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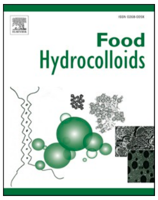

Recent advances in the conjugation approaches for enhancing the bioavailability of polyphenols

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ABSTRACT

In recent years, the consumption of functional foods containing health-beneficial ingredients has become increasingly popular. Polyphenols are among the most important functional and bioactive molecules found in a variety of fresh produce and food products. However, the limited solubility of most polyphenols in water can significantly affect their bioavailability, thereby reducing their potential health benefits. To overcome this limitation, various approaches have been explored, including molecular enhancers, nanoparticles, encapsulation systems, and conjugation methods. In this review, we focus on recent advances in conjugation methods for enhancing the bioavailability of polyphenols. We provide a concise overview of the types of polyphenols and bioavailability determination methods and, subsequently, discuss the concept of conjugation methods, including different synthesizing methods, confirmation procedures, and the effects of conjugation on polysaccharides and polyphenols. Overall, this review provides a comprehensive update on recent advances in conjugation methods that can be used to improve the bioavailability of polyphenols and highlights the potential of these approaches to enhance the health benefits of polyphenol-rich foods.

1. Introduction

Natural polyphenols are bioactive substances and secondary metabolites that are widely present in plant-based sources such as fruits and vegetables. These compounds serve as protectors against UV light and pathogenic microorganisms (Rasouli, Farzaei, & Khodarahmi, 2017). Based on their chemical structure, polyphenols can be divided into four groups: flavonoids, phenolic acids, lignans, and stilbenes (Abbas et al., 2017). They offer numerous health advantages in the treatment of cardiovascular illnesses, cancer, diabetes, and a variety of other degenerative, aging-related, and infectious conditions (Catalkaya et al., 2020; Raman et al., 2019; Yoshioka, Ohishi, Nakamura, Fukutomi, & Miyoshi, 2022).

As people shift their choices toward healthier lifestyles, natural polyphenols have become increasingly popular as they are perceived to possess health-beneficial properties. Additionally, these phytochemicals are considered safe for human consumption due to their insignificant toxicity to the human body. Their antioxidant and antimicrobial activities have been proven, making them a popular candidate for food ingredients. For example, 1–2% of people throughout the world suffer from epilepsy, which is the most prevalent neurological illness characterized by recurring spontaneous seizures. Many investigations have been conducted in the hope of finding a suitable replacement for benzodiazepines and a natural remedy for this illness. It was found that the structure of flavonoids is similar to the structure of benzodiazepines, making them potential GABA agonists (Park et al., 2007; Ramalingam, Nath, Madhavi, Nagulu, & Balasubramaniam, 2013). Hence, the addition of polyphenolic compounds to food and pharmaceutical products improves their health-beneficial quality. However, the bioavailability of polyphenols is limited due to their low solubility and uptake in the gastrointestinal tract. Furthermore, because these compounds possess numerous –OH groups, they are susceptible to light, heat, and alkaline environments (Oliver, Vittorio, Cirillo, & Boyer, 2016). Numerous studies have shown that only a small fraction of dietary polyphenols can be absorbed and reach their target cells to exert their biological effects. For example, Rasmussen, Frederiksen, Struntze Krogholm, and Poulsen (2005) concluded that only proanthocyanidins with a degree of polymerization (DP) < 2 are metabolized in the gut. A high degree of hydrophobicity and rapid metabolization and excretion are the primary reasons for the low absorption of curcumin and naringenin (Anand, Kunnumakkara, Newman, & Aggarwal, 2007; Erlund, 2004). The inherent instability of anthocyanins, especially when subjected to food

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processing and gastrointestinal conditions, leads to their limited absorption (Di Lorenzo, Colombo, Biella, Stockley, & Restani, 2021). Several food rich in polyphenolic compounds induce astringency in the mouth cavity due to their capability to precipitate salivary proteins (Cai et al., 2020). While astringency is considered a desirable characteristic in certain foods and beverages (e.g., wine), it is important to note that the binding capacity of polyphenols to proteins represents a significant limitation of these compounds. Therefore, it is not unexpected to restrict the activities of digestive enzymes such as pepsin, elastase, and trypsin, when polyphenols reach the gastrointestinal tract (Cirkovic Velickovic & Stanic-Vucinic, 2018). Additionally, polyphenol-protein complexes can be developed in food products during processing and storage, thus influencing the nutritional value of proteins and lowering their digestibility rate (Dufour et al., 2018). It is also reported that the presence of anti-nutrients, such as phytates, tannins, and some polyphenols, can lead to a decrease in the bioavailability of essential minerals such as iron, zinc, and copper, thereby hindering their absorption by the body (Feitosa et al., 2018). However, it is also disclosed that the antinutritive effect of polyphenols is dose-dependent and affected by the food matrix and the presence of other dietary compounds. Additionally, scientists have been reporting that the antinutritive activities of these compounds may be offset by their functionalities and health-beneficial effects (Manach, Scalbert, Morand, Rémésy, & Jiménez, 2004; Nath, Samtiya, & Dhewa, 2022).

To address challenges in the bioavailability of polyphenols, it is crucial to recognize the factors affecting the bioavailability of these compounds. These factors can be divided into three different categories: molecule-related, food-related, and host-related factors. The former includes the nature and the structure of molecules while food-related factors can be regarded as the food matrix and liberation condition of polyphenols, food processing method, interaction with other compounds, the concentration of these compounds in the food formulation, etc. Host-related factors also include age, gender, health condition, and other factors related to the consumer.

The term “bioactivity” refers to the beneficial physiochemical effects of a compound, and “bioaccessibility” refers to any condition by which a bioactive compound can be absorbed in the gastrointestinal tract and be presented in the circulatory system of the human body. Furthermore, “bioavailability” is regarded as the capability of a bioactive compound to be digested, absorbed, distributed, metabolized, and/or stored in human cell/culture or organs (Cardoso, Afonso, Lourenço, Costa, & Nunes, 2015; Wood, 2005). Therefore, any condition that affects the bioaccessibility of a bioactive compound directly affects its bioavailability.

In this review, our main focus is on the utilization of conjugates as innovative techniques to enhance the bioaccessibility and bioavailability of polyphenols. To overcome the challenge of low bioavailability associated with polyphenols, several approaches have been explored. These include investigating different food processing conditions to minimize polyphenolic compound degradation, as well as employing techniques such as encapsulation and chemical and structural modifications to modify their bioavailability. Among these approaches, the use of conjugates has demonstrated significant advantages over other methods, positioning them as promising candidates for various food and pharmaceutical formulations. Therefore, this review centers on the synthesis procedures for polyphenolic conjugates based on proteins and polysaccharides. Additionally, we discuss various approaches for measuring the bioavailability of these conjugates, methods for analyzing them, and their potential applications.

The detailed information presented in this study serves as a valuable resource for scientists, providing them with procedures, ideas, and references to consider in their prospective research endeavors related to the production of polyphenolic conjugates. Furthermore, it offers insights into enhancing the bioavailability of these conjugates and exploiting them as modified functional ingredients. To illustrate a suitable approach for enhancing bioavailability, it is crucial to recognize various types of polyphenolic compounds, which are delineated in the following section. By understanding the different classes of polyphenols and their structural variations, researchers can tailor conjugation techniques to optimize bioavailability. Finally, the findings of this study can lead to the understanding of the factors that influence the bioavailability of polyphenols and the appropriate techniques, such as conjugation, that can significantly improve the efficacy of polyphenols in promoting human health. By harnessing the potential of polyphenolic conjugates, researchers can develop innovative strategies to maximize the bioavailability of these compounds and unlock their full therapeutic potential.

2. Types of polyphenols and their structure

Polyphenols are a large class of phytochemicals that are found in various fruits and vegetables. They are chemically diverse substances that possess antioxidant and anti-inflammatory properties and are known to offer numerous health benefits to consumers. Polyphenols exist in the outer layers of plant tissues and their seeds as a protective mechanism against environmental stressors. As shown in Fig. 1, the main types of polyphenols are classified into two categories: flavonoids and non-flavonoids (Tsimogiannis & Oreopoulou, 2019).

Flavonoids are a subclass of polyphenols that are further classified into several subcategories based on their chemical structure. They are widely distributed in plant foods and include compounds such as anthocyanins, flavones, flavanones, flavonols, and isoflavones. Anthocyanins are the most pigmented flavonoids and are responsible for the blue, purple, and red colors in many fruits and vegetables. They are glycosides of anthocyanidins, which are unstable and can be converted into stable anthocyanins by attaching glucose molecules to their structure. Non-flavonoid polyphenols are also chemically diverse and include several subtypes, including phenolic acids, stilbenes, and lignans. Phenolic acids are the most abundant type of non-flavonoid polyphenols, and they are found in many plant foods, such as coffee, tea, and fruits. The most common phenolic acids include salicylic acid, gallic acid, syringic acid, hydroxybenzoic acid, and protocatechuic acid. Hydroxycinnamic acids, such as caffeic acid, ferulic acid, and synaptic acid, are also included in this category.

Complex polyphenolic compounds, such as tannins, are also present in some plant foods. Tannins are polyphenols with a condensed structure that can be hydrolyzed. They can bind to proteins and are called “tanning” compounds. Tannins are found in various plant sources, such as tea, wine, and fruits. Understanding the chemical composition and structure of polyphenols can provide insight into their health benefits and bioavailability in the body.

2.1. Flavonoids

Flavonoids are a group of polyphenolic compounds that constitute around two-thirds of the polyphenols in plants, while phenolic acids make up the other third (Li et al., 2020). They have a basic structure of C6–C3–C6 and are subcategorized into flavanols, flavonols, flavones, flavanones, and anthocyanins. The basic structures of flavonoids are shown in Fig. 2. Quercetin and kaempferol are two well-known compounds found in the flavonol group. These compounds are typically found in glycosylated forms, which are more soluble and stable. The sugar portion consists of glucose or rhamnose, although other sugar molecules such as rhamnose (in quercitrin and naringin), arabinose (in Quercetin 3-*O*-alpha-ᴅ-arabinopyranoside), and rutinose (in rutin) are also found (Amaretti, Raimondi, Leonardi, Quartieri, & Rossi, 2015; Dai, Tuan, Thang, & Ogunwande, 2014; Kanaze, Bounartzi, Georgarakis, & Niopas, 2007; Morand, Manach, Crespy, & Remesy, 2000).

2.1.1. Anthocyanins

Anthocyanins are water-soluble polyphenolic compounds found in the vacuole, and their color is pH-dependent. These compounds are

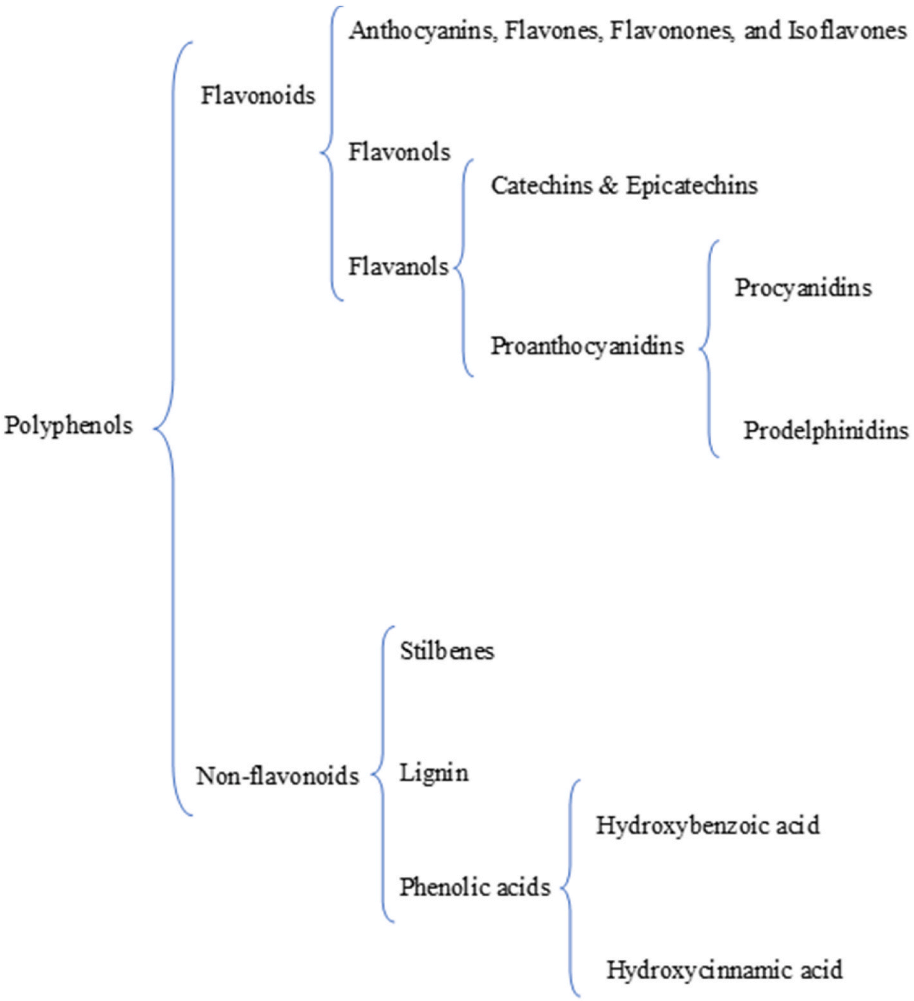


Fig. 1. Classification of polyphenols.

glycosylated forms of anthocyanidins, which are ubiquitously found in Vaccinium species such as cranberries, blueberries, and bilberries (Davies, 2004). Generally, more than one sugar molecule is attached to the anthocyanidins at the position of the OH of the C3 group in the C-ring. However, 3-deoxyanthocyanidins are exceptions as they are not in glycosylated forms due to their instability in natural conditions (Archetti et al., 2009). Most anthocyanins include pelargonidin, cyanidin, peonidin, delphinidin, petunidin, and malvidin, and R′3, R′4, and R′5 are responsible for their color (Wallace & Giusti, 2015).

2.1.2. *Flavones*

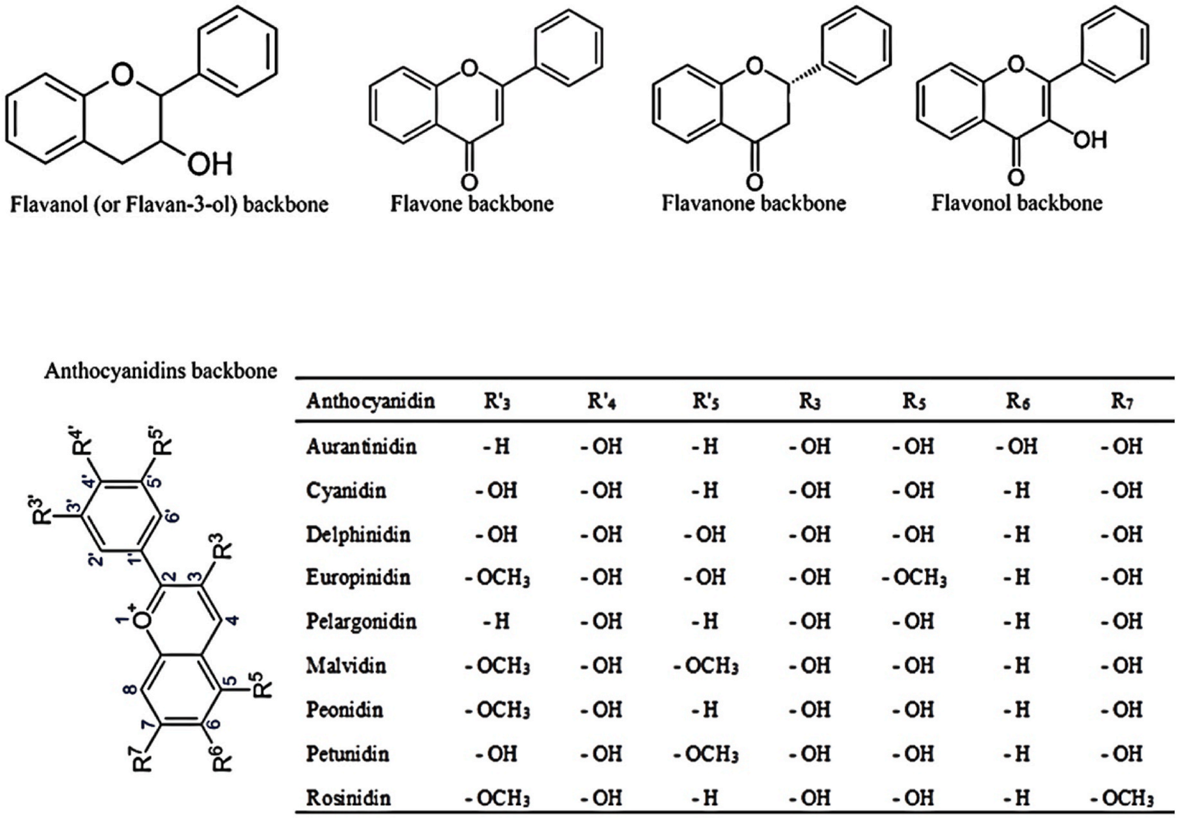
Flavones are another group of flavonoids that have the structure of C6–C3–C6, which are called A-ring, C-ring, and B-ring, respectively. Their crystals are dissolved in alkaline solutions and exhibit a yellow color, while they are mostly uncolored in other solutions (Singh et al., 2014). Chrysin, luteolin, and apigenin are three well-known flavones with high antioxidant capacity even at low concentrations (Greeff, Joubert, Malan, & van Dyk, 2012; McCord, 1995). Chrysin has been reported to have high activity against different kinases, including cyclin-dependent kinases and glycogen synthase kinase-3 (Nguyen et al., 2012). Other flavones include amentoflavone, baicalein, capitavine, chrysoeriol, eupafolin, flavopiridol, morelloflavone, nobiletin, and wogonin.

