Nanoformulated Polyphenols and Their Therapeutic Applications in Human Diseases

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**Abstract:** Plant polyphenols have gained significant attention in recent years as a promising area for the creation of innovative functional foods. Polyphenols, which are bioactive substances, encompass flavonoids, phenolic acids, and lignans. They are frequently present in plant-based diets and exhibit diverse biological activities, such as antioxidant, anti-inflammatory, and anticancer properties. Regrettably, the utilization of polyphenols in nutraceuticals is limited due to the inadequate oral bioavailability of several of the chemical compounds found in polyphenols. Fortunately, polyphenols may be enclosed and conveyed utilizing nanocarriers derived from biological sources, enhancing their ability to be absorbed and utilized by the body. The practical application of polyphenols is hindered by their restricted solubility in water and low ability to be absorbed by the body. However, this problem can be overcome by developing appropriate delivery systems that can encapsulate and transport polyphenolic chemicals. This work presents a comprehensive examination of the use of nanocarriers to improve the absorption of polyphenols when taken orally. Additionally, it provides a concise explanation of the various health benefits of polyphenols in the prevention and treatment of multiple diseases.

Keywords: Nanoformulations, Polyphenols, Therapeutic activity, Pharmaceutical uses

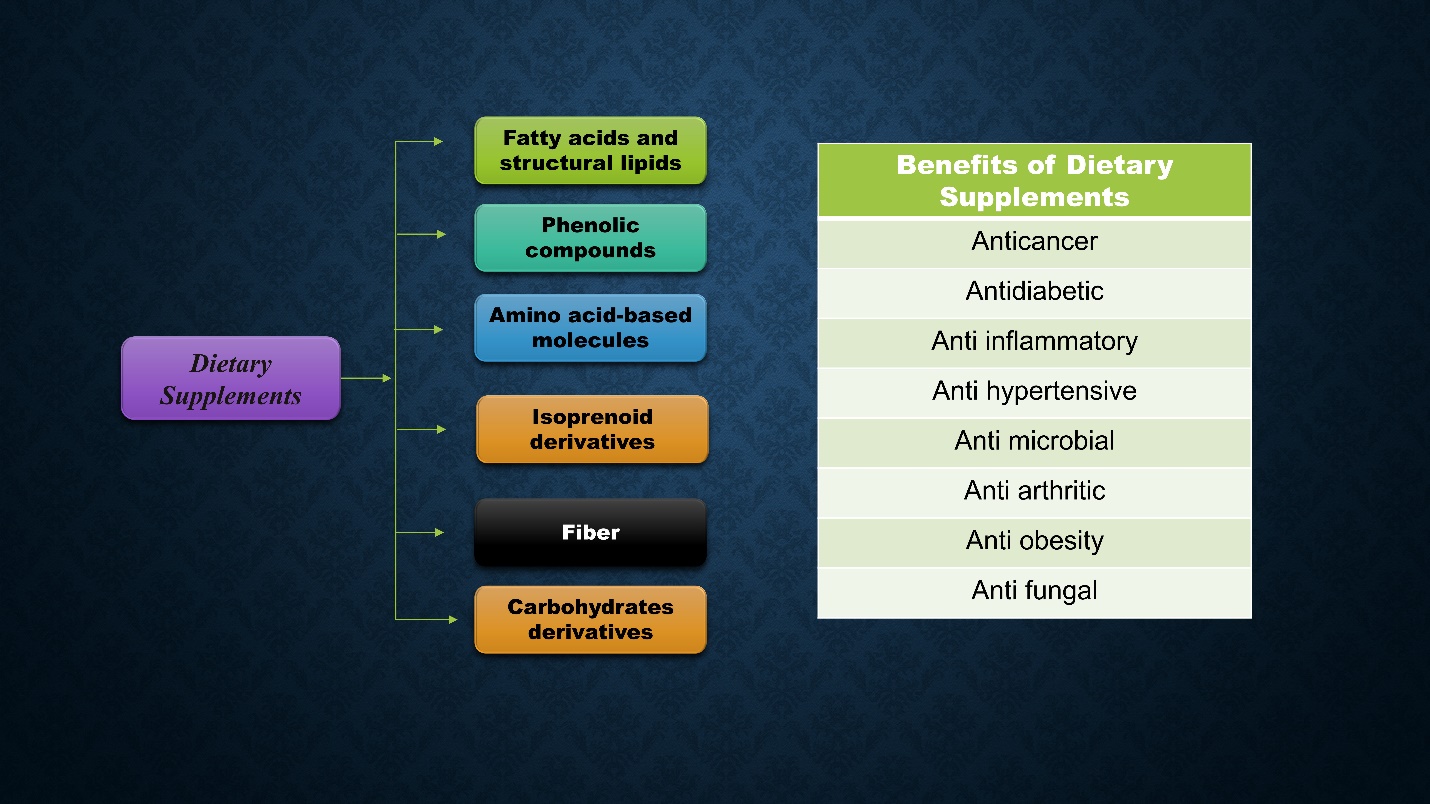
**1. Introduction**

Plant polyphenols, one of the most frequent chemical components of plants, have garnered special attention due to the growing scientific interest in the health advantages of a plant-based functional diet. Polyphenols can be found in their natural forms in foods such as vegetables, fruits, cereals, tea, and coffee. Polyphenolic substances can be subdivided into phenolic acids, flavonoids, anthocyanins, and tannins, all of which have structures based on phenolic rings [1,2]. There are a number of foods that contain bioactive compounds [2,3]. Polyphenols can be obtained in two main ways: either by recycling already existing natural compounds or by isolating and extracting them from whole foods. The rate of absorption and the scope of effect of polyphenols in the digestive tract are both influenced by their chemical composition [4]. Polyphenols are powerful prophylactic agents against chronic and degenerative diseases [3,4,5] due to their distinct chemical composition. Numerous studies [6,7,8,9,10,11,12] have shown that polyphenols protect against cardiovascular disease, neurological disease, liver disease, diabetes, and cancer.

Multiple studies have demonstrated the positive effects of polyphenols on intestinal health, including reduced inflammation and cancer protection via flora regulation [2,13]. This is why you will often find them on menus for "functional diets," or diets that attempt to promote health through food. The market for polyphenols is expected to continue growing as the world population rises and more people become aware of the importance of leading a healthy lifestyle. However, the limited oral bioavailability of many polyphenolic compounds limits their utility in nutraceuticals.

