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REVIEW ARTICLE

Plant-derived polyphenolic compounds: nanodelivery through polysaccharide-based systems to improve the biological properties

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ABSTRACT

Plant-derived polyphenols are naturally occurring compounds widely distributed in plants. They have received greater attention in the food and pharmaceutical industries due to their potential health benefits, reducing the risk of some chronic diseases due to their antioxidant, anti-inflammatory, anticancer, cardioprotective, and neuro-action properties. Polyphenolic compounds orally administered can be used as adjuvants in several treatments but with restricted uses due to chemical instability. The review discusses the different structural compositions of polyphenols and their influence on chemical stability. Despite the potential and wide applications, there is a need to improve the delivery of polyphenolics to target the human intestine without massive chemical modifications. Oral administration of polyphenols is unfeasible due to instability, low bioaccessibility, and limited bioavailability. Nano-delivery systems based on polysaccharides (starch, pectin, chitosan, and cellulose) have been identified as a viable option for oral ingestion, potentiate biological effects, and direct-controlled delivery in specific tissues. The time and dose can be individualized for specific diseases, such as intestinal cancer. This review will address the mechanisms by which polysaccharides-based nanostructured systems can protect against degradation and enhance intestinal permeation, oral bioavailability, and the potential application of polysaccharides as nanocarriers for the controlled and targeted delivery of polyphenolic compounds.

KEYWORDS

Antioxidants; bioavailability; flavonoids; nanoencapsulation; polyphenolic compounds; polysaccharides; target delivery

1. Introduction

In recent years, several biological, epidemiological, and clinical studies have established the association between a plant-based diet with health benefits and potentially reducing the prevalence of various non-communicable diseases in the population (Koch 2019). Indeed, the regular intake of bioactive food (Tahir et al. 2021) has been widely associated with decreased risk for the development of cardiovascular diseases (Kasprzak-Drozd et al. 2021), cancer (Gharibzahedi et al. 2022), diabetes (Zamora-Ros et al. 2018), obesity (Jamar, Estadella, and Pisani 2017), and mental disorders (Lin et al. 2021). In addition, food-bioactive compounds can reduce and attenuate the inflammatory reaction intrinsically linked to age-associated chronic diseases (Cory et al. 2018).

The growing evidence of the biological effects of plant-derived food components and their metabolites in improving human health has contributed to boosting research and innovation in the nutraceuticals industry over the years. Polyphenolic compounds are extensive and heterogeneous phytochemicals in vegetable-based foods (Suleria, Barrow, and Dunshea 2020); they are considered the primary group of non-nutrients due to their diversity and biological properties. Polyphenols have been studied for their potential benefits as anti-aging, anti-inflammatory, antioxidant, and antiproliferative agents (Fraga et al. 2019; Lin et al. 2021). Due to their potential benefits on human health, polyphenolic compounds have attracted great interest as functional food ingredients and dietary supplements (Wang, Barrow, and Dunshea 2021). However, the limitation in oral intake due to difficulties in maintaining stability implies a decrease in functional properties and the ability to reach specific tissues in the human body (Jiao, Jin, and Qiu 2022). Low bioaccessibility and insufficient bioavailability are ting factors for oral administration and limiting effective therapeutic results (Faridi Esfanjani, Assadpour, and Jafari 2018; Jiao, Jin, and Qiu 2022).

Over the years, efforts have been directed toward exploring technologies to maximize the benefits of these phytochemicals to human health. However, the vast diversity of molecular structures of these compounds, the complexity of interactions with the intestinal microbiota and their variability, and the scarcity of studies *in vivo* models indicate that a broad discussion on the topic should be deepened (Bié et al. 2023; Zamora-Ros et al. 2018). In the search for effective

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alternatives to overcome the challenges of oral ingestion of polyphenolic compounds, enhance the biological effects and maintain their functionality, nanotechnology has been incorporated as a new alternative for the food enrichment, nutraceuticals, and pharmaceutical industries (Ayala-Fuentes and Chavez-Santoscoy 2021; Khalil et al. 2020). Recent studies have demonstrated the applicability of nano-encapsulated polyphenolic compounds to increase bioaccessibility, bioactivity, and their biological use (Garavand et al. 2021; Salarbashi, Bazeli, and Rad 2020). Despite studies reporting the advantages of nanoencapsulation for polyphenolic compounds (Andishmand et al. 2023; Caballero et al. 2022; Frosi et al. 2022; Siddiqui et al. 2022; Suhag et al. 2022) studies on polysaccharide-based nano-delivery systems are not described. However, it is necessary to deepen the discussions to include them as nanocarriers for controlled direct delivery to specific tissues, mainly intestinal, and to potentiate the biological effects of these bioactive compounds.

Several nanotechnological approaches, techniques, and encapsulating materials have been investigated (Salarbashi, Bazeli, and Rad 2020). Natural polysaccharides are especially highlighted for their ability to form nanostructures to encapsulate bioactive compounds (Lu et al. 2019; Zhang, Jia, et al. 2021). Food polysaccharides – such as starch, pectin, chitosan, and cellulose – can (1) protect bioactive compounds which are sensitive to factors intrinsic to human digestion; (2) be used for targeted drug delivery system, and; (3) promote the absorption of intact structures while favoring a more effective production of active metabolites (Akbari-Alavijeh, Shaddel, and Jafari 2020; Bié et al. 2023). They are biodegradable, biocompatible, and easily obtained by consolidated extraction techniques and with various natural sources for extraction (such as by-products from the food industry). Polysaccharides have biological functionality, such as control of intestinal homeostasis. They are compounds without toxicity, so they are safe for human consumption. Also, they have thermally, chemically, mechanically resistant, and flexible physical and chemical structures since modifications can be induced on their molecular structure (Lu et al. 2019; Shen et al. 2022). They have a natural affinity for polyphenolic compounds and are compatible with nano foods and nutritional formulations, favoring their use in nanostructured polysaccharide-based delivery systems (Fernandes et al. 2020; Song et al. 2022). In this regard, there is a current need for studies to discuss the applications of nanotechnology to increase the bioavailability of polyphenols to support future studies. Therefore, this article provides an overview of the physicochemical properties of common polysaccharides used in nanostructured systems and their nanoparticle formation mechanisms. In addition, it addresses the potential of nanoformulations for adjuvant treatments in some diseases, such as intestinal cancer. It highlights the applications of nanoencapsulation for the oral administration of polyphenolic compounds and increasing their bioavailability.

2. Polyphenolic compounds: structural diversity and bioactivities

Polyphenolics are compounds derived from the secondary metabolism of plants (Jiao, Jin, and Qiu 2022); they are responsible for fundamental functions for physiology and morphology in vegetables (Khalid et al. 2019). They consist of water-soluble compounds (phenolic acids, phenylpropanoids, and quinones) and water-insoluble compounds (condensed tannins, lignin); most flavonoids are water-soluble and some insoluble in water (such as quercetin and lignans). Due to their wide occurrence in plant sources, these compounds are part of the daily human diet (Carnauba et al. 2022). The primary sources are fruits, vegetables, whole grains, chocolate, and beverages such as tea and wine. Also, they are widely distributed in vegetable peels and can be extracted from food by-products (Comunian, Silva, and Souza 2021). Polyphenols also contribute to foods' color, flavor, organoleptic qualities, and various food functionalities (Câmara et al. 2020).

In the last decades, polyphenolic compounds have been extensively studied, and recent research has explored their potential as functional ingredients for addition by the food and pharmaceutical industries (Fernandes, Mateus, and Freitas 2023). Plant-derived polyphenol compounds are one of the natural compounds reported promising to decrease the risks of developing several chronic diseases (Cosme, Rodríguez, and Espino 2020). The broad spectrum of biological effects attributed to polyphenols has been described in the literature in several *in vitro*, *in vivo,* and clinical trial studies (Curtis et al. 2019; Jiao, Jin, and Qiu 2022; Yahfoufi et al. 2018; Zhang and Tsao 2016). The main beneficial properties associated with these compounds described in the literature are antioxidant activity (Cosme, Rodríguez, and Espino 2020; Imran et al. 2018; Kumar and Pandey 2013), anti-inflammatory effect (Grgić et al. 2020; Pandima et al. 2015), anticancer activity (Dobrzynska, Napierala, and Florek 2020; Salehi et al. 2020), prevention of cardiovascular diseases (Câmara et al. 2020; Carvalho et al. 2022; Zamora-Ros et al. 2018), anti-obesity effect and weight-reducing properties (Cialdella-Kam et al. 2017.; Panchal et al. 2022), antidiabetic activity (Hossain et al. 2016; Salehi et al. 2020), intestinal homeostasis (Gu et al. 2019; Kasprzak-Drozd et al. 2021), central nervous system (Parkinson's and Alzheimer's disease) and mental disorders (depression and anxiety) (Magni et al. 2022; Sato et al. 2019; Zhou et al. 2020). The therapeutic and health-promoting properties of polyphenols indicate the promising administration of these bioactive to reduce the risk of developing certain diseases and as a powerful adjunct in treating various conditions (Henriques et al. 2020; Semwal et al. 2016; Siddiqui et al. 2014; Verediano et al. 2021).

It is known that the complex interaction between polyphenolic compounds and the intestinal microbiota contributes to its benefits in the various biological systems (Adan et al. 2019; Liang et al. 2018; Osadchiy, Osadchiy, Martin, and Mayer 2020). Intestinal bacteria can biotransform polyphenolic compounds into more active metabolites, promoting more efficient absorption, influencing bioavailability, and preserving the anti-inflammatory action (Horn et al. 2022; Lin et al. 2021; Needham, Daouk, and Mazmanian 2020). At the same time, polyphenols can maintain the intestinal barrier, contributing to microbiota homeostasis (Estruel-Amades et al. 2019). Some polyphenolic compounds can modify the

microbiota composition by increasing the proportion of beneficial bacteria among the pathogenic ones and promoting immunomodulatory and prebiotic action (Tomas-Barberan, Selma, and Esp 2018). The biotransformation of these compounds by the microbiota produces essential metabolites. However, this process also reduces the amount of absorbed whole compounds or intact molecules in more distal intestinal portions (De Ferrars et al. 2014; Duda-Chodak et al. 2015); this interconnection mechanism will be explored in the next section, especially detailing this interaction's impact on biological use.

Polyphenolic compounds have many structures directly related to their functional properties (Hanhineva et al. 2010). Structurally, polyphenols comprise two aromatic rings (benzene) with one or more hydroxyl substituents, such as organic acids, sugars (mono-, di- or oligosaccharides), and acylated sugars linked to the primary structure with hydrophilic groups (Van de Velde, Pirovani, and Drago 2018). They are distributed into two main classes: flavonoids, consisting of a C_6-C_3-C_6 core, and non-flavonoids formed by a C_1-C_6, C_3-C_6, or a core C_6-C_2-C_6 (Dias et al. 2021; Panche, Diwan, and Chandra 2016). They are formed by two phenyl groups, complexed by a three-carbon bridge with different degrees of oxidation and unsaturation; sugar molecules can be linked to hydroxyl groups in flavonoids (Dobrzynska, Napierala, and Florek 2020; Jakobek 2015), and the phenolic acids are formed by a single phenyl ring (Dobson et al. 2019). The main classes identified in plants are flavonoids, phenolic acids, lignans, and stilbenes; the most abundant foods are flavonoids, which include flavonols, flavones, flavanones, flavanols, isoflavones, and anthocyanidins (Figure 1). Phenolic acids (caffeic, chlorogenic, ferulic, coumaric acid), stilbenes (resveratrol), and lignans (secoisolariciresinol) are non-flavonoid compounds in foods (Figure 2).