2.1.3. *Flavanones*

Flavanones are found in citrus fruits, tomatoes, and aromatic herbs such as mint. Hesperetin, naringenin, prunin, eriodictyol, isosakuranetin, and their glycosides, such as naringenin chalcone, are some well-known flavanones. Naringenin is the aglycone portion of naringin, and its sugar portion is neohesperidose, a disaccharide that causes skin cancer prevention. In a study by Park, Choi, Hong, Jung, and Suh (2017), the effect of quercetin, a flavonol, on UVB-induced skin carcinogenesis in hairless mice was evaluated. The results showed that quercetin significantly suppressed tumor incidence and tumor multiplicity, and also inhibited the expression of pro-inflammatory cytokines and oxidative stress markers. Another study by Fotsis et al. (1997) investigated the effect of genistein, a flavonoid found in soy products, on the growth of breast cancer cells. The results indicated that genistein inhibited the growth of cancer cells by inducing apoptosis, and it was also found to inhibit the growth of blood vessels supplying the tumor. In addition, some studies have reported that the intake of flavonoids and other polyphenols may help reduce the risk of various chronic diseases, such as cardiovascular disease, diabetes, and neurodegenerative diseases (Dryden, Song, & McClain, 2006; Ferretti, Turco, & Bacchetti, 2014; Renaud & Martinoli, 2019).

2.1.4. *Flavanols*

Flavanols, which are called flavan-3-ols, can be subclassified into two distinct categories, including catechins (and epicatechin) and proanthocyanidins, which are in monomeric and polymeric forms, respectively. The latter is found to be broken down into monomers or dimers through digestion before uptake. These compounds are profoundly found in cocoa, red wine, red grapes, and berries (Luo et al., 2022). In fact, proanthocyanidins are further divided into two groups,



Anthocyanidin	R'₃	R'₄	R'₅	R₃	R₅	R₆	R₇
Aurantinidin	- H	- OH	- H	- OH	- OH	- OH	- OH
Cyanidin	- OH	- OH	- H	- OH	- OH	- H	- OH
Delphinidin	- OH	- OH	- OH	- OH	- OH	- H	- OH
Europinidin	- OCH_3	- OH	- OH	- OH	- OCH_3	- H	- OH
Pelargonidin	- H	- OH	- H	- OH	- OH	- H	- OH
Malvidin	- OCH_3	- OH	- OCH_3	- OH	- OH	- H	- OH
Peonidin	- OCH_3	- OH	- H	- OH	- OH	- H	- OH
Petunidin	- OH	- OH	- OCH_3	- OH	- OH	- H	- OH
Rosinidin	- OCH_3	- OH	- H	- OH	- OH	- H	- OCH_3

Fig. 2. The basic structures of flavonoids: Flavanols, flavonols, flavones, flavanones and anthocyanidins.

including procyanidin and prodelphinidin. Every flavonoid that has been discussed till now is said to be found mostly in the glycosidic form, while flavanols are reported to be frequently in the form of aglycon. However, as shown in Fig. 3, flavanols can be esterified with gallic acid in the form of epigallocatechin gallate (EGCG), epigallocatechin (EGC), and epicatechin gallate (ECG) (Hackman et al., 2008). In addition to these compounds, epiafzelechin, epicatechin, fisetinidol, guibourtinidol, mesquitol, and robinetinidol are also included as flavanols (Jang et al., 2010; Mouton, 1989; Porter, 2017).

While flavones, flavanones, and flavanols share some similarities in

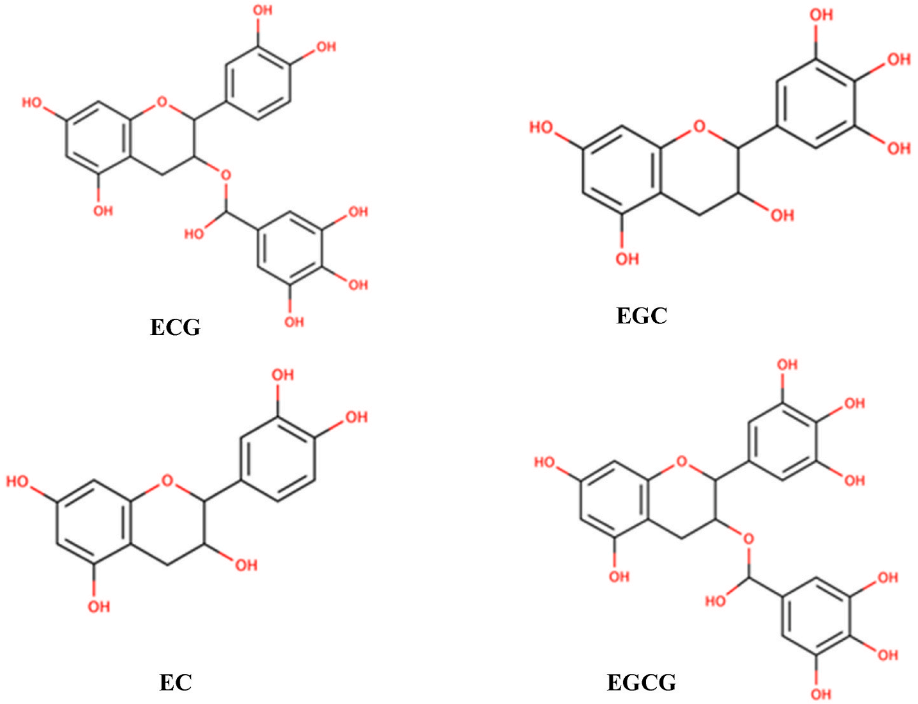


Fig. 3. The chemical structure of epigallocatechin gallate (EGCG), epigallocatechin (EGC), epicatechin gallate (ECG), and epicatechin (EC).

their chemical structures and biological properties, they also exhibit some differences in their sources, taste, and specific health benefits. For example, flavones are found in a variety of fruits, vegetables, and herbs, while flavanones are abundant in citrus fruits, and flavanols are found in tea, cocoa, and some fruits and vegetables (Manach et al., 2004). Flavanols have a bitter taste, which can be perceived by the taste buds on the tongue. The activation of bitter taste receptors by monomeric flavanols is found to induce the secretion of ghrelin (hunger hormone). Conversely, the release of ghrelin was found to be inhibited by oligomeric flavanols (Serrano et al., 2016). It is acknowledged that flavones, flavanones, and flavanols have antioxidant and anti-inflammatory properties; however, they exhibit some differences in their biological activities. For instance, flavones have demonstrated potential as anticancer agents. Certain flavones, such as apigenin and chrysin, have been found to possess anxiolytic and sedative properties (Wang et al., 2023). In contrast, flavanones have been reported to have cardiovascular benefits, including reducing blood pressure and enhancing endothelial function, in addition to their potential anticancer effects. Similarly, flavanols, like catechins and epicatechins, are recognized to promote cardiovascular health through other biological activities (Alotaibi et al., 2021).

2.2. *Non-flavonoid polyphenols*

As mentioned earlier, non-flavonoid polyphenols include stilbenes, lignin, and phenolic acids. The former is said to be less frequent in the human diet (Manach et al., 2004). Among stilbenes, resveratrol is a well-known compound that is present in low amounts in red wine, and has been shown to have several health benefits such as immunomodulatory, anti-inflammatory, and anti-angiogenic properties (Dubrovina & Kiselev, 2017). Structurally, these compounds are in the form of either monomeric or oligomeric (Shen, Wang, & Lou, 2009). For example, bibenzyls, phenanthrenes, macrocyclic lactones, and combretastatins are included as monomeric stilbenes (Goufo, Singh, & Cortez, 2020; Kiselev & Dubrovina, 2021). In addition, resveratrols, isorhapontigenins, piceatannols, and oxyresveratrols are in the form of oligomers (Aja et al., 2020; Chen, Luo, Ye, & Hu, 2001).

Lignin has a complex structure in which phenolic precursors are cross-linked with each other. This compound is profoundly found in cell walls in wood or bark to support tissues. Several phenolic compounds are found to be the monomers of lignin (Vanholme, Morreel, Ralph, & Boerjan, 2008, 2012). For example, coniferyl alcohol, sinapyl alcohol, and paracoumaryl alcohol are prevalent in lignin (Fig. 4). Despite its limited application in the food industry, lignin remains an important and valuable polyphenol with a wide range of applications. For example, one of the most significant applications of lignin is as a bio-based alternative to fossil fuels. A vast amount of lignin is produced by various industries such as paper production factories, and exploiting them as an alternative to fossil fuels can significantly reduce waste (Saini et al., 2023; Sjostrom, 2013). On the other hand, the term "lignan" refers to small water-soluble molecules, while lignin is substantially dense, undigestable, and insoluble in water. Lignan and lignin are related, but they are not the same substances. In fact, lignans are the building blocks of lignin in plants and both of them have the same precursors. To illustrate their relationship, monolignols are good examples. It is reported that in plant cells oxidative enzymes such as laccase and peroxidase may polymerize monolignols through radical coupling to produce lignans prior to the biosynthesis of lignin (Zitterman, 2003). As shown in Fig. 5, lignans are divided into eight groups, including furofuran, furan, arylnaphthalene, aryltetralin, dibenzylbutyrolactone, dibenzylbutane, dibenzocyclooctadiene, and dibenzylbutyrolacto. These compounds also consist of monolignols such as matairesinol (in debenzylbutyrolactone), secoisolariciresinol (in dihydroxydibenzylbutane), justicidin A (in arylnaphthalene), pinoresinol (in furofuran), steganacin (in dibenzocyclooctadienelactone), and podophyllotoxin (in aryltetralin) as their monomers (Al-Juaid & Abdel-Mogib, 2004; Broomhead, Rahman, Dewick, Jackson, & Lucas, 1991; Hemmati & Seradj, 2016; Johnsson, Kamal-Eldin, Lundgren, & Åman, 2000; Kupchan et al., 1973; Markulin et al., 2019).

As shown in Fig. 1, phenolic acids, or phenolcarboxylic acids, can be divided into benzoic acid derivatives (hydroxybenzoic acids) and cinnamic acid (hydroxycinnamic acids) derivatives (see Fig. 6) (Shahidi & Naczk, 1995; Tomás-Barberán & Clifford, 2000). It is reported that in comparison to other polyphenolic compounds such as flavonoids, plants have lower concentrations of phenolic acids, except for tea leaves, red fruits, black radishes, and onions. In addition, phenolic acids exist in both free and esterified (parabens) forms. Some parts of hydrolyzable tannins, such as gallotannins and ellagitannins, consist of these compounds. Phenolic acids are soluble in water in small amounts, while they are miscible in polar organic solutions such as alcohol and acetone (Gracin & Rasmuson, 2002).

Salicylic acid, 4-hydroxybenzoic acid, protocatechuic acid, gentisic acid, vanillic acid, syringic acid, gallic acid, ellagic acid, and hexahydroxydiphenic acid (ellagic acid dilactone) are included as hydroxybenzoic acids (Tomás-Barberán & Clifford, 2000). On the other hand, hydroxycinnamic acids or hydroxycinnamates, which have a basic structure of phenylpropanoid C6–C3 structure, are more prevalent in comparison to hydroxybenzoic acids. Some of the compounds in this group are α-cyano-4-hydroxycinnamic acid, caffeic acid, quinic acid, chlorogenic acid, cichoric acid, cinnamic acid, coumaric acid, diferulic acids, ferulic acid, and sinapinic acid. These compounds are not found in free form but are present in the form of glycosides or esters of quinic acids. However, small amounts of them can be found in processed food products (Teixeira, Gaspar, Garrido, Garrido, & Borges, 2013). A comprehensive study by Möller and Herrmann (1983) showed that free quinic acid was not detectable in numerous varieties of fruits while its esters including 5′-caffeoylquinic acid, 3′-caffeoylquinic acid, and 4′-*p*-coumaroylquinic acid were determined.

Chlorogenic acids consist of caffeic acid and quinic acid and are found prevalently in coffee and fruits (Clifford, 1999). Caffeic acid is the predominant phenolic acid in fruits (Birková, Hubková, Bolerázska, Mareková, & Čižmárová, 2020). In contrast, ferulic acid is prevalent in cereals and found mostly in the outer parts (aleurone layer and the pericarp) (Renger & Steinhart, 2000).

3. Bioavailability and bioaccessibility of polyphenols

In order to broaden our understanding of the bioavailability of polyphenolic compounds, it is important to acquire information about their absorption mechanism through the gastrointestinal tract.

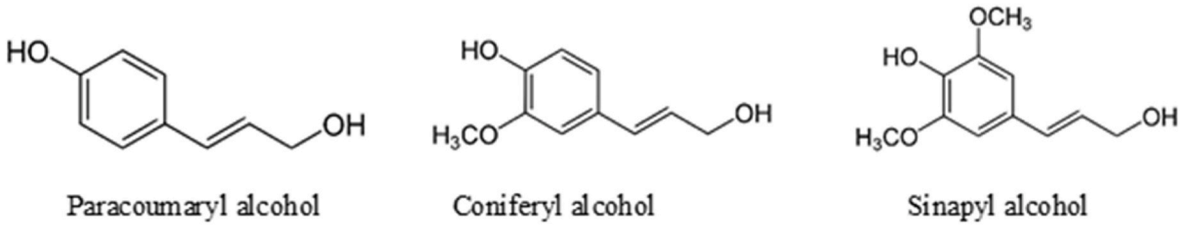


Fig. 4. The chemical structures of prevalent monomers of lignin, paracoumaryl alcohol, coniferyl alcohol, and sinapyl alcohol.

