a laptop or desktop computer. Some features may be less compatible for use on a mobile device.*

---

Please enter your study code: \_\_\_\_\_

Please indicate all the types of feeds given to your baby since he/she was born. (Mark all that apply to you.)

- Breastfeeding
- Antenatal expressed colostrum
- Expressed colostrum/breast milk after your baby was born
- Donor's breast milk (including donor's colostrum)
- Formula
- Oral Rehydration Salts
- Drops and syrups (vitamins, minerals, medicines)
- Other \_\_\_\_\_

Please recall all the ways you have fed your baby since she/he was born. (Mark all that apply to you.)

- At the breast
- From wet nurse
- Spoon or cup feeding
- Finger feeding
- From a bottle
- From a syringe
- Supplementary nursing system (lactation aid)
- Other \_\_\_\_\_

*Display This Question:*

*If Please indicate all the types of feeds given to your baby since he/she was born. (Mark all that a... = Breastfeeding*

*Or Please recall all the ways you have fed your baby since she/he was born. (Mark all that apply to... = At the breast*

How often did you feed your baby at the breast since your baby was born?

- Whenever she/he wants (feed on demand)
- Every 2-3 hours as scheduled
- Both (scheduled + demand feeding)
- Other \_\_\_\_\_

**End of Block: Default Question Block**

**Start of Block: Pumping**

Have you pumped or expressed since your baby was born?

- Yes
- No

*Display This Question:*

*If Have you pumped or expressed since your baby was born? = Yes*

Why have you pumped or expressed? (Mark all that apply to you.)

- Allow others to feed the baby
- Breast problems (inverted nipple, sore/cracked nipple etc.)
- I will be away from my baby (back to work, travel etc.)
- Illness
- My baby is not able to feed from my breasts (tongue-tie, in neonatal unit, difficulty with latching etc.)
- Increase my milk supply
- Too much milk
- To store some milk for the future
- Donate some milk
- Other \_\_\_\_\_

**End of Block: Pumping**

---

**Start of Block: Formula**

Is your baby having any formula or donor's milk? (If chose 'Yes', please enter how many millilitres (mL) of formula/donor milk was fed yesterday, for example 300.)

- Yes, formula \_\_\_\_\_
  - Yes, donor's milk \_\_\_\_\_
  - No
- 

*Display This Question:*

*If Is your baby having any formula or donor milk? (If chose 'Yes', please enter how many millilitres... = Yes, formula*

*Or Is your baby having any formula or donor milk? (If chose 'Yes', please enter how many millilitres... = Yes, donor milk*

Was yesterday a typical day, in as much as any day is typical?

- Yes
- Every day is very different
- No (please explain) \_\_\_\_\_

**End of Block: Formula**

---

**Start of Block: Other foods**

Is your baby having other drinks or foods besides breast milk and/or formula?

- Yes
- No

**End of Block: Other foods**

---

**Start of Block: Reasons to stop EBF/BF**

*Display This Question:*

*If Please indicate all the types of feeds given to your baby since he/she was born. (Mark all that a... = Formula*

*Or Please indicate all the types of feeds given to your baby since he/she was born. (Mark all that a... = Oral Rehydration Salts*

*Or Please indicate all the types of feeds given to your baby since he/she was born. (Mark all that a... = Drops and syrups (vitamins, minerals, medicines)*

*Or Please indicate all the types of feeds given to your baby since he/she was born. (Mark all that a... = Other*

*Or Is your baby having any formula or donor milk? (If chose 'Yes', please enter how many millilitres... = Yes, formula*

*Or Is your baby having any formula or donor milk? (If chose 'Yes', please enter how many millilitres... = Yes, donor milk*

*Or Is your baby having other drinks or foods besides breast milk and/or formula? = Yes*

Why have you fed your baby with formula, donor's milk and/or other foods? (Mark all that apply to you.)

- My baby had trouble sucking or latching on
- I had nipple problems (e.g. inverted nipple, sore/cracked nipple)
- Breastfeeding was too painful
- I was ill
- My baby was ill or in neonatal unit
- Premature baby
- My baby was not gaining enough weight
- I don't have enough milk
- My partner wanted to feed the baby
- To help baby sleep
- My baby is ready for solid food
- Breastfeeding is time consuming
- I need to go back to work
- Pumping or expressing is too stressful
- I can't get enough milk with pumping
- Other \_\_\_\_\_

*Display This Question:*

*If Why have you fed your baby with formula, donor milk and/or other foods? (Mark all that apply to y... = My baby had trouble sucking or latching on*

*Or Why have you fed your baby with formula, donor milk and/or other foods? (Mark all that apply to y... = I had nipple problems (e.g. inverted nipple, sore/cracked nipple)*

*Or Why have you fed your baby with formula, donor milk and/or other foods? (Mark all that apply to y... = Breastfeeding was too painful*

*Or Why have you fed your baby with formula, donor milk and/or other foods? (Mark all that apply to y... = I was ill*

*Or Why have you fed your baby with formula, donor milk and/or other foods? (Mark all that apply to y... = My baby was ill*

*Or Why have you fed your baby with formula, donor milk and/or other foods? (Mark all that apply to y... = My baby was not gaining enough weight*

*Or Why have you fed your baby with formula, donor milk and/or other foods? (Mark all that apply to y... = I don't have enough milk*

*Or Why have you fed your baby with formula, donor milk and/or other foods? (Mark all that apply to y... = My partner wanted to feed the baby*

*Or Why have you fed your baby with formula, donor milk and/or other foods? (Mark all that apply to y... = To help baby sleep*

*Or Why have you fed your baby with formula, donor milk and/or other foods? (Mark all that apply to y... = My baby is ready for solid food*

Or Why have you fed your baby with formula, donor milk and/or other foods? (Mark all that apply to y... =  
 Breastfeeding is time consuming  
 Or Why have you fed your baby with formula, donor milk and/or other foods? (Mark all that apply to y... =  
 I need to go back to work  
 Or Why have you fed your baby with formula, donor milk and/or other foods? (Mark all that apply to y... =  
 Pumping or expressing is too stressful  
 Or Why have you fed your baby with formula, donor milk and/or other foods? (Mark all that apply to y... =  
 I can't get enough milk with pumping  
 Or Why have you fed your baby with formula, donor milk and/or other foods? (Mark all that apply to y... =  
 Other  
 Carry Forward Selected Choices from "Why have you fed your baby with formula, donor milk and/or other  
 foods? (Mark all that apply to you.)"

Please rank the reasons for giving expressed milk, formula or other food. These are the reasons you have given in last question ('1' means that the reason is most important). If more than 5 reasons are given please just rank the top 5 reasons.

- \_\_\_\_\_ My baby had trouble sucking or latching on
- \_\_\_\_\_ I had nipple problems (e.g. inverted nipple, sore/cracked nipple)
- \_\_\_\_\_ Breastfeeding was too painful
- \_\_\_\_\_ I was ill
- \_\_\_\_\_ My baby was ill
- \_\_\_\_\_ My baby was not gaining enough weight
- \_\_\_\_\_ I don't have enough milk
- \_\_\_\_\_ My partner wanted to feed the baby
- \_\_\_\_\_ To help baby sleep
- \_\_\_\_\_ My baby is ready for solid food
- \_\_\_\_\_ Breastfeeding is time consuming
- \_\_\_\_\_ I need to go back to work
- \_\_\_\_\_ Pumping or expressing is too stressful
- \_\_\_\_\_ I can't get enough milk with pumping
- \_\_\_\_\_ Other

**End of Block: Reasons to stop EBF/BF**

---

**Start of Block: Milk supply**

Generally speaking, I believe my breasts make the right amount of milk to satisfy my baby.

- No, I make too much
- Yes, just right
- Sometimes not enough
- Often not enough
- Not sure

*Display This Question:*  
 If Generally speaking, I believe my breasts make the right amount of milk to satisfy my baby. != Yes, just right

Please explain what happened to make you think that? \_\_\_\_\_ A

*Display This Question:*  
 If Generally speaking, I believe my breasts make the right amount of milk to satisfy my baby. != Yes, just right

What have you done about it?

- Just carried on
- Block feeding (feed on one side for 2-3 hours or more)
- Expressed milk
- Added formula
- Talked to health professionals (midwife, lactation consultant, GP etc.)
- Talked to complementary or alternative practitioner (homeopath, naturopath, herbalist, traditional Chinese medicine practitioner etc.)
- Talked to family and/or friends
- Searched for information from books/magazines/Internet
- Took special herbs/herbal products
- Took special foods
- Other \_\_\_\_\_

Please indicate your agreement or disagreement with each following statement by marking the best answer:

	Strongly agree	Somewhat agree	Neither agree nor disagree	Somewhat disagree	Strongly disagree	N/A
I think it's extremely difficult to breastfeed my baby	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
I think my milk is of good quality	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
I think my milk is nutritious enough to nourish my baby	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
My baby generally appears satisfied with the amount of breast milk received from feedings at my breasts	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Most of the time my baby seems settled	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
I think my baby is crying a lot because of not getting enough milk	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
I think my baby sleeps well during the night even if he/she wakes up for breastfeeding	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
My partner believes that I have adequate milk for my baby/ never questions my milk supply	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

	Strongly agree	Somewhat agree	Neither agree nor disagree	Somewhat disagree	Strongly disagree	N/A
My important family members (e.g. mother, grandmother or mother-in-law etc.) believe that I have adequate milk for my baby / never questions my milk supply	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
My friends believe that I have adequate milk for my baby / never questions my milk supply	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
The health professionals I have seen since my baby was born (midwife, lactation consultant etc.) believe that I have adequate milk for my baby / never question my milk supply	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

*Display This Question:*

*If Please indicate your agreement or disagreement with each following statement by marking the best... = I think it's extremely difficult to breastfeed my baby [ Strongly agree ]*

*Or Please indicate your agreement or disagreement with each following statement by marking the best... = I think it's extremely difficult to breastfeed my baby [ Somewhat agree ]*

Please tell us what was it about your baby's behavior that made it difficult to breastfed your baby.

**End of Block: Milk supply**

**Start of Block: BF problems**

Have you had any of the following problems with your breasts since your baby was born? (Mark all that apply to you.)

- I have not had any problems with my breasts or nipples
- Engorgement
- Sore nipple
- Cracked nipple
- Thrush
- Blocked ducts
- Breast pain
- Mastitis
- Psoriasis / Skin problems on breast
- Raynaud's / Nipple blanching and vasospasm
- Ulcer
- Other \_\_\_\_\_

Did your baby have any of the following problems since he/she was born? (Mark all that apply to you.)

- Did not have any problems
- Difficulty with latching on to the breast
- Tongue-tie/lip-tie
- Cleft lip/palate
- Thrush
- Very sleepy
- Very Jaundiced
- Abdominal/tummy pain
- Reflux
- Colic
- Failure to thrive
- Unsettled/ cry a lot
- Other \_\_\_\_\_

**End of Block: BF problems**

**Start of Block: Postnatal distress**

Please read each statement and circle a number 0, 1, 2 or 3 which indicates how much the statement applied to you over the past week. There are no right or wrong answers. Do not spend too much time on any statement.

*The rating scale is as follows:* 0 Did not apply to me at all 1 Applied to me to some degree, or some of the time 2 Applied to me to a considerable degree, or a good part of time 3 Applied to me very much, or most of the time

I found it hard to wind down	▼ 0 ... 3
I was aware of dryness of my mouth	▼ 0 ... 3
I couldn't seem to experience any positive feeling at all	▼ 0 ... 3
I experienced breathing difficulty (eg, excessively rapid breathing, breathlessness in the absence of physical exertion)	▼ 0 ... 3
I found it difficult to work up the initiative to do things	▼ 0 ... 3
I tended to over-react to situations	▼ 0 ... 3
I experienced trembling (eg, in the hands)	▼ 0 ... 3
I felt that I was using a lot of nervous energy	▼ 0 ... 3
I was worried about situations in which I might panic and make a fool of myself	▼ 0 ... 3
I felt that I had nothing to look forward to	▼ 0 ... 3
I found myself getting agitated	▼ 0 ... 3
I found it difficult to relax	▼ 0 ... 3
I felt down-hearted and blue	▼ 0 ... 3
I was intolerant of anything that kept me from getting on with what I was doing	▼ 0 ... 3
I felt I was close to panic	▼ 0 ... 3
I was unable to become enthusiastic about anything	▼ 0 ... 3

I felt I wasn't worth much as a person	▼ 0 ... 3
I felt that I was rather touchy	▼ 0 ... 3
I was aware of the action of my heart in the absence of physical exertion (eg, sense of heart rate increase, heart missing a beat)	▼ 0 ... 3
I felt scared without any good reason	▼ 0 ... 3
I felt that life was meaningless	▼ 0 ... 3

**End of Block: Postnatal distress**

**Start of Block: Health status and life style**

*Now I would like to know what happened in your life relating to your health status since your baby was born.*

Have you taken any medications or natural/herbal products with the purpose of influencing your milk supply since your baby was born?

- Yes
- No

Have you taken any other supplements or natural/herbal products since your baby was born?

- Yes
- No

Have you taken oral contraceptive pills (birth control pills) since your baby was born?

- Yes
- No

Have you taken any other medications (including prescribed and/or Over the Counter) since your baby was born?

- Yes
- No

*Display This Question:*

*If Have you taken any medications or natural/herbal products with the purpose of influencing your mi... = Yes*

*Or Have you taken any other supplements or natural/herbal products since your baby was born? = Yes*

*Or Have you taken oral contraceptive pills (birth control pills) since your baby was born? = Yes*

*Or Have you taken any other medications (including prescribed and/or Over the Counter) since your ba... = Yes*

Please fill in the table below with information about the medication(s), supplements, and/or natural/herbal products you have taken since your baby was born.

	Product name	Reason for taking	When started (date dd/mm/yyyy)	Dose (xx mg/day or xx tablets/capsules per day)	When stopped (date dd/mm/yyyy) or for how long taken (xx days)
Product 1					
Product 2					
Product 3					
Product 4					
Product 5					
Product 6					
Product 7					
Product 8					

Have you taken any special foods (either manufactured or homemade) with the purpose of influencing your milk supply since your baby was born?

- No
- Yes

*Display This Question:*

*If Have you taken any special foods (either manufactured or homemade) with the purpose of influe... = Yes*

Please fill in the table below with information about the special food(s) you have taken with the purpose of influencing milk supply since your baby was born.

	Food name	Recipe or main ingredients	When started (date)	How much did you take every day (xx g or xx serves)	When stopped (date dd/mm/yyyy) or for how long taken (xx days)
Food 1					
Food 2					
Food 3					
Food 4					
Food 5					
Food 6					
Food 7					
Food 8					

Did you have any health problems since your baby was born?

- Yes
- No

*Display This Question:*

*If Did you have any health problems since your baby was born? = Yes*

Please specify the problem. \_\_\_\_\_

Do you have any of the following problems since your baby was born?

	Always	Most of the time	About half the time	Sometimes	Never
Constipation	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Nausea	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Decreased appetite	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Skin rash	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

How often do you smoke since your baby was born?

- Not at all
- Occasionally
- 1-5 cigarette per day
- 6-10 cigarette per day
- More than 11 cigarette per day
- Other \_\_\_\_\_

---

How often have you drunk alcohol since your baby was born?

- Not at all
  - Occasionally
  - 1-3 times a week
  - 4-6 times a week
  - Daily
  - More than once per day
  - Other \_\_\_\_\_
- 

*Display This Question:*

*If How often have you drunk alcohol since your baby was born? != Not at all*

How much did you usually drink each time?

- Less than or up to one standard drink (one bottle (330mL) of beer or a glass (100mL) of wine or 30mL of straight spirits @ 42% alcohol)
- More than one standard drink (one bottle (330mL) of beer or a glass (100mL) of wine or 30mL of straight spirits @ 42% alcohol)
- Sometimes one standard drink or less and sometimes more than one standard

**End of Block: Health status and life style**

---

**Start of Block: Birth information**

*Now I would like to ask you some questions about your labour and birth, and early hours after birth.*

When was your baby born (please enter as dd/mm/yyyy)? \_\_\_\_\_

What was your estimated due date of birth (please enter as dd/mm/yyyy)? \_\_\_\_\_

What is the gender of your baby?

- Male
- Female
- Undetermined

What was your baby's birth weight (please enter as "xxxx" g, e.g. 3560)? \_\_\_\_\_

Where was your baby born?

- Hospital
  - Birth unit
  - Home
  - Other place
- 

*Display This Question:*

*If Where was your baby born? = Hospital  
Or Where was your baby born? = Birth unit*

In hospital/birth unit was your baby in the same room with you?

- Not in the same room
- Most time
- 24 hours/day

Did you have caesarean delivery?

- Yes
- No

---

Were any of the following medications used during the labour and birth? (Mark all that apply to you.)

- Didn't use any medications
- Don't know if used anything
- Entonox
- Epidural/Spinal
- Oxytocin
- Pethidine
- Morphine
- Fentanyl
- Other \_\_\_\_\_

Was your baby admitted to the neonatal care unit?