Isoflavones are the most stable polyphenolics, and anthocyanins are the most unstable molecules (Shivashankara and Acharya 2010). The molecular structure of polyphenolic compounds (flavonoids and non-flavonoids) can directly affect absorption, functional properties, biological effects, and stability (Dobson et al. 2019; Kardum and Glibetic 2018). Recent research attributes essential influences on the metabolites of polyphenolic compounds; for some, it is assumed that the biological activity is mainly due to the products of the catabolism of these bioactive compounds. However, some factors (which will be discussed in the next topic of this article) may prevent or reduce the content of

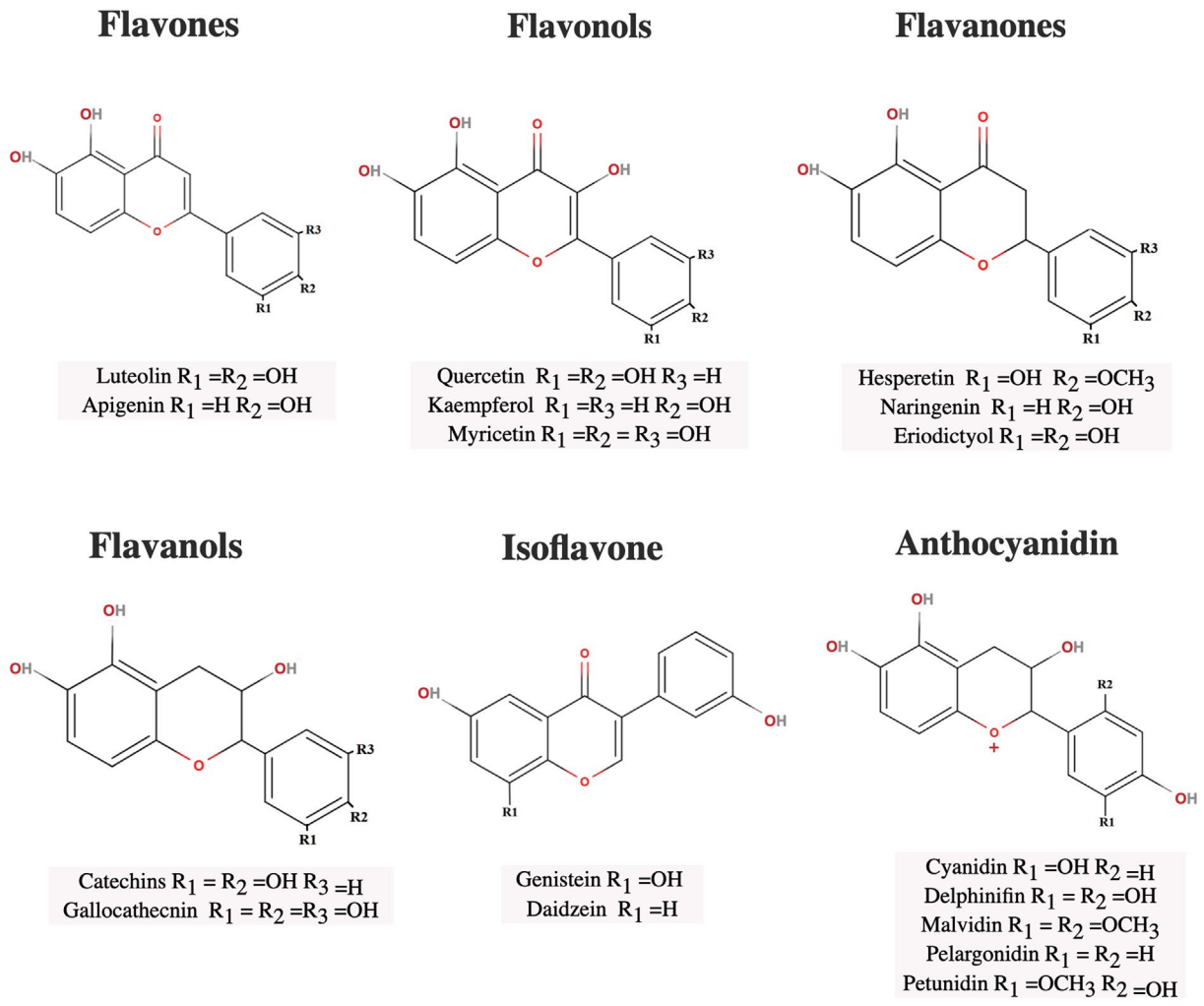

Figure 1. Chemical structures of flavonoids in foods. The primary forms of the main groups are depicted: flavonols, flavones, flavanones, flavanols, isoflavones, and anthocyanidins. The figure was created with MolView (https://molview.org) and Mind the Graph (https://mindthegraph.com) (accessed on 09 March 2023).

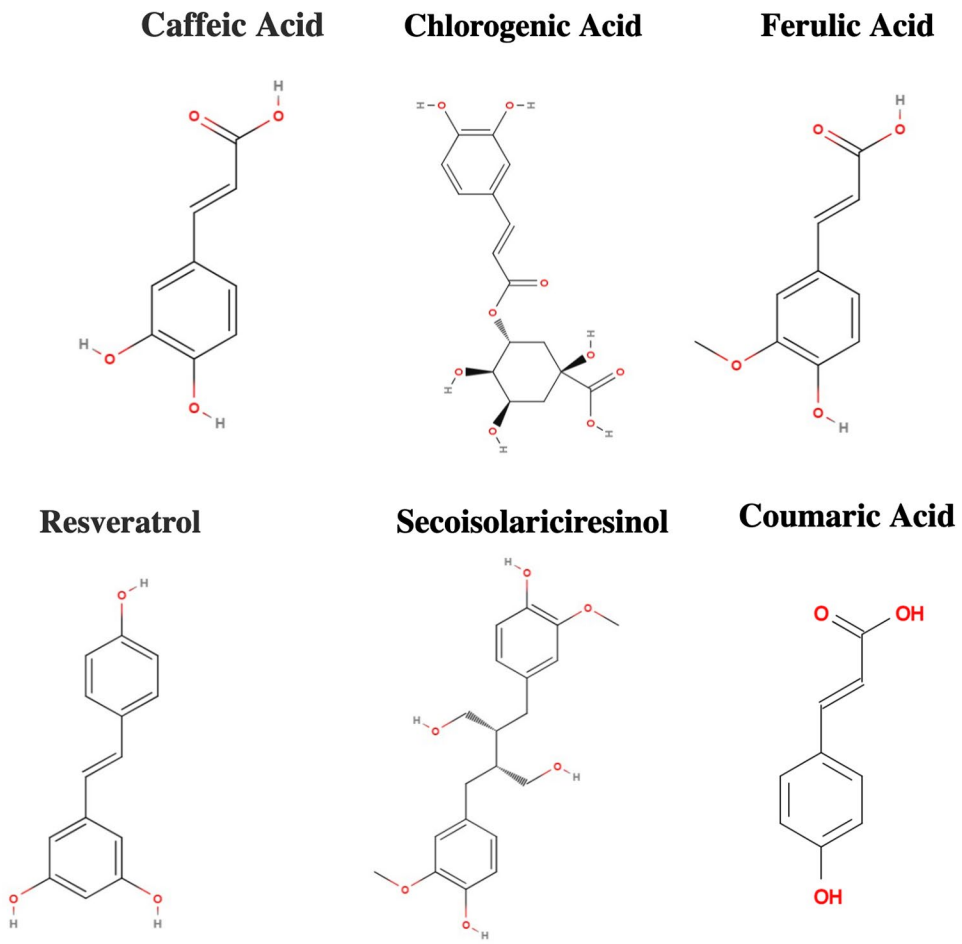

Figure 2. Chemical structures of non-flavonoids in foods. The primary forms of the main groups are depicted: phenolic acids (caffeic, chlorogenic, and ferulic acid), stilbenes (resveratrol), and lignans (secoisolariciresinol). the figure was created with MolView (https://molview.org) and Mind the Graph (https://mindthegraph.com) (accessed on 09 March 2023).

compounds that reach more distal portions of the large intestine, limiting the amount of metabolism by the local microbiota and, consequently, reducing the absorption of metabolites (Jakobek 2015; Victoria-Campos et al. 2022), and decreases the amount of intact structures of polyphenolic compounds, limiting essential biological properties in the small intestine (Akbari-Alavijeh, Shaddel, and Jafari 2020). Our previous studies discuss other characteristics, classifications, metabolism, and beneficial health effects in more detail (Rosales et al. 2022; Rosales & Fabi, 2023b).

3. Molecular stability and bioavailability: challenges to enable oral ingestion

Despite the numerous advantages and protective effects of polyphenolic compounds, there is a limitation to oral ingestion and use as therapeutic agents (Dima et al. 2020b). Most of these compounds are not biologically used to their full potential. The main limitations of oral ingestion of intact molecules are moderate solubility, low stability, high excretion, and inefficient biological use (Jokioja, Yang, and Linderborg 2021; Tanaka et al. 2019). When ingested orally, polyphenolic compounds can be degraded in the small intestine, where they can be absorbed – intact or in aglycone form – the unabsorbed fraction goes to the large intestine. However, the intense degradation can reduce the intact molecules in the large intestine, where they are metabolized by the local microbiota, reducing the systemic effects of colonic fermentation (Tian et al. 2019; Toydemir et al. 2013).

Due to the vast diversity of molecular structures of polyphenolic compounds, the estimation of total polyphenol content in foods is inaccurate (Jiao, Jin, and Qiu 2022). The effects observed *in vivo* initially depend on the concentration of the food and subsequently on its bioaccessibility and bioavailability after ingestion (Braga et al. 2018; Jaime and Santoyo 2021). The bioavailability of these compounds is intricately linked to the preservation of molecular integrity – external factors related to raw material, processing, and storage – and factors intrinsic to human digestion can also directly affect these compounds' molecular stability, leading to molecules' biotransformation, as already discussed in the previous section (Chen et al. 2017; De Ferrars et al. 2014; Fleschhut et al. 2006). Due to these interconnected complex factors, a higher content of polyphenol compounds in food does not result in a higher bioavailability (Manach et al. 2004; Polia et al. 2022).

Some factors may prevent or decrease the content of compounds that reach more distal portions of the large intestine, limiting the amount of metabolism by the local microbiota and, consequently, reducing the metabolites absorption (Ozdal et al. 2016; Salehi et al. 2020). Furthermore, the intact structure of polyphenolic compounds preserves essential biological properties, and maintaining chemical integrity can have numerous advantages for some biological systems (De Ferrars et al. 2014; Enaru et al. 2021; Van de Velde et al. 2022). In the human body, polyphenolic compounds are intensely degraded, and molecular stability results from exposure to other food constituents (nutrients and non-nutrients), intestinal pH, digestive enzymes, and intestinal bacteria (Chen et al. 2017; Neilson, Goodrich, and Ferruzzi 2017).

