Review Article

A brief review on encapsulation of natural poly-phenolic compounds

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Abstract

Polyphenol research and use have lately sparked significant interest in the functional foods, nutraceutical, and pharmaceutical sectors due to their potential health advantages for humans. Polyphenols' success, however, is dependent on sustaining the stability, bioactivity, and bioavailability of their active components. The disagreeable taste of most phenolic compounds also restricts their use. The use of encapsulated polyphenols rather than free molecules can successfully address these inadequacies. This study focuses on polyphenolic chemical nanoencapsulation technology, its applications in the food and pharmaceutical industries, as well as safety and biocompatibility. This also discusses the health benefits and disease prevention properties of encapsulated polyphenolic compounds in animals and humans. This review discusses polyphenol encapsulation technologies such as spray drying, coacervation, liposome entrapment, inclusion complexation, co-crystallization, nanoencapsulation, freeze drying, yeast encapsulation, and emulsion. The latest studies, advances, and trends are also highlighted.

Keywords**:** Encapsulation, nanoencapsulation, Microencapsulation, Polyphenols, polymers

Introduction

"Encapsulation is a medicine or food ingredient-loaded delivery method that entraps active components, preventing them from decomposing or degrading during processing and storage, and facilitating their transport to the target tissue/organ, hence increasing their bioactivities". Because dietary bioactive components, such as polyphenols, are sensitive to environmental and/or gastrointestinal conditions, the use of this technology is increasingly shifting from pharmaceuticals to the food business. Encapsulation can be used effectively in the development of poly-phenol-based functional foods, potentially increasing their bio-accessibility and/or bioavailability. Furthermore, encapsulation can help in the targeted distribution of polyphenols and perhaps reduce side outcomes (Ozkan et al., 2024). Several processes are used to encapsulate bioactive substances, including emulsion phase separation, emulsification/internal gelation, film creation, spray drying, spray bed drying, fluid-bed coating, spray chilling, spray cooling, and melt injection. Polyphenols are the most abundant category of plant secondary metabolites, with a wide range of biological effects. The literature has shown that they can prevent a variety of ailments and pathologies, ranging from basic allergy problems to more complicated metabolic syndromes, and cardiovascular and neurological diseases. Despite promising health effects in preclinical investigations, dietary polyphenols' clinical application remains limited due to their poor bio-accessibility and/or bioavailability. Dietary polyphenols may alter multiple signaling pathways at the cellular and molecular levels, protecting humans from oxidative stress and inflammation, which are at the root of many chronic degenerative diseases. They serve as a cardio-protective, anti-diabetic, anti-microbial, anti-platelet, anti-asthmatic, neuro-protective, anxiolytic, anti-depressant, and anti-carcinogenic drugs, to mention a few.

The literature (Table 1) shows that in-vitro as well as in vivo, poly-phenols can:

- Reduce inflammation by inhibiting edema,
- Stop the development of tumors,

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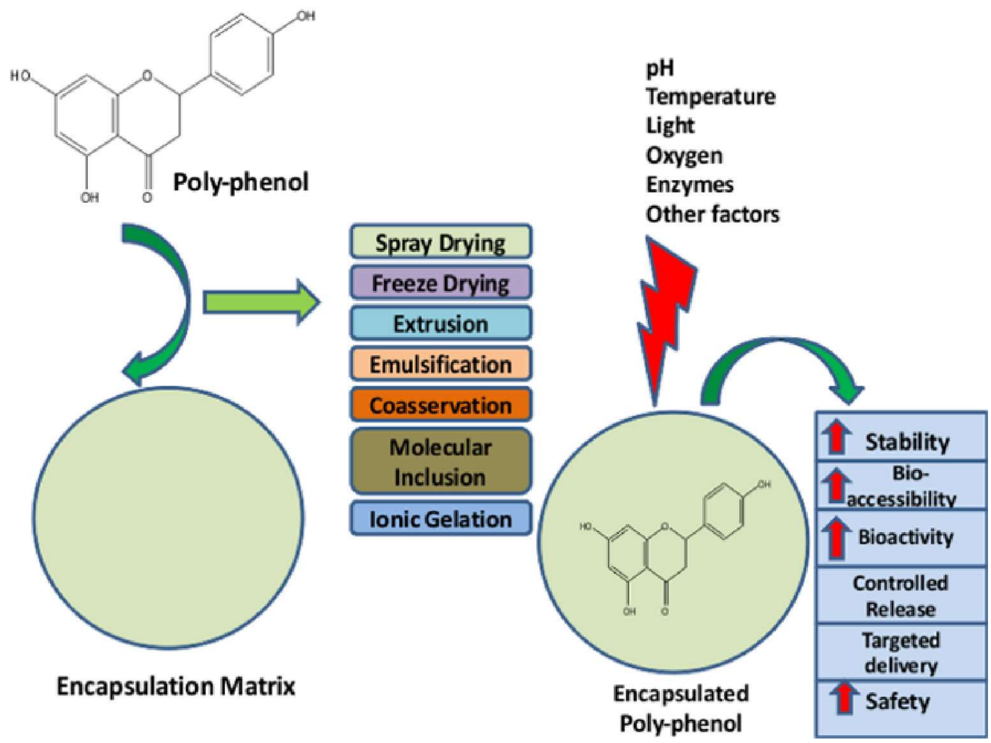