- Yes
- No

*Display This Question:*

*If Was your baby admitted to the neonatal care unit? = Yes*

Please describe the reason the baby was in neonatal unit. \_\_\_\_\_

*Display This Question:*

*If Was your baby admitted to the neonatal care unit? = Yes*

How old was your baby when he/she was finally discharged from the neonatal care unit? \_\_\_\_\_

When was your baby put to your breast after birth?

- ≤ 1 hour
- 1-2 hours
- 2-5 hours
- 5 hours+

---

Did you (or anyone else) hold your baby skin-to-skin within 30 minutes of birth?

- Yes
- No

**End of Block: Birth information**

---

**Start of Block: Demographics**

*At last I would like to ask a few questions about you so we can compare the participants to the NZ population.*

---

How many children do you have? \_\_\_\_\_

What is your age? \_\_\_\_\_

Which Ethnic group do you belong to? (Mark all that apply to you.)

- New Zealand European
- Māori
- Samoan
- Cook Islands Māori
- Tongan
- Niuean
- Chinese
- Indian
- Other (eg Dutch, Japanese, Tokelauan), please state:  
\_\_\_\_\_

What is the highest level of education you have completed?

- No secondary school qualification
- Secondary school qualification or NCEA 1-3 or NZQF 1–4
- Diploma or Trade Certificate or NZQF 5–6
- Bachelors Degree or NZQF level 7 qualification
- Higher Degrees (postgraduates, masters, PhD)

Who are you currently living with? (Here, 'people living with you' means people who share a private dwelling and normally spend four or more nights a week in the household. They must share consumption of food OR contribute some portion of income towards the provision of essentials for living as a group. Please mark all that apply to you.)

- My partner
- Child(ren)
- My parent(s)
- My partner's parent(s)
- Other
- Just myself

What is your total annual household income before tax? (Here 'household' means all the persons living with you together as marked in the last question.)

- ≤ \$34,100
- \$34,101-\$60,299
- \$60,300-\$89,799
- \$89,800-\$135,099
- \$135,100+
- Prefer not to say

*Thank you for your time and input. Next survey will be taken at one week after you start to take the study capsules. We look forward to hearing from you again.*

Appendix 9 Supplementary Table: Effectiveness of *Saccharomyces cerevisiae* yeast-based supplement (SCYS) on milk production in animals (Chapter 6)

References	Study animal	Study design	Daily dose	Administration	Daily milk yields or litter weight	Other benefits
<b>Ruminant animals</b>						
Dobicki et al. [1]	Cow, Holstein-Friesian N = 75	No information. Daily milk yield were determined once a month at the Milk Analysis Laboratory.	*SCYS: 200 g/animal *YCWP: 20 g/animal	Supplementation from 7 days prior to the estimated calving date to 100 days of lactation. SCYS group: dried yeast (Leiber BT) containing 40% yeast cells. YCWP group: MOS (Biolex MB 40) containing 40-50% MOS and beta-glucans.	Milk yields at 100 day: SCYS: 26.780 ± 4.459 <sup>A</sup> kg MOS: 25.993 ± 5.707 <sup>A</sup> kg Control: 23.810 ± 4.765 <sup>B</sup> kg <sup>A,B</sup> P≤0.01	Milk SCC was significantly lower (P≤0.01) in SCYS group. The number of bacteria in the rumen fluid was significantly higher (P≤0.01) in SCYS and MOS groups (n = 24).
Kuczaj et al. [2]	Cow, Holstein-Friesian (Red-white) N = 50	Animals randomly assigned to 2 groups. Daily milk yield was conducted once a month (official control).	*SCYS: 200 g/animal	Supplementation from 3 weeks before calving to 100 days lactation with added SCYS (Leiber BT) containing 40% yeast cells.	Milk yields at 100 day: SCYS: 29.84 ± 4.80 kg Control: 28.60 ± 4.82 kg P> 0.05	Milk fat and dry matter were significantly higher (P< 0.05) in SCYS group in the first month. Maternal blood urea was significantly higher (P≤0.01) and blood albumins and globulins were significantly lower (P≤0.01 and ≤0.05 respectively) in SCYS group (n = 16). Milk SCC was significantly lower (P<0.05) in SCYS group in the first two months.
Westland et al. [3]	Cow, Holstein cross Friesian N = 80	80 cows randomly assigned to 2 groups prepartum with colostrum obtained from 59 cows. Colostrum collected by Fullwood® mobile milking machine (Fullwood Ltd,	*MOS: 2 g/animal	Supplementation prepartum from drying off until point of calving over 6 months. No information of the MOS.	Colostrum yields immediately post-calving: MOS: 7.5 ± 0.69 kg Control: 5.6 ± 0.43 kg P = 0.02	No significant differences of IgG in colostrum between two groups.

References	Study animal	Study design	Daily dose	Administration	Daily milk yields or litter weight	Other benefits
		Ellesmere, Shropshire, UK) within 40 minutes of calving.				
Aung et al. [4]	Cow, Holstein N = 32	2×2 factorial arrangement (2 treatments × 2 LP) LP = lactation period, early lactation means day in milk <120, and mid lactation means >120 Cows were milked twice a day and milk yields were automatically recorded at each milking.	*YCWP: 10 g/animal	Ten-week experiment with first 2 weeks as adaptation period and last 8 weeks as experimental period, with added YCWP (SafMannan; Phileo, Lesaffre Animal Care, France)	Milk yields: Control: Early lactation: 25.52±1.96 kg Mid lactation: 24.48±1.73 kg YCWP: Early lactation: 28.97±1.54 kg Mid lactation: 22.83±1.82 P = 0.627 (treatment) P = 0.117 (treatment × LP)	In early lactation groups, maternal blood total cholesterol and non-esterified fatty acid/total cholesterol ratio was significantly lower in treatment group. In early lactation groups, 4% fat corrected milk and energy corrected milk was higher (p = 0.063 and 0.065 respectively) in treatment group.
Milewski & Sobiec [5]	Ewe, Polish long-wool Kamieniec N = 26	Animals divided into 2 equal groups. No information of randomisation and blind assessment. Daily milk yield was determined by the results of milking after an injection of oxytocin.	*SCYS: 30 g/animal	Supplementation for 70 days lactation period after birth, with added SCYS (Inter Yeast®, Krośniewice).	Milk yields: Day 28: SCYS: 1895.00 ml Control: 1603.31 ml P< 0.01 Day 70: SCYS: 1121.54 ml Control: 970.77 ml P< 0.05	On day 28 blood erythrocytes and leukocytes, blood glucose and Na+ (P≤0.05), blood haemoglobin and haematocrit and blood Cl- (P≤0.01) were significantly higher and blood creatinine was significantly lower (P≤0.01) in SCYS group. On day 70 blood leukocyte, blood glucose and Na+ (P≤0.05), blood Cl- (P≤0.01) were significantly higher and blood creatinine was significantly lower (P≤0.01) in SCYS group.
Zabek et al. [6]	Ewe, Polish long-wool Kamieniec N = 26	Animals divided into 2 equal groups. No information of randomisation and blind assessment. No information of milking.	*Beta-glucan: 0.18g/animal (adding beta-glucan as 3 g/kg of CJ mixture at the daily dose of	Supplementation from birth to 70 days of lactation with added beta-glucan (Biolex®-Beta S Leiber GmbH) containing 70% of beta-1,3/1,6-D-glucan not	Milk yields: Day 28: Control: 1596.15 ± 181.90 ml Glucan: 1812.31 ± 231.31 ml P< 0.01 Day 70: Control: 998.46 ± 187.69 ml	Milk SCC was significantly lower (P≤0.05) in glucan group on day 28. Milk fat was significantly higher (P≤0.01) in glucan group on both day 28 and day 70. Milk protein was significantly higher (P≤0.05) in glucan group on day 70.

References	Study animal	Study design	Daily dose	Administration	Daily milk yields or litter weight	Other benefits
			0.6 kg/animal). Assume feeding at equal level.	changing the chemical composition of the feed.	Glucan: 1138.69 ± 155.46 ml P< 0.01	Blood gamma globulin, lysozyme activity, respiratory burst activity, potential killing activity, MTT-ConA (RI) and MTT- LPS (RI) were significantly higher (p≤0.01) in glucan group on both day 28 and day 70.
Zabek et al. [7]	Ewes, Kamieniec N = 39	Animals divided into 3 equal groups. No information of randomisation and blind assessment. Daily milk yield was determined by the results of morning milking after an injection of oxytocin.	*SCYS: 15 g/animal	Experimental group I supplementation from late pregnancy to 70 days of lactation, experimental group II supplementation from birth to 70 days of lactation. Supplementation with SCYS (Inter Yeast S).	Milk yields: Day 28 Group I: 1868.46±268.88 <sup>a</sup> ml Group II: 1927.54±439.58 <sup>a</sup> ml Control: 1603±164.89 <sup>b</sup> ml Day 70 Group I: 1078.46±168.22 ml Group II: 1164.61±286.84 <sup>a</sup> ml Control: 970.77±158.87 <sup>b</sup> ml <sup>a,b</sup> P<0.05	Milk SCC was significantly lower in supplementation groups on day 28 and day 70 (P≤0.01 and ≤0.05 respectively). Higher value of blood gamma globulin, lysozyme activity, respiratory burst activity, MTT-ConA (RI) and MTT- LPS (RI) were observed in group I on both day 28 and day 70, compared to the other two groups (P≤0.01). Ceruloplasmin activity and potential killing activity in group I were significantly higher (P≤0.01) than control on both days. All these parameters except for gamma globulin in group II were significantly higher (P≤0.01) than control on both days.
Zabek et al. [7]	Ewes, Kamieniec N = 26	Animals divided into 2 equal groups. No information of randomisation and blind assessment. Daily milk yield was determined by the results of morning milking after an injection of oxytocin.	*SCYS: 15 g/animal	Supplementation from birth to 70 days of lactation with added SCYS (Inter Yeast S).	Milk yields: Day 28 SCYS: 1860.15±320.46 ml Control: 1596.15±181.90 ml P<0.05 Day 70 SCYS: 1277.92±175.47 ml Control: 998.46±187.69 ml P<0.01	Milk SCC was significantly lower (P≤0.05) in SCYS group on day 28. Blood gamma globulin, lysozyme activity and MTT-ConA (RI) (P≤0.01) as well as respiratory burst activity, potential killing activity and MTT- LPS (RI) (p≤0.05) were significantly higher in SCYS group on day 28.

References	Study animal	Study design	Daily dose	Administration	Daily milk yields or litter weight	Other benefits
						All these 6 parameters were significantly higher ( $P \leq 0.01$ ) in SCYS group on day 70.
Zaleska et al. [8]	Ewe, Polish long-wool N = 120	Animals divided into 3 equal groups. Milk yield evaluated from 8 randomly selected ewes nursing singleton in each group. Daily milk yield was determined by the results of morning milking after an injection of oxytocin.	*SCYS: 50 g/kg feed Beta-glucan: 3 g/kg feed	Supplementation 3-week preparation for tugging + from lambing to 70 days lactation. SCYS group: dried yeast (Inter Yeast®) Glucan group (G): beta-glucan (Biolex® Beta-S) containing over 70% (1,3)-(1,6)- $\beta$ -D-glucan.	Milk yields: Day 28 SCYS: 1850.00 $\pm$ 231.02 <sup>a</sup> ml G: 1795.00 $\pm$ 211.59 <sup>a</sup> ml Control: 1567.50 $\pm$ 172.69 <sup>b</sup> ml Day 70 SCYS: 1373.50 $\pm$ 212.86 <sup>A</sup> ml G: 1268.50 $\pm$ 70.05 <sup>A</sup> ml Control: 1055.00 $\pm$ 155.56 <sup>B</sup> ml <sup>a,b</sup> $P < 0.05$ , <sup>A,B</sup> $P < 0.01$	On day 28 milk fat and dry matter were significantly higher ( $P \leq 0.01$ ) in glucan group and milk dry matter was significantly higher ( $P \leq 0.01$ ) in SCYS group, compared to the control group. On day 70 milk fat and dry matter were significantly higher ( $P \leq 0.01$ and $\leq 0.05$ respectively) in glucan group and milk fat was significantly higher ( $P \leq 0.05$ ) in SCYS group, compared to the control group.
Gomes et al. [9]	Goat, Saanen N = 24	Animals randomly assigned to 3 $\times$ 2 factorial design (3 diets $\times$ 2 parity orders). Goats were milked manually twice a day and milk yields of individual goat was measured at each milking.	**SCYS group: 234.1 g/kg feed SCYS plus soybean meal group (SCYS+S): 97.2 g/kg feed Goats were fed <i>ad libitum</i> .	SCYS in substitution to soybean meal. Diet in SCYS groups provided the same crude protein in dry matter as in soybean meal group (S). The experiment was conducted from 21 days to 200 days of lactation. No information of source of yeast.	Milk yields (an average of daily milking): 21 – 60 days: SCYS: 3.06 $\pm$ 0.23 kg SCYS+S: 2.94 $\pm$ 0.23 kg S: 3.21 $\pm$ 0.23 kg 60 – 130 days: SCYS: 2.88 $\pm$ 0.37 kg SCYS+S: 2.79 $\pm$ 0.37 kg S: 3.75 $\pm$ 0.37 kg 130 – 200 days: SCYS: 2.71 $\pm$ 0.24 kg SCYS+S: 2.69 $\pm$ 0.24 kg S: 3.34 $\pm$ 0.24 kg No significant difference.	

References	Study animal	Study design	Daily dose	Administration	Daily milk yields or litter weight	Other benefits
De Lima et al. [10]	Goat, Saanen N = 18	Completely randomized design. Goats were milked twice a day and milk yields of individual goat was recorded at each milking.	**SCYS group: 229.0 g/kg feed SCYS plus soybean meal group (SCYS+S): 102.0 g/kg feed Goats were fed <i>ad libitum</i> .	SCYS in substitution to soybean meal. Diet in SCYS groups provided the same crude protein in dry matter as in soybean meal group (S). The experiment was conducted from 60 days to 150 days of lactation. Yeast grown on sugar cane.	Milk yields: SCYS: 2.2 kg SCYS+S: 2.3 kg S: 2.3 kg P = 0.923	Milk produced by SCYS+S group contained significantly higher fat and total solids than SCYS group (P<0.05). Milk production efficiency (kg of milk produced/kg of crude protein ingested) was significantly higher in SCYS group compared to SCYS+S and S groups (P<0.05).
<b>Pigs</b> Czech et al. [11]	Sow, Polish Landrace breed N = 32 in Experiment 1 and Experiment 2 respectively	No information.	*MOS: 8 g/animal	Supplementation 4 weeks prepartum and 4 weeks postpartum with added MOS (Bio-MOS, Alltech, US). The diet in Experiment 1 contained 40% wheat; Experiment 2 contained 40% triticale.	Litter weight in Experiment 1 At birth: MOS: 22.29 kg Control: 19.43 kg P = 0.032 Day 14: MOS: 59.67 kg Control: 48.17 kg P = 0.016 Day 28: MOS: 103.77 kg Control: 84.69 kg P = 0.013 No difference in Experiment 2	In both experiments, MOS groups had significantly lower piglet losses compared to the control groups (P≤0.05). In Experiment 1, MOS group had significantly higher contents of colostrum IgG and IgM from 1 hour to 48 hours after birth (P≤0.05). In Experiment 2, MOS group had significantly higher content of colostrum IgG from 1 hour to 48 hours after birth (P≤0.05), and significantly higher content of colostrum IgM from 1 hour to 12 hours after birth (P≤0.05). In both experiments, MOS group had significantly higher content of milk IgG at 21st day of age (P≤0.05).

