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FROM FUNCTIONAL FOODS TO PHARMACEUTICAL NUTRACEUTICALS: ADVANCES IN POLYPHENOL DELIVERY SYSTEMS, BIOAVAILABILITY, AND THERAPEUTIC APPLICATIONS

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ABSTRACT
Polyphenols are bioactive compounds and have a variety of pharmaceutical properties, such as antioxidant, anti-inflammatory, anticancer, cardioprotective, neuroprotective and antidiabetic effects. Yet, these are in need of improvement due to their poor aqueous solubility, bioavailability, rapid metabolism, and limited stability for clinical applications. This review highlights recent developments of pharmaceutical strategies that could be used to overcome these shortcomings and enhance the therapeutic potential of polyphenols. The literature search was performed to identify peer-reviewed publications on PubMed, Scopus, Web of Science, ScienceDirect, Google Scholar, and SpringerLink between 2015 and 2025 to retrieve articles. The relevant studies were screened and the relevant literature critically synthesized to assess the progress made in polyphenol bioavailability, drug delivery systems and therapeutic applications. In recent years, the desired bioavailability and therapeutic efficacy of polyphenols has been achieved through their formulation in nano-systems such as liposomes, phytosomes, polymeric nanoparticles, solid lipid nanoparticles, nano-emulsions, micelles, and cyclodextrin inclusion complexes, which have improved the stability, absorption, controlled release, and targeted delivery of polyphenols. Notwithstanding these developments, there is a need to address the issues of scale up manufacturing, regulatory approval, long-term safety and clinical validation. Going forward, development of formulation science and nanotechnology will make it easier to progress polyphenols in the realms of functional food components to actual pharmaceutical nutraceuticals for prevention and management of chronic diseases.

KEYWORDS: Polyphenols, Pharmaceutical nutraceuticals, Bioavailability, Nanoencapsulation, Drug delivery systems, Nanotechnology

INTRODUCTION
Polyphenols are one of the largest and most structurally diverse classes of plant secondary metabolites, with over 8,000 compounds found in fruits and vegetables, cereals, legumes, tea, coffee, cocoa, herbs and spices and various medicinal plants. These include the flavonoids, phenols acids, stilbenes and lignans, which all have critical physiological functions in plants as a protection against environmental stress, pathogens and ultraviolet damage, as well as a role in pigmentation, growth and defense. The dietary polyphenols have gained significant research interest in the last few decades due to their potential in human health promotion and for reducing the risk of chronic non-communicable diseases.(El-Saadony et al., 2024) In the era of greater prevalence of cardiovascular diseases, diabetes mellitus, obesity, neurodegenerative diseases, cancer and chronic inflammatory diseases worldwide, its search for naturally occurring bioactive compounds to complement conventional therapeutic approach has gained a tremendous momentum. Due to their various biological activities, such as antioxidant, anti-inflammatory, antimicrobial, cardioprotective, neuroprotective, antidiabetic, and anticancer properties, polyphenol rich foods are considered as a key ingredient in functional foods and nutraceuticals. Dietary polyphenols are generally considered safe, whereas many of the synthetic pharmaceuticals have been linked to undesirable side effects after long-term use, and have multiple functions that affect multiple physiological pathways. These properties have made polyphenols good candidates for prevention of disease and health promotion (El-Saadony et al., 2024; Quesada-Vázquez et al., 2024). There are a wealth of experimental and epidemiological studies documenting the therapeutic benefits of polyphenols, but attempts to translate these findings into clinically viable nutraceuticals and/or pharmaceutical products are still challenging. Most