Natural bio-based nanocarriers are the optimum solution for encapsulating, conserving, and transporting polyphenols, which enhances their bioavailability (Figure 1) [2,14]. Bio-based polymers (such as those containing proteins and polysaccharides) are suitable delivery systems when used as nutritional treatments because they are biocompatible, biodegradable, resource-sustainable, and nutritionally valuable [2,14]. In addition to their excellent nutritional value, protein bio-based polymers possess a wide range of beneficial characteristics including emulsification, amphiphilicity, gelation, and foaming [14]. Nanoparticles, nanogels, nano-emulsions, nanofilms, and nanofibers are just some of the nanoscale delivery vehicles that can transport hydrophilic and hydrophobic polyphenolic chemicals [14,15] due to their typical or distinctive molecular structure and functional properties. Polyphenolic substances can be transported using nanocarriers that are constructed from bio-based polymeric polysaccharides [1,2]. Lipid-based nanocarriers have emerged as an important technology for delivering polyphenols in the food and nutrition industry because they are biocompatible and biodegradable [2]. Some polyphenol products have been placed in an attempt to further develop new polyphenol-based health nutrition products [2,15] in order to further explore and build unique polyphenol-based health nutrition products. Protecting fat-soluble polyphenols from degradation in the digestive system and increasing their bioavailability [1,2,4,12,15] are two benefits of lipid-based delivery vectors including liposomes, nano-emulsions, and solid lipid nanoparticles.

The favorable benefits of polyphenols on human health are thoroughly evaluated, and their classification within the broader category of polyphenolic compounds is introduced. The article details the ways to increase the bioavailability of polyphenolic compounds, such as the design and implementation of food-grade bio-based nanocarriers to encapsulate, store, and disperse these compounds. In conclusion, it is fascinating to consider the possibility of using polyphenol food-grade bio-based nano-complexes in nutraceuticals, which would combine nano-delivery methods with polyphenol health benefits.



**Figure 1.** Human health benefits associated with dietary supplement consumption based on polyphenols.

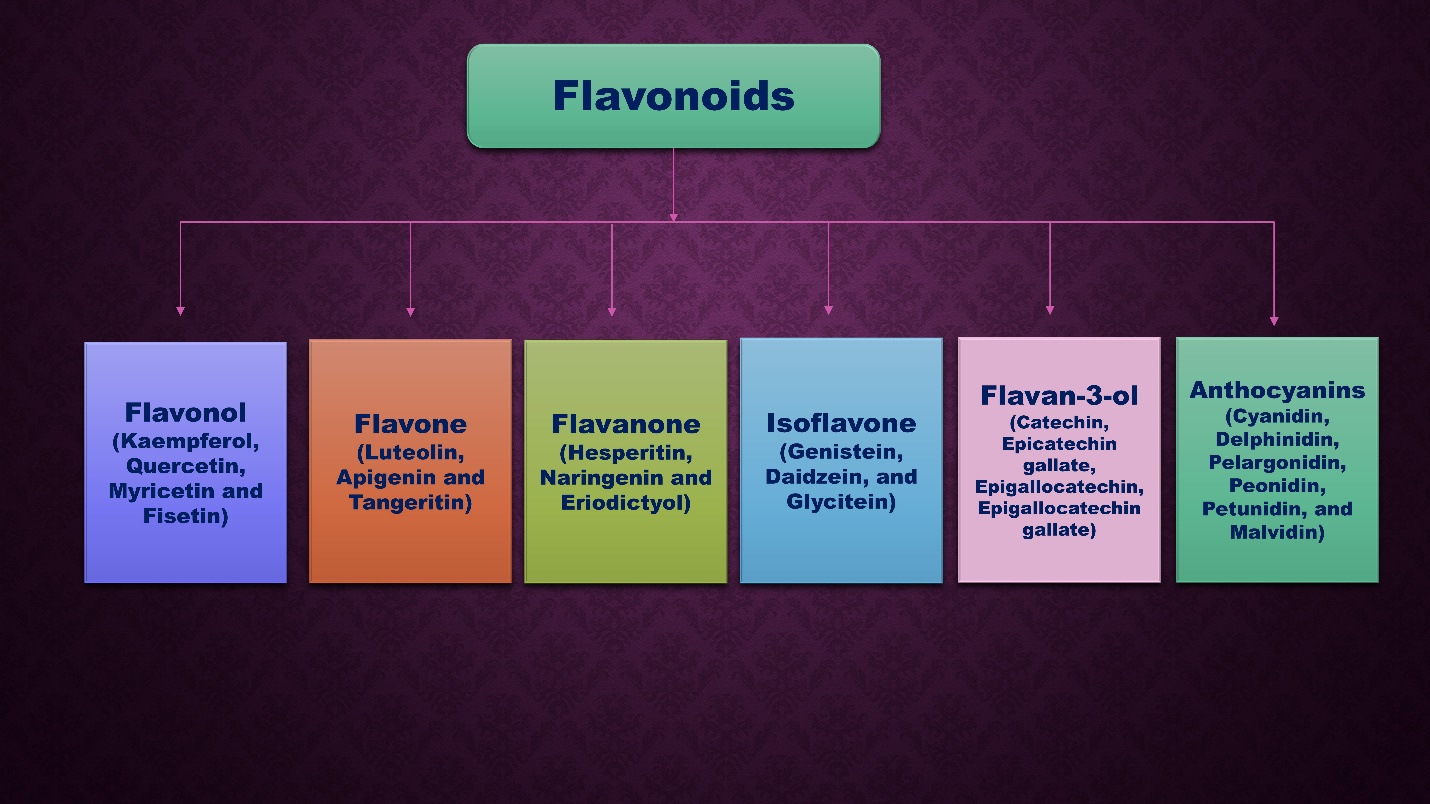
**2. An Overview of Polyphenols in Plants: Classification, Characteristics, and Impact on Human Health**

2.1 Classification and Properties of Polyphenols

Plant polyphenols, found in a wide variety of meals, have gained popularity for their possible health benefits. Polyphenols are chemicals that have two or more phenolic hydroxyl groups and a benzene ring structure [1,2,15]. Based on their chemical structures, these substances can be broken down into two subgroups: flavonoids and phenolic acids.