References	Study animal	Study design	Daily dose	Administration	Daily milk yields or litter weight	Other benefits
Szuba-Trznadel et al. [12]	Sow, crossbred (Polish Large White × Polish Landrace) N = 40	No information.	*Beta-glucan: Experimental group I: 100 ppm feed, Experimental group II: 200 ppm feed, Experimental group III: 300 ppm feed	Supplementation from day 80 of gestation to day 21 of lactation (weaning) with added purified (1,3)-(1,6)-β-D-glucan (Betamune®, 80% purity). Piglets started supplementation from day 10 of lactation to the end of experiment with the same dose as sows.	Piglet body weight Day 2: Experimental I: 1.64 ± 0.23 kg Experimental II: 1.66 ± 0.12 kg Experimental III: 1.63 ± 0.12 kg Control: 1.58 ± 0.25 kg No significant difference. Day 21: Experimental I: 7.20 ± 0.70 kg Experimental II: 6.98 ± 0.70 kg Experimental III: 6.95 ± 0.67 kg Control: 6.73 ± 0.80 kg No significant difference. Day 45: Experimental I: 14.63 ± 0.58 kg Experimental II: 15.11 ± 0.62 <sup>b</sup> kg Experimental III: 15.05 ± 0.60 <sup>b</sup> kg Control: 14.27 ± 0.62 <sup>a</sup> kg <sup>a,b</sup> P<0.05	Milk whey γ-globulin was significantly higher (p<0.01) in Experimental I and Experimental II groups compared to control group on day 21. Sow serum α-globulin was significantly higher (p<0.01) in Experimental II group compared to control group on day 2. Sow serum γ-globulin was significantly higher (p<0.01) in Experimental II group compared to control group on day 21. Piglet serum α-globulin was significantly higher (p<0.05) in all Experimental groups compared to control group on day 2. Piglets in experimental groups had significantly lower (p<0.01) feed conversion ratio from day 21 to day 45 compared to control group.
Graugnard et al. [13]	Sow, no information of breed N = 218	Randomized complete block design 62 milk samples collected from individual sows from week 1 to week 4, 22 from control and 40 from treatment group	*MOS: 900 mg/kg feed	Supplementation from day 100 of gestation to day 23 of lactation (weaning) with added MOS (Actigen™, Alltech Inc., Nicholasville, KY, US)	Litter weight At birth: MOS: 19.7 kg Control: 19.1 kg P = 0.2 Adjusted wean weight MOS: 7.0 kg Control: 7.0 kg P = 1.0	Milk protein, total solids less fat and IgG were significantly higher (p = 0.01, p = 0.03 and p = 0.03 respectively) in MOS group. Intestinal gene expression in piglets from MOS group shown significantly higher (p<0.01) number of issue development, cell proliferation, cell growth and cell differentiation, as well as significantly lower (p<0.01) cell migration.

References	Study animal	Study design	Daily dose	Administration	Daily milk yields or litter weight	Other benefits
Duan et al. [14]	Sow, crossbred (Large White × Yorkshire, 4 ± 1 parity) N = 60	Completely randomized design with a 2 × 2 factorial treatment arrangement (2 treatment × 2 animal groups). Colostrum and milk samples were collected from 6 sows per group.	*MOS: Sow diet: 400 mg/kg feed Piglet diet: 800 mg/kg feed	Supplementation from day 86 of gestation to day 20 of lactation (weaning) with added MOS (Actigen, Alltech Inc., Nicholasville, US). Piglets started supplementation from day 7 of lactation to the end of experiment with the same MOS.	Piglet body weight At birth: MOS: 1.56 kg Control: 1.57 kg P = 0.86 Weaning: MOS: 6.10 kg Control: 5.69 kg P = 0.03	Piglet serum IgA and IgG concentrations at weaning were significantly higher (p<0.01) in group of sow diet supplementing MOS. Piglet serum complement 3, complement 4 and lysozyme were significantly higher (p<0.01, p = 0.05 and p<0.01 respectively) in group of sow diet supplementing MOS.
<b>Other animals</b>						
Wu et al. [15]	Doe, New Zealand White N = 30	Completely randomized design.	*Beta-glucan: Experimental group I: 0.064% of feed Experimental group II: 0.128% of feed	Supplementation from day 14 of gestation to day 28 of lactation (weaning) with added (1,3)-(1,6)-β-D-glucan (Allamond, Inc.) containing 16% glucan.	Litter weight: At birth: Experimental I: 364 ± 32 g Experimental II: 296 ± 46 g Control: 319 ± 41 g At weaning: Experimental I: 2245 ± 334 g Experimental II: 1960 ± 409 g Control: 2205 ± 421 g No significant difference.	Doe serum IgM was significantly (p<0.05) higher in experimental group I on lactation day 28. Does serum IgG was significantly (p<0.05) higher in experimental group II on lactation day 3 and significantly (p<0.05) higher in both experimental groups on lactation day 28.

MOS: manna oligosaccharides, SCC: somatic cell count, YCWP: yeast cell wall product.

\* Added in addition to the feeds.

\*\* Added as the substitute for soybeans as protein source.

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## Appendix 10 The calculation of nicotinic acid and folic acid intake from *Saccharomyces cerevisiae* yeast-based supplement and risk of approaching upper level, and estimation of Ochratoxin A intake for New Zealand women (Chapter 6)

The Australia/New Zealand Nutrient Reference Values (NRV) of nicotinic acid and folic acid are used for comparison the risk of approaching the upper level (UL) of each vitamin [1]. The upper level (UL) of nicotinic acid for lactation is set at 35 mg/day for women aged 19 and above; and folic acid from fortified foods or supplement for lactation is set at 1 mg/day for women aged 19 and above.

The calculation on nicotinic acid intake from SCYS is based on the following assumptions:

1. a breastfeeding woman (>18 years) consumes 30 g/day SCYS;
2. the concentration of nicotinic acid in SCYS is 1 mg/g, as per the highest value in Ahmad and Moat's study of SCY grown in culture added with 500 µg/ml tryptophan [2].

The estimated nicotinic acid intake is  $1 \text{ mg/g} \times 30 \text{ g/day} = 30 \text{ mg/day}$ , which is 85.7% of UL.

The calculation on folic acid intake from SCYS is based on the following assumptions:

1. a breastfeeding woman (>18 years) consumes 30 g/day SCYS;
2. the concentration of folic acid in SCYS is 0.045 mg/g, as per the highest value in Table 2 (75 µg DFE = 45 µg folic acid).

The estimated folic acid intake is  $0.045 \text{ mg/g} \times 30 \text{ g/day} = 1.35 \text{ mg/day}$ , which is 135% of UL.

The calculation of Ochratoxin A (OTA) intake is based on the following assumptions:

1. a breastfeeding woman (>18 years) consumes 30 g/day SCYS;
2. the SCYS contains 4.24 ng/g OTA as the highest level reported in Germany study [3];
3. the body weight of the woman is 70 kg;
4. the consumption of OTA from other source is 2.1 ng/kg body weight/day as the highest OTA dietary exposure for New Zealand women [4]

The estimated OTA intake is  $4.24 \text{ ng/g} \times 30 \text{ g/day} \times 7 \text{ days} \div 70 \text{ kg body weight} + 2.1 \text{ ng/kg body weight/day} \times 7 \text{ days} = 27.42 \text{ ng/kg body weight/week}$ .

We used the Provisional Tolerable Weekly Intake (PTWI) of OTA (100 ng/kg body weight/week) assessed by the FAO/WHO Expert Committee on Food Additives (JECFA) to do the calculation [5]. The estimated OTA intake is 27.4% of PTWI.

### Uncategorized References

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2. Ahmad, F. and A.G. Moat, *Nicotinic acid biosynthesis in prototrophs and tryptophan auxotrophs of *Saccharomyces cerevisiae**. Journal of Biological Chemistry, 1966. **241**(4): p. 775-780.
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4. Cressey, P. and A. Pearson, *FW14019 Dietary exposure to ochratoxin A and trichothecene mycotoxins: Risk estimates and proportionality of exposure source*, in *The New Zealand Mycotoxin Surveillance Program 06-14 Report Series*. 2014: Wellington.
5. JECFA, *Safety evaluation of certain food additives. Prepared by the sixty-eighth meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA)*. WHO Food Additive Series: 59, in *WHO Food Additive Series: 59*. 2008, World Health Organization: Geneva.



## BaBY Study - screening eligibility

*Thank you for your interest in our study. The purpose of the study is to evaluate how a yeast-based supplement influences breastfeeding. Participation in this study would last 4 weeks after your enrollment and you will be followed up to 6 months postpartum.*

*To see if you are eligible for this study, I need to ask you some questions about your health history and present condition. Some of these questions may be sensitive, such as questions about breast surgery and medication use. I may need to contact you to clarify or get more details. If you are eligible for the study, I will contact you within two days. If you are not eligible for this study or finally decide not to participate in this study, the information you give me will be destroyed immediately.*

What was your estimated due date of birth (please enter as dd/mm/yyyy)? \_\_\_\_\_

Do you have the following breast problems: (Mark the space or spaces that apply to you.)

- No (history of) breast problems
- History of breast surgery or breast cancer
- Previously diagnosed lack of breast tissue (by GP, gynaecologist, midwife or other health professionals)
- Others \_\_\_\_\_

Are you taking any medications (including prescribed and Over The Counter) regularly?

- No
- Yes

*Display This Question:*

*If Are you taking any medications (including prescribed and Over The Counter) regularly? = Yes*

Please give the name of the medication(s) you are taking in the text entry box bellow. \_\_\_\_\_

Have you ever been told by a doctor that you have chronic diseases or long-term illnesses? (A chronic disease is a physical or mental illness that has lasted, or is expected to last, for more than six months. The symptoms may come and go or be present all the time.)

- No
- Yes

*Display This Question:*

*If Have you ever been told by a doctor that you have chronic diseases or long-term illnesses? (A chr... = Yes*

Please describe your health problem in the text entry box bellow. \_\_\_\_\_

Is your baby having any formula or donor's milk? (If chose 'Yes', please enter how many millilitres (mL) of formula/donor's milk was fed yesterday, for example 300.)

- Yes, formula \_\_\_\_\_
- Yes, donor's milk \_\_\_\_\_
- No

Was your baby admitted to the neonatal unit?

- No
- Yes

*Display This Question:*

*Does your baby stay at the neonatal unit or hospital? = Yes*

Please describe what happened in the text entry box bellow. \_\_\_\_\_

Do you have any concerns regarding to your baby's health?

- No
- Yes

*Display This Question:*

*Do you have any concerns regarding to your baby's health? = Yes*

Please describe your concerns in the text entry box bellow. \_\_\_\_\_

Now please leave your contact details and we will contact you soon.

- Name \_\_\_\_\_
- Contact number \_\_\_\_\_
- Email \_\_\_\_\_

---

*Thank you for your input. We will contact you as soon as possible.*

## BaBY Study - Week 1/2/3

### Start of Block: Default Question Block

Welcome back to the "BaBY" study. And thank you very much for giving your precious time to participate in this study. It will take 5-10 minutes to answer all the questions. Be assured that all answers you provided will be confidential. If you are not able to answer all the questions at once, please feel free to come back later. Your answers will be auto saved by the system.

Now I would like to know how you managed breastfeeding in the last week and if there were any concerns, problems of taking the capsules. Some of the questions are open ended. You are welcome to give more details if all the options provided do NOT describe your situation.

Please note that this survey will be best displayed on a laptop or desktop computer. Some features may be less compatible for use on a mobile device.

Please enter your study code: \_\_\_\_\_

Please indicate all the types of feeds given to your baby since the last survey (about one week ago). (Mark all that apply to you.)

- Breastfeeding
- Expressed breast milk
- Donor's breast milk
- Formula
- Oral Rehydration Salts
- Drops and syrups (vitamins, minerals, medicines)
- Other \_\_\_\_\_

Please indicate all the ways you have fed your baby since the last survey. (Mark all that apply to you.)

- At the breast
- From wet nurse
- Spoon or cup feeding
- Finger feeding
- From a bottle
- Supplementary nursing system (lactation aid)
- Other \_\_\_\_\_

#### Display This Question:

If Please indicate all the types of feeds given to your baby since the last survey (about one week a... = Breastfeeding  
Or Please recall all the ways you have fed your baby since the last survey. (Mark all that apply to... = At the breast

How often did you feed your baby at the breast since the last survey?

- Whenever she/he wants (feed on demand)
- Every 2-3 hours as scheduled
- Both (scheduled + demand feeding)
- Other \_\_\_\_\_

Are you breastfeeding your baby currently (including feeding at the breast and expressed milk from you)?

- Yes
- No

*Display This Question:*

*If Are you breastfeeding your baby currently (including feeding at the breast and expressed milk fro... = No*

When did you stop breastfeeding your baby (including feeding at the breast and expressed milk from you)?

\_\_\_\_\_

*Display This Question:*

*If Are you breastfeeding your baby currently (including feeding at the breast and expressed milk fro... = No*

Do you plan to breastfeed this baby in the future?

- Yes
- No
- Not sure

**End of Block: Default Question Block**

**Start of Block: Pumping**

Have you pumped or expressed breast milk since the last survey (about one week ago)?

- Yes
- No

*Display This Question:*

*If Have you pumped or expressed breast milk since the last survey (about one week ago)? = Yes*

Why have you pumped or expressed? (Mark all that apply to you.)

- Allow others to feed the baby
- Breast problems (inverted nipple, sore/cracked nipple etc.)
- I will be away from my baby (back to work, travel etc.)
- Illness
- My baby is not able to feed from my breasts (tongue-tie, in neonatal unit etc.)
- Increase my milk supply
- Too much milk
- To store some milk for the future
- Donate some milk
- Other \_\_\_\_\_

**End of Block: Pumping**

**Start of Block: Formula**

Is your baby having any formula or donor's milk? (If chose 'Yes', please enter how many millilitres (mL) of formula/donor's milk was fed yesterday, for example 300.)

- Yes, formula \_\_\_\_\_
- Yes, donor's milk \_\_\_\_\_
- No

*Display This Question:*

*If Is your baby having any formula or donor's milk? (If chose 'Yes', please enter how many millilitr... = Yes, formula  
Or Is your baby having any formula or donor's milk? (If chose 'Yes', please enter how many millilitr... = Yes, donor's  
milk*

Was yesterday a typical day, in as much as any day is typical?

- Yes
- Every day is very different
- No (please explain) \_\_\_\_\_

**End of Block: Formula**

**Start of Block: Other foods**

Is your baby having other drinks or foods besides breast milk and/or formula?

- Yes
- No

**End of Block: Other foods**

**Start of Block: Reasons to stop EBF/BF**

*Display This Question:*

*If Please indicate all the types of feeds given to your baby since the last survey (about one week a... = Formula  
Or Please indicate all the types of feeds given to your baby since the last survey (about one week a... = Oral  
Rehydration Salts  
Or Please indicate all the types of feeds given to your baby since the last survey (about one week a... = Drops and  
syrups (vitamins, minerals, medicines)  
Or Please indicate all the types of feeds given to your baby since the last survey (about one week a... = Other  
Or Is your baby having any formula or donor's milk? (If chose 'Yes', please enter how many millilitr... = Yes, formula  
Or Is your baby having any formula or donor's milk? (If chose 'Yes', please enter how many millilitr... = Yes, donor's  
milk  
Or Is your baby having other drinks or foods besides breast milk and/or formula? = Yes*

Why have you fed your baby with formula, donor's milk and/or other foods? (Mark all that apply to you.)

- My baby had trouble sucking or latching on
- I had nipple problems (e.g. inverted nipple, sore/cracked nipple)

- Breastfeeding was too painful
- I was ill
- My baby was ill
- My baby was not gaining enough weight
- I don't have enough milk
- My husband wanted to feed the baby
- To help baby sleep
- My baby is ready for solid food
- Breastfeeding is time consuming
- I need to go back to work
- Pumping or expressing is too stressful
- I can't get enough milk with pumping
- Other \_\_\_\_\_

**Display This Question:**

*If Why have you fed your baby with formula, donor milk and/or other foods? (Mark all that apply to y... = My baby had trouble sucking or latching on*

*Or Why have you fed your baby with formula, donor milk and/or other foods? (Mark all that apply to y... = I had nipple problems (e.g. inverted nipple, sore/cracked nipple)*

*Or Why have you fed your baby with formula, donor milk and/or other foods? (Mark all that apply to y... = Breastfeeding was too painful*

*Or Why have you fed your baby with formula, donor milk and/or other foods? (Mark all that apply to y... = I was ill*

*Or Why have you fed your baby with formula, donor milk and/or other foods? (Mark all that apply to y... = My baby was ill*

*Or Why have you fed your baby with formula, donor milk and/or other foods? (Mark all that apply to y... = My baby was not gaining enough weight*

*Or Why have you fed your baby with formula, donor milk and/or other foods? (Mark all that apply to y... = I don't have enough milk*

*Or Why have you fed your baby with formula, donor milk and/or other foods? (Mark all that apply to y... = My husband wanted to feed the baby*

*Or Why have you fed your baby with formula, donor milk and/or other foods? (Mark all that apply to y... = To help baby sleep*

*Or Why have you fed your baby with formula, donor milk and/or other foods? (Mark all that apply to y... = My baby is ready for solid food*

*Or Why have you fed your baby with formula, donor milk and/or other foods? (Mark all that apply to y... = Breastfeeding is time consuming*

*Or Why have you fed your baby with formula, donor milk and/or other foods? (Mark all that apply to y... = I need to go back to work*

*Or Why have you fed your baby with formula, donor milk and/or other foods? (Mark all that apply to y... = Pumping or expressing is too stressful*

*Or Why have you fed your baby with formula, donor milk and/or other foods? (Mark all that apply to y... = I can't get enough milk with pumping*

*Or Why have you fed your baby with formula, donor milk and/or other foods? (Mark all that apply to y... = Other*

**Carry Forward Selected Choices from "Why have you fed your baby with formula and/or other foods? (Mark all that apply to you.)"**

Please rank the reasons you have given in the last question ('1' means that the reason is most important). If more than 5 reasons are given please just rank the top 5 reasons.

