REVIEW PAPER

Advances in nanocarriers for *Zingiber officinale* phytochemicals: enhancing bioavailability and therapeutic potential

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ABSTRACT

Zingiber officinale, commonly known as ginger, is a medicinal plant esteemed for its diverse pharmacological properties, including antioxidant, anti-inflammatory, anticancer, and antimicrobial properties. The primary bioactive compounds found in ginger, particularly gingerol and shogaol, have shown notable therapeutic benefits but are limited by poor solubility, instability, and low bioavailability. Recent advancements in nanotechnology have introduced innovative delivery systems that address these limitations by enhancing stability, improving bioavailability, and facilitating targeted delivery of these bioactive compounds. Notable nanocarrier systems include polymeric nanoparticles, micelles, nanoemulsions, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and metal-based nanoparticles. Research indicates that polymeric and chitosan-based systems significantly enhance the oral absorption, antibacterial efficacy, and DNA-protective properties of ginger constituents. Micellar carriers, specifically, have demonstrated increased oral bioavailability and hepatoprotective benefits of 6-shogaol. Lipid-based nanoparticles have also made notable advances, offering sustained release, enhanced tissue penetration, and high entrapment efficiency for both topical and oral applications. Additionally, green-synthesized metal nanoparticles, including silver, zinc oxide, and iron oxide, have exhibited potent antioxidant, antimicrobial, and anti-inflammatory activities, further establishing their role in expanding the therapeutic potential of ginger. Despite these promising developments, further research is imperative to optimize formulations, assess long-term safety, and determine the feasibility of large-scale clinical application. The integration of nanotechnology into ginger-based therapies holds significant promise for overcoming the limitations associated with traditional formulations and enhancing their therapeutic efficacy.

Keywords*: Zingiber officinale; Gingerol; Nanoparticles; Bioavailability; Nanocarriers.*

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INTRODUCTION

Zingiber officinale Roscoe (Zingiberaceae), commonly known as ginger, has been widely used for centuries as both a culinary spice and a traditional medicine. The ginger rhizome is the most frequently used part and contains a complex phytochemical profile with abundant bioactive constituents. The major constituents of the ginger rhizome are carbohydrates, lipids, terpenes, and phenolic compounds. Moreover, it contains more than 400 bioactive compounds, including alkaloids, saponins, flavonoids, steroids, oleoresin, phytosterols, tannins, glycosides, terpenoids, and various vitamins. Among these, shogaol, paradol, and gingerol are regarded as the principal active compounds and are primarily responsible for the characteristic pungent flavors and aroma of ginger. Ginger has been extensively studied for its various pharmacological action potentials, demonstrating its efficacy in the treatment and prevention of multiple conditions, including diabetes, inflammation, cancer, nausea, and vomiting. Consequently, ginger exhibits various biological activities, including antioxidant, hypocholesterolaemia, antimicrobial, neuroprotective, anti-ulcer, antiemetic, and hepatoprotective effects [1–6] Ginger (*Zingiber officinale* Roscoe) has long been valued as both a culinary spice and a medicinal plant, with numerous reported pharmacological effects. Conventional ginger dosage forms, including capsules, tablets, and syrups, continue to play an essential role due to their simplicity, accessibility, and patient familiarity, making them practical choices for daily maintenance.

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However, despite these advantages, conventional formulations face inherent challenges in fully harnessing ginger's therapeutic potential. The main bioactive constituents, such as gingerols and shogaols, possess poor aqueous solubility, are rapidly metabolized, and exhibit low oral bioavailability, which collectively reduce their clinical effectiveness [7,8]. In addition, these compounds are chemically unstable and prone to degradation during processing, storage, or exposure to gastric conditions, which further compromises their pharmacological activity [6]. Rapid systemic clearance and short half-life further hinder their sustained bioavailability, while high doses needed to achieve therapeutic effects may increase the risk of gastrointestinal irritation (e.g., heartburn, reflux, and diarrhea, especially at doses exceeding 5-6 g daily) and inconsistent clinical outcomes [9]. Such limitations limit the consistency and magnitude of therapeutic outcomes achieved with conventional dosage forms.

To overcome these challenges, recent research has focused on developing advanced delivery systems designed to complement conventional preparations rather than replace them. These systems enhance antioxidant activity, as reflected in higher levels of antioxidant enzymes and reduced oxidative stress markers[10]. They also demonstrated the feasibility of large-scale production, supporting their potential application in the pharmaceutical industry and making it a valuable approach for future drug formulation and delivery systems[11]. For example, encapsulation of ginger essential oil within carrier systems not only improves absorption across mucosal membranes but also protects the oil from hydrolysis, oxidation, and volatilization, thereby maintaining its pharmacological activity [8]. Encapsulation protects the oil from hydrolysis, oxidation, and volatilization, thereby preserving its therapeutic properties. Furthermore, such delivery approaches may reduce adverse effects and achieve therapeutic efficacy at lower doses, ultimately contributing to improved patient compliance [12].

In Indonesia, there are three known types of ginger, including *Zingiber officinale* var. Amarum (*jahe emprit*), *Zingiber officinale* var. Roscoe (*jahe gajah*), and *Zingiber officinale* var. Rubrum (*jahe merah*). *Zingiber officinale* (ginger) contains a diverse range of bioactive compounds that account for its broad spectrum of pharmacological activities. The major pungent principles—gingerols, shogaols, and paradols—together with sesquiterpenes such as zingiberene and β-bisabolene, have been widely reported to exhibit antihepatotoxic, anti-inflammatory, analgesic, antimicrobial, and cardiotonic effects (26–28). Among these, zingerone and shogaols demonstrate powerful antioxidant properties, with free radical scavenging activity even greater than that of ascorbic acid. These compounds also contribute to anti-inflammatory, anticancer, antimicrobial, and hepatoprotective actions (29). Moreover, ginger oleoresin supports immune function and has been traditionally applied as an antiemetic, antiallergenic, and anti–motion sickness agent (30). Taken together, these findings highlight the multifaceted pharmacological actions of *Zingiber officinale*, supporting its long-standing use in traditional medicine and its potential for further development in modern therapeutic applications. Despite these therapeutic benefits, they exhibit clinical properties such as poor aqueous solubility, instability, and low bioavailability [13]. Recent advances in nanotechnology have offered promising strategies to overcome these barriers (Figure 1).

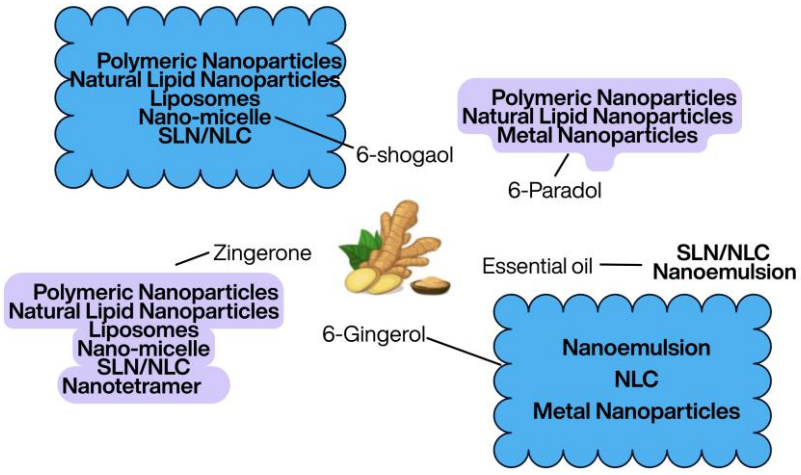

Fig. 1. Nanotechnology-based delivery systems for ginger bioactive compounds (6-shogaol, 6-paradol, zingerone, and essential oils)

Literature search

This review systematically collects and analyses the published literature on the formulation, characterization, and pharmacological applications of ginger-based nanoparticles. A literature search was conducted utilizing electronic databases such as PubMed, Scopus, and Google Scholar for studies published from 2010 to 2025. The search strategy utilized combinations of the following terms: “ginger”, “Zingiber officinale”, “gingerol”, “shogaol”, “paradol”, “zingerone”, “Polymeric nanoparticles”, “Polymeric micelles”, “Nanoemulsions”, “Solid Lipid Nanoparticles”, “Nanostructured Lipid Carriers”, “Metal Nanoparticles. Boolean operators, specifically AND and OR, were employed to refine the results. Data were manually extracted, and essential information was gathered from each study. A narrative synthesis was used to compare findings across studies, emphasizing the methods used to develop nanocarriers, excipients, characterize nanocarriers, and assess pharmacological activities.

Polymeric-based nanoparticles for ginger bioactives

Polymeric nanoparticles are submicron-sized colloidal polymer particles in which therapeutic agents can be embedded, encapsulated, adsorbed, or conjugated onto the particle surface [14]. In this review, eight studies (Table 1) were identified that developed polymeric nanoparticle systems incorporating ginger-derived bioactive compounds. The delivery platforms reported across these studies primarily included Poly (Lactic-co-Glycolic Acid) (PLGA) nanoparticles, chitosan-based nanoparticles, and natural lipid nanoparticles, highlighting the versatility of these carriers in addressing the intrinsic properties of ginger compounds. The ginger-derived bioactive compounds were 6-shogaol, 6-paradol, zingerone, and crude ginger extracts.

Table 1. Formulation of Ginger Bioactives Using Polymeric and Natural-Lipid Nanoparticles

No	Delivery System	Active ingredient (dose)	Excipients	Method	Limitations of Active Ingredients	Therapeutic	Reference
1.	Oral Nanoparticles PLGA/PLA-PEG-FA	6-Shogaol 6 mg	PBA PLA-PEG/PLA-PEG-FA	Versatile single-step surface functionalizing	Oral bioavailability is poor	-Improves clinical symptoms in the DDS-induced colitis model	[50]
3.	Nanoparticles	6-paradol (30 mg/kg)	Not reported	Not reported	Low bioavailability and biological efficacy	Antioxidant and superhydrogen depressant of peptides in the liver	[51]
4.	Polymeric Nanoparticle	Zingerone (10 mg/ml)	Dextrab sulfate solution, chitosan.	Ion-gelation method	Low solubility and rapid degradation in biological fluids	Antibacterial, anti-virulence, and anti-inflammatory age	[52]
6.	Nanoparticle colloid dispersion (nanosuspension)	Ginger extract methanolic 50 mg	Chitosan, tripolyphosphate	Ionic gelation	Not reported	Antimicrobial	[19]
7.	Nanoparticle	Ginger root extract ethanolic 200 mg	Chitosan, TPP	Ionic gelation	Low bioavailability and poor delivery	Antidiabetic	[17]
8.	Natural-Lipid Nanoparticle	6-Shogaol 0.2 mL	Lipids isolated from ginger-derived exosomal nanoparticles are mainly composed of phosphatidic acid (PA), monogalactosyl diacylglycerol (MGDG) and digalactosyl diacylglycerol (DGDG)	Thin lipid film complex	Long onset time of action of 6-shogaol on the compositional change of the microbiota	Anti-inflammatory	[53]

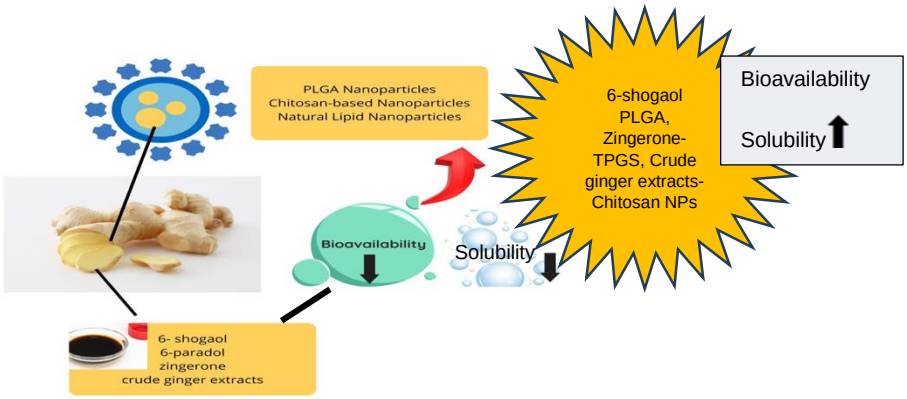

Fig. 2. Polymeric-Based Nanoparticles improve the bioavailability and solubility of ginger bioactives

These compounds are generally limited by their poor solubility, low oral bioavailability, and rapid degradation in biological fluids, which restrict their clinical efficacy (Figure 2). Incorporation into polymeric, chitosan-based, and lipid nanoparticle systems prepared primarily by ion-gelation, thin-film, or colloid-dispersion methods has been shown to overcome these limitations. Polymeric nanoparticles (e.g., PLA-PEG and PLA-PEG-FA) encapsulating 6-shogaol have shown enhanced oral delivery and significant anti-colitis effects by modulating inflammatory biomarkers [15] Lipid-based nanoparticles derived from ginger vesicles demonstrated targeted interaction with gut microbiota, accelerating anti-inflammatory and wound-healing responses [16] Similarly, chitosan-based nanoparticles prepared by ionic gelation improved the antibacterial activity of ginger extracts and protected against pancreatic Deoxyribonucleic acid (DNA) damage in diabetic models [17] 6-paradol-loaded nanoparticles provided hepatoprotection with reduced toxicity [18]. Chitosan has been a popular polymer for ionic gelation nanoparticles; it has been used to encapsulate ginger extract, increasing antibacterial effects and providing protective activity in pancreatic tissues [19]. Beyond enhancing activity, nanoparticle-based systems have also shown potential to reduce the side effects of ginger bioactives, such as 6-paradol. Interestingly, naturally derived nanovesicles, such as ginger-derived exosomes, have emerged as innovative delivery platforms. In their study, Yang et al. [20] demonstrated that ginger-derived exosomes could effectively deliver bioactive compounds to the colon, enhancing anti-inflammatory activity and mucosal healing. Collectively, these findings highlight that nanotechnology offers promising strategies to overcome the intrinsic limitations of gingerol and its derivatives, thereby expanding their therapeutic applications in inflammatory, metabolic, and infectious diseases.

Polymeric Micelle-Based Nanoparticles for Ginger Bioactives

Micelle-based delivery systems have also been developed to enhance the therapeutic efficacy of ginger-derived bioactive compounds. Polymeric micelles offer notable advantages, including improved solubilization of hydrophobic drugs, controlled release via polymer design, and ease of preparation (Figure 2). Their hydrophilic corona also enhances their biocompatibility. Nevertheless, their clinical application remains limited by their poor stability in systemic circulation, which can reduce drug delivery efficiency [21] Compared with other nanocarriers, micelles are attractive for early formulation development but often require modification or combination strategies to achieve high drug delivery efficiency. One particularly promising approach involves the oral administration of 6-shogaol encapsulated within self-assembled micelles formed from a polyethylene glycol (PEG)-linoleic acid (LA) conjugate, specifically mPEG2k-LA (Table 2) [22]. This nanocarrier system, prepared via nanoprecipitation, achieved a remarkably small particle size of 76.8 nm and an encapsulation efficiency of 81.6%. In vivo studies revealed a 3.2-fold increase in oral bioavailability, indicating a substantial improvement in systemic absorption. These results underscore the critical role of micellar nanocarriers in optimizing the delivery, bioavailability, and therapeutic impact of ginger-derived compounds such as 6-shogaol, especially in hepatic and neurological applications [22]. A nanomicelle formulation of zingerone was developed using the thin-film dispersion method for liquid oral administration. The micelles were prepared using D-α-tocopheryl polyethylene glycol succinate (TPGS) as the carrier, resulting in zingerone-loaded micelles (ZTMs) that overcome their low solubility and bioavailability and exhibit significant antitumor and antiproliferative effects [24].

Table 2. Formulations of Ginger Bioactives Using Polymeric Micelles

No	Delivery System	Active ingredient (dose)	Excipient	Method	Limitations of the Active Ingredients	Therapeutic	Reference
1.	Nanoemulsion	Ginger extract 10% (%b/v)	Tween 80, Buffer Sodium dihydrogen phosphate (pH 7)	Homogenizer	Lipophilic, less soluble in water, and low bioavailability	Not reported	[54]
2.	Hydrogel-loaded nanoemulsion	Ginger essential oil	Carboxymethyl chitosan/double formaldehyde cellulose-based hydrogel	High-pressure homogenization	Low viscosity and the spreading ability	Antibacterial and preservative	[26]
3.	Nanoemulsion Oral	Essential oil (20% v/v)	Tween 20, Tween 40, dan Tween 80 (surfaktan); Propilen glikol (cosurfaktan); air	High-pressure homogenization	Low oral absorption	Antiproliferative effect	[56]
4.	Nanoemulsion Topical	Essential oil	Tween 80 (surfaktan); ethanol, propylene glycol, PEG 400 (kosurfaktan); air	Spontaneous emulsification	Low absorption and stability of the essential oil	Antioxidant agent	[57]
5.	Nanoemulsion Oral	Essential oil	Gelatin, chitosan, tween 80, sodium tripolyphosphate.	Mixing and solution casting method	Instability can affect the unique taste and sensory characteristics of food products during packaging and storage.	Antimicrobial agent	[58]
6.	Nanoemulsion oral	Ginger essential oil (5%v/v)	Tween 80 (30% wt of GEO).	Ultrasonic emulsification.	Low water solubility	Antimicrobial agent	[59]
7.	Nanoemulsion	Ginger essential oil	Essential oil, organic and aqueous phase.	Nanoprecipitation (bottom-up solvent displacement technique)	Instability	Preservative or flavor modifier agent	[29]
8.	Nanoemulsi	Ginger essential oil 125 μl/ml	Tween 20, distilled water	Low-energy emulsification (transition phase inversion approach)	Instability, poor solubility, and durability	Antibacterial agent	[61]
9	Nanoemulsion intranasal	6-Gingerol	Lauroglycol 90, Tween80, PEG-400, chitosan	Microtitration	Poor solubility, low absorption, and low bioavailability	Neuroprotective	[28]

Nanoemulsions-Based Nanoparticles for Ginger Bioactives

Several studies (Table 3) have explored nanoemulsion formulations to improve the solubility, stability, and bioavailability of ginger extracts and essential oils. The reported formulations employed a range of techniques, including high-pressure homogenization, ultrasonic emulsification, spontaneous emulsification, solution casting, nanoprecipitation, and phase inversion methods. Despite their potential, ginger-derived nanoemulsions are often limited by instability, poor solubility, low oral bioavailability, and reduced stability during storage. Notably, intranasal nanoemulsions of 6-gingerol have shown promise in improving brain delivery and neuroprotective activity, highlighting their potential in targeting neurological disorders. Studies have shown that additives in nanoemulsions can facilitate particle penetration through the nasal epithelium to the brain, such as chitosan, which can prolong the residence time of the nanoemulsion in the nasal cavity and enhance drug delivery from the nose to the brain. However, a significant drawback is their limited stability, as nanoemulsions are thermodynamically unstable systems that may degrade during delivery, leading to the efflux of the encapsulated drug [25]. Overall, nanoemulsion-based delivery provides a versatile approach to overcoming the intrinsic limitations of ginger bioactives and expanding their therapeutic applications.

Table 3. Formulations of Ginger Bioactives Using Nanoemulsions

No	Delivery System	Active ingredient (dose)	Excipient	Method	Limitations of Active Ingredients	Therapeutic	References
1.	Oral Micelle PEG and linoleic acid conjugate	6-Shogaol 10 mg	mPEG2k-LA	Nanoprecipitation	Poor water solubility, poor oral absorption, and rapid metabolism.	Anticancer and anti-inflammatory (hepatoprotective)	[22]
2.	Nano-micelle	Zingerone (IC50 7,56 µg/mL)	Liquid Oral	The thin-film dispersion method	Poor solubility and bioavailability	Antitumor and antiproliferative effects.	[63]

Nanoemulsion-based delivery systems have emerged as an effective strategy to harness and enhance the pharmacological potential of volatile, sensitive natural compounds, such as ginger essential oil. Functionally, the hydrogel-nanoemulsion composite demonstrated excellent bactericidal efficacy against a broad spectrum of pathogenic bacteria, including *Escherichia coli*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*. This suggests that integrating ginger essential oil into a nanoemulsion-hydrogel matrix not only stabilizes the oil's volatile constituents but also significantly enhances its antibacterial potency, positioning it as a promising candidate for biomedical and wound care applications [26].

Recent studies have demonstrated that ginger and its bioactive constituents have been successfully incorporated into diverse nanoemulsion systems for oral, topical, and intranasal applications. High-pressure homogenization and ultrasonic emulsification consistently produced smaller droplets (<100 nm) [26–28], whereas nanoprecipitation yielded a wider size range (68-1035 nm), indicating that method selection strongly influences physicochemical outcomes [29]. Surfactants such as Tween 20 and Tween 80, and co-surfactants such as propylene glycol, were most frequently used, with chitosan or gelatin occasionally added to enhance stability or provide mucoadhesive properties [30,31]. Functionally, ginger nanoemulsions have shown broad pharmacological potential: improving oral bioavailability and antiproliferative activity in vivo [30], exhibiting antioxidant and antimicrobial effects in food preservation [26,29], enhancing topical antioxidant efficacy [27], and even improving brain delivery of 6-gingerol via intranasal administration [25]. Interestingly, while most systems maintained negative zeta potentials conducive to stability, the intranasal gingerol nanoemulsion showed a near-neutral charge, possibly due to the chitosan coating, which may facilitate mucosal adhesion but raises concerns regarding long-term stability [28]. Collectively, these findings highlight that ginger nanoemulsions not only improve the solubility and stability of hydrophobic actives but also expand their therapeutic and industrial applications. However, optimizing surfactant ratios, preparation methods, and delivery routes remains essential.

Lipid-based nanocarriers for ginger bioactives (Solid Lipid Nanoparticles (SLNs) and Nanostructured Lipid Carriers (NLCs)

Lipid-based nanocarriers, including solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs), have been widely applied for the delivery of ginger-derived compounds such as ginger oil, ginger extract, 6-gingerol, shogaol, and zingerone. Various lipid excipients, including glyceryl monostearate, Precirol ATO 5, soya lecithin, cholesterol, and medium-chain triglycerides, have been employed in combination with surfactants such as Tween 80, Poloxamer 188, and Span 80 (Table 4). Common preparation methods include high-pressure homogenization, ultrasonication, double emulsification, microemulsion techniques, and thin-film methods. Although SLNs and NLCs improve encapsulation and stability, several limitations remain, including poor water solubility, rapid metabolism, limited release performance, instability under light, heat, or air, and susceptibility of the essential oil to degradation. Despite these drawbacks, lipid-based nanocarriers have demonstrated promising therapeutic outcomes, including anti-inflammatory, antimicrobial, depigmenting, and anti-gout activities, with some systems designed for controlled release to overcome rapid metabolism.

Overall, SLNs and NLCs offer a versatile delivery approach to enhance the stability and bioavailability of ginger-derived compounds. However, further optimization of formulation parameters is required to achieve consistent therapeutic performance.

Table 4. Formulation of Ginger Bioactives Using Solid Lipid Nanoparticles (SLNs) and Nanostructured Lipid Carriers (NLCs)

No	Delivery System	Active ingredient (dose)	Excipient	Method	Limitations of the Active Ingredients	Therapeutic	References
1.	Topical NLC and SLN	Ginger oil (1,0% w/w) 4-hexylresorcinol	SLN: Precirol ATO 5 (glyceryl palmitostearate), NLC: Labrafac, GO Surfactant: Poloxamer P188, sucrose distearate (SP30) Lutrol, span 85	High shear homogenization	Might not reach the deepest skin layer and have low release performance.	Depigmenting effect by inhibitory effect on tyrosinase activity.	[43]
2.	Topical suspension of solid lipid nanoparticles	Ginger extract 0,7% w/w	Stearic acid as a solid lipid Cremophor RH 40 as the surfactant and ethanol as the co-surfactant	Microemulsion technique	Unstable in the presence of light, heat, and air	Not reported	[36]
3.	Nanostructured Lipid Carrier	6-gingerol	Solid lipid: Glyceril monostearate; liquid oil: VCO Surfactant: Tween 80 and soy lechitin	Ultrasonication	Low solubility	Not reported	[65]
4.	Solid Lipid Nanoparticles	Essential oil	Lipid: Soya lecithin and cholesterol; Hydrophilic Polymer (PVA); Surfactants (tween 80)	Double emulsification	Ginger oil was susceptible to degradation	Antimicrobial activity	[38]
5.	Nanostructured Lipid Carriers	**6** Gingerol 200 mg/kg	Solid lipid (glyceryl monostearate), liquid lipid (decanoyl/octanoyl-glycerides), and mixed surfactants (Tween 80 and Poloxamer 188),	High Pressure Homogenization	Poor water solubility and oral biological availability	Not reported	[67]
6.	*Oral solution Solid Lipid Nanoparticles* (SLN)	Zingerone (25 µM)	Compritol ATO 888, Vitamin E TGPS, and transcutol P	Modified emulsification	Very few zingerone nano-biomaterials have been developed	Anti-inflammatory agent.	[68]
7.	Nanolipid	Essential oil (1,16 mg/mL)	Lecithin, cholesterol, and Span 80	Thin-film method	Not reported	Antibacterial agent	[69]
8.	NLC (Nanostructured Lipid Carrier)	Ginger oil	VCO, tween 80, soy lecithin, glyceryl monostearate	Hot homogenization and ultrasonication	Poor water solubility and poor bioavailability	Not reported	[46]
9.	Natural lipid nanoparticle controlled release	6-Shogaol (rapid metabolism)	Total lipids from fresh ginger roots	Thin lipid complex film	Hidrophobic and rapid metabolism result in poor bioavailability.	Anti-inflammatory agent.	[70]
10.	Nanostructured Lipid Carrier	Ginger oil	Tween 80, soy lecithin, VCO, GMS	High-pressure homogenization	Not reported	Not reported	[71]

Nanostructured lipid carriers (NLCs) are lipid-based nanoparticles developed to overcome the limitations of solid lipid nanoparticles (SLNs). They are composed of a mixture of solid and liquid lipids. Because hydrophobic molecules are more soluble in liquid lipids than in solid lipids, NLCs can achieve higher drug entrapment efficiency compared to SLNs and are suitable for both hydrophobic and hydrophilic materials [32]. The lipids used in this type of nanoparticle are biocompatible and well-tolerated by the body, such as triglycerides, fatty acids, steroids, and waxes. NLCs also offer the advantage of being easily scalable for industrial production based on their fabrication methods.

However, the limitations of NLCs include low entrapment efficiency when combining two or more drugs, and limited capacity for hydrophilic drug loading [33,34] chitosan-coated NLCs for the intranasal delivery of buspirone to the brain, using the solvent diffusion evaporation method. A mixture of glycerol monostearate and oleic acid was used as the lipid phase, with Tween 80 as the surfactant.

Lipid-based nanocarriers such as solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) have shown significant promise for improving the delivery and performance of ginger-derived bioactives. In a comprehensive topical formulation study, ginger oil was incorporated with 4-hexylresorcinol into both SLN and NLC systems using Precirol ATO 5 as the solid lipid and Labrafac as the liquid lipid for the NLCs. Surfactants such as Poloxamer 188 and sucrose distearate facilitated emulsification during high shear homogenization. These systems were evaluated for depigmenting efficacy, and both demonstrated noticeable improvements in skin lightness over 28 days of topical application. However, the NLCs outperformed the SLNs in terms of the lightening effect and skin barrier restoration, likely due to their superior drug loading and release properties. In a separate SLN system using ginger extract and stearic acid as the lipid matrix, prepared via the microemulsion technique, the particles exhibited a spherical morphology with sizes ranging from 453.1 to 551.7 nm. Despite their larger size, they achieved high entrapment efficiencies (85.23–90.07%). They were stable under various temperature and light conditions, effectively addressing the instability issues associated with gingerol, which is sensitive to heat, light, and oxygen [35].

A topical suspension of ginger extract-loaded solid lipid nanoparticles (SLNs) was prepared using stearic acid as the solid lipid, Cremophor RH 40 as the surfactant, and ethanol as the co-surfactant via a microemulsion technique. The SLNs exhibited mean particle sizes ranging from 453.1 to 551.7 nm, with high entrapment efficiency (85.23-90.07%) and loading capacity (1.41-1.49%) as determined by HPLC. Notably, the formulation demonstrated good stability when stored at 4 °C and 30 °C under light-protected conditions, which is particularly relevant given the known instability of gingerol in light, heat, and air [36]

Nanostructured lipid carriers (NLCs) of 6-gingerol were prepared using glyceryl monostearate as the solid lipid, virgin coconut oil (VCO) as the liquid lipid, and Tween 80 with soy lecithin as the surfactant through ultrasonication. The resulting nanoparticles ranged from 100 to 250 nm, with a notably high encapsulation efficiency of 92.7 ± 3.03%, suggesting an efficient entrapment of gingerol [37]. Similarly, ginger essential oil-loaded solid lipid nanoparticles (SLNs) formulated with soya lecithin, cholesterol, polyvinyl alcohol (PVA), and Tween 80 via double emulsification exhibited potent antimicrobial activity, further supporting the potential of lipid-based nanocarriers to enhance ginger bioactivity [38].

Beyond essential oils, zingerone-loaded SLNs formulated with Compritol ATO 888, vitamin E TGPS, and Transcutol P demonstrated promising oral delivery properties for targeting inflammatory bowel disease (IBD), underscoring the versatility of lipid nanocarriers in addressing diverse therapeutic targets [39]. In another study, 6-gingerol was encapsulated in NLCs comprising glyceryl monostearate and a blend of decanoyl and octanoyl glycerides as liquid lipids, stabilized with Tween 80 and Poloxamer 188. Following oral administration, these NLCs significantly enhanced the systemic exposure of 6-gingerol, increasing serum concentrations, mean residence time, and overall bioavailability compared with the free suspension [40]. Similarly, natural lipid nanoparticles derived directly from ginger roots were used to encapsulate 6-shogaol. These nanoparticles provided delayed release and improved anti-inflammatory outcomes in a DSS-induced colitis model, although drug levels remained below the effective therapeutic threshold [41].

Further evidence of NLC efficacy comes from a formulation containing Chinese ginger oil, soy lecithin, Tween 80, and glyceryl monostearate (GMS), in which high-pressure homogenization effectively reduced particle size and improved uniformity, both essential for consistent drug delivery [42]. Collectively, these studies highlight the versatility and effectiveness of SLNs and NLCs in enhancing the pharmacological delivery of ginger-based compounds for both topical and oral therapeutic applications, ranging from skin depigmentation and barrier repair to systemic anti-inflammatory and hepatoprotective effects. Table 4. Highlights advanced nanocarrier systems that go beyond conventional polymeric and lipid-based nanoparticles. A shogaol-loaded liposomal formulation was developed using D-α-)- tocopherol polyethylene glycol succinate (TPGS), sodium cholate, and cholesterol via the thin-film dispersion method (Table 5), which significantly improved drug solubility and stability. Similarly, zingerone was incorporated into niosomal suspensions prepared with Span 60, cholesterol, and PEG 3000 via thin-layer hydration, offering enhanced encapsulation and controlled release properties [43][44]

Table 5. Formulation of Ginger Bioactives Using Solid Lipid Nanoparticles (SLNs) and Nanostructured Lipid Carriers (NLCs)

No	Delivery System	Active ingredient (dose)	Excipient	Method	Limitation of the Active Ingredients	Therapeutic	Reference
1.	D-a-tocopheryl polyethylene glycol (PEG) succinate (TPGS)-modified Liposome	Shogaol 15 mg	Sodium cholate, cholesterol, and vitamin E-TPGS	Thin film dispersion	Poor water solubility	Brain delivery	[72]
2.	Niosome suspension	Zingerone (250 dan 500 µg/mL)	Span 60, cholesterol, polyethylene glycol (PEG 3000), chloroform-methanol solution.	Thin-layer hydration	Not reported	Antibacterial and antibiofilm against methicillin-resistant *Staphylococcus aureus* (MRSA)	[73]

Metal-based nanocarriers for ginger bioactives

In addition to polymeric, micellar, lipid, and nanoemulsion systems, ginger extracts and bioactive compounds have also been widely used in the green synthesis of metallic nanoparticles (Table 6). The reported systems include zinc oxide, silver, gold, copper, and iron oxide nanoparticles, synthesized primarily through eco-friendly green chemistry approaches using ginger extract as a reducing and stabilizing agent. The techniques employed range from ion-exchange and ultrasonic centrifugation to plant-mediated green synthesis and nanocomposite formulations. In addition to lipid-based carriers, inorganic nanoparticles have also been explored for ginger-derived compounds. For instance, zinc oxide nanoparticles encapsulating 6-paradol (20 and 40 mg/kg) via ion exchange demonstrated significant physiological effects in streptozotocin-induced diabetic rats. Compared with untreated diabetic controls, 6-paradol–loaded ZnO nanoparticles not only improved body, testis, and epididymis weight but also restored testosterone, luteinizing hormone, and follicle-stimulating hormone levels. Furthermore, sperm concentration, motility, and viability improved, while abnormal sperm percentages decreased, highlighting their potential in mitigating diabetes-induced reproductive dysfunction [45]. The application of metal-based nanoparticles synthesized from ginger extracts has attracted considerable attention for their therapeutic, catalytic, and antimicrobial properties. Among the most extensively studied are silver nanoparticles (AgNPs), zinc oxide, and iron oxide nanoparticles, each offering distinct functional benefits when synthesized with ginger-derived phytochemicals. The AgNPs were also deemed biocompatible based on L929 cell viability studies, highlighting their therapeutic safety [46].

In addition to lipid-based carriers, several studies have demonstrated the utility of inorganic nanocarriers for ginger-derived compounds. Gold nanoparticles (AuNPs) loaded with gingerol (50 and 100 mg/kg, intraperitoneal) prepared via ultrasonic centrifugation exhibited neuroprotective potential. Specifically, AuNP administration reduced oxidative DNA damage and apoptosis in rat hippocampal tissues while restoring brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) levels, highlighting their promise for managing neurodegenerative conditions [47]. Similarly, iron oxide nanoparticles synthesized through a green method using ginger extract as a reducing agent demonstrated a cubic crystalline structure (~5.1 nm). These nanoparticles displayed potent antibacterial activity against *Escherichia coli,* with an inhibition zone of 22 mm, indicating their potential as natural, ginger-mediated antimicrobial agents [48].

Similarly, a green synthesis approach using ethanolic ginger rhizome extract and silver nitrate yielded AgNPs ranging from 80 to 100 nm, with a zeta potential of -17.1 mV and crystalline morphology confirmed by XRD. These nanoparticles showed broad-spectrum antibacterial activity against *E. coli*, *Bacillus subtilis*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*, along with antioxidant activity and cytotoxicity at concentrations as low as 0.6–6 µg/mL in Vero cell lines [49]. An even smaller nanoparticle size (~2 nm) was achieved via ultrasound-assisted green synthesis using different parts of the ginger plant, producing highly spherical AgNPs. These biogenic particles demonstrated exceptional catalytic degradation of synthetic dyes, including DB15 and DO26, with performance surpassing that of standard antioxidants, such as BHT. However, the ginger extract alone did not display catalytic activity [48].

Table 6. Formulation of Ginger Bioactives Using Metal Nanoparticles

No	Delivery System	Active ingredient (dose)	Excipient	Method	Limitation of the Active Ingredients	Therapeutic	Reference
1.	Nanoparticle Zinc oxide	6-paradol (20 and 40 mg/kg BB)	Zinc oxide	Ion exchange	Not reported	The protective effect on spermatogenesis in the diabetic rat.	[45]
2.	Silver nanoparticles	Ginger extract 10 mg/ml	Silver nitrate	Aq extract at different pH, gradually added to the silver nitrate solution	Not reported	Anti-inflammatory agents and antioxidants	[46]
3.	Gold nanoparticles (AuNPs) (intraperitoneal)	6-Gingerol 50 mg/kg dan 100 mg/kg	Gold nanoparticles, normal saline	Ultrasonic centrifugation	Not reported	Antioxidant and neuroprotective	[74]
4.	Iron oxide nanoparticles	Ginger extract 80 ml and 100 ml	Ferric chloride precursor and ginger extract as the reducing agent	Green synthesis	Not reported	Antibacterial agent	[48]
5.	Silver Nanoparticles	Ethanolic ginger rhizome extract	AgNO3	Green synthesis	Not reported	Antioxidant and antibacterial	[49]
6.	Silver nanoparticles (solution)	Different parts of the ginger extract	Silver nitrate	Green synthesis and ultrasound	Not reported	Antioxidant agent	[77]
7.	Copper Nanoparticles (Solid Oral)	Ginger extract 1 g/100 ml, from which 45 ml was used.	Copper sulfate	Green synthesis	Not reported	Antibacterial agent	[78]
8.	Silver nanoparticle (solution)	Ginger extract 20 g/100 ml, from which 10 ml was used	Silver nitrate	Green synthesis	Not reported	Antibacterial agent	[79]
9.	Zinc oxide nanoparticle (pellet in solution)	Ginger extract 10 mL in 50 mL	Zn(NO3)2 hexahydrate NaOH	Green synthesis	Not reported	Anticancer	[80]
10.	Silver nanoparticles	Ginger oleorosein 20, 40, 60, 80, and 100 μl.	Silver nitrate solution	Eco-friendly green synthesis	Not reported	Anti-inflammatory	[81]
11.	ZnO Nanoparticles	1 mg of ginger and 1 mg of clove powder were dissolved in 100 mL of distilled water.	Zinc nitrate, sucrose, sodium benzoate, sodium lauryl sulfate.	Formulated with a combination of clove and ginger mediated by zinc oxide nanoparticles.	Not reported	Anti-inflammatory	[82]
12.	Ginger-loaded nanoparticles	50 mg fresh ginger	Iron (II) chloride-hexahydrate (FeCl3.6H2O), Ammonium iron (II) sulfate hexahydrate (NH4) 2Fe(SO4)2.6H2O.	Superparamagnetic iron oxide@Silver nanocomposites (SPION@Ag) were prepared through a green nanoformulation.	Not reported	Anti-inflammatories for acute ulcerative colitis	[83]

In addition to silver, iron oxide nanoparticles were synthesized using fresh ginger extract as both a reducing and a stabilizing agent. These particles exhibited a crystal size of 5.10 nm, a cubic morphology (confirmed by SEM), and characteristic peaks in FTIR and XRD analyses. Functionally, they displayed potent antibacterial activity against *E. coli*, forming inhibition zones up to 22 mm in diameter, demonstrating their potential for microbial control [45].

Zinc oxide nanoparticles synthesized with 6-paradol through ion-exchange methods were also explored for their reproductive toxicology. When administered to STZ-induced diabetic rats, the 6-

paradol-ZnO nanoparticles mitigated testicular weight loss and hormonal imbalances, including reductions in testosterone, LH, and FSH, which STZ otherwise induced. Moreover, sperm count, motility, and viability were significantly improved, while the percentage of abnormal sperm cells decreased in the treated groups [45]. These findings indicate the potential of metal-based ginger nanoparticles not only in the antimicrobial and antioxidant domains but also in fertility preservation and toxicological mitigation.

Overall, ginger-mediated metal nanoparticles represent a promising and sustainable nanoplatform, combining the intrinsic pharmacological activity of ginger bioactives with the unique physicochemical and biomedical properties of metallic nanocarriers. However, further studies are required to address the safety profiles, stability, and clinical translation.

Nanotechnology has emerged as a powerful platform for improving the pharmacological performance of *Zingiber officinale* (ginger) and its derivatives. Various delivery systems—including polymeric nanoparticles, solid lipid nanoparticles (SLN), nanostructured lipid carriers (NLC), micelles, nanoemulsions, and metal-based nanoparticles—have been explored to address challenges such as poor bioavailability, instability, and limited therapeutic targeting.

Polymeric systems such as PLA-PEG-FA and PEG-linoleic acid micelles significantly enhanced the oral bioavailability and targeted the anti-inflammatory effects of 6-shogaol. Chitosan-based nanoparticles encapsulating ginger methanolic or ethanolic extracts showed superior antibacterial and DNA-protective effects. Lipid-based systems, such as SLNs and NLCs, enabled sustained release and deeper skin penetration, thereby improving outcomes in skin depigmentation and oral delivery models. The nanoemulsions integrated into the hydrogels also enhanced the antibacterial activity against multiple pathogens.

Metal nanoparticles synthesized via green methods using ginger extracts, such as silver, zinc oxide, and iron oxide, demonstrated potent antioxidant, antimicrobial, anti-inflammatory, and even fertility-protective effects. These systems not only stabilized volatile compounds such as gingerol and shogaol but also extended their therapeutic windows.

Collectively, these diverse nanocarrier approaches underscore the promise of nanotechnology in unlocking the full therapeutic potential of ginger across anti-inflammatory, antimicrobial, hepatoprotective, and cosmetic applications. In addition to these well-established systems, more novel strategies have also been reported (Table 7). Edible nanoparticles isolated from ginger rhizomes using polyethylene glycol (PEG-6000) ultracentrifugation demonstrated potential as natural nanocarriers. At the same time, carbon-based nanotetramers were synthesized to encapsulate zingerone via a one-pot heat-condensation process, thereby improving molecular stability at low concentrations.

Collectively, these delivery platforms, ranging from polymeric and lipid-based nanoparticles to innovative edible nanovesicles and nanotetramers, highlight the versatility of nanotechnology in overcoming the intrinsic limitations of ginger bioactives, including poor solubility, instability, and low bioavailability. Their development not only enhances the therapeutic efficacy but also broadens the potential applications of ginger-derived compounds across inflammatory, metabolic, infectious, and degenerative diseases.

Table 7. Formulations of Ginger Bioactives Using Other Nanoparticles

No	Delivery System	Active ingredient (dose)	Excipient	Method	Limitation of the Active Ingredients	Therapeutic	Reference
1.	Edible nanoparticles (nanovesicle suspensions)	Ginger rhizome 250 g	PEG 6000-ENPs	Ultra-centrifugation to develop a polyethylene glycol-6000 (PEG6000) based ginger ENP purification (PEG-ENPs) method.	Not reported	Anti-inflammatory drugs for bowel diseases and colon cancer	[84]
2.	Nanotetramer	Zingerone (25 μM)	Carbon-based nanoparticles	A one-pot heat condensation synthesis process.	Not reported	Antiproliferation, antitumorigenicity	[85]

Advantages and limitations

The use of nanoparticle-based systems to deliver ginger extracts and their derivatives offers several notable advantages, significantly enhancing the therapeutic utility of these natural compounds. One of the most prominent benefits is the substantial improvement in bioavailability. Compounds such as 6-shogaol, which are typically rapidly metabolized and poorly soluble, exhibit markedly increased absorption and systemic retention when encapsulated in polymeric micelles or lipid-based carriers. This enhanced pharmacokinetic profile translates to more effective dosing and better clinical outcomes.

In addition, nanoparticles enable targeted delivery and site-specific accumulation, which is particularly beneficial in inflammatory conditions or localized diseases. Functionalized carriers, such as folic acid-conjugated PLA-PEG nanoparticles, exhibit selective uptake in inflamed or cancerous tissues, thereby enhancing therapeutic efficacy while minimizing off-target effects. These systems also offer the advantage of protecting the bioactive components of ginger—especially the unstable constituents, such as gingerol and paradol—from degradation caused by environmental factors, including light, heat, and oxygen. By stabilizing the active ingredients within a protective matrix, the nanoparticles ensured sustained potency throughout storage and administration.

Moreover, the controlled and sustained release properties of lipid-based systems, such as SLNs and NLCs, enable prolonged drug action, reducing the need for frequent dosing and improving patient compliance. These nanoformulations have been shown to significantly enhance the pharmacological activities of ginger, including its antioxidant, antibacterial, anti-inflammatory, hepatoprotective, and even reproductive-protective effects. Notably, most studies report good biocompatibility of these systems, particularly those that use natural polymers such as chitosan or lipids derived from ginger itself. Their versatility, which allows them to be tailored for oral, topical, or injectable use, further underscores their potential across diverse therapeutic contexts.

However, despite these promising outcomes, there are notable limitations that must be addressed. The formulation processes for such nanoparticles—ranging from high-pressure homogenization to green synthesis of metal particles—are often technically demanding and cost-intensive, posing challenges for large-scale manufacturing. Additionally, some systems exhibit issues related to particle size and uniformity; for example, certain SLNs incorporating ginger extract produced relatively large particles, which could affect their pharmacokinetics and tissue penetration.

Another limitation lies in the still-limited body of in vivo data, particularly in human subjects. Although the preclinical results are promising, the transition to clinical application requires robust toxicological assessments and pharmacokinetic studies. Some metal-based nanoparticles, although effective, also face potential stability issues in biological environments and may raise concerns regarding long-term safety. Furthermore, the mechanisms by which these nanoformulations exert their enhanced effects are not always fully understood, with some studies reporting outcomes without comprehensive mechanistic elucidation. Finally, the regulatory pathways for such novel delivery systems remain complex, especially when they incorporate metals or synthetic surfactants. Regulatory approval may require extensive documentation, safety validation, and environmental risk assessments, potentially delaying or limiting commercialization. In summary, while nanoparticle-based delivery systems for ginger extracts and derivatives hold transformative potential, especially in enhancing bioactivity and stability, their development and application must be accompanied by careful optimization, detailed safety studies, and regulatory foresight to ensure successful translation into clinically viable products.

CONCLUSION

In conclusion, the future of ginger-derived nanoparticle therapeutics is bright and multidimensional. The compound 6-shogaol, when encapsulated in polymeric micelles or lipid-based carriers, could enhance its pharmacokinetic profile, translating into more effective dosing and better clinical outcomes. Unstable constituents, such as gingerol and paradol, could serve as functionalized carriers, such as folic acid-conjugated PLA-PEG nanoparticles; these systems also offer the advantage of protecting the bioactive components of ginger. With continued scientific innovation, rigorous validation, and responsible development, these systems could evolve into a new class of bioactive delivery platforms—offering potent, stable, and targeted therapies derived from one of nature's oldest and most versatile remedies.

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DECLARATION OF ORIGINALITY

We hereby declare that the content presented in this article is original. All sources employed in this article have been correctly referenced.

DATA AVAILABILITY

All the data have been included in the manuscript and will be made available upon publication.

ETHICAL APPROVAL

This article does not contain any studies with human participants or animals performed by any of the authors.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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