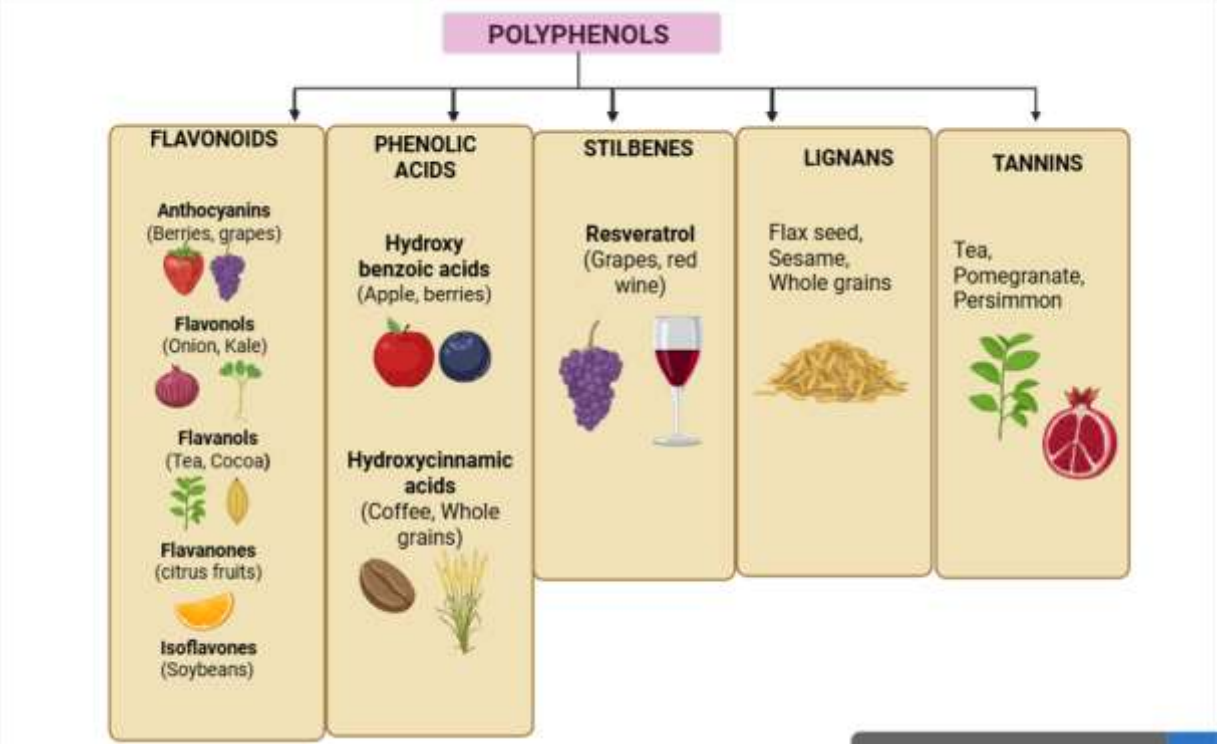
polyphenols found in nature are poorly soluble in water, have limited intestinal permeability, and are unstable to gastrointestinal metabolism, phase II metabolism, and food processing, and are extensively metabolized in the liver during the first-pass. As such, systemic activity of the ingested dose of the agent is greatly reduced, and only a small amount actually enters systemic circulation in its active form. Besides, significant inter-individual differences among the variability of absorption, metabolism and excretion (extensively dependent on gut microbiota composition, genetic polymorphisms, age, dietary habits and physiological status) make it more complex to predict clinical responses after polyphenol intake(Favari et al., 2024; Tomas et al., 2025). These pharmacokinetic challenges have led to the search for more than just bioactive polyphenols; advanced pharmaceutical strategies are being developed to enhance the stability, bioavailability, targeted delivery, and therapeutic efficacy of these compounds. New technologies have been developed for pharmaceutical sciences that allow the development of innovative delivery platforms such as liposomes, phytosomes, polymeric nanoparticles, solid lipid nanoparticles, nanostructured lipid carriers, nanoemulsions, micelles, cyclodextrin inclusion complexes, hydrogels or other nanoencapsulation technologies. These delivery systems help to safeguard polyphenols against degradation, increase gastrointestinal uptake, maintain longer circulation in the body, control release and target specific tissues, significantly boosting the therapeutic potential of polyphenols. These new technological developments are reshaping the traditional view of dietary polyphenols as food components to new, next-generation pharmaceutical nutraceuticals that have further clinical application(Aatif, 2023; Sahraeian, Rashidinejad and Golmakani, 2024; Kalita et al., 2025)**.** The opportunities for polyphenols to be incorporated in formulations with functional properties for specific diseases have been further extended by the parallel developments that have taken place in nutraceutical science, nanotechnology, biomaterials engineering and precision medicine. New formulation strategies are increasingly directed towards enhancing the pharmacokinetic performance of the drug with maintaining the safety, scalability, regulatory compliance, and commercial feasibility. While there has been promising progress, there are still several challenges to overcome – such as manufacturing costs, formulation stability, long term toxicity assessment, regulatory harmonisation and successful translation of promising preclinical data to strong and compelling clinical evidence. To unlock the full pharmaceutical potential of polyphenol-based products, it is crucial to tackle these challenges(Peng and Shahidi, 2024).

The present review, unlike in most conventional reviews, takes a translational pharmaceutical view of the dietary polyphenols, not just their antioxidant qualities or potential therapeutic effects. It critically reviews the bioavailability challenges, recent innovations in delivery systems and formulation technologies, novel applications of advanced formulations, and the state of the art in clinical translation and commercialization of polyphenols as pharmaceutical nutraceuticals. The purpose of this review is to highlight the latest developments of food science, pharmaceutics and nanotechnology for the development of safer and more effective nutraceutical products of polyphenol origin that can be clinically relevant.

METHODOLOGY OF LITERATURE SEARCH AND DATA SELECTION

A thorough literature review was carried out to find peer-reviewed studies related to pharmaceutical applications of polyphenols. Articles published from 2015 to 2025 were searched from the electronic databases such as PubMed, Scopus, Web of Science, Science Direct, Google Scholar, and SpringerLink focusing on the most recent studies (2020–2025). The search strategy used was a combination of keywords and boolean operators such as "polyphenols", "functional foods", "pharmaceutical nutraceuticals", "bioavailability", "pharmacokinetics", "nanoencapsulation", "liposomes", "phytosomes", "polymeric nanoparticles", "solid lipid nanoparticles", "nanoemulsions", "micelles", "cyclodextrin inclusion complexes", "drug delivery" and "therapeutic applications". English-language articles were included if they were original research articles or review papers. Conference abstracts, editorials, letters, duplicate records, studies which were not in English language and those which did not contain sufficient scientific data or were not relevant to pharmaceutical formulation and therapeutic applications were not included. Selected articles were critically assessed, classified into thematic areas and synthesized to get a holistic overview over polyphenol classification, therapeutic applications, bioavailability challenges, advanced pharmaceutical delivery systems and future research directions.