Flavonoids (a major class of polyphenols) are primarily found in plant cells as glycosides contained in vesicles. The molecular backbone of flavonoids is a C6-C3-C6 tricyclic structure. The chemical structure is used to classify flavonoids into subclasses; for example, flavonols, flavones, isoflavones, anthocyanins, flavanones, and flavanols are all subclasses of flavonoids (Figure 2). The ubiquitous flavonoids have been linked to positive effects on plant health, including improved growth, flowering, fruiting, resistance to disease, and antibacterial activity [2]. Most of these flavonoids have physiological activities that may be beneficial to human health, including those that are anti-inflammatory, antibacterial, antioxidant, and anticancer [12].

Phenolic acids can be found in food and drinks such as fruit, vegetables, tea, and coffee. It is stated that low-molecular-weight phenolic acids are water-soluble; however, after enduring condensation processes with glucose and quinic acid, they become water-insoluble, resulting in poor bioavailability [13,16]. Phenolic acids are used extensively in the manufacturing of functional meals [17] due to their beneficial biological properties.



**Figure 2.** Types of flavonoids and some representative molecules of those classes.

2.2 Health Advantages of Polyphenols

Plant-based polyphenols offer multiple health benefits to humans. Incorporating these ingredients into foods has the potential to improve people's health due to their high antioxidant and antibacterial content, as well as their accessibility and biocompatibility. Some of the positive benefits of plant polyphenols (particularly flavonoids) on human health are presented in Table 1, illustrating the potential use of polyphenols in food compositions. Functional foods rich in polyphenolic compounds may play a significant role in lowering the rates of diabetes, hypertension, and cancer.

**Table 1**. Flavonoid subclasses found in the diet along with their food sources [2]

|  |  |  |
| --- | --- | --- |
| Flavonoid Subclass | Representative Flavonoids | Food Sources |
| Flavanol | Catechin, epicatechin, epigallocatechin-3-gallate | Tea |
| Flavanone | Naringin, naringenin, herperidin | Citrus fruits, oranges, grapefruits, lemons |
| Anthocyanins | Cyanidin, peonidin | Blackberry, blueberry, cherry, strawberry |
| Flavones | Chrysin, apigenin,  luteolin | Celery, green peppers, parsley, peppermint |
| Flavonols | Kaempferol,  quercetin,  myricetin, rutin | Blueberries, apple, cabbage, broccoli, cherries, garlic, onion, tea, red wine |
| Isoflavonoids | Daidzein, genistein, glycitein | Legumes, soy |

2.3 Antioxidant properties

Plant polyphenolic chemicals have significant antioxidant action due to their distinctive molecular structure. Polyphenols are an example of an antioxidant that can prevent DNA damage. Cancer risk is reduced by EGCG because it inhibits reactive oxygen species (ROS) production, and in vitro research shows that it hastens programmed cell death by reducing DNA synthesis in cancer cells without impacting healthy ones [2,3]. Human colon cancer cell lines HCT-116 and SW-480 have their development slowed by EGCG due to their phenolic composition [2,3]. Cell signaling system components protein kinase B (Akt) and c-Jun N-terminal kinase (JNK) are involved in EGCG's regulation of oxidative stress-induced apoptosis [2]. The antioxidant defense system of a cell is strengthened by EGCG because it stimulates the expression of genes in the antioxidant response element (ARE) and mitogen-activated protein kinase (MAPK) pathways [2,3]. Important cellular pathways for antioxidants in the body include nuclear factor-kappa B (NF-kB), nuclear factor-erythroid 2-related factor 2 (Nrf2), and others [2,3]. Increased serum levels of antioxidant enzymes such as catalase (CAT), glutathione peroxidase (GSH-Px), and superoxide dismutase (SOD) have been linked to EGCG's anti-oxidant effects [2,18]. Clinical results from a study [19] suggest that patients undergoing radiation therapy for esophageal cancer who also suffer from acute radiation-induced esophagitis (ARIE) may benefit from taking an EGCG solution orally [2] from the available databases. While EGCG does not boost radiation's effectiveness, it may mitigate some of the risks involved [19]. Patients with chronic lymphocytic leukemia (CLL) who took EGCG in the Polyphenon E formulation once daily over the duration of the trial reported no adverse events [20]. Absolute lymphocyte count (ALC) and/or lymphadenopathy improved significantly over time for the great majority of patients. New, potentially more effective oral EGCG formulations are now in research and development [20]. Research and published literature suggest that plant polyphenols have powerful antioxidant properties that could be used to improve human health [2].

2.4 Anti-inflammatory properties

Plant polyphenols have the ability to hinder and eliminate some inflammatory cells via interacting with cytokines and their receptors, or by altering the release of cytokines. As per the study [21], hydrogels containing rutin showed comparable anti-inflammatory efficacy to conventional medications. Scientists have analyzed the anti-inflammatory effects of hesperidin by studying its impact on RAW264.7 cells and a model of acute liver injury induced by CCl4. The findings demonstrated that the compound effectively suppressed the production of nitric oxide (NO), interleukin 6 (IL-6), and tumor necrosis factor-alpha (TNF-α) in both laboratory experiments and living organisms. Scientific research has demonstrated and verified that polyphenols possess the ability to safeguard the body against inflammation [2].

2.5 Anti-cancer properties

Specific types of cancer exhibit greater susceptibility to the preventative benefits of polyphenols. Furthermore, apart from inhibiting tumor growth, their cytotoxic properties can induce apoptosis in cells. A study discovered that resveratrol possesses inhibitory properties on cell development, induces apoptosis, and exhibits favorable antioxidant features [22]. These effects have the potential to modify the progression of cancer and associated illnesses. The paper emphasized the extensive utilization of quercetin for treating and preventing esophageal cancer [22]. Additional studies have discovered that polyphenolic compounds, including EGCG, genistein, naringin, and curcumin, have anti-cancer properties [23,24,25,26]. These polyphenols have the ability to eradicate cancer cells by modifying signaling pathways, obstructing cell cycle events, and triggering apoptosis, among other methods to combat cancer. Polyphenol regulation also targets enzymes involved in the proliferation of tumor cells. Current studies indicate that natural polyphenols possess anti-cancer properties through many pathways, such as their capacity to impede angiogenesis, metastasis, and DNA interaction [27,28].