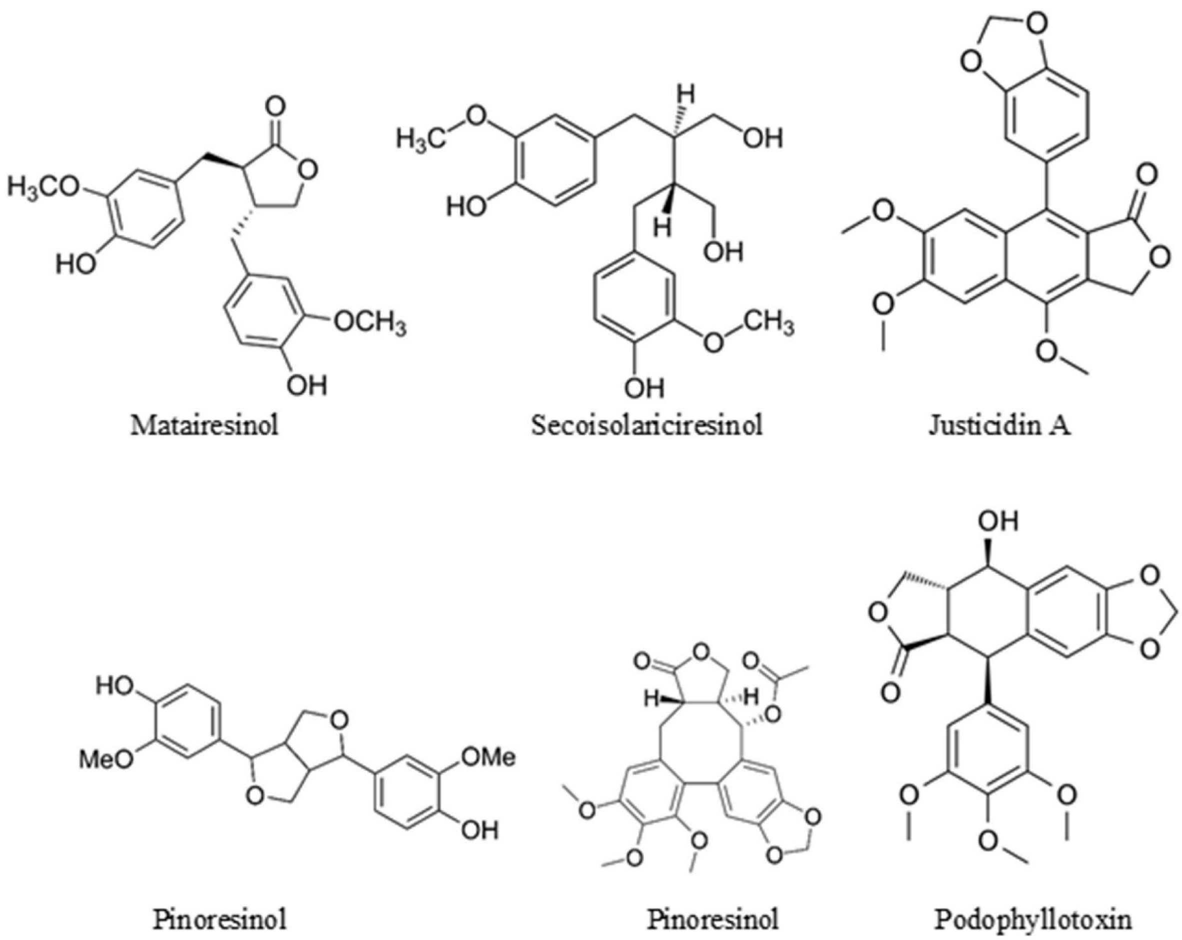


Fig. 5. The chemical structure of some frequent monolignols.

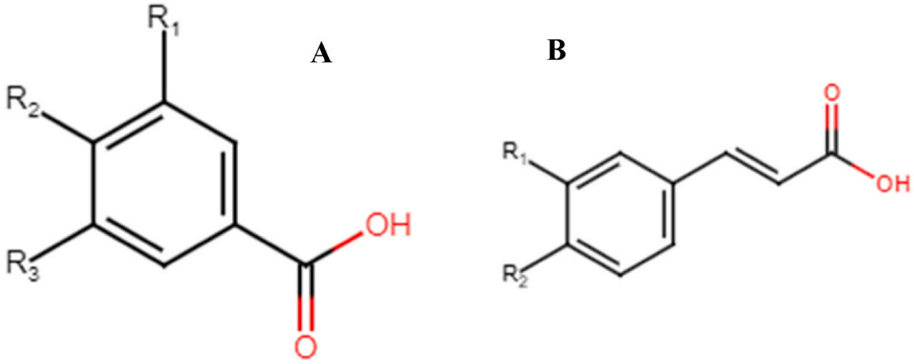


Fig. 6. The basic skeleton of hydroxybenzoic acids (A) and hydroxycinnamic acids (B).

Polyphenols that are not ingested and uptaken are metabolized by colonic microflora and transformed into their simple aglycon forms if they were in conjugated form (Aura et al., 2005). For example, the formation of equol (an isoflavandiol estrogen) from diazine (an isoflavone) is one such transformation that produces active forms of polyphenols by colonic microflora (Setchell, Brown, & Lydeking-Olsen, 2002). On the other hand, oligomeric polyphenols are hydrolyzed into their monomeric form in the stomach. The colon is the absorption venue of the aglycon portion, where the polyphenolic compound undergoes hydrolyzation through which the glycosidic bond is dissociated and results in the aglycon portion. After the absorption of the aglycons, these compounds are structurally modified in the liver before reaching the blood circulation system or being excreted. It is said that the polyphenols that reach cells or tissues are distinct from the original chemical structure or functionality in comparison with the consumed molecules. However, anthocyanins are absorbed in their glycosidic form and present in blood circulation (D'Archivio, Filesi, Varì, Scazzocchio, & Masella, 2010).

Different approaches are employed to evaluate the bioavailability and bioaccessibility of polyphenols. Based on the definition of bioactivity, bioavailability, and bioaccessibility, bioactivity can be assessed through *in vitro*, *ex vivo*, and *in vivo* methodologies, while bioaccessibility and bioavailability can be evaluated through *in vitro* and *in vivo* approaches, respectively (Fernández-García, Carvajal-Lérida, & Pérez-Gálvez, 2009). These methods, which have their advantages and disadvantages, are as follows: *in vitro* models such as simulated gastrointestinal digestion, artificial membranes, Caco-2 cell cultures, isolated/reconstituted cell membranes, *ex vivo* models such as human immune cells or gastrointestinal organs in laboratory conditions, and *in situ* models including intestinal perfusion in animals, and *in vivo* models including animal and human studies (Carbonell-Capella et al., 2014). *In vivo* assays provide direct data on the bioavailability of polyphenols, while *in vitro* tests are quicker, cheaper, and do not require ethical and legal commitment. For example, isoflavones and simple phenolic acids such as gallic acid are taken up in the small intestine, while complex polyphenols are absorbed in lower amounts (Hackman et al., 2008; Martin & Appel, 2009). In the following section, the aforementioned approaches are discussed in detail.

3.1. *In vitro models*

Scientists have commonly employed *in vitro* models such as simulated gastrointestinal digestion to evaluate the bioaccessibility of polyphenols (Bermúdez-Soto, Tomás-Barberán, & García-Conesa, 2007; Bouayed, Hoffmann, & Bohn, 2011; Chen et al., 2013; Dupas, Marsset Baglieri, Ordonaud, Tomé, & Maillard, 2006; Gil-Izquierdo, Zafrilla, & Tomás-Barberán, 2002). Generally, *in vitro* digestion methods used for food are categorized as static or dynamic. The aim of these models is to replicate the physiological conditions of the oral, gastric, and small intestinal phases of the upper gastrointestinal tract. While dynamic models have been proven to be effective for simulating food and pharmaceutical digestion in various populations and for diverse purposes, they are complex and expensive to establish and maintain, and may not be accessible to the majority of food researchers (Thuenemann, 2015). On the other hand, static models have been extensively employed for food, animal feed, and pharmaceutical purposes due to their simplicity. These models use a fixed ratio of food to enzymes and electrolytes, as well as a constant pH for each digestive phase. This approach has been in use for several decades. *In vitro* static digestion models have demonstrated their performance in prognosticating the outcomes of *in vivo* digestion (Alegría, Garcia-Llatas, & Cilla, 2015). Standardized static models are available in varying degrees of complexity, such as the United States Pharmacopeia methods and Bioaccessibility Research Group of Europe (BARGE). However, these models were deemed unsuitable for digesting food due to the complexity and variability of food structures, as well as differences in research questions in food science. Consequently, there was a need to standardize digestion conditions, leading to the establishment of the international INFOGEST network in 2005. This network comprises multidisciplinary experts from over 35 countries in fields such as food science, nutrition, gastroenterology, engineering, and enzymology (Brodkorb et al., 2019).

The INFOGEST technique was intentionally developed to be compatible with standard laboratory equipment and requires only minimal expertise, thereby promoting its adoption among a diverse pool of researchers. According to Brodkorb et al. (2019), this digestion method is static in nature and constant ratios of food to digestive digestion fluids, as well as a fixed pH value for each stage are used. Such an approach ensures uniformity throughout the digestion process. It is noteworthy that INFOGEST approach is not a valid study of digestion kinetics simulation. In this method, food specimens undergo a stepwise process of oral, gastric, and intestinal digestion. The electrolytes, enzymes, bile, dilution, pH, and duration of each stage of digestion are determined based on existing physiological data. By analyzing the products of digestion, this technique enables the assessment of endpoints resultant from food digestion. The *in vitro* digestion method involves three phases: preparation, digestion procedure, and sample treatment with subsequent analysis. It is crucial to determine the concentrations of bile salts and activities of all digestive enzymes experimentally during the preparation stage, using recommended standardized assays. Failure to do so accurately can lead to incorrect digestion rates and alter the overall digestion of the food. The digestion process exposes the food to three successive phases: oral, gastric, and intestinal, with constant experimental conditions during each phase. The oral phase involves diluting the food with simulated salivary fluid and, if necessary, subjecting it to simulated mastication and exposure to salivary amylase. The oral phase is essential in all simulated digestion procedures to maintain consistency of dilution (Brodkorb et al., 2019). It should be noted that the pH of the stomach can vary between individuals and can depend on factors such as the type of food consumed and the person's age and health status. In general, the pH of the stomach can range from 1.5 to 3.5. Due to the dynamic pH condition in the stomach, in some food digestion studies, researchers may choose to conduct the gastric phase at pH 2.0, while others may choose to conduct it at pH 3.0 (Akritidou et al., 2022).

In the static *in vitro* models, the phenol-containing sample is homogenized in simulated saliva prior to mixing in the oral phase. This is followed by the gastric phase in which pepsin enzymes are added at a pH of 2 and incubated at 37 °C. Subsequently, the mixture undergoes a transition process in which the pH value increases. In the small intestine step, porcine bile extract, porcine pancreatin, and lipase are added at a pH of approximately 7 and incubated at 37 °C for 2 h. After this step, the separation process is conducted to evaluate the hydrolyzed polyphenolic compounds. Additionally, Dupas and colleagues used Caco-2 cells to simulate the uptake process (Dupas et al., 2006). For example, Gil-Izquierdo and colleagues used this method to assess the bioavailability of some polyphenolic compounds in orange juice. They reported that narirutin, hesperidin, total flavanones, and vicenin-2 showed 10.5%, 16.2%, 12.0%, and 18.6% bioavailability, respectively (Gil-Izquierdo, Gil, Ferreres, & Tomás-Barberán, 2001). Furthermore, Chiang, Kadouh, and Zhou (2013) assessed the bioavailability of polyphenols in Invicta gooseberry using the aforementioned approach. They found that caffeic acid, kaempferol, ρ-coumaric, quercetin hydrate, resveratrol, and rutin showed 59.5%, 82.8%, 73.4%, 154.7%, 94.6%, and 101.0% bioavailability (Chiang et al., 2013).

The Parallel Artificial Membrane Permeability Assay (PAMPA) is a filter-based approach used to examine the passive transportation of bioactive molecules and their derivatives across artificial membranes, mimicking the skin barrier, blood-brain, and gastric barriers (Bélair et al., 2021). As shown in Fig. 7 (a), this device consists of a well containing digested polyphenols called a "donor compartment" placed at the bottom, a lipid-based membrane mimicking the cell membrane, and an acceptor compartment without polyphenols placed on top. After a predetermined incubation time, the content of the acceptor well is examined using UV–vis spectroscopy or mass-spectrometric analysis (Navarro del Hierro, Piazzini, Reglero, Martin, & Bergonzi, 2020). In this method, *in vitro* gastrointestinal digestion is also required if the digested polyphenols are involved in the assay.

In 1977, Fogh and colleagues established the Caco-2 cell culture at the Sloan-Kettering Institute for Cancer Research. Caco-2 cells, derived from human colon carcinoma, are human intestinal epithelial cells used to examine the absorption of polyphenolic compounds, which is a good indication of absorption in the human intestine. Despite their colonic origin, Caco-2 cells have morphological and functional traits of small intestine cells. The cells are seeded into filter-based wells (see Fig. 7 (b)) and allowed to proliferate and differentiate into confluent monolayers for approximately three weeks after seeding to conduct transport tests. Prior to the transport experiment, the transepithelial electrical resistance (TEER) or the permeability of paracellular markers such as mannitol, inulin, dextran, and lucifer yellow are measured to ensure the Caco-2 monolayer's cohesion (Kamiloglu, Capanoglu, Grootaert, & Van Camp, 2015; Sun, Chow, Liu, Du, & Pang, 2008). In this method, polyphenolic compounds are first subjected to an *in vitro* gastrointestinal digestion process prior to examining the absorption process using Caco-2 cells. Several scientists have used cell lines to assess the bioavailability of various polyphenols (Manna et al., 2000; Manzano & Williamson, 2010; Xu, Kong, & Tian, 2022).

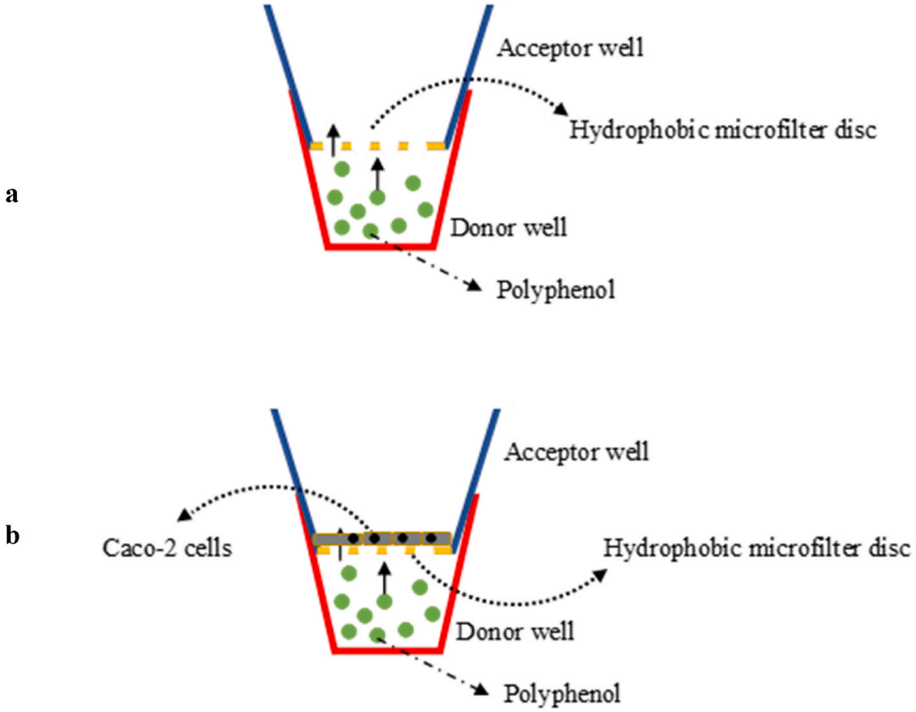


Fig. 7. The schematic of (a): Parallel Artificial Membrane Permeability Assay (PAMPA) and (b): Caco-2 cell line transportation assay.

3.2. *Ex vivo models*

In *ex vivo* models, scientists usually use human immune cells or gastrointestinal tissues in laboratory conditions. For example, Magiera et al. (2022) evaluated the antioxidant and anti-inflammatory activity in human neutrophil and monocyte cells. First, neutrophils were precipitated using dextran, and lysis of red blood cells was done using a hypotonic solution. Monocyte cells were also isolated through Ficoll–Hypaque gradient centrifugation. After isolation, cells were treated with polyphenols for a specific time at a predetermined temperature (usually 37 °C for human cells) followed by treating them with degenerative substances such as free radicals or other reactive species. Finally, the viability of these cells was compared to the control ones (Magiera et al., 2022). When digested polyphenols are considered, polyphenols are subjected to an *in vitro* digestion before the *ex vivo* test (Annunziata et al., 2021). In addition to using neutrophil and monocyte cells, exploiting Ussing chamber is a widely used laboratory model for studying the transport and bioaccessibility of bioactive compounds across biological membranes, particularly in the intestine. This model typically involves the use of animal or, in some cases, human biopsy samples of the intestinal tissue (Józsa et al., 2023). Franz cell is also a commonly used laboratory model for studying the bioaccessibility and diffusion of drugs and bioactive compounds across the buccal region of the oral cavity (Meng et al., 2023).