CLASSIFICATION AND DIETARY RESOURCES



Error! Reference source not found. **Shows the classification and dietary sources of polyphenols.**

THERAPEUTIC APPLICATIONS OF POLYPHENOLS

Due to their wide range of biological activities such as antioxidant, anti-inflammatory, antimicrobial, cardioprotective, antidiabetic, neuroprotective and anticancer, polyphenols have shown great promise as therapeutic agents. Epidemiological association of polyphenol-rich diet with lower risk of chronic diseases, but the application of polyphenols in the clinics has been limited due to their poor water solubility, chemical instability, high metabolism, and low oral bioavailability (El-Saadony et al., 2024; Rudrapal et al., 2024). In recent years, the use of polyphenols has been greatly extended, thanks to new technologies in the field of drugs. The incorporation of liposomes, phytosomes, polymeric nanoparticles, solid lipid nanoparticles, nanostructured lipid carriers, nanoemulsions and cyclodextrin inclusion complexes has increased their physicochemical stability and their resistance to the gastrointestinal tract, as well as their systemic circulation and tissue-specific delivery. Therefore, these pharmaceutical formulations have been evaluated to be more effective in treating various diseases in preclinical and emerging clinical research studies than conventional free polyphenols (Guo et al., 2024; Ozkan et al., 2024). Cancer is one of the most thoroughly-studied therapeutic areas. The antitumor effect of polyphenol loaded nanocarriers have been shown to be improved due to increased intracellular accumulation, induction of apoptosis, inhibition of tumor angiogenesis, inhibition of metastasis and overcoming of multidrug resistance. The advanced drug delivery systems, such as nanoformulations of curcumin, resveratrol, quercetin, and epigallocatechin gallate (EGCG), have proven to be more bioavailable and effective in terms of therapeutic responses when compared to their native counterparts, underscoring their potential role in cancer management (Aatif, 2023; Rudrapal et al., 2024). Another large application area for the polyphenol-based nutraceuticals is cardiovascular diseases. The advanced formulation has been found to benefit endothelial function, decrease oxidative stress, inhibit vascular inflammation and regulate lipid metabolism which helps in preventing hypertension, atherosclerosis and ischemic cardiovascular diseases. Improved bioavailability due to nanoencapsulation and lipid-based drug delivery systems may lead to greater systemic levels of bioactive polyphenols and potential for long-term cardioprotective benefits (Ciupei et al., 2024; El-Saadony et al., 2024). Pharmaceutical preparations of polyphenols also have shown great potential in the prevention and control of metabolic disorders, such as type 2 diabetes mellitus and obesity. Optimized delivery systems increase intestinal absorption and release, thus supporting glucose metabolism regulation, insulin sensitivity, reducing oxidative stress and chronic inflammation. The formulations may also have longer systemic action and precision targeting of metabolically active tissues, thereby exhibiting anti-diabetic effects.These formulations can also have prolonged systemic activity and precision targeting of metabolically active tissues, making them anti-diabetic (Guo et al., 2024; Rudrapal et al., 2024). Neurodegenerative diseases have special delivery challenges due to the blood–brain barrier (BBB) that impedes the delivery of many bioactive molecules. Polymeric nanoparticles, liposomes, and lipid nanoparticles have proven to be promising carriers for the targeted delivery of polyphenols to the brain by use of nanotechnology. These delivery systems can enhance the stability of the drug in the body, improve its blood–brain barrier penetration and boost the concentration of the drug in the neural tissues, which is beneficial for therapeutic applications in Alzheimer's disease, Parkinson's disease, and other neurodegenerative disorders (Aatif, 2023; Ozkan et al., 2024). In addition to systemic diseases, a wide range of therapeutic potential

of the polyphenol based pharmaceutical nutraceuticals has been seen in gastrointestinal health. Colon targeted delivery systems are used to ensure polyphenols are not exposed to the upper gastrointestinal tract, but are released in the intestine. These strategies have a beneficial effect on the therapeutic response in inflammatory bowel disease, colorectal cancer prevention, intestinal inflammation and modulation of gut microbiota. Recent studies indicate that the gut homeostasis is further improved by the use of the biopolymer-based nanosystems, which can improve the stability of polyphenol and its retention in the intestine and its release in a controlled manner (Guo et al., 2024; Tomas et al., 2025). Polyphenols also have been used topically in pharmaceutical formulations in dermatology and wound management. Hydrogels, nanofibers and polymeric dressings containing polyphenols have the ability to release the compounds at the wound site for a prolonged period of time, stimulate tissue regeneration, inhibit microbial growth and accelerate wound healing by boosting antioxidant and anti-inflammatory effects at the wound site. Such formulations have opened the doors to the use of polyphenols in local therapeutic interventions (Ozkan et al., 2024) besides their use in oral nutraceuticals.

All of these advances suggest that polyphenols can be successfully formulated to substantially enhance their therapeutic efficacy, overcoming some of their intrinsic pharmacokinetic limitations. Advances in research to date justify the shift of polyphenols from traditional functional food ingredients to clinically important pharmaceutical nutraceuticals with therapeutic potential in combating the spectrum of chronic diseases (Ali Redha, Kodikara and Cozzolino, 2024; Ciupei et al., 2024).

Table ***1*** Shows the summary of classification and therapeutic applications of polyphenols.

Table 1 Classification of dietary polyphenols according to chemical subclasses, representative compounds, major food sources, and reported therapeutic applications.

Class	Subclass	Representative compounds	Major dietary resources	Major therapeutic applications (citation)
Phenolic acids	Hydroxybenzoic acids	Gallic acid, Protocatechuic acid, Vanillic acid	Berries, pomegranate, tea, walnuts, cloves	Antioxidant, antimicrobial, anti-inflammatory, hepatoprotective and anticancer (Ciupei et al., 2024; Rudrapal et al., 2024)
Phenolic acids	Hydroxycinnamic acids	Caffeic acid, Ferulic acid, p-Coumaric acid, Sinapic acid	Coffee, cereals, whole grains, apples, tomatoes	Cardioprotective, antidiabetic, neuroprotective and antioxidant (Ciupei et al., 2024; Rudrapal et al., 2024)
Flavonoids	Flavonols	Quercetin, Kaempferol, Myricetin	Onion, broccoli, kale, apples, grapes	Antioxidant, anti-inflammatory, antihypertensive and anticancer (Ciupei et al., 2024; Rudrapal et al., 2024)
Flavonoids	Flavones	Apigenin, Luteolin	Parsley, celery, chamomile, oregano	Neuroprotective, anti-inflammatory and anticancer (Rudrapal et al., 2024)
Flavonoids	Flavanones	Hesperidin, Naringenin, Eriocitrin	Citrus fruits	Cardioprotective, lipid-lowering, antidiabetic and anti-inflammatory (Ciupei et al., 2024; Rudrapal et al., 2024)
Flavonoids	Flavan-3-ols	Catechin, Epicatechin, EGCG	Green tea, cocoa, dark chocolate, grapes	Antioxidant, anti-obesity, cardioprotective and anticancer (Rudrapal et al., 2024)
Flavonoids	Anthocyanins	Cyanidin, Delphinidin, Malvidin, Pelargonidin	Blueberries, blackberries, cherries, purple grapes, black rice	Neuroprotective, cardioprotective, antidiabetic and anti-inflammatory (Ciupei et al., 2024; Rudrapal et al., 2024)
Flavonoids	Isoflavones	Genistein, Daidzein, Glycitein	Soybeans, soy products, legumes	Phytoestrogenic, anticancer, osteoporosis prevention and cardiovascular protection (Ciupei et al., 2024; Rudrapal et al., 2024)
Stilbenes	—	Resveratrol, Pterostilbene	Grapes, blueberries, peanuts, red wine	Cardioprotective, neuroprotective, anti-aging and anticancer (Ciupei et al., 2024; Rudrapal et al., 2024)
Lignans	—	Secoisolariciresinol, Matairesinol, Lariciresinol	Flaxseed, sesame seeds, rye, whole grains	Hormone modulation, antioxidant, cardioprotective and anticancer (Ciupei et al., 2024; Rudrapal et al., 2024)

Tannins	Hydrolysable tannins	Ellagic acid, Ellagitannins	Pomegranate, walnuts, strawberries, raspberries	Antioxidant, antimicrobial, anti-inflammatory and anticancer (Ciupei et al., 2024)
Tannins	Condensed tannins	Procyanidins, Prodelphinidins	Cocoa, cranberries, grapes, apples	Cardioprotective, antimicrobial, anti-inflammatory and antioxidant (Ciupei et al., 2024)
Other polyphenols	Curcuminoids	Curcumin, Demethoxycurcumin	Turmeric	Anti-inflammatory, anticancer, neuroprotective and wound healing (Rudrapal et al., 2024)
Other polyphenols	Phenolic secoiridoids	Oleuropein, Hydroxytyrosol	Olives, extra virgin olive oil	Cardioprotective, antioxidant, anti-inflammatory and neuroprotective (Ciupei et al., 2024)