Figure 1: Possible and clinical benefits of Encapsulated Polyphenols in Health and Disease.

- Present pro-apoptotic and anti-angiogenic actions,
- Modulate the immune system,
- Prevent the osseous disturbances incriminated in osteoporosis,
- Increase capillary resistance by acting on the constituents of blood vessels,
- Protect the cardiovascular system,
- Protect the retina,
- Limit.

The economic consequences of poly-phenolic chemicals are therefore significant. They are utilized as natural additives in a wide range of food-processing industries. However, the most significant economic impact of polyphenols is likely to be in the realm of human health. Many plant extracts high in phenolic compounds of interest are utilized as dietary supplements or can be used in cosmetic or medicinal formulas. Some important plant polyphenols, their structures, sources, specifications, and biological characteristics are summarized below. Unfortunately, the applications of these precious natural chemicals are severely limited (Munin and Edwards-Lévy, 2011).

Natural Polyphenols

Natural polyphenols' biological activity in scavenging free radicals and interacting with proteins makes them theoretically attractive for a range of applications, but their realization is restricted by their inherent instability. Instability might be seen as breakdown during manufacturing and storage (temperature, oxygen, light) or in vivo delivery (pH, enzymes in the gastrointestinal system). Encapsulating polyphenols (typically plant extracts) is intended to retain biological activity, increase the stability of active chemicals, and ensure regulated release of the latter. Encapsulation has the benefit of being a non-thermal stabilization technique that is appropriate for temperature-sensitive natural biologically active chemicals, such as those isolated from various plants for medicinal uses (Bartosz and Irene, 2019). Nano-encapsulation is the process of encapsulating nano-particles of an active component in the form of a solid, liquid, or gas, also known as the core or active, into a secondary material, known as the matrix or shell, to create nano-capsules. The core (depending on design) is often released by diffusion or in reaction to triggers like shear, pH, or enzyme activity, allowing for regulated and timed delivery to a specific spot. Nano-encapsulation can be used to study the effects on dynamic behavior, electrical properties, and phase transitions of non-therapeutically active substances, in addition to bioactive materials. Chitosan, gelatin, sodium alginate, and albumin are the most often utilized natural biopolymers for creating nano-encapsulated compounds. Synthetic polymers include PLA, PGA, PLGA, and PVA, to mention a few. Copolymers include poly (lactide)-poly (ethylene glycol) (PLA-PEG) and poly (lactide-co-glycolide)-poly(ethylene glycol) (PLGA-PEG). Polymeric

Table 1. Types of plant polyphenols, their structures, sources, specifications, and biological characteristics