3.3. *In situ models*

Another method to evaluate the bioavailability of polyphenols is to use *in situ* models, which are intermediate of *in vivo* and *in vitro* models. Among various *in situ* models, the *in situ* rat intestinal perfusion model is well-known. It is worth mentioning that these investigations need to be approved ethically. For example, Fong et al. (2012) investigated the effect of different polyphenolic compounds on the absorption and bioavailability of a flavonoid named “baicalein.” In this investigation, they prepared a perfusion buffer using KCl, KH2PO4, Na2HPO4, CaCl2, MgCl2, and polyethylene glycol. The perfusion buffer containing the polyphenol as well as other polyphenols was injected into the rat jejunum. In predetermined intervals, samples were collected from the mesenteric vein and outlet of the intestine of rats. Finally, the collected samples were analyzed in terms of absorbed and transformed polyphenols (Fong et al., 2012). As described, it can be perceived that in such models, polyphenols are subjected to a real location of absorption-this is why it is called an *in situ* model- and the output of the veins, which are responsible for transporting the absorbed compound, is collected for further investigations.

3.4. *In vivo models*

Firstly, it should be stated that *in vivo* models including animals or humans also need ethical and legal permission. In the case of animal studies, scientists tend to exploit mice, rats, dogs, cats, rabbits, pigs, fish, and other animals (Ansari, Ahmad, & Haqqi, 2020; Espín et al., 2007; Kapetanovic et al., 2009; Román, Jackson, Gadhia, Román, & Reis, 2019). For example, mice are divided into a specific number of groups that are given different diets, in which some parameters differ from others. After a period of receiving diets, animals are sacrificed, and target tissues will be analyzed. To illustrate this, Wang, Heber, and Henning (2012) exploited mice and fed them with quercetin, and their lung, kidney, and liver tissues were analyzed. They used β-glucuronidase to generate free forms of polyphenols followed by monitoring the methylated polyphenols using a CoulArray detector (Wang et al., 2012).

In human studies, scientists concentrate on critical health problems such as cardiovascular diseases, diabetes mellitus, obesity, neurodegenerative diseases, digestive disease, and cancers to be alleviated using polyphenols (Dryden et al., 2006; Ferretti et al., 2014; Renaud & Martinoli, 2019; Tan, Konczak, Ramzan, & Sze, 2011). In these studies, participants with the target diseases receive predetermined dosages of polyphenols, and their related risk factors are assessed. For example, “following a 28-day course of supplements containing a number of phenolic compounds, subjects with stage 1 or 2 hypertension and metabolic syndrome had their diastolic blood pressure significantly reduced and their systolic blood pressure significantly decreased,” as reported by Biesinger et al. (2016). In another study conducted by Filippini et al. (2020), the cancer-preventive effect of tea polyphenols using several human participants was investigated. A significant reduction in cancer cells was observed (Filippini et al., 2020). For more detailed information, please refer to the aforementioned studies.

3.5. Challenges in the bioavailability of polyphenolic compounds

When it comes to the challenges in the bioavailability of polyphenolic compounds, they are not fully liberated from the food matrix, and the released portion is not properly absorbed in the gastrointestinal tract (Dong et al., 2020; Wojtunik-Kulesza et al., 2020). Furthermore, the absorbed polyphenolic compounds may not be properly metabolized or transported to the target sites. These vital events crucial to the bioavailability of polyphenolic compounds are influenced by various factors.

The liberation and digestion rate of polyphenolic compounds is among the factors that can limit their bioavailability. The composition of the food matrix and the conditions during food processing can affect these compounds and result in different forms, including free, conjugated, and insoluble complexes. In the case of flavonols, studies have shown that oral administration of quercetin glucosides in the form of a water-alcohol solution to fasted volunteers can result in higher bioavailability compared to the administration of an equivalent quantity of the compound in the form of foods such as onions, apples, or a complex meal (Hollman et al., 1997). During digestion, several enzymes are responsible for breaking down complex polyphenols into simpler molecules. Insoluble complexes consist of a phenolic portion and indigestible polysaccharides such as arabinoxylan, hemicellulose, cellulose, and pectin (Sun, Warren, & Gidley, 2018), rod-shaped proteins (Morzel, Canon, & Guyot, 2022), and other polyphenols which are highly dense such as condensed tannin and lignin (Ajayi, Otemuyiwa, Adeyanju, & Falade, 2021). Consequently, these complexes are less likely to be solubilized in gastric juice, leading to only a small quantity passing through the intestinal epithelium and reaching the bloodstream, resulting in low bioavailability of insoluble polyphenols. It has been reported that only about one-tenth of polyphenols can pass through the intestinal cells, enter the blood circulation, and ultimately reach target cells to exhibit their bioactivity (Shahidi & Yeo, 2016). Undigested polyphenols reach the colon where they can be metabolized by colon microflora and released again as digestible metabolites (Zhang, Hu, et al., 2023).

The next step is digestion and metabolism, which can be categorized into three consecutive phases: phase I (structural modification), phase II (bioconjugation), and phase III (excretion). Phase I involves structural changes that occur in polyphenols. Depending on their structure, polyphenols may be metabolized and reach the blood circulation through either phase I or phase II or be excreted via feces or urine. In phase I, polyphenols with low molecular weight can be absorbed through paracellular pathways and reach the liver and other tissues (Kosińska & Andlauer, 2012; Lu et al., 2011; Terahara, 2015). In these tissues, polyphenols undergo structural modifications such as amination, carboxylation, or hydroxylation (Shahidi & Peng, 2018). Subsequently, these conjugates either reach target cells through the bloodstream or may be excreted to the colon via bile. These excreted metabolites can be further metabolized by colon microflora, as mentioned earlier (Augusti et al., 2022). The metabolites produced by these microflora can be absorbed into the enterocytes (Phase II). On the other hand, polyphenols that do not undergo Phase I metabolism may be metabolized through Phase II. After passing through the cell membrane of enterocytes via active transportation, facilitated transportation, or passive diffusion, polyphenols undergo bioconjugation. Methylation, glucuronidation, and sulfation are well-known biotransformation processes for polyphenols occurring in enterocytes (Wang, Li, Hu, & Zhao, 2022). Subsequently, the conjugated polyphenols are transported to the liver for distribution. While numerous pieces of evidence indicate that polyphenols are absorbed in the small intestine, some polyphenols, including isoflavonoids (daidzein and genistein), phenolic acids (gallic acid, caffeic acid, and chlorogenic acid), flavonols (quercetin), and anthocyanins, are absorbed in the stomach (Crespy et al., 2002; Fernandes, de Freitas, Reis, & Mateus, 2012; Konishi, Zhao, & Shimizu, 2006; Morand et al., 2000; Piskula, Yamakoshi, & Iwai, 1999). However, as mentioned earlier, most polyphenols are not properly liberated, digested, or metabolized.

Another limiting factor may be the degree of polymerization of polyphenols, especially when their concentration is high enough and their liberation from the food matrix into the gastrointestinal tract is sufficient. It has been reported that monomeric phenolic compounds such as epicatechin are properly absorbed in the small intestine (Sun et al., 2023), while dimers, trimers, and oligomers such as proanthocyanidins are poorly absorbed (Chen, Wang, et al., 2022). Additionally, some polyphenols may be attached to rhamnose, which negatively affects their absorption in the small intestine, and these molecules are metabolized by colon microflora (Liu, Cheng, et al., 2023). Polyphenols such as curcumin and naringenin possess a high degree of hydrophobicity, which hampers their absorption due to the low solubility. However, it is worth noting that the relative hydrophobicity is also necessary for their permeability and uptake by enterocytes. For example, the absorption rate of some polyphenols follows the order: Genistin = daidzin < daidzein < genistein < flavonoid aglycones (Bohn, 2014). As evident, several limiting factors restrict the bioavailability of polyphenolic compounds, and scientists strive to identify the weak points of such compounds to modify their bioavailability.

4. Recent approaches for enhancing the bioavailability of polyphenols

As previously discussed, investigations on the absorption, biodistribution, metabolism, and elimination of hydrophobic polyphenols have identified polyphenol solubility and structure as the primary causes of the low bioavailability of polyphenolic substances. This section concentrates on the recent conjugation approaches applied to raise the bioavailability of hydrophobic polyphenols. Several investigations developed conjugates in which hydrophobic polyphenols were conjugated through weak interactions, and on the other hand, some other researchers focused on the covalently bonded polyphenolic compounds. However, this review revolves around the basic systems that have been applied to develop polyphenolic conjugates in which carriers possess either organic sources or inorganic origins. To have a better understanding of the methods employed to enhance the bioavailability of polyphenols, these methods are concisely described below. Generally, other recent approaches applied in the hope of raising the bioaccessibility and bioavailability of polyphenolic compounds include molecular enhancers, nanoparticles, encapsulation systems, and developing derivatives and analogs of polyphenols. In the latter case, conjugates of these compounds are regarded as their derivatives, which is the emphasis of this study.

4.1. Molecular enhancers

Some scientists have exploited compounds called “molecular enhancers” or “adjuvants”, which manipulate step I of polyphenol metabolization by suppressing the activity of enzymes, multidrug efflux pump (MDR), or P-glycoprotein, which act as barriers to the absorption of polyphenols and other xenobiotic compounds. In addition, adenosine triphosphate-binding cassette (ABC) transporters are responsible for effluxing xenobiotic compounds from human cells by consuming ATP molecules. Therefore, co-administration of molecular enhancers with polyphenols has been shown to enhance their bioavailability by improving their absorption in the gut. For example, piperine is a renowned molecular enhancer that can enhance the bioavailability of curcumin and epigallocatechin-3-gallate (Lambert, Hong, Kim, Mishin, & Yang, 2004; Shoba et al., 1998). It was also reported that the combination of lipids and emulsifiers leads to a higher absorption rate of quercetin through an *in vivo* test (Azuma, Ippoushi, Ito, Higashio, &

Terao, 2002). Agulló and colleagues investigated the effect of noncaloric sweeteners, including stevia and sucralose, on the bioavailability of polyphenols in citrus-maqui soft drinks. They applied a predetermined regime of drink intake to 138 healthy overweight adults. Twenty-four bioavailable derivatives of polyphenolic compounds were detected, indicating the enhancing effects of these sweeteners in comparison with sucrose (Agulló, García-Viguera, & Domínguez-Perles, 2022). Further investigations revolving around this method are summarized in Table 1. In these studies, a mixture of polyphenols may be used, and the synergistic effects were investigated, or researchers used polyphenolic compounds as enhancers to raise the bioavailability of target drugs.

4.2. Nano-encapsulation systems

A diverse range of nanoparticles has been applied to encapsulate and enhance the bioavailability of hydrophobic polyphenols, including both organic and inorganic nanoparticles. The former include protein-based, carbohydrate-based, and protein-polysaccharide conjugate nanoparticles, while the latter mainly consists of gold, silver, and silica nanoparticles (Salah, Mansour, Zogona, & Xu, 2020). Encapsulation methods endow several advantages to improve the bioavailability of different polyphenols. Some encapsulation systems such as gelatin nanoparticles protect core polyphenols (e.g., resveratrol) against harsh gastric conditions and deliver them to the intestinal sites where they can be absorbed efficiently (Song et al., 2019). Controlled release of polyphenols (e.g., rutin) by applying encapsulation systems such as bovine serum albumin improves their bioavailability and lowers their excretion rate (Pedrozo, Antônio, Khalil, & Mainardes, 2020). Additionally, some carriers such as alginate/chitosan-based encapsulation systems possess mucoadhesive properties which can guarantee better uptake (Bhunchu, Muangnoi, & Rojsitthisak, 2016). β-Lactoglobulin nanoparticles have been used as encapsulation systems for anthocyanins, showing higher antioxidant activity and retention rates throughout an *in vitro* gastrointestinal tract (Salah et al., 2020). Prolamine-based nanoparticles have also been explored as nano-delivery systems for polyphenols, due to their specific characteristics and potential application in various food formulations. Several recent studies have shown their potential in enhancing the bioavailability of polyphenols (Chen, Lin, et al., 2023; Chen, Wu, et al., 2023; Voci, Fresta, & Cosco, 2021; Wiggers, Fin, Khalil, & Mainardes, 2022; Wu et al., 2023). Gliadin nanoparticles have been developed as delivery systems for curcumin, which showed increased bioavailability and stability after prolonged irradiation, heating, and storage (Guo et al., 2022b).

Polysaccharide-based nano-encapsulation systems, owing to their abundance and high stability during harsh processes and gastrointestinal conditions, have been extensively applied to enhance the bioavailability of polyphenolic compounds (Leena, Anukiruthika, Moses, & Anandharamakrishnan, 2022; Walbi et al., 2022; Yuan, Ma, Zhang, Wang, & Xu, 2022). For example, curcumin was successfully encapsulated in chitosan-based nano-delivery systems, which exhibited sustained release behavior and released 90% of curcumin after 24 h in an aqueous solution (Walbi et al., 2022). Chitosan and alginate-based nano-delivery systems were also developed to increase the bioavailability and anticancer activity of curcumin, showing a sustained release behavior and high curcumin protection against UV light and gastrointestinal conditions. *In vitro* studies revealed that this system significantly increased the bioaccessibility of free curcumin from 12.3% to 72.3% (Sorasitthiyanukarn, Muangnoi, Rojsitthisak, & Rojsitthisak, 2021).

Solid lipid nanoparticles (SLN) have also received attention as nano-delivery systems for hydrophobic polyphenols, showing the potential in enhancing their bioavailability (Kim, Ban, Kim, Lim, & Choi, 2022; Tang, Chen, & Dong, 2023; Trapani et al., 2022). For example, ellagic acid was successfully encapsulated in an SLN and added to chocolate bar formulations, with the best formulation containing 5% of ellagic acid and an IC50 value of about 174 (Subroto, Andoyo, Indiarto, Lembong, & Rahmani, 2022). Curcumin and resveratrol were embedded in an SLN system to enhance skin penetration and anticancer efficacy, showing about 70% skin-bounding properties and higher anti-tumor characteristics (Palliyage et al., 2021). Table 2 summarizes the most recent nano-delivery systems applied for polyphenolic compounds to enhance their bioavailability.

4.3. Metal-based nanocarriers

Due to their controllable size and shape, as well as their great specific surface area, metal nanoparticles have gained attention in enhancing the bioavailability of polyphenolic compounds. Gold and silver nanoparticles are the most widely used nanocarriers to enhance the bioavailability of polyphenols (Meena et al., 2020). In addition, silica, titanium dioxide, and magnetic iron oxide nanoparticles have also been used in drug-delivery systems (Enteshari Najafabadi, Kazemipour, Esmaeili, Beheshti, & Nazifi, 2018; Li, Li, et al., 2021; Niu et al., 2022).

Table 1
Various molecular enhancers that can be used to increase the bioavailability of polyphenols.

Target compound	Enhancer	Rise in bioavailability (%)	Main findings	References
Curcumin	Piperine	2000 (humans), 154 (rats)	• Among eight novel derivatives of curcumin, fluoropropyl-substituted curcumin was a suitable radioligand for amyloid plaques due to its higher bioavailability	Shoba et al. (1998)
Anthocyanins	Phytic acid	N/A[1]	• Compared to the administration of anthocyanins without phytic acid, coadministration of phytic acid and anthocyanins led to an increase in the levels of anthocyanins in both plasma and urine.	Matsumoto et al. (2007)
Glabridin	Norfloxacin	N/A	• When used in combination against multidrug-resistant clinical isolate of *Staphylococcus aureus*, a synergistic interaction was observed between norfloxacin and glabridin at significantly lower concentrations. • Findings suggest that glabridin may be a promising candidate for combination therapy.	Singh, Pal, and Darokar (2015)
Doxorubicin	Capsaicin & piperine	N/A	• Capsaicin and piperine exhibit chemosensitizing activity and act as substrates for P-glycoprotein. • Findings suggested that these compounds could be useful for the development of new modulators for multidrug resistance.	Li, Krstin, Wang, and Wink (2018)
Apigenin and quercetin	–	300 (quercetin), 150 (apigenin)	• By coadministration of flavonoids from cereals and pulses, their bioavailability can be increased. • The rise in bioavailability may be through a synergistic effect that inhibits the function of membrane transporters and phase II enzymes.	Ravisankar et al. (2019)
EGCG[2] and green tea polyphenols	–	N/A	• The results suggested that EGCG can serve as an effective treatment for multidrug-resistant *Vibrio cholerae*.	Siriphap et al. (2022)

[1] Not applicable,
[2] Epigallocatechin gallate.

