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Sustainability spotlight

Nutraceuticals are bioactive compounds derived from food sources with purported health benefits and offer great potential for promoting wellness and preventing diseases. However, they pose certain limitations including poor bioavailability, high sensitivity to light and oxygen, low water solubility, limited stability, and probable chemical changes after delivery that restrict their applications and health benefits. The integration of advancement of nanotechnology into sustainable nutraceutical manufacturing is driving impactful innovation in industry. Nanotechnology offers promising avenue for delivery of nutraceuticals to improve the bioavailability and targeted delivery. Natural and biodegradable polymers like chitosan, alginate, lignin, zein, casein, etc. are being employed for development of nanocarriers. These biopolymers are non-toxic, non-irritant, easily available, and biodegradable, making them excellent candidates for the delivery of nutraceutical and dietary supplements. Nanotechnology in the food and pharmaceutical industry holds a great potential to transform food and agricultural practices as it presents enormous benefits and sustainable production methods to shape the future of nutraceuticals. This review provides a comprehensive overview of the latest advancements in nanotechnological approaches aimed at improving the encapsulation of bioactive compounds emphasizing their targeted applications in disease management.

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Recent overview of nanotechnology based approaches for targeted delivery of nutraceuticals

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Abstract

Nutraceuticals and dietary supplements have experienced a remarkable surge in demand over the past decade, driven by growing emphasis on preventive healthcare and heightened consumer preference for bioactive products. Nutraceuticals serve as an interface between pharmaceuticals and bioactives, offering therapeutic potential with minimal adverse effects. However, their clinical applications are often hindered by their inherent physicochemical characteristics, including low bioavailability, susceptibility to environmental degradation, poor aqueous solubility, instability, and post-delivery structural degradation. To address these challenges, nanotechnology has emerged as a promising avenue for enhancing the therapeutic efficacy and bioavailability of nutraceuticals. Nano-sized cargos such as liposomes, nanoparticles, nano-emulsions, and nanogels enable improved encapsulation, stability, bioavailability, cellular internalization, and targeted delivery of nutraceuticals. Furthermore, the sustainable manufacturing of nutraceuticals has undergone substantial technological advancements to enhance the bioavailability, therapeutic effect, and long-term stability. This review provides a comprehensive overview of recently published literature addressing different nano-enabled approaches employed for nutraceuticals, highlighting their targeted applications in disease prevention and management. Additionally, it critically examines the regulatory challenges associated with their production scalability, safety concerns, and environmental impact, while offering insights into existing regulatory frameworks and future considerations for the pervasive use of nanotechnology in the nutraceutical industry.

Keywords: Nanotechnology, Nanomaterials, Nutraceuticals, Biomaterials, Targeted delivery, Sustainable manufacturing

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1. Introduction

Nutraceuticals are bioactive compounds that provide therapeutic benefits beyond basic nutrition, contributing to disease prevention and overall health maintenance. The term is a combination of 'nutrition' and 'pharmaceutical', reflecting their dual role in nourishment and therapeutic efficacy [1]. These compounds encompass a wide range of bioactive substances, including vitamins, minerals, antioxidants, prebiotics, probiotics, herbal products, spices, as well as a range of polyunsaturated fatty acids (PUFA) [2]. They are commonly incorporated into functional foods, dietary supplements, and fortified food products such as cereals, soups, and beverages [3].

Dietary supplements, a subset of nutraceuticals, are formulated to augment dietary intake and may contain a combination of essential nutrients, herbs, botanicals, amino acids, metabolites, or bioactive extracts. Regulatory authorities such as the United States Food and Drug Administration (USFDA) mandate that dietary supplements must be appropriately labeled and are permitted to bear specific health claims only when supported by robust scientific evidence [4,5]. They provide various benefits, including anti-aging properties, antioxidant properties, promoting good health and preventing diseases, fewer side effects, easy availability, and a holistic approach to wellness [5]. The consumption of nutraceuticals and dietary supplements has increased substantially due to growing consumer interest in naturally derived compounds and preventive healthcare strategies [6]. Extensive research highlights their therapeutic potential in mitigating oxidative stress-related disorders, including cardiovascular diseases [7,8] and cancer[9,10], neurodegenerative conditions such as Alzheimer's disease[11] and Parkinson's disease [12,13], metabolic disorders like diabetes mellitus

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[14,15], and obesity [16,17], as well as immunological [18,19] and inflammatory disorders [20,21]. The global nutraceutical market is experiencing significant expansion, driven by increasing consumer awareness and advancements in functional food development [22]. As of 2022, the market was valued at approximately $317.22 billion and is projected to grow at a compound annual growth rate (CAGR) of 9.6%, reaching nearly $600 billion by 2030 [23] (see Figure 1). While India accounted for only 2% of the global nutraceutical market in 2017 [24], recent estimates suggest it is anticipated to expand at a CAGR of 15% between 2023 and 2028, with the preventive healthcare segment anticipated to reach $195 billion by 2025 at a CAGR of 22% [25]. This illustrates both the economic potential and the increasing significance of nutraceuticals in the global health sector.

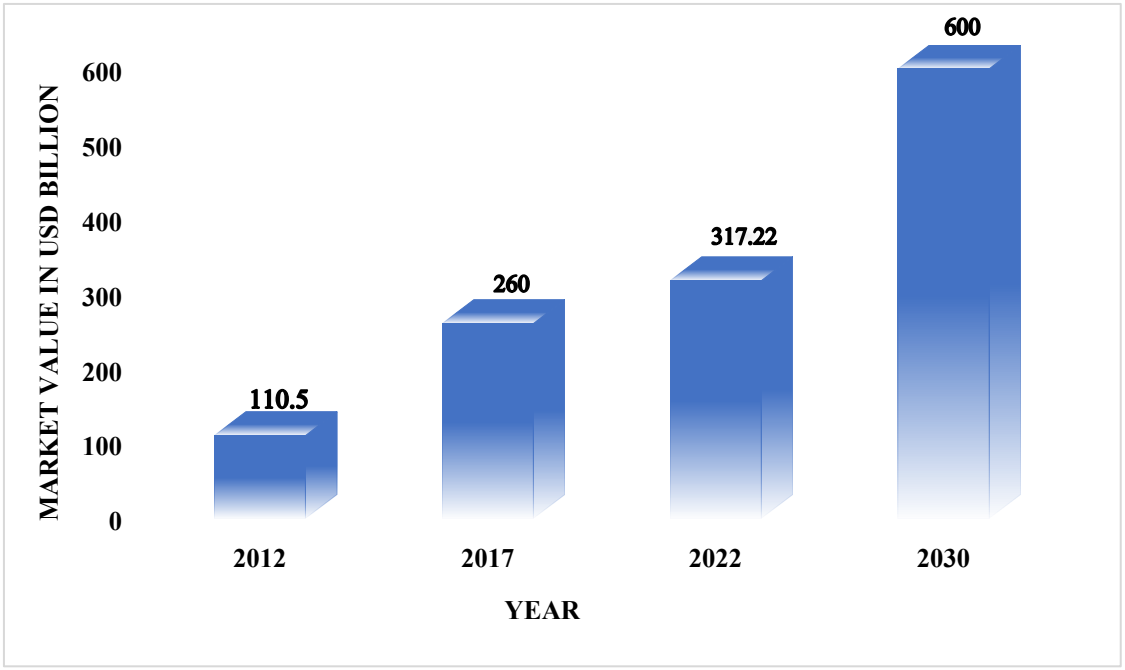

Figure 1. The global market value of nutraceuticals in USD Billion from year 2012 to 2027 [24,26]

Despite their promising therapeutic applications, the efficacy of many nutraceuticals is hindered by inherent physicochemical limitations, including poor bioavailability, low aqueous solubility,

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high sensitivity to light and oxygen, limited stability, and probable chemical changes after their delivery [27]. These challenges necessitate innovative delivery strategies to enhance their absorption, protect them from environmental degradation, and ensure targeted delivery to specific physiological sites [28]. Thus, nanotechnology has been seen as a breakthrough invention for the efficient delivery of nutraceuticals and dietary supplements and in activating the positive characteristics of human health, hence improving their efficacy in a variety of ailments [29].

This literature review intends to provide a comprehensive analysis of nanotechnology-based delivery systems for nutritional supplements, highlighting their targeted applications in disease prevention and management. It further examines how various nanocarriers address the physicochemical limitations of conventional nutraceutical formulations, thereby advancing their clinical and commercial viability. Additionally, it provides limitations of existing regulatory frameworks and a comparative analysis of different nanoformulations based on their production costs, scalability, regulatory challenges, and environmental concerns.

2. Strategies to improve nutritional properties of foods using nanotechnology

Nutraceuticals exhibit several physicochemical limitations that hinder their therapeutic efficacy, including poor bioavailability, low aqueous solubility as a result of their hydrophobic nature, sensitivity to temperature, light, pH, free radicals, or oxygen, limited stability, as well as potential structural degradation during their delivery [27,28]. Many bioactive compounds derived from natural sources, such as curcumin and quercetin, face significant challenges in achieving their full therapeutic potential due to inefficient absorption, short systemic circulation time, and rapid metabolic degradation [30,31]. To overcome these limitations, nanotechnology has emerged as a

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promising approach for effectively delivering nutritional supplements [32,33]. Nanoencapsulation offers several advantages, including the ability to protect bioactive compounds from environmental degradation (e.g., pH fluctuations, photodegradation, temperature variations, and oxidative stress), enhance bioavailability, facilitate targeted delivery, and permit controlled and sustained release of the encapsulated compound [34,35] (Figure 2).

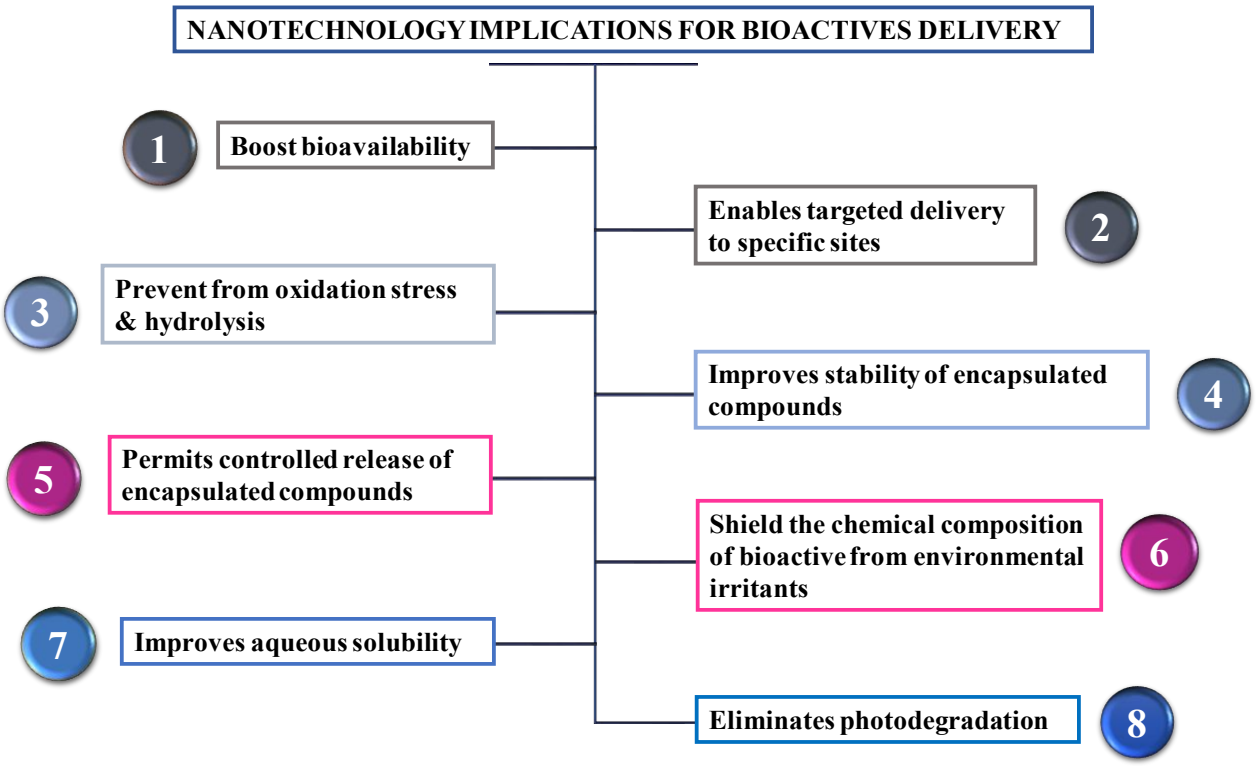

Figure 2: Nanotechnology implications to nutraceuticals and dietary supplements delivery

The encapsulation process must be carefully designed to ensure precise regulation of release kinetics, allowing for controlled dosage at the intended site of action [36]. An optimal delivery system should protect external destabilizing factors such as enzymatic degradation, moisture, and temperature fluctuations, thereby preserving the structural and functional integrity of the encapsulated compound [37]. Additionally, once encapsulated within nanocarriers, the

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physicochemical properties of nutraceuticals are largely influenced by the characteristics of the carrier system rather than the entrapped bioactive, thereby enhancing solubility and stability. Moreover, nanocarrier-based systems enable the co-delivery of hydrophilic and lipophilic bioactives, facilitating their synergistic therapeutic effects and improved bioavailability [38,39].