- \_\_\_\_\_ My baby had trouble sucking or latching on
- \_\_\_\_\_ I had nipple problems (e.g. inverted nipple, sore/cracked nipple)
- \_\_\_\_\_ Breastfeeding was too painful

- \_\_\_\_\_ I was ill
- \_\_\_\_\_ My baby was ill
- \_\_\_\_\_ My baby was not gaining enough weight
- \_\_\_\_\_ I don't have enough milk
- \_\_\_\_\_ My husband wanted to feed the baby
- \_\_\_\_\_ To help baby sleep
- \_\_\_\_\_ My baby is ready for solid food
- \_\_\_\_\_ Breastfeeding is time consuming
- \_\_\_\_\_ I need to go back to work
- \_\_\_\_\_ Pumping or expressing is too stressful
- \_\_\_\_\_ I can't get enough milk with pumping
- \_\_\_\_\_ Other

**End of Block: Reasons to stop EBF/BF**

**Start of Block: Milk supply**

Generally speaking, I believe my breasts make the right amount of milk to satisfy my baby.

- No, I make too much
- Yes, just right
- Sometimes not enough
- Often not enough
- Not sure

*Display This Question:*

*If Generally speaking, I believe my breasts make the right amount of milk to satisfy my baby. != Yes, just right*

Please explain what happened make you think that? \_\_\_\_\_

*Display This Question:*

*If Generally speaking, I believe my breasts make the right amount of milk to satisfy my baby. != Yes, just right*

What have you done about it?

- Just carried on
  - Block feeding (feed on one side for 2-3 hours or longer)
- 
- Expressed milk
  - Added formula
  - Talked to health professionals (midwife, lactation consultant, GP etc.)
  - Talked to complementary or alternative practitioner (homeopath, naturopath, herbalist, traditional Chinese medicine practitioner etc.)
  - Talked to family and/or friends
  - Searched for information from books/magazines/Internet
  - Took special herbs/herbal products (please enter the herb name or product name and brand) \_\_\_\_\_
  - Took special foods (please enter the food name or recipe) \_\_\_\_\_
  - Other \_\_\_\_\_

Please indicate your agreement or disagreement with each following statement by marking the best answer:

	Strongly agree	Somewhat agree	Neither agree nor disagree	Somewhat disagree	Strongly disagree	N/A
I think it's extremely difficult to breastfeed my baby	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
I think my milk is of good quality	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
I think my milk is nutritious enough to nourish my baby	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
My baby generally appears satisfied with the amount of breast milk received	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Most of the time my baby seems settled	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
I think my baby is crying a lot because of not getting enough milk	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
I think my baby sleeps well during the night even if he/she wakes up for breastfeeding	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
My partner/husband believes that I have adequate milk for my baby/ never questions my milk supply	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
My important family members (e.g. mother, grandmother or mother-in-law etc.) believe that I have adequate milk for my baby / never questions my milk supply	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
My friends believe that I have adequate milk for my baby / never questions my milk supply	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
The health professionals I have seen after I took the last survey (midwife, lactation consultant etc.) believe that I have adequate milk for my baby / never question my milk supply	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

*Display This Question:*

*If Please indicate your agreement or disagreement with each following statement by marking the best... = I think it's extremely difficult to breastfeed my baby [ Strongly agree ]*

*Or Please indicate your agreement or disagreement with each following statement by marking the best... = I think it's extremely difficult to breastfeed my baby [ Somewhat agree ]*

Please tell us what was it about your baby's behavior that made it difficult to breastfed your baby. \_\_\_\_\_

**End of Block: Milk supply**

**Start of Block: Side effect assessment**

*At last I would like to know if there's any concerns or problems for taking the capsules.*

Do you have any of the following problems since the last survey (about one week ago)?

	Always	Most of the time	About half the time	Sometimes	Never
Constipation	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Nausea	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Decreased appetite	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Skin rash	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

---

Do you notice any problems you think may be caused by taking the capsules you were given for this study?

- No
- Yes

---

*Display This Question:*

*If Do you notice any problems you think may be caused by taking the capsules you were given for this... = Yes*

Please describe the problem(s). \_\_\_\_\_

**End of Block: Side effect assessment**

---

*Thank you for your time and input. Next survey will be taken about a week later. We look forward to hearing from you again.*

# BaBY Study - endpoint

## Start of Block: Default Question Block

*Thank you so much for giving your precious time to participate in “BaBY” study. It will take 15-20 minutes to answer all the questions. Be assured that all answers you provide will be confidential. If you are not able to answer all the questions at once, please feel free to come back later. Your answers will be auto saved by the system.*

*Now I would like to ask you some questions about your feeding experience since the last survey, what was working well and if there were any concerns, problems or difficulties. Some of the questions are open ended. You are welcome to give more details if all the options provided do NOT describe your situation. Please note that this survey will be best displayed on a laptop or desktop computer. Some features may be less compatible for use on a mobile device.*

Please enter your study code: \_\_\_\_\_

Please indicate all the types of feeds given to your baby since the last survey (about one week ago). (Mark all that apply to you.)

- Breastfeeding
- Expressed breast milk
- Donor's breast milk
- Formula
- Oral Rehydration Salts
- Drops and syrups (vitamins, minerals, medicines)
- Other \_\_\_\_\_

Please indicate all the ways you have fed your baby since the last survey (about one week ago). (Mark all that apply to you.)

- At the breast
- From wet nurse
- Spoon or cup feeding
- Finger feeding
- From a bottle
- Supplementary nursing system (lactation aid)
- Other \_\_\_\_\_

### Display This Question:

*If Please indicate all the types of feeds given to your baby since the last survey (about one week a... = Breastfeeding  
Or Please indicate all the ways you have fed your baby since the last survey (about one week ago). (... = At the breast*

How often did you feed your baby at the breast since the last survey?

- Whenever she/he wants (feed on demand)
- Every 2-3 hours as scheduled
- Both (scheduled + demand feeding)
- Other \_\_\_\_\_

Are you breastfeeding your baby currently (including feeding at the breast and expressed milk from you)?

- Yes
- No

Display This Question:

If Are you breastfeeding your baby currently (including feeding at the breast and expressed milk fro... = No

When did you stop breastfeeding your baby (including feeding at the breast and expressed milk from you)?

---

Display This Question:

If Are you breastfeeding your baby currently (including feeding at the breast and expressed milk fro... = No

Do you plan to breastfeed this baby in the future?

- Yes
- No
- Not sure

**End of Block: Default Question Block**

---

**Start of Block: Pumping**

Have you pumped or expressed since the last survey (about one week ago)?

- Yes
  - No
- 

Display This Question:

If Have you pumped or expressed since the last survey (about one week ago)? = Yes

Why have you pumped or expressed? (Mark all that apply to you.)

- Allow others to feed the baby
- Breast problems (inverted nipple, sore/cracked nipple etc.)
- I will be away from my baby (back to work, travel etc.)
- Illness
- My baby is not able to feed from my breasts (tongue-tie, in neonatal unit, difficulty with latching etc.)
- Increase my milk supply
- Too much milk
- To store some milk for the future
- Donate some milk
- Other \_\_\_\_\_

**End of Block: Pumping**

**Start of Block: Formula**

Is your baby having any formula or donor's milk? (If chose 'Yes', please enter how many millilitres (mL) of formula/donor's milk was fed yesterday, for example 300.)

- Yes, formula \_\_\_\_\_
  - Yes, donor's milk \_\_\_\_\_
  - No
- 

Display This Question:

If Is your baby having any formula or donor's milk? (If chose 'Yes', please enter how many millilitr... = Yes, formula  
Or Is your baby having any formula or donor's milk? (If chose 'Yes', please enter how many millilitr... = Yes, donor's  
milk

Was yesterday a typical day, in as much as any day is typical?

- Yes
- Every day is very different
- No (please explain) \_\_\_\_\_

**End of Block: Formula**

**Start of Block: Other foods**

Is your baby having other drinks or foods besides breast milk and/or formula?

- Yes
- No

**End of Block: Other foods**

---

**Start of Block: Reasons to stop EBF/BF**

*Display This Question:*

*If Please indicate all the types of feeds given to your baby since the last survey (about one week a... = Formula*

*Or Please indicate all the types of feeds given to your baby since the last survey (about one week a... = Oral*

*Rehydration Salts*

*Or Please indicate all the types of feeds given to your baby since the last survey (about one week a... = Drops and syrups (vitamins, minerals, medicines)*

*Or Please indicate all the types of feeds given to your baby since the last survey (about one week a... = Other*

*Or Is your baby having any formula or donor's milk? (If chose 'Yes', please enter how many millilitr... = Yes, formula*

*Or Is your baby having any formula or donor's milk? (If chose 'Yes', please enter how many millilitr... = Yes, donor's milk*

*Or Is your baby having other drinks or foods besides breast milk and/or formula? = Yes*

Why have you fed your baby with formula, donor's milk and/or other foods? (Mark all that apply to you.)

- My baby had trouble sucking or latching on
  - I had nipple problems (e.g. inverted nipple, sore/cracked nipple)
  - Breastfeeding was too painful
  - I was ill
  - My baby was ill
  - My baby was not gaining enough weight
  - I don't have enough milk
  - My husband wanted to feed the baby
  - To help baby sleep
  - My baby is ready for solid food
  - Breastfeeding is time consuming
  - I need to go back to work
  - Pumping or expressing is too stressful
  - I can't get enough milk with pumping
  - Other \_\_\_\_\_
-

**Display This Question:**

*If Why have you fed your baby with formula, donor milk and/or other foods? (Mark all that apply to y... = My baby had trouble sucking or latching on*  
*Or Why have you fed your baby with formula, donor milk and/or other foods? (Mark all that apply to y... = I had nipple problems (e.g. inverted nipple, sore/cracked nipple)*  
*Or Why have you fed your baby with formula, donor milk and/or other foods? (Mark all that apply to y... = Breastfeeding was too painful*  
*Or Why have you fed your baby with formula, donor milk and/or other foods? (Mark all that apply to y... = I was ill*  
*Or Why have you fed your baby with formula, donor milk and/or other foods? (Mark all that apply to y... = My baby was ill*  
*Or Why have you fed your baby with formula, donor milk and/or other foods? (Mark all that apply to y... = My baby was not gaining enough weight*  
*Or Why have you fed your baby with formula, donor milk and/or other foods? (Mark all that apply to y... = I don't have enough milk*  
*Or Why have you fed your baby with formula, donor milk and/or other foods? (Mark all that apply to y... = My husband wanted to feed the baby*  
*Or Why have you fed your baby with formula, donor milk and/or other foods? (Mark all that apply to y... = To help baby sleep*  
*Or Why have you fed your baby with formula, donor milk and/or other foods? (Mark all that apply to y... = My baby is ready for solid food*

*Or Why have you fed your baby with formula, donor milk and/or other foods? (Mark all that apply to y... = Breastfeeding is time consuming*  
*Or Why have you fed your baby with formula, donor milk and/or other foods? (Mark all that apply to y... = I need to go back to work*  
*Or Why have you fed your baby with formula, donor milk and/or other foods? (Mark all that apply to y... = Pumping or expressing is too stressful*  
*Or Why have you fed your baby with formula, donor milk and/or other foods? (Mark all that apply to y... = I can't get enough milk with pumping*  
*Or Why have you fed your baby with formula, donor milk and/or other foods? (Mark all that apply to y... = Other*  
**Carry Forward Selected Choices from "Why have you fed your baby with formula, donor milk and/or other foods? (Mark all that apply to you.)"**

Please rank the reasons for giving expressed milk, formula or other food. These are the reasons you have given in last question ('1' means that the reason is most important). If more than 5 reasons are given please just rank the top 5 reasons.

- \_\_\_\_\_ My baby had trouble sucking or latching on
- \_\_\_\_\_ I had nipple problems (e.g. inverted nipple, sore/cracked nipple)
- \_\_\_\_\_ Breastfeeding was too painful
- \_\_\_\_\_ I was ill
- \_\_\_\_\_ My baby was ill
- \_\_\_\_\_ My baby was not gaining enough weight
- \_\_\_\_\_ I don't have enough milk
- \_\_\_\_\_ My husband wanted to feed the baby
- \_\_\_\_\_ To help baby sleep
- \_\_\_\_\_ My baby is ready for solid food
- \_\_\_\_\_ Breastfeeding is time consuming
- \_\_\_\_\_ I need to go back to work
- \_\_\_\_\_ Pumping or expressing is too stressful
- \_\_\_\_\_ I can't get enough milk with pumping
- \_\_\_\_\_ Other

**End of Block: Reasons to stop EBF/BF**

**Start of Block: Milk supply**

Generally speaking, I believe my breasts make the right amount of milk to satisfy my baby.

- No, I make too much
- Yes, just right
- Sometimes not enough
- Often not enough
- Not sure

*Display This Question:*

*If Generally speaking, I believe my breasts make the right amount of milk to satisfy my baby. != Yes, just right*

Please explain what happened to make you think that? \_\_\_\_\_

*Display This Question:*

*If Generally speaking, I believe my breasts make the right amount of milk to satisfy my baby. != Yes, just right*

What have you done about it?

- Just carried on
- Block feeding (feed on one side for 2-3 hours or more)
- Expressed milk
- Added formula
- Talked to health professionals (midwife, lactation consultant, GP etc.)
- 

- 
- Talked to complementary or alternative practitioner (homeopath, naturopath, herbalist, traditional Chinese medicine practitioner etc.)
  - Talked to family and/or friends
  - Searched for information from books/magazines/Internet
  - Took special herbs/herbal products
  - Took special foods
  - Other \_\_\_\_\_

Please indicate your agreement or disagreement with each following statement by marking the best answer:

	Strongly agree	Somewhat agree	Neither agree nor disagree	Somewhat disagree	Strongly disagree	N/A
I think it's extremely difficult to breastfeed my baby	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
I think my milk is of good quality	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
I think my milk is nutritious enough to nourish my baby	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
My baby generally appears satisfied with the amount of breast milk received	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Most of the time my baby seems settled	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
I think my baby is crying a lot because of not getting enough milk	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
I think my baby sleeps well during the night even if he/she wakes up for breastfeeding	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
My partner/husband believes that I have adequate milk for my baby/ never questions my milk supply	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
My important family members (e.g. mother, grandmother or mother-in-law etc.) believe that I have adequate milk for my baby / never questions my milk supply	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
My important family members (e.g. mother, grandmother or mother-in-law etc.) believe that I have adequate milk for my baby / never questions my milk supply	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
My friends believe that I have adequate milk for my baby / never questions my milk supply	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
The health professionals I have seen since my baby was born (midwife, lactation consultant etc.) believe that I have adequate milk for my baby / never question my milk supply	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

*Display This Question:*

*If Please indicate your agreement or disagreement with each following statement by marking the best... = I think it's extremely difficult to breastfeed my baby [ Strongly agree ]*

*Or Please indicate your agreement or disagreement with each following statement by marking the best... = I think it's extremely difficult to breastfeed my baby [ Somewhat agree ]*

Please tell us what was it about your baby's behavior that made it difficult to breastfed your baby.

**End of Block: Milk supply**

**Start of Block: BF problems**

Have you had any of the following problems with your breasts since you participated in this study? (Mark all that apply to you.)

- I have not had any problems with my breasts or nipples
- Engorgement
- Sore nipple
- Cracked nipple
- Thrush
- Blocked ducts
- Breast pain
- Mastitis
- Psoriasis / Skin problems on breast
- Raynaud's / Nipple blanching and vasospasm
- Ulcer
- Other \_\_\_\_\_

Did your baby have any of the following problems since you participated in this study? (Mark all that apply to you.)

- Did not have any problems
- Difficulty with latching on to the breast
- Tongue-tie/lip-tie
- Cleft lip/palate
- Thrush
- Very sleepy
- Abdominal/tummy pain
- Reflux
- Colic
- Failure to thrive
- Unsettled/ cry a lot
- Other \_\_\_\_\_

**End of Block: BF problems**

**Start of Block: Postnatal distress**

Please read each statement and circle a number 0, 1, 2 or 3 which indicates how much the statement applied to you over the past week. There are no right or wrong answers. Do not spend too much time on any statement. *The rating scale is as follows:* 0 Did not apply to me at all 1 Applied to me to some degree, or some of the time 2 Applied to me to a considerable degree, or a good part of time 3 Applied to me very much, or most of the time

I found it hard to wind down	▼ 0 ... 3
I was aware of dryness of my mouth	▼ 0 ... 3
I couldn't seem to experience any positive feeling at all	▼ 0 ... 3
I experienced breathing difficulty (eg, excessively rapid breathing, breathlessness in the absence of physical exertion)	▼ 0 ... 3

I found it difficult to work up the initiative to do things	▼ 0 ... 3
I tended to over-react to situations	▼ 0 ... 3
I experienced trembling (eg, in the hands)	▼ 0 ... 3
I felt that I was using a lot of nervous energy	▼ 0 ... 3
I was worried about situations in which I might panic and make a fool of myself	▼ 0 ... 3
I felt that I had nothing to look forward to	▼ 0 ... 3
I found myself getting agitated	▼ 0 ... 3
I found it difficult to relax	▼ 0 ... 3
I felt down-hearted and blue	▼ 0 ... 3
I was intolerant of anything that kept me from getting on with what I was doing	▼ 0 ... 3
I felt I was close to panic	▼ 0 ... 3
I was unable to become enthusiastic about anything	▼ 0 ... 3
I felt I wasn't worth much as a person	▼ 0 ... 3
I felt that I was rather touchy	▼ 0 ... 3
I was aware of the action of my heart in the absence of physical exertion (eg, sense of heart rate increase, heart missing a beat)	▼ 0 ... 3
I felt scared without any good reason	▼ 0 ... 3
I felt that life was meaningless	▼ 0 ... 3

**End of Block: Postnatal distress**

**Start of Block: Health status and life style**

*At last I would like to know what happened in your life relating to your health status since you participated in this study.*

Have you taken any medications or natural/herbal products with the purpose of influencing your milk supply since you participated in this study?