Table 2
The most recent nano-delivery systems applied for polyphenolic compounds to improve their bioavailability and/or bioaccessibility.

Polyphenolic compound	Nano-delivery systems	Improved targeted properties	Reference
Malus baccata polyphenols	Protein/ polysaccharides	Physicochemical stability and release rate	Li, An, et al. (2023)
Curcumin, quercetin, and resveratrol	Protein	Anti-inflammatory activity	Ruiz-Alcaraz et al. (2023)
EGCG[1]	Metal-organic frameworks	Tumor-targeting	Jannatun et al. (2023)
Chlorogenic acid and ECG[2]	Protein	Gastrointestinal stability and bioaccessibility	Ren et al. (2023)
Quercetin	Protein/ polysaccharides	Bioavailability	Zhang, Hu, et al. (2023)
Resveratrol	Protein/ polysaccharides	pH, storage, and ionic stability	Li, Bi, et al. (2023)
Apple polyphenols	Protein/ polysaccharides	Antioxidant activity and stability	Chen, Wu, et al. (2023)
Curcumin and EGCG	Protein/ polysaccharides	Thermal, light and storage stabilities	Li, He, et al. (2023)
EGCG	Selenium nanoparticles	Bioactivity and anticancer property	Zhou et al. (2023)
EGCG	Poly-lactic poly-glycolic copolymer	Anticancer properties	Minnelli et al. (2023)
Red wine polyphenols	Protein	Gastrointestinal stability	Paladines-Quezada et al. (2023)

[1] Epigallocatechin gallate.
[2] Epigallocatechin.

Similar to other nanoparticles, top-down and bottom-up methodologies are employed to prepare these nanocarriers. These methodologies also can be categorized as physical, chemical, and biological procedures (Chamundeeswari, Jeslin, & Verma, 2019). Several studies have shown that silver and gold nanoparticles are promising nanocarriers to rise the bioavailability of curcumin (Mahmoudi, Kesharwani, Majeed, Teng, & Sahebkar, 2022). Smaller size and fluoresce under visible light (550 nm) make gold nanoparticles superior nanocarriers to monitor the absorption of polyphenols through imaging methods (Khandelwal, Alam, Choksi, Chattopadhyay, & Poddar, 2018). Generally, in chemical methods, reducing agents such as sodium borohydride, sodium citrate, and ascorbic acid are employed to produce gold and silver nanoparticles. However, it has been reported that epigallocatechin gallate (EGCG) can also be used as a reducing agent to produce gold nanoparticles. The findings showed that EGCG -gold nanoparticles possess more anticancer properties than free EGCG and EGCG -gold nanoparticles prepared using the citrate method (Yang, Dong, Wang, & Zhang, 2020).

5. Conjugation approaches for enhancing polyphenol bioavailability

Numerous investigations on the conjugation of polyphenols with natural polymers have been conducted to date. The development of such structures may serve purposes and applications in the food and pharmaceutical industries. A novel, alternative, and hopeful method is creating emerging substances to enhance a chosen food component's qualities or produce new traits for the targeted applications. The purpose of developing such compounds can be to use them as antioxidants, anticancers, wound-healing agents, preservatives, or to raise the bioavailability of polyphenols. As the latter is the core of this study, recent progress in the application of such structures to raise the bioavailability of polyphenols is discussed. Glycosylation, hydroxylation, methylation, acylation, sulfation, glucuronidation, and conjugation with biopolymers are effective in enhancing the bioavailability of polyphenols. The polymer for developing polyphenolic conjugates can be either proteins or polysaccharides. It is noteworthy that conjugation differs from nano-delivery systems. Generally, in the conjugation methods, covalent bonds play a key role in the system to carry and enhance the bioavailability of polyphenols or other bioactive molecules, while in the nano-delivery systems, the encapsulation of bioactive molecules is carried out through non-covalent interactions (Faya et al., 2018).

One of the primary polymers, proteins, has unique capabilities such as emulsifying, gelling, and foaming characteristics. For example, enhancing the antioxidant activity of proteins has drawn growing interest. Therefore, it is possible to develop new functionalities for the proteins to apply them in more fields (Liu, Sun, Yang, Yuan, & Gao, 2015). On the other hand, many researchers have isolated natural polysaccharide-polyphenol conjugates and investigated their application. Such compounds have been isolated from different herbal medicines, and their role in protecting human platelets was studied (Pawlaczyk, Czerchawski, Pilecki, Lamer-Zarawska, & Gancarz, 2009, 2011). Moreover, developing such compounds has also been recently investigated in the hope of enhancing the bioavailability of hydrophobic polyphenols. More information is provided in the following sections.

5.1. Hydroxylation

The process of adding a hydroxyl group (-OH) to an organic compound is known as hydroxylation, and it can also refer to the amount or distribution of OH groups in a molecule or substance. Enzymes referred to as hydroxylases are frequently used in biochemistry to catalyze hydroxylation reactions. Inserting an oxygen atom into a C–H bond causes it to become an alcohol group. The hydroxylation of polyphenols is a key step in their biosynthesis, which is a process that plants use to produce these secondary metabolites to protect themselves from other organisms. It is important to note that polyphenols exhibit various patterns of hydroxylation, methylation, and glycosylation, and these modifications can affect their properties and potential applications (ncbi.nlm.nih.gov). For example, flavonols, a subgroup of flavonoids, have a ketone and a hydroxyl group in position 3 of ring C and can exhibit different hydroxylation patterns. For example, in addition to the hydroxylation of Position 3 of the C ring, it can be occurred in positions 5 and 7, which can result in different polyphenolic compounds (Hano & Tungmunnithum, 2020). To synthesize hydroxylated polyphenols, bacterial tyrosinases are exploited as biocatalysts. The synthesis of quercetin and myricetin from kaempferol using a bacterial tyrosinase from Bacillus megaterium can be a good example of a hydroxylation process. Tricetin derived from apigenin and 3′-hydroxyeriodictyol biosynthesized from naringenin are other examples of hydroxylated polyphenolic compounds via tyrosinase. It is noteworthy that polyphenols are unstable at the reaction condition of tyrosinase, which leads scientists to conduct the biotransformation at a pH value of about 6 (Vaezi, 2022). For example, myricetin and quercetin are highly oxidized under alkaline conditions (Atala, Fuentes, Wehrhahn, & Speisky, 2017).

5.2. Methylation

Methylation of polyphenols is said to result in more stable, soluble, antioxidant, antimicrobial, and bioavailable polyphenolic derivatives (Walle, 2009). The methylation of rutin was done using methyl iodide to synthesize tetra-methylated rutin, which was hydrolyzed under acidic conditions to produce 5,7,30,4′-tetra-*O*-methylated quercetin (El Mahdi, Ouakil, & Lachkar, 2022). Permethylated rutin was also synthesized via methyl iodide under alkaline conditions (Farha et al., 2022). As perceived, the methylation reactions that scientists tend to conduct are rather chemical, while this reaction is biotransformation of polyphenols in human tissue and colon microbiota, which exploit enzymes such as catechol-*O*-methyltransferase (COMT) (Gonçalves et al., 2022). Methyl groups can be introduced to various positions of the polyphenol molecular structure, such as 7-, 4'-, and 3′-hydroxyl groups in flavonols (Liu et al., 2022).

5.3. Acylation

The esterification of polyphenols with fatty acids is regarded as an acylation reaction, which can lead to higher hydrophobicity and stability in polyphenolic compounds. Chemical, enzymatic, and microbial approaches are employed to generate acylated polyphenols (Peng & Shahidi, 2023). Enzymatic acylation of quercetin with oleic acid was studied by Saik, Lim, Stanslas, and Choo (2017). Lipase is the catalysis exploited in the enzymatic acylation of polyphenols. In this study, quercetin was dissolved in acetonitrile followed by the addition of an excess amount of oleic acid in the presence of lipase. Quercetin 4′-oleate, Quercetin 7,3′,4′-trioleate, and Quercetin 3′,4′-dioleate were developed from the enzymatic reaction and it was found that the stability these compounds was substantially higher than the native molecule. The hydrophobicity of quercetin increased by approximately 152% after modification.

5.4. Sulfation

Chemical sulfation of polyphenols can be achieved through microwave-based sulfation, as described by Al-Horani, Karuturi, Verespy, and Desai (2015). In several studies, the sulfating agent in this approach is sulfur trioxide trimethylamine complex ($(CH_3)_3N–SO_3$), and microwave heating at 90–100 °C in the absence of air provides the activation energy for the reaction (Duenas, Gonzalez-Manzano, Surco-Laos, Gonzalez-Paramas, & Santos-Buelga, 2012; Kolaříková et al., 2022; Shi, Gao, & Liu, 2022). On the other hand, in the chemoenzymatic approach, 3′-phosphoadenosine-5′-phosphosulfate (PAPS)-dependent sulfotransferases or PAPS-independent aryl sulfotransferases are used as catalysts. It is reported that sulfated molecules of quercetin still possessed antioxidant activities, although they were less active than the native form of quercetin. Moreover, higher bioavailability has been reported for these compounds in comparison with native quercetin (Valentová et al., 2017), which can be due to the introduction of sulfate groups to quercetin which resulted in more water solubility.

5.5. Glucuronidation

Glucuronidated polyphenols are crucial in health-related investigations due to numerous reports indicating that such metabolites are found in the brain after being orally administered (Fernández-Ochoa et al., 2022; Sarubbo, Moranta, Tejada, Jiménez, & Esteban, 2023; Scott, Styring, & McCullagh, 2022). In the chemical synthesis of glucuronidated polyphenols through the Koenig–Knorr method, glycosyl bromide donors such as methyl 2,3,4-tri-*O*-acetyl-1-bromo-α-ᴅ-glucuronate 5/silver oxide or methyl (2,3,4-tri-*O*-acetyl-α-ᴅ-glucopyranosyl) uronate bromide in the presence of silver oxide (Ag2O) are used (Ahmadi, Hosseini, Rostamizadeh, & Anoush, 2021; Dini & Grumetto, 2022). This is reported to yield relatively less, but it is reliable (Dini & Grumetto, 2022).

Sometimes scientists are required to obtain specific glucuronidated polyphenols in their research, which can be done by protecting other hydroxyl groups against glucuronidation (Hanioka et al., 2022; Xia, 2021). For example, it is reported that hydroxyl groups of quercetin were protected using benzyl bromide and potassium carbonate at ambient temperature in dimethylformamide (DMF) (Kajjout & Rolando, 2011; Rajaram, 2020). Additionally, it has been found that the mixture of benzyl chloride/sodium bicarbonate/benzyl(triethyl)ammonium chloride could serve as a securing solution for quercetin and other polyphenols (Bouktaib, Atmani, & Rolando, 2002). To glucuronidate a single hydroxyl group of epicatechin without introducing sugar to other groups, some researchers (Zhang et al., 2013) suggested reacting it with the methoxymethyl (MOM) group, while securing the other hydroxyl groups using benzyl bromide.

5.6. Protein-polyphenol conjugates

Proteins and polyphenols are capable of interacting with each other through covalent or non-covalent bonds (You, Luo, & Wu, 2014). Covalent bonding is preferred due to its higher stability during different food processing conditions (Liu, Pu, Liu, Kan, & Jin, 2017). Hydrogen bonding and hydrophobic interactions are primary non-covalent interactions between polyphenols and proteins. Enzymes such as polyphenol oxidase and tyrosinase or even chemicals including free radical grafting and alkaline solutions have been exploited to develop covalent bonds between proteins and polyphenols (Gu, Peng, et al., 2017; Liu, Pu, et al., 2017).

Polyphenols are reported to be excellent hydrogen donors, making them good candidates to interact with the C═O bonding of proteins (Buitimea-Cantúa, Gutiérrez-Uribe, & Serna-Saldivar, 2018). Hydrogen bonds can also be developed by the interaction between hydroxyl groups of polyphenols and hydroxyl or amine groups of proteins (Yildirim-Elikoglu & Erdem, 2018). Moreover, hydrophobic-hydrophobic interactions can be formed between hydrophobic proteins such as leucine, methionine, and cysteine and aromatic groups of polyphenolic compounds (Richard, Lefeuvre, Descendit, Quideau, & Monti, 2006).

Polyphenolic compounds are indeed prone to oxidation in alkaline solutions, leading to the formation of semi-quinone species, which rapidly convert to quinones. These quinones can readily interact with nucleophilic groups found in amino acids such as tryptophan and methionine. As a result, covalent bonds can be formed between polyphenols and proteins under alkaline conditions. This non-enzymatic method relies on the reactivity of the quinone intermediates with nucleophilic residues in proteins, facilitating the covalent binding process. (Waterhouse & Laurie, 2006). Furthermore, utilizing ascorbic acid and hydrogen peroxide as triggers to facilitate the development of covalent bonds between polyphenols and proteins is considered a convenient, rapid, and environmentally friendly process. By combining ascorbic acid and hydrogen peroxide, the oxidative environment is enhanced, promoting the formation of reactive species that can react with the nucleophilic groups present in proteins. This approach offers a sustainable and efficient method for generating covalent bondings between polyphenols and proteins (Gu, Peng, et al., 2017; Liu et al., 2015).

Trigger compounds, such as hydrogen peroxide or other reactive oxygen species, can generate hydroxyl radicals in the side chains of proteins. These hydroxyl radicals create a favorable environment for the formation of covalent bonds between proteins and polyphenols. The highly reactive hydroxyl radicals can react with both the polyphenolic compounds and the nucleophilic groups present in the protein side chains, leading to the formation of covalent linkages. This process allows for the establishment of stable and specific interactions between proteins and polyphenols, contributing to various biological and biochemical phenomena (Feng, Cai, Wang, Li, & Liu, 2018). In enzymatic methods, the production of *o*-diphenols from monophenols can be achieved using oxidative enzymes like cresolases. This enzymatic reaction creates a suitable condition for the subsequent production of o-quinones using catecholases. These o-quinones, formed from the oxidation of *o*-diphenols, are highly reactive and can undergo nucleophilic addition reactions with the nucleophilic groups present in amino acids such as lysine, tryptophan, and others. This interaction leads to the formation of covalent bonds between the o-quinones and the nucleophilic amino acid residues, resulting in the attachment of polyphenols to proteins. This enzymatic process enables specific and controlled modifications of proteins, allowing for the study of protein-polyphenol interactions and their biological effects (Chung et al., 2003; Prigent, Voragen, Visser, van Koningsveld, & Gruppen, 2007).

The conjugates of chlorogenic acid, whey protein isolate, and casein revealed higher solubility and foaming capacity. It was also reported that the affinity of chlorogenic acid to non-covalently bond with whey protein isolate was higher than casein (Jiang, Zhang, Zhao, & Liu, 2018). Similarly, Somu and Paul (2018) conjugated curcumin onto the nanoparticles of casein to assess the therapeutic properties of the polyphenol. Higher antioxidant activity and cytotoxicity against different cancer cells were observed, and this was enhanced when folic acid was also conjugated into the system. The stability of the system was about one month with an insignificant reduction in bioactivity (Somu & Paul, 2018).

In 2021, Somu and Paul developed surface-modified lysozyme using curcumin, which led to higher antimicrobial, antioxidant, and anticancer properties compared to their counterpart individuals (Somu & Paul, 2021). Zhang and colleagues prepared conjugates of EGCG and β-lactoglobulin in the hope of desensitization to allergens through *in vivo* experiments (Zhang, Li, Shao, Li, & Hemar, 2021). They reported that interestingly, further conjugation was inhibited or decreased due to the reduction in β-sheet content. Moreover, due to an increase in hydroxyl groups of protein after conjugation, the antioxidant activity of the system was higher than in their native samples (Zhang et al., 2021).