2.6 Antimicrobial properties

Polyphenols exhibit potent antibacterial properties against a wide range of bacterial strains. Flavonoids exhibit significantly higher antibacterial activity compared to other polyphenolic compounds. According to certain research, polyphenolic compounds can synergistically enhance the effectiveness of antibiotics against bacteria. Curcumin applied to chitosan films showed potent antibacterial effects against Staphylococcus aureus and Rhizopus solani [29]. The antibacterial action of tea polyphenols (EGCG, EGC, ECG), silymarin, and rutin has been extensively documented and verified in multiple investigations [30,31]. The aforementioned polyphenols reduced cellular viability, extracellular DNA, and exopolysaccharide levels. The therapy resulted in a moderate reduction in bacterial adhesion to human keratinocytes. These polyphenols hindered the mechanism of membrane permeability [29,30,31,32].

2.7 Anti-hypertensive properties

Polyphenolic chemicals, specifically those present in cocoa, such as flavanol components like catechins and proanthocyanidins, have been associated with enhanced endothelial function, reduced oxidative susceptibility of low-density lipoproteins, and increased vasodilation. The European Food Safety Authority (EFSA) extensively recognizes the impact of polyphenols. The study extensively discusses the beneficial effects of several polyphenolic compounds on vasodilation and other mechanisms involved in blood pressure control [33]. A study revealed that curcumin, amlodipine, and a combination of both substances exhibited vasodilatory effects in isolated rat aortic rings. The co-delivery of curcumin and amlodipine resulted in a more potent vasorelaxant effect compared to the treatment of amlodipine alone [34]. These findings indicate that individuals with hypertension who are prescribed amlodipine can ingest curcumin without compromising the drug's antihypertensive properties, whether for dietary or medicinal purposes [34].

**3. Bioavailability of Polyphenols**

There is no relationship between the amount of polyphenols present in food and their ability to be absorbed and utilized by the body. Polyphenols, when ingested, enter the bloodstream through the digestive mucosa and then reach the desired tissues. Several research validates the increasing fascination with nutraceuticals [35]. One's food habits have a dramatic impact on the regulation of multiple metabolic activities. Food serves as more than mere sustenance for the body's metabolic functions; it also contains bioactive compounds that exert beneficial effects on health, such as antioxidants, vitamins, polyunsaturated fatty acids, and fiber. Therefore, consuming a nutritious diet and its various components can enhance individuals' well-being, reduce their susceptibility to specific ailments, and overall enhance their standard of living [36,37,38].

The types of molecules that have been extensively researched for their physiological activity include fatty acids and lipids, substances based on amino acids, carbohydrates, fiber, derivatives of isoprenoid, and phenolic compounds. When evaluating the bioavailability of these beneficial compounds [39,40,41], it is important to consider their intestinal absorption and bio-accessibility. Polyphenols exert a regulatory impact on the gut microbiota by inhibiting harmful bacteria and promoting beneficial bacteria, thus benefiting the overall health of the host. The mucus layer, composed of epithelial cells, can function as a barrier for some nutraceutical compounds, hence restricting their absorption following consumption [42]. However, bioactive compounds have beneficial effects on human health when they are absorbed from food and become soluble in the fluids of the gastrointestinal tract.

Microencapsulated bioactive molecules, such as flavonoids, phenolic compounds, antioxidant molecules, carotenoids, and general plant metabolites, are types of nutraceutical chemicals that can be easily absorbed by the body. Active compounds, such as pigments, antioxidants, vitamins, minerals, peptides, and proteins, are effectively shielded and stabilized, and their capacity to be absorbed and utilized by the body is enhanced and regulated using micro/nano-encapsulation techniques. Nutraceuticals are more resilient to the challenges of the digestive system, allowing them to effectively interact with it and maintain their solubility and bioavailability [43,44,45].