It is imperative to ensure that nanotechnology-based delivery systems utilize biocompatible, non-toxic, and non-immunogenic materials that pose no threat to human health [40]. The materials commonly employed in nanocarrier fabrication include lipid, polymer, and protein-based systems, all of which must comply with regulatory standards and be categorized as Generally Recognized as Safe (GRAS) [40]. The selection of an appropriate nanocarrier system is determined by the physicochemical properties of the encapsulated nutraceutical, the intended site of action, and the specific therapeutic application [41,42]. Among the key nanocarriers explored in recent research are nanogels, nanoemulsions, nanoparticles (lipidic, polymeric, or protein-based), niosomes (non-ionic surfactant vesicles), liposomes, nanocrystals, and polymeric nanocapsules (Figure 3). The following sections provide a comprehensive discussion of these nanocarrier systems and their applications in enhancing nutraceutical delivery.

2.1 Nanogels

Nanogels are hydrogel particles with remarkable versatility in nutraceutical delivery due to their nanoscale size (typically <1000 nm), high loading capacity, stability, and ability to protect and control the release of bioactive compounds [43]. They are predominantly synthesized through self-assembly, chemical modifications, ionic gelation, and ultrasonication techniques, often incorporating proteins and polysaccharides as core materials. Recent advancements in nanogel formulation have demonstrated significant improvements in encapsulation efficiency, bioavailability, and functional properties of encapsulated nutraceuticals.

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He M et al. developed soy protein isolate (SPI)-based nanogels modified with dextran and succinic acid anhydride to encapsulate curcumin. The Maillard reaction and succinic acid anhydride modification enhanced the functional properties of SPI, such as hydrophobicity and charge distribution, facilitating self-assembly into nanogels. This resulted in nanogels with a particle size of 143nm, a dispersion index of 0.20, an encapsulation efficiency of 93%, and a loading capacity of 54%[44]. These nanogels exhibited excellent stability and antioxidant activity, making them suitable for addressing oxidative stress-related diseases. Similarly, Wang et al. formulated self-assembled nanogels using acylated rapeseed protein isolate (ARPI) through a process of chemical acylation and heat-induced protein denaturation [45]. This approach imparted the nanogels with unique secondary and tertiary structures, reduced sulfhydryl groups, and increased hydrophobic surfaces, resulting in spherical particles with a hydro-diameter of 170 nm and a light core-dark shell morphology. ARPI nanogels were effective in enclosing curcumin with an exceptional encapsulation efficiency of 95% which significantly boosted its potential to fight cancer in different cell lines. However, the study lacks data on pH stability and performance in complex food matrices and in vivo studies to prove their safety and efficacy [45]. In another approach, Yu et al. formulated acylated kidney bean protein isolate (AcKPI) nanogels via the self-assembly method, achieving uniform particles of particle size of 137 nm and PDI of 0.3. They exhibited excellent encapsulation efficiency of 92%, significant antioxidant properties, and pH and temperature tolerance. The study provides the application scope of AcKPI-nanogels to be potentially used as an innovative and ideal delivery system for bioactive compounds for controlled release [46].

Beyond protein-based nanogels, Xu et al. designed an innovative nanogel encapsulating lutein in ovomucin and chitosan oligosaccharide blend through the self-assembly technique [47]. The

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encapsulated lutein showed remarkable stability across a wide pH range and ionic concentrations, retained its amorphous state, and achieved controlled release with significant antioxidant activity. The nanogels demonstrated no cytotoxicity toward L929 fibroblast cells at higher concentrations. The study presents the potential application of lutein-loaded ovomucin and chitosan oligosaccharide blend nanogels as the promising and effective oral carrier of lutein. However, the absence of in vivo studies left uncertainties regarding their oral bioavailability and long-term safety [47]. Another study encapsulated folic acid (vitamin B_9) in soy proteins and polysaccharides using a self-assembling technique to prevent deterioration due to pH, temperature, and light [48]. The folic acid-encapsulated nanogels could be used for intestinal release, as folic acid was gradually released under neutral pH. Furthermore, the nano-encapsulated substance remained stable at high temperatures, high light exposure, and high oxygen pressures, making it a feasible option for employing the nanogels in a variety of food and drink formulations without worrying about the risk of deterioration [48]. Additionally, Sun et al. utilized a Maillard reaction and self-assembly to fortify orange juice with curcumin [49]. The encapsulated curcumin demonstrated superior stability and antioxidant activity, expanding its potential for acidic beverage applications. Despite their advantages, they may pose allergenicity risks and limit their applicability in certain populations. Nevertheless, self-assembled nanogels can effectively encapsulate a variety of nutraceuticals and drugs, improving their stability and bioavailability. The process avoids the use of toxic solvents, aligning with green chemistry principles.

The ultrasonication technique is another widely employed method for nanogel synthesis, offering advantages such as controlled particle size tuning (30–200 nm), crosslink density modulation, and adjustable drug release profiles by varying ultrasonication time, amplitude, and polymer concentration [50]. Jin et al. encapsulated vitamin B_2 in nanogels made with dextran and thermally

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denatured soy protein using an ultrasonication technique, having a diameter of 40 nm and maintaining their spherical shape at pH 6 [51]. Encapsulation efficiency was 65.9%, with gradual intestinal release, making them suitable for specific gastrointestinal applications. The study demonstrated that nanogels made with dextran and thermally denatured soy protein had low dispersion, nanoscale sizes, and fair encapsulation efficiency when riboflavin was delivered in an intact form, supporting their potential as functional nutraceutical carriers [51].

Another promising approach in nanogel synthesis is ionic gelation, a simple and mild technique that enables the fabrication of nanogels under physiological pH and ambient temperatures, making it particularly suitable for encapsulating sensitive bioactive compounds [52]. Buosi et al. developed resveratrol-loaded chitosan-sodium tripolyphosphate nanogel targeted for ophthalmic delivery[53]. The nanogel demonstrated remarkable protection of encapsulated bioactive from UV light. It exhibited biocompatibility with human retinal pigment epithelial cell line (ARPE-19). These findings underscore the ability of ionic gelation-derived nanogels to serve as protective carriers for bioactives while maintaining cellular compatibility.

Collectively, these studies showcase innovative methods to prepare nanogels with tailored properties for nutraceutical delivery. The techniques employed, such as chemical modification, self-assembly, ionic gelation, and Maillard reaction enhance the functional capabilities of protein-based carriers. However, a significant limitation across most studies is the absence of in vivo validation, which remains crucial for assessing the clinical efficacy, safety, and scalability of these systems. Future research should focus on optimizing nanogel formulations to address allergenicity concerns, improving stability in complex biological environments, and conducting comprehensive in vivo evaluations to establish their commercial viability. Other recent studies related to the entrapment of bioactives into polymeric nanogels are summarised in Table 1.

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192 **Table 1. Polymers employed for the encapsulation of bioactive compounds into nanogels.**

Loaded Bioactive Compounds	Polymers used for encapsulation	Methods of preparation	Outcomes	Targeted Applications	Ref.
Curcumin	Soy protein isolate (SPI)	Heat-induction	• Reported particle size, PDI, and EE% of 143nm, 0.2 and 93%, respectively. • Revealed sustained release of curcumin (approx. 80%). • Showed enhanced stability and antioxidant nature.	Targeted therapy for numerous ailments like cancer, diabetes, and cardiovascular diseases	44
	Rapeseed protein isolate	Chemical acylation and heat-induced protein denaturation	• Reported a hydro-diameter of 170 nm and encapsulation efficiency of 95%. • Had significantly different spatial secondary and tertiary structures. • Demonstrated enhanced hydrophobic surfaces and reduced levels of free sulfhydryl groups.	Anti-cancer therapy for several cell lines	45
	Polyglutamate	Esterification reaction with vitamin B_6	• Exhibited remarkable anti-inflammatory activity in vitro as well as in vivo. • Macrophages incorporated curcumin-loaded nanogels to release it under acidic conditions.	Targeted anti-inflammatory effect	54
	Soy protein isolate and dextran	Maillard reaction and self-assembly technique	• Reported EE% and DL% of 89% and 17%, respectively. • Exhibited remarkable bioavailability of 55%, enhanced stability, and excellent antioxidant activity.	Fortification of acidic beverages like orange juice	49

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Vitamin B_2 (Riboflavin)	Dextran and modified soy protein	Ultrasonication	• Reported spherical shape with 40nm and EE% of 66% • Exhibited low dispersion, nanoscale sizes, and fair encapsulation efficiency.	Targeted delivery system for vitamin B_2	51
Vitamin B_9 (Folic acid)	Soy protein isolate	Self-assembly	• The stability of vitamin B_9 was independent of the presence of a singlet oxygen atom. • Stable at high temperatures, light exposure, and oxygen pressures.	Targeted delivery of folic acid	48
Capsaicin	Poly (vinyl alcohol) and gelatin	Esterification	• Crystallinity was inversely proportional to gelatin concentration. • Exhibited excellent sensitivity to both pH and temperature.	Innovative delivery system for capsaicin	55
Resveratrol	Chitosan and sodium tripolyphosphate	Ionic gelation	• Reported particle size, ZP, and EE% of 140 nm, 32 mV, and 59%, respectively. • Demonstrated biocompatibility with human pigment epithelial cell line (ARPE-19) and remarkable protection from UV light. •	Targeted ophthalmic delivery	53
	Tribasic acid and 1,2,5-pentanetriol	Esterification precipitation reaction	• Reported an encapsulation effectiveness of 94.5% and a spherical shape with a particle size of 220nm. • In vitro results showed high protective activity of resveratrol against oxidative stress in	For the enhancement of protective effects in oxidative stress cells	56

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			fibroblast and neuroblastoma cells.		
Quercetin	Chitosan	Ionic-gelation	• Nanogel particle size, PDI, and zeta-potential were reported to be 370nm, 0.528, and -24.8 mV, respectively. • Reported an entrapment efficiency of 98%. • Exhibited sustained release of the drug up to 48 hours.	Targeted transdermal delivery of quercetin as an antioxidant	57
	Poly-ε-caprolactone (PCL) and poly ethylene glycol (PEG)	Crosslinking with folic acids	• Reported particle size ranges from 44 to 194 nm. • Revealed remarkable drug loading and entrapment efficiencies. • Nanogels with greater crosslinking densities disintegrated in buffer solution too quickly.	Targeted delivery system for a wide range of cancer	58
Lutein	Ovomucin and chitosan oligosaccharide	Self-assembly method	• Demonstrated particle size, PDI, ZP, EE%, and DL% of 210 nm, 0.25, -20.71 mV, 90%, and 6.5%, respectively. • Exhibited remarkable stability over a wide range of pH values. • Exhibited significant antioxidant activity and no cytotoxicity toward L929 fibroblast cells.	Novel oral delivery system for lutein and other hydrophobic drugs	47
β-Carotene	Chitosan and carboxymethyl starch	Chemical cross-linking	• Demonstrated excellent protection from UV light and high temperature. • Exhibited remarkable stability indicated by	Targeted oral delivery of β-carotene and other bioactives	59

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			enhanced retention (56% - 69%) of encapsulated β-carotene upon one month storage. • Showed improved bioavailability of encapsulated β-carotene.		