Baba and colleagues successfully conjugated whey proteins with quercetin through ultrasonication and redox pair methods. It was revealed that the conjugates resulting from the ultrasonication method had higher solubility, foam, and emulsification properties, while the other method resulted in higher antioxidant activity of the conjugates (Baba, Abdelrahman, & Maqsood, 2021). Li and colleagues evaluated the conjugates of lactoferrin and EGCG formed through enzymatic or non-enzymatic approaches (Li, Li, et al., 2021). The results showed that the enzymatic method resulted in a higher yield. In addition to the higher solubility of the system compared to the native samples, the antioxidant and emulsification properties of lactoferrin increased after conjugation (Li, Li, et al., 2021).

5.7. *Protein-polysaccharide-polyphenol conjugates*

Engineering functional ingredients can be achieved by developing ternary conjugates. These conjugates may differ from other ternary conjugates with the same constituents due to the sequence of reactions, as it plays a crucial role in the resulting conjugates (Liu, Cheng, et al., 2023). There are three possible reaction sequences that scientists have been following to develop protein-polysaccharide-polyphenol conjugates (Fig. 8). In one method, the appropriate conditions are provided for proteins and polysaccharides to react with each other through the Maillard reaction. Subsequently, accessible nucleophilic molecules in proteins, such as cysteine and tyrosine, and polysaccharides, such as carboxylic acid, become probable reaction sites for polyphenolic compounds. However, it is essential to carefully select the reaction conditions to avoid altering the protein structure (Liu, Pu, et al., 2017). On the other hand, when proteins or polysaccharides are first reacted with polyphenols, several advantages can be gained. These include easier purification due to the separation of unreacted polyphenols and catalysts. In the enzymatic approach, similar to other conjugation methods, polyphenol oxidases such as laccase and tyrosinase are utilized in the presence of air to generate reactive species (o-quinones and quinones), which then react with proteins or polysaccharides (Liu, Cheng, et al., 2023).

Generally, these novel ternary systems are fabricated to be applied as emulsifiers or interfacial functional ingredients with antioxidant, antimicrobial, and anticancer properties. Soy protein isolate-EGCG-maltose conjugates were developed and exploited as emulsifiers to encapsulate β-carotene. The conjugates revealed high solubility, emulsification, and foaming properties. It was reported that more than half of the β-carotene was retained after one month of storage at 55 °C, and about three-quarters of this compound was retained after storage in exposure to UV light for 8 h. Finally, it was shown that the

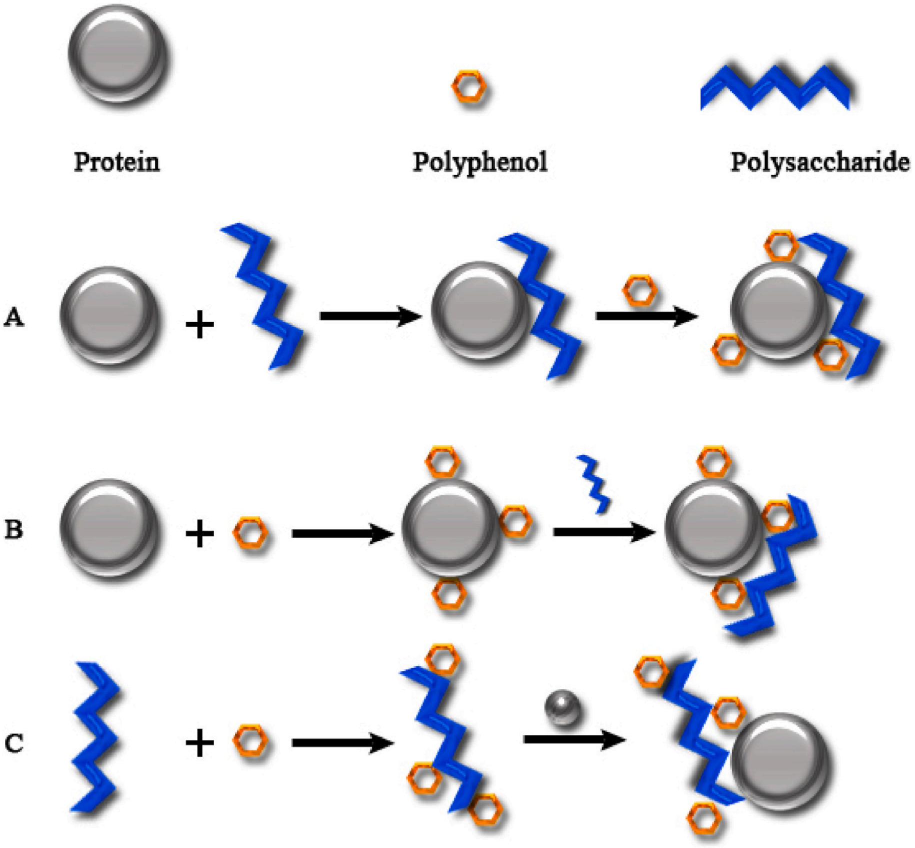


Fig. 8. Three possible interactions between proteins, polyphenols, and polysaccharides.

nanoemulsions based on these ternary conjugates as emulsifiers were a suitable candidate to encapsulate and protect β-carotene from environmental degenerative factors (Geng et al., 2023).

Catechin was also applied to prepare ternary conjugates based on dextran-egg white protein and used as an emerging emulsifier with antioxidant activities. In this study, the conjugation of catechin into the dextran via radical grafting was the first step, followed by a Maillard reaction to graft the conjugate into egg white proteins. The system revealed higher hydrophilicity and emulsification properties than egg-white proteins, and as a result, a higher interfacial tension was observed. It was claimed that due to the presence of the polyphenolic compound, the antioxidant activity of egg-white proteins increased (Gu et al., 2023). Numerous investigations were conducted to show an emulsifier with antioxidant activities based on catechin and its derivatives (Chen, Wang, et al., 2022; Gu et al., 2022; Wei & Huang, 2019). Man et al. (2023) prepared conjugates based on κ-carrageenan, chlorogenic acid, and soybean protein isolate. The hydrogels formed by these conjugates showed higher antioxidant and mechanical properties than soybean protein isolate hydrogels. Similar to the aforementioned study, the conjugation process caused lower hydrophobicity and free amino groups as well as higher thermal properties, water-holding capacity, and antioxidant activity (Man et al., 2023).

In another study, whey protein isolate, inulin, and cyanidin-3-glucoside were exploited to develop ternary conjugates as emulsifiers for Pickering emulsions. The reduced size of particles in the emulsion was reported to be due to the strong repulsion of droplets as a result of the presence of such conjugates. As expected, such systems showed strong antioxidant activity against external factors due to the presence of polyphenolic compounds in the structure (Tao et al., 2023). To summarize the applications of such emerging systems in food formulation, Table 3 shows the most recent ternary conjugate systems used as functional ingredients.

Table 3

The most recent ternary conjugate systems used as functional ingredients (sorted chronologically).

Ternary conjugates	Applications	Main findings	References
Egg white protein-dextran-catechin	Emulsifier	Highest bioaccessibility of lutein loaded emulsions stabilized by the ternary conjugate	Gu et al. (2022)
Polysaccharides-ovalbumin-ferulic acid	Emulsifier	Higher emulsion stability	Huang et al. (2022)
WPC[1]-pectin -chlorogenic acid or rosmarinic acid	Antioxidant	Higher antioxidative and emulsification properties	Zhang, Li, Yang, Wang, and Zhang (2022)
Ferulic acid-chitosan- EGCG[2]	Pharmaceutical	Good skin regeneration and whitening capacity	Li et al. (2022)
Myofibrillar protein-dextran-EGCG or catechin or gallic acid	Antioxidant	Enhanced heat stability and antioxidant activity	Xu, Han, Huang, and Xu (2021)
Gelatin-pectin-apple polyphenol	antioxidant	High antioxidant activity	Lin et al. (2021)
Pupa protein–glucose-cyanidin-3-*O*-glucose	(Multiple)	High thermal stability and antioxidant activity	Attaribo et al. (2021)
Bovine serum albumin- dextran-chlorogenic acid	Antioxidant	Antioxidant emulsifier with higher bioaccessibility	Yan et al. (2020)
Soy protein isolate-anionic polysaccharides-EGCG	Antioxidant	Better stability index and decreased particle sizes	Zhao et al. (2020)
Lactoferrin-hyaluronic acid-EGCG	Antioxidant	Antioxidant activity: pH 5 ≫ pH 3	Liu et al. (2019)

[1] Whey protein concentrate,

[2] Epigallocatechin gallate.

5.8. *Polysaccharide-polyphenol conjugates*

5.8.1. *Naturally occurring conjugates*

Many scientists have shown the presence of naturally occurring polysaccharide-polyphenol conjugates in various medicinal herbs, and numerous health-beneficial properties have been assigned to such compounds. Hence, these compounds are crucial in health-related investigations because polyphenolic compounds in these structures possess higher bioavailability stemming from their higher solubility and stability against heat, light, gastrointestinal conditions, and other destructive factors. In this section, different naturally occurring polysaccharide-polyphenol conjugates are discussed first, before a comprehensive discussion revolving around synthetic ones with desired properties and bioavailability.

Most of the polysaccharide-polyphenol conjugates have been extracted with a similar outline form seeds, stems, leaves, and roots. For example, the leaves and flowers of *Sanguisorba officinalis* L. are washed, dried, and milled prior to the defatting process. The main extraction process is done using sodium hydroxide or distilled water. After filtration of the extract, another extraction process is done using *n*-hexane followed by diethyl ether. Subsequently, conjugates are precipitated using methanol, dialyzed, and lyophilized for further investigations (Pawlaczyk-Graja et al., 2016). It is important to report the phenolic and total carbohydrate content of the extract, which is done by Folin–Ciocalteu and phenol-sulfuric acid methods, respectively (DuBois, Gilles, Hamilton, Rebers, & Smith, 1956; Singleton, Orthofer, & Lamuela-Raventós, 1999).

Till now, various publications have been published regarding the biological activities of these compounds. For example, based on the partial thromboplastin time (APTT) and prothrombin time (PT) examinations, it is reported that the polysaccharide-polyphenol conjugates extracted from seventeen medicinal plants named Asteraceae and Rosaceae families have anticoagulant activity (Pawlaczyk et al., 2009). Furthermore, Pawlaczyk et al. (2010) found out that flowers of *Lythrum salicaria* L. contain polysaccharide-polyphenol conjugates with anticoagulant activity in the plasma of both humans and rats (Pawlaczyk et al., 2010). Radioprotective characteristics of bioactive compounds refer to their ability to protect cells or organisms from the harmful effects of ionizing radiation through their antioxidant activities. Radioprotective agents have potential applications beyond medical and therapeutic settings, and may also be beneficial for individuals who work in facilities with radiation sources, such as radiographers, or those who are exposed to radiation in their professions, such as naval cadets in nuclear submarines, armed forces personnel, flight pilots, and astronauts (Mishra & Alsbeih, 2017). The radioprotective characteristics of polysaccharide-polyphenol conjugates are another property that has been widely studied. For example, the radioprotective activity of polysaccharide-polyphenol conjugates extracted from the Rosaceae/Asteraceae family is reported. These conjugates have the potential to inhibit the oxidation of thiol groups in plasma caused by gamma rays (Zbikowska et al., 2016). The presence of phenolic compounds in such structures is responsible for this protective characteristic because the strong radical scavenging activities of polyphenolic compounds have been proven. On the other hand, the antitussive and bronchodilatory properties of many medicinal syrups are due to such compounds, and numerous papers have been published in this respect. Antitussive properties cause stopping coughing, and the bronchodilatory activity of a compound results in facile breathing due to widening the bronchi and relaxing the muscles of the lungs. It was reported that alkaline extracted polysaccharide-polyphenolic conjugates from Purple loosestrife resulted in lower quantities of cough in human studies that endure for 5 h

(Šutovská, Capek, Fraňová, Pawlaczyk, & Gancarz, 2012).

Finally, the antioxidant activity of polysaccharide-polyphenol conjugates extracted from plants is widely investigated. Grafting to a polysaccharide results in a higher solubility of polyphenols and as a result, their antioxidant activity can be extended to interfacial regions in emulsion and aqueous solutions. On the other hand, applying such antioxidants has many advantages over synthetic ones concerning health, financial issues, and chemicals used in the production process. In an investigation, it was reported that polysaccharide-polyphenol conjugates extracted from Conyza canadensis L. from the family of Asteraceae possess substantial antioxidant properties. Findings of the *in vitro* test revealed that these compounds have a protective effect against peroxynitrite for platelet proteins (Saluk-Juszczak et al., 2010).

5.8.2. Synthetic polysaccharide-polyphenol conjugates

In addition to naturally occurring polysaccharide-polyphenol conjugates, scientists tend to exploit synthetic ones with desired or tailored properties because, as mentioned previously, these macromolecules have shown numerous health-beneficial and technological characteristics. First, it is important to understand how these conjugates can be synthesized. The main methods used to produce protein-polyphenol conjugates can also be applied to polysaccharide-polyphenol conjugates (Guo, Xiao, et al., 2022a; Zhang et al., 2020).

5.8.2.1. Synthesis methods

5.8.2.1.1. Immobilized enzymes. Polyphenol oxidase enzymes, including laccase, tyrosinase, horseradish peroxidase, and chloroperoxidase, are the predominant enzymes used to develop polysaccharide-polyphenol conjugates (Aljawish et al., 2014; Hu and Luo, 2016; Vuillemin et al., 2020). These enzymes are often immobilized in biopolymer films or hydrogels to enhance their reaction efficiency. This method has advantages such as being environmentally friendly, cost-effective, and allowing for enzyme recovery (Vittorio et al., 2016). However, it has drawbacks such as low stability in long-term usage, a complicated enzyme recovery process, and potential protein contamination (Spizzirri et al., 2016). Furthermore, these enzymes can convert phenol hydroxyl groups into quinones via the oxidation reaction, leading to colored polysaccharide derivatives with lower biological activities than conjugates prepared by other methods (Rui et al., 2017). The concept of this method is based on the formation of o-quinones from polyphenols, which are highly reactive and have a great tendency to react with nucleophilic amine groups of chitosan through Schiff-base or Michael-type reactions (Fig. 9) (Hu and Luo, 2016).

5.8.2.1.2. Free radical grafting. In the radical grafting method, the carbohydrate is dissolved in an acetic acid solution followed by adding a solution containing hydrogen peroxide and ascorbic acid. This solution initiates the conjugation process with a redox system, which is regarded as cost-effective, safe, and eco-friendly. Ascorbic acid and hydroperoxide react with each other to produce hydroxyl and ascorbate radicals. These radicals tend to detach hydrogen atoms on the polysaccharide chains, leading to the production of polysaccharide radicals. Finally, the polyphenols in the vicinity of these radicals act as acceptors, and the final conjugates are produced. The schematic of the formation of a catechin-illunine conjugate through the free radical grafting reaction is depicted in Fig. 10. The concentration of polyphenols and temperature are the main factors that affect the reaction efficiency (Gianfranco Spizzirri et al., 2014; Oliver, Thomas, Kavallaris, Vittorio, & Boyer, 2016).

5.8.2.1.3. Esterification. Another method used to develop polysaccharide-polyphenol conjugates is the esterification approach, which involves using *N*,*N*′-dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) as coupling agents (Mundlia, Ahuja, & Kumar, 2021). These reagents activate the carboxyl groups of carbohydrates and hydroxyl groups of the polyphenols, allowing them to react and form esterified polysaccharides. The reaction process of gellan-curcumin conjugates using DMAP/DCC is depicted in Fig. 11.

5.8.2.1.4. Epichlorohydrin chemistry. In some studies, epichlorohydrin has been utilized as the conjugating agent in an alkaline solution to activate the carboxyl groups of solubilized pectin to react with the hydroxyl groups of polyphenols (Ahn, Halake, & Lee, 2017). The polysaccharide aqueous solution is prepared in this procedure, followed by the preparation of the intermediate conjugation solution, which involves dissolving polyphenolic compounds in a solution containing 7.5% NaOH and 1 mmol of ECH. Finally, the intermediate solution is gradually added to the polysaccharide solution and reacted for approximately 5 h at 40 °C (Ahn et al., 2017). In the following paragraphs, confirmation of the synthesis of polysaccharide-polyphenol conjugates, and the most recent studies on developing such conjugates will be discussed.