BIOAVAILABILITY AND PHARMACOKINETIC CHALLENGES

Although the clinical benefits of dietary polyphenols have been well established, their clinical efficacy is often confined by suboptimal bioavailability and pharmacokinetic traits. Bioavailability is the percentage of the dose that reaches the systemic circulation in an active form and is bioavailable to produce biological effects. The poor aqueous solubility, low intestinal permeability, high gastrointestinal tract instability, extensive metabolism, and rapid elimination are the reasons for the low oral bioavailability of most polyphenols (El-Saadony et al., 2024; Rudrapal et al., 2024). After oral ingestion, polyphenols enter into a series of steps of pharmacokinetics such as absorption, distribution, metabolism and excretion (ADME). Some polyphenols are sensitive to degradation by either acidic digestion or enzymes of the gastrointestinal tract, which decreases their bio-accessibility during gastrointestinal digestion. Moreover, their release and absorption from the diet may be further restricted by interactions with macromolecules in the food including proteins and polysaccharides (Tomas et al., 2025). The structure, molecular weight, glycosylation (the presence of a saccharide component) and lipophilicity of polyphenols affect their intestinal absorption. In general, aglycone forms are absorbed more efficiently than the glycosylated/polymerized forms. Polyphenols are metabolized extensively in the intestine and liver, primarily by glucuronidation, sulfation and methylation, producing a large proportion of conjugates that leave the body in a systemic circulation with low levels of free metabolites (Rudrapal et al., 2024). The gut microbiota is also critical in the metabolism of polyphenols, as it is able to transform them into low molecular weight phenolic metabolites, which can have improved or different biological properties. But inter-individual differences in gut microbial composition are associated with wide inter-individual variation in polyphenol bioavailability and therapeutic responses (Favari et al., 2024). Many polyphenols have short biological half-lives, due to their rapid renal and biliary excretion, which will not allow to maintain therapeutically significant plasma levels. The PK profile and efficacy of dietary polyphenols (DPs) is therefore impacted by the chemical structure, food matrix, processing techniques, gut microbiota, age, genetic and physiological factors (El-Saadony et al., 2024). The pharmacokinetic limitations have encouraged development of new pharmaceutical delivery systems such as liposomes, phytosomes, polymeric nanoparticles, solid lipid nanoparticles, nanostructured lipid carriers and nano-emulsions. These delivery systems can contribute to a more stable, soluble, absorbed, controlled release, and target tissue delivery of polyphenols, leading to a greater therapeutic effect and the transition from food components to pharmaceutical nutraceuticals (Tomas et al., 2025). Table 2 Shows the limitations of dietary polyphenols.

Table 2 Major pharmacokinetic limitations of dietary polyphenols and their implications for therapeutic efficacy.

Challenge	**Mechanism**	**Impact on therapeutic efficacy**
Poor aqueous solubility	Limited dissolution	Reduced absorption
Chemical instability	Oxidation and degradation	Loss of bioactivity
Low intestinal permeability	Restricted membrane transport	Poor systemic availability
First-pass metabolism	Extensive hepatic and intestinal metabolism	Low plasma concentration
Rapid elimination	Renal and biliary clearance	Short half-life
Gut microbial variability	Differences in microbial metabolism	Variable clinical response

PHARMACEUTICAL DELIVERY SYSTEMS FOR POLYPHENOLS

1.1 Rationale for pharmaceutical formulation

Dietary polyphenols have been shown to have great therapeutic potential against chronic diseases but their clinical application is greatly restricted due to the poor pharmacokinetic properties. The low aqueous solubility, gastrointestinal instability, low intestinal permeability, high first-pass metabolism and rapid elimination in plasma after oral administration are the main drawbacks of most polyphenols, accounting for low oral bioavailability and inadequate levels at target sites (Ali Redha, Kodikara and Cozzolino, 2024; Rudrapal et al., 2024). Thus, in vitro and animal studies report beneficial effects that are not always reflected in the clinical trial studies performed in humans.

To overcome these limitations, the formulation strategies have been developed for polyphenols in order to enhance their clinical translation. The advanced delivery systems such as liposomes, phytosomes, polymeric nanoparticles, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), nanoemulsions, micelles, cyclodextrin inclusion complexes and hydrogels prevent the chemical and enzymatic degradation of polyphenols, increase their solubility in water, promote intestinal absorption, increase their residence time in the bloodstream, and allow controlled and site-specific drug release (Ozkan et al., 2024; Kalita et al., 2025). Nano sized delivery systems also provide more surface area for dissolution of the active ingredients and aid endocytosis into the cell to enhance the therapeutic efficacy. Modification of these carriers at the surface with targeting ligands also allows for targeted accumulation in diseased tissues and off-target effects and systemic toxicity is reduced. The targeted delivery schemes are especially beneficial for delivering drugs to specific locations, such as cancer, neurodegenerative diseases, cardiovascular diseases, and inflammatory conditions, where adequate drug concentrations at the site of action are essential (Liu et al., 2023). Pharmaceutical formulations have the advantage of not only improving pharmacokinetic performance, but also increasing the physicochemical stability of polyphenols during storage and processing, protecting them from environmental factors (such as light, oxygen, moisture and temperature) and extend them shelf-life. The formulations also allow for the dose to be standardized, make it easier for patients to take due to decreased frequency of dosing, and offer increased therapeutic outcome reproducibility than traditional dietary supplements (Pandey et al., 2024). In recent years, the use of nanotechnology and biomaterials has greatly advanced the development of multifunctional delivery systems that are able to deliver multiple bioactive compounds, respond to physiological stimuli (such as pH, enzymes, or reactive oxygen species) and contain both diagnostic and therapeutic components. The innovations have revolutionized polyphenols from traditional non-pharmaceutical food ingredients into attractive pharmaceutical nutraceuticals with better bioavailability, targeted delivery and clinical applicability (Song et al., 2024). In summary, formulation is a key approach to be taken to overcome the natural challenges of dietary polyphenols and to exploit their therapeutic effects. Advances in formulation science and strict clinical validation and regulatory standardization are anticipated to pave the way towards successful product translation into evidence-based pharmaceutical products of polyphenols.

1.2 Nano-encapsulation

Nanoencapsulation is an advanced pharmaceutical approach that improves the stability, bioavailability, and therapeutic efficacy of polyphenols by protecting them from oxidation, light, pH variations, and enzymatic degradation during processing, storage, and gastrointestinal transit (Chowdhury, Kar and Mazumder, 2024; Rezagholizade-Shirvan et al., 2024). Nanocarriers (1–1000 nm) possess a high surface area-to-volume ratio, enhancing solubility, intestinal absorption, cellular uptake, and controlled or targeted release. This is particularly beneficial for polyphenols with poor bioavailability, such as curcumin, resveratrol, quercetin, and catechins (Ali Redha, Kodikara and Cozzolino, 2024; Ozkan et al., 2024). Biocompatible materials, including chitosan, alginate, pectin, gelatin, zein, and whey protein, are widely used to develop nanocarriers, alongside lipid-based nanoparticles, polymeric nanoparticles, nanoemulsions, nanogels, and hybrid systems (Akbarzadeh et al., 2013). Nanoencapsulation has been shown to improve the stability, plasma bioavailability, and antioxidant, anti-inflammatory, anticancer, neuroprotective, and cardioprotective activities of polyphenols compared with their free forms (Ali Redha, Kodikara and Cozzolino, 2024; Ozkan et al., 2024). However, challenges related to large-scale production, formulation stability, regulatory approval, and safety evaluation continue to limit their widespread clinical application. Future research should focus on developing safe, biodegradable, and scalable nanocarriers to accelerate the translation of polyphenol-based pharmaceutical nutraceuticals into clinical practice (Chowdhury, Kar and Mazumder, 2024; Rezagholizade-Shirvan et al., 2024)**.**

1.3 Liposomes

Liposomes are among the earliest and most extensively studied nanocarriers for polyphenol delivery owing to their excellent biocompatibility, biodegradability, and ability to encapsulate both hydrophilic and lipophilic compounds. Structurally, they consist of one or more phospholipid bilayers surrounding an aqueous core, enabling the incorporation of hydrophilic polyphenols into the aqueous compartment and lipophilic compounds within the lipid bilayer (Lian and Ho, 2001; Akbarzadeh et al., 2013). Liposomal encapsulation protects polyphenols from oxidation, hydrolysis, enzymatic degradation, and photodegradation during storage and gastrointestinal transit, thereby enhancing their stability, shelf life, and biological activity. Additionally, liposomes improve the aqueous dispersibility, intestinal absorption, and bioavailability of poorly soluble polyphenols (Chelliah et al., 2025). Their structural similarity to biological membranes facilitates cellular uptake through membrane fusion or endocytosis,

while PEGylation and ligand modification further prolong systemic circulation and enable targeted delivery (Lian and Ho, 2001). Liposomal formulations of curcumin, resveratrol, quercetin, and epigallocatechin gallate (EGCG) have demonstrated enhanced bioavailability and improved anticancer, cardioprotective, neuroprotective, antioxidant, and anti-inflammatory activities compared with their free forms(Lian and Ho, 2001; Chelliah et al., 2025). Despite limitations such as phospholipid oxidation, drug leakage, and manufacturing costs, advances including PEGylated, deformable, and stimuli-responsive liposomes have significantly improved formulation stability and therapeutic performance, supporting their potential in polyphenol-based pharmaceutical nutraceuticals(Chelliah et al., 2025).

1.4 Phytosomes

Phytosomes are phospholipid-based delivery systems that consist of molecular complexes of polyphenols with phospholipids, typically phosphatidylcholine, which increase the bioavailability of polyphenols. Contra to the traditional liposomes, phytosomes enhance the permeability of the membrane, along with the absorption from the gastrointestinal tract, by increasing the lipophilicity of polyphenols. They also increase the stability of bioactives by reducing chemical and enzymatic degradation and thus improve their therapeutic effects. The antioxidant, anti-inflammatory, hepatoprotective and cardioprotective activities of the phytosome forms of curcumin, quercetin, resveratrol, and EGCG have been found to be more effective than their free counterparts (Riva et al., 2019; Wong, Tomura and Yamamoto, 2023).

1.5 Polymeric nanoparticles

Polymeric nanoparticles are biodegradable colloidal carriers that have been extensively applied to enhance the stability, solubility and bioavailability of polyphenols by their delivery. They are typically made using natural polymers like chitosan, alginate, gelatin, zein or synthetic polymers like polylactic-co-glycolic acid (PLGA) and polycaprolactone (PCL). Polyphenols are able to be protected from enzymatic degradation and oxidation by polymeric nanoparticles; they can be released from the nanoparticles at a controlled rate and they can enhance intestinal absorption and the uptake into the cells. Moreover, they possess a surface that can be modified to include targeting ligands, which can facilitate site-specific delivery, while minimizing systemic toxicity. Enhanced antioxidant, anti-inflammatory, anticancer, neuroprotective, and cardioprotective activities have been observed for polymeric nanoparticle formulations of curcumin, quercetin, resveratrol and epigallocatechin gallate (EGCG) than their free counterparts. Although polymeric nanoparticles have some drawbacks in large-scale production, reproducibility and regulatory approval, they are one of the most promising pharmaceutical delivery systems to make polyphenols clinically effective nutraceuticals (Kumari, Yadav and Yadav, 2010; Crucho and Barros, 2017; Kalita et al., 2025; Oliveira et al., 2025).

1.6 Solid lipid nanoparticles (SLNs)

Solid lipid nanoparticles (SLNs) are lipid based nanocarriers that consist of biocompatible and biodegradable solid lipids, with the help of surfactants. They have attracted a lot of interest for delivering polyphenols due to the enhanced solubility, stability, and oral bioavailability of poorly water-soluble substances in these products. The solid lipid matrix can provide protection from chemical degradation, oxidation, and enzymatic hydrolysis during storage and in the gastrointestinal tract, and provide controlled and sustained drug release. SLNs also exhibit better intestinal absorption, cellular uptake and tissue distribution, which results in better therapeutic efficacy. Encapsulation of polyphenols like curcumin, resveratrol, quercetin and epigallocatechin gallate (EGCG) in SLNs has shown to have improved antioxidant, anti-inflammatory, anticancer and neuroprotective activities than their free forms. Second generation lipid carriers, however, with a higher drug-loading capacity and without drug expulsion during storage, have been developed due to the limitations of the first generation, such as nanostructured lipid carriers (NLCs) (MÃ¼ller, 2000; Beloqui et al., 2016; Ozkan et al., 2024; Kalita et al., 2025).

1.7 Nano-emulsions

Nano-emulsions are oil-in-water nano-colloidal delivery systems containing oil, water, surfactants, and co-surfactants, and usually consisting of droplets ranging from 20 to 200 nm in size. They have been found to be useful carriers for polyphenols due to their ability to increase the water solubility, stability, and oral bioavailability of poorly soluble polyphenols. The small droplet size will increase the surface area that will enhance the dissolution, gastrointestinal absorption and cellular uptake. Nanoemulsions also shield polyphenols against oxidation and/or hydrolysis and environmental degradation and allow controlled release and tissue distribution. Nanoemulsion formulation of curcumin, resveratrol, quercetin and epigallocatechin gallate (EGCG) have been shown to exhibit greater antioxidant, anti-inflammatory, antimicrobial and anticancer properties than free polyphenols. Despite the potential issues of long-term stability and surfactant selection, nanoemulsions are being explored for pharmaceutical and nutraceutical applications, due to their high physical stability, ease of preparation and scalability (McClements, 2012; Guttoff, Saberi and McClements, 2015; Ozkan et al., 2024; Kalita et al., 2025).

1.8 Micelles

In an aqueous medium, a micelle is a colloidally self-assembled nanosized system consisting of a hydrophobic core and a hydrophilic shell, either through the amphiphilic properties of block copolymers or due to the presence

of some surfactant (or amphiphilic molecules). This unique architecture allows for efficient encapsulation of poorly water-soluble polyphenols like curcumin, resveratrol and quercetin, enhancing both their aqueous solubility, stability, and oral bioavailability. Recent studies have shown that polymeric micelles can improve the gastrointestinal stability and prevent bio-actives from being degraded by enzymes and oxidative stress, thus increasing the bioavailability of the bio-actives (Song et al., 2024; Wang, Liang and Zhao, 2024). Polymeric micelles also help to improve pharmacokinetics, by enhancing cellular uptake and prolonging the circulation time. The nanoscale size facilitates passive accumulation within the tumor through the enhanced permeability and retention (EPR) effect and the surface engineering strategy provides tumor-specific ligand targeting and pH or redox responsive drug release. Further, the development of PEG-based and temperature-responsive micellar systems have exhibited better drug loading efficiency and controlled release characteristics, positioning them as highly promising for precision delivery of hydrophobic therapeutics (Jamirad, Seif and Montazeri, 2025; Manna, Roy and Pal, 2026). The delivery of polyphenol into the cell was demonstrated to be significantly greater and to result in enhanced antioxidant, anti-inflammatory and anticancer activities, which was attributed to encapsulation in micellar systems. But there are also challenges like dilution induced instability in physiological fluids, low drug loading and scale-up limitations which still hinder clinical translation. These challenges are addressed through the development of stimuli-responsive and hybrid micellar systems that are under investigation (Song et al., 2024).

1.9 Cyclodextrin Inclusion Complexes

Due to the advantages of the cyclodextrin inclusion complex for improving the pharmaceutical function of polyphenols from the perspective of solubility, chemical stability, and bioavailability in aqueous solutions, it is widely used. Cyclodextrins are cyclic oligosaccharides with a hydrophilic outer surface and a hydrophobic inner cavity that can host the hydrophobic polyphenols through non-covalent host–guest interaction(Musuc, 2024). This encapsulation ensures better resistance to oxidative, photodegradation and enzymatic degradation of polyphenols, and better dissolution, gastrointestinal stability and controlled release. It has been found that hydroxypropyl-β-cyclodextrin (HP-β-CD) and sulfobutyl ether-β-cyclodextrin (SBE-β-CD) exhibit significant efficacy in curcumin, tea polyphenols, flavonoids and resveratrol encapsulation and release, leading to better antioxidant and therapeutic effects(Li et al., 2024; Ming Liu et al., 2024). Recently, the research has focused on modified cyclodextrins as targeted delivery and enhanced pharmacokinetic characteristics, as potential carriers for pharmaceutical nutraceuticals(Nicolaescu et al., 2025).

Therapeutic applications of advanced polyphenol formulations

Table ***3*** Shows therapeutic applications of advanced pharmaceutical formulations of polyphenols, highlighting their delivery systems, therapeutic targets, and pharmaceutical advantages.