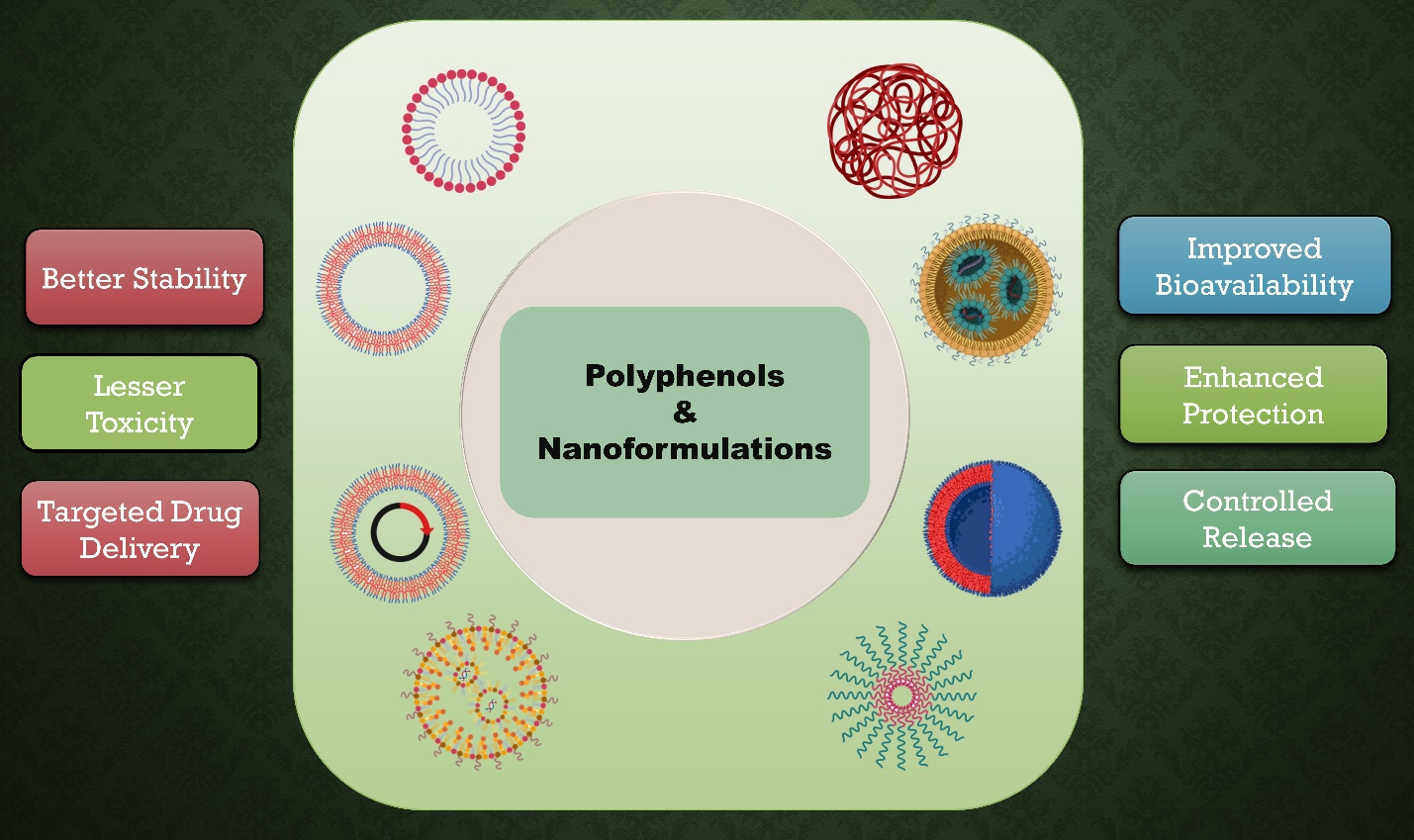
Apples and berries are examples of fruits that have a polyphenol content above 200 mg per 100 g of fresh fruit [46]. The quantity and capacity of these phenolic compounds to be absorbed by the body, however, are influenced by the specific method(s) of food processing employed. For example, as numerous food-processing methods involve the use of heat, it is often observed that exposure to higher temperatures might have a detrimental impact on the nutritional composition of fruits and vegetables. However, certain studies have discovered contradictory results [47]. A systematic examination of approximately more than 150 polyphenols and associated food-processing modifications revealed that domestic cooking leads to substantial reductions in polyphenols, with significant variance observed among different meals. Moreover, the study revealed that the food being examined had a greater impact than the method employed, highlighting the importance of the food matrix [48]. The transformation of polyphenolic compounds during food processing is influenced by numerous factors, such as the specific food-processing methods used in both commercial and domestic kitchens. This relationship is briefly examined in this discussion.

Heat treatments are commonly employed both in domestic settings and in industrial food-processing facilities. These preparations can be executed using cooking techniques such as stovetop cooking, microwave cooking, and steam oven cooking. Toasting, coffee roasting, drying, canning, pasteurizing, and sterilizing are all instances of prevalent heat-dependent transformation techniques. The fate of polyphenols under heating is contingent upon the specific processing procedure employed. Heat enhances the release of phenolic chemicals that are otherwise trapped in the plant by breaking down cell walls [49]. However, they have a higher susceptibility to oxidation, and only a limited number of them exhibit true thermostability. The polyphenol compositions of foods exhibit variations based on the duration of boiling. As an example, kale leaves experienced a 51% reduction in their polyphenol content after undergoing blanching (a brief boiling process), with caffeic acid showing the smallest decrease (28%) and ferulic acid showing the largest decrease (55%). Nevertheless, the overall polyphenol content experienced a reduction of 73% because of the heightened destruction resulting from prolonged cooking durations [50].

In order to improve the absorption and health benefits of dietary polyphenols, it is essential for future research and analyses to explore the potential of alternative methods to optimize processing conditions for different food compositions [51,52,53,54].

**4. Nanoformulations composed of dietary macromolecules for the encapsulation and transportation of polyphenols**

Dietary proteins possess a distinct characteristic of exhibiting a remarkable affinity with different medications or nutraceuticals. This quality makes them an excellent and renewable source material for fabricating nanocarriers used in the administration of medication or nutraceuticals (Figure 3). Food proteins offer numerous health benefits and advantages, including their antigenicity and biodegradability. Protein nanoparticles can be easily synthesized and produced on a large scale with minimal obstacles [55,56]. The following text provides a review and discussion of commonly utilized food-grade proteins in the creation of nanoparticle delivery systems for encapsulating dietary polyphenols. These could facilitate the enhanced assimilation of polyphenols in the human body.



#### Figure 3. Benefits of utilizing various nanoformulations based on polyphenols.

#### 4.1 Casein Nanoformulations

Caseins with a high proportion of proline and an open structure have distinct regions that are hydrophobic and hydrophilic. Caseins, comprising 95% of the composition, undergo spontaneous self-assembly to form casein micelles. These micelles are colloidal particles that have a spherical shape and range in size from 50 to 500 nm, with an average size of 150 nm [57]. Curcumin's solubility was significantly enhanced via hydrophobic interactions, resulting in a minimum 2500-fold increase when incorporated into camel β-casein micelles. The antioxidant activity of curcumin is higher when it is encapsulated in a β-casein micelle compared to when it is in its free form together with β-casein. The K-562 cell line, which is a kind of human leukemia cell, exhibited greater sensitivity to curcumin when it was encapsulated compared to when it was in its free form [57]. The researchers examined the spray-dried curcumin-loaded casein nanoparticles, which were produced by dissolving sodium caseinate and curcumin in a warm aqueous ethanol solution [58]. The antioxidant and cytotoxic effects of curcumin with casein nanoparticles were shown to be stronger compared to pure curcumin. The researchers have suggested a cost-effective and energy-efficient encapsulation technique that does not require the use of organic solvents. This method relies on the pH-dependent solubility of curcumin and the self-assembly properties of sodium caseinate [58]. Curcumin was encapsulated within self-assembled casein nanoparticles by neutralization at a pH of 12 and a temperature of 21 °C. Curcumin, when encapsulated in casein nanoparticles, enhanced the development of colorectal and pancreatic cancer cells in humans [58]. Casein was found to enhance the stability of curcumin when attached to it at a pH of 7.2, as noted by another research group [59]. The interaction between curcumin and casein did not influence the hemolysis prevention effect of curcumin [59]. This demonstrates a really encouraging approach to the absorption of polyphenols.

4.2 Gelatin Nanoformulation

Gelatin is a protein derived from collagen that undergoes denaturation through acid and alkaline hydrolysis. The Food and Drug Administration has approved its use in pharmaceuticals, cosmetics, and food products for several years without any reported safety concerns. The study found that gelatin-based nanoparticles containing EGCG effectively inhibited intracellular signaling caused by hepatocyte growth factor in MBA-MD-231 breast cancer cells, similar to the effects of free EGCG [60]. Furthermore, it was noted that the combination of high concentrations of resveratrol-loaded gelatin nanoparticles led to cell death via modifying the expression of p53, p21, caspase-3, Bax, Bcl-2, and NF-κB [61]. According to the observations, it is feasible to utilize polyphenols in conjunction with gelatin for the treatment of life-threatening illnesses like cancer.

4.3 Food Polysaccharide Nanoformulations

Polysaccharides play a role in determining the texture, flavor, and caloric content of food. Glycosidic connections connect individual monosaccharide units to form polysaccharides. The bio adhesion of polysaccharides, particularly on mucosal surfaces, has been utilized to specifically target organs or cells and prolong the presence of polyphenols in the colon. Chitosan is a commonly utilized polysaccharide in nanoparticle systems for oral delivery [62]. The most widely distributed biopolymer is a positively charged, non-toxic, biodegradable, and biocompatible polyelectrolyte with a lethal dose (LD50) when taken orally in mice of more than 16 g/kg [62]. Japan, Italy, and Finland have granted approval for its use in diets. It enhances the uptake of active compounds in the intestines, particularly water-soluble molecules such as EGCG that have limited permeability in the small intestine. Chitosan exhibits strong interactions with polymers that carry a negative charge and can be altered with different functional groups to acquire features that enable nanoparticle targeting [62].

4.4 Conjugated Protein-Polysaccharide Nanoformulations

The Maillard reaction generates glycosylated proteins that prevent protein precipitation caused by high concentrations or interaction with polyphenols, which are materials used for polyphenol encapsulation [63]. The gelatin-dextran conjugate nanoparticles produced through the Maillard reaction included tea polyphenols in their protein core. The EGCG-loaded conjugate nanoparticles exhibited a mean diameter of 86 nm and a narrow distribution under optimal conditions. EGCG exhibits a loading capacity of 360 wt.% and its encapsulation effectiveness is not affected by changes in pH. In the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) experiment, encapsulated EGCG demonstrated cytotoxicity against MCF-7 cells that was either equal to or greater than that of free EGCG [64]. The dextran-glycosylated casein nanoparticles effectively encapsulated and preserved EGCG, exhibiting excellent stability as colloidal particles over a wide range of concentrations during storage. EGCG was safeguarded by glycosylated casein in an alkaline pH environment and exhibited controlled release in the intestinal fluid [64]. The Maillard process was used to link dextran and bovine serum albumin, resulting in the formation of EGCG for protein glycosylation [65].

4.5 Dietary Lipid-based Nanoformulations

Solid lipid nanoparticles (SLNs) enhance the solubility and bioavailability of lipid-soluble polyphenols. The delivery of curcumin was investigated in a coculture system consisting of absorptive Caco-2 cells and mucus-secreting HT29-MTX cells using solid lipid nanoparticles (SLN). It was observed that curcumin encapsulated in SLN exhibited superior delivery compared to unencapsulated curcumin while maintaining the integrity of cellular junctions [66]. A separate investigation discovered that solid lipid nanoparticles (SLNs) containing curcumin demonstrated the capacity to extend the effectiveness of anticancer treatment in laboratory conditions, enhance cellular absorption, and improve the availability of the drug in living organisms [67]. In a study, resveratrol was incorporated and enclosed within two types of solid lipid nanoparticles (SLN) [68]. Resveratrol caused a modification in the crystal structure of the nanoparticle, indicating its entrapment. Resveratrol mostly remained associated with lipid nanoparticles when exposed to digestive juices throughout incubation [68]. A study developed solid SLNs using glyceryl behenate as a substrate to encapsulate and disperse resveratrol [69]. The cytotoxicity assay demonstrated that Resveratrol-loaded Solid Lipid Nanoparticles (SLNs) had comparable efficacy to free Resveratrol as an anticancer agent. In a study examining the distribution of resveratrol in Wistar rats, it was found that solid lipid nanoparticles (SLNs) significantly enhanced the amount of resveratrol in the brain (p < 0.001) [69]. Resveratrol-loaded solid lipid nanoparticles (SLNs) containing stearic acid and coated with poloxamer 188 were effectively manufactured using a solvent diffusion–solvent evaporation method. These nanoparticles demonstrated prolonged release of the medication in a laboratory setting for up to 120 hours. The lipid formulation significantly enhanced the oral bioavailability of resveratrol by a factor of eight, as demonstrated in comparison to the alternative solution [70]. The solubility, stability, and intracellular transport of resveratrol enhanced after being loaded into SLNs. Regardless of the presence or absence of resveratrol, submicron lipid nanoparticles (SLNs) with a size below 180 nm rapidly traversed the cell membrane, dispersed throughout the cytoplasm, progressively traveled among several cellular levels, and localized in the perinuclear region without causing any harm to the cells. The cytostatic effect of resveratrol in solution was lower compared to SLN-resveratrol. The administration of Resveratrol by SLN may boost its effects in suppressing cell growth [71]. Thus, it may be inferred that nanoformulations utilizing dietary lipids can be regarded as a dependable means of delivering polyphenols.

Thus, it can be inferred that polysaccharides, whether in isolation or bound to proteins, are frequently used for the nanoencapsulation of quercetin, EGCG, and resveratrol, as outlined in Table 2. The polyphenolic compounds were encapsulated at the nano level to preserve their physicochemical stability and inherent properties, including antibacterial, anticancer, antioxidant, and antiproliferative action. In addition, the process of nanoencapsulation can enhance the rate at which substances are released in the intestines, increase their bio accessibility and bioavailability, prevent degradation in the gastrointestinal tract, ensure stability during storage and protect color, be used in food packaging, improve thermal stability, and enable oral administration of these compounds.