- Yes
- No

Have you taken any other supplements or natural/herbal products since you participated in this study?

- Yes
- No

Have you taken oral contraceptive pills (birth control pills) since you participated in this study?

- Yes
- No

Have you taken any other medications (including prescribed and/or Over the Counter) since you participated in this study?

- Yes
- No

**Display This Question:**

*If Have you taken any medications or natural/herbal products with the purpose of influencing your mi... = Yes  
Or Have you taken any other supplements or natural/herbal products since you participated in this st... = Yes  
Or Have you taken oral contraceptive pills (birth control pills) since you participated in this study? = Yes  
Or Have you taken any other medications (including prescribed and/or Over the Counter) since you par... = Yes*

Please fill in the table below with information about the medication(s), supplements, and/or natural/herbal products you have taken since you participated in this study.

	Product name	Reason for taking	When started (date dd/mm/yyyy)	Dose (xx mg/day or xx tablets /capsules per day)	When stopped (date dd/mm/yyyy) or for how long taken (xx days)
Product 1					
Product 2					
Product 3					
Product 4					
Product 5					
Product 6					
Product 7					
Product 8					

Have you taken any special foods (either manufactured or homemade) with the purpose of influencing your milk supply since you participated in this study?

- No
- Yes

**Display This Question:**

*If Have you taken any special foods (either manufactured or homemade) with the purpose of influe... = Yes*

Please fill in the table below with information about the special food(s) you have taken with the purpose of influencing milk supply since you participated in this study.

	Food name	Recipe or main ingredients	When started (date dd/mm/yyyy)	How much did you take every day (xx g or xx serves)	When stopped (date dd/mm/yyyy) or for how long taken (xx days)
Food 1					
Food 2					
Food 3					
Food 4					
Food 5					
Food 6					
Food 7					
Food 8					

Did you have any health problems since you participated in this study?

- Yes
- No

**Display This Question:**

*If Did you have any health problems since you participated in this study? = Yes*

Please specify the problem. \_\_\_\_\_

Do you have any of the following problems since the last survey (about one week ago)?

	Always	Most of the time	About half the time	Sometimes	Never
Constipation	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Nausea	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Decreased appetite	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Skin rash	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Do you notice any problems you think may be caused by taking the capsules you were given for this study since the last survey (about one week ago)?

- No
- Yes

*Display This Question:*

*If Do you notice any problems you think may be caused by taking the capsules you were given for this... = Yes*

Please describe the problem(s). \_\_\_\_\_

How often do you smoke since you participated in this study?

- Not at all
- Occasionally
- 1-5 cigarette per day
- 6-10 cigarette per day
- More than 11 cigarette per day
- Other \_\_\_\_\_

How often have you drunk alcohol since you participated in this study?

- Not at all
- Occasionally
- 1-3 times a week
- 4-6 times a week
- Daily
- More than once per day
- Other \_\_\_\_\_

*Display This Question:*

*If How often have you drunk alcohol you participated in this study? != Not at all*

How much did you usually drink each time?

- Less than or up to one standard drink (one bottle (330mL) of beer or a glass (100mL) of wine or 30mL of straight spirits @ 42% alcohol)
- More than one standard drink (one bottle (330mL) of beer or a glass (100mL) of wine or 30mL of straight spirits @ 42% alcohol)
- Sometimes one standard drink or less and sometimes more than one standard

**End of Block: Health status and life style**

*Thank you for your time and input. Next survey will be taken when your baby is six months old. We look forward to hearing from you again.*

# BaBY Study - follow up

## Start of Block: Default Question Block

Welcome back to the "BaBY" study. And thank you very much for giving your precious time to participate in this study. It will take 5-10 minutes to answer all the questions. Be assured that all answers you provided will be confidential. If you are not able to answer all the questions at once, please feel free to come back later. Your answers will be auto saved by the system.

Now I would like to know how you managed breastfeeding since the last survey and if there were any concerns, problems of taking the capsules. Some of the questions are open ended. You are welcome to give more details if all the options provided do NOT describe your situation.

Please note that this survey will be best displayed on a laptop or desktop computer. Some features may be less compatible for use on a mobile device.

Please enter your study code: \_\_\_\_\_

Please indicate all the types of feeds given to your baby since the last survey (after you stopped taking the study capsules). (Mark all that apply to you.)

- Breastfeeding
- Expressed breast milk
- Donor's breast milk
- Formula
- Oral Rehydration Salts
- Drops and syrups (vitamins, minerals, medicines)
- Other \_\_\_\_\_

Please indicate all the ways you have fed your baby since the last survey (after you stopped taking the study capsules). (Mark all that apply to you.)

- At the breast
- From wet nurse
- Spoon or cup feeding
- Finger feeding
- From a bottle
- Supplementary nursing system (lactation aid)
- Other \_\_\_\_\_

### Display This Question:

*If Please indicate all the types of feeds given to your baby since the last survey (after you stoppe... = Breastfeeding  
Or Please indicate all the ways you have fed your baby since the last survey (after you stopped taki... = At the breast*

How often did you feed your baby at the breast since the last survey (after you stopped taking the study capsules)?

- Whenever she/he wants (feed on demand)
- Every 2-3 hours as scheduled
- Both (scheduled + demand feeding)
- Other \_\_\_\_\_

Are you breastfeeding your baby currently (including feeding at the breast and expressed milk from you)?

- Yes
- No

Display This Question:

If Are you breastfeeding your baby currently (including feeding at the breast and expressed milk fro... = No

When did you stop breastfeeding your baby (including feeding at the breast and expressed milk from you)?

Display This Question:

If Are you breastfeeding your baby currently (including feeding at the breast and expressed milk fro... = No

Do you plan to breastfeed this baby in the future?

- Yes
- No
- Not sure

**End of Block: Default Question Block**

**Start of Block: Pumping**

Have you pumped or expressed breast milk since the last survey (after you stopped taking the study capsules)?

- Yes
- No

Display This Question:

If Have you pumped or expressed breast milk since the last survey (after you stopped taking the stud... = Yes

Why have you pumped or expressed? (Mark all that apply to you.)

- Allow others to feed the baby
- Breast problems (inverted nipple, sore/cracked nipple etc.)
- I will be away from my baby (back to work, travel etc.)
- Illness
- My baby is not able to feed from my breasts (tongue-tie, in neonatal unit etc.)
- Increase my milk supply
- Too much milk
- To store some milk for the future
- Donate some milk
- Other \_\_\_\_\_

**End of Block: Pumping**

**Start of Block: Formula**

Is your baby having any formula or donor's milk? (If chose 'Yes', please enter how many millilitres (mL) of formula/donor's milk was fed yesterday, for example 300.)

- Yes, formula \_\_\_\_\_
- Yes, donor's milk \_\_\_\_\_
- No

Display This Question:

If Is your baby having any formula or donor's milk? (If chose 'Yes', please enter how many millilitr... = Yes, formula  
Or Is your baby having any formula or donor's milk? (If chose 'Yes', please enter how many millilitr... = Yes, donor's  
milk

Was yesterday a typical day, in as much as any day is typical?

- Yes
- Every day is very different
- No (please explain) \_\_\_\_\_

**End of Block: Formula**

**Start of Block: Other foods**

Is your baby having other drinks or foods besides breast milk and/or formula?

- Yes
- No

**End of Block: Other foods**

**Start of Block: Reasons to stop EBF/BF**

*Display This Question:*

*If Please indicate all the types of feeds given to your baby since the last survey (after you stoppe... = Formula*

*Or Please indicate all the types of feeds given to your baby since the last survey (after you stoppe... = Oral*

*Rehydration Salts*

*Or Please indicate all the types of feeds given to your baby since the last survey (after you stoppe... = Drops and syrups (vitamins, minerals, medicines)*

*Or Please indicate all the types of feeds given to your baby since the last survey (after you stoppe... = Other*

*Or Is your baby having any formula or donor's milk? (If chose 'Yes', please enter how many millilitr... = Yes, formula*

*Or Is your baby having any formula or donor's milk? (If chose 'Yes', please enter how many millilitr... = Yes, donor's milk*

*Or Is your baby having other drinks or foods besides breast milk and/or formula? = Yes*

Why have you fed your baby with formula, donor's milk and/or other foods? (Mark all that apply to you.)

- My baby had trouble sucking or latching on
- I had nipple problems (e.g. inverted nipple, sore/cracked nipple)
- Breastfeeding was too painful
- I was ill
- My baby was ill
- My baby was not gaining enough weight
- I don't have enough milk
- My husband wanted to feed the baby
- To help baby sleep
- My baby is ready for solid food
- Breastfeeding is time consuming
- I need to go back to work
- Pumping or expressing is too stressful
- I can't get enough milk with pumping
- Other \_\_\_\_\_

Display This Question:

*If Why have you fed your baby with formula and/or other foods? (Mark all that apply to you.) = My baby had trouble sucking or latching on*

*Or Why have you fed your baby with formula and/or other foods? (Mark all that apply to you.) = I had nipple problems (e.g. inverted nipple, sore/cracked nipple)*

*Or Why have you fed your baby with formula and/or other foods? (Mark all that apply to you.) = Breastfeeding was too painful*

*Or Why have you fed your baby with formula and/or other foods? (Mark all that apply to you.) = I was ill*

*Or Why have you fed your baby with formula and/or other foods? (Mark all that apply to you.) = My baby was ill*

*Or Why have you fed your baby with formula and/or other foods? (Mark all that apply to you.) = My baby was not gaining enough weight*

*Or Why have you fed your baby with formula and/or other foods? (Mark all that apply to you.) = I don't have enough milk*

*Or Why have you fed your baby with formula and/or other foods? (Mark all that apply to you.) = My husband wanted to feed the baby*

*Or Why have you fed your baby with formula and/or other foods? (Mark all that apply to you.) = To help baby sleep*

*Or Why have you fed your baby with formula and/or other foods? (Mark all that apply to you.) = My baby is ready for solid food*

*Or Why have you fed your baby with formula and/or other foods? (Mark all that apply to you.) = Breastfeeding is time consuming*

*Or Why have you fed your baby with formula and/or other foods? (Mark all that apply to you.) = I need to go back to work*

*Or Why have you fed your baby with formula and/or other foods? (Mark all that apply to you.) = Pumping or expressing is too stressful*

*Or Why have you fed your baby with formula and/or other foods? (Mark all that apply to you.) = Other*

*Or Why have you fed your baby with formula and/or other foods? (Mark all that apply to you.) = I can't get enough milk with pumping*

*Carry Forward Selected Choices from "Why have you fed your baby with formula and/or other foods? (Mark all that apply to you.)"*

Please rank the reasons you have given in the last question ('1' means that the reason is most important). If more than 5 reasons are given please just rank the top 5 reasons.

- \_\_\_\_\_ My baby had trouble sucking or latching on
- \_\_\_\_\_ I had nipple problems (e.g. inverted nipple, sore/cracked nipple)
- \_\_\_\_\_ Breastfeeding was too painful
- \_\_\_\_\_ I was ill
- \_\_\_\_\_ My baby was ill
- \_\_\_\_\_ My baby was not gaining enough weight
- \_\_\_\_\_ I don't have enough milk
- \_\_\_\_\_ My husband wanted to feed the baby
- \_\_\_\_\_ To help baby sleep
- \_\_\_\_\_ My baby is ready for solid food
- \_\_\_\_\_ Breastfeeding is time consuming
- \_\_\_\_\_ I need to go back to work
- \_\_\_\_\_ Pumping or expressing is too stressful
- \_\_\_\_\_ I can't get enough milk with pumping
- \_\_\_\_\_ Other

**End of Block: Reasons to stop EBF/BF**

**Start of Block: Milk supply**

Generally speaking, I believe my breasts make the right amount of milk to satisfy my baby.

- No, I make too much
  - Yes, just right
  - Sometimes not enough
  - Often not enough
  - Not sure
- 

*Display This Question:*

*If Generally speaking, I believe my breasts make the right amount of milk to satisfy my baby. != Yes, just right*

Please explain what happened make you think that? \_\_\_\_\_

---

*Display This Question:*

*If Generally speaking, I believe my breasts make the right amount of milk to satisfy my baby. != Yes, just right*

What have you done about it?

- Just carried on
- Block feeding (feed on one side for 2-3 hours or longer)
- Expressed milk
- Added formula
- Talked to health professionals (midwife, lactation consultant, GP etc.)
- Talked to complementary or alternative practitioner (homeopath, naturopath, herbalist, traditional Chinese medicine practitioner etc.)

- Talked to family and/or friends
- Searched for information from books/magazines/Internet
- Took special herbs/herbal products (please enter the herb name or product name and brand)
- \_\_\_\_\_
- Took special foods (please enter the food name or recipe) \_\_\_\_\_
- Other \_\_\_\_\_

Please indicate your agreement or disagreement with each following statement by marking the best answer:

	Strongly agree	Somewhat agree	Neither agree nor disagree	Somewhat disagree	Strongly disagree	N/A
I think it's extremely difficult to breastfeed my baby	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
I think my milk is of good quality	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
I think my milk is nutritious enough to nourish my baby	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
My baby generally appears satisfied with the amount of breast milk received	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Most of the time my baby seems settled	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
I think my baby is crying a lot because of not getting enough milk	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
I think my baby sleeps well during the night even if he/she wakes up for breastfeeding	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
My partner/husband believes that I have adequate milk for my baby/ never questions my milk supply	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
My important family members (e.g. mother, grandmother or mother-in-law etc.) believe that I have adequate milk for my baby / never questions my milk supply	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
My friends believe that I have adequate milk for my baby / never questions my milk supply	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
The health professionals I have seen after I took the last survey (midwife, lactation consultant etc.) believe that I have adequate milk for my baby / never question my milk supply	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

*Display This Question:*

*If Please indicate your agreement or disagreement with each following statement by marking the best... = I think it's extremely difficult to breastfeed my baby [ Strongly agree ]*

*Or Please indicate your agreement or disagreement with each following statement by marking the best... = I think it's extremely difficult to breastfeed my baby [ Somewhat agree ]*

Please tell us what was it about your baby's behavior that made it difficult to breastfed your baby.

---

**End of Block: Milk supply**

*Thank you for your time and input. This is the end of the study.*

Appendix 13 Twenty-four hour feeding and nappy change record (Chapter 7)

## Feeding and nappy changing record (sample)

Please fill in the form right after you finish every activity. The activities includes BF (breastfeeding), F (formula feed), EM (expressed milk from the mother), DM (donor milk), N (nappy change). Please indicate if the record is estimated. Please record EVERY breastfeed. In this study we define a feed as **completion of latching on, sucking, swallowing and latching off**. Please indicate how many sides are offered in cluster feeds.

Activities	Start time	Finish time	Amount (formula, expressed/donor milk)	Wet nappy	Soiled nappy	Estimated	Numbers of sides
BF	6.15 am	6.30 am					1
N	7.00 am			Y			
BF	8.30 am	30 minutes				Y	2
F	9.00 am	9.15 am	40mL			Y	
N	9.30 am			Y			
BF	11.30 am	11.45 am					1
N	11.45 am			Y	Y		
BF	11.50 am	12.10 pm					1
N	2.30 pm			Y	Y		
BF	2.50 pm	3.00 pm					1

N	3.02 pm				Y		
<b>Activities</b>	<b>Start time</b>	<b>Finish time</b>	<b>Amount (formula, expressed/donor milk)</b>	<b>Wet nappy</b>	<b>Soiled nappy</b>	<b>Estimated</b>	<b>Numbers of sides</b>
BF	3.05 pm	3.30 pm					2
EM	3.35 pm	3.45 pm	30 mL				
N	5.00 pm			Y	Y		
BF	5.10 pm	6.15 pm				Y	3

Please record EVERY breastfeed. In this study we define a feed as **completion of latching on, sucking, swallowing and latching off**. Here are some examples to help you record a feed:

1. It may take a few minutes for nappy change or winding, and then you may carry on the feed. In this study, you have to record this feed as TWO feeds, because your baby latches off for the nappy change or winding and latches on again for another feed.
2. Sometimes you feed your baby on one side in a feed but the other times you may feed on both sides. In this study, you have to record it as TWO feeds if you feed on both sides, since your baby latches off and latches on again when switching sides.
3. If your baby finishes one side and switches to the other side but you forget to record the time for switch side, please record it as one feed and record how many sides you have offered to your baby. For example, you first latched on the right side and then changed to left side, you need to put "2" at the column of "Numbers of sides".
4. When your baby has cluster feeds, it may be very difficult to decide how many feeds your baby has. If it happens, please record how many sides you have offered to your baby. For example, you first latched on the left side and then changed to right side and changed back to left side, you need to put "3" at the column of "Numbers of sides".