5.8.2.2. Synthesis confirmation. Various approaches can be used to confirm the successful conjugation process, including Fourier Transform

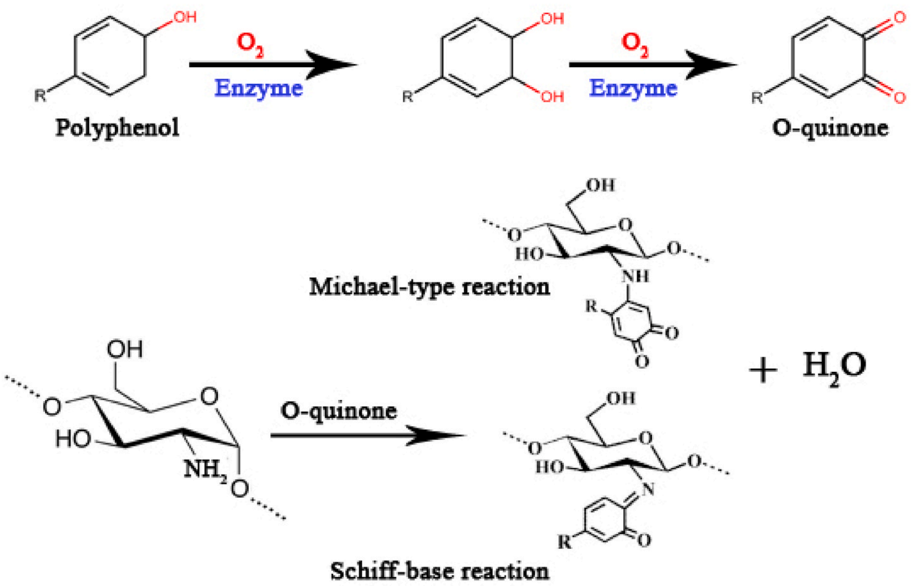


Fig. 9. The mechanism of formation of chitosan-polyphenol conjugates through immobilized enzyme method.

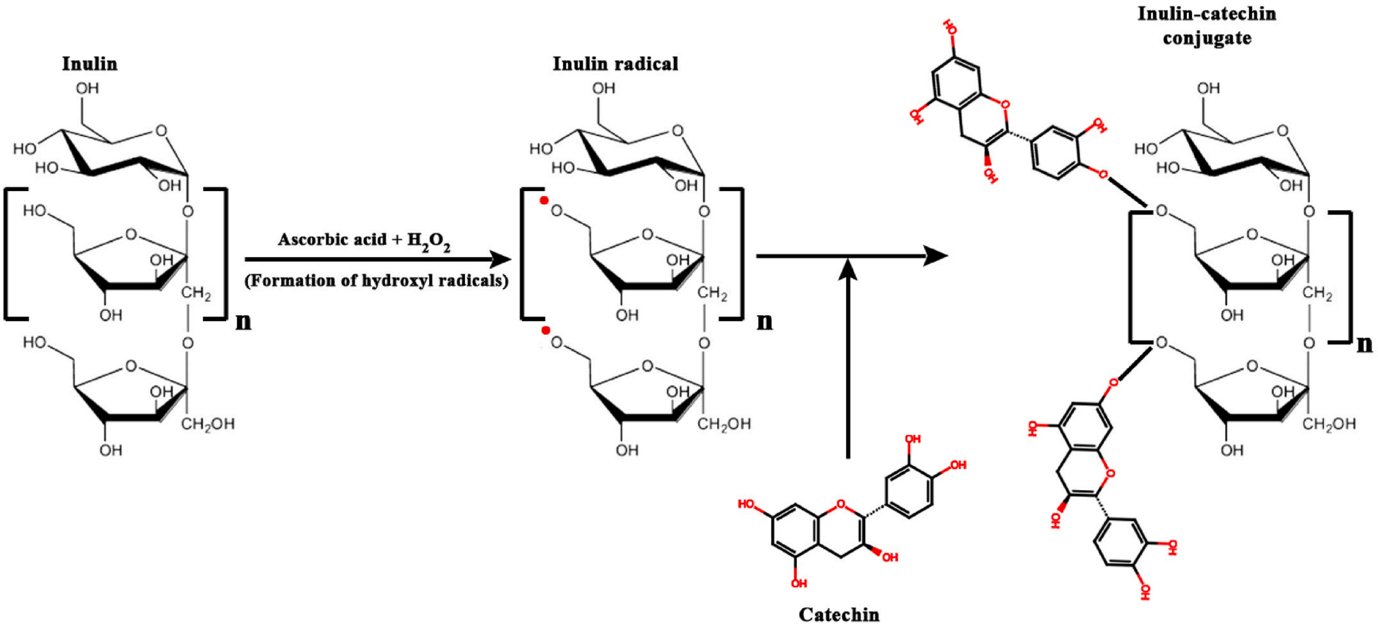


Fig. 10. The schematic presentation of the process of producing a catechin-inulin conjugate using free radical grafting.

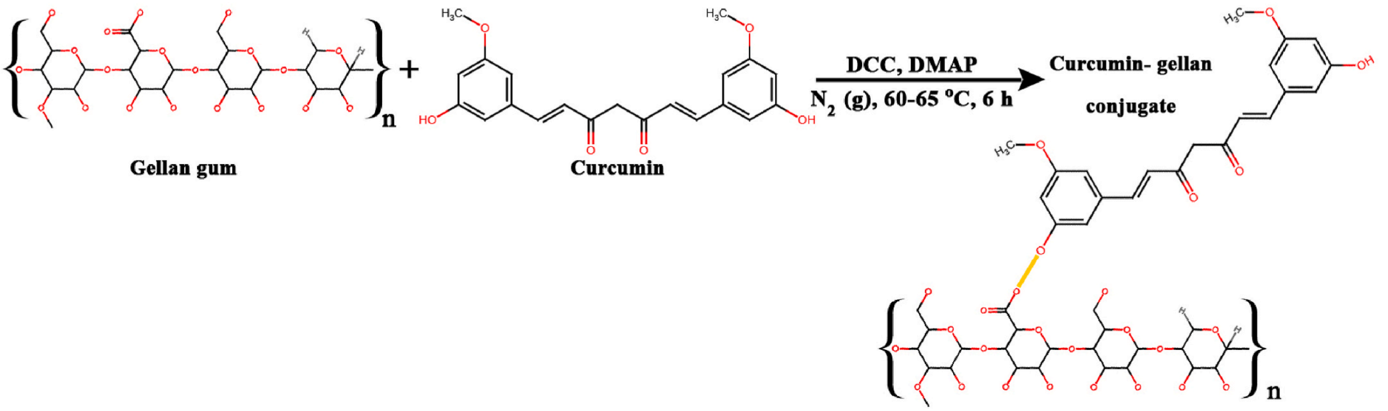


Fig. 11. The schematic presentation of the development of gellan-curcumin conjugates through 4-dimethylaminopyridine (DMAP)/dicyclohexylcarbodiimide (DCC) reaction.

Infrared Spectroscopy (FTIR), Nuclear Magnetic Resonance (NMR), ultraviolet–visible spectroscopy, and molecular weight changes. FTIR analysis shows the characteristic peaks of both polysaccharides and polyphenols, whether they are covalently or non-covalently bonded (Moreno-Vásquez et al., 2017). For polyphenols, the –OH stretching and bending vibrations (3300–3500 cm^{-1}), C=C stretching vibration of aromatic rings (1400–1600 cm^{-1}), and C–O or C–C stretching vibrations (1200–1300 cm^{-1}) are critical peaks (Woranuch & Yoksan, 2013). When the polysaccharide is covalently conjugated with polyphenol, two new peaks appear compared to the non-covalent case, including 1730 and 1640 cm^{-1}. The former is attributed to C=O stretching of esters, and the latter is attributed to C=O stretching in amide groups of chitosan.

Native polyphenols usually exhibit one or two characteristic absorption bands when analyzed through UV–vis spectroscopy, which are attributed to the benzene rings in the structure of polyphenols (Gu et al., 2022). Polysaccharides, however, do not show any absorption peaks at the wavelength used in UV–vis spectroscopy. Nevertheless, polyphenol-polysaccharide conjugates reveal an absorption peak similar to the corresponding polyphenol, and sometimes a slight shift may occur due to an alteration in the state of electrons in phenolic chromophores (Moreno-Vásquez et al., 2017). Table 4 summarizes the UV–vis characteristic peak absorption of different polyphenols and the shifts that occurred due to conjugation with polysaccharides.

5.8.2.3. Effect of conjugation on polysaccharides and polyphenols: an overview.

When polyphenols are conjugated onto polysaccharides, some changes occur in the structure and chemistry of the polysaccharides, leading to a substantial alteration in functionalities and nutritional properties. For example, sometimes the addition of polyphenols to the polysaccharide structure results in a change in crystallinity, and the intermolecular interactions are dissociated due to the occupation of polyphenols in the network of the polysaccharide. This can result in a higher water solubility of the polysaccharides (Gu, Su, et al., 2017).

Thermogravimetric analysis (TGA)and differential scanning calorimetry (DSC) are applied to evaluate the thermal properties of conjugates in which two main stages of weight loss can be observed. The first one is attributed to water loss, and the second one is related to depolymerization. Therefore, the more temperature required to reach the loss regions, the more stable the conjugates. It has been reported that thermal stability increases if the conjugation leads to more crystallinity in the structure of polysaccharides (Ahn et al., 2017; Liu et al., 2016). However, in the case of chitosan, controversial results have been

Table 4

UV–vis characteristic peak absorption of different polyphenols and shifts in their absorption due to the conjugation.

Polyphenol	ABS (nm)	Polyphenol-polysaccharide conjugate	ABS (nm)	Reference
Banana condensed tannins	209 & 272	Tannins- inulin	207 & 271	Zeng, Du, Ding, Zhao, and Jiang (2020)
Catechin	274	Catechin-arabinoxylan	274	Guo et al. (2021)
Chlorogenic acid	322	Chlorogenic acid-chitosan	322	Rui et al. (2017)
Curcumin	420	Curcumin-alginate	427	Dey & Sreenivasan. (2014)
Curcumin	420	Curcumin-hyaluronic acid	440	Manju and Sreenivasan (2011)
Curcumin	400	Curcumin-gellan gum	440	Mundlia et al. (2021)
Naringenin	280	Naringenin-gellan gum	300	
Gallic acid	211 & 259	Gallic acid-chitosan	259 & 261	Hu et al. (2016)
Gallic acid	260	Gallic acid-soluble dietary fibers	280	Li et al. (2020)
Rutin	265	Rutin-pectin	257	Ahn et al. (2017)
Hesperidin	285	Hesperidin-pectin	283	
Quercetin	274	Quercetin-pectin	258	
Tannic acid	288	Chitosan-pectin	~288	Jing, Diao, and Yu (2019)
Tyramine	275	Tyramine-gum tragacanth	275	Tavakol, Dehshisri, et al. (2016)

reported (Liu, Wen, Lu, Kan, & Jin, 2014; Moreno-Vásquez et al., 2017). This reduction in thermal stability can be attributed to the loss of crystallinity and hydrogen bonds after the conjugation (Wang, Mao, Dai, Yuan, & Gao, 2018).

Regarding alterations in crystallinity that occur during the conjugation of polyphenols and polysaccharides, contradictory results have also been reported. For example, some studies have reported that the crystallinity of starch reduced after being conjugated with polyphenols (Li et al., 2022; Liu, Wang, Yong, et al., 2018). However, other reports showed that conjugation brought about higher crystallinity (Liu et al., 2016; Liu, Wang, Yong, et al., 2018). To the best of our knowledge, this can be rationalized by forming or deforming the bonds through conjugation, which means if the conjugation process leads to more intermolecular associations, the crystallinity increases (Guo, Xiao, et al., 2022a).

Conjugation of various polysaccharides with polyphenols has been reported to reveal shear-thinning flow behavior, which was due to the chain entanglements of polysaccharides (Karaki, Aljawish, Muniglia, Humeau, & Jasniewski, 2016; Lv, Ye, Li, Ming, & Zhao, 2016; Wei & Gao, 2016). In contrast, other studies have shown higher viscosity after conjugation, which was attributed to the development of a higher molecular weight of polysaccharides (Wei & Gao, 2016). Based on these reports, it can be deduced that functional properties, including antioxidant, antimicrobial, anticancer, antidiabetic, and anti-inflammatory activities of polysaccharide-polyphenol conjugates, stem from the polyphenol portion of such systems.

5.8.2.3.1. Curcumin. According to our current understanding, curcumin is the most commonly used polyphenol in conjugation systems due to its lower solubility, followed by catechin and gallic acid. The polysaccharide portion is often made up of gellan gum, dextran, gum Arabic, alginate, or hyaluronic acid. Hyaluronic acid has been successfully esterified with curcumin to improve its solubility and stability, but the high hydrophilicity of hyaluronic acid and low solubility of curcumin can present potential drawbacks. A mixture of water and DMSO has been reported as a viable solution to this problem. In a study by Manju and Sreenivasan (2011), the conjugation process led to a substantially higher solubility of curcumin.

Dey and Sreenivasan (2014) developed alginate-curcumin conjugates using the esterification method to enhance the solubility and stability of curcumin. They confirmed the conjugation linkages through FTIR spectroscopy, with a sharper peak at 3441 cm^{-1} and 1617 cm^{-1} indicating hydroxyl groups and enol linkage of curcumin in the conjugates, respectively. They found that the micelles developed from the self-assembly effect of the conjugates in an aqueous solution were nano-sized, with curcumin and alginate located in the interior and exterior parts of these structures, respectively. This could potentially be used to encapsulate other hydrophobic compounds in the micelles. In another study, gum Arabic was used as a delivery system for hepatocarcinoma cells. The solubility of curcumin was about 900-fold greater than intact curcumin, and the conjugates showed more efficacy in human hepatocellular carcinoma (HepG2) cells compared to human breast carcinoma (MCF-7) cells (Sarika, James, Kumar, Raj, & Kumary, 2015).

Dextran is a predominant polysaccharide portion in the investigation of curcumin-polysaccharide conjugates, often developed using the free radical conjugation method. These conjugates were synthesized to inhibit pathogens and cancer cells and were confirmed through FTIR and 1H NMR. Dextran-curcumin conjugates were reported to be more efficient against gram-positive bacteria than gram-negative ones, and by adding more conjugates to the medium, more bacteria were inhibited from growing. The conjugates were also reported to have more cytotoxic properties against gastric adenocarcinoma, human breast adenocarcinoma (MCF-7 cells), and fibroblast cell lines than free curcumin (Curcio et al., 2019; Zare, Norouzi Sarkati, Tashakkorian, Partovi, & Rahaiee, 2019) developed similar conjugates through the immobilized laccase method. In this study, laccase was fixed on an acrylate hydrogel film acting as a solid-state catalyst. The conjugates were used as delivery systems for methotrexate and demonstrated a sustained release of the drug through an *in vitro* assay. This delivery system had a synergistic effect on the therapeutic properties of methotrexate against MCF-7 cells. The techno-functional properties of curcumin-polysaccharides conjugates have not been extensively investigated; it seems scientists are more interested in the health-beneficial effects of curcumin conjugates than their technological roles in food formulations. For instance, conjugates have been used as drugs to inhibit prostate cancer cells, with the half IC-50 value of conjugates proving the higher efficacy of this polyphenol. Similarly, dextran-curcumin demonstrated a synergistic effect on doxorubicin against prostate cancer cells (Bevacqua et al., 2021). It can be stated that a suitable method to develop polyphenol-gum conjugates is employing the esterification reaction which is used by many scientists.