**Table 2.** Nanoformulations consisting of several polyphenolic chemicals [72]

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Polyphenol | Method | Encapsulating material | Size (nm) | Result |
| Quercetin | Self-assembly | Hohenbuehelia serotina polysaccharides | 360 | Stability and anti-proliferative effects following GI digestion in vitro |
| Anthocyanin | Ionic gelation | Chitosan Beta Lactoglobulin | 580 | Longevity of storage and resistance to oxidation during in vitro digestive models |
| Malvidin | Emulsification | Soybean insoluble dietary fiber | 300 | Long-term durability and safeguarding against color degradation |
| EGCG | Ionic gelation | Chitosan and Beta Lactoglobulin | 100 - 500 | Administer EGCG within the gastrointestinal tract |
| Anthocyanin | Self-assembly | Pectin – Whey Protein Isolate | 200 | Enhanced stability |
| Olive leaf polyphenol | Nanoemulsion | Pectin – Whey Protein Concentrate | 347 | Enhanced antioxidant capabilities and accelerated release rate |
| Pomegranate peel extract polyphenol | Nanoemulsion | Pectin - Cellulose | 200 | Enhanced antimicrobial efficacy |
| Resveratrol | Antisolvent precipitation and electrostatic deposition | Pectin | 120 | Antioxidant, bioavailability, and stability |
| Quercetin and Resveratrol | Antisolvent precipitation | Zein-Caboxymethyl cellulose | 217 | Temperature Stability |
| EGCG | Ionic cross-linking | Carboxymethyl chitosan | 400 | Enhanced the efficacy of tumor suppression |

**5. Polyphenol Nanoformulations with Enhanced Therapeutic Effects**

5.1 Cardioprotective action

Oxidative stress is widely believed to play a significant role in the pathogenesis of cardiovascular disease. Both acute and chronic heart failure are linked to elevated levels of oxidative stress and a reduced capacity for antioxidants [73]. Polyphenols have the ability to safeguard against oxidative-related illnesses, such as cardiovascular disease, including ischemic heart disease, and stroke caused by atherosclerosis. Several studies [74,75] have demonstrated that polyphenols have a protective effect on the heart against illnesses caused by oxidative stress. A layer of a bioactive polymer (PLGA) was applied onto a superparamagnetic SiN.SiN@QC-PLGA nano-bio-composite [76] to alter the drug release pattern and enhance its similarity to the local myocardial tissue. This modification facilitates the recruitment, expansion, attachment, and interaction of cardiac proteins with the composite material. A study has examined the efficacy of newly developed nano-formulated natural treatments in combating hypertension, atherosclerosis, thrombosis, and myocardial infarction [77]. A recent study investigated the cardioprotective effects of a curcumin nanoformulation on cardiomyocytes [78]. The compound Cur-Res-mP127, which consists of curcumin and resveratrol loaded in Pluronic® F127 micelles at a molar ratio of 5:1, was discovered to have cardioprotective effects in a rat embryonic cardiomyocyte (H9C2) model. It achieved this by decreasing apoptosis and reactive oxygen species (ROS) levels [78].

5.2 Neuroprotective action

Oxidative stress occurs when an excessive amount of free radicals is generated, overpowering the antioxidant system. Superoxide anions, hydroxyl radicals, hydrogen peroxide radicals, and peroxyl radicals are all instances of reactive oxygen species. As the most metabolically active organ in the body, the brain consumes 20% of the total baseline oxygen and experiences one of the highest levels of oxidative stress [79]. Endogenous mechanisms that neutralize oxidative damage consist of catalase, glutathione/glutathione peroxidase, superoxide dismutase, and vitamins E and C, among other substances. In numerous disorders, oxidative stress is intensified due to the excessive creation of free radicals beyond the body's defensive mechanisms. Neurodegenerative illnesses commonly exhibit elevated levels of oxidative stress in the brain [80]. The diseases encompassed in this list are Parkinson's disease, Alzheimer's disease, Huntington's disease, multiple sclerosis, traumatic brain injury, ischemia, and the process of aging. Research has demonstrated that polyphenols possess neuroprotective advantages by reducing oxidative stress in the brain [81]. Cerium oxide nanoparticles are currently under assessment for their potential application in biomedicine, owing to their robust regenerative antioxidant properties. These properties have resulted in their extensive utilization in the materials industry. Scientists are conducting research on cerium oxide nanoparticles due to their potential as a therapeutic option for several neurological disorders [82]. The study investigated the neuroprotective properties of CeO2@SiO2-PEG nanoparticles (CSP-NPs) in delivering proanthocyanidin and curcumin [83]. Curcumin (Cur), which is water-loving, and proanthocyanidin (PAC), which is water-repelling, were separately attached to CeO2@SiO2-PEG nanoparticles to create Cur-NPs and PAC-NPs. Curcumin nanoparticles (Cur-NPs) and polymeric micelles containing curcumin (PAC-NPs) suppressed the activity of acetylcholinesterase (AchE) and shielded neurons from the harmful effects of A1-42 in PC-12 cells. Multiple studies have documented various nanoparticle systems containing curcumin. The systems encompass poly (-caprolactone) (PCL), poly (lactide-co-glycolide) (PLGA), and methoxy poly (ethylene glycol) poly (-caprolactone) (MPEG-PCL). The inclusion of curcumin into nanoparticle systems enables the prevention of enzymatic and pH degradation of curcumin, as well as the demonstration of its neuroprotective potential [84]. An effective and secure therapeutic strategy for addressing Alzheimer's disease could involve the creation of PEGylated PLGA nanoparticles with a combination of EGCG and acetyl acid medications. The administration of EGCG/ascorbic acid NPs orally resulted in the accumulation of the chemical in many organs, including the brain. Studies have demonstrated that this formulation has the capacity to enhance the drug's longevity in both the bloodstream and the brain [85]. A study has discovered that the use of 4-hydroxyisophthalic acid (4-HIA)-encapsulated PLGA-NPs resulted in a considerable decrease in the harmful effects of H2O2 on PC12 cells [86]. Therefore, the use of nanoformulations with polyphenols has been proven to have significant neuroprotective effects.

5.3 Anti-cancer action

Cancer is characterized by the unregulated proliferation of cells, resulting in the development of malignant tumors that pose a significant risk of mortality and impose substantial financial burden on patients and the healthcare system. Natural polyphenols have conventionally been utilized for the treatment and prevention of several ailments. Therefore, because of their ability to combat cancer, these phytochemicals can potentially serve as chemotherapeutic and chemopreventive medications for many types of malignancies [87]. The study investigated the cytotoxic properties of curcumin-loaded PLGA nanoparticles combined with anti-P-glycoprotein in human cervical cancer KB-3-1 and KB-V1 cells. The findings demonstrated enhanced solubility and cellular uptake of curcumin, along with reduced cell viability [88]. In order to initiate PTT-assisted ferrous therapy for cancer treatment, the researchers in developed nanoparticles that are coordinated with ferric polyphenols [89]. The combination of ellagic acid, schizophyllan, and chitin nanoparticles demonstrates anti-cancer properties in MCF-7 breast cancer cells [90]. The viability experiments demonstrated a considerable inhibition of proliferation in MCF-7 cells, with a greater effect observed at higher dosages. A recent study revealed the process of nanoencapsulating quercetin and curcumin in a model based on casein [91]. The effectiveness of these chemicals against MCF-7 cell lines was then examined. The encapsulated polyphenols had a greater inhibitory effect on tumor cell proliferation compared to the unencapsulated polyphenols. The cerium nanoparticles produced by the environmentally friendly method exhibited all the characteristic features of a functional nanoparticle and enhanced the expression of the genes responsible for the two primary antioxidant enzymes, catalase (CAT) and superoxide dismutase (SOD). Cerium oxide nanoparticles (CeO-NPs) exhibited enhanced cytotoxicity against breast cancer cells in comparison to normal cells. CeO-NPs demonstrated the ability to safeguard healthy cells against oxidative stress and inflammation induced by free radicals, making them a potentially effective therapeutic agent for treating breast cancer cells [92].

**6. Nanoformulations Derived from Polyphenols: The Bigger Picture**

In the future, it is necessary to overcome several significant concerns in order to accelerate the development and clinical application of nanoformulations containing polyphenols. The production of nanoformulations containing polyphenols necessitates the creation of uncomplicated and universal techniques, together with the implementation of logical design and synthesis that may be tailored to specific needs. Gaining a deeper understanding of the properties and capabilities of materials is crucial. The present nanoformulations incorporating polyphenols possess several limitations, such as insufficient physiological stability and biodegradability, suboptimal drug encapsulation and loading efficiency, limited reactivity to stimuli, inadequate traceability, and a lack of active targeting capability. The combination of chemical grafting and supramolecular self-assembly has the potential to generate novel viewpoints. Polyphenol-containing nanoformulations have emerged as a promising platform for cancer combination therapy. Potential advancements in anticancer strategies could be achieved by creating multifunctional nanoplatforms based on polyphenols that combine different cancer treatment methods, including chemotherapy, radiation, and immunotherapy. Additional investigation is required to explore the various possible medicinal applications of nanoformulations using polyphenols. Although the majority of research has focused on cancer treatment, polyphenols have demonstrated several health advantages that extend to the prevention and management of bacterial infections, neurological illnesses, cardiovascular issues, diabetes, and various other ailments. Moreover, it is expected that the nanoformulations containing polyphenols will have the capacity to incorporate diverse enzymes for the aim of biocatalysis. There should be a greater emphasis on incorporating imaging agents (such as fluorescence probes, MRI agents, and radioactive agents) into different disease treatments. It is essential to conduct systematic evaluations of the safety and fate within a living organism of nanoformulations that contain polyphenols. Research on nanoformulations including polyphenols should prioritize investigating their capacity to specifically target tumor or inflamed tissues, long-term toxicity, ability to degrade in vivo, renal clearance, and interaction mechanisms with biological systems.

It is crucial to comprehend the interactions between these polyphenol-containing materials and blood, immunological, and normal tissue cells in order to guarantee their safe utilization in therapeutic situations. Furthermore, it is recommended to do additional biosafety assessments in the future using animal models. Research on nanoformulations containing polyphenols has been focused on in vitro or pilot animal experiments. The potential for polyphenol-containing nanoformulations to cause cancer, genetic damage, mutations, harm to reproductive health, and birth defects, as well as other relevant clinical effects, is mostly uncertain.

Presently, the predominant techniques, such as ionic gelation and emulsification, are employed in conjunction with well-established procedures to fabricate nanoformulations. These procedures need more complex implementation and may necessitate more stringent reaction conditions or the inclusion of additional chemicals, both of which contribute to the cost of preparation. Electrostatic spinning and electrostatic spraying are emerging technologies that show promise for enhancing the manufacturing of nanoformulations in the future. These technologies employ simple techniques and mild reaction conditions to achieve more efficient production.

Ultimately, polyphenol-based nanoformulations hold great potential in the field of biomedical research due to their adaptable structures, straightforward production process, and few harmful effects. If these problems can be successfully addressed, then these nanoformulations will offer researchers powerful resources to address some of the most challenging scientific and technical obstacles in the biomedical field. This study aims to offer readers a comprehensive grasp of the current status of polyphenol-containing nanoformulations in the field of biomedicine. It also seeks to inspire further research in this domain and guide the development of innovative functional materials that incorporate polyphenols.

**7. Conclusion**

The phenolic chemicals, including EGCG, resveratrol, curcumin, and quercetin, are present in plants in significant amounts and exhibit diverse advantageous biological activities. In addition, the compounds' inadequate stability, solubility, and bioavailability greatly restrict their application in the fields of food and medicine. Nanoparticle encapsulation enables enhanced targeting precision, controlled release, and the ability to bypass existing limitations. Nanotechnology offers an optimal method for enhancing the pharmacokinetics and bioavailability of polyphenols. Nanoparticles possess highly desirable characteristics as carriers, but it is crucial to carefully evaluate and address their potential side effects and toxicity prior to their application in a therapeutic context. It is crucial to comprehend the hazardous side effects associated with the accumulation of nanoparticles in the physiological system, as polyphenols, which are natural substances, need to be consumed over a prolonged duration for the treatment and prevention of diseases. More precisely, if the nanoparticles have a low encapsulation efficiency, this will occur. Therefore, it is necessary to create standardized models for testing nanoparticles both in laboratory settings (in vitro) and in living organisms (in vivo). Additionally, the safety testing techniques for in vivo experiments must be validated to ensure the successful creation and use of nanoparticles that are advantageous for human health.

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