2.2 Nano-emulsions

Nano-emulsions (NEs) are small-sized colloidal particulate systems utilized for the transportation of numerous drug molecules [60]. They differ from traditional emulsions due to their smaller droplet size, typically in the nanometre range. They typically consist of water, oil, and an emulsifier, which plays a crucial role in reducing the interfacial surface tension between water and oil phases, stabilizing the NEs, and preventing coalescence [61]. Surfactants, proteins, and lipids are commonly used emulsifiers [62,63]. NEs offer multiple advantages such as, shielding active ingredients, enhancing their effectiveness, and serving as delivery systems for nutraceuticals and food components [64,65].

Recent studies have extensively investigated the potential of NEs as advanced nutraceutical delivery systems, focusing on their ability to enhance bioavailability, stability, and functional properties. In one such study, researchers encapsulated co-enzyme Q10 into chitosan-based NEs, demonstrating excellent stability, reducing oxidative stress and inflammation in cardiomyoblast cells and hepatocytes against the damaging effects of the potent anticancer drug doxorubicin [66]. They also increased cell viability by 35-40% in hepatocytes and cardiomyocytes and decreased the production of nitric oxide, interleukins, and TNF-α. The chitosan surface provided biocompatibility and enhanced bio-adhesion, improving cellular uptake [66]. Similarly, another

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study encapsulated clove oil in whey-protein NEs utilizing the ultrasonication method, achieving a droplet size of 280 nm, a PDI of < 2, and a zeta potential (ZP) of -35 mV [67]. These properties contributed to stability across various pH levels, temperatures, and ionic concentrations. These NEs exhibited potent antimicrobial efficacy against *E.coli* and *B.subtilis* strains with a minimum inhibitory concentration and minimum bactericidal concentration of 50 and 90 μg/mL, respectively, suggesting their potential for food safety applications. The small droplet size and negative zeta potential likely enhanced interaction with microbial membranes, improving efficacy. This study heralds a promising avenue for leveraging clove oil's antimicrobial property in practical applications within food systems [67]. Another study utilizing a NE mixture of whey protein isolate (WPI) and gardenia fruit oil encapsulated three different bioactive compounds, named β-carotene, hesperetin, and naringenin, exhibiting remarkable encapsulation efficiencies of 80%, 51%, and 46%, respectively [68]. Small droplet sizes (< 300 nm) achieved through ultrasound application stabilized the NEs under challenging environments i.e., lower temperatures, alkaline conditions, and reduced cationic concentrations. They impressively curtailed the generation rate and amount of peroxide value (PoV) and thiobarbituric acid reactive substances (TARS) during the 14-day accelerated oxidation experiment, affirming the improved oxidation stability of gardenia fruit oil [68].

In terms of functional bioavailability and cellular uptake, albumin-stabilized NEs encapsulating resveratrol exhibited neuroprotective effects by mitigating postoperative cognitive dysfunction in older rats by decreasing hippocampal inflammation [69,70]. The smooth surface and bioactive encapsulation protected resveratrol from degradation and improved its interaction with cellular targets. The neuroprotective effects were linked to the activation of the SIRT1 signaling pathway, highlighting the role of surface characteristics in influencing biological pathways [70]. Additionally,

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N. Walia and L. Chen demonstrated that pea protein-stabilized NEs encapsulating vitamin D, enhanced its bioavailability and potentially alleviated vitamin insufficiency in older adults. The protein surface enhanced cellular absorption, highlighting the value of protein-emulsifier interactions in optimizing nutrient delivery [71]. V. Campani et al. utilized low-energy techniques to prepare vitamin K_1 (VK_1)-loaded PLGA NEs, which exhibited intriguing droplet size and stability across different storage conditions. The porous surface facilitated skin penetration and transdermal delivery. Nebulization studies confirmed the potential for spray formulations without altering the NE properties, suggesting commercial viability for topical applications [72].

From an antioxidant and food system perspective, black rice bran phenolics (ferulic and p-coumaric acids) were successfully entrapped in sunflower oil NEs using homogenization and ultrasonication, exhibiting sustained antioxidant activity across varying thermal and ionic conditions (0.2-1 mol L^{-1}), thereby suggesting their utility in food preservation [73]. Similarly, Li J et al. incorporated lycopene from tomato waste into oil-in-water NEs utilizing isopropyl myristate (oil phase) and Pluronic F-127 (emulsifier) through high-speed homogenization combined with spray-drying technology. The spray-drying technique preserved lycopene's bioactivity, and small droplet sizes enhanced its dispersion and uptake in food systems [74].

Despite these promising attributes, several challenges remain in the development and commercialization of NE-based nutraceuticals. While NEs demonstrate superior EE%, payload capacity, and protection from degradation, their stability is highly dependent on the selection of appropriate surfactants and emulsifiers. Expanding in vivo studies to validate their bioavailability and therapeutic efficacy is essential for their clinical and commercial translation. Future innovations should explore hybrid NE systems integrating multiple encapsulation strategies to achieve synergistic effects. Table 2 summarizes studies on nutraceutical delivery via NEs,

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257 highlighting natural and synthetic polymers used for encapsulating nutritional supplements and
258 their targeted applications.

259 **Table 2. Polymers used for the entrapment of bioactive compounds into nano-emulsions.**

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Loaded Bioactive Compounds	Polymers used for encapsulation	Methods of preparation	Outcomes	Targeted Applications	Ref.
Coenzyme Q10	Chitosan	High-pressure homogenization	• Cell viability increased by 35-40% in coenzyme Q10-loaded nanoemulsions. • Decreased the production of nitric oxide, interleukins and TNF-α. • Reduced oxidative stress and inflammation in cardiomyoblast cells (HCF cell line) and hepatocytes (THLE-2 cell line).	Protection of cardiomyocytes and hepatocytes against the damaging effects of doxorubicin and trastuzumab	66
Eugenol from clove oil	Whey protein	Ultrasonication	• Reported droplet size, PDI, and zeta potential of 280 nm, less than 0.2, and -35mV, respectively. • Exhibited astonishing resistance to different pH values (3-7), temperatures (60-120ºC), and ionic concentrations (0.1-1M NaCl). • Demonstrated potent antimicrobial efficacy against *E.coli* and *B.subtilis* strains after a rigorous contact period of 8 hours.	Antimicrobial agent for various food products	67
β-carotene, hesperetin, and naringenin	Whey protein isolate (WPI) and gardenia fruit oil	High-speed homogenization and ultrasonication techniques	• Reported small droplet sizes (< 300nm) at 10% v/v concentration of oil. • Demonstrated excellent stability at low temperature, high pH, and low ionic strength. • All three NEs exhibited remarkable encapsulation efficiencies.	Targeted and controlled delivery of lipid-soluble nutraceuticals	68
Resveratrol	Albumin	Low-energy emulsification	• Reduced the cognitive impairment brought on by surgery and associated hippocampus neuroinflammation. • The concurrent injection of sirtinol decreased the	Prevention of cognitive dysfunction	70

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			neuroprotective effects of resveratrol's nano-emulsion.		
Vitamin D	Pea protein	High-pressure homogenization	• Revealed excellent stability, reduced droplet sizes (170 - 350 nm), and remarkable encapsulation efficiency (94-96%). • Exhibited high cellular uptake in the Caco-2 cell line.	Alleviation of vitamin insufficiency in elderly people	71
Vitamin K_1 (Phytonadione)	PLGA (Polylactic-co-glycolic acid)	Spontaneous emulsification	• Exhibited intriguing droplet size and stability over time at various storage temperatures. • Had the potential to be used for the commercial production of an aqueous spray formulation for the topical administration of VK_1.	Targeted transdermal delivery of VK_1	72
Curcumin	Chitosan	Homogenization	• Chitosan improved the spreadability, feel, and consistency of nano-emulsion. • Showed improved skin permeability.	For the transdermal delivery of curcumin	75
	Polyacrylic acid	Low-energy emulsification	• Increased the solubility and skin permeability of curcumin. • Droplet size, PDI, and zeta potential were 10.57 nm, 0.094, and -18.7 mV, respectively. • Results showed fast recovery of psoriasis in rat models.	For the management of psoriasis	76

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Ferulic acid and p-coumaric acid	Polysorbate 80 and soy lecithin	Homogenization and ultrasonication	• All NEs reported droplet sizes within 128 – 226 nm. • Exhibited excellent stability at high temperature (65ºC) over a one-month storage period. • Demonstrated remarkable stability and antioxidant activity at different ionic strengths (0.2, 0.5, and 1 mol L^{-1}).	Targeted drug delivery system for polyphenols	73
Lycopene	Isopropyl myristate and Pluronic F-127	High-speed homogenization and spray-drying techniques	• Reported droplet sizes in the range of 259-276 nm with uniform spherical shape • Evaluated the effect of different coating agents, drying temperatures (120-170ºC), and feed flow rates (3-9 ml min^{-1}) on droplet size. • Maltodextrin (coating agent) enhanced the stability of NEs.	Novel drug delivery system for lycopene and other bioactives	74

2.3 Liposomes and Niosomes

Liposomes and niosomes are advanced vesicular nanocarriers used for the efficient delivery of hydrophilic and lipophilic substances. Unlike nanogels and nanoemulsions, these vesicles can encapsulate a wide range of bioactives due to their unique multilamellar structure [77]. Both hydrophilic and lipophilic molecules, as well as amphiphilic substances, can be incorporated into their structures (Figure 3)[78] . Multilamellar liposomes, for instance, offer additional versatility by hosting substances within their multiple bilayers. Liposomes primarily consist of phospholipids and surfactant molecules, while niosomes are synthesized from non-ionic surfactants, making them cost-effective [79]. Numerous techniques are employed for the preparation of these vesicles, including lipid layer hydration, reversed-phase evaporation, transmembrane pH gradient, micro-

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fluidization, ether injection, and extrusion techniques [80]. Critical factors influencing their synthesis include the type of vesicles, phospholipid properties, their interactions with the dispersion medium, and bioactive molecules being encapsulated [81].

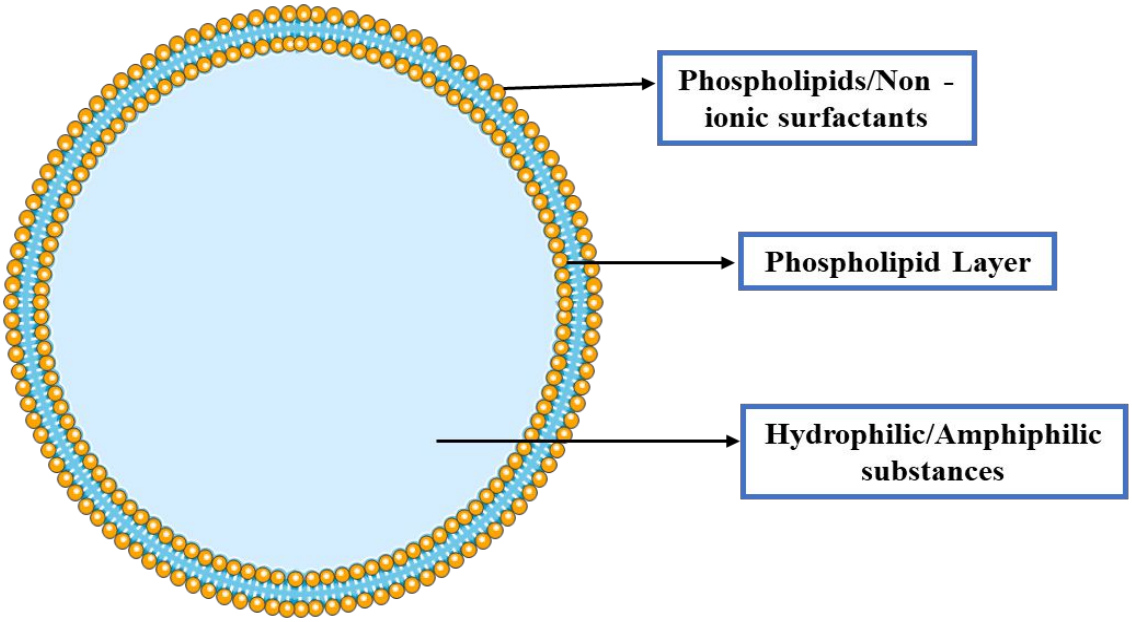

Figure 3. Schematic representation of Liposomes and Niosomes.