Please keep this form or your cell phone with you during the day so that you can record every feed when it happens. If you forget to record the finish time, please **estimate the total time of feeding and write it down in "Finish time" column and put "Y" in "Estimated" column.**

Please record the start time and finish time of the feeds during sleep. If you fell asleep too, please **estimate the duration of the feed and write it down in "Finish time" column and put "Y" in "Estimated" column.**

Please indicate if the record is **estimated when the amount of a formula/donor milk feed was estimated.**

You could also practice estimating a feed by using this record. After your baby finishes a feed, please estimate how long the feed lasts and then look at the clock. This will help you to record the estimated feed closer to the truth if you miss recording a feed.

# Feeding and nappy changing record

Please fill in the form right after you finish every activity. The activities includes BF (breastfeeding), F (formula feed), EM (expressed milk from the mother), DM (donor milk), N (nappy change). Please indicate if the record is estimated. Please record EVERY breastfeed. In this study we define a feed as **completion of latching on, sucking, swallowing and latching off**. Please indicate how many sides are offered in cluster feeds.

Activities	Start time	Finish time	Amount (formula, expressed/donor milk)	Wet nappy	Soiled nappy	Estimated	Numbers of sides

Was it a typical feeding day, in as much as any day is typical?

Was it a typical nappy changing day, in as much as any day is typical?

- Yes
- Every day is very different
- No (please explain) \_\_\_\_\_

- Yes
- Every day is very different
- No (please explain) \_\_\_\_\_

**Appendix 14 Infant anthropometric measurements for the randomised placebo-controlled trial (Chapter 7)**

Study code:

Date:

Time:

Pump: Study / Self (E / M, Brand and model \_\_\_\_\_)

Breast: L / R (productive)

Infant anthropometric measurements (Visit 1)

Weight (g) nearest 10 g	
Length(mm) nearest mm	
Head circumference(mm) nearest mm	

Date:

Time:

Infant anthropometric measurements (Visit 2)

Weight (g) nearest 10 g	
Length(mm) nearest mm	
Head circumference(mm) nearest mm	

**Appendix 15 Multivariate linear regression of the intervention (group) and confounders (secretor status, maternal age, and breastfeeding status) and HMO concentration change from baseline to the endpoint of individual and total HMO among 67 participants (Chapter 7)**

Predictors	Model for 2FL				Model for 3FL				Model for LNFP I				Model for LNFP II			
	$\beta$	B	95% CI	<i>p</i>	$\beta$	B	95% CI	<i>p</i>	$\beta$	B	95% CI	<i>p</i>	$\beta$	B	95% CI	<i>p</i>
Group (Ref. = placebo)	-	-126.86	-	0.282	0.03	29.46	-	0.840	-	-23.31	-	0.682	0.04	19.84	-96.48,	0.807
Yeast	0.14		331.63,				202.76,		0.06		125.10,				129.71	
Secretor – yes	-	-78.20	-	0.440	-	-79.87	-	0.611	-	-89.70	-	0.033	0.14	74.30	-42.73,	0.295
	0.08		265.73,		0.06		364.37,		0.20		167.37,				197.98	
			127.02				245.06				-16.20					
Maternal age	-	-3.04	-32.13,	0.882	-	-0.10	-29.29,	0.995	0.01	0.57	-11.05,	0.944	0.11	5.24	-8.59,	0.532
	0.03		30.16		0.00		31.73				11.52				20.10	
Exclusively breastfeeding – yes	-	-205.42	-	0.063	0.01	10.89	-	0.946	-	-61.58	-	0.198	-	-28.97	-	0.596
	0.22		385.86,				261.15,		0.14		157.29,		0.06		140.37,	
			-49.73				278.64				24.31				91.11	
Adjusted R <sup>2</sup>	0.01				0.06				0.00				0.03			

Predictors	Model for LNFP III				Model for LNFP V				Model for LNnFP				Model for Fucosylated HMOs			
	$\beta$	B	95% CI	<i>p</i>	$\beta$	B	95% CI	<i>p</i>	$\beta$	B	95% CI	<i>p</i>	$\beta$	B	95% CI	<i>p</i>
Group (Ref. = placebo)	-	-13.64	-91.48,	0.744	-0.00	-0.26	-14.00,	0.976	0.01	0.16	-3.87,	0.948	-	-114.61	-	0.729
Yeast	0.04		58.05				14.06				4.20		0.04		666.41,	
Secretor – yes	0.09	32.32	-51.78,	0.464	0.16	10.35	-5.80,	0.227	0.10	2.11	-2.41,	0.374	-	-127.68	-	0.680
			120.20				26.73				6.37		0.04		712.36,	
															492.80	
Maternal age	0.09	3.27	-7.13,	0.611	0.14	0.82	-0.74,	0.336	0.22	0.46	-0.13,	0.181	0.03	7.22	-72.50,	0.925
			14.62				2.41				1.10				95.15	
Exclusively breastfeeding – yes	-	-31.74	-	0.482	-0.12	-7.34	-19.96,	0.293	-	-1.40	-6.01,	0.618	-	-325.56	-	0.342
	0.09		112.07,				5.76		0.07		2.48		0.12		912.90,	
			30.01												176.46	
Adjusted R <sup>2</sup>	0.04				0.00				0.00				0.04			

Predictors	Model for 3SL				Model for 6SL				Model for Sialylated HMOs			
	$\beta$	B	95% CI	$p$	$\beta$	B	95% CI	$p$	$\beta$	B	95% CI	$p$
Group (Ref. = placebo)	-0.07	-7.08	-26.45, 11.86	0.530	-0.03	-3.63	-28.96, 21.88	0.804	-0.06	-10.71	-48.08, 28.19	0.651
Yeast												
Secretor – yes	0.29	3.08	-22.70, 28.83	0.830	-0.03	-3.86	-26.75, 18.87	0.758	-0.00	-0.79	-44.82, 45.15	0.959
Maternal age	-0.05	-0.50	-2.81, 2.11	0.711	-0.03	-0.41	-4.38, 3.48	0.854	-0.04	-0.91	-7.24, 5.48	0.765
Exclusively breastfeeding – yes	-0.25	-25.38	-49.74, 0.76	0.060	-0.41	-54.34	-81.23, -27.94	<0.001	-0.40	-79.72	-122.51, -35.73	<0.001
Adjusted R <sup>2</sup>	0.01				0.12				0.11			

Predictors	Model for LNT				Model for LNnT				Model for non-fucosylated, non-sialylated HMOs				Model for total HMOs			
	$\beta$	B	95% CI	$p$	$\beta$	B	95% CI	$p$	$\beta$	B	95% CI	$p$	$\beta$	B	95% CI	$p$
Group (Ref. = placebo)	0.02	15.54	-171.05, 214.17	0.881	-0.03	-3.92	-37.30, 28.62	0.841	0.01	11.63	-198.27, 211.05	0.916	-0.03	-113.67	-937.24, 610.12	0.805
Yeast																
Secretor – yes	0.06	49.60	-134.50, 220.84	0.609	-0.03	-4.61	-32.32, 24.31	0.737	0.05	44.99	-153.74, 233.72	0.678	-0.02	-83.48	-739.74, 679.26	0.851
Maternal age	0.12	9.79	-11.46, 29.79	0.433	0.14	2.11	-2.07, 6.40	0.393	0.13	11.90	-10.81, 36.18	0.395	0.05	18.21	-85.65, 135.64	0.801
Exclusively breastfeeding – yes	-0.08	-68.79	-261.44, 110.12	0.475	-0.13	-18.38	-48.79, 11.50	0.268	-0.10	-87.17	-286.81, 99.72	0.436	-0.14	-492.46	-1247.97, 272.55	0.275
Adjusted R <sup>2</sup>	0.04				0.02				0.03				0.04			

**Appendix 16 Participants' scores on the DASS-21 and subscales at baseline and endpoint (n = 68) (Chapter 7)**

DASS scores (Median [Q1, Q3])	Baseline		Endpoint		$p_1$	$p_2$	$p_3$
	Placebo (n = 35)	Yeast (n = 33)	Placebo (n = 35)	Yeast (n = 33)			
Depression	2 (2, 6)	2 (1, 6)	2 (0, 4)	2 (0, 4)	0.501	0.020	0.313
Anxiety	4 (2, 6)	2 (0, 7)	2 (0, 4)	0 (0, 4)	0.474	0.004	0.522
Stress	10 (4,14)	8 (4, 15)	6 (2, 12)	6 (2, 8)	0.434	0.004	0.334
DASS-21 total	14 (8, 22)	14 (6, 27)	12 (6, 18)	6 (4, 15)	0.279	0.001	0.440

Nonparametric factorial ANOVA using ART method,  $p_1$  shows comparison between the two groups,  $p_2$  shows comparison of time,  $p_3$  shows interactions.

**Appendix 17 Infant anthropometry measurements and Z-scores at the baseline and the endpoint (n = 67)  
(Chapter 7)**

Infant anthropometry and Z-scores	Baseline				Endpoint				$p_1$	$p_2$	$p_3$
	Placebo (n = 34)	Yeast (n = 33)	Placebo (n = 34)	Yeast (n = 33)	Placebo (n = 34)	Yeast (n = 33)	Placebo (n = 34)	Yeast (n = 33)			
Weight (g)	6561.5 ± 1331.7	6545.0 ± 1259.0	7008.4 ± 1300.2	7074.1 ± 1232.4	0.925	0.000	0.261				
WAZ	-0.02 (-1.07, 0.74)	-0.07 (-0.83, 1.00)	-0.08 (-1.08, 0.54)	0.15 (-0.94, 1.06)	0.708	0.230	0.440				
Length (mm)	629.3 ± 45.0	627.6 ± 33.4	651.0 ± 42.7	649.2 ± 30.1	0.860	0.000	0.975				
LAZ	0.18 ± 1.17	0.09 ± 1.32	0.24 ± 1.14	0.13 ± 1.19	0.739	0.849	0.349				
WLZ	-0.25 ± 1.24	-0.22 ± 1.26	-0.39 ± 1.25	-0.20 ± 1.34	0.722	0.304	0.138				
Head circ (mm)	415.3 ± 20.2	417.9 ± 20.4	424.1 ± 18.0	427.0 ± 19.6	0.563	0.000	0.768				
HCAZ	1.16 (0.59, 1.83)	1.54 (0.86, 2.38)	0.56 (-0.10, 0.99)	0.90 (0.04, 1.50)	0.263	0.285	0.493				

WAZ: weight-for-age Z-score. LAZ: length-for-age Z-score. WLZ: weight-for-length Z-score. Head circ: head circumference. HCAZ: head circumference-for-age Z-score. Nonparametric factorial ANOVA using ART method:  $p_1$  shows comparison between the two groups;  $p_2$  shows comparison of time;  $p_3$  shows interactions.

**Appendix 18 Infant breastfeeding frequency and duration over 24 hours at baseline and the endpoint (n = 68) (Chapter 7)**

Feeding record (Median [Q1, Q3])	Baseline		Endpoint		$p_1$	$p_2$	$p_3$
	Placebo (n = 34)	Yeast (n = 34)	Placebo (n = 34)	Yeast (n = 34)			
Total feeding time (minutes)	134 (78.25, 202.25)	128.5 (94.5, 208)	129 (88, 169)	117 (79, 151.25)	0.740	0.014	0.123
Day feeding time (minutes)	79 (54.25, 114.5)	76 (54.75, 103.25)	79 (42, 98.75)	62.5 (49.5, 93.75)	0.791	0.004	0.502
Night feeding time (minutes)	54 (27.5, 85)	53.5 (28.75, 90)	51.5 (32.25, 87.5)	46.5 (30.25, 66.5)	0.847	0.539	0.182
Total number of feeds	15.5 (11, 19.25)	13 (11.75, 18.25)	13 (12, 17.25)	14 (11, 16)	0.398	0.174	0.169
Number of day feeds	9.5 (8, 12)	8 (6.75, 11)	8 (6, 10.25)	8 (6, 11)	0.414	0.006	0.103
Number of night feeds	6 (3, 8.25)	5 (3.75, 7.25)	5 (4, 7.25)	5 (3.75, 7.25)	0.553	0.562	0.716

Day: 6 am – 6 pm. Night: 6 pm – 6 am. Nonparametric factorial ANOVA using ART method:  $p_1$  shows comparison between the two groups;  $p_2$  shows comparison of time;  $p_3$  shows interactions.

**Appendix 19 Infant nappy changes in 24 hours at baseline and the endpoint (n = 68) (Chapter 7)**

Nappy change record (Median [Q1, Q3])	Baseline		Endpoint	
	Placebo (n = 34)	Yeast (n = 34)	Placebo (n = 34)	Yeast (n = 34)
Number of wet nappies	7 (6, 8)	6 (5, 7)	7 (5.75, 7)	6 (5, 7.25)
Number of soiled nappies	3 (1, 4)	2 (1, 4)	2 (1, 3.25)	2.5 (1, 3.25)

Mann-Whitney U test for the numbers of wet nappies and for the numbers of soiled nappies found no significant differences between two groups at each time point.

**Appendix 19 Participants' self-reported adverse effects at baseline and the endpoint (n = 66) (Chapter 7)**

Adverse effects (Median [Q1, Q3])	Baseline		Week 1		Week 2		Week 3		Endpoint	
	Placebo (n = 33)	Yeast (n = 33)	Placebo (n = 33)	Yeast (n = 33)	Placebo (n = 33)	Yeast (n = 33)	Placebo (n = 33)	Yeast (n = 33)	Placebo (n = 33)	Yeast (n = 33)
Constipation *	4 (4, 5) <sup>§</sup>	4 (4, 4.5) <sup>§</sup>	5 (4, 5) <sup>§</sup>	5 (4, 5) <sup>§</sup>	5 (4, 5)	5 (4, 5)	5 (4, 5)	5 (4, 5)	4.5 (4, 5)	5 (4, 5)
Nausea	5 (4, 5)	5 (5, 5)	5 (5, 5)	5 (5, 5)	5 (5, 5)	5 (5, 5)	5 (5, 5)	5 (5, 5)	5 (5, 5)	5 (5, 5)
Decreased appetite <sup>†</sup>	5 (4, 5)	5 (4, 5)	5 (5, 5)	5 (5, 5)	5 (5, 5)	5 (5, 5)	5 (5, 5)	5 (5, 5)	5 (4.5, 5)	5 (5, 5)
Skin rash	5 (5, 5)	5 (5, 5)	5 (5, 5)	5 (5, 5)	5 (5, 5)	5 (5, 5)	5 (5, 5)	5 (5, 5)	5 (5, 5)	5 (5, 5)

Mann-Whitney U test for each adverse effect tests found no significant differences between two groups at each time point. Friedman's ANOVA for each adverse effect tests within each group. \* In the placebo group,  $\chi^2(4) = 16.78, p = 0.002$ ; and in the SCYS group,  $\chi^2(4) = 37.89, p < 0.001$ . <sup>†</sup> In the SCYS group,  $\chi^2(4) = 11.69, p = 0.020$ . <sup>§</sup> *post hoc* test using Wilcoxon signed ranks test with a Bonferroni correction, in the placebo group from baseline to week 1,  $Z = -3.50, p < 0.001$ ; and in the SCYS group from baseline to week 1,  $Z = -3.39, p = 0.001$ .