Phenolic compounds and Caumarines	Carbon Skeleton	Example	Sources	Specifications	Main Biological Properties
Hydroxybenzoic Acids	C6-C1	Gallic acid, Vanillic acid, Protocatechuic acid, p-Hydroxybenzoic acid	Tea Red fruit (raspberry, black currant, strawberry)	Very common, in free form as well as combined, not much studied and not considered to be of great nutritional interest, sensitive to temperature, oxidation, light, and pH, water-soluble	Very limited therapeutic interest, antimicrobial activity, and fungitoxicity, anti-inflammatory properties of salicylates
Hydroxy-cinnamic Acids	C6-C3	Caffeic acid, p-coumaric acid, Sinapic acid Ferulic acid	Fruit (kiwis, blueberries, apples) Cereal grains (wheat, rice, oat flours)	Rarely found in free form, often esterified, sensitive to oxidation and pH, slightly soluble in water	
Caumarines		OmbelliferoneAesculetin, Scopoletin	Tonka bean, bark (chestnut), medicinal plants (Melilotus officinalis, Angelica Officinalis)	Free coumarines are soluble in alcohols and organic solvents, the heterosidic forms are less soluble in water.	Anti-inflammatory and antiviral activities, limited pharmacological applications: hepatotoxicity
Stilbenes	C6-C2-C6	Resveratrol	Medicinal plants (vine)	Found only in low quantities in the human diet	Anticarcinogenic effects, anti-inflammatory activity
Flavonoids			C6-C3-C6		
Flavonols		Myricetin, Quercetin, Kaempferol, and their glycosylated forms	Fruit and vegetables (Onions, curly kale, leeks, broccoli, blueberries), red wine and tea	Flavonols are the most ubiquitous flavonoids in food	Vitamin P factor protects capillaries and veins, It is often anti-inflammatory, antiallergenic, antiviral, anti-spasmodic, antibacterial, antioxidant, and anti-carcinogenic properties, hepatoprotective, some are powerful enzymatic inhibitors
Flavones		Aspigenin, Luteolin, Tangeretin, Nobiletin, Sinensetin	Parsley, celery, cereals (millet and wheat) Skin of citrus	Flavones are much less common than flavonols in fruit and vegetables	
Flavanones		Hesperetin, Naringenin, Eriodictyol	Citrus fruit (grapefruit, orange, lemon), tomatoes and some aromatic plants (mint)	Sensitive to oxidation, light, and pH, bitter taste	
Isoflavones		Genistein, Daidzein, Glycitein	Leguminous plants (soya and its processed products)	Structural similarities with estrogens confer pseudo-hormonal properties	
Flavanols					
Monomer Form		Catechin, Epicatechin	Fruit (apricot, cherry, grape, peach, apple), green and black tea, red wine and cider	Sensitive to oxidation, light, and pH, astringent and bitter taste, slightly soluble in water	
Polymer Form Proanthocyanidins	(C15)n	Castalin, Vescalin	Fruit (grapes, peaches, kakis, apples, berries), beverages (wine, cider, tea, beer), chocolate	Responsible for the astringent character and bitter taste, sensitive to high temperature and oxidation, water and alcohol soluble	
Anthro-cyanins		Cyanidin, Pelargonidin, Delphinidin, Petunidin	Red wine, some varieties of cereals, some leafy and root vegetables (aubergines, cabbage, beans, onions, radishes), flowers, and most abundant in fruit	Plant pigments, highly sensitive to temperature, oxidation, pH, and light, water-soluble	
Lignans	(C6-C3)2	Pinoresinol, Podophyllotoxin, Steganacin	Flax seed, sesame seed, cereals (rye, wheat, oat, barley), cruciferous vegetables (broccoli, cabbage), and fruit (apricots, strawberries)	One of the major classes of phytoestrogens, relatively stable under normal conditions, water-soluble, unpleasant flavor	Hepatoprotector, antimitotic, antiviral, antihypertensive, and cytostatic activities, inhibitors of enzymatic reactions