Liposomes and niosomes have demonstrated remarkable potential in delivering various vitamins (A, C, and E), phytosterols, and other bioactive substances [82]. Encapsulation in liposomes improved all-trans retinoic acid's (ATRA's) photo-stability, and anti-cancer efficacy, enhancing cellular uptake and reducing degradation [83,84]. The anticancer effects of retinoic acid were enhanced on thyroid carcinoma cell lines (FRO, PTC-1, and B-CPAP) when ATRA was delivered via liposomes. The intracellular uptake of the vesicular formulation in the in vitro assays on FRO and B-CPAP cell lines demonstrated a more pronounced anticancer effect when compared with free drug [85]. Similarly, niosomes synthesized using the film hydration technique demonstrated a narrow size distribution (107–190 nm) and high encapsulation efficiency, enhancing stability and reducing lipid peroxidation [86].

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In a parallel investigation, liposomal formulations of curcumin and α-tocopherol, prepared with the homogenization method, retained the antioxidant activity in fortified cookies without compromising sensory attributes. Their encapsulation efficiencies were reported to be above 90%. DPPH and ferric-reducing antioxidant power assays reported the successful liposomal encapsulation of curcumin and α-tocopherol into the fortified cookies, preserving the antioxidant properties of both [87]. Another group of researchers explored niosomal formulations for co-delivering nutraceuticals and dietary supplements. They encapsulated gallic acid with curcumin and ascorbic acid with quercetin in niosomes, which significantly boosted solubility and antioxidant efficacy [88]. This enhanced synergistic antioxidant activity, making it more promising for chronic disease management. A separate investigation highlighted the encapsulation of gallic acid extracted from Indian gooseberry and sappan wood heartwood using the ethanol injection method to produce mucus-penetrating niosomes with potent anti-inflammatory activity. The addition of poloxamer 407 influenced diffusion mechanisms, enabling efficient intestinal absorption [89].

Incorporating bioactive lipids into vesicular systems has also demonstrated promising outcomes. Zelikina D et al. incorporated curcumin and fish oil PUFAs (n-3 and n-6) into liposomes made from WPI-chitosan conjugate via the Maillard reaction. The liposomes exhibited sustained release, enhanced bioavailability, and mucoadhesiveness of the encapsulated nutraceuticals during gastric and small intestinal stages [90]. Semenova M et al. encapsulated a combination of lipophilic (n-3 PUFAs, vitamin D3, and eugenol) and hydrophilic (γ-aminobutyric acid) nutraceuticals in phosphatidylcholine liposomes coated with WPI-chitosan conjugate. These liposomes exhibited small particle size, remarkable encapsulation efficiencies (> 80% for lipophilic and > 49% for hydrophilic), and improved interaction with bile salts and mucin in the intestine. The study

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demonstrated the potential of phosphatidylcholine liposomes as novel oral carriers for lipophilic and hydrophilic bioactive compounds [91].

Liposomes and niosomes, with their tunable shape, surface properties, and multi-compartment structure, serve as efficient carriers for bioactives, ensuring improved stability, bioavailability, and targeted delivery. These attributes position them as promising candidates for nutraceutical and functional food applications. Despite their significant advantages, further research is needed to optimize these delivery systems by improving their stability in biological environments, ensuring large-scale reproducibility, and conducting extensive in vivo evaluations to confirm their therapeutic potential (Table 3).

Table 3. Bioactive compounds loaded in liposomes and niosomes.

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Loaded Bioactive Compounds	Phospholipids and surfactants used	Methods of preparation	Outcomes	Potential Applications	Ref.
All-trans retinoic acid (ATRA)	Phosphatidylcholine, cholesterol, and polyethylene glycol (PEG)	Reversed-phase evaporation	• Reported particle size and EE% of 200 nm and 82%, respectively. • Exhibited remarkable stability in 60% FBS. • Enhanced anticancer effect on thyroid carcinoma cell lines (FRO, PTC-1, and B-CPAP).	Potential therapy for anaplastic thyroid carcinoma	85
α-Tocopherol	Dicetyl phosphate (DCP), cholesterol, Span 60, and Tween 60	Film hydration technique	• Showed particle size range, ZP, EE%, and PDI of 107-190 nm, -30 mV, > 80%, and 0.34. • Improved stability with DCP and cholesterol. • Exhibited initial burst release followed by sustained release.	Novel oral carrier for α-Tocopherol and other lipophilic bioactives	86
Curcumin and α-tocopherol	Cholesterol and soy lecithin	Homogenization method	• Reported particle size range and EE% of 14-16 μm and more than 90%, respectively. • Encapsulated nutraceuticals did not alter the sensory attributes of the cookies. • Retained antioxidant activities of the loaded bioactives.	Fortification of cookies and other food products with curcumin and α-tocopherol	87

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Gallic acid/curcumin and quercetin/vitamin C	Tween 60	Film hydration method	• All niosomes had particle sizes from 500 nm to 700 nm. • Combination of two nutraceuticals substantially increased the antioxidant activity and aqueous solubility.	Alleviation of diseases caused by oxidative stress	88
Gallic acid from Indian gooseberry and sappan wood	Poloxamer 407, cholesterol, Span 60, and Tween 80	Ethanol injection technique	• Reported particle sizes between 96-400 nm. • Decrease in mucus penetration caused by incorporation of poloxamer 407. • Enhanced anti-inflammatory activity due to the combination of two extracts.	Targeted transmucosal delivery system for mitigation of mucositis	89
Curcumin and fatty acids of fish oil (n-3 and n-6 PUFAs)	Phosphatidylcholine and biopolymers (WPI and chitosan)	Maillard reaction	• Exhibited ZP and EE% of 29 mV and >92%, respectively. • Enhanced bioavailability, sustained release, and increased mucoadhesiveness of the encapsulated nutraceuticals at pH 1.2 and pH 6.8. • Increased solubility and stability of curcumin.	Novel oral delivery system for lipophilic bioactives	90
Lipophilic: n-3 PUFAs, vitamin D3, and eugenol ***Hydrophilic:*** γ-aminobutyric acid	Phosphatidylcholine and biopolymers (WPI and chitosan)	Maillard reaction	• Reported remarkable encapsulation efficiencies for lipophilic (> 80%) and hydrophilic bioactives (> 49%). • Reduced microviscosity and	Targeted oral delivery system for lipophilic and hydrophilic nutraceuticals	91

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			particle size leading to enhanced aqueous solubility and excellent stability. • Increased bioavailability of the encapsulated nutraceuticals resulting in their interaction with bile salts and mucin in the small intestine.		

2.4 Nanoparticles

Nanoparticles (NPs) are extensively employed as drug delivery systems due to versatility in composition, which composes a variety of materials, including proteins [92], lipids [93], and polymers such as poly-D, L-lactide-co-glycolide(PLGA) [94], polylactic acid (PLA) [95], poly-ε-caprolactone (PCL) [96], chitosan [97], alginate [98], and lignin [99] . These materials offer unique properties for encapsulating bioactives and ensuring controlled release. The use of food-grade materials is imperative to ensure safety and compliance for applications in the food and nutraceutical industries. Zein [100], chitosan [101], gelatin [102], and lignin [103] are a few examples of the food-grade materials employed in NP formulation (Figure 4). These materials not only provide biocompatibility and biodegradability but also align with the regulatory requirements, making them suitable candidates for delivering bioactive compounds in functional foods and dietary supplements.

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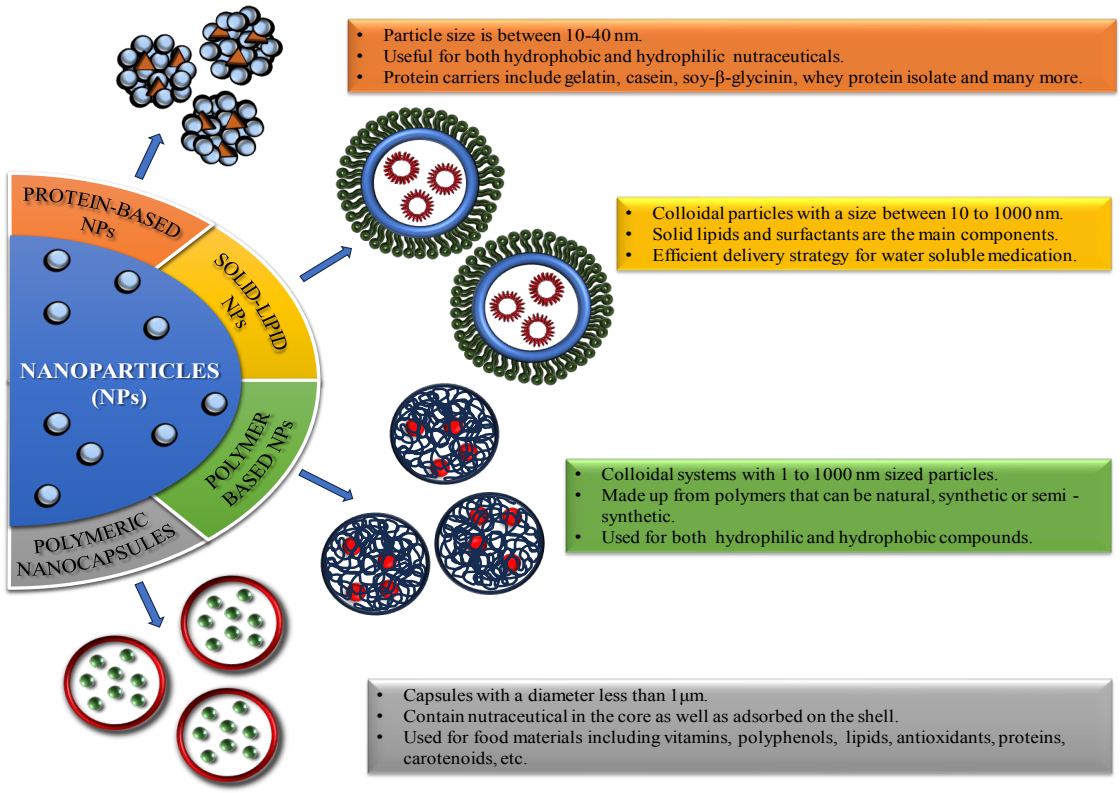

Figure 4. Classification of nanoparticles based on material used to prepare them for delivery of nutraceuticals.

2.4.1 Protein-based Nanoparticles

Protein-based NPs, with particle sizes ranging from 10 to 40 nm, exhibit several desirable characteristics, such as bioavailability, biodegradability, non-antigenicity, high nutritional value, and exceptional binding capacity for various bioactive compounds [92]. These properties, combined with their non-toxic and biodegradable attributes, have increased research interest in their development. They can effectively deliver hydrophilic and hydrophobic nutraceuticals and are derived from sources such as bacteria, plants, animals, and fungi. Key methods for their synthesis include nanoprecipitation, emulsification, nano-spray drying, coacervation, desolvation, self-assembly, and cross-linking [104]. Protein carriers include gelatin, casein, whey protein, albumin,

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and collagen derived from animals, as well as soy-β-glycinin, wheat gliadin, and zein from plants [105–107].

Sunflower seed protein isolate (SFPI) NPs encapsulated curcumin, a hydrophobic anti-inflammatory compound, significantly enhancing its solubility, stability, anti-oxidant, and anti-inflammatory properties. The encapsulation efficiency was observed at 83 ± 3%, with improved curcumin solubility (8.1μg/ml). Additionally, encapsulated curcumin demonstrated higher lipoxygenase activity (IC_{50} = 45.3 μM) compared to free curcumin. However, the study did not explore the long-term stability or in vivo performance of SFPI-encapsulated curcumin, limiting its translational applicability [108]. Similarly, Liu L et al. synthesized soy-β-glycinin NPs employing urea-induced disassembly and reassembly techniques to deliver curcumin. These core-shell nanostructures, comprising an aggregated β-subunit core and hydrophilic α- and α'- subunit shell, achieved a remarkable EE% (79%) and improved curcumin bioaccessibility (40%) compared to free curcumin (20%). These soy β-conglycinin nanostructures offer a potential biocompatible delivery mechanism for hydrophobic substances [109]. In a parallel investigation, casein NPs, synthesized via coacervation and stabilized with lysine or arginine, demonstrated gastro-resistance and enabled controlled intestinal release of vitamin B_9. These NPs, with an average size of 150 nm, contained 25 mg of vitamin B_9 per mg and improved oral bioavailability in vitro. However, the absence of in vivo pharmacokinetic data limits the conclusions regarding their efficacy as an oral delivery system for vitamin B_9 [110].

Another study brought attention to the development of plant-based protein NPs encapsulating quercetin that were resistant to gastric digestion, antioxidant, and stable enough to withstand higher temperatures [111]. High-intensity sonication was employed to prepare soybean, rice, and walnut protein-based NPs with particle size < 110 nm and PDI < 0.20. These NPs exhibited remarkable

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thermal stability, antioxidant activity, and resistance to gastric digestion while maintaining morphology during digestion. This study provided valuable insights into the development of plant protein-based NPs as promising delivery systems for bioactive compounds [111].

Beyond nutraceutical delivery, protein-based NPs have emerged as promising candidates for targeted drug delivery in cancer therapy. A novel study synthesized capsaicin-encapsulated lactoferrin-functionalized carboxymethyl dextran-coated egg albumin NPs (Cap-LF-CMD-EA-NPs) for the treatment of colorectal cancer. The preparation involved esterification, Maillard reaction, and gelation, where hydrophobic interactions between capsaicin and protein polymers facilitated nanoparticle formation [112]. Spectral analyses reported the successful synthesis of smooth and spherical NPs with excellent EE% and DL%. Drug release studies revealed sustained release of capsaicin (up to 80% in 24 hours) in pH 5.8 with anomalous transport attributed to CMD and EA matrix shell. Moreover, enhanced cytotoxicity against HCT116 and LoVo cell lines was observed owing to the overexpression of lactoferrin receptors in colorectal HCT116 cells. This study illustrates the potential of functionalized protein carriers for the treatment of colorectal cancer [112].

Overall, protein-based NPs present a versatile and biocompatible platform for the encapsulation and delivery of bioactive compounds. Their tunable physiochemical properties, combined with high encapsulation efficiency and controlled release capabilities, make them promising candidates for applications in nutraceuticals and targeted drug delivery. However, future research is warranted to optimize their stability, large-scale production, and in vivo performance to facilitate clinical translation.

2.4.2 Polymer-based nanoparticles

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Polymeric NPs have emerged as promising vehicles for the targeted and controlled delivery of nutraceuticals, offering enhanced stability, biocompatibility, and therapeutic efficacy. These nanocarriers, composed of natural, synthetic, or semi-synthetic polymers, exhibit particle sizes ranging from 1-1000 nm [113]. Their biocompatibility, biodegradability, and capacity for surface modification make them ideal candidates for addressing challenges associated with conventional drug and nutraceutical delivery systems. The natural polymers most commonly employed are gelatin, chitosan/chitosan derivates, alginate, and lignin. Synthetic polymers include PLGA, PLA, PCL, and PAMAM (polyamidoamine) [114].

Chitosan nanoparticles (CS-NPs) have been extensively studied for their potential in targeted cancer therapy. In one of the studies, liver-targeting nanosystems were developed that utilized trans-resveratrol-loaded (CS-NPs) to target hepatic carcinoma. The researchers modified the nanoparticle surface with biotin (B-CS-NPs) or biotin and avidin (A-B-CS-NPs) to enhance cellular uptake and adhesion to cancer cell lectins [115]. NPs were prepared via ionic gelation, a technique known for its simplicity and ability to encapsulate hydrophilic drugs. In vitro studies on HepG2 cells revealed that modified CS-NPs exhibited superior anticancer activity compared to free trans-resveratrol, showcasing enhanced cellular internalization and sustained drug release. However, chitosan's solubility limitations at physiological pH may restrict systemic applications, necessitating further optimization [115].

A separate investigation brought attention to the development of PLGA-NPs encapsulating resveratrol modified with chitosan-folate (RSV-CS-F-PLGA-NPs), prepared using a single emulsion solvent evaporation method, as an innovative targeted delivery system for prostate cancer [116]. This technique yields highly stable nanoparticles with remarkable drug-loading efficiency. Biological assays on the PC-3 prostate cancer cell line indicated that these NPs induced oxidative

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stress and apoptosis more effectively than free resveratrol. This study affirms the potential of RSV-CS-F-PLGA-NPs as an efficacious treatment option for prostate cancer. Despite their advantages, PLGA NPs may suffer from burst release effects, though chitosan coating helps mitigate this limitation by providing an additional diffusion barrier [116].

Another study explored the application of PLA nanoparticles to deliver quercetin, prepared using the solvent evaporation method, as a novel approach. The resulting NPs exhibited a particle size of 130 nm, remarkable EE% of 96.7%, and controlled quercetin release, preserving quercetin's bioactivity [117]. Fluorescence quenching studies confirmed the protective effect of PLA NPs on quercetin stability. This study paved the way for encapsulating anti-oxidant nutraceuticals toward the development of better therapeutic compounds [117].

Vitamin D_3 (VD_3)-loaded tyrospheres were developed for topical applications to enhance bioactive stability and skin penetration. These polymeric nanospheres demonstrated high drug loading efficiency and protected VD_3 from photodegradation and hydrolysis. The ease of formulation and improved drug retention made tyrospheres attractive for dermatological applications, though their limited penetration depth may require complementary techniques for systemic effects [118]. Furthermore, Prabhuraj et al. developed PLGA NPs loaded with curcumin, coated with polyethylene glycol (PEG), and conjugated with various targeting moieties, folic acid, hyaluronic acid, and transferrin. The solvent evaporation method produced homogenous, well-coated NPs with enhanced circulation time and reduced macrophage uptake. TEM imaging confirmed particle size increase from 85 nm to 124 nm upon PEGylation, correlating with prolonged drug release and enhanced efficacy against aggressive and metastatic MDA-MB-231 breast cancer cells. Nevertheless, PEGylation can sometimes trigger immune responses, which may limit clinical translation [119].

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A composite nanoparticle system incorporating hydroxyapatite and PLA NPs encapsulating capsaicin (Cap-HA/PLA-NPs) was developed utilizing the ultrasound-assisted dispersion method. SEM imaging revealed uniform, spherical NPs (approximately 50 nm), while pharmacokinetic studies demonstrated prolonged drug release and significantly enhanced bioavailability [120]. The biphasic release profile, influenced by HA concentration, allows for initial rapid release followed by sustained release. They exhibited remarkable biocompatibility and served as effective long-term controlled release carriers, thereby improving the solubility and bioavailability of lipophilic drugs. However, the complex synthesis process and potential for aggregation may present formulation challenges [120].

Various other studies related to biodegradable polymers used to encapsulate nutritional supplements into polymeric nanoparticles along with their targeted applications have been summarized in Table 4. These studies highlight the versatility of polymeric NPs in nutraceutical delivery. While natural polymers offer superior biocompatibility and safety, synthetic polymers provide adjustable drug release kinetics and structural stability. The choice of polymer, surface modification strategy, and fabrication method must be tailored to the desired therapeutic outcome. Future research should focus on optimizing formulation parameters, scaling up production, and conducting comprehensive in vivo studies to facilitate clinical translation. By addressing these challenges, polymeric nanocarriers hold immense potential to revolutionize nutraceutical and drug delivery systems.

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456 **Table 4. Polymers used for encapsulating bioactive compounds in polymeric nanoparticles**
457 **and nanocapsules.**

458

Loaded Bioactive Compounds	Polymers used for encapsulation	Methods of preparation	Outcomes	Targeted Applications	Ref.
Capsaicin	α-lactalbumin	Self-assembly	• Enhanced rate of capsaicin endocytosis. • Deep penetration and anti-lipogenesis impact on steatotic HepG2 spheroid model.	Treatment of Non-Alcoholic Fatty Liver Disease (NAFLD)	121
	Alkali Lignin	Modified nanoprecipitation	• Enhanced cellular internalization of Cap-LNPs in HepG2 cells. • Decreased intracellular triglyceride accumulation in OA-induced HepG2 cell model confirmed by Oil Red O staining and triglyceride quantification.	NAFLD and other chronic liver-inflammatory conditions	99
Curcumin	β-lactoglobulin (BLG)	Desolvation	• Loading efficiency(LE) upto 157%. • The ideal level of glutaraldehyde dropped by 50% when the curcumin/protein ratio rose.	Targeted delivery of curcumin	122
	PLGA(Polylactic-co-glycolic acid)	Solvent displacement	• Hyaluronic acid and folic acid were superior targeting moieties amongst hyaluronic acid, folic acid, and transferrin.	Targeted therapy for breast cancer	119

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			• Highly effective against metastatic MDA-MB-231 breast cancer cells		
	Chitosan	Oil-in-water emulsification and ionotropic gelation technique	• Formed NPs demonstrated superior biopharmaceutical and biological activities compared with free curcumin. • Improved mucoadhesion, cytotoxicity, and cellular uptake against Caco-2 cells. • Showed improved antioxidant and anti-inflammatory properties in activated RAW264.7 cells.	Targeted therapy for colon cancer	123
	Alginate	Self-assembly	• Hydrophilicity and bioavailability of curcumin increased. • Alg-Cur effectively reduced inflammation in RAW264.7 cells.	Ulcerative colitis treatment	124
	Albumin	Self-assembly	• Encapsulation efficiency and loading capacity were 83.22% and 8.33%. • Showed glutathione (GSH)-triggered curcumin release. • *In vitro* results showed increased cytotoxicity against MDA-MB-231 triple-negative human breast cancer cells	Targeted drug delivery system for breast cancer	125

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Resveratrol	Chitosan	Conjugation with biotin alone and along with avidin Solvent displacement method	• Both B-CS-NPs and A-B-CS-NPs had improved anti-cancer activity against HepG2 cells. • Conjugation with biotin enhanced the hepatic tissue penetrability. • B-CS-NPs were less cytotoxic than A-B-CS-NPs.	Targeted resveratrol delivery for hepatic carcinoma	115
	Chitosan/γ-polyglutamic acid (γ-PGA)	Ionic gelation	• Stability and solubility of resveratrol-loaded NPs were affected by their particle size. • Nanoencapsulation improved resveratrol solubility and stability. • Stability rose but solubility dropped with an increase in particle size.	Targeted delivery system for resveratrol	126
	Alkali lignin	Self-assembly	• Exhibited improved stability and anti-neoplastic activity of RSV. • Demonstrated remarkable drug loading efficiency (above 20% wt).	Targeted delivery system for lipophilic drugs.	127
Silibinin (SIL)	Bovine serum albumin (BSA)	Nano-precipitation	• SIL/BSA NPs reported to have a diameter of 90nm. • Reduced acute liver damage caused by APAP and LPS/D-GaIN in mice. • Exhibited antioxidant benefits	Innovative treatment strategy for acute liver injury	128

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			against intracellular oxidative stress.		
	PLGA/PCL	Double emulsion solvent evaporation technique	• Reported particle size of 284 nm. • Exhibited sustained release upto 48h. • Improved cell inhibition in human lung cancer cell line.	Targeted delivery system for pulmonary carcinoma	129
Quercetin	Chitosan	Ionic gelation	• NP's size (< 200nm) and encapsulation efficiency of 79.78% were reported. • *In vitro* results showed quercetin release of about 67.28%. • IC_{50} value reduced in *in vitro* cytotoxicity assay.	For the treatment of lung and breast cancer	130
	PCL	Modified nanoprecipitation technique	• Particle size, ZP, PDI, and EE% of NCs reported to be 230nm, -17.5mV, 0.383 and 93%, respectively. • Demonstrated biphasic release i.e., initial burst release followed by sustained release. • More effective intranasally as compared with the oral route of administration.	Innovative targeted delivery system for anxiety treatment	131
	Prunus armeniaca gum exudate	Ionotropic gelation	• Exhibited remarkable EE% and sustained drug release.	Targeted drug-delivery system for quercetin against	132

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			• Demonstrated significant reduction in bacterial load, IL-6 and IL-1β in the kidney tissues. • Greatly improved intestinal permeation and stability of bioactive.	antibiotic-resistant *S.aureus* bacteria	
	Eudragit L-100	Sonication along with emulsification solvent evaporation	• Administered orally to streptozotocin-induced diabetic rats for 21 days. • Exhibited significant anti-diabetic effect on rats.	Innovative targeted drug delivery system for diabetes	133
	PLA (Polylactic acid)	Solvent evaporation	• Exhibited remarkable antioxidant activity. • Reported to have a particle size of 130nm and EE% of 97%. • Demonstrated initial burst release followed by sustained release.	Innovative delivery system for quercetin and other anti-oxidant bioactives.	117
Fucoxanthin	Alginate and chitosan	O/W emulsification and ionic gelation	• Exhibited particle size, ZP, and EE% of 225nm, 35.3mV and 81%, respectively. • Displayed remarkable stability in simulated environmental conditions. • Improved bioavailability, anti-oxidant property, and cytotoxicity in various cancer cells.	Innovative delivery system for fucoxanthin as well as other bioactives	134

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Vitamin B_9 (Folic acid)	PLA	Nanoprecipitation technique	• NP's size, PDI, and EE% were reported to be 180nm, 0.18, and 89% respectively. • Exhibited higher cellular uptake for breast(MDA-MB-231) and bladder (RT4) cancer cells.	Targeted glycoalkaloidic delivery strategy for breast and bladder cancer treatment	135
	PLGA	Nanoprecipitation	• Cytotoxicity in normal and tumor cells was reported. • IC_{50} for folic acid was 4 times lower than 5-fluorouracil-loaded PLGA NPs.	Targeted 5-fluorouracil delivery system for treatment of colon and breast cancer	136
Vitamin D_3 (VD_3) (Cholecalciferol)	Tyrospheres (tyrosine-derived nanospheres)	Centrifugation and dispersion	• Shielded the bioactive compound against photodegradation and hydrolysis. • Enhanced the stability of VD_3.	Topical delivery of vitamin D_3	118
	Ovalbumin	Water-in-oil-in-water double emulsion solvent evaporation method	• Inhibited the production of ovalbumin-specific-CTLs by intravenous administration of NPs.	Anti-specific immune suppression	137
Vitamin K_1 (VK_1)	Alginate	Nanoprecipitation	• Reported to have an average diameter of 211 nm and ZP of -15 mV. • Exhibited enhanced stability of VK_1 • Demonstrated higher retention of VK_1 in the epidermal layer of skin.	Transdermal delivery of VK_1	138
α-tocopherol	Alginate	Ionotropic gelation	• Reported particle size of 21.9nm and EE% of 77%	Spinal cord injury treatment	139

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			• Exhibited improved cell viability and anti-oxidant activity in human astrocyte spinal cord cells.		
	PLGA	Nanoprecipitation	• Reported to have a mean diameter of 165nm and 172nm at lab and pilot scale, respectively. • Greatly improved antioxidant activity of vitamin E.	Innovative delivery system for vitamin E	140

2.4.3 Polymeric nanocapsules

Polymeric nanocapsules represent a cutting-edge approach for encapsulating bioactive compounds within a polymeric membrane, enhancing stability, bioavailability, and therapeutic efficacy. Unlike polymerosomes, nanocapsules have a hydrophobic liquid core, and their properties are highly influenced by polymer composition, molecular geometry, and relative monomer length (Figure 5). Encapsulation boosts product storage stability, safeguards the bioactive chemical from the environment, and maintains the health-promoting activities of nutraceuticals [141]. The most popular encapsulation method for food materials including vitamins, polyphenols, lipids, antioxidants, proteins, carotenoids, etc, is spray drying, though other methods like nanoprecipitation, double emulsion, and self-assembly are widely employed [142]. Various polymeric wall materials, including sodium alginate, arabic gum, trehalose, whey protein, and modified starch are commonly used to form the nanocapsule wall, each influencing the final nanoparticle properties [143].

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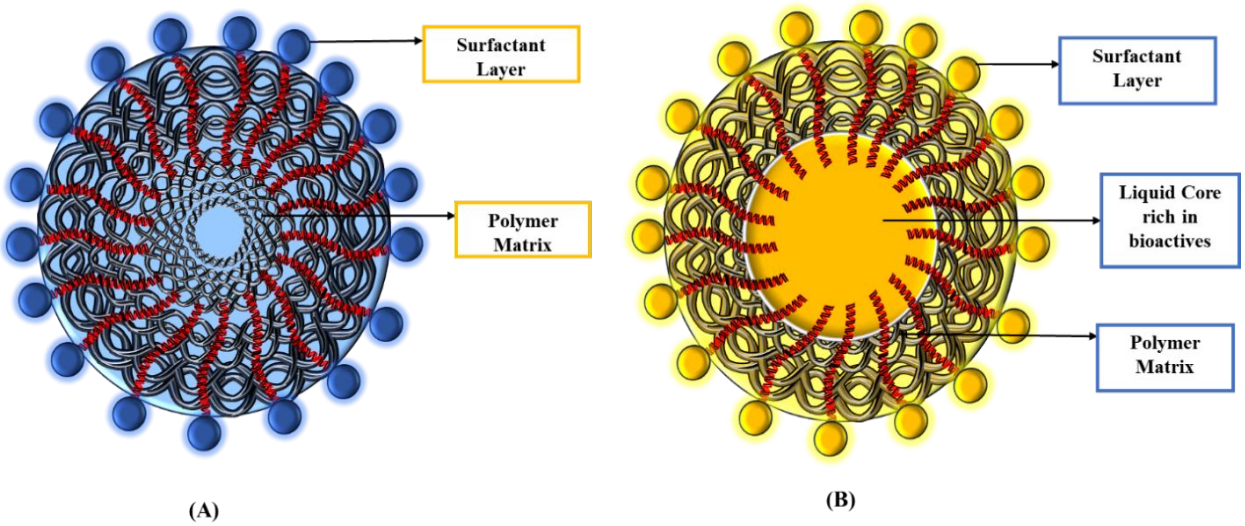

Figure 5. (A) Polymeric nanoparticles (B) Polymeric nanocapsules

One of the significant applications of polymeric nanocapsules is improving the bioavailability of essential nutrients. A study investigated the encapsulation of vitamin K_1 (VK_1) into sodium alginate nanocapsules using the nanoprecipitation method [138]. These nanocapsules reported an average diameter of 211nm and a negative zeta potential of 15 mV. Franz-type diffusion and tape-stripping assays revealed enhanced VK_1 retention in the dermis while reducing unwanted systemic absorption. This highlights nanocapsules' potential in transdermal delivery, though their negative zeta potential may impact long-term stability [138].

Similarly, Khayata et al. developed α-tocopherol-loaded nanocapsules (α-T NCs) utilizing the membrane contractor approach, showcasing their promising potential at lab and pilot scales [140]. These nanocapsules exhibited particle sizes of 165 and 172 nm at the lab and pilot scales, respectively, with remarkable encapsulation efficiencies of 98% and 97%. A six-month accelerated stability study revealed that α-T NCs were stable without significant changes in mean diameter,

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zeta potential, and drug encapsulation efficiency. More importantly, the antioxidant activity of vitamin E was significantly improved due to its nano-encapsulation, underscoring the potential of nanocapsules in improving the functionality of dietary antioxidants. Despite these benefits, membrane contractor methods may require precise parameter control for scalability [140].

Expanding on the application of natural bioactives, Abbas et al. developed multilayered curcumin-loaded nanocapsules using the self-assembly method [144]. The study utilized the ultrasound-assisted NEs as templates, where the polyelectrolytes such as chitosan, partially deacylated chitosan, sodium carboxymethylcellulose (Na-CMC), and purity gum ultra (OSA-modified starch) were employed for the fabrication of stable multilayered curcumin nanocapsules. The outcomes suggested that regulated sonication played a crucial role in producing uniform NE droplets, providing a scalable approach for encapsulating hydrophobic bioactives with enhanced stability [144].

Beyond improving bioavailability, polymeric nanocapsules have shown remarkable therapeutic potential in the treatment of colorectal cancer [145]. For instance, the co-encapsulation of curcumin and salicylic acid within mucoadhesive copolymer m-PEG-b-PCL NCs demonstrated a sustained release profile and strong adhesion to colonic mucosa. They exhibited particle size of less than 500 nm and a remarkable EE% of 14% and 91% for curcumin and salicylic acid, respectively. The ability to co-deliver multiple therapeutic agents highlights the versatility of nanocapsules in colorectal cancer treatment [145].

For advancing cancer treatment, dual-targeted folic acid-PLGA NCs encapsulating pterostilbene were developed for alleviating hepatocellular carcinoma (HCC) [146]. They exhibited a particle size of 220 nm and sustained release of pterostilbene for up to 48 hours. More importantly, they demonstrated superior anticancer activity compared to free pterostilbene, with a 20-fold reduction

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in IC_{50} against HepG2 cells. In-vivo investigations conducted on HCC-induced animals further showcased the superiority of dual-targeted nanocapsules over the free pterostilbene while enhancing apoptotic signaling, reinforcing their potential for targeted cancer therapy [146].

In addition to synthetic polymeric carriers, natural nanocarriers have also been explored for bioactive delivery. A study utilizing lotus sporopollenin-based exine capsules for anthocyanin delivery, isolated from red cabbage, demonstrated their potential as an oral delivery system [147]. The prolonged acidolysis technique successfully converted microcapsules into nanocapsules with a hydrodynamic size of less than 220 nm and a PDI of less than 0.25, indicating uniform size distribution. HRSEM images confirmed the structural stability of these nanocapsules, even under gastric acid conditions, underscoring their potential as a promising vehicle for various plant-derived bioactive compounds. The natural origin of sporopollenin enhances biocompatibility, though the acidolysis process may affect production efficiency [147].

These studies underscore the versatility of polymeric nanocapsules in improving the bioavailability, stability, and targeted delivery of bioactive compounds. The integration of natural and synthetic polymers further expands the potential of nanocapsules, paving the way for innovative advancements in bioactive encapsulation. The choice of polymer, encapsulation method, and surface modification strategy directly impact the efficacy and practicality of the delivery system. Future research should focus on optimizing these parameters, exploring alternative biodegradable polymers, and conducting long-term in vivo studies to ensure clinical translation.

2.4.4 Lipid-based nanoparticles

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Lipid-based nanocarrier systems, particularly solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs), have gained significant attention for their ability to enhance the stability, bioavailability, and therapeutic efficacy of lipophilic bioactive compounds [148,149]. SLNs consist of solid lipids and surfactants, forming colloidal particles ranging from 10 to 1000 nm, and serve as an efficient delivery strategy for corrective dynamic therapy and water-soluble medication [150]. In contrast, NLCs contain an aqueous phase with surfactants and an unstructured solid lipid matrix, typically comprising a solid-to-liquid lipid ratio of 70:30 to 99:9:0.1, with surfactant concentrations between 1.5% and 5% (w/v) [149]. Various techniques, including ultrasonication, solvent evaporation, solvent emulsification-diffusion, and supercritical fluid methods, are employed for their synthesis [151].

Liposoluble nutraceuticals, including carotenoids, vitamins A, D, and E, omega-3 fatty acids, and essential oils, are compatible and miscible with the lipid matrix used in these nanovehicles [152–154]. For instance, researchers have improved the physicochemical stability of β-carotene by encapsulating it within WPI-stabilized SLNs containing palmitic acid and corn oil. The palmitic acid crystals developed a protective shell around the oil droplets' surface, enhancing the oxidative stability, while WPI contributed to colloidal stability. This strategy highlights the potential of SLNs in improving the shelf life and bioavailability of carotenoids in functional foods and supplements[155].

Another promising nutraceutical, lutein, acts as a free radical scavenger and blue light filter, making it a valuable candidate for skincare applications [156,157]. Researchers formulated lutein into SLNs, NLC, and NEs using high-pressure homogenization technique, with particle sizes ranging from 150 to 350 nm [158]. NE exhibited the highest in vitro release of lutein among the three forms.

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554 The study underscored the potential of these nanocarriers as novel antioxidant, and photoprotective
555 agents, capable of shielding the skin from blue-light induced oxidative stress and photodamage [158].

556 In another study, ergocalciferol (vitamin D_2) was encapsulated in tripalmitin-based SLNs
557 stabilized with Tween 20 using a nozzle-type high-pressure homogenizer and the hot
558 homogenization method. The SLN dispersion, formulated with 5% w/w ergocalciferol , exhibited
559 particle sizes between 65 and 120 nm, depending on the vitamin concentration. The outcomes
560 indicated that the higher vitamin D_2 concentrations enhanced the stability of the lipid crystal
561 structure, improving protection against oxygen and light exposure. This approach presents an
562 alternative delivery strategy for vitamin D_2 in functional foods, such as fortified milk and
563 margarine, though further studies are needed to ensure sustained bioavailability post-ingestion [159].

564 Beyond nutraceuticals, SLNs have also been explored for their therapeutic applications. One study
565 focused on improving the intestinal permeability and bioavailability of γ-Tocotrienol (γ-T_3), a
566 member that belongs to the vitamin E family with limited absorption due to its lipophilicity [160,161].
567 Encapsulation of γ-T_3 in SLNs via the solvent evaporation technique led to a marked enhancement
568 in oral bioavailability by increasing passive permeability, as confirmed by in-vivo investigations.
569 However, the study emphasized the need for further optimization to maximize absorption
570 efficiency and metabolic stability [161].

571 The therapeutic potential of lipid nanocarriers extends to cancer treatment. Researchers developed
572 quercetin-encapsulated SLNs employing stearic acid and tripalmitin, stabilized with Tween 80 and
573 Span 80 , and optimized their formulation using the Box-Behnken design approach [162]. The
574 resulting SLNs exhibited spherical shapes with reduced particle size of 132 nm and outstanding
575 EE% of 98%, facilitating gradual release of quercetin for up to two days. Furthermore, the in-vitro
576 cytotoxicity investigations conducted on the Caco-2 cell line at IC_{50} of 49µM/ml demonstrated the

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therapeutic effectiveness of quercetin-loaded SLNs by inducing apoptosis along with minimal necrosis and oxidative stress in the cancer cells. However, challenges such as large scale production, long-term stability, and in-vivo biodistribution remain areas for future research [162].

Overall, SLNs and NLCs offer a versatile platform for the delivery of nutraceuticals and therapeutics, with applications ranging from functional foods to cancer therapy. Despite their advantages, challenges such as scale-up feasibility, long-term stability, and precise control over drug release kinetics must be addressed. Future research should focus on optimizing formulation parameters, improving biocompatibility, and conducting extensive in vivo studies to validate their efficacy and safety for clinical applications.

2.5 Nanocrystals

Nanocrystals are nanosized formulations composed of drug particles stabilized using appropriate stabilizers or surfactants, which typically fall within the nanometre size range, often between a few nanometres and 1000 nm [163]. These nanocrystals are often formulated as nanosuspensions by dispersing them in an aqueous media [164]. Unlike polymeric or lipidic nanoparticles, nanocrystals consist entirely of the active pharmaceutical ingredient or nutraceutical molecule, offering a pure drug delivery system. Their synthesis involves either the application of high-energy size reduction techniques to macro-sized drug dispersions in the presence of stabilizers or precipitation of the drug from an organic solvent upon the addition of an aqueous solution of surfactant or stabilizer [165].

Recent studies have demonstrated the potential of nanocrystals in improving the bioactivity and stability of various bioactive compounds. For instance, Akhlagi et al. encapsulated vitamin C (VC) in cellulose nanocrystals grafted with chitosan oligosaccharide via ionic complexation with

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tripolyphosphate. This formulation significantly improved the stability and free radical scavenging activity of VC. Notably, these nanocrystals exhibited encapsulation efficiencies of 72% and 91% at pH 3 and 5, respectively. These findings underscore the potential of nanocrystals in preserving the functionality of antioxidant molecules; however, further investigation into their long-term stability and release kinetics is warranted [166].

Similarly, another notable study investigated the synthesis of quercetin-loaded-cellulose nanocrystals (QCT-CNCs) derived from celery stalks. Morphological analysis using FESEM and TEM revealed spherical nanocrystals with a reduced particle size from 600nm to 400nm [167]. X-ray diffraction analysis confirmed the successful hydrolysis of the cellulose, and FTIR analysis indicated reduced crystallinity due to quercetin-cellulose interactions. Furthermore, binding affinity studies with human holo transferrin (HHT) demonstrated fluorescence quenching, confirming the interaction between QCT-CNCs and HHT. These findings suggest that QCT-CNCs represent a promising nanocarrier delivery strategy for quercetin and other bioactive compounds. However, challenges such as optimizing drug loading efficiency, stability, and in vivo biodistribution require further investigation [167].

Beyond preserving the natural structure and bioactivity of nutraceuticals, nanocrystals also aid in improving the therapeutic index of various bioactive compounds. One such study by Ndong Ntoutoume et al. explored the application of curcumin-loaded-cyclodextrin/cellulose nanocrystals (Cur-CdxCNs) for the treatment of colorectal and prostate cancer. These nanocrystals were prepared via ionic association with cationic β-cyclodextrin (CD). The in vitro assessments demonstrated promising anticancer activity on colorectal and prostatic cell lines, although the study was limited by the absence of in vivo validation, highlighting the necessity for further preclinical evaluation to assess its pharmacokinetics and therapeutic efficiency [168].

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Delving further into the therapeutic potential of nanocrystals, Manca et al. synthesized quercetin nanosuspensions via the wet media milling technique, employing Tween 80 and Poloxamer 188 as stabilizers for treating skin disorders [169]. The resulting quercetin nanocrystals, characterized by DSC, FTIR, and X-ray powder diffractometry, exhibited mean particle diameters ranging from 326 to 474 nm with a PDI below 0.30. This nanosizing approach significantly improved the solubility and bioavailability of quercetin, enhancing its potential for treating skin disorders. In vitro evaluations utilizing keratinocytes confirmed its dermatological applications, however, further clinical studies are required to determine its efficacy in human subjects and asses potential cytotoxicity concerns at higher concentrations [169].

While nanocrystals offer a versatile platform for enhancing drug solubility, stability, and bioavailability, several limitations must be addressed before their clinical translation. These include the need for comprehensive pharmacokinetic studies, optimization of large-scale production techniques, and assessment of potential toxicity associated with prolonged exposure. Future research should emphasize refining nanocrystal formulations for targeted delivery, controlled release, and enhanced therapeutic outcomes in diverse biomedical applications.

3. Navigating the pros and cons of nanocarriers

Nanoformulations provide significant advantages for the encapsulated nutraceuticals, including enhanced bioavailability, improved physicochemical stability, targeted delivery, controlled release, protection against photodegradation, thermal, and oxidative degradation[170,171]. Their nano-size enables superior drug delivery efficiency compared to conventional formulations, facilitating improved therapeutic outcomes. Given these attributes, nanoformulations hold immense potential as preventive and therapeutic alternatives for various diseases such as cancer, diabetes, ocular

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diseases, neurodegenerative disorders, NAFLD, cardiovascular diseases, obesity, mucositis, and many more[172–180].

Despite their numerous merits and potential applications, concerns regarding their safety, environmental impact, and biocompatibility are ambiguous. The reduced particle size of the nanoparticles, liposomes, niosomes, and nanocrystals increases their surface reactivity, potentially contributing to undesirable interactions in the biological systems, cytotoxicity, and other adverse health problems [181]. The different materials used in nanoformulation development, such as polymers, surfactants, cross-linkers, solvents, drugs, and probes, pose additional risks, including cytotoxicity and hemotoxicity. Furthermore, there is a lack of comprehensive, evidence-based studies addressing the long-term toxicity, absorption, clearance, and biodistribution of nutraceutical-loaded nanoformulations in biological systems, contributing to concerns regarding their safety profile [53,90,91]. Another critical challenge is the stability of nanoformulations during storage and transportation. Nanoparticles are prone to aggregation and degradation due to environmental conditions, which can significantly compromise their efficacy[182]. Additionally, the high production cost associated with nanoformulations, driven by the requirement for sophisticated technology, specialized equipment, and stringent manufacturing conditions, limits their large-scale commercialization[183]. Regulatory challenges further complicate the widespread adoption of nanoformulations. The absence of standardized guidelines and discrepancies among regulatory authorities create inconsistencies in evaluating the safety and efficacy of these formulations [184]. Consequently, extensive preclinical and clinical investigations are necessary to establish their therapeutic potential, prolonging the approval process and delaying market entry. Table 5 illustrates a comparative analysis of different nanoformulations discussed in this review based on their production cost, scalability concerns, regulatory challenges, and environmental impact.

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667 **Table 5. Comparative analysis of different nanoformulation strategies.**

Nanoformulations	Production cost	Scalability	Regulatory complexity	Environmental impact	Ref.
Nanogels	High due to the need for specialized polymers and cross-linking agents.	Complex synthesis may hinder large-scale manufacturing.	Limited clinical data may delay regulatory approval.	Potential environmental persistence raises concerns.	185,186
Nanoemulsions	Moderate due to the utilization of relatively straightforward manufacturing techniques.	Amenable to industrial-scale production due to established emulsification methods.	Generally safe, but novel formulations still require comprehensive evaluation.	Generally considered eco-friendly depending on constituent materials.	186,187
Liposomes	Substantial costs as they incorporate high-purity phospholipids and necessitate stringent production conditions.	Feasible but requires meticulous control over size and encapsulation efficiency.	Several FDA-approved liposomal drugs exist; however, new formulations must undergo rigorous testing.	Biodegradable components minimize environmental risks.	188–190
Niosomes	Cost-effective alternative to liposomes as they employ non-ionic surfactants.	Simpler preparation methods facilitate scalability.	Face uncertain regulatory pathways as they are emerging carriers.	Biocompatibility suggests low ecological impact.	188,189
Nanoparticles	Cost is determined by the materials used for production. For instance, gold nanoparticles are notably more expensive than polymeric nanoparticles.	Scalability is material-dependent. For instance. Polymeric nanoparticles are generally easier to produce in bulk compared to metallic ones.	Concerns about toxicity and long-term effects necessitate extensive safety assessments.	Non-biodegradable variants, such as certain metals, may accumulate in ecosystems, leading to potential toxicity.	188,191,192
Nanocrystals	Moderate to high costs due to the involvement of sophisticated crystallization techniques.	Challenges in controlling crystal size and purity can impede large-scale production.	Regulatory bodies require detailed characterization and proof of stability.	Environmental effects are largely material-specific and require thorough investigation.	187,190,193

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4. Regulatory considerations and limitations

The integration of nanotechnology in nutraceuticals necessitates stringent compliance and safety regulations to protect consumers and maintain public confidence[194,195]. However, the current global landscape lacks standardized, mandatory legal frameworks specifically governing nano-encapsulated nutraceutical products[196]. Consequently, major global regulatory authorities such as the United States Food and Drug Administration (USFDA), the European Chemical Agency (ECHA), the European Food Safety Authority (EFSA), and the World Health Organization (WHO) have introduced comprehensive guidelines and frameworks to regulate nanotechnology applications in nutraceuticals worldwide [197]. In 2021, EFSA established a structured risk assessment approach for nanomaterials in numerous food and feed products, emphasizing physicochemical characterization, scientific evaluation procedures, transparency in regulatory communication practices, and active stakeholder engagement through public consultations [198]. Similarly, in 2022, the USFDA issued guidance on key regulatory considerations, including quality assurance, manufacturing protocols, safety assessment, characterization techniques, analytical validation, risk management strategies, and regulatory submission requirements of nano-based drug and biological products, ensuring transparency in procuring new materials, addressing ethical and environmental issues, and promoting international trade and conformity worldwide. [199]. ECHA governs nanomaterials under the Registration, Evaluation, Authorisation, and Restriction of Chemicals (REACH) regulation, yet its adaptation to nano-specific risks remains a challenge due to the evolving nature of nanotechnology [200]. WHO, recognizing the increasing global reliance on nanotechnology, has recommended a risk-based regulatory framework that incorporates both hazard identification and lifecycle assessments of nano-nutraceuticals, addressing potential long-term implications, bioaccumulation risks, and

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environmental impact in humans [201,202]. WHO also emphasizes the need for interdisciplinary research collaborations, promoting the integration of nanotechnology risk management strategies into global public health policies [203].

International initiatives have launched to harmonize risk assessment methodologies to enhance regulatory oversight and ensure the development of standardized testing protocols. The 'Malta Initiative' fosters collaboration between ECHA, Member States, the European Commission, and industry to refine test guidelines that address nano-specific regulatory requirements [204,205]. Similarly, the Horizon 2020-funded NanoHarmony project aims to accelerate the development of harmonized test methods by aligning research institutions with the OECD and ECHA [206,207]. The 'MACRAMÉ Project', an initiative between the European Green Deal and Chemical Strategy for Sustainability, is intended to ensure the safety and sustainability of advanced materials such as carbon nanofibers, polymeric nanoparticles, etc, by developing standardized methodologies for their detection, characterization, and risk assessment throughout their life cycle [208]. Complementing traditional toxicity assessments, computational modeling techniques, including quantitative structure-activity relationships (QSARs) and read-across frameworks, are being increasingly adopted to predict nanomaterial behaviour based on existing datasets. Organizations such as OECD, ECHA, and EFSA are actively supporting research efforts to advance these predictive modeling approaches, thereby improving the efficiency and reliability of safety evaluations. These initiatives collectively contribute to a more robust regulatory landscape, facilitating transparent risk assessments, promoting scientific advancements, and ensuring the safe integration of nanotechnology into nutraceutical applications [209,210].

Despite significant advancements in regulatory guidelines, several gaps persist in understanding the long-term safety implications of nano-encapsulated nutraceutical products in biological

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systems, potentially contributing to ambiguities in risk assessments and insufficient safety measures. The rapid evolution of nanotechnology further complicates regulatory adaptation, rendering guidelines susceptible to obsolescence [211]. The absence of a globally unified regulatory environment exacerbates these challenges, as discrepancies between international regulatory bodies result in inconsistencies in the requirements and standards imposed [212]. This regulatory fragmentation leads to duplicity, market barriers, and potential discrepancies in product safety and quality across different jurisdictions. Furthermore, while current regulatory frameworks prioritize human and animal health, the potential environmental impact of nanomaterials remains an underexplored domain [213]. The fate of nanoformulations in ecosystems, their bioaccumulation potential, and their long-term environmental interactions require systematic evaluation to prevent unforeseen ecological consequences. Addressing these challenges necessitates dynamic and evolving standards of regulatory mechanisms that can adapt to new emerging technologies and scientific enlightenment.

A multifaceted approach must be adopted to enhance the effectiveness of regulatory oversight in nanonutraceuticals. A key priority is harmonizing global standards, which requires a collaborative effort among international regulatory bodies to establish unified guidelines. Furthermore, advancements in risk assessment methodologies are essential to accurately evaluate the interactions of nanomaterials at both molecular and systemic levels. The development of advanced toxicological models and in vitro/in vivo studies to assess nanomaterial interactions at the molecular and systemic levels. Regulatory bodies must integrate continuous scientific advancements to ensure relevance and efficacy in risk management.

Conclusion and Future Perspectives

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Nutraceuticals and dietary supplements play a pivotal role in promoting health and preventing various chronic conditions, including cardiovascular diseases, neurodegenerative disorders, dermatological problems, cancer, NAFLD, ocular diseases, and inflammatory conditions. However, their clinical efficacy is often limited by inherent physicochemical drawbacks such as low bioavailability, high susceptibility to environmental degradation (light, oxygen, and temperature), instability during storage and delivery, and poor aqueous solubility. Nanotechnology has emerged as a transformative strategy in the food and pharmaceutical industries, offering solutions that enhance the bioavailability, stability, and controlled release of nutraceuticals encapsulated in nanocarriers enhancing their biological efficacy. Despite many significant advantages of nano-enabled strategies, several challenges hinder their widespread adoption, including scalability constraints, the requirement of sophisticated equipment, potential toxicity concerns, regulatory ambiguities, and environmental impact. This comprehensive review underscores the applications of nanotechnology in nutraceutical delivery, demonstrating how polymeric and lipid-based nanocarriers facilitate targeted and controlled release of bioactives. The utilization of GRAS biopolymers, including chitosan, alginate, lignin, zein, and casein, further ensures safety, biodegradability, and non-toxicity, making nanotechnology a viable approach for nutraceutical delivery. Additionally, this review critically evaluates existing regulatory frameworks, highlighting the need for harmonized guidelines, robust safety assessments, and transparent policies to enable the integration of nanotechnology into the nutraceutical industry.

Advancements in nanotechnology continue to open new frontiers in nutraceutical delivery. Future research should focus on the development of sustainable nanocarriers derived from eco-friendly, biodegradable polymers to mitigate environmental concerns. Innovations in biopolymeric nanoparticles present significant potential for improving targeted delivery in conditions such as

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NAFLD, cardiovascular diseases, and metabolic disorders. Additionally, nanogels and nano-emulsions hold promise for transdermal and ocular delivery of nutraceuticals, enhancing the therapeutic efficacy for eye and skin disorders. Emerging technologies such as artificial intelligence (AI) and machine learning are set to revolutionize nanocarrier design by optimizing formulation parameters, predicting stability and encapsulation efficiency, and improving drug release kinetics. AI-driven models can accelerate the development of next-generation nanocarriers by simulating interactions between encapsulated nutraceuticals and biological systems, thus reducing reliance on extensive in-vivo experimentation. The integration of AI and sustainable materials in nanocarrier development not only enhances the efficacy and safety of nutraceutical delivery systems but also paves the way for more cost-effective, scalable, and environmentally responsible solutions. Moreover, the integration of wearable biosensors with nanotechnology could enable real-time monitoring of nutraceutical delivery and metabolic responses, facilitating personalized nutrition and precision medicine approaches. With increasing concerns about nanotoxicity and environmental impact, future research should focus on the development of biodegradable smart nanocarriers composed of bioresorbable polymers to ensure safe degradation and minimal ecological footprint. Expanding beyond conventional drug delivery, stimuli-responsive nanocarriers could be tailored for precise gene editing and RNA-based therapies. These systems could enhance CRISPR-Cas9 and siRNA delivery, enabling targeted genetic interventions with minimized off-target effects. The combination of microfluidic nanocarrier synthesis with organ-on-a-chip platforms could accelerate preclinical validation of nanoformulations, reducing the reliance on animal studies and improving translational research outcomes.

To further advance nanotechnology-based nutraceuticals, interdisciplinary collaboration among material scientists, biotechnologists, regulatory bodies, and industry stakeholders is imperative.

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Addressing regulatory challenges, ensuring scalability, and prioritizing safety assessments will be crucial for translating laboratory-scale innovations into commercial products. In conclusion, nanotechnology holds immense potential to revolutionize nutraceutical formulations, paving the way for enhanced therapeutic efficacy, precision-targeted interventions, and sustainable health solutions.

Abbreviations:

PUFA, polyunsaturated fatty acids; CAGR, compound annual growth rate; GRAS, Generally Recognized as Safe; SPI, soy protein isolate; ARPI, acylated rapeseed protein isolate; WPI, whey protein isolate; BSA, Bovine serum albumin; PLGA, Polylactic-co-glycolic acid; PCL, Poly-ε-caprolactone; PLA, Polylactic acid; PAMAM, Polyamidoamine; γ-PGA, γ-polyglutamic acid; TNF-α, Tumor Necrosis Factor alpha; NE, Nano-emulsion; SIRT1, sirtuin 1; VK_1, vitamin K_1; VD_3, vitamin D_3; PDI, Poly Dispersity Index; EE, Encapsulation efficiency; AcKPI, Acylated kidney bean protein isolate; PoV, Peroxide value; TARS, Thiobarbituric acid reactive substances; ATRA, All-Trans Retinoic Acid; DCP, dicetyl phosphate; Chol, Cholesterol; HLB, Hydrophilic-lipophilic balance; ZP, zeta potential; SFPI, sunflower seed protein isolate; NPs, nanoparticles; β-CG, soy-β-conglycinin; IC_{50}, half-maximal inhibitory concentration; SDS-PAGE, sodium dodecyl sulphate polyacrylamide gel electrophoresis; DPPH, 2,2-diphenyl-1-picrylhydrazyl; CS-NPs, chitosan nanoparticles; B-CS-NPs, Biotin chitosan nanoparticles; AIA, anti-inflammatory activity; A-B-CS-NPs, Biotin and Avidin chitosan nanoparticles; BLG, β-lactoglobulin; Cap-LF-CMD-EA-NPs, capsaicin-encapsulated lactoferrin-functionalized carboxymethyl dextran-coated egg albumin NPs; NAFLD, Non-Alcoholic Fatty Liver Disease; LE, Loading Efficiency; GSH, glutathione; SIL/BSA NPs, Silibinin bovine serum albumin nanoparticles; APAP,

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Acetaminophen; LPS/D-GaIN, Lipopolysaccharide/D- galactosamine-induced acute liver injury; CTLs, Cytotoxic T lymphocytes; MRT, mean retention time; Cap-HA/PLA-NPs, capsaicin loaded hydroxyapatite and polylactic acid NPs; TEM, Transmission Electron Microscope; PEG, Poly ethylene glycol; Cur, curcumin; RA, Retinoic acid; HCT116, human colorectal carcinoma cell line; ARPE-19, human retinal pigment epithelial cell line Dopaminergic; RA-NPs, Retinoic acid nanoparticles; m-PEG-b-PCL NCs, copolymer m-PEG-b-PCL nanocapsules; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; SN, Substantia Nigra; PD, Parkinson's disease; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; AFP, α-fetoprotein; Bcl2, B-cell lymphoma 2; HCC, hepatocellular carcinoma; Na-CMC, sodium carboxymethylcellulose; OSA, octenyl-succinic- anhydride; α-T NCs, α-tocopherol-loaded nanocapsules; SLNs, Solid Lipid Nanoparticles; NLCs, Nanostructured Lipid Carriers; γ-T3, γ-Tocotrienol; VC, vitamin C; Cur-CdxCNs, curcumin-loaded-cyclodextrin/cellulose nanocrystals; CD, β-cyclodextrin; DSC, Differential Scanning Calorimetry; FT-IR, Fourier Transform Infrared Spectroscopy; QCT-CNCs, Quercetin-loaded-cellulose nanocrystals; HHT, Human Holo Transferrin; USFDA, United States Food and Drug Administration; ECHA, European Chemical Agency; EFSA, European Food Safety Authority; WHO, World Health Organization; REACH, Registration, Evaluation, Authorisation, and Restriction of Chemicals; OECD, Organization for Economic Cooperation and Development; QSARs, Quantitative Structure-Activity Relationships; AI, Artificial Intelligence.

Author contribution

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JM: Collection of the information, drafting of the manuscript, and writing review; KP: Writing review; SVP: Data curation; conceptualization, planning, analysis, review, and editing. All authors approved the final submitted version of the manuscript.

Conflict of interest

None

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No primary research results have been included and no new data were generated as part of this review.

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