It is a consensus in the literature that polyphenolic compounds have low bioaccessibility and limited bioavailability. Bioaccessibility can be defined as the portion of the available nutrient or bioactive compound released from the food matrix or nanostructure and available to be absorbed. In turn, bioavailability is the proportion of the compound effectively absorbed, reaches the target tissue or organ, and is available for biological use (Cardona et al. 2013; Fisher et al. 2010). Low bioavailability results in limited bio-efficacy and all attributed health benefits (Yahfoufi et al. 2018), and the significant structural differences of polyphenolics can affect their biological use efficiency (Jiao, Jin, and Qiu 2022).

Due to the rapid occurrence in the blood plasma after ingestion (in minor quantity), these compounds can be absorbed by the stomach mucosa in smaller amounts than by the intestine. Most of them are absorbed in the small intestine. On the other hand, due to the instability, compounds that are not absorbed reach the colon and are biotransformed by intestinal bacteria. For most polyphenols, such as flavonoids, especially anthocyanins, quercetin, and daidzein, the acidic environment of the stomach (pH 2-3) does not cause acid hydrolysis of the structure, and only in the intestine (pH 7-8) they can be degraded (Fernandes et al. 2015; Neilson, Goodrich, and Ferruzzi 2017). Those whose composition has a rhamnose portion can reach the colon hydrolyzed by rhamnosidases and absorbed as aglycones (Maaliki et al. 2019).

It has been reported that the passive mass diffusion of polyphenolic compounds in the intestine is inefficient due to the hydrophilicity of most of them, making it difficult to penetrate the intestine layer (Obayashi et al. 2013; Rastogi and Jana 2016; Rein et al. 2013). Another factor is that at pH 7 and 8 (intestinal pH), the state of ionization (hydrogen bonds) of polyphenols directly influences absorption *via* passive diffusion. Those compounds with lower molecular weight, hydrophobic character, and a neutral charge have a greater possibility of passive absorption. Active absorption can also occur *via* membrane transporters (sodium-dependent). However, all membrane transporters involved in polyphenol absorption have already been fully elucidated. Although the polyphenolics (glycosylates and aglycones) can be absorbed in the small intestine, many of these compounds in food have esters, glycosides, or polymers in their compositions, which complicates the absorption of the intact (native) structures (Manach et al. 2004; Obayashi et al. 2013; Rastogi and Jana 2016; Rein et al. 2013; Tian et al. 2019). The absorption of flavonoid glycosides involves the enzyme cleaving and releasing the aglycon moiety (to be absorbed by passive diffusion in the epithelial cells). Then, the compounds are metabolized to phenolic acids by intestinal microbiota and can be absorbed or excreted (Talavéra et al. 2004). Polyphenolic compounds and their metabolites are conjugated in the small intestine and the liver after absorption, including methylation, sulfation, and glucuronidation (Faria et al. 2014; Kamiloglu et al. 2021). During digestion, these compounds in the intestine can bind to other molecules – polysaccharides, such as fiber – forming structural complexes, decreasing or improving their bioaccessibility (Ashley et al. 2019; Lila et al. 2016).

The presence of glucose in the polyphenolic structure has strong relevance for their chemical stability. The process of deglycosylation is related to bioaccessibility and bioavailability. Among the polyphenolic compounds, bioaccessibility differs depending on the chemical structure and the presence of glucose. Some phenolic compounds can form condensed structures that are not absorbed, such as catechin and epicatechin monomers that can form oligomers and proanthocyanidins that are condensed tannins, resulting in poor absorption and less bioavailability (Ashley et al. 2019; Lee et al. 2006).

Two main factors determine the biotransformation of polyphenols in the gastrointestinal tract. Structural rearrangement (polyphenol scaffolding) can be formed primarily by the molecular structure, and responses to external factors can be attenuated. The nanoparticle design will minimize access to intestinal enzymes and bacteria, limiting the structural biotransformation (Duda-Chodak et al. 2015; Marín et al. 2015). Gut microbiota is the second factor that impacts polyphenols' bioavailability. The intestinal microbiota plays an essential role in bioavailability. Polyphenols, especially flavonoids, strongly interact with the intestinal microbiota, and different biotransformation can occur depending on the microbiome's composition (variety of species). Some intestinal bacteria possess enzymatic apparatus that processes polyphenols, such as the deglycosylation process. However, some alterations only occur in the presence of specific bacteria (strains determined) to certain polyphenolic compounds. Therefore, the individuality of the microbiota and the composition of polyphenols in the diet are complex and interfere with biological utilization. The interaction between flavonoids and microbiome results in phenolic compounds metabolites, for example, phenyl propionic, protocatechuic, phenylacetic, and benzoic acids (different hydroxylation levels) (Braga et al. 2018; Fernández et al. 2015; Hidalgo et al. 2012).

This two-way interaction has been explored in many studies (Braga et al. 2018; Neilson, Goodrich, and Ferruzzi 2017; van Dorsten et al. 2010). In general, the gut microbiota influences the bioavailability of polyphenolic compounds, and their presence in the intestine modulates the microbiota composition (Ashley et al. 2019; Neilson, Goodrich, and Ferruzzi 2017; Rodríguez-Daza et al. 2020).

A prebiotic effect can be attributed to some polyphenols. For example, flavonoids and their metabolites migrate from the small intestine to the large intestine and reach the colon, interacting with the local microbiota. The fermentation can benefit the intestine and promote epithelial growth (increase absorptive capacity), production of short-chain fatty acids and inhibit the growth of some pathogenic bacteria, and stimulate the growth of beneficial genera (*Lactobacillus* spp. and *Bifidobacterium* spp.) (Singh et al. 2019; Fernández et al. 2015). Thus, more significant compounds precisely delivered to the intestine could represent better local use by the microbiota. On the other hand, it would allow the absorption of non-biotransformed compounds, positively influencing their bioavailability. The metabolism of dietary polyphenols is linked to inter-individual variability concerning the compositional profile of intestinal bacteria (Faria et al. 2014; Fernández et al. 2015). Also, flavonoids occur predominantly in the form of glycosides in nature, which makes absorption difficult. In addition, molecular instability, oxidative degradation, and enzymatic and bacterial metabolism further limit efficient biological utilization, leading to high excretion, poor absorption, and reduced bioactivity. In this regard, nano-delivery systems are considered options to overcome these factors (Faridi Esfanjani, Assadpour, and Jafari 2018; Gaber Ahmed, Fernández-González, and Díaz García 2020; Garavand et al. 2021). Figure 3 summarizes the main challenges for the oral intake of polyphenolic compounds from food matrices, supplements, and extracts. The enzymatic action and pH initiate the degradative process in the oral phase. Some of these compounds in the stomach tend to maintain their structure due to the acidic pH; others can be degraded and are poorly soluble; absorption in the gastric phase is low. The intestinal stage is responsible for intense degradation, leading to low absorption, loss of bioactivity, high excretion, decreased bioefficacy, and active metabolite production. The metabolites and intact molecules in plasma and organs are limited.

4. Polysaccharides-based nanoencapsulation of polyphenolic compounds

Nanoparticles as delivery systems for bioactive compounds have become important in recent decades. Natural biopolymers have been exploited to encapsulate various phytochemicals and drugs. Food and pharmaceutical industries have benefited from the application of nanotechnology in developing nano foods (smart foods) and new supplements. Nanotechnology ($10< d<1000$ nm) can be used throughout the food chain, from production to processing and packaging (Baliyan et al. 2020). Nanoencapsulation is an effective tool with wide application for many unstable molecules to improve quality, safety, and nutrition and enhance the benefits of different bioactive compounds (Assadpour and Jafari 2019). Encapsulation traps a central (bioactive compound at the internal phase) inside another immiscible substance – carrier or wall – in a solid or liquid state (Câmara et al. 2020). The encapsulation process preserves the structural

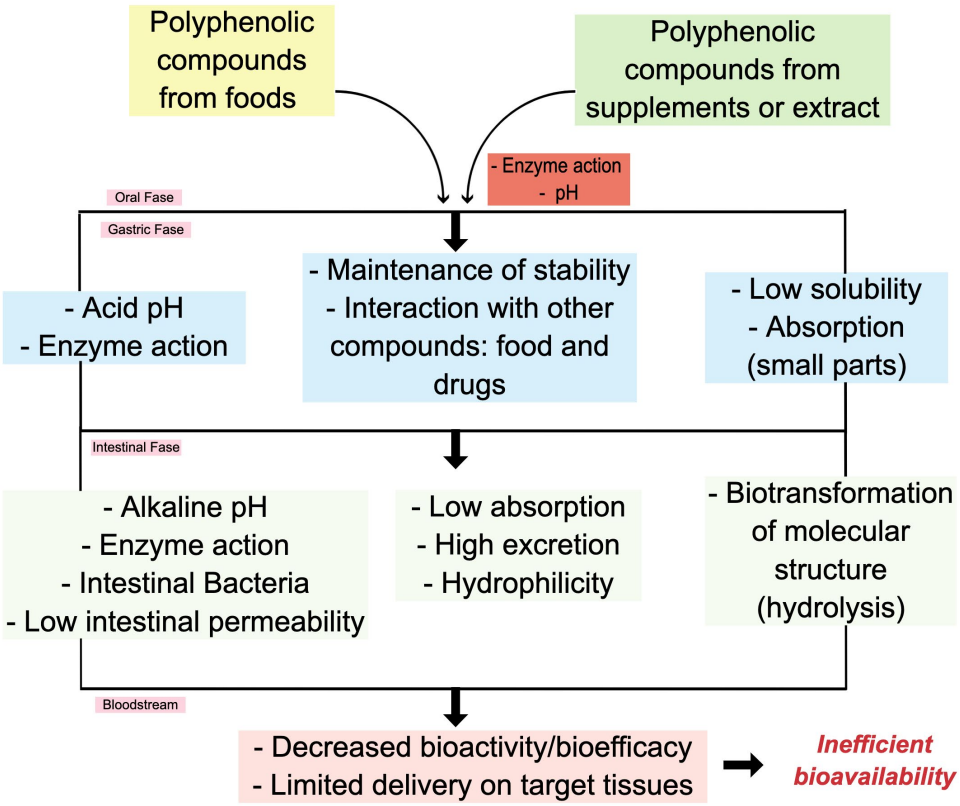

Figure 3. The main challenges for the oral ingestion of dietary polyphenols start in the oral phase until absorption and reaching tissues and organs. Several factors are involved and are responsible for the massive degradation. The scheme represents the biological aspects that converge in inefficient oral bioavailability. The figure was created with Mind the Graph (https://mindthegraph.com) (accessed on 26 may 2023).

properties of polyphenolic compounds, preventing degradation and loss of their biopotency (Adefegha et al. 2022). Elaborating nanostructures may enhance the compound's protective ability to control and precisely release in biological systems (Sadeghi et al. 2017).

There is growing interest in technological approaches that increase the physicochemical stability of bioactive compounds and enable the development of new products with beneficial human health attributes (Jafari and McClements 2017). For polyphenolic compounds, many benefits are attributed to their application. In addition to maintaining functional properties, astringency and unwanted flavors can be improved, as are some other sensory characteristics (Bajpai et al. 2018). Nanoencapsulated polyphenols can be fortified in food products, dietary supplements, and nutraceuticals (Mohammed 2022).