colloidal stabilizers, such as dextran, polysorbate 20, and polysorbate 80, are commonly used to avoid aggregation in nano-encapsulation operations. Nano-materials may be created utilizing a variety of nanocarriers, which operate as transport modules for bioactive materials. Pharmaceutical nanocarriers include nanospheres, nanocapsules, nanoparticles, nanoemulsions, nanoliposomes, and nanoniosomes (nonionic surfactant vesicles). These nanoscale drug delivery systems might be natural or manufactured, and they can transport lipophilic or hydrophilic compounds. They can be classed depending on their origin (e.g., lipid-based and biopolymer nanocarriers), and mode of synthesis (e.g., electrospun and electrosprayed nano-carriers). Nanoencapsulation creates active particles with sizes of 1–1000 nm. The term nanoparticle refers to both nanospheres and nanocapsules. Nanospheres have a matrix-type structure. Actives might be absorbed in the spherical surface or contained inside the particle. Nanocapsules are vesicular systems in which the active is contained within a cavity composed of an inner liquid core surrounded by a polymeric membrane (Fang and Bhandari, 2010). Nano-encapsulation strategies for synthesizing nano-materials might be top-down or bottom-up. A top-down approach, as the name implies, involves the size reduction and structure shaping of the material using specific methods (e.g., emulsification-sol-vent evaporation), whereas the bottom-up approach allows for the self-assembly and self-organization of molecules to yield nano-materials (e.g., Coacervation). A nano-material's physical and chemical characteristics have a significant impact on its efficacy. Additionally, its surface features can impact its functional and physicochemical qualities, as well as its application. Characterization of nano-particles is thus crucial to ensuring the requisite features for optimal efficiency and safety. There are multiple characterization approaches that may be used to examine various properties of a nano-material. These strategies differ in terms of relative advantages, drawbacks, cost, efficiency, and complexity, so choosing one requires careful study (Rambaran, 2020). This work established the potential of utilizing zein to nano-encapsulate bioactive substances via an electro-spraying technique, successfully photo and thermo-stabilizing the polyphenolic chemicals found in Biloxi blueberry extracts. This approach produced nano-capsules with homogenous morphology, no fractures or dents, and no changes to their thermal characteristics. The necessity of using an adjuvant like glycerol to improve the encapsulation effectiveness of hydrophilic molecules in partly hydrophobic matrices was also proven (González-Cruz et al., 2023). Phenolic compounds are the most abundant secondary metabolites generated by the shikimic acid pathway in plants during growth or in response to environmental stressors. Their content in the plant is determined by the plant variety, growth circumstances, ripening, harvest, and processing and storage conditions (Grgić et al., 2020). Polyphenols are currently receiving a lot of interest in the pharmaceutical and medical fields because of their health-promoting qualities.

Uses of Polyphenols

They may have anti-inflammatory, anti-oxidative, and anti-cancer properties by inhibiting the production of pro-inflammatory cytokines and enzymes or factors associated with carcinogenesis (e.g., matrix metalloproteinases, vascular endothelial growth factor), implying that they may have therapeutic potential for IBD and CRC. However, their utilization is restricted under both processing conditions and gastrointestinal interactions, lowering their stability and hence bio-accessibility and bioavailability. Polyphenols are currently receiving a lot of interest in the pharmaceutical and medical fields because of their health-promoting qualities. They may have anti-inflammatory, anti-oxidative, and anti-cancer properties by inhibiting the production of pro-inflammatory cytokines and enzymes or factors associated with carcinogenesis (e.g., matrix metalloproteinases, vascular endothelial growth factor), implying that they may have therapeutic potential for IBD and CRC. However, their utilization is restricted under both processing conditions and gastrointestinal interactions, lowering their stability and hence bio-accessibility and bioavailability. As a result, there is a need for more effective carriers capable of encapsulating polyphenols (Caban and Lewandowska, 2023). There are two types of polymers used in the preparation of nano-particles- Natural polymers and synthetic polymers. The polymers should be adaptable (non-toxic) and non-antigenic to the human body, as well as biodegradable and biocompatible. The polymers utilized are of two kinds (Varsha, Krishnakumar, and Dineshkumar, 2017).

Table 2: Polymers types

Natural Polymers	Synthetic Polymers
Chitosan	Polyacticides (PLA)
Gelatin	Polyglycolides (PGA)
Sodium Alginate	Poly (lactide co-glycolides) (PLGA)
Albumin	Polycyanoacrylates Poly (N-vinyl pyrrolidine) Poly (vinyl alcohol) Poly (acrylic acid) Poly (ethylene glycol) Poly (methacrylic acid)