# Hourly expression record

Study code:

Date:

Visit: 1 / 2 / 3

Pump: Study / Self (E / M, Brand and model \_\_\_\_\_)

Breast: L / R (productive)

Expression	Start time	Empty bottle (g)	Bottle with milk (g)	Expressed milk (g)
First				
Second				
Third				
Fourth				

## Appendix 21 Summary of studies on galactagogues published in 2022 and 2023 (Chapter 9)

Study and design	Galactagogue and study aims	Dosage and timeframe	Study Subjects and recruiting criteria	Effect on milk volume	Other effects on milk production	Reported side effects
<b>Preterm</b>						
Asztalos and Kiss (2022) [1] Multicentre, double-masked RCT, intention-to-treat analysis Canada	Domperidone Aim: To evaluate the response pattern to domperidone in mothers with varying low breast milk volumes prior to initiating this treatment.	10 mg, 3× day Domperidone group: 28 days Placebo group: placebo for 14 days, then domperidone for 14 days. Infants aged 8 to 21 days at the baseline.	Three groups were formed based on the baseline breast milk volumes: A (n = 46) ≤100 mL/kg/d; B (n = 25) 101–200 mL/kg/d; and C (n = 19) ≥201–250 mL/kg/d. Inclusion criteria: Preterm (<29 weeks gestation), pumping ≥ 6x/day in the 4 days prior to study entry. Lactation inadequacy within the 72 hrs prior to study entry: 1) ≤ 150 ml/kg/d (based on infant's birthweight); or 2) milk volume reduction ≥ peak volume. Exclusion criteria: Cardiac dysrhythmias or receiving an anti-arrhythmic medication; mastitis; previous breast surgery; any illness; receiving medications alter the metabolism and pharmacokinetics of domperidone or medications affect prolactin levels; triplet or higher; and cigarette smoking.	Mean milk volume (SD) (mL/day) by exclusively pumping and self-recorded in 24 hours. Days 14: A: 155.9 (160.3) B: 303.0 (147.8) C: 375.8 (154.6) <i>p</i> < 0.0001 Day 28: A: 199.6 (203.1) B: 349.1 (163.5) C: 454.3 (212.9) <i>p</i> < 0.0001	<b>Mean % volume change day 0 to day 14 (SD):</b> <i>p</i> = 0.001 A: 356.2 (465.8) Domperidone (n = 23) 400.64 (571.10); Placebo (n = 23) 304.80 (310.53), <i>p</i> = 0.99 B: 106.1 (99.2) Domperidone (n = 13) 123.72 (117.58); Placebo (n = 12) 85.33 (71.77), <i>p</i> = 0.41 C: 45.2 (62.5) Domperidone (n = 9) 81.50 (47.24); Placebo (n = 10) 8.95 (55.85), <i>p</i> = 0.01 <b>Mean % volume change day 15 to day 28 (SD):</b> No significant differences.	Not reported.
Khalili et al. (2023) [2] RCT with three parallel groups Iran	Pimpinella Anisum herbal tea (Anise tea) Aim: To determine the effect of Pimpinella Anisum herbal tea on human milk volume and preterm infant weight.	2 g of dried Anise plant, 3× day Tea bag was brewed in 150 ml boiling water for 10 minutes. Study duration: 7 days. Infant age not reported.	Intervention (n = 45), Placebo (n = 45), Control (n = 39) Inclusion criteria: ≥ 18 years old women willing to breastfeed and accept to pump milk via an electric pump from the third day postpartum; preterm infant (≥32 weeks' gestation) admitted to the intensive care unit and fed by orogastric or nasogastric tube. Exclusion criteria: Smoking; alcohol; drug use; infectious diseases transmitted through human milk; pulmonary tuberculosis; history of infertility; taking anticoagulants contraindicated with Anise; history of cancer estrogen-dependent diseases (e.g., uterine cancer, breast cancer, endometrial hyperplasia) and/or mastectomy; nipple fractures, breast abscesses and/or infectious mastitis;	<b>Mean milk volume (SD) (mL/day)</b> by exclusively pumping and self-recorded in 24 hours. Day 3: I: 169.2 (66.2); P: 138.3 (52.0); C: 125.5 (55.2) <i>p</i> values (three groups, I vs C, I vs P): 0.001, 0.001, 0.025. Day 4: I: 193.7 (78.8); P: 148.7 (53.9); C: 130.2 (60.7) <i>p</i> values: <0.001, <0.001, 0.002. Day 5: I: 220.5 (89.7); P: 155.0 (56.8); C: 141.2 (69.1)	No significant differences of infant weights between groups at Day 3 or Day 7. Infant was weighed by the researcher prior to the first human milk feed and after the infant's first bowel and urinary outputs.	No adverse effects were reported by participants.

Study and design	Galactagogue and study aims	Dosage and timeframe	Study Subjects and recruiting criteria	Effect on milk volume	Other effects on milk production	Reported side effects
			multiple birth; infant with congenital anomalies (e.g., cleft lip and palate).	<i>p</i> values: <0.001, <0.001, <0.001. Day 6: I: 244.3 (102.2); P: 164.7 (63.9); C: 151.4 (80.4) <i>p</i> values: <0.001, <0.001, <0.001. Day 7: I: 268.1 (98.5); P: 170.1 (66.7); C: 154.8 (82.1) <i>p</i> values: <0.001, <0.001, <0.001.		
Yimyam et al. (2023) [3] RCT Thailand	Commercial banana flower beverage. Aim: To investigate the effects of banana flower beverages on breast milk production among mothers with preterm infants.	Treatment group had banana beverage 100 mL (containing 14 mg of banana flower), 3× day. Control group had 100 mL water. Study duration: 3 days, starting from day 1 postpartum.	Treatment (n = 20), Control (n = 21) Inclusion criteria: Healthy lactating mothers aged 18 years and over, with preterm neonates (≤ 37 weeks' gestation, birth weight between 1500 g and 2499 g). Exclusion criteria: Mothers with serious chronic diseases or medical conditions; maternal abnormalities of breasts and nipples; having decreased breast milk production; having a contraindication to breastfeeding; having any other herbal or pharmaceutical galactagogues; contraindication or allergic to banana flower; or the infant having any contraindication to enteral feeding during the first three days postpartum.	<b>Mean milk volume (SD) (mL)</b> evaluated by expressing at Day 1 (24 ± 2 h after delivery), Day 2 (48 ± 2 h after delivery), and Day 3 (72 ± 2 h after delivery). Day 1: Treatment: 12.1 (11.2) Control: 6.1 (6.9) <i>p</i> = 0.015 Day 2: Treatment: 41.3 (23.3) Control: 12.1 (12.4) <i>p</i> < 0.001 Day 3: Treatment: 42.4 (11.3) Control 25.5 (9.6) <i>p</i> < 0.001	Milk flow level (no definition): Treatment group have higher milk flow level than those in the control group at Day 2 (48 ± 2 h) ( <i>p</i> = 0.0043) and Day 3 (72 ± 2 h) ( <i>p</i> = 0.0001) of postpartum.	No adverse effect recorded. Maternal adverse effects included gastrointestinal discomfort, allergic reactions, urticaria, pruritus, edema, decreased urine volume and other complications.
<b>Term infant, ≤ 7 days postpartum at the baseline</b>						
Chanpraph et al. (2022) [4] RCT Thailand	Ayurved Siriraj Prasa-Nam-Nom (ASPNN) recipe, containing garden spurge (Euphorbia hirta Linn.) with proposed galactagogue effects. Aim:	3x 500 mg capsules (1500 mg), 3x day Study duration: 10 days, including 3 days in the hospital and 7 days at home (after discharge).	ASPNN (n = 27), Placebo (n = 26) Inclusion criteria: ≥ 18 years old; first vaginal delivery at term; expressed milk volume at 24-hour after the delivery <49 ml. Exclusion criteria: Medical disorders (hypertension, type 2 diabetes, thyrotoxicosis, and hypothyroidism); previous allergy to ASPNN or its ingredients; inability to eat	<b>Median (min, max) expressed milk volume (mL)</b> from one pumping session at Day 3 (no information of timing and duration of the session): ASPNN: 19 (0, 139) Placebo: 30 (0.01, 110) No significant difference.	At Day 3, no significant differences between two groups in creatinocrit or blood prolactin concentration. No significant differences between two groups in changes in breast milk volume, creatinocrit, or blood prolactin concentration from Day 1 to Day 3.	1 case of skin rash and 1 case of mild diarrhoea in the ASPNN group.

Study and design	Galactagogue and study aims	Dosage and timeframe	study	Subjects and recruiting criteria	Effect on milk volume	Other effects on milk production	Reported side effects
	To explore the effectiveness of ASPNN on milk volume in women with inadequate milk during early postpartum period.			vegetables or spicy food; severe breastfeeding problems (abnormal breast anatomy, short nipples, mastitis, breast abscess and severe fetal tongue-tie); taking other medications (domperidone, metoclopramide, anti-depressive drugs, caffeine and alcohol).		Proportion or exclusive breastfeeding on day 11: ASPNN: 92.6% Placebo: 88.5%	
Fungtam masan and Phupong (2022) [5] RCT Thailand	Moringa oleifera Aim: To evaluate the efficacy of Moringa oleifera leaves in increasing the volume of breast milk in early postpartum days.	One 450 mg Moringa oleifera leaves powder capsule, 2× day (900 mg/day) Study duration: 3 days, starting within 6 hours postpartum.	Moringa (n = 44), Placebo (n = 44) Inclusion criteria: Women ≥ 18 years old; gestation age ≥ 37 weeks; intend to breastfeed; uncomplicated full-term delivery; accomplished similar antenatal breastfeeding promotion protocol. Exclusion criteria: HIV; taking chemotherapeutic drugs; on radioactive substances; postpartum haemorrhage, sepsis, or other unstable conditions; allergy to Moringa oleifera; insufficient glandular tissue or breast surgery; hypothyroidism; twins or higher order births; preterm infants; infant with galactosemia or needed phototherapy; infants with sucking problems or structural oral anomalies affecting sucking (e.g., tongue tie, birth asphyxia, clefts, etc.).	<b>Median (Q1, Q3) milk volume at day 3 postpartum (ml/day) by 24-hr test weighing:</b> Moringa: 73.5 (35.7, 138.7) Placebo: 50 (26.3, 126.5) No significant difference.	No significant differences in the percentage of women who noticed breast fullness, the time of breast fullness or scores in satisfaction or Quality of life (WHOQoL-BREF). Proportion of exclusive breastfeeding at 6 months postpartum: Moringa: 23 (52.3%) Placebo: 20 (45.5%) No significant difference.	2 cases of constipation, 1 case of heartburn, 1 case of infant hypotension.	
Maenpue n et al. (2022) [6] Single blind, multi-centre RCT Thailand	<i>Lysiphyllum strychnifolium</i> (Craib) A. Schmitz (LS) tea Aim: To determine the clinical effects of LS tea on breast milk volume, nutrients in the milk, and the infant weight.	2 g of LS tea mixed in 200 mL warm water before meals 3× day. Control group took 200 mL warm water. Study duration: 10 days and the participants took LS tea for 7 days, starting within 6 hours postpartum.	LS tea (n = 42), Control (n = 42) Inclusion criteria: Women aged 20 to 40 years, normal delivery, exclusive breastfeeding, with full term and healthy neonates. Exclusion criteria: Postpartum haemorrhage; history of smoking or drug use; food or herb allergy; chronic illness; breast problem; any drug use for improving breast milk production; twin delivery; hepatitis B; AIDS; syphilis; infant birth weight < 2500 g; APGAR scores < 7; or intrauterine growth retardation.	<b>Mean milk volume (SD) by pumping (by an electric pump) both breasts simultaneously for 15 minutes after a 2-hour interval from the last breastfeeding.</b> Day 4: LS tea: 62.9 (44.9) Control: 47.4 (32.2) Non-significant difference. Day 10: LS tea: 75.8 (45.6) Control: 80.7 (46.2) Non-significant difference.	Mean (SD) milk energy (kcal/100 mL) at Day 4: LS tea, 52.6 (9.1); Control, 60.1 (8.7); $p < 0.001$ . No significant differences at Day 10. No significant differences in milk protein between two groups at Day 4 or Day 10. No significant differences in Mean (SD) milk carbohydrate (g/100 mL) at Day 4. Day 10: LS tea, 8.7 (1.4); Control, 7.9 (0.8); $p = 0.002$ . Mean (SD) milk fat (g/100 mL) at Day 4: LS tea, 1.3 (1.1); Control, 2.3 (0.9); $p < 0.001$ . Day 10: LS tea, 2.3 (1.6); Control, 3.1 (1.0); $p = 0.013$ .	No adverse effects were found. Maternal symptoms were dry throat, frequent urination, headache, muscle weakness, diarrhoea, insomnia, stomach pain, rash, nausea, swelling and bloating. Infant symptoms were diarrhoea, flatulence, and constipation.	

Study and design	Galactagogue study aims	and Dosage and timeframe	and study Subjects and recruiting criteria	Effect on milk volume	Other effects on milk production	Reported side effects
Roosita et al. (2022) [7] Experimental study with post-controlled design Indonesia	Galohgor nutraceutical lactation cookies (NLC) Aim: To evaluate the effect of NLC on breast milk production and lactose concentration in early postpartum period.	4 pieces (40 g) per day of NLC containing 1 g/piece galohgor nutraceutical powder that has obtained Indonesian patent (IDP000058958). Nutrient composition of the NLC/100g: 146 kcal, 58.3 g carbohydrate, 6.22 g protein, and 29.22 g fat. Study duration: 14 days, starting from Day 1 postpartum.	NLC (n = 9), Placebo (n = 11) Inclusion criteria: Women aged 26 to 40 years, single pregnancy, normal delivery, multiparous, willing to exclusively breastfeed their infants, consent to follow-up visits, with a term and healthy infant. Exclusion criteria: Any medical condition or complications during previous pregnancies or delivery; breast problems such as inverted nipples and mastitis using a medicine; smoking; alcohol; separated from the infant; infant with low birth weight, intrauterine growth retardation and any illness or congenital abnormalities.	<b>Mean milk volume (95% CI) mL/day</b> , adjusted for parity, gestation age and head circumference of infants, measured by 24-hour test weighing of the infants. Day 14: NLC: 557.0 (497.3 – 616.6) Placebo: 435.9 (382.3 – 489.6) $p < 0.05$	No significant differences in infant weight between groups at Day 4 or Day 10. Mean milk lactose concentration (95% CI), adjusted for parity, carbohydrate intake of mother and water content of breast milk. Day 14: NLC: 6.03% (5.66%–6.40%) Placebo: 5.18% (4.85%–5.51%) $p < 0.05$	No adverse effects were found. Maternal symptoms were headache, rash, itching, nausea, abdominal pain, and excessive rectal gas.
Saejueng et al. (2022) [8] Three-armed, double-blinded RCT Thailand	Wang Nam Yen herbal tea and domperidone. Aim: To compare the efficacy of Wang Nam Yen herbal tea, domperidone, and a placebo in increasing milk production in mothers that have undergone caesarean delivery.	Wang Nam Yen herbal tea bag diffusion in 200 mL of warm water for 5 minutes, 3x day after meals. Wang Nam Yen herbal tea bag contained 500 mg sappan ( <i>Caesalpinia sappan</i> Linn.), 500 mg licorice ( <i>Glycyrrhiza glabra</i> Linn.), 500 mg bale fruit ( <i>Aegle marmelos</i> L. Corr), 500 mg ginger ( <i>Zingiber officinale</i> Roscoe), and 500 mg jewel vine ( <i>Derris scandens</i> (Roxb.) Benth). Domperidone: 10 mg, 3x day. Treatment group (T) received Wang Nam Yen herbal tea and placebo tablets, Domperidone group (D) received placebo tea and domperidone	T (n = 40), D (n = 40), P (n = 40) Inclusion criteria: Women aged 15 to 41 years, caesarean section at 28 to 42 weeks gestational age. Exclusion criteria: Contraindications for breastfeeding and/or serious illness affecting mother or infant, such as HIV infection, postpartum haemorrhage with hypovolemic shock, HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count), eclampsia with respiratory failure; history of allergy to domperidone or ingredients in the herbal tea; neonates-mother separation before participation.	<b>Mean milk volume (SD) at 72 hours postpartum (mL)</b> measured by pumping (by an electric pump) both breasts simultaneously for 15 minutes after a 2-hour interval from the last breastfeeding: T: 57.5 (50.7) D: 60.9 (70.7) P: 31.9 (27.7) T vs P: $p = 0.007$ D vs P: $p = 0.018$ T vs D: NS.	Mean milk volume (SD) at 24 hours postpartum (mL): T: 10.0 (21.4) D: 3.8 (7.6) P: 2.6 (6.2) T vs P: $p = 0.039$ D vs P: NS T vs D: NS. No significant differences in mean milk volume (SD) at 48 hours postpartum (mL) between the three groups.	One case of dry mouth in the domperidone group; one case of diarrhoea in the herbal tea group during the first 24 hours postpartum and the symptoms persisted for 72 hours postpartum.