The elaboration of nanoparticles to encapsulate different polyphenolics may be a viable alternative for the compounds (intact structure) to reach more distal portions of the large intestine and to instigate fermentation by the local microbiota, leading to better-absorbed metabolites and improved bioavailability (Tsirigotis-Maniecka et al. 2017). Controlled and gradual delivery can promote more significant interaction with intestinal bacteria in all colon segments (Mas-Capdevila et al. 2020). Despite the difficulties, oral ingestion is the most used treatment route, although it should be optimized for more successful therapeutic results. As discussed earlier in this article, the intense degradation decreases the delivery of polyphenols to several target tissues (Guadarrama-Escobar et al. 2023). The first-pass effect in the human intestine is one of the main challenges polyphenolic compounds must overcome to achieve a fair biological result (Kamiloglu et al. 2021). Currently, alternatives way for prevention and treatments for the administration of polyphenolics have gained attention (Mitchell et al. 2021).

Some polyphenols and metabolites are associated with anti-inflammatories, such as ellagic acid, caffeic acid, quercetin, and hesperidin; their metabolites produced by intestinal microbiota fermentation may have a local and systemic immunomodulatory and anti-inflammatory effect (Estruel-Amades et al. 2019; Iskender et al. 2017; Pacheco-Ordaz et al. 2018). Conditions of intestinal inflammation, cancer, and other systemic diseases could benefit if a more significant amount were delivered to the colon through a nano-system, enhancing the production of active molecules derived from their metabolism (Tsirigotis-Maniecka et al. 2017).

Thus, for these reasons, controlled release systems based on natural nanoparticles have been reported to be very efficient in enabling oral administration and improving absorption in multiple studies (Bulatao et al. 2017; Chatterjee et al. 2021; Gonçalves et al. 2022; Lu et al. 2019; Matalanis, Jones, and McClements 2011). Food-derived polysaccharides have been shown to have a wide range of properties and roles in the nanotechnology areas to encapsulate and transport various bioactive compounds within the body and amplify the interaction of these compounds with target cells, maximizing biological properties (Lu et al. 2019; Park et al. 2010). Combined or isolated food biopolymers (with binding affinity for polyphenolics) can be a protective barrier. They are resistant carriers that facilitate polyphenols to pass through the gastrointestinal tract. Polysaccharides can transport, protect, and respond to determined biological stimuli (Gopi Krishna et al. 2021; Rashidinejad et al. 2021; Rehman et al. 2020). Nanoencapsulation based on polysaccharides has unique opportunities for controlling the body's dose and time of release, directing precise adjuvant treatments in several diseases, such as intestinal cancer. Due to their natural characteristics, polysaccharides are used for oral ingestion because they are multi-responsive to diverse biological stimulants that release the encapsulated compound. They are sensitive to swelling in a wide range of pH. Also, they can be accurately tailored according to their specific application (Gopinath et al. 2018; Karimi, Eslami, Sahandi-Zangabad, Mirab, Farajisafiloo, et al. 2016). Elaborating polysaccharide nanostructures may intensify the polyphenols' protection, thus controlling a targeted release (Sadeghi et al. 2017).

Nanoencapsulated polyphenolic compounds could pass through the gastrointestinal tract with fewer structural changes. In the stomach, polysaccharide protection would be against acidic pH, and there could be attenuation of the action of digestive enzymes. In the intestine, nanocapsules can protect against alkaline pH and the activity of digestive enzymes, directing more absorption capacity, favoring mucoadhesive ability, improving bioaccessibility, and gradually releasing the trapped compounds. Overcoming challenges during digestion can facilitate access to tissues/organs and maintain functional properties (Manzoor et al. 2020; McClements 2012; Paredes et al. 2016). Figure 4 resumes this process.

Food biopolymers, such as polysaccharides, have many excellent properties for creating nanoparticles (Adrian, Mihai, and Vodnar 2019). Polysaccharides are biodegradable, biocompatible, and ideal biomaterials for carrying polyphenolic compounds. Strategies have been investigated over the last few years to stabilize natural compounds and increase their bioavailability to overcome physical and chemical limitations. Systems of nanocarriers with a practical design for protecting and delivering polyphenolic compounds based on polysaccharides have been created (Garavand et al. 2021). Charged (negative or positive) polysaccharides can form nanostructures for compound entrapment. The different groups that make up the structures can have a positive or negative charge according to pH (Stenger et al. 2017). Polysaccharides mostly have degradable, fermentable, and hydrophilic structures and can pass intact through the gastrointestinal tract, resisting digestive factors (Muvva et al. 2020; Nasrollahzadeh et al. 2021).

Natural polysaccharides have homogeneous properties, show bio-specific interactions with other biopolymers, demonstrate adhesiveness to the intestinal mucosa, and release encapsulated compounds controlled according to specific stimulation or cell interaction (Gopinath et al. 2018; Gopinath et al. 2018). Polysaccharides are used alone or combined with other biopolymers (additional polysaccharides and proteins). Many studies have been based on using food biopolymers as nanocarriers (Dogan Ergin et al. 2021;

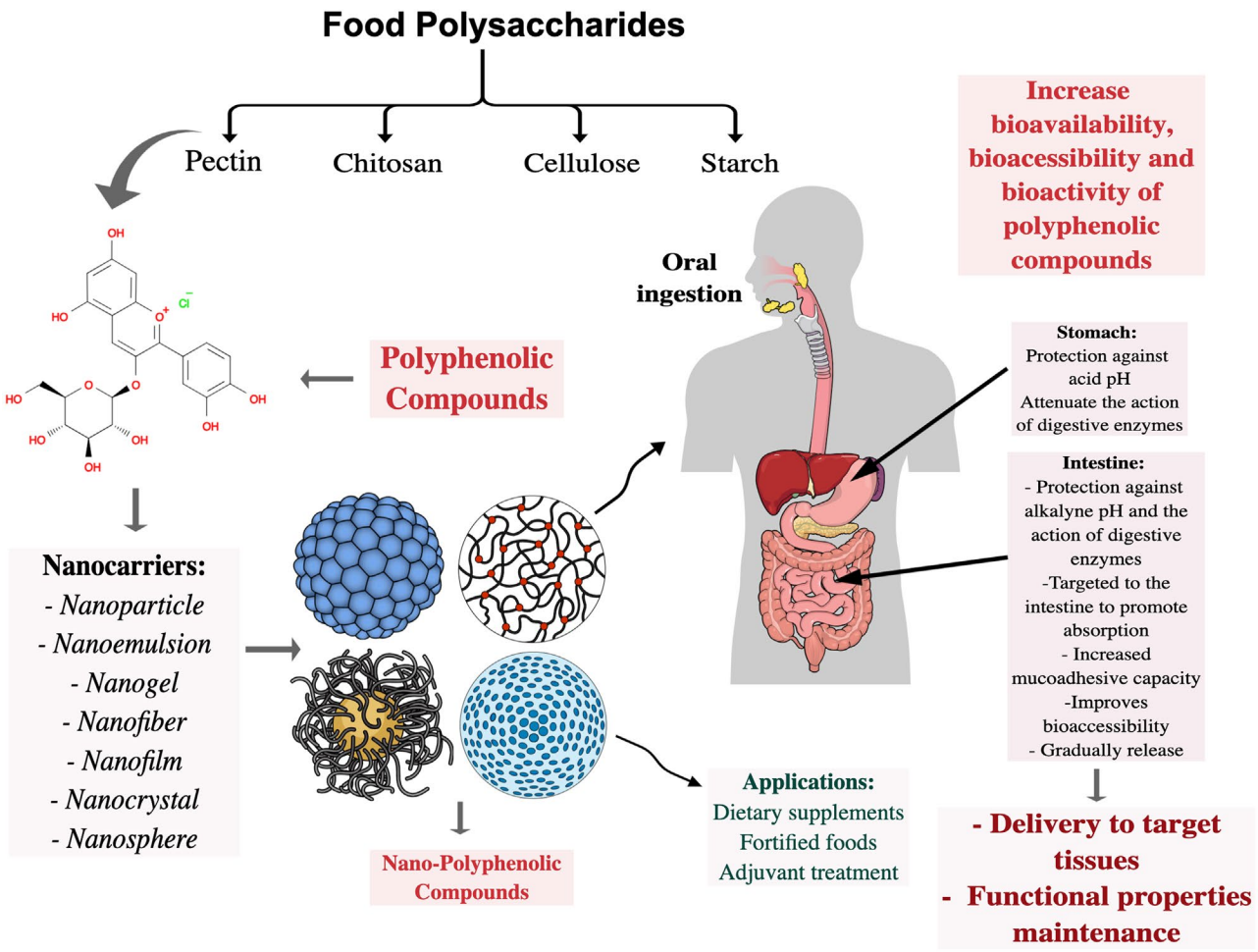

Figure 4. Food polysaccharides are excellent biomaterials to form nanostructures for encapsulating phenolic compounds, enabling oral ingestion and industrial application. Biological advantages occur at all stages of digestion, from the mouth to reaching the tissues, maintaining the functional properties of these natural antioxidants. The figure was created with Mind the Graph (https://mindthegraph.com) (accessed on 09 March 2023).

Rosales and Fabi 2023a). Polysaccharides, such as starch, pectin, chitosan, glycogen, and cellulose, can form nanostructures for the protection and targeted delivery of polyphenolic compounds. Different types of nanocarriers can be developed based on diverse polysaccharides, such as nanoparticles, nanoemulsions, nano-gels, nanofibers, nanofilms, nanocrystals, nanospheres, nano helical, and nanocapsules. Table 1 shows some of the sources of these food compounds, the main advantages of application as a biomaterial to form nanostructures, and the different types of nanocarriers included.

Table 1 shows the variability of the polysaccharides, the natural sources of extraction, and the advantages that should be used to guide the choices of each of the compounds to be encapsulated. The wall material determines the selected nanoencapsulation method and the core characteristics (e.g., nano-encapsulated material). Stability tests are crucial in evaluating the carrier composition and the influence on the product's final properties (desired qualities). The encapsulation efficiency and the ability of compounds to encapsulate and release from their entrapment must be carefully analyzed initially in precise *in vitro* tests and subsequently *in vivo* tests to ensure efficacy and safety (Câmara et al. 2020; Manzoor et al. 2020; Zhang et al. 2020). The wide variability of natural sources for obtaining biomaterials lights the advantages of using these biopolymers to form nanostructures to encapsulate polyphenolic compounds. In addition, it is essential to know the primary methods for elaborating polysaccharide-based delivery nano-systems. A large variety of technologies for elaborating nanoparticles are described in the literature; the most cited are self-assembly, emulsification, coacervation, ionic gelation, nanoprecipitation, and ionic crosslinking. Some of the main techniques are described below.

The self-assembly technique is widely used for different bioactive compounds; in particular, polyphenols can benefit from this methodology for stabilization and targeted and responsive delivery to other biological stimuli. This technique uses homogenized biopolymers (aqueous solution) for electrostatic interaction. Various forces induce the nano complexes formation: hydrogen bonds, hydrophobic interaction, and *Van der Waals*, for example. This methodology does not include potentially toxic products and can be used for safety in food (Antonov et al. 2019; Gummel et al. 2006; Zhang, Jia, et al. 2021; Zhao et al. 2020b).

Emulsification is a nanoencapsulation process characterized by mixing immiscible liquids with the addition of an interface agent, such as surfactant and co-surfactants. It is

Table 1. Advantages for nanoencapsulation based on food polysaccharides: main nanocarriers and sources for extraction.

Food-polysaccharide	Main Nanocarriers	Source for Extraction	Advantages of an encapsulating material	Disadvantages of encapsulating biomaterial	Reference
Starch	Nanoparticles, Nanocrystals, Nanofibers Nano helical	Grains, tubers.	Most abundant carbohydrate, variety of sources for extraction; consolidated extraction techniques, biocompatible, absence of toxicity, availability, and economic aspects.	The native form needs to be modified (physical, chemical, or enzymatic) as an encapsulating material. Limited studies have been focused on food delivery systems using starch nanostructures.	(Rostamabadi, Falsafi, and Jafari 2019)
Pectin	Nanoparticles, Nanogel, Nanocapsules, Nanoemulsion, Nanosphere, Nanocapsules	Citrus peel (orange, lemon, lime, and pomelo), apple peel, chayote peel, and passion fruit albedo.	Self-assembly abilitiesThermal and mechanical resistance, nontoxic, biodegradable, can be extracted from by-products, high affinity with polyphenols, resistant to digestion factors (pH and enzymes).	Premature swelling and release need other biomaterials or ions for more excellent stability.	(Arroyo-Maya and McClements 2015; Rosales and Fabi 2023a)
Chitosan	Nanoparticles, Nanogel, Nanocapsules, Nanoemulsion, Nanosphere, Nanocapsules	Shrimp and crab.	Biocompatibility, biodegradability, versatility, ability to target delivery of polyphenols to the colon, stimuli-responsive nanocarriers, mucoadhesive and mucus-penetrating, interaction with the intestinal barrier.	Lower mechanical resistance, difficulty controlling pore size, low solubility in neutral and alkaline pH; the crosslinking method can affect the intrinsic properties, may contract, and need deacetylation.	(Garg et al. 2019; Tie and Tan 2022; Wu et al. 2020)
Glycogen	Nanoparticle, Nanofibers	Animal liver and muscles, certain species of bacteria, and yeast.	Biocompatibility and biodegradability, high availability, high water solubility, ease of functionalization, and comprises short linear chains.	It must be modified before being applied to nanostructures, and extraction can be more complex.	(Besford, Cavalieri, and Caruso 2020; Gopinath et al. 2018; Gopinath et al. 2018)
Cellulose	Nanoparticles, Nanofibers, Nanocrystal, Nanofilms	Seeds, vegetable peel, and wheat flour.	Most widely distributed and abundant polysaccharide in nature, excellent physical and chemical properties, protection of unstable compounds, self-assembly abilities, large surface area, high crystallinity, good mechanical properties, high thermal stability, and rheological properties of shear.	Insolubility in water. It must be modified beforehand to interact with other components and form nano complexes.	(Gopinath et al. 2018; Mu et al. 2019)

used to increase some polyphenolic compounds' solubility and kinetic stability. Systems based on this process can provide an efficient matrix to promote stability, protection, and targeted delivery (Akhavan et al. 2018; Cao et al. 2021; Garavand et al. 2021). Using coacervation to encapsulate polyphenols can be indicated as a technique that provides adequate stability and high encapsulation efficiency. This process involves interacting two biopolymers with opposite charges to form complexes trapping the bioactive (Antonov et al. 2019; Ban and Kim 2022; Singh and Yethiraj 2020).

Another widely used method for forming nanostructures to encapsulate polyphenolic compounds is the application of ionic gelation. In this technique, biopolymers with different electrical charges interact in an aqueous solution. Spherical particles can be formed by adding a polysaccharide dissolved in acid and added to a polycationic solution. The ionic interaction creates nanostructures to encapsulate labile compounds. The structure formed from this interaction has characteristics distinct from the original compounds. Polyphenolic compounds can be stabilized using this principle without the addition of potentially toxic products (Ahirrao et al. 2014; Antonov et al. 2019; Dogan Ergin et al. 2021). Ionic crosslinking is another process that can also stabilize polyphenol compounds. This technique concerns the formation of polyelectrolyte complexes by binding divalent cations (Mg^{2+}, Ca^{2+}, and Ba^{2+}). This methodology is based on ionic crosslinking through the interaction between tripolyphosphate anions and protonated amine groups of biopolymers. The structure is formed due to polyelectrolyte interaction resulting from opposite charges (Andersen, Auk-Emblem, and Dornish 2015; Dogan Ergin et al. 2021; Prabaharan and Mano 2005). Also, nanoprecipitation is a process that occurs with biopolymers and non-solvent addition to a polymeric solution. Nanocomplexes such as polymeric aggregates encapsulate polyphenolic compounds with stability and controlled delivery. Nanostructures are formed by supersaturation, nucleation, growth by condensation, and coagulation (Chen et al. 2019; Martínez Rivas et al. 2017).

Several production factors must be carefully selected to nano-encapsulate polyphenols because they have high sensitivity and propensity to degradation (Munin and Edwards-Lévy 2011). The methodology chosen, as well as other variables, are undoubtedly steps that need to consider the particularities of each polyphenol individually. In general, to be successful in the nanoencapsulation process, pH is one of the main factors; the adjustment must be made considering the factors related to the availability of electrical charges and the ability to dissociate - isoelectric point (PI) and dissociation constant (PKa) - as well as other characteristics of biopolymers (protonated and deprotonated molecules) in a specific range of pH which is subject to the various intermolecular interactions (Antonov et al. 2019, 2022; Dogan Ergin et al. 2021). The proportion is another factor that must be considered through mathematical models to optimize and prepare more effective, stable, and release-capable nanostructures. The concentration between biopolymers (polysaccharides and proteins) and the molecular concentration of the encapsulating compound (polyphenol) needs to be considered, as well as the homogenization time of the necessary components for interaction (Faridi Esfanjani, Assadpour, and Jafari 2018; Gonçalves et al. 2018; Shen et al. 2022; Yan et al 2023).

The choice of method for nanoencapsulation must be based on the ability of the biopolymer and the technique to produce particles on a nanometric scale and on the ability to reproduce it on industrial scales with the same results (Santos and Savina 2023). Table 2 summarizes the main advantages of each of the methods discussed.

In addition to these factors, the characteristics of biopolymers are crucial to determine the methodology for forming a nano-system for targeted delivery and increased bioavailability of biologically active compounds. Also, the final applicability, stability in certain pH and thermal ranges, solubility, and other critical molecular affinities of each polyphenolic compound, must be considered when choosing the biopolymer (Lu et al. 2019; McClements 2012). Natural biopolymers are polymeric organic molecules from renewable, sustainable, biocompatible, nontoxic sources with resistant structures, availability in nature, and are easily modified (Nasrollahzadeh et al. 2021). The characteristics of the encapsulating material are crucial in this process, and most of those polysaccharides form gels at mid to high concentrations. So they must be used more diluted to form nanostructures, such as nanogels. The main properties of these polysaccharides – starch, pectin, chitosan, and cellulose – are discussed below. We also discussed the properties of arabinogalactans.

4.1. Starch

Biopolymers are abundant in several plants as a reserve carbohydrate; starch is a natural polysaccharide that is abundant in nature (stems, roots, and seeds). Many plants produce this natural, renewable polymer as a source of stored energy (Ahmad et al. 2019). Starch is a vital carbohydrate component of our diet and is used in food in the industry. It is biocompatible and biodegradable (Escobar-Puentes et al. 2020).

This biomaterial consists of two main types: amylose and amylopectin. Structurally, starch is formed by 3D granules, architecture with crystallinity in the range of 15-45%, and comprises D-glucose molecules, including amylopectin, branched (1→6) α-*D*-glucan, amylose, and linear (1→4)-linked α-D-glucan (Lopez-Rubio et al. 2008; Sadeghi & Bardajee, 2018). Recent advances in starch-based materials point to promising applications for the controlled release of different biologically active compounds (Fathi, Martín, and McClements 2014; Gopinath et al. 2018). The native form of starch can be modified to increase hydrophobicity and for other applications - such as nanoencapsulation and controlled release of phenolic compounds. Due to its biocompatibility, vast sources for extraction, and ease of modification (physical, chemical, and enzymatic methods), starch has been used as a biomaterial for nanoencapsulation Starch-based nanoparticles and nanocrystals have numerous advantages and applicability. They can give rise to particles with a small diameter and high surface-to-volume ratio, favoring the

Table 2. Advantages and disadvantages of the different techniques using polysaccharides.

Nanoencapsulation Techniques	Description	Some Advantages	Some Disadvantages	Reference
Emulsification	Mixing immiscible liquids with the addition of an interface agent, such as surfactant and co-surfactants.	Good stability, adequate solubility, effective targeted delivery, and protection.	Use of surfactant, potentially toxic.	(Akhavan et al. 2018; Walia et al. 2019; J. Zhang, Jia, et al. 2021)
Self-Assembly	Interaction between biopolymers with opposite charges. Formation of a complex network of intermolecular bonds naturally.	There is no addition of potentially toxic compounds. The technique is safe for food application. Easy application. Does not require expensive equipment.	Encapsulation efficiency and stability, in some cases, can be compromised.	(Peng et al. 2016; Zhang, Jia, et al. 2021; Zhao et al. 2020b)
Coacervation	Interaction between two oppositely charged polymers where a complex between these polymers is formed around particles, protecting the bioactive molecules.	Use of biodegradable materials. There is no addition of potentially toxic compounds—good stability during storage.	Requires equipment, effective control of numerous variables, high cost, and more complexity for elaboration.	(Ban and Kim 2022; Singh and Yethiraj 2020)
Ionic Gelation	Biopolymers with different electrical charges interact in an aqueous solution. Polysaccharides dissolved in acid and added to a polycationic solution.	Provides stability and encapsulation efficiency.	Limited controlled release. Particles, in some cases non-homogeneous.	(Dogan Ergin et al. 2021; Wu et al. 2017)
Nanoprecipitation	It consists of the formation of nanoparticles or polymeric aggregates. Polymer precipitation occurs due to the addition of a component (non-solvent). Steps: 1. supersaturation; 2. nucleation; 3. growth by condensation; 4. coagulation.	Technique with low cost and easy elaboration. Non-solvent addition to a polymeric solution.Stability and Controlled Delivery.	More detailed preparation methodology.	(Busato et al. 2020; Ezhilarasi et al. 2013; Walia et al. 2019)
Ionic Crosslinking	Formation of polyelectrolyte complexes by binding divalent cations (Mg2+, Ca2+, and Ba2+).	Simple procedure, without potentially toxic,Biocompatible, reversible process, and fast and good dissolution for analysis	pH-sensitive swelling,poor mechanical properties, and a tendency to dissociate early.	(Dogan Ergin et al. 2021; Sun et al. 2020)
Mechanochemical transformations in mixtures of solids organic substances	Formation of intermolecular compounds by mixing solid substances	Formation of supramolecular complexes for efficient delivery of poorly water-soluble molecules. Formation of complexes of drugs/bioactive molecules (hydrophilic and hydrophobic) as a solid dispersion. Composed of a technological stage and without the use of toxic organic solvents.	This technique may partly destroy the material and pose scaling problems.	(Dushkin et al. 2012)

encapsulation of different bioactive molecules, such as phenolic compounds, and facilitating transport *via* biological barriers (Hasanvand et al. 2015; Yu and Huang 2010). The application as a starch-based nanoencapsulation has grown substantially in numerous pharmaceutical products and foods (Zhu 2017).

4.2. Pectin

Pectin is a promising biomaterial for encapsulating and delivering polyphenolic compounds in the intestine (Rosales and Fabi 2023a). Heterogeneous complexes of non-starch polysaccharides form pectin, a structural part of the plant cell walls (Lara-Espinoza et al. 2018). The content of vegetables varies from 10% to 30% of the total weight of the fruit (Sriamornsak 2011). They are natural anionic biopolymers and are composed of α-*D*-galactopyranuronic acid – Gal*p*A (galacturonic acid) linked by α-1,4 glycosidic bonds (Mohnen 2008; Ninan et al. 2013) and comprises about 70% of the structure (Bauer 2012; Mohnen 2008; Reichembach, and Petkowicz 2021). Pectin with a low/medium degree of esterification is negatively charged at neutral pH (pKa pH ~3.6). It can interact with positively charged ions or molecules, such as calcium salts and proteins, such as lysozyme and lactoglobulin (pH dependent), to form stable structures for encapsulating chemically unstable compounds (Bealer et al. 2020; Dogan Ergin et al. 2021; Lin et al. 2015; Manzoor et al. 2020). Pectin is a resistant, nontoxic, biocompatible, and biodegradable

biomaterial with sources for sustainable extraction such as citrus, apple, chayote peel, and Passiflora fruit albedo (by-products of the food industries) with consolidated techniques for extraction and purification (Rosales & Fabi, 2023b). Among the various properties of pectin, the ability to produce highly viscous gels or solutions that have broad applicability in multiple solutions to emulsify and thicken stands out, thus forming nano gels for various technological applications (Moreira et al. 2014; Viebke, Al-Assaf, and Phillips 2014).

When ingested, pectin passes intact through the gastrointestinal tract. It resists the stomach's acidic pH and digestive enzymes' action, reaching the intestine's distal portions intact. In the intestine, the microbiota bacteria ferment the pectin into SCFA (short-chain fatty acids, e.g., butyrate, propionate, and acetate) that are used as an energy substrate by intestinal cells resulting in their growth, which have several positive effects and tend to the absorptive capacity of the intestine (Duda-Chodak et al. 2015; Fathi, Martín, and McClements 2014; Prado et al. 2019).

Recent reports have highlighted the extended applicability of pectin in several nano-carrier systems for phenolic compounds. The interaction is promising due to the natural affinity between these two compounds (Fernandes et al. 2020; Tomas 2022). The pectin-based nanostructures intensify cell permeation and inhibit enzymes (proteases) (Gottesmann et al. 2020; Morris et al. 2010). Enhancing the absorption of intact molecules in the small intestine and carrying more significant amounts to the large intestine – even more distal portions – provides more effective therapeutic results (Feng et al. 2019; Li, Xu, and Li 2022; Zhao et al. 2020a). However, the pectic matrix can suffer swelling under physiological conditions that can lead to the premature release of compounds in some cases, which can be prevented by developing pectin-based nanostructures combined with other polymers (polysaccharides or proteins) (Khotimchenko 2020; Morris et al. 2010). Due to its swollen polymeric matrix, bioactive compounds could be gradually released, thus improving passive or active absorption. Moreover, pectin can keep its covering intact through the intestine, in which case absorption could occur from the entire nanostructure (*via* endosomes), releasing the intact bioactive compounds into the cell interior (Fathi, Martín, and McClements 2014; Khotimchenko 2020; Nguyen et al. 2011).

Some studies have explored pectin in nanostructures to protect phenolic compounds (Arroyo-Maya and McClements 2015; Song et al. 2022; Tomas 2022). The hesperidin-pectin nano complex represents a possible increase in the bioavailability of molecular structures targeted to the colon (Tahir et al. 2021); it is a practical approach to benefit the human microbiota for systemic effects (Horn et al. 2022; Liang et al. 2018). Recently, a study analyzed the release of a flavonoid (anthocyanin) nano encapsulated in a pectin-based structure and combined with a protein (lysozyme). The nanoparticles were stable under simulated human physiological conditions using the INFOGEST protocol (Brodkorb et al. 2019). The release started at the end of the gastric phase and was gradually released from the matrix until the last stage of digestion. Despite this, a significant part of the anthocyanins remained trapped in the nanostructure, with the possibility of being fully absorbed. In addition, the study evaluated *in vitro* – two cellular models, bi and three-dimensional – the possible cytotoxicity of these nanostructures, concluding that they are potentially safe and were absorbed through the formation of endosomes (Rosales et al. 2023).

4.3. Chitosan

Chitosan is an amphiphilic polysaccharide with broad technological applicability, safe and effective in composing nanostructures. It is a cationic molecule with neutral and acidic pH (Liang et al. 2014; Park et al. 2010). Chitosan has extensive variability and essential properties for encapsulating and transporting phenolic compounds within the body and enhancing the compound's interaction with target cells, improving absorption and effectiveness (Guadarrama-Escobar et al. 2023; Quadrado and Fajardo 2020; Rinaudo 2006). Chitosan's physicochemical characteristics indicate that it can provide targeted delivery of polyphenolic compounds in the body to specific sites and improve their bioavailability (Carrasco-Sandoval et al. 2021; Dacoba et al. 2019; Goodarzi et al. 2013; Pateiro et al. 2021).

Chitosan is biodegradable, nontoxic, soluble in organic and inorganic acids, and insoluble in water and organic solvents; to increase the solubility in water, it is necessary to deacetylate process (chitosan is produced after alkalinization and chitin deacetylation) (Kumar et al. 2004; Leiva et al. 2015). Some factors are crucial for applying this polysaccharide in nanostructures, such as the degree of deacetylation and molecular weight. Furthermore, the greater the degree of deacetylation, the more excellent the solubility. In alkaline solutions, it precipitates; in acid, it has a predominantly negative charge and forms gels (Luo and Wang 2014; Park et al. 2010). The functional groups in the structure of chitosan are mostly free amino acids, primary and secondary hydroxyl groups, and acetamido groups. Hydroxyl groups can undergo chemical reactions (etherification, esterification, crosslinking, graft copolymerization, and *O*-acetylation). Modifications to these functional groups generate a variety of derivatives and a wide range of compounds. The main chemical changes are alkylation, acylation, hydroxy alkylation, carboxy alkylation, phosphorylation, sulfation, oligomerization, enzymatic modifications, and co-polymerizations (Goodarzi et al. 2013; Park et al. 2010).

In the formation of nanostructures, chitosan can be covalently crosslinked. The electrostatic interaction and ionotropic gelling need to use chitosan, and another oppositely charged biopolymer to prepare nanostructures based on chitosan. Chitosan and its derivatives are used for controlled delivery nanoencapsulation due to essential factors such as adhesion capacity to the intestinal mucous membranes (promotes better absorption) and influences the bioavailability. The interaction occurs between mucin (a glycoprotein in intestinal mucus) and residues of N-acetyl neuraminic acid, sulfated galactose, and hydrophobic fucose containing methyl, increasing the interaction between the nanostructures and the intestinal

epithelium (Park et al. 2010; Sogias, Williams, and Khutoryanskiy 2008; Takeuchi et al. 2005).

4.4. Cellulose

One of the most abundant components in plants is cellulose. They are responsible for forming microfibrils and maintaining the structure of plant cell walls, contributing to giving shape, support, and mechanical resistance to plants (Fathi, Martín, and McClements 2014; Posocco et al. 2015; Williamson, Burn, and Hocart 2002). Structurally, this polysaccharide is a homopolymer composed of glucose in long, linear chains (units linked by β-1,4-glycosidic bonds), with groups of three hydroxyl groups for glucose fraction and generally has a high molecular weight (Mudgil and Barak 2013; Pérez and Samain 2010; Williamson, Burn, and Hocart 2002). Intermolecular interactions, cross-link polymerization, chain elongation, and side-chain functional group effects (hydroxyl, methyl, and hydroxypropyl ether) occur between structural groups (Kamel et al. 2008; Pérez and Samain 2010). Cellulose is resistant to temperature and pH changes (Gopinath et al. 2018; Nurkeeva, Mun, and Khutoryanskiy 2003). Cellulose and its derivatives are considered suitable biomaterials for the nanoencapsulation of polyphenols. They have biocompatible properties, are biodegradable, and have been investigated extensively for nanotechnology applications (Wijaya et al., 2021).

One of the difficulties of applying natural cellulose is its insolubility in water. Cellulose is a delivery vehicle for natural compounds and drugs; compared to starch, water solubility is the main obstacle that makes the widespread use of cellulose for nanostructures formation. To overcome this limitation, hydrolysis of higher molecular weight of cellulose to smaller fragments is carried out (Calvini et al. 2006; Pandey, Mohamad, and Amin 2014). Cellulose can be chemically altered, forming its soluble derivatives, such as carboxymethylcellulose, methylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, and hydroxyethyl cellulose (Nurkeeva, Mun, and Khutoryanskiy 2003). The modifications can facilitate the nanoencapsulation of phenolic compounds, increasing their functionality. Derivatives have improved properties for targeted delivery, such as biocompatibility, adhesion, water retention, greater thickening capacity, and emulsification (Cordeiro et al. 2021; Sun et al. 2020; Wang et al. 2011).

Cellulose and derivatives resist gastric pH and can release nano-encapsulated compounds in the intestine, mainly by protecting them from enzymatic action (Sarkar et al. 2017b). Thus, nano-encapsulated bioactive compounds in a polymeric cellulose matrix can be protected from factors intrinsic to digestion (gastric protection) (Bai et al. 2012; Gopinath et al. 2018; Zhai et al. 2018). Cellulose is biocompatible, mucoadhesive, and capable of direct delivery to intestinal cells, with widespread use for protecting labile compounds (Pandey, Mohamad, and Amin 2014; Sarkar et al. 2017a).

4.5. Arabinogalactan

Another encapsulating polysaccharide for the delivery of bioactive compounds described in the literature is arabinogalactan. They are a branched natural polymer consisting of arabinose and galactose units and a molecular weight of around 16 kDa. They show a high water solubility with the production of low-viscosity solutions. They are considered an important source of dietary fiber without toxicity, biodegradability, biocompatibility, and hydrophilicity. The functional groups that form the structure are hydroxyl, carboxylic acid for intermolecular interaction with other compounds to form nanostructures (Focsan and Polyakov 2019; Khvostov et al. 2017; Kong et al. 2018). In nanostructures, arabinogalactans are indicated to increase the solubility of hydrophobic compounds. Some features should be highlighted, such as adherence adequate to the surface of the membranes and the ability to permeate them. Studies indicate that due to the solubility of these polysaccharides in aqueous solution, compounds that are insoluble in water can be nanostructured through techniques that use the compounds in the solid state without the use of organic solvents, being a sustainable and effective option for protection, increased solubility, and absorption (Noore et al. 2021; Selyutina et al. 2017).

5. Nanoencapsulation directs the delivery and the release, improving the absorption and bioavailability of polyphenolic compounds

Encapsulated polyphenolic compounds can overcome the limitations of oral therapy and be transported across biological barriers (systemic and cellular). The intelligent design of nanostructures can be applied as a targeted precision therapy for certain specific metabolic situations (Martínez-Ballesta et al. 2018; Mitchell et al. 2021). An effective carrier of polyphenolic compounds must have – in addition to the nanoscale size – the ability to protect the phenolic structures in ambient processing or storage conditions without a tendency for chemical interactions with other compounds (Assadpour and Jafari 2019; Dima et al. 2020a). Another important aspect is the potential ability to protect bioactive compounds from factors related to human digestion, attenuating the action of digestive enzymes and the consequences resulting from changes in physiological pH and promoting bioavailability due to improved solubility, enhanced surface-to-volume ratios, increased mucoadhesive capacity in the intestine, and ability to gradually release bioactive molecules into the intestinal lumen or after cellular absorption (Ayala-Fuentes and Chavez-Santoscoy 2021; Faridi and Mahdi 2016; Mohammadi et al. 2016). Also, they must be incorporated by cells, easily pass through cell walls, reach the bloodstream, target tissues, and release their encapsulated content. The release of polyphenolic compounds from polysaccharide matrices can occur by the following mechanisms: swelling of the polymeric matrix, diffusion, weakening of hydrogen bonds by enzymatic degradation, and colonic fermentation (Akbari-Alavijeh, Shaddel, and Jafari 2020; Sadeghi et al. 2017). Nanostructures and improving bioavailability and mucoadhesive properties can be valuable for intracellular delivery (Zhang et al. 2020).

Nanostructures can improve the stability and solubility of polyphenolic compounds, promote transport across membranes and prolong blood circulation (Kou et al. 2018).

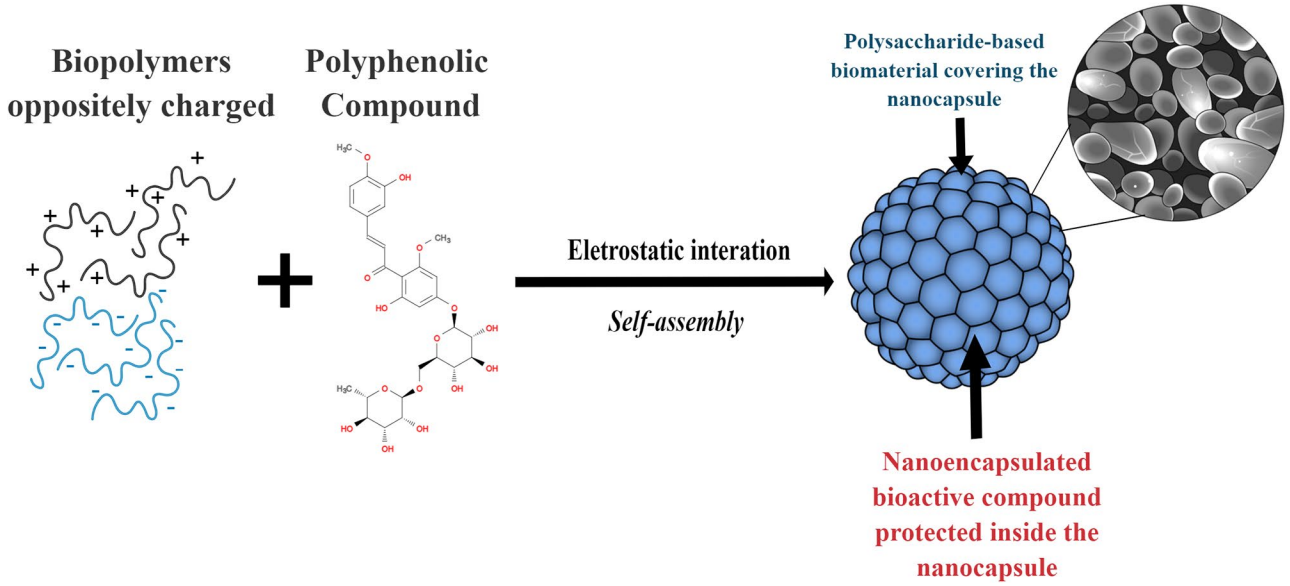

Figure 5. Nanocapsules can be formed by coating polysaccharides (combined with each other or with proteins) and protect the bioactive compound (polyphenols) encapsulated when interacting with different recognition systems and controlled delivery. The figure was created with Mind the Graph (https://mindthegraph.com) (accessed on 26 may 2023).

Research has been dedicated to *in vitro* and *in vivo* tests (animal models) to enhance safety and effectiveness, and the findings indicate promising clinical applications (Hua et al. 2018). There needs to be more information available on the protection of polyphenols in nanostructures in the literature. Only some studies have analyzed dose and administration time *in vivo* models, demonstrating an emerging need for conducting such experiments. Although polysaccharides are biodegradable and safe for human consumption, administration at the nanometer scale may cause some safety challenges, mainly when used as nanofillers in food delivery systems (Bao et al. 2019). Specific characteristics such as size, stability, absorption, and delivery to different organs should be fully explored to rule out biological reactions that cause adverse consequences (Jafari, Esfanjani, and Katouzian 2017). Figure 5 represents a mechanism for forming polysaccharide nanocapsules (biopolymers with opposite charges) through molecular self-organization to encapsulate unstable polyphenolics. The formed nanocapsules have an external coating based on polysaccharides, protecting the internal content (bioactive compounds) from the environmental factors responsible for its degradation.

In adjuvant therapy, nano-encapsulated polyphenolic compounds can be used as more complex engineered delivery systems and in synergy with some specific drugs, including combination therapies between different polyphenolics in addition to enhancing their biological action; nanostructures can alter multiple pathways and maximize therapeutic efficacy in specific clinical treatments (Mitchell et al. 2021). Simultaneous loading and co-delivery of different polyphenolic compounds and drugs can achieve beneficial synergistic therapeutic impacts to treat some diseases, such as intestinal cancer (Martínez-Ballesta et al. 2018; Posocco et al. 2015). Even under normal physiological conditions, effective biodistribution and delivery of polyphenols are challenging to achieve (for the reasons already discussed), mainly due to chemical and biological barriers. In an altered physiological process, as in many pathological situations, oral administration can be even more difficult for these compounds. Thus, nanoencapsulation is the viable option for optimizing its effects (Jiang, Eliaz, and Sliva 2013; Karimi et al. 2017; Shen et al. 2022). In addition, nanoencapsulation in auxiliary treatments can standardize and control bioactive compounds (accurate dosage) (Karimi et al. 2016; Rehman et al. 2020).

Smart nanoparticle rationally designed drugs for targeted delivery are a practical and plausible approach applicable to most polyphenolic compounds. As well as it is indicated that aspects of the use of sustainable techniques for the extraction of phenolics and elaboration of nanostructures are carefully evaluated, and the potential for toxicity will be investigated (Dima et al. 2020a; Zamora-Ros et al. 2018).

The current research has been stating that there is a close enhancement between the microbiota-intestine-brain axis. Furthermore, a broad approach is being undertaken to assess the impact of polyphenolic ingestion on the human microbiome and its systemic effects and support that some diseases may have their risk reduced with these phytochemicals in various conditions such as neural disorders (Bié et al. 2023; Kim et al. 2019; Westfall and Pasinetti 2019). Thus, nano-formulations that promote stability and protect these bioactive against damage in the gastrointestinal tract, minimizing metabolization and massive degradation are necessary to enable their use in targeted nutritional supplements to reach more distant portions in the intestine and intensify absorption and bioavailability, resulting in responses more effective therapies (Bao et al. 2019; Estruel-Amades et al. 2019; Gopi Krishna et al. 2021).

The interaction between polysaccharides and proteins is extensively explored to form nanostructures to encapsulate biologically active compounds. The connection between these biomolecules can provide different and promising

nano-system functionalities for controlled delivery (Chang et al. 2017; Wusigale et al. 2020). Furthermore, polysaccharides linked to proteins are indicated as more stable nanostructures. Based on this potential, several studies cite successful results in encapsulating polyphenols based on the polysaccharide-protein interaction (Chi et al. 2019; Gaber Ahmed, Fernández-González, and Díaz García 2020; Song et al. 2022). One crucial aspect is the microbiota's role in metabolizing a wide range of polyphenols. Intestinal bacteria interact with these compounds, producing an essential portion of biologically active metabolites. Phenolic compounds modulate the microbiota (prebiotic effect), as described in section 3. The promising interaction between these bioactive and intestinal bacteria regulates several biological systems. Nanostructures carrying polyphenols can promote intestinal delivery directed to the colon, which could favor the effects of the polyphenol-microbiota interaction (Fernández et al. 2015; Neilson, Goodrich, and Ferruzzi 2017). Some polyphenolic compounds can preserve their structure and subsequent bioactivity by maintaining molecular stability. Anthocyanins are examples of flavonoids that, to promote their biological effects, the action of the intestinal microbiota, enzyme action, and intestinal pH must be attenuated; in this sense, nanoencapsulation can protect them and induce the absorption of intact anthocyanins (Rosales et al. 2022).

In the last decades, studies have been proposed to encapsulate different types of polyphenolic compounds on a nanometric scale. Anthocyanins – flavonoids with potent antioxidant action and a natural dye – due to their high tendency to degradation, high excretion, and low bioavailability, it is a flavonoid susceptible to biotransformation. To enhance its action in the human body, several studies have proposed some methods to maintain the integrity of the molecular structure and protection the color, antioxidant activity, and other properties are compounds with many efforts aimed at stabilizing them and enabling their use in the food industry as a naturally dyed instead of synthetics, and as a functional ingredient in foods and supplements (Gonçalves et al. 2022).

Anthocyanins were nano-encapsulated to improve stability and increase bioavailability through ionic pre-gelation and complex polyelectrolyte formation, using chitosan and alginate as wall material. The methodology effectively formed particles of 358.5 nm to 635.9 nm in diameter, with 68.9% encapsulation efficiency (Bulatao et al. 2017). To improve stability, anthocyanins were also encapsulated using pectin and whey protein isolate (WPI) through the molecular self-organization technique; the nanoparticles had an average diameter of 200 nm, the zeta potential of −36 mV and 55% efficiency of encapsulation (Arroyo-Maya and McClements 2015).

Carboxymethyl-chitosan was also used to encapsulate anthocyanin through ionic interaction, forming particles from 63.15 nm to 219.53 nm to promote molecular stability and inhibit degradation in the gastrointestinal tract (He et al. 2017). Isolated chitosan stabilized color and maintained anthocyanin antioxidant activity by ionic gelation on nanostructures from 160 nm to ~1,000 nm (Ko et al. 2017). To improve the stability and bioavailability of anthocyanins, nanoparticles (91.71 nm to 69.33 nm) based on chitosan linked to β-lactoglobulin encapsulated anthocyanin by ionic gelation (Ge et al. 2019).

Chitosan and β-Lactoglobulin were also used as anthocyanin encapsulants in another study through ionic gelation. The obtained nanoparticles had an average diameter of 580.4 nm, zeta potential of + 49.6 mV, and encapsulation efficiency of 77.4%. Storage and oxidant stability during *in vitro* simulated digestion were the study's objectives (Chen et al. 2023). The combination between chitosan and β-lactoglobulin was also used to encapsulate another phenolic compound, epigallocatechin gallate. For controlled release in the gastrointestinal tract, nanostructures (100 nm to 500 nm) were prepared by ionic gelation with zeta potential from + 10 mV to + 35 mV, encapsulating ~60% of the bioactive (Liang et al. 2016).

In a targeted delivery system, a study was developed to protect nano-encapsulated chitosan-based catechins by gelation, obtaining stable nanoparticles with a size ranging from 169.0 nm to 201.4 nm, with a zeta potential of ~ +30 mV and an encapsulation capacity of 24% to 53% (Ing et al. 2008).