Encapsulated polyphenols have the advantage of alleviating their sensory impact, overcoming their instability, enhancing their skin penetration, and the formulation flexibility of the cosmetic final product. Encapsulation technologies offer a wide range of approaches that aim to protect the inner bioactive molecules from environmental factors (i.e., light, oxygen, moisture, pH, temperature, and enzymes) thus preserving their biological activity Encapsulated poly-phenols have the advantage of alleviating their sensory impact, overcome their instability, enhance their skin penetration, and the formulation flexibility of the cosmetic final product. Encapsulation technologies offer a wide range of approaches that aim to protect the inner bioactive molecules from environmental factors (i.e., light, oxygen, moisture, pH, temperature, and enzymes) thus preserving their biological activity (Rispo et al., 2023). Polyphenols are plant secondary metabolites with hydroxylated phenyl moieties that have received a lot of attention due to their broad bioactivity. They have been shown to promote human health by contrasting oxidative stress and thus play a protective role in preventing various pathologies such as cardiovascular disease. The phenolic acid group is made up of molecules with a single phenyl ring and is mostly composed of benzoic and cinnamic acid derivatives. Flavonoids are composed of two aromatic rings joined by an oxygenated heterocyclic ring and are classified into various sub-groups, including flavonols, flavones, flavanones, isoflavones, flavanols, and anthocyanidins. Stilbenoids, lignans, ellagic acids, phenolic acids, and flavonoid polymers, known as hydrolyzable and condensed tannins, represent other phenolic component groups. Finally, and most crucially for the food industry, polyphenols' low stability under denaturing conditions induced by heat, pH, light, oxygen, enzymes, and so on restricts their use as functional additives, natural antioxidants, and supplements. Depending on the combination and intensity of these factors, the amount of intact polyphenols that remain in the food and can reach the intestine—where their absorption is thought to occur primarily-varies greatly, influencing the extent of their bioavailability and subsequent metabolism (Cao et al., 2021).

Microencapsulation

Microencapsulation is a novel technique that protects food components or functional elements from various processing conditions by encasing them in a polymeric or nonpolymeric material and allowing for controlled release under certain conditions. Coating materials are selected based on their rheological properties, capacity to distribute and stabilize the active molecule, inertness to the active component, and ability to properly retain the active molecules. Carrier materials include lipids like wax, paraffin, beeswax, and diacylglycerols; proteins like glutein, casein, and gelatin; carbohydrates like starch, maltodextrin, modified starch, cyclodextrin, and cellulose; and gums like gum acacia, agar, and carrageenan. Several microencapsulation techniques include spray chilling, spray cooling, fluidized bed coating, liposome entrapment, extrusion, freeze drying, and coacervation (Adefegha et al., 2022). Encapsulation is a proven method for modifying characteristics and delivering polyphenolic chemicals. This approach boosts polyphenol bioavailability, conceals astringency, extends shelf life, and directs molecules to specific areas of the gut for metabolism or absorption.