Table 3 .Therapeutic applications of advanced polyphenol formulations

Polyphenol	Advanced formulation	Target disease/application	Key therapeutic advantages	Reference
Curcumin	Liposomes	Cancer	Enhanced tumor accumulation, improved bioavailability, increased apoptosis, reduced systemic toxicity	(Ozkan et al., 2024)
Curcumin	Polymeric nanoparticles (PLGA/chitosan)	Inflammation, cancer	Sustained release, improved cellular uptake, enhanced anti-inflammatory and anticancer activity	(Kalita et al., 2025)
Curcumin	Solid lipid nanoparticles (SLNs)	Neurodegenerative disorders	Improved blood–brain barrier penetration, enhanced neuroprotection	(Rudrapal et al., 2024)
Resveratrol	Nanoemulsions	Cardiovascular diseases	Improved oral absorption, enhanced antioxidant and cardioprotective effects	(Ozkan et al., 2024)
Resveratrol	Polymeric micelles	Cancer	Improved stability, prolonged circulation, enhanced anticancer efficacy	(Song et al., 2024)
Quercetin	Phytosomes	Inflammatory disorders	Increased bioavailability, enhanced antioxidant and anti-inflammatory activity	(Riva et al., 2019)
Quercetin	Polymeric nanoparticles	Diabetes	Improved intestinal absorption and glycemic control	(Kalita et al., 2025)
EGCG	Liposomes	Cancer, inflammation	Enhanced stability, increased cellular uptake, improved antioxidant activity	(Ozkan et al., 2024)
EGCG	Cyclodextrin inclusion complexes	Oxidative stress-related disorders	Improved aqueous solubility, controlled release, enhanced stability	(Li et al., 2024)
Anthocyanins	Nanoemulsions	Cardiovascular diseases	Enhanced gastrointestinal stability and bioavailability	(Kalita et al., 2025)

Polyphenol	Advanced formulation	Target disease/application	Key therapeutic advantages	Reference
Catechins	Polymeric nanoparticles	Neurodegenerative diseases	Improved brain delivery and neuroprotective effects	(Rudrapal et al., 2024)
Grape seed polyphenols	Phytosomes	Cardiovascular disorders	Improved absorption and vascular protective effects	(Wong, Tomura and Yamamoto, 2023)
Tea polyphenols	Cyclodextrin inclusion complexes	Diabetes, oxidative stress	Enhanced stability, α-glucosidase inhibition, improved antioxidant activity	(Li et al., 2024)
Naringenin	Nanoemulsions	Liver disorders	Improved solubility, hepatoprotective activity, enhanced bioavailability	(Ozkan et al., 2024)

FUTURE PROSPECTS

The study of polyphenol-based pharmaceutical nutraceuticals in the future needs to be an advanced delivery system, where the issues of low bioavailability, stability, and target specificity need to be overcome. Stimuli-responsive nanocarriers, ligand-targeted nanoparticles, hybrid delivery systems, and multifunctional nanoplatforms are promising strategies that will improve the controlled delivery, targeted delivery, and therapeutic action of nanocarriers (Kalita et al., 2025)**.** In addition, the use of artificial intelligence, computational modeling, and quality-by-design (QbD) in formulation development can aid in optimizing and clinical translation of polyphenol-containing formulations (Ozkan et al., 2024). Large scale manufacturing, long-term safety studies, regulatory harmonization, and well-designed clinical trials to determine the dosage regimen and prove clinical efficacy should also be given importance for future investigation (Ali Redha, Kodikara and Cozzolino, 2024)**.** Further, precision nutrition and microbiome-directed formulations can enable the creation of personalized polyphenol formulations based on individual metabolic and genetic makeup (Rudrapal et al., 2024)**.** These innovations are likely to help speed the polyphenols' journey from functional food ingredients to proven pharmaceutical nutraceuticals for the prevention and management of chronic diseases.

CONCLUSION

The antioxidant, anti-inflammatory, cardioprotective, neuroprotective, anticancer and antidiabetic properties of polyphenols show that they have great potential for the prevention and management of chronic diseases. Despite their therapeutic potential, the therapeutic use of these is greatly restricted due to poor solubility, low bioavailability, rapid metabolism and limited stability. The delivery of polyphenols using novel pharmaceutical delivery systems has been revolutionized recently, for example by using systems like nanoencapsulation, liposomes, phytosomes, polymeric nanoparticles, solid lipid nanoparticles, nano-emulsions, micelles and cyclodextrin inclusion complexes. The use of these technologies allows to increase the stability, absorption, controlled release and targeted delivery of polyphenols, thus increasing their pharmacokinetic profile and therapeutic efficacy. All of this has reinforced the shift of polyphenols from traditional functional food to potential pharmaceutical nutraceuticals.

While a great deal has been achieved, there are issues with manufacturing on a large scale, with formulation stability, getting the product approved, making it produce a consistent quality product, and clinical validation. Optimization of delivery systems, clinical studies with sound design, and setting up standardized protocols for safety, efficacy and commercialization of polyphenol-based formulations should all be emphasized for further research. Breaking through the years and the ongoing progress of nanotechnology, pharmaceutical sciences and personalized medicine are anticipated to further propel the clinical usage of polyphenols and introduce their involvement in the evidence-based healthcare and development of next-generation nutraceuticals.

Conflict of Interest

The authors declare that there are no conflicts of interest regarding the publication of this review.

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