5.8.2.3.2. Naringenin. Researchers (Mundlia et al., 2021) have previously synthesized esterified curcumin and naringenin conjugates with gellan gum and conducted an *in vitro* drug release study to simulate the release of these polyphenols. They also evaluated the antioxidant, antibacterial, and anticancer properties of these conjugates using *in vitro* models. The higher release of polyphenols from the conjugates under acidic conditions suggests a promising treatment for malignant cells since these cells often exist in such pH conditions. This feature is considered positive because the higher release of polyphenols at acidic pH values can lead to a greater inhibition of such cells (Sarika et al., 2015). The results of antioxidant and minimum inhibitory concentration assays showed significantly higher activities of these conjugate systems, as expected due to the higher solubility of polyphenols in their conjugated form with polysaccharides. The researchers reported that the conjugates had significantly greater anticancer activities against NIH: OVCAR-5 cells compared to their corresponding native forms. However, curcumin-gellan conjugates revealed higher anticancer activities than naringenin-gellan conjugates at the same concentration, which can be attributed to the higher anticancer activity of curcumin (Mundlia et al., 2021). Although this study revealed the potential of these conjugate systems, further investigations using *in vitro* 3D spheroid cell cultures and *in vivo* tests are necessary. The same authors had previously investigated naringenin-pectin conjugates to increase the aqueous solubility of this polyphenol and studied the consequences of this effect. Similarly, they found that naringenin was released at higher rates under acidic conditions (Mundlia, Ahuja, Kumar, & Pillay, 2019). It has been found that when the polysaccharide used for conjugation has a larger particle size, the efficiency of the conjugation process increases, and the particle morphology undergoes more alteration (Chanphai & Tajmir-Riahi, 2017).

5.8.2.3.3. Catechin. Catechin was grafted onto dextran using the immobilized laccase method to create a functionalized system. It was reported that the resulting conjugates had antitumor properties while nonmalignant cells remained unaffected in their presence (Vittorio et al., 2016). The functionalization of polysaccharides through catechin conjugation has gained the interest of scientists, leading to further research on polysaccharide-catechin conjugates. As previously mentioned, the radical grafting method can be used to control the reaction efficiency by adjusting the reaction temperature and polyphenol concentration. However, Oliver, Thomas, et al. (2016) utilized the radical grafting method to develop dextran-aldehyde-catechin conjugates and discovered that the aldehyde content on the dextran also affects the conjugation yield. The conjugation of catechin and arabinoxylan had an interesting effect, leading to a decrease in molecular weight, thermal properties, apparent viscosity, and *in vitro* digestibility of this polysaccharide. This means that this novel dietary fiber offers not only health benefits but also functional properties in food formulations (Guo et al., 2021). The effect of particle size on the conjugation yield was also reported by Chanphai and Tajmir-Riahi (2018), who developed chitosan-tea polyphenol conjugates, including (+)-catechin, (−)-epicatechin gallate, and (−)-epigallocatechin gallate. They found that the epigallocatechin gallate conjugates had the highest thermal stability, while (+)-catechin conjugates had the lowest. This could be due to the thermodynamic properties of these conjugates, and the catechin-chitosan conjugates seemed to have more enthalpy and free binding energy than other conjugates (Chanphai & Tajmir-Riahi, 2018).

5.8.2.3.4. Gallic acid. The presence of gallic acid and other phenolic acids in the network of chitosan has been shown to reduce the crystallinity and enhance the solubility of chitosan-phenolic acid conjugates compared to native chitosan and phenolic acids (Hu, Wang, Zhou, Xue, & Luo, 2016; Pasanphan & Chirachanchai, 2008; Pasanphan, Buettner, & Chirachanchai, 2008). However, it has been reported that the conjugation of gallic acid and sinapic acid with pre-gelatinized rice starch leads to an increase in crystallinity, ordered network, and resistant starch content (Chumsri, Panpipat, Cheong, Nisoa, & Chaijan, 2022), possibly due to the development of V-type inclusion complexes (Obiro, Sinha Ray, & Emmambux, 2012; Zhu, 2015). Similar results were found by Wu et al. (2022), who prepared gallic acid-starch and quercetin-starch conjugates. Additionally, strong interaction between these polyphenols and corn starch resulted in a reduction in the swelling ability (Wu et al., 2022). Furthermore, when gallic acid and catechin are mixed with soluble dietary fibers such as D-galactose, L-rhamnose, D-glucose, D-arabinose, and xylose, pH is the most important factor in conjugation yield, followed by temperature and mass ratio, respectively (Jakobek & Matić, 2019; Li et al., 2020).

5.8.2.3.5. Quercetin. Starch aldehyde was functionalized through conjugation with quercetin by Yong et al. (2020); however, their results showed controversy in the crystallinity of corn starch. In contrast to the abovementioned results, they reported a reduction in the crystallinity of corn starch after conjugation (Yong et al., 2020). Since the process was according to the radical grafting method, it is not unexpected if oxidation reactions and acidic hydrolysis destroyed the ordered structure. Additionally, the dissolution of starch in DMSO solution could be another factor that disrupted the crystalline regions (Liu, Wang, Bai, et al., 2018; Liu, Wang, Yong, et al., 2018; Zuo et al., 2017). For more information about other polyphenol conjugates, please refer to the references listed (alphabetically) in Table 5.

6. Potential applications of conjugated polyphenols

Apart from enhancing the bioavailability of polyphenols through conjugation methods, such conjugates have been increasingly used as functional ingredients in a wide range of formulations across the food, pharmaceutical, and cosmetic industries. As previously mentioned, polyphenolic conjugates exhibit various functionalities, including emulsification capacity, foam-forming ability, encapsulation of bioactives, and film-forming ability, making them highly suitable for diverse formulations. This section will discuss different applications of polyphenolic conjugates as functional ingredients. The preparation of emulsions with acceptable stability and enhanced characteristics using protein/polysaccharide-polyphenol conjugates has been widely studied. For example, Feng et al. (2018) prepared stabilizers based on fish oil and conjugated ovalbumin with catechin. The resulting emulsion exhibited lower droplet size, higher stability, and lower oxidation compared to emulsions prepared with ovalbumin alone. The introduction of

Table 5
Other synthesized polyphenol-polysaccharide conjugates.

Polyphenol	Polysaccharide	Main findings	Reference
4-Methoxyphenol	β-Cyclodextrin	• The system had the potential to reduce the negative impacts of the drug therapy during treatment.	Swiech, Mieczkowska, Chmurski, and Bilewicz (2012)
Chlorogenic acid	Chitosan	• The system can be exploited as supplement to prepare functional food	Rui et al. (2017)
Condensed Tannin	Inulin	• Enhanced hypoglycemic effects of inulin was observed and the conjugate have the potential to be developed as an effective anti-diabetic agent.	Zeng et al. (2020)
Proanthocyanidin	Chitosan	• The antioxidant and antibacterial activities of chitosan was enhanced through conjugation with proanthocyanidin	Jing, Huang, and Yu (2018)
Quercetin-DHA[1] Ester	Pectin	• The system was protective and transporting for quercetin and the bioavailability of quercetin was enhanced through the conjugation with pectin	Carullo et al. (2022)
Rosmarinic acid	Dextran	• The conjugates exhibited a prolonged efficacy and enhanced stability in comparison with free polyphenols. • Th system are innovative bioactive ingredient and whitening agent in cosmetic formulations	Parisi et al. (2017)
Salicylic acid	Chitosan film	• Enhanced antioxidant and antibacterial properties of chitosan film • Enhanced mechanical and water vapor barrier properties of chitosan film	Hu, Du, et al. (2021)
Tannic acid	Chitosan	• 6.4 times higher antioxidant activities of conjugate films in comparison with native chitosan films	Jing et al. (2019)
Tyramine	Gum tragacanth	• The use of electron beam irradiation was a viable technique for fabricating tyramine conjugated gum tragacanth	Tavakol, Dehshiri, and Vasheghani-Farahani (2016)
Tyramine	Gum tragacanth	• The conjugate was found to be a suitable candidate for preparation of hydrogels with sustained release properties	Tavakol, Vasheghani-Farahani, Mohammadifar, Soleimani, and Hashemi-Najafabadi (2016)

[1] Docosahexaenoic acid.

polyphenols increased the surface hydrophobicity and provided stronger repulsion between conjugates, resulting in improved emulsification capacity and stability. Studies have also reported enhanced emulsification and encapsulation capacity as well as emulsion stability for polysaccharide-polyphenol conjugates (Singh, Mittal, & Benjakul, 2023; Zhao, Fan, Liu, & Li, 2022b). Zhao, Fan, Liu, and Li (2022a) prepared emulsions using chitosan-protocatechuic acid conjugates as stabilizers for encapsulating β-carotene. These conjugates exhibited higher physical, oxidation, and thermal stability compared to chitosan alone. The molecular weight of chitosan also influenced the emulsion properties and β-carotene retention, with chitosan of 200 kDa showing better performance compared to conjugates prepared with chitosan of 400 and 100 kDa.

Biodegradable packaging materials have gained attention due to their biocompatibility and safety. Proteins such as corn zein, soy and milk proteins, collagen, and gelatin, as well as polysaccharides including chitosan, pectin, cellulose, and starch, are widely exploited as biopolymer-based packaging materials. Additionally, the development of biodegradable active packaging is of interest due to its ability to extend the shelf life and maintain the quality of food products. Protein/polyphenol and polysaccharide/polyphenol conjugates possess numerous functional and health-beneficial properties, making them attractive for active packaging applications. Wu et al. (2022) developed a biodegradable film based on chitosan-tea polyphenol conjugates and silica aerogel, which exhibited a smooth surface and high biodegradability. The incorporation of polyphenols into the chitosan matrix enhanced the antimicrobial and antioxidant properties of the packaging material. Similarly, De Carli et al. (2022) created an active packaging material using chitosan derived from crayfish shell waste and polyphenols extracted from propolis. The addition of polyphenols resulted in lower light transmission, increased thermal and mechanical stability, and improved antioxidant and antimicrobial properties of the chitosan films.

Crosslinking is a method commonly employed to prepare gels in food formulations (Liu, Pu, et al., 2017), and polyphenols in their oxidized form have a strong tendency to bond with proteins and polysaccharides. Therefore, polyphenol conjugates are considered beneficial candidates for gel-based formulations. For instance, Von Staszewski et al. (2012) demonstrated that the conjugation of β-lactoglobulin with tea polyphenols resulted in gels with improved gelling properties, including decreased set time and set temperature. In another study, hydrogels were developed based on ternary conjugates of sodium alginate, soy protein isolate, and epigallocatechin gallate (EGCG). These hydrogels exhibited low porosity, higher antioxidant activity, and enhanced stability during digestion in the upper gastrointestinal tract (Hu, Sun, et al., 2021).

Another notable capacity of polyphenolic conjugates is their potential as encapsulation and delivery systems (Zhou et al., 2020). Zhou, Pan, et al. (2022) developed a delivery system for anthocyanins using sinapic acid-chitosan conjugates. These conjugates not only exhibited higher antioxidant activity but also demonstrated sustained release properties with improved encapsulation efficiency and retention of anthocyanins. Additionally, Sun et al. (2019) prepared a nano-delivery system in the form of a core-shell system using chitosan, lysozyme, and tannin conjugates. The incorporation of polyphenols into the system enhanced bioavailability, antioxidant activity, and antimicrobial properties. The introduction of polyphenols to biopolymers such as proteins and polysaccharides enhances their capacity in various applications due to the hydrophobicity, therapeutic capability, and antioxidant and antimicrobial properties of polyphenols. Furthermore, as previously described, astringency in wine arises from the interaction between concentrated tannins and saliva proteins, leading to the formation of aggregates and precipitates. Polysaccharides can compete with saliva proteins to non-covalently bond with tannins, thereby reducing astringency (Watrelot, Schulz, & Kennedy, 2017).

Polyphenolic conjugates also hold pharmaceutical potential. Pawlaczyk et al. (2009) reported that naturally occurring polysaccharide-polyphenol conjugates in C. Canadensis effectively inhibit oxidative and nitrative stresses caused by peroxynitrite, which contribute to cardiovascular diseases and inflammatory conditions. In another study, phenolic conjugates of phenolic acids extracted from swallow root (Decalepis hamiltonii) exhibited cytoprotective activity on NIH 3T3 fibroblast cells and a protective effect on DNA (Nayaka, Sathisha, & Dharmesh, 2010). Additionally, polyphenolic conjugates extracted from Annurca apple demonstrated a chemoprotective effect and inhibition of colorectal cancer cells (Fini et al., 2011). Overall, the wide range of applications of polyphenolic conjugates as functional ingredients in various formulations highlights their versatility and potential for use in the food, pharmaceutical, and cosmetic industries.

7. Challenges and future directions

The development of polyphenolic conjugates, despite their recognized health-promoting effects and techno-functional applications, presents several challenges that need to be addressed. One of the main difficulties lies in the synthesis of polyphenolic conjugates with specific health-promoting and functional characteristics, as there is currently no standardized procedure for their production. Consequently, the ability to establish a predetermined approach for generating novel conjugates with desired properties would greatly benefit the food and pharmaceutical industries. Furthermore, the application of polyphenol conjugates in these industries lacks clear evidence and established practices. While the potential of polyphenolic conjugates is widely acknowledged, there is a need for further research and substantiation of their practical utilization in food and pharmaceutical formulations. Therefore, it is crucial to develop facile, cost-effective, and safe procedures for the production of polyphenolic conjugates to facilitate their widespread application and integration into various products.

To achieve optimal conjugation efficiency, it is necessary to consider various factors that influence the process, including reaction conditions, the types of proteins/polysaccharides involved, and the specific polyphenols used. Identifying the ideal conjugation conditions and establishing guidelines that other scientists can refer to and replicate will be instrumental in advancing the field. Standardizing the conjugation process will enable the development of reproducible and scalable methods for producing polyphenolic conjugates with consistent quality and properties. Moreover, there is a pressing need for the discovery and development of novel polyphenolic conjugates with unique potentials and characteristics. As researchers and industries increasingly recognize the significant role of polyphenols in promoting health and enhancing product formulations, exploring new conjugates becomes imperative. These novel conjugates can offer innovative applications and benefits, expanding the possibilities for incorporating polyphenols into a wide range of products.

In summary, while polyphenolic conjugates hold great promise in various industries, addressing the challenges related to synthesis, standardization, and evidence generation is crucial. Developing an optimized conjugation process, establishing clear protocols, and exploring novel conjugates will contribute to the advancement and utilization of polyphenolic conjugates in the future. By overcoming these challenges and focusing on future directions, the potential of polyphenolic conjugates can be fully realized, leading to novel functional ingredients with diverse applications in food, pharmaceutical, and other related industries.

8. Conclusion

Polyphenols are widely recognized as highly beneficial functional ingredients found in fresh produce and food products. The consumption of such compounds has been shown to provide numerous health benefits, making them a desirable component for both consumers and manufacturers. However, the low solubility and corresponding poor bioavailability of most polyphenols have limited their application in various sectors including the food industry. Several techniques have been employed to enhance the bioavailability of these compounds, with conjugation methods being the most recent and promising ones. Conjugation methods involve the chemical and physical grafting of polyphenols onto edible biomacromolecules such as proteins and polysaccharides. Successful synthesis of protein-polyphenol, protein-polysaccharide-polyphenol, and polysaccharide-polyphenol conjugates has been reported in several studies, all of which have improved the bioavailability of these nutraceuticals. Protein and polysaccharide conjugation methods include immobilized enzymes, free radical grafting, esterification, and epichlorohydrin chemistry methods. However, polysaccharide-polyphenol conjugates have shown greater success in enhancing the bioavailability of polyphenols due to the higher solubility of polysaccharides compared to protein-based conjugates.

There are still numerous polysaccharides and polyphenols to be explored as conjugates, including novel polysaccharides extracted from plants and synthesized polyphenols. Additionally, optimal procedures are required to develop polysaccharide-polyphenol conjugates with the highest efficiency and several functional properties, such as emulsification capacity, foam-forming ability, and taste contrast effects. This presents an opportunity for food manufacturers to utilize these conjugates instead of synthetic functional ingredients. Furthermore, consumers will have the option to choose healthier diets for their lifestyles. Taken together, the development and application of polysaccharide-polyphenol conjugates have opened up new avenues for enhancing the bioavailability of polyphenols, thus providing numerous health benefits for consumers. Future research should focus on exploring novel conjugates and optimizing their functional properties to provide even more benefits for consumers and manufacturers alike.

Author statement/CRediT roles

Shahriyar Sahraeian: Conceptualization; Data curation; Methodology; Formal analysis; Software; Investigation; Writing - original draft. Ali Rashidinejad: Supervision; Investigation; Validation; Writing - review & editing. Mohammad-Taghi Golmakani: Supervision; Writing - review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

Data availability

Data will be made available on request.

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