Technologies for polyphenol encapsulation

Encapsulation technologies used in modern research include freeze-drying, extrusion coating, fluidized bed encapsulation, liposome capture, simple/complex coacervation, gelation, and more. There are two types of encapsulation methods: top-down and bottom-up. The top-down approach is used in the extrusion of emulsion. It splits huge solid or liquid objects into smaller fragments by external force, such as cutting, collision, or pressure. This approach necessitates specific equipment, such as homogenizers, which raises the operating and maintenance expenses. The bottom-up method employs self-organization potential to create bigger molecules. Microcapsules form when the components are enclosed and the carrier is combined in a solution. The technique is sensitive to pH, temperature, and ionic strength, yet it is energy-efficient and produces microcapsules with predetermined form and size. Coacervation, spray drying, electro-spinning, bonding, and anti-solvent precipitation are the most common bottom-up approach techniques. Polyphenols have limited hydrophilicity, limiting their absorption in the gastrointestinal system. Cyclodextrin glucans-transferase promotes the formation of cycloamylose. It encapsulated resveratrol, increasing its solubility in water by 6000 times, while maintaining chemical stability, antioxidant impact, and anti-inflammatory capabilities.The matrix material influences the stability of the encapsulated active ingredient. Capsules containing alginate and guar gum were able to maintain anthocyanins for two weeks. Other study teams observed similar findings. Furthermore, alginate capsules were particularly successful in preserving phenolic acids. Polyphenol concentration may rise or decrease during storage when condensed molecules depolymerize and monomers attach to the capsule matrix. Composite matrices, particularly those containing guar gum, sustain greater polyphenol antioxidant values in new capsules as well as after two or three weeks of storage. Anthocyanins are the most frequent plant pigments, making them ideal culinary coloring agents. The color intensity of encapsulated concentrates has been shown to increase with storage, particularly when a composite matrix is used. Chitosan enhanced the intensity of the yellow color, whilst alginate or its mixture with guar gum boosted the red color. Liposomes have progressed through clinical trials, and numerous liposomal-based drug delivery systems are now clinically licensed to treat a variety of conditions, including cancer, fungal infections, and viral infections. Liposomes make polyphenols more bioavailable. Milk or whey proteins have also proven useful for a variety of causes (Sakshi, 2014). First, they hide the astringent taste, allowing for the inclusion of more polyphenols in functional food compositions. Second, the final product is fortified with beneficial proteins and vital amino acids. Third, high polyphenol concentrations provide sufficient antioxidant capabilities to extend the shelf life. Polyphenol encapsulation is a useful way of functional product design, particularly in the field of foods intended for dietary nutrition, sports, preventative diets, and so on (Bobrysheva et al., 2024). Protein has been utilized as a carrier to preserve and target polyphenols, extending their shelf life. Interactions between protein molecules and polyphenols are crucial because they modify the complex's activities and physiochemical characteristics while also protecting polyphenols. Protein-polyphenol interactions are typically noncovalent. pH, temperature, and the structure of proteins and polyphenols all have a role in such interactions. Phytochemicals derived from fruit and vegetable waste show promise for improving nutritional and health-promoting characteristics. These phytochemicals are extremely sensitive since direct incorporation into food items impairs their sensory and functional properties. These beneficial chemicals degrade during food storage and processing, resulting in a decrease in antioxidant action. As a result, including these sensitive bioactive components in food poses a significant challenge to the food industry in developing a functional meal with better attributes. Encapsulation technology is a good approach for protecting these delicate bioactive chemicals, which have higher antioxidant properties and regulated release as compared to non-encapsulated bioactive substances (Thakur and Borah, 2021). Furthermore, nanoencapsulation methods such as emulsion, nanohydrogel, and nanocomplex creation can provide high stability for polyphenols. Protein mixed with other substances such as lipids and carbs was shown to be the best carrier for polyphenol encapsulation (Xiao et al., 2023). Several promising results for future Nano sponge development emerged from an analysis of the manufactured Nano sponges' various parameters (Kumar et al., 2022). Polyphenolic compounds are microencapsulated to protect them from interactions with milk components during dairy product preparation or storage, which reduces their bioavailability and overall acceptability (El-Messery et al., 2019). Natural extracts, with their unique multi-component composition, as well as individual polyphenols, have the potential to improve the performance of medicines and functional foods by delivering sustained concentrations to a specific site in a minimally invasive manner. The future of encapsulated polyphenols and site-specific carrier targeting is promising (Haponska et al., 2020).

Summary and Conclusion

According to the literature, using encapsulated polyphenols instead of free compounds can increase the compounds' stability and bioavailability in vivo and in vitro, as well as optimize routes of administration. Although the majority of encapsulation technologies used for other chemicals have been adopted in polyphenol encapsulation, some technologies, such as spray cooling/chilling, spinning disc and centrifugal co-extrusion, extrusion, and fluidized bed, are still not being used for these special phytochemicals. However, this does not imply that these technologies are ineffective for polyphenol encapsulation. Future polyphenol encapsulation research will most likely focus on factors of distribution and the possible application of co-encapsulation techniques, in which two or more bioactive substances can be combined to provide a synergistic effect. Over the next decade, encapsulated polyphenols are expected to play an important role in increasing the efficacy of functional foods or even pharmaceuticals, thanks to advances in manufacturing technologies, new strategies for stabilizing fragile nutraceuticals, and the development of novel approaches to site-specific carrier targeting. Future research in polyphenol encapsulation is likely to focus on aspects of delivery and the potential use of co-encapsulation methodologies, where two or more bioactive ingredients can be combined to have a synergistic effect. It can be predicted that, with a deep understanding of the health benefits of polyphenols, improvements in manufacturing technologies, new strategies for stabilizing fragile nutraceuticals, and the development of novel approaches to site-specific.

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