Soybean-insoluble dietary fiber was used to encapsulate anthocyanin (Malvidin-3-*O*-glycoside) by emulsification (300 nm), increasing storage stability and color protection (He et al. 2022). Isolated chitosan improved anthocyanins' *in vivo* antioxidant potential by elaborating nanoparticles by ionotropic gelation. The nanostructures showed characteristics of stable particles (−5.04 mV to −35.4 mV) with a size of 274 nm to 455 nm and an encapsulation efficiency of 70% (Chatterjee et al. 2021).

Some studies combined pectin and chitosan to encapsulate anthocyanins. The self-assembly methodology was used to maintain molecular stability and induce release into the intestine, obtaining nanoparticles from 100 nm to 300 nm with 66.68% encapsulation efficiency (Zhao et al. 2020b)·To keep the color and enable the application in food packaging feasible, nanoparticles were elaborated through the polyelectrolyte complex, stable, zeta potential from + 37 mV to + 55.5 mV and with 60% efficiency in trapping (Borges et al. 2015), and nanoliposomes were elaborated to investigate the protective effect of hepatocytes injury (*in vitro*), nanostructures with 64 nm to 352 nm in diameter, zeta potential indicating stability (−30 mV to + 21 mV) and efficiency to encapsulate anthocyanin of 28.54% to 61.17% (Karim et al. 2022).

By self-assembly, pectin interacting with lysozyme was used to nano-encapsulate cyanidin-3-*O*-glycoside (from Blackberry). The mathematical model optimized the concentrations, and the ratio of 1:2 (pectin and lysozyme, respectively) was the most promising one analyzed. The nanoparticles showed stability (−26 mV), an average diameter of 198.5 nm, and an encapsulation efficiency of 73%. The nanoparticles were stable in a wide pH range (2 to 14), invariably spherical, with homogeneous morphology and a polydispersity index of 0.2. The structures can be added to various food systems as dyes or enrichment and have shown potential for future studies in developing supplements and nutraceuticals (Osvaldt Rosales et al. 2021). In addition to anthocyanin, pectin was used as a wall material to increase the stability, bioaccessibility, and maintenance of the antioxidant capacity of resveratrol. Using the antisolvent precipitation method, the formed nanostructures obtained a size of 120 nm and stability at −30 mV zeta potential (Huang et al. 2019).

The potential of pectin bound to cellulose and pectin was analyzed to increase the antimicrobial activity of a mixture of phenolic compounds extracted from pomegranate peel through a nanoemulsion formulation with approximately 200 nm diameter (Hassan et al. 2022). To promote excellent thermal stability to enable oral administration, quercetin and resveratrol were nano-encapsulated by zein-carboxy-methylcellulose by antisolvent precipitation; the nanoparticles had a diameter of 217 nm, were stable (zeta potential from −33.6 mV to −45.6 mV) and efficiently of 25.1% in the encapsulation of these compounds (Yang et al. 2023).

Starch-based nanoparticles were designed for catechin nanoencapsulation. The authors used three sources: horse chestnut, water chestnut, and lotus stem. The average particle size was 322.7, 559.2, and 615.6 nm with an encapsulation efficiency of 59.09, 48.30, and 55.00% and zeta potential of − 18.05, − 21.5, and − 18.05 mV, respectively. Several spectroscopic and calorimetric techniques have demonstrated the interaction between catechin and starch. Also, the study ensured controlled release in the intestine of these compounds and the preservation of their properties (Ahmad et al. 2019). Considering the results already found, it is possible to establish the probable potential of nanoencapsulation to increase the bioaccessibility and bioavailability of these plant-based compounds (Faridi Esfanjani, Assadpour, and Jafari 2018; Garavand et al. 2021; Rosales et al. 2023). Although this consensus has already been established, most studies were analyzed using *in vitro* models. Approaches in animal, human, and interventional models are highly suggested to validate the potentiality of enhancing biological effects. Table 3 highlights recent studies using polysaccharides to encapsulate polyphenols. The main objectives of the nano-system formed, the results of the characterization analysis are shown, and the method chosen to encapsulate. Studies indicate that maintaining stability and functional properties is the research's primary and common objective.

6. Future perspectives in the use of nano-encapsulated bioactive compounds

Some considerations should be pointed out to increase the bioavailability of polyphenolics; throughout this review article, some of the main ones were highlighted, such as 1) the influence of the diversity of chemical structures of these plant-derived compounds; 2) the content of compounds in a food source does not correspond to the ability to be absorbed in the body; 3) molecular instability limits the biological use of these natural antioxidants; 4) the intestinal microbiota plays a fundamental role in the biotransformation of these phytochemicals, the composition of the strains interferes with the bioavailability of phenolics, as it limits absorption and metabolism; 5) the bio-efficacy of these compounds must be maintained and delivered directly to different biological systems in the body; 6) nano-systems correspond to tools that facilitate this process and can improve bioavailability.

The development of nanostructures is in vast expansion; the polyphenols encapsulated can be used in a diverse range of clinical applications, including preventive treatments to therapeutics. Identifying potential therapeutic pathways of natural compounds can be an effective strategy in the prevention and adjuvant treatment of some diseases; this is considered an innovative application, mainly in cancer treatments. In the coming years, there should be a better approximation of nanotechnology in the food and pharmaceutical industry. This perspective imposes the need for studies with an *in vivo* approach so that new formulations are used safely and effectively. New materials and methodologies must be carefully selected; food polysaccharides are potential biomaterials. The possibility of having more bio-accessible and bioavailable polyphenolic compounds in foods and dietary supplements is possible due to applying a wide range of construction of these nano-vehicles. Various studies have proven that polysaccharide-based nanostructures are adequate and appropriate delivery agents for diverse bioactive foods, such as polyphenolics.

However, despite several indications that nanoparticles are effective systems for the targeted delivery of bioactive compounds, much remains to be explored. The possible deleterious effects and toxicity *in vitro* and *in vivo* models attest to the safety of oral administration. To ensure safety for widespread application in food, future research should focus efforts on assessing toxicity that provides ingestion without adverse risks to human health.

Despite the advances, some challenges still need to be overcome, such as establishing structure-activity for the full range of polyphenols in foods and elucidating all mechanisms involved in absorption and that impact on bioavailability. Determining recommended doses of polyphenolic compounds in nutritional guidelines and studies of chronic and long-term intake of nano-encapsulated bioactive compounds have already been conducted. More dedicated efforts must soon be planned through more comprehensive biological studies to fill this gap. *In vivo* studies are essential to obtain data about absorption, excretion, and the natural destination after oral ingestion of polyphenols and their metabolites. Supporting studies on the interaction of these compounds with the intestinal microbiota are fundamentally defined as an essential factor for bioavailability.

The elaboration of nano-projected vehicles can systematically promote delivery systems of polyphenolic compounds in different tissues and organs. This indicates that adjuvants could be used with more bioactivity in clinical treatment. In addition, more active metabolites can be observed of polyphenols delivered to the intestine (more distal portions), promoting more considerable interaction with cells and more excellent absorption of both integral structures and metabolites. This article proposed a discussion on the bioavailability of nano-encapsulated polyphenolic compounds based on polysaccharides as a basis for future *in vivo* studies, given the undeniable potential of nanotechnology to promote most excellently physical-chemical stability that can positively interfere with the bioavailability of bioactive compounds, especially polyphenolic compounds. Notably, there is an emerging need for more studies to identify nanostructured materials (and techniques) that form targeted delivery systems for specific metabolic situations, representing a substantial advance in food and nutrition science.

Table 3. Recent studies on applying polysaccharides (alone or combined with other biopolymers) to nano-encapsulate polyphenolic compounds.

Polysaccharide	Polyphenolic Compound	Nanoencapsulation Method	Size (nm)	Zeta Potential (mV)	Encapsulation Efficiency (%)	Purpose of Nanoencapsulation	Reference
Chitosan - Alginate	Anthocyanin	Ionic pre-gelation and complex polyelectrolyte	358.5 – 635.9	–	68.9	Improve stability and increase bioavailability.	(Bulatao et al. 2017)
Pectin – WPI	Anthocyanin	Self-assembly	200	−36	55	Improve Stability	(Arroyo-Maya and McClements 2015)
Carboxymethyl-chitosan	Anthocyanin	Ionic gelation	63.15 – 219.53	–	–	Improve Stability during digestion.	(He et al. 2017)
Chitosan - β-Lactoglobulin	Anthocyanin	Ionic gelation	91.71 – 69.3	–	–	To improve the stability and bioavailability	(Ge et al. 2019)
Chitosan - β-Lactoglobulin	Anthocyanin	Ionic gelation	580.4	+ 49.	77.4	Storage and oxidant stability during *in vitro* simulated digestion	(Chen et al. 2023)
Chitosan - β-Lactoglobulin	Epigallocatechin gallate	Ionic gelation	100 - 500	+ 10 to + 35	60	Control release in the gastrointestinal	(Liang et al. 2016)
Chitosan	Catechins	Ionic gelation	169.0 – 201.4	+ 30	24 - 53	Protection and stability	(Ing et al. 2008)
Soybean-insoluble dietary fiber	Anthocyanin	Emulsification	300	–	–	Increasing storage stability and color protection	(He et al. 2022)
Chitosan	Anthocyanin	Ionotropic gelation	274 - 455	−5.04 to −35.4	70	Antioxidant potential	(Chatterjee et al. 2021b)
Pectin - WPI	Phenolic compound (mixture)	Nanoemulsion	> 675	–	96.64	Stability	(Mohammadi et al. 2016)
Cellulose - Pectin	Phenolic compound (mixture)	Nanoemulsion	200	–	–	Antimicrobial Activity	(Hassan et al. 2022)
Chitosan	Anthocyanin	Ionic gelation	160 - ~1,000	–	–	Antioxidant Activity	(Ko et al. 2017)
Zein-carboxy-methylcellulose	Quercetin and Reveratrol	Antisolvent precipitation	217	−33.6 to −45.	25.1	Thermal stability to enable oral administration	(Yang et al. 2023)
Pectin	Resveratrol	Antisolvent precipitation and electrostatic deposition	120	−30	–	Stability, Bioaccessibility, and Antioxidant Capacity Maintenance	(Huang et al. 2019)
Pectin-Chitosan	Neohesperidin	Polyelectrolyte complex	87–225	−19.2 to 24.4	72	Antioxidant Property, Released and Improve Absorption	(Shishir et al. 2019)
Pectin - Chitosan	Anthocyanins	Self-assembly	100 - 300	–	66.68	Molecular Stability and Control Released	(Zhao et al. 2020b)
Pectin - Lysozyme	Anthocyanins	Self-assembly	198.5	−26	73	Molecular Stability	(Osvaldt Rosales et al. 2021)
Starch	Catechin	–	322.7, 559.2, and 615.6	− 18.05, − 21.5, and − 18.05	59.09, 48.30, and 55.00	Controlled release in the intestine and protection of properties	(Ahmad et al. 2019)

Disclosure statement

The authors declare no conflicts of interest.

Author contributions

T.K.O.R.: Conceptualization, data curation, and writing (original draft and review and editing); F.F.A.S.: writing (review and editing); E.S.B: writing (review and editing); J.P.F.: conceptualization, supervision, and writing (review and editing). All authors have read and agreed to the published version of the manuscript.

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