Study and design	Galactagogue and study aims	Dosage and study timeframe	Subjects and recruiting criteria	Effect on milk volume	Other effects on milk production	Reported side effects
		tablets, Placebo group (P) received placebo tea and placebo tablets. Study duration: 3 days, starting from day 1 postpartum.				
Shen et al. (2023) [9] Repeated measures by questionnaire survey	24 galactagogue food items were included in the questionnaire. Aim: To investigate galactagogue food consumption patterns during “doing the month” and how they relate to perceived insufficient milk supply and exclusive breastfeeding.	Galactagogue foods included in this study are crucian carp soup, chicken soup, pigs’ feet soup, lean meat soup, millet congee, rice wine with egg soup, vegetable with pork liver soup, sponge gourd soup, red bean soup, soybean milk, minced pork congee, carp soup, papaya congee, shrimp congee, day lily soup, pork liver congee, hairtail soup, sautéed sesame, silver carp soup, catfish soup, lamb congee, taraxacum soup, semen coicis tea, and human placenta. Study duration: 4 months, starting before hospital discharge.	N = 218. Inclusion criteria: Women aged 18 to 45 years, singleton pregnancy and with healthy term infants aged 1 to 7 days, intention to breastfeed, able to read, write, and communicate in Mandarin. Exclusion criteria: History of pregnancy complications, acute disease, severe function disorders, or genetic disease; hypoplastic breasts; history of breast surgery; abnormal nipples; maternal and child separation; or galactagogue medication consumption.	Not evaluated.	No association between galactagogue food consumption and perception of insufficient milk supply (measured by the Chinese version of the Hill and Humenick Lactation Scale). women who consumed galactagogue foods were less likely to breastfeed exclusively during the entire study period (OR = 0.34 [0.19, 0.59], $p < .001$ ). Mixed feeding rate in the group of consumers were significantly higher than that in the group of non-consumers at 1 month, 2 months, 3 months and 4 months postpartum.	Not reported.
Nasution et al. (2023) [10] Quasi-experimental non-equivalent control group pretest-	Moringa leaves Aim: To determine the effectiveness of Moringa leaves in increasing breast milk production and the health status of postpartum mothers.	100 g boiled Moringa vegetables, 3x day. Study duration: 7 days, starting from the day 1 after birth.	Intervention (n = 30), Control (n = 30) Inclusion criteria: Women giving birth to live and uncomplicated babies, not having blisters on the breasts, and being willing to become research respondents. No exclusion criteria. Gestation age unknown.	Not evaluated.	Milk production evaluated by self-designed questionnaire (not provided), mean score (SD) at the endpoint: Intervention: 1.57 (0.68) Control: 3.00 (1.02) $p < 0.001$ Exclusively breastfeeding rate at the endpoint: Intervention, 83.3%; Control, 46.7%. Day of copious milk, n (%):	Not reported.

Study and design	Galactagogue study aims	and	Dosage and timeframe	and	study	Subjects and recruiting criteria	Effect on milk volume	Other effects on milk production	Reported side effects
protest design Indonesia								Day1: Intervention, 16 (53.3%); Control, 2 (6.7%) Day 2: Intervention, 11 (36.7%); Control, 7 (23.3%) Day 3: Intervention, 3 (10%); Control, 12 (40%) Day 4: Control 7 (23.4%) Day 5: Control 2 (6.7%)	
<b>Term infant, &gt; 7 days postpartum at the baseline or unclear</b>									
Azevedo et al. (2022) [11] One group pre-test post-test design Brazil	Corn-based preparation Aim: To verify whether corn-based preparation can increase breast milk production in women with hypogalactia		100 g green corn cake (229.4 kcal, 22.1 g carbohydrate, 5.7 g protein, and 13.2 g fat) and 150 g white hominy (260.8 kcal, 40.3 g carbohydrate, 6.5 g protein, and 8.2 g fat) per day (500 kcal/day) Study duration: 14 days. Baseline week – standard hospital meals; the second week – same daily energy intake with minor changes in hospital meals to include corn-based preparations. Infant aged 5 – 20 days at the baseline.			N = 35 Inclusion criteria: Infants in the NICU for ≥ 15 days; diagnosis of hypogalactia; manually expressing milk; to breastfeed their child. Exclusion criteria: Hypogalactia was not diagnosed; medications hinder lactation (e.g., diuretics, piridoxina); using galactagogues; not like corn products; children had an expected discharge date of <15 days; lack of exclusively breastfeeding; children had allergic reactions, even if not directly related to the mother's diet; diabetes mellitus or lactase deficiency. No inclusion criteria for study infants. Gestation age unknown.	Mean milk volume (SD) mL/day, measured by manual expressing every three hours with instruction from the hospital nurse at each expression. Baseline: 343.6 (155.8) Intervention: 397.6 (182.6) $p < 0.01$	The paired mean difference of milk volume (SD) between the 2 weeks: 53.5 (14.3) mL/day. Median energy intake: Baseline: 2,685.6 kcal/day Intervention: 2,779.2 kcal/day Percentage distribution of energy and macronutrients (carbohydrate: protein: lipid): Baseline: 59.9:14.7:24.8 Intervention: 58.2:14.4:27.2 The difference in intake between the study periods differed statistically from zero ( $p < 0.001$ ) for both energy and macronutrients.	Not reported.
Karapati et al. (2022) [12] Retrospective survey Greece	Silitidil (Silymarin from milk thistle with incorporated phospholipids) Aim: To assess the effect on milk production and the duration of breastfeeding in mothers with high risks of not exclusive breastfeeding		5 g/day for 14 days. Started during hospital stay. Unclear starting time at the baseline.			N = 161. Inclusion criteria: Mothers of twins or premature newborns, or those whose neonates had weight loss ≥ 10% of BW, needed phototherapy, required transport to a tertiary NICU, and mothers unable to breastfeed due to any other reason. Exclusion criteria: not reported. Gestation age < 37: 39 (24%); ≥ 37: 122 (76%).	Not evaluated.	Proportion of breastfeeding at: 1 week: 161 (100%) 1 month: 159 (98.8%) 4 months: 140 (87%) 6 months: 91 (56.5%) 12 months: 66 (41%) >12 months: 31 (19.3%)	Not reported.

Study and design	Galactagogue and study aims	Dosage and study timeframe	Subjects and recruiting criteria	Effect on milk volume	Other effects on milk production	Reported side effects
Palacios et al. (2023) [13] RCT US	Lactation cookies (LCs) containing ingredients suggested to increase breast milk production such as oatmeal, flaxseed meal, fenugreek, brewer's yeast. Aim: To evaluate the effectiveness of commercially available LCs on breast milk production.	~57 g LCs with unclear proportion of galactagogue ingredients (260 kcal, 38 g carbohydrate, 5 g protein, 11 g fat). Study duration: 1 month, starting from 2 months postpartum.	LCs (n = 88), Placebo (n = 88) Inclusion criteria: Exclusively breastfeeding women aged 18 to 45 years, with one healthy term infant (gestation age > 37 weeks), healthy pregnancy, uncomplicated birth, living in the contiguous 48 US states, intention to exclusively breastfeed infant for ≥3 months, and intention to take the infant to the CDC-recommended well-child visits. Exclusion criteria: Allergy to or dislike of cookie ingredients; any other contraindications to consuming cookies; thyroid disease, epilepsy, psychosis, and bipolar disorder; currently receiving treatment of depression or anxiety or using medications that may interfere with milk production (e.g., metoclopramide, chlorpromazine, domperidone, medroxyprogesterone, and thyroid hormone); substance use disorder; consuming LCs in the previous 2 week; feeding the infant with formula more than once during the study; or consuming any products marketed to boost lactation in the 2 week prior or at any point during the study.	Mean (SD) milk production rate (mL/h) evaluated by hourly expression for 3 hours: Baseline: Intervention: 39.2 (14.7) Placebo: 41.4 (16.1) Endpoint: Intervention: 43.1 (15.7) Placebo: 46.7 (20.2) No significant difference.	<b>Baseline-to-endpoint difference (SEs) in milk production rate:</b> Intervention: 5.5 (17.6) Placebo: 5.8 (15.7) No significant difference. No significant differences in the baseline-to-endpoint difference (SEs) in perceived insufficient milk scores (Perception of Insufficient Milk questionnaire) or breastfeeding self-efficacy scores.	Not reported.
Simbar et al. (2022) RCT [14] Iran	Honey and fenugreek. Aim: To compare the effect of a combination of "honey and fenugreek" with "fenugreek" on breastfeeding success.	Honey and fenugreek group (HF group) used fenugreek extract mixed with 70% honey syrup. Fenugreek group (F group) used same amount of fenugreek added into the hydro-aqueous solution. Both groups had 30 liquid drops 3x day. The concentration of fenugreek extract was 8.4 mg/mL solvent. The dosage of fenugreek was not reported. Study duration: 4 weeks.	HF (n = 36), F (n = 39) Inclusion criteria: Exclusively breastfeeding women aged 18 to 38 years, with normal single fetus pregnancy, normal term delivery, maternal body mass index (19.8 – 26 kg/m <sup>2</sup> ), having a 1 to 5 months aged infant that were mature at birth and weighed 2.5 – 4 kg, and were seeking advice for a natural galactagogue. Exclusion criteria: Women with history of known medical and psychological diseases; any mental or physical illness during the study that interferes with breastfeeding such as hepatitis, cancer, and breast problems; smoking; use of other herbal and chemical drugs that increase milk during the intervention; use of dopamine antagonists (domperidone, metoclopramide, risperidone, and	Not evaluated.	Pre-test post-test comparison of mean scores (SD) of the breastfeeding success questionnaire (measured by a self-designed questionnaire containing 21 items): F: before, 77.46 (7.30); after, 76.33 (8.08); NS. HF: before, 72.97 (6.72); after, 77.80 (12.19); <i>p</i> = 0.035. Endpoint mean scores (SD): F: 75.53 (1.64) HF: 78.67 (1.71) <i>p</i> = 0.023.	1 case of nausea and vomiting in the HF group, 2 cases of gastrointestinal problems in the F group and 1 case in the HF group, 6 cases of infant diarrhoea in the F group and 1 case in the HF group.

Study and design	Galactagogue study aims	and Dosage and timeframe	and study	Subjects and recruiting criteria	Effect on milk volume	Other effects on milk production	Reported side effects
				phenothiazine); cessation of breastfeeding for any reason; infant with any abnormalities, diseases, or nutritional problems; or unwillingness to continue the intervention.			

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Appendix 22 DRC 16 forms for Chapter 4, 5, 6, 7, and 8


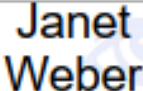


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In which chapter is the manuscript/published work?	Chapter 4
What percentage of the manuscript/published work was contributed by the student?	70%
Describe the contribution that the student has made to the manuscript/published work: The student prepared the ethics application for this study, interviewed the study participants, analysed the data, drafted the manuscript and made revisions based on supervisors' feedback.	
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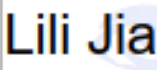
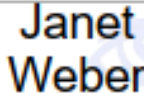
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We, the student and the student's main supervisor, certify that all co-authors have consented to their work being included in the thesis and they have accepted the student's contribution as indicated below in the Statement of Originality.	
Student name:	<b>Lili Jia</b>
Name and title of main supervisor:	<b>Dr Janet Weber</b>
In which chapter is the manuscript/published work?	<b>Chapter 8</b>
What percentage of the manuscript/published work was contributed by the student?	<b>70%</b>
Describe the contribution that the student has made to the manuscript/published work: <b>The student prepared the ethics application, collected the data, conducted the data analysis, wrote the first draft of the manuscript and revised it based on supervisors' feedback.</b>	
Please select one of the following three options:	
<input type="radio"/>	<b>The manuscript/published work is published or in press</b> Please provide the full reference of the research output:
<input type="radio"/>	<b>The manuscript is currently under review for publication</b> Please provide the name of the journal:
<input checked="" type="radio"/>	<b>It is intended that the manuscript will be published, but it has not yet been submitted to a journal</b>
Student's signature:	<div style="display: flex; justify-content: space-between;"> <div style="text-align: center;">   <b>Lili Jia</b>  <small>Digitally signed by Lili Jia            DN: cn=Lili Jia, o=Massey University, ou=School of Food and Advanced Technology, email=lja@massey.ac.nz            Date: 2023.02.02 00:04:57 +1300</small> </div> <div style="text-align: center;">   <b>Janet Weber</b>  <small>Digitally signed by Janet Weber            DN: cn=Janet Weber, o=Massey University, ou=School of Food and Advanced Technology, email=j.l.weber@massey.ac.nz            Date: 2023.02.03 10:34:24 +1300</small> </div> </div>
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## Appendix 23 Researchers' contributions

Stage	Task	Contribution
<b>Qualitative study</b>		
Preparation	Study design	Developed concepts and designed the study based on the literature and in collaboration with supervisors.
	Ethics application	Completed the ethics application through the Massey University Human Ethics Committee.
	Interview guide development	Developed the interview guide with probes.
	Participant forms	Developed the information sheet and consent form.
Recruitment and interviews	Advertisement	Created all advertising materials including letters and emails to organisations such as College of Midwives, Plunket, La Leche League and Playcentres.
	Site visits	Visited Playcentres to meet breastfeeding mothers; attended College of Midwives meetings to meet midwives.
	Conference Interviews	Recruited and interviewed three postnatal healthcare professionals from La Leche League Conference 2014. Conducted interviews either face-to-face or via phone calls.
Data management and analysis	Transcription	Transcribed all interviews manually.
	Coding	Imported transcripts to NVivo to manage codes.
	Data analysis	Created coding frame and discussed with supervisors regularly.
<b>Randomised Controlled Trial (RCT)</b>		
Preparation	Study design	Co-designed the study based on the literature and in collaboration with supervisors.
	Ethics application	Completed the ethics application through the Massey University Human Ethics Committee; submitted amendments (i.e., change in study design, sample size, and recruiting area) as required throughout the study period.
	Trial registration	Registered the trial with the Australian New Zealand Clinical Trials Registry (ANZCTR); updated trial status annually
	Funding application	Assisted with Massey University Research Fund application.
	Participant forms	Developed the information sheet and consent form.
	Questionnaires	Developed all study questionnaires online via Qualtrics platform.
	Record forms	Developed 24-hr feeding and nappy change record, hourly expression record and infant anthropometry record.
	Information of support	Developed a list of online and local breastfeeding support; developed a list of support for postnatal depression.
	Standard operating procedures (SOPs)	Developed SOPs for hourly expression, infant anthropometry, Human Nutrition Research Unit (HNRU) visits.
Trial protocol	Developed a trial protocol for data collection.	
Recruitment	Advertisement	Designed all advertising materials including posters and flyers; developed letters and emails to organisations such as College of Midwives, Plunket, La Leche League, Playcentres and childcare centres.

<b>Stage</b>	<b>Task</b>	<b>Contribution</b>
	Site visits	Visited Playcentres, childcare centres, healthcare centres, Parent Centre, midwife clinics, pharmacies, and supermarkets to distribute study flyers; attended, La Leche League meetings, breastfeeding mother groups (i.e., Milk Cafe), antenatal classes to meet mothers.
	Trial Facebook page	Created trial Facebook page to communicate with potential participants and to promote study via over 100 Facebook groups in Manawatu and Wellington areas.
	Advertisement campaign	Developed a paid advertisement campaign via Facebook and Google.
	Press release	Reviewed press release to promote recruitment that were published on the Massey University website and Stuff.
	Parent Centre Magazine	Created a paid targeted advertisement for Palmerston North Parent Centre Magazine.
Administration	Study contact	Was the main contact for all participants.
	Study schedules	Scheduled all the appointments for HNRU and home visits, as well as the follow up surveys.
	Equipment and consumables	Purchased the manual capsule filler, study breast pump and consumables such as breast milk storage bags, tubes etc.
	Participant documentation	Kept all participant information up to date in an Excel sheet with password.
	Participant pack	Arranged all packs for participants including study information sheet, 24-hr feeding and nappy change record, information sheet of contacts of local and online breastfeeding support, and the study capsules.
Study capsules	Capsule filling procedure	Established a procedure for capsule filling to determine the number of capsules for daily dose and to minimise the weight variation between capsules.
	Supplement pack	Filled the capsules, labelled the containers, and made the supplement pack for every participant.
Data collection and management	Study visits	Conducted all visits in the HNRU or at participant's home. Accomplished infant anthropometric measurements: height, weight, head circumference. Completed the hourly expression protocol for the first 24 participants. Collected 24-hr feeding and nappy change records.
	Milk sample	Transferred the collected breast milk to 5mL storage tubes and stored at – 80 °C freezer. Transported the breast milk samples to Te Ohu Rangahau Kai for human milk oligosaccharides (HMOs) analysis.
	Questionnaires	Created and managed all questionnaires using Qualtrics. Identified incorrect, or incomplete answers and contacted the participants to obtain correct information.
	Data cleaning and transformation	Identified incorrect, duplicate, or incomplete data and removed from dataset as necessary. Formatted, organised and/or combined multiple datasets for SPSS analysis. Transformed normal datasets to long format for linear mixed model analysis for hourly expression.

<b>Stage</b>	<b>Task</b>	<b>Contribution</b>
Covid-19 management	Protocol adjustment Participant communication	Reviewed the protocol and changed study design (i.e., changed the main aim and primary outcome to evaluate the effect on HMOs and reduced the visits to two). Obtained the ethics approval on these changes. Drafted email to participants providing protocol updates and to request for consent of HMO analysis; acted as primary contact for participant queries
Data analysis	SPSS	Analysed data from milk sample analysis, questionnaires, 24-feeding and nappy change records, and anthropometry using SPSS.
Thesis writing and publications	Manuscripts Thesis	Drafted all manuscripts and amended the manuscripts according to co-authors' comments. Submitted manuscripts to peer-review journals and drafted the response to reviewers and amended the manuscripts with support from co-authors. Completed the first draft of the entire thesis and amended according to supervisors' comments.