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Lipid-based nano-carriers for the delivery of anti-obesity natural compounds: advances in targeted delivery and precision therapeutics

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Abstract

Obesity is a major global health challenge, contributing to metabolic disorders such as type 2 diabetes, cardiovascular diseases, and hypertension. The increasing prevalence of obesity, driven by sedentary lifestyles, poor dietary habits, and genetic predisposition, underscores the urgent need for effective therapeutic strategies. Conventional pharmacological treatments, including appetite suppressants and metabolic modulators, often fail to provide sustainable weight loss due to side effects, poor adherence, and limited long-term efficacy. As a result, natural bioactive compounds have gained attention for their anti-obesity potential. However, their clinical application is hindered by poor bioavailability, rapid metabolism, and inefficient delivery. Lipid-based nano-carriers, including liposomes, solid lipid nanoparticles, and nanostructured lipid carriers, offer a promising solution by enhancing the solubility, stability, and targeted delivery of these compounds. These advanced delivery systems improve bioactive retention, enable controlled release, and enhance therapeutic action on adipose tissue and metabolic pathways. Additionally, functionalized and stimulus-responsive nanocarriers present innovative approaches for precision obesity treatment. Despite these advancements, challenges remain in large-scale production, regulatory approval, and long-term safety. Overcoming these barriers is critical to ensuring the successful clinical translation of nano-formulated therapies. This review explores the potential of lipid-based nano-carriers in optimizing the therapeutic efficacy of natural anti-obesity compounds and highlights their role in advancing next-generation obesity management strategies.

Keywords Lipid-based nanocarriers, Anti-obesity natural compounds, Bioavailability, Drug delivery systems, Obesity treatment, Nanotechnology

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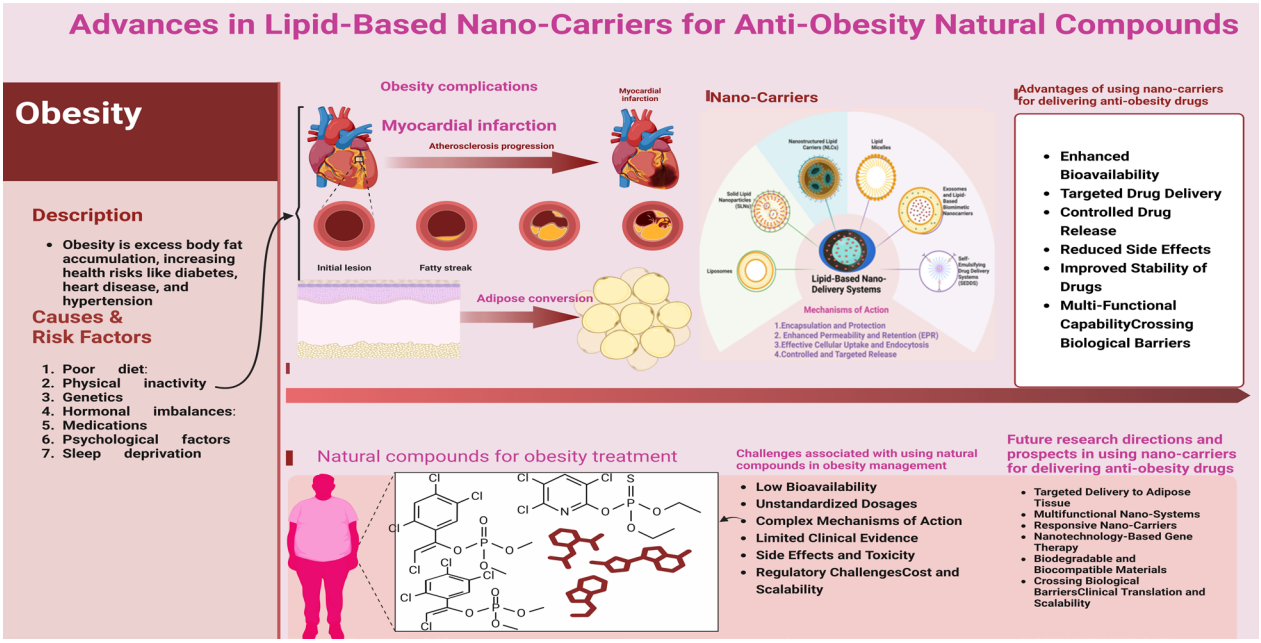
Graphical Abstract

Lipid-based nano-carriers for the delivery of anti-obesity natural compounds (created in https://BioRender.com)



Introduction

The increasing global epidemic of obesity features abundant body fat leading to multiple health dangers for both the body and metabolic system [1–3]. The global epidemic of obesity now affects millions of people worldwide while creating additional health problems including cardiovascular diseases and type 2 diabetes and certain cancers that have become more widespread [2, 4, 5]. The World Obesity Federation (WOF) revealed that all countries are off track to meet the 2025 global targets which predicted that by 2025, global obesity prevalence could reach 18% in men and surpass 21% in women, with many countries experiencing higher levels [6]. Five countries—the US, China, Brazil, India, and Russia—account for around a third of all cases of obesity in adults globally [6]. Obesity has significant financial and social impacts, with the total cost of high Body Mass Index (BMI) to health services globally being around US$990 billion per year. Organizations around the world are calling for a re-evaluation of the approach to addressing obesity, which affects over 650 million adults and 125 million children worldwide [6]. A concerning global phenomenon shows that high-income countries are not the only ones with rising obesity rates because low- and middle-income nations witness similar fast-growing obesity statistics together with ongoing food deficiencies [7–9]. The combination of obesity with other health conditions creates substantial medical expenses which burdens both healthcare systems and economies as well as strain individual healthcare needs so effective obesity management strategies require urgent public health attention.

The origins of obesity combine elements from biological inheritance and interaction with external environmental and human behavioural influences. The combination of dietary factors containing numerous calories together with nutrition-deficient food combined with inactive behaviours serves as the main cause in obesity epidemic expansion [10]. The challenge becomes more difficult because socioeconomic differences along with cultural patterns create obstacles to modifying dietary choices and boosting physical exercise. Current obesity intervention methods show insufficient results while medical practitioners recognize that innovative prevention solutions are necessary for obesity control because of its unrelenting prevalence [11, 12].

Clinical approaches to obesity treatment mainly depend on three components: lifestyle changes and medication administration and surgical treatment methods. Lifestyle alterations which combine food adjustments with physical activity level increases serve as the initial approach for obesity management

[13–15]. The long-term commitment to obesity treatment presents major obstacles because of human behaviour elements together with societal pressures and external environment factors which produce widespread treatment dropout rates [16, 17]. The treatment of obesity and related metabolic risks relies on pharmaceutical choices that include orlistat and liraglutide and phentermine-topiramate [18]. The medical drugs available for weight control demonstrate inconsistent success rates and expensive costs together with side effects which primarily affect digestive health and elevated cardiovascular health risks [19–22]. The treatments struggle to help entire segments of potential candidates because their effectiveness remains limited to select patient types. For patients dealing with severe obesity bariatric surgery combines gastric bypass and sleeve gastrectomy to provide better weight-loss results [23]. The weight loss potential of these procedures remains significant yet patients must face expensive invasive surgery alongside possible surgical complications including long-term nutritional deficiencies and high costs [18]. These operations exist primarily for obese patients who cannot benefit from standard interventions or people with severe obesity [24–26].

New medical treatments still require development because existing methods do not deliver both adequate safety and acceptable accessibility and wild success. Bio-resource compounds obtained from plant and marine organism and microorganism sources display substantial promise to fill the therapeutic void [3, 27, 28]. Through traditional medicine people have employed natural compounds since ancient times to manage diverse health disorders especially metabolic conditions [29, 30]. Current scientific investigations emphasize bioactive molecules as treatment candidates for obesity reduction. The pharmacological properties of drugs like polyphenols and alkaloids with terpenoids and saponins and flavonoids show broad potential in targeting multiple obesity-related mechanisms [31, 32]. Research shows that these compounds reduce inflammation while providing antioxidant protection and breaking down fats and triggering thermogenic responses as well as controlling hunger levels and improving insulin response [2, 33].

Fighting oxidative stress through antioxidants such as epigallocatechin gallate (EGCG) and quercetin combines the potent anti-inflammatory properties of curcumin and resveratrol [34–36]. The natural substances berberine and chlorogenic acid activate better insulin function while enhancing glucose processing abilities [37]. The use of natural compounds remains preferred because these substances demonstrate greater clinical effectiveness with reduced safety risks and lower adverse effects than pharmaceutical drugs. In resource-limited settings their widespread availability combined with less expensive costs make them highly desirable for use [37–40]. The therapeutic pathways of natural compounds remain underexplored because they encounter limitations relating to their stability and bioavailability requirements and targeted delivery frameworks.

Traditional delivery methods limit the clinical effectiveness of natural compounds because they suffer from low aqueous solubility and poor absorption as well as rapid metabolism together with essential delivery limitations and instability [41, 42]. The therapeutic advantages of such compounds require sophisticated delivery technology because current challenges persist. The delivery of drugs through lipid-based nano-carriers such as liposomes along with solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) corrects the deficiencies of traditional delivery approaches [2, 42]. Lipid-based delivery systems increase drug solubility and stability and boost bioavailability and controlled drug release capabilities and provide targeted delivery within safe biocompatible frameworks [34]. Results from recent research showcase potential benefits through these delivery systems. The incorporation of curcumin into liposomes led to enhanced metabolic function and decreased body fat accumulation compared to unencapsulated curcumin while solid lipid nanoparticles containing [43, 44]. EGCG produced superior anti-obesity effects to free EGCG. Using natural compounds alongside lipid-based nano-carriers enables researchers to transform the way they approach obesity treatment [45–47]. By integrating these delivery methods, traditional issues fade away while establishing avenues toward customized precision medicine. Future research must focus on both improving nano-carrier technology advancement and assessing their safety profile and enduring efficacy potential. Regulatory institutions must develop updated guidelines which recognize these new treatments as they enter the market. The extensive problems caused by obesity call for strategies which extend past existing medical strategies. Natural compounds used with lipid-based nano-carriers provide a growing solution for practical obesity treatments. The optimization of natural products into clinical applications through this therapeutic strategy presents a meaningful contribution to obesity treatment efforts.

Our previous studies have demonstrated the efficacy of bioactive compounds from natural sources in modulating lipid metabolism and mitigating obesity-related complications. Okoh et al. [48] identified bioactive compounds from *Trigonella foenum-graecum* as potential inhibitors of peroxisome proliferator-activated receptor gamma (PPARγ) through molecular docking, indicating their therapeutic potential in metabolic disorders.

Aja et al. [49] reported that *Cucumeropsis mannii* seed oil ameliorated bisphenol A-induced adipokine dysfunction and dyslipidemia, underscoring the lipid-modulating capabilities of plant-based compounds, and *Cucumeropsis mannii* seed oil is rich in unsaturated fatty acids (USFA), with linoleic acid being the dominant fatty acid, followed by oleic acid [50]. In vivo studies further support the anti-obesity effects of natural compounds. Uti et al. [2] demonstrated that African walnuts (*Tetracarpidium conophorum*) mitigate hepatic lipid accumulation by modulating HMG-CoA reductase and paraoxonase activity. Umoru et al. [3] extended these findings by showing that African walnuts upregulate adiponectin and PPARγ expression while suppressing TNF-α gene expression in obesity models, providing a mechanistic basis for their lipid-lowering and anti-inflammatory effects. Additionally, Uti et al. [51] reported that *Buchholzia coriacea* leaves attenuated dyslipidemia and oxidative stress in hyperlipidemic rats, reinforcing their potential role in obesity management. Histological and biochemical evidence from Atangwho et al. [52] demonstrated the benefits of *Vernonia amygdalina* supplementation in obese rats, highlighting the metabolic health improvements associated with natural compounds. More recently, Puri et al. [53] emphasized the role of nanotechnology in modern healthcare, integrating traditional medicine, green chemistry, and biogenic metallic phytonanoparticles to enhance the bioavailability and efficacy of therapeutic compounds.

Other studies with similar viewpoints on the role of natural compounds in obesity management include; Mahboob et al. [54] who examined the anti-obesity effects of flavonoids, particularly quercetin and resveratrol, in modulating lipid metabolism via AMPK activation and adipogenesis inhibition, Zhang et al. [55] investigated berberine's effects on lipid metabolism and its potential in reducing obesity-related complications by targeting gut microbiota and mitochondrial function, Zou et al. [56] reported the role of curcumin in attenuating obesity-induced inflammation and lipid dysregulation through the modulation of PPARγ and NF-κB pathways, and Basu et al. [57] demonstrated that green tea catechins promote thermogenesis and improve lipid metabolism by upregulating UCP1 in adipose tissues, and Feng et al. [58] studied the effects of ginsenoside Rg3 on adipocyte differentiation and lipid accumulation, highlighting their role in regulating key metabolic pathways in obesity management.

Building on these recent findings, this review explores cutting-edge advancements in lipid-based nano-carrier systems for delivering anti-obesity natural compounds. We highlight how these innovative platforms address limitations of conventional therapies, opening avenues for targeted and personalized obesity treatment. Key classes of bioactive phytochemicals such as polyphenols, alkaloids, terpenoids, and saponins are examined for their therapeutic potential, alongside challenges like poor bioavailability and stability. Advanced delivery systems, including liposomes, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs), are discussed for their roles in enhancing solubility, targeted delivery, and sustained release. We also look into recent strides in precision therapeutics, emphasizing nanotechnology's promise in tissue-specific targeting and stimuli-responsive drug release. Finally, the review addresses safety, regulatory challenges, and the translational prospects of these systems in clinical obesity management.

Methodology

A thorough literature search was conducted using electronic databases, including PubMed, Scopus, Web of Science, and Google Scholar, to retrieve relevant studies on lipid-based nano-carriers for the delivery of anti-obesity natural compounds. The search strategy incorporated key terms such as "lipid-based nano-carriers," "anti-obesity natural compounds," "nanotechnology in obesity treatment," "bioavailability enhancement," and "targeted drug delivery." Selected articles comprised studies that focused on lipid-based nano-formulations, evaluated their bioavailability and therapeutic efficacy, and assessed their role in obesity management. Studies exploring nano-carrier types such as liposomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and other advanced lipid-based delivery systems were prioritized. Non-peer-reviewed publications, studies that did not specifically address lipid-based nano-carrier applications in obesity, research lacking mechanistic insights or therapeutic assessments, and studies published before 2019 were excluded. However, exceptions were made in a few cases where the studies were deemed significant and formed the foundation of this review.

Natural compounds with anti-obesity potential

Categories of natural anti-obesity compounds

Polyphenols

The bioactive compounds called polyphenols found throughout multiple plant-based sources demonstrate potential for fighting obesity [59, 60]. Natural polyphenolic compounds create a comprehensive weight loss solution through their multiple pathways which control energy and lipid metabolism while reducing inflammation. The diverse biological characteristics of these compounds prove their capacity to reduce inflammation and protect cells from damage and

manage metabolic functions [61, 62]. The modulation of adipogenesis signaling pathways together with thermogenesis and mitochondrial pathways and lipid metabolism pathways demonstrates potential in combating obesity alongside its related medical complications. Manufactured from natural resources and exhibiting minimal adverse effects they become appealing as therapeutic options [63].

Table 1 presents comprehensive information about polyphenols that show anti-obesity potential through an analysis of their sources and mechanisms and research status with identified challenges. The table presents ten essential polyphenols including resveratrol catechins curcumin quercetin which exhibit distinct anti-obesity mechanisms through enhancing fatty acid oxidation and inhibition of lipogenesis combined with stimulation of mitochondrial biogenesis and their promotion of beneficial gut microbiota. The diverse results achieved through preclinical and clinical work demonstrate the vast difficulty in developing these drugs into successful medical interventions. The clinical use of polyphenols faces major problems including poor chemical accessibility and fast destruction in the human body as well as reduced stability in natural environments. The limited therapeutic potential of polyphenols requires innovative delivery systems including nanoparticles and liposomes combined with sustained-release formulations to enhance their therapeutic outcomes. Large-scale clinical studies of polyphenols must occur to validate their safety practices with effectiveness across various population groups. This analysis examines the obesity prevention capacity of these polyphenols while discussing their action pathways and investigation progress along with existing obstacles and upcoming research objectives.

Alkaloids

The research community is strongly interested in alkaloids and other natural products because these substances show multiple bioactive properties and show promise for managing essential metabolic pathways controlling energy balance along with lipid levels [83, 84]. The pharmacologically active compounds known as alkaloids derive from plants and contain nitrogen structures are known to produce anti-obesity effects [85–87]. An Assessment of Selected Alkaloids Exhibiting Anti-Obesity Potential can be Found in Table 2; This document shows the alkaloids' natural origins and their mechanisms of action as well as the research progress and effectiveness along with obstacles to their adoption as weight loss agents and future development targets. Berberine and caffeine among other alkaloids alongside harmine and quinidine demonstrate anti-obesity effects through multiple mechanisms such as thermogenic activation and appetite control and adipocyte differentiation blockade. The clinical application of these substances faces multiple roadblocks which include poor bioavailable properties and issues with safety and approval process requirements. A detailed discussion regarding alkaloid research for obesity management presents both development achievements in this field but stresses the requirement for imaginative approaches to increase their therapeutic effectiveness along with sophisticated delivery systems and optimized alkaloid structures while employing holistic wellness practices has been summarized as given in Table 2.

Terpenoids

Terpenoids represent a widespread group of naturally existing organic substances which have become prominent targets for researchers developing anti-obesity therapeutic strategies [110–112]. Terpenoids derived from multiple plant substances possess distinctive chemical designs which exhibit specific active properties that represent a promising solution beyond traditional drug therapies [34, 113]. Table 3 summarizes the anti-obesity benefits of terpenoids showing their methods of operation together with their effectiveness throughout different study stages and existing barriers. The four terpenoids forskolin and ginsenoside Rb1 along with limonene and curcumin influence distinct metabolic processes that involve changes in lipid levels and increased energy utilization and diminished fat cell formation. The table presents a summary of compound translational progression beginning with preclinical assessment moving onto clinical trials and featuring several compounds that display both fat mass reduction and improved metabolic health metrics.

The clinical application of terpenoids for anti-obesity treatment remains hindered by restricted bioavailability and high extraction costs as well as inadequate human clinical research data. Certain terpenoids require additional development because they produce side effects involving blood pressure reduction and gastrointestinal distress. Future studies focusing on bioavailability improvement and dosage refinement and combinatorial treatment methods will help to overcome current terpenoid utilization constraints and improve their clinical potential. Table 3 examines terpenoids' therapeutic potential through mechanistic understanding and effectiveness reviews coupled with documented limitations toward their application for obesity treatment.

Saponins with anti-obesity potentials

Plants produce naturally occurring glycoside compounds known as saponins have been identified as effective agents for obesity treatment along with associated

Table 1 Polyphenols with anti-obesity potentials, their sources, mechanism of action, and associated challenges

S. no.	Polyphenol	Source	Mechanism of action	Level of study	Clinical phase	Route of administration	Level of success	Challenges	Future direction	References
1	Resveratrol	Red grapes, berries, peanuts	Stimulates Sirtuin 1; promotes mitochondrial biogenesis, fatty acid oxidation, and browning of white adipose tissue	Clinical	Phase II/III	Oral	High	Low bioavailability, rapid metabolism	Development of advanced delivery systems like liposomes and nanoparticles	[64, 65]
2	Catechins	Green tea, black tea	Enhances thermogenesis and fat oxidation; inhibits lipogenic enzymes (ACC, FAS); promotes beneficial gut bacteria growth	Clinical	Phase II/III	Oral	High	Stability and low solubility in aqueous solutions	Improving formulations for stability; conducting large-scale clinical trials	[2, 66]
3	Quercetin	Onions, apples, berries	Inhibits lipid accumulation and promotes mitochondrial biogenesis; reduces inflammation by downregulating pro-inflammatory cytokines	Preclinical	NA	Oral	Moderate	Poor bioavailability; inconsistent results in human studies	Enhancing delivery systems; conducting large-scale human trials to confirm efficacy	[67–69]
4	Epigallocatechin Gallate (EGCG)	Green tea	Promotes fat oxidation; reduces adipogenesis through modulation of AMPK and downregulation of FAS and ACC	Clinical	Phase II	Oral	High	Poor stability and low bioavailability	Nanoencapsulation and structural modifications to improve stability and absorption	[2, 70, 71]
5	Curcumin	Turmeric (*Curcuma longa*)	Inhibits adipogenesis and promotes lipolysis by modulating inflammatory cytokines and activating AMPK pathways	Preclinical	NA	Oral	High	Low bioavailability and rapid degradation in the gastrointestinal tract	Use of nanoformulations, liposomal delivery systems, and prodrugs to enhance absorption	[72, 73]
6	Hesperidin	Citrus fruits	Reduces lipid accumulation and promotes fat oxidation by regulating PPAR-γ and AMPK signaling pathways	Preclinical	NA	Oral	Moderate	Limited clinical data and poor water solubility	Conducting more clinical trials; structural modifications for improved solubility	[2, 2, 74]

Table 1 (continued)

S. no.	Polyphenol	Source	Mechanism of action	Level of study	Clinical phase	Route of administration	Level of success	Challenges	Future direction	References
7	Chlorogenic Acid	Coffee, green coffee beans	Inhibits glucose absorption in the gut, reduces fat deposition, and promotes fat metabolism via AMPK activation	Clinical	Phase II	Oral	High	Limited bioavailability due to metabolism in the gut	Development of sustained-release formulations; further clinical validation in diverse populations	[75–77]
8	Ellagic Acid	Pomegranate, berries	Modulates lipid metabolism by inhibiting pancreatic lipase activity and reducing oxidative stress-induced adipogenesis	Preclinical	NA	Oral	Moderate	Limited clinical studies; rapid degradation	Use of co-delivery systems with other polyphenols for synergistic effects	[78, 79]
9	Apigenin	Parsley, chamomile, celery	Inhibits adipogenesis and promotes mitochondrial activity by modulating PPAR-γ and AMPK pathways	Preclinical	NA	Oral	Moderate	Limited bioavailability and clinical studies	Development of bioenhanced formulations and conducting large-scale human studies	[80, 81]
10	Genistein	Soybeans, legumes	Reduces adipogenesis and promotes fat metabolism by modulating estrogen receptors and AMPK signaling	Preclinical	NA	Oral	High	Hormonal effects; limited bioavailability	Conducting targeted delivery studies to minimize side effects; validating efficacy in clinical trials	[2, 82]

NA not applicable

Table 2 Alkaloids with anti-obesity potentials, their sources, mechanism of action, and associated challenges

S. no.	Alkaloid	Source	Mechanism of action	Level of study	Clinical phase	Route of administration	Level of success	Challenges	Future direction	References
1	Berberine	*Berberis* species	Activates AMPK, suppresses adipogenesis, reduces hepatic lipid accumulation	Clinical	Phase II/III	Oral	High	Low bioavailability, gastrointestinal side effects	Development of better delivery systems and derivatives with enhanced bioavailability	[88, 89]
2	Ephedrine	*Ephedra sinica*	Increases thermogenesis, basal metabolic rate, and lipolysis; suppresses appetite	Clinical	Phase III	Oral	Moderate	Cardiovascular risks, regulatory restrictions	Safer ephedrine analogs; combination with natural compounds to reduce risks	[2, 90]
3	Caffeine	*Coffee, tea, cocoa*	Enhances thermogenesis, fat oxidation, and energy expenditure; reduces appetite	Clinical	Phase IV	Oral	High	Tolerance development, overstimulation, and sleep disruption	Controlled-dose formulations; integration with diet and exercise programs	[91–94]
4	Capsaicin	*Chili peppers* (Capsicum)	Activates TRPV1, promotes thermogenesis, reduces appetite, and enhances fat oxidation	Clinical	Phase III	Oral	High	Tolerance to spicy foods, gastrointestinal discomfort	Alternative delivery methods (e.g., capsules, patches); improving palatability	[95–98]
5	Harmine/Harmaline	*Peganum harmala*	Inhibits MAO activity, affects serotonin and dopamine pathways, promotes fat cell apoptosis	Preclinical	NA	Oral	Moderate	Limited clinical studies, potential toxicity	Preclinical validation and toxicological assessment; development of safer analogs	[99, 100]
6	Nicotine	*Tobacco plants* (Nicotiana)	Activates nicotinic acetylcholine receptors, suppresses appetite, increases thermogenesis, and promotes lipolysis	Clinical	Phase IV	Oral	High (short-term)	Addiction, long-term health risks	Non-addictive derivatives; safer delivery systems (e.g., transdermal patches)	[101–104]
7	Quinidine	*Cinchona bark*	Reduces lipid accumulation and enhances thermogenesis	Preclinical	NA	Oral	Moderate	Limited preclinical data, potential side effects	Validation in obesity models; structural optimization for efficacy and safety	[2, 2]

Table 2 (continued)

S. no.	Alkaloid	Source	Mechanism of action	Level of study	Clinical phase	Route of administration	Level of success	Challenges	Future direction	References
8	Piperine	*Black pepper (*Piper nigrum*)*	Inhibits fat cell differentiation, enhances thermogenesis, and improves nutrient bioavailability	Preclinical/Clinal	Phase I/II	Oral	High	Limited clinical validation, poor solubility	Clinical trials; development of bioenhanced formulations	[2, 2]
9	Reserpine	*Rauwolfia serpentina*	Depletes catecholamines in adrenergic nerve endings, reducing appetite and modulating stress-related obesity	Preclinical	NA	Oral	Moderate	Potential neurological side effects such as depression and sedation	Safer analogs with targeted delivery systems to minimize neurological risks	[105, 106]
10	Yohimbine	*Pausinystalia johimbe*	Blocks alpha-2 adrenergic receptors, enhancing fat breakdown and energy expenditure	Preclinical	NA	Oroal	High	Dose-dependent side effects like anxiety, hypertension, and tachycardia	Controlled-dose studies; integration with lifestyle modifications for weight management	[107–109]

NA not applicable

Table 3 Terpenoids with anti-obesity potentials, their sources, mechanism of action, and associated challenges

S. no.	Alkaloid	Source	Mechanism of action	Level of study	Clinical phase	Route of administration	Level of success	Challenges	Future direction	References
1	Forskolin	*Coleus forskohlii*	Activates adenylate cyclase, increases cAMP levels, enhances lipolysis	Preclinical, clinical	Phase II	Oral	Moderate success in weight and fat loss	Limited clinical trials, side effects like low blood pressure	Larger clinical trials; development of targeted formulations	[114–116]
2	Ginsenoside Rb1	*Panax ginseng*	Modulates adipogenesis, increases energy expenditure, and improves insulin sensitivity	Preclinical, clinical	Phase I/II	Oral, intravenous	Promising anti-obesity effects in animal studies	Limited human studies, high extraction costs	Conduct human trials; optimize extraction techniques	[117, 118]
3	Limonene	*Citrus fruits*	Reduces fat accumulation by modulating lipid metabolism and increasing fatty acid oxidation	Preclinical, clinical	Phase I/II	Oral	Effective in reducing BMI and improving lipid profiles	Lack of human data, low bioavailability	Enhance bioavailability; conduct clinical studies	[34, 119, 120]
4	Curcumin	*Curcuma longa*	Suppresses adipocyte differentiation and inflammation, enhances AMPK activity	Preclinical, clinical	Phase II	Oral, nanoformulations	Effective in reducing fat in animal models	Low bioavailability, rapid metabolism	Develop bioenhanced curcumin formulations for sustained activity	[121–124]
5	Berberine	*Berberis* spp.	Activates AMPK, reduces adipogenesis, and improves mitochondrial function	Preclinical, Clinical	Phase II/III	Oral	Moderate success in weight management	Limited long-term studies, potential gastrointestinal side effects	Evaluate long-term safety; explore combinatorial therapy with other agents	[125–127]
6	Carnosic acid	*Rosmarinus officinalis*	Enhances lipolysis, reduces oxidative stress, and suppresses adipocyte differentiation	Preclinical, Clinical	Phase I/II	Oral	Effective in reducing fat accumulation in models	Limited human data, potential interactions with other medications	Conduct clinical studies; investigate synergistic effects with dietary compounds	[128–130]
7	Genistein	*Soy products*	Modulates PPARγ and inhibits adipogenesis; reduces oxidative stress	Preclinical, clinical	Phase I/II	Oral	Promising results in weight loss and metabolic regulation	Low bioavailability, limited clinical validation	Optimize formulations; explore mechanisms in diverse populations	[2, 131]

Table 3 (continued)

S. no.	Alkaloid	Source	Mechanism of action	Level of study	Clinical phase	Route of administration	Level of success	Challenges	Future direction	References
8	Humulone	*Hops* (Humulus lupulus)	Inhibits lipogenesis by suppressing sterol regulatory element-binding protein (SREBP)-1	Preclinical	NA	Oral, topical	Promising results in reducing lipid accumulation	Lack of human data, potential for dose-dependent side effects	Clinical trials focusing on dose optimization and safety	[132, 133]
9	Betulinic acid	*Birch bark* (Betula spp.)	Induces apoptosis in pre-adipocytes and inhibits differentiation into mature adipocytes	Preclinical	NA	Oral, injectable	Effective in fat mass reduction in animal studies	Limited bioavailability, toxicity at high doses	Develop drug delivery systems to improve safety and efficacy	[134, 135]
10	Ursolic acid	*Apples, rosemary*	Promotes muscle growth, inhibits fat deposition, enhances brown fat activity, and thermogenesis	Preclinical, clinical	Phase I/II	Oral, topical	Effective in improving metabolic health markers	Low bioavailability, limited long-term safety data	Formulate derivatives with improved absorption and stability; conduct more human trials	[136, 137]

metabolic disorders [2, 138]. Research has found that these bioactive compounds are distributed in plant species and these compounds have demonstrated several pharmacological activities which include anti-inflammatory, antioxidant properties and glucose-lowering effects [139–141]. The potential therapeutic effects of saponins on essential metabolic pathways which target insulin signaling and glucose uptake while inhibiting carbohydrate-digesting enzymes position them as possible agents for new anti-obesity treatments [2, 142, 143].

A review of some selected anti-obesity saponins is presented in Table 4 which details source species and study levels together with operational mechanisms of these compounds. The saponins obtained from *Dioscorea nipponic*a dioscin and from *Astragalus membranaceus* astragaloside IV have shown promising outcomes in preclinical research yet their translation into clinical practice encounters obstacles because of restricted bioavailability and transient human trials and toxicity risks. The future of saponin therapy benefits from improvements in formulation research and delivery system design that should overcome these scientific hurdles. Future research must determine the underlying mechanisms of saponin anti-obesity properties while concurrently resolving existing hurdles to enable their utilization in obesity treatment programs. A detailed exploration of saponins' distinct features and weight-loss aspirations and associated research hurdles leads this section towards future perspectives for obesity treatment.

Other bioactives in obesity management

The rising epidemic of obesity has motivated researchers to explore bioactive compounds which might fight obesity alongside conventional treatment methods [164, 165]. Multiple bioactive compounds have shown anti-obesity potential as documented in Table 5. Bioactive compounds from diverse natural sources such as plants, algae and marine organisms operate through distinct weight management mechanisms that support fat metabolism while boosting heat generation and suppressing hunger and regulating metabolic processes.

The analyzed compounds cover preclinical and clinical research work that demonstrates variable success rates for obesity management according to the table. Multiple factors control weight management success with bioactive compounds such as bioavailability levels and prescribed dosages as well as how individuals react differently to them. The development of these compounds as anti-obesity agents faces ongoing constraints including limited proven therapeutic value together with high operational costs and safety implications for public use. Even with their present challenges many bioactive substances demonstrate impressive potential through positive results in preclinical research while demonstrating reasonable effects during clinical testing.

The data strongly indicates we need more research to maximize the potential of bioactives for obesity prevention and therapy. The research will develop better drug delivery systems to increase compound absorption while scientists will test optimal medication doses on many patients for complete safety understanding and practitioners will investigate combining drugs to develop most effective therapies. Our enhanced knowledge of these bioactive compounds has the potential to produce ground-breaking prevention and treatment solutions for obesity that offer fresh hope against this common health issue.

Mechanisms of action of natural compounds in obesity management

The growing global incidence of obesity has made natural bioactive compounds more appealing than ever as prospective therapeutic agents. Compounds extracted from plants including polyphenols together with alkaloids terpenoids saponins and other substances attack central obesity-linked biological processes (Fig. 1, Tables 1–5). Briefly, Fig. 1, outlines the mechanisms of phytochemicals in obesity management, including enhancement of fatty acid oxidation through polyphenolic compounds like resveratrol, epigallocatechin gallate (EGCG), and quercetin, inhibition of lipogenesis by blocking fat synthesis enzymes, activation of thermogenesis by alkaloids like synephrine and yohimbine, modification of gut microbiota by promoting beneficial gut bacteria growth, suppression of appetite by modulating hunger-related hormones like leptin and ghrelin, and anti-inflammatory and antioxidant effects by curcuminoids and omega-3 fatty acids. These mechanisms collectively contribute to obesity management by targeting multiple metabolic pathways.

Research shows that polyphenolic compounds including resveratrol and EGCG, and quercetin and curcumin enhance fatty acid oxidation while blocking lipogenesis and stimulating mitochondrial growth [34, 187]. The compounds cause changes to the composition of gut microbiota while promoting better metabolic outcomes. Some alkaloids like caffeine along with capsaicin and yohimbine and synephrine elevate thermogenesis while decreasing appetite and boosting energy expenditure but they present cardiovascular safety concerns [188]. Although terpenoids including limonene, linalool, carvone, and menthol successfully regulate lipid metabolism and boost energy expenditure while blocking adipocyte differentiation these

Table 4 Saponins with anti-obesity potentials, their sources, mechanism of action, and associated challenges

S. no.	Saponins	Source	Mechanism of action	Level of study	Clinical phase	Route of administration	Level of Success	Challenges	Future direction	References
1	Dioscin	*Dioscorea nipponica*	Enhances glucose uptake, inhibits α-glucosidase, and modulates insulin signaling	Preclinical (in vitro, in vivo)	Not yet in clinical trials	Oral	Significant glucose-lowering effects in animal models	Poor bioavailability and stability	Develop novel formulations to improve bioavailability	[2, 144]
2	Astragaloside IV	*Astragalus membranaceus*	Activates AMPK pathway and regulates oxidative stress	Preclinical (in vitro, in vivo)	Not yet in clinical trials	Oral	Effective in reducing glucose and improving insulin sensitivity	Limited clinical evidence	Conduct clinical trials for efficacy and safety	[145, 146]
3	Ginsenoside Rb1	*Panax ginseng*	Enhances glucose uptake and insulin secretion	Clinical and preclinical studies	Phase I/II	Oral	Effective in improving glucose homeostasis	Dose optimization for human studies	Large-scale clinical trials for long-term safety	[147, 148]
4	Soyasaponin I	*Glycine max* (Soybean)	Inhibits α-amylase and α-glucosidase, reduces postprandial glucose levels	Preclinical (in vivo)	Not yet in clinical trials	Oral	Moderate glucose-lowering potential	Poor absorption and metabolism	Improve pharmacokinetics through formulation design	[149–151]
5	Quillajasaponin	*Quillaja saponaria*	Stimulates insulin secretion and reduces oxidative stress	Preclinical (in vivo)	Not yet in clinical trials	Oral	Significant anti-hyperglycemic effects in diabetic rats	Limited human studies	Explore combination therapy with other antidiabetic agents	[2, 152]
6	Saikosaponin A	*Bupleurum falcatum*	Activates PPAR-γ, enhances insulin sensitivity, and inhibits inflammation	Preclinical (in vitro, in vivo)	Not yet in clinical trials	Oral	Promising glucose-lowering effects in animal models	Toxicity concerns at high doses	Assess safety profile and dose standardization	[153, 154]
7	Aescin	*Aesculus hippocastanum*	Improves glucose metabolism by regulating GLUT4 translocation	Preclinical (in vivo)	Not yet in clinical trials	Oral	Effective in reducing fasting blood glucose levels in diabetic models	Poor systemic absorption	Develop nanoparticle-based delivery systems for enhanced absorption	[155, 156]
8	Bacopaside I	*Bacopa monnieri*	Modulates insulin signaling pathways and reduces oxidative stress	Preclinical (in vitro, in vivo)	Not yet in clinical trials	Oral	Promising in improving glucose tolerance	Limited clinical validation	Conduct human trials to evaluate safety and long-term effects	[157–159]
9	Gypsosaponin	*Gypsophila oldhamiana*	Inhibits carbohydrate-digesting enzymes and improves glucose utilization	(Preclinical (in vitro, in vivo)	Not yet in clinical trials	Oral	Significant anti-hyperglycemic effects	Limited research on pharmacokinetics	Perform advanced pharmacokinetic and toxicological studies	[160, 161]

Table 4 (continued)

S. no.	Saponins	Source	Mechanism of action	Level of study	Clinical phase	Route of administration	Level of Success	Challenges	Future direction	References
10	Escin	*Horse chestnut*	Anti-inflammatory effects that enhance insulin sensitivity and glucose uptake	Preclinical (in vivo)	Not yet in clinical trials	Oral	Promising in controlling hyperglycemia	Toxicity and side effects	Investigate dose optimization and long-term safety	[162, 163]

Table 5 Other bioactives with anti-obesity potentials, their sources, mechanism of action, and associated challenges

S. no.	Bioactive compound	Source	Mechanism of action	Level of study	Clinical phase	Route of administration	Level of success	Challenges	Future direction	References
1	Capsaicin	*Chili peppers* (*Capsicum*)	Increases energy expenditure, stimulates thermogenesis, and reduces appetite	Preclinical and clinical	Phase I–III	Oral, topical	Moderate	Limited bioavailability, tolerance development	Explore improved formulations for sustained effects	[166, 167]
2	Fucoxanthin	*Brown seaweed* (e.g., *Undaria*)	Increases fat oxidation and reduces fat accumulation by enhancing thermogenesis	Preclinical and clinical	Phase I–III	Oral	High	Limited bioavailability, cost of extraction	Investigate more efficient extraction methods, clinical trials	[168, 169]
3	Pterostilbene	*Blueberries, grapes*	Activates SIRT1, increases fatty acid oxidation, and improves mitochondrial function	Preclinical and clinical	Phase I–III	Oral	High	Bioavailability issues, limited human studies	Develop improved delivery methods, conduct large trials	[170, 171]
4	Gingerol	*Ginger* (*Zingiber officinale*)	Increases thermogenesis and energy expenditure while reducing fat accumulation	Preclinical and clinical	Phase I–III	Oral	Moderate	Potential for irritation in sensitive individuals, limited clinical evidence	Further clinical trials to assess long-term effects and safety	[172–174]
5	Garcinia cambogia extract	*Garcinia cambogia*	Inhibits fat synthesis by blocking citrate lyase and increases fat oxidation	Clinical and preclinical	Phase I–III	Oral	Moderate	Mixed clinical results, risk of gastrointestinal side effects	Further studies on the ideal dosage and long-term use	[175–177]
6	Glucomannan	*Konjac root*	Absorbs water to form a gel, promoting satiety and reducing appetite	Clinical and preclinical	Phase I–III	Oral	Moderate	Bloating, possible digestive discomfort, and risk of esophageal obstruction	Optimize dosage and combine with other appetite-suppressing agents	[178–180]
7	CLA (Conjugated Linoleic Acid)	*Dairy, meat* (*ruminants*)	Reduces fat mass by regulating adipocyte differentiation and lipogenesis	Preclinical and Clinical	Phase I–III	Oral	High	Variability in individual responses, potential liver damage at high doses	Explore optimal dosages and long-term safety	[181, 182]
8	Silymarin	*Milk thistle* (*Silybum marianum*)	Modulates lipid metabolism, reduces oxidative stress, and improves insulin sensitivity	Preclinical and clinical	Phase I–III	Oral	Moderate	Limited clinical evidence on weight loss, liver-focused research	Investigate combined effect with other metabolic modulators	[183, 184]

Table 5 (continued)

S. no.	Bioactive compound	Source	Mechanism of action	Level of study	Clinical phase	Route of administration	Level of success	Challenges	Future direction	References
9	Astaxanthin	*Microalgae, shrimp, salmon*	Inhibits inflammation, reduces oxidative stress, and improves lipid metabolism	Preclinical and clinical	Phase I–III	Oral	Moderate	Limited human data, expensive production costs	Explore cost-effective sources and enhanced human trials	[185, 186]

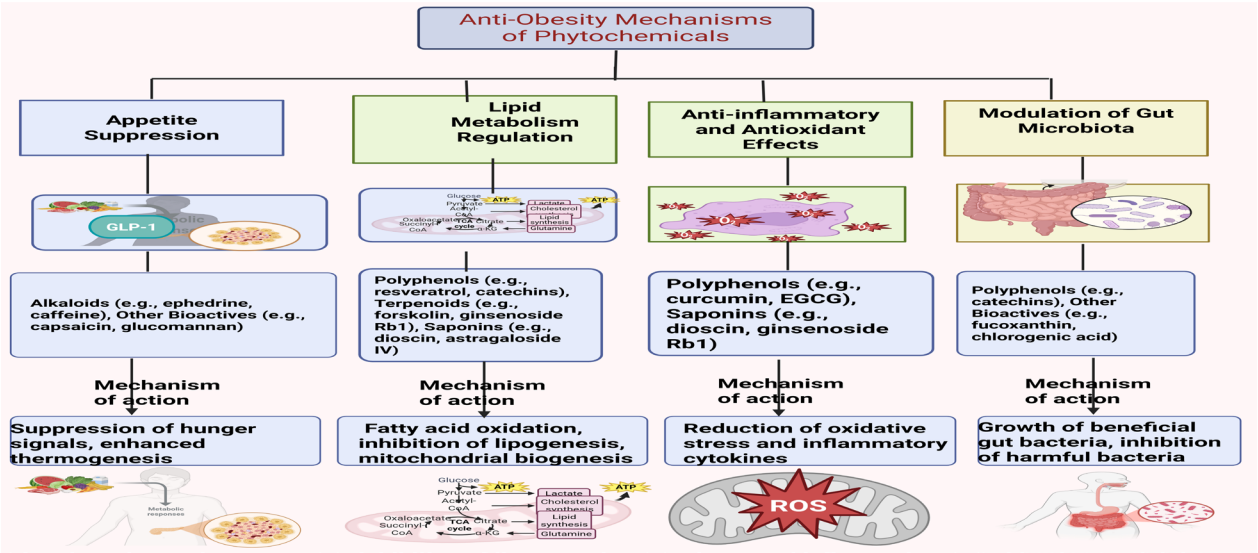


Fig. 1 Mechanisms of Phytochemicals in Obesity Management (Created in https://BioRender.com). This figure illustrates the diverse mechanisms through which phytochemicals exert anti-obesity effects. It shows that polyphenols such as resveratrol, epigallocatechin gallate (EGCG), and quercetin enhance fatty acid oxidation, inhibit lipogenesis by downregulating fat synthesis enzymes, and promote mitochondrial biogenesis. Additionally, alkaloids like synephrine ephedrine, and caffeine stimulate thermogenesis and increase energy expenditure, while also suppressing appetite by modulating hormones such as leptin and ghrelin. The figure further highlights how certain bioactives influence gut microbiota composition, encouraging the proliferation of beneficial bacteria. Moreover, compounds like curcumin and omega-3 fatty acids contribute anti-inflammatory and antioxidant effects, thereby mitigating metabolic stress. Collectively, these phytochemicals act on multiple molecular pathways to provide a comprehensive approach to obesity management

compounds face obstacles due to gastrointestinal side effects and their high manufacturing costs [34, 34]. Advanced delivery systems are needed to overcome the poor absorption and variable efficacy of saponins which include diosgenin, ginsenosides, quillaic acid, and escin properties that enhance glucose uptake while improving insulin signaling and reducing oxidative stress [189–191]. The bioactive compounds curcuminoids and gingerols along with omega-3 fatty acids and conjugated linoleic acid (CLA) display anti-inflammatory action and impact gut microbiota regulation and lipid metabolic efficiency despite requiring improved stability and scaling methods [192–194].

Lipid-based nano-delivery systems

Nanocarriers constructed from lipids have evolved into a ground-breaking massive approach for obesity management which offers new solutions to standard therapeutic obstacles [34, 34]. The nanocarriers provide superior biological tolerance in addition to drug molecule encapsulation capabilities and natural barrier penetration properties [34, 195]. Engineers at the nanoscale level have developed lipid-based nanocarriers which improve active agent delivery efficiency by solving obesity treatment challenges of poor bioavailability and nonspecific targeting [196, 197]. The structural composition of these systems consists mainly of lipids because these molecules naturally attract cellular membranes which enables better drug uptake and precise medication release and enhanced therapeutic effectiveness [198, 199]. The extensive loading capacity of these platforms allows them to contain drugs and peptides alongside nucleic acids therefore enabling use across metabolic complication investigation of obesity pathways. Lipid-based nanocarriers present therapeutic opportunities for obesity treatment and their current applications together with remaining barriers to reach their full therapeutic capabilities in managing this worldwide health issue are analyzed in this section.

Types of lipid-based nanocarriers

Lipid-based nanocarriers can be broadly classified into several types (Fig. 2) each with distinct structures, properties, and applications [200–202]: Fig. 2 summarizes various lipid-based nano-delivery systems for delivering phytochemicals in obesity management. These systems include liposomes, solid lipid nanoparticles, nanostructured lipid carriers, exosomes and lipid-based biomimetic nanocarriers, and self-emulsifying drug delivery systems. Liposomes are spherical vesicles with phospholipid bilayers, while solid lipid nanoparticles enhance drug stability and

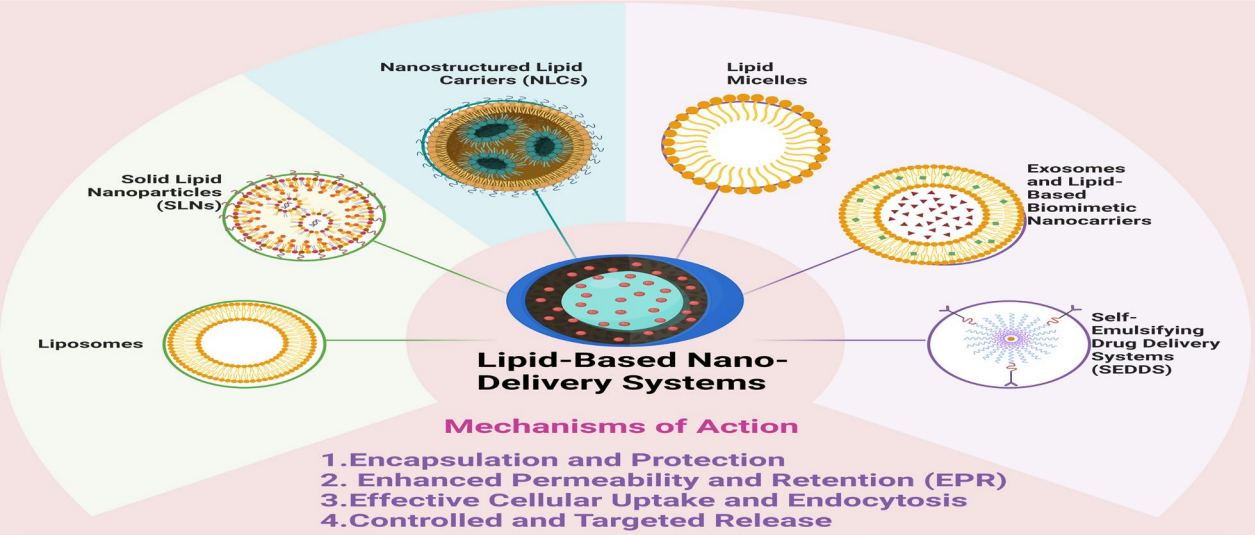


Fig. 2 Lipid-based nano-delivery systems for phytochemicals (drugs) delivery in obesity management (created in https://BioRender.com). This Figure provides a schematic overview of various lipid-based nano-delivery systems designed to enhance the therapeutic efficacy of natural anti-obesity compounds. It presents liposomes as spherical vesicles with phospholipid bilayers capable of encapsulating both hydrophilic and hydrophobic molecules, thereby improving solubility and stability. Solid lipid nanoparticles (SLNs) are highlighted for their enhanced drug stability and controlled release properties, whereas nanostructured lipid carriers (NLCs) combine solid and liquid lipids to provide greater drug loading capacity and reduce premature release. The figure also illustrates lipid micelles, which are self-assembled amphiphilic carriers that improve the solubility and absorption of poorly water-soluble phytochemicals. Exosomes and biomimetic nanocarriers mimic biological lipid bilayers and offer efficient cell targeting with minimal immunogenicity. Lastly, self-emulsifying drug delivery systems (SEDDS) are shown to enhance gastrointestinal absorption by forming fine emulsions that improve solubility and bioavailability of lipophilic compounds. Together, these systems represent advanced strategies for improving the delivery, stability, and efficacy of phytochemicals in obesity therapy

controlled release. Nanostructured lipid carriers combine solid and liquid lipids, while exosomes and lipid-based biomimetic nanocarriers mimic biological lipid bilayers. Self-emulsifying drug delivery systems form oil-based formulations in the gastrointestinal tract, improving drug solubility and absorption. These lipid-based nanocarriers offer advantages such as enhanced solubility, increased bioavailability, better stability, controlled drug release, and targeted delivery of natural compounds.

Liposomes

Liposomes with a phospholipid bilayer can offer a hydrophilic core for hydriphilic drugs with a hydrophobic shell for hydrophobic drugs [34]. These lipid-based nanocarriers emerged during the 1960s and subsequently established themselves as the most investigated delivery systems in modern drug delivery. Fluid expertise separates liposomes into unilamellar vesicles which combine single lipid bilayers with small unilamellar vesicles (SUVs) and large unilamellar vesicles (LUVs) categories alongside multilamellar vesicles (MLVs) that use multiple lipid bilayers [203]. Because of their distinctive design and compatibility with biological substances liposomes serve as fundamental elements of pharmaceutical creation to ensure targeted drug delivery systems. Doxil® (doxorubicin liposomes) represents a liposome-based formulation that now holds FDA approval for cancer therapy through improved therapeutic index and reduced agent-related systemic toxicity [204, 205].

Solid lipid nanoparticles (SLNs)

Solid lipid nanoparticles (SLNs) represent sophisticated drug delivery methods that incorporate solid lipids which stay structurally sound at normal temperatures and body temperatures for improved delivery flexibility and consistency [206]. The hydrophobic core of these nanoparticles stays solid and protected by a protective phospholipid or surfactant monolayer that promotes both structural protection and biological compatibility. SLN solid matrices function both to protect drugs by creating barriers against environmental elements while providing physical stability through their protective barrier formation which improves drug shelf life and pharmacological effectiveness [207, 208]. SLNs represent an ideal drug delivery method for lipophilic substances because they both enhance drug solutions and increase drug availability when drugs remain dissolved in their hydrophobic core. Trapped within SLNs patients

experience controlled release properties because the materials provide a gradual time-release mechanism that also means less frequent dosing [209, 210]. The controlled drug release capability has clear value for medication delivery of precise amounts when combined with drugs whose body clearance rates remain rapid over time. The special features of solid lipid nanoparticles position them as an effective delivery method that benefits complex medicinal formulations.

Nanostructured lipid carriers (NLCs)

Nanostructured Lipid Carriers (NLCs) function as improved derivatives of SLNs because they expand upon solid lipid nanoparticles to overcome specific formulation constraints. NLCs achieve their functional enhancements through the combination of solid and liquid lipids which leads to formation of an imperfect crystalline matrix [211, 212]. This matrix improves drug storage capacity while protecting drug contents from unexpected release during storage periods which often affects SLN systems. Liquid lipids added to systems loosen solid lipids' perfect crystal arrangement which allows larger Active Pharmaceutical Ingredient (API volumes to fit within created spaces. NLCs demonstrate excellent suitability for trapping drugs that resist water dissolution making them valuable for drug delivery applications. Supercritical carbon dioxide processed NLCs demonstrate multiple medical applications because they improve both the drug bioavailability and delivery while minimizing systemic chemical reactions in cancer treatments [213, 214]. Science-based dermatological applications use NLCs to deliver active compounds within skincare products where they enhance penetration depth and maintain compound availability over time. Their ability to penetrate biological barriers enables their use in central nervous system (CNS) disorders thereby providing promising drug delivery methods to regions where traditional methods prove inadequate [214]. NLCs continue to gain significance in pharmaceutical therapies because these systems demonstrate fundamental versatility in diverse drug delivery settings.

Lipid micelles

Lipid Micelles are simple structure of amphiphilic lipids caused by self-assembly in aqueous solutions. Lipid self-organization occurs through their amphiphilic behaviour which produces small spheres that combine their lipophilic tails into a central hydrophobic domain while their hydrophilic heads reside at the exterior to connect with aqueous environments [215]. Lipid micelles possess a hydrophobic core combined with a hydrophilic shell that creates a structure which effectively encapsulates poorly soluble drugs located inside the core. Through their encapsulating ability lipid micelles optimize therapeutic outcomes by improving the absorption of water-solubility limited drugs that are vital in pharmaceutical products. Lipid micelles effectively solubilize drug compounds while they protect the drugs through stability maintenance alongside prevention of degradation and facilitate greater systemic absorption [216]. Drug delivery systems utilizing biocompatible lipid micelles at the nanoscale work effectively to address delivery challenges in clinical conditions.

Exosomes and lipid-based biomimetic nanocarriers

Nature produces exosomes as extracellular vesicles that enable cellular intercommunication through the transfer of proteins and nucleic acids and lipids between cells. Researchers apply exosome-inspired biomimetic lipid-based nanocarriers to construct therapeutic platforms that replicate exosome features [217]. The engineered nanocarriers duplicate exosomal lipid bilayers through engineered design enhancements which improve stability and enhance delivery targeting with minimized compatibility issues [218]. Nanocarriers built with biomimetic lipid structures display exceptional potential as drug delivery platforms for obesity therapy. Nanocarriers can transport anti-obesity drugs towards adipose tissues and metabolic organs by wrapping ligands, peptides, or antibodies which bind receptors present on both adipocytes and hepatic cells. Nanocarriers provide a vehicle to carry nucleic acids while enabling gene therapy affecting obesity-relevant genes and generating anti-inflammatory outcomes [219–221].

The delivery of exosome-like nanocarriers through the body leads to microbiome restoration along with improvements in lipid metabolism and energy balance and reduced obesity-linked systemic inflammation [222]. These nanocarriers shield natural compounds including curcumin and resveratrol and catechins from gastrointestinal breakdown while enabling their better absorption and targeted transport to adipose tissues and metabolic organs [223]. Biomimetic lipid-based nanocarriers' applications to manage obesity encounter obstacles stemming from complicated production methods alongside storage requirements and regulatory approval difficulties. Future investigators should concentrate their efforts on three main research aspects: developing precise target delivery through advanced ligand engineering [224, 225], creating manufacturing methods with scalability and low production costs and performing extensive proof-of-concept experiments

coupled with clinical investigations to assess therapeutic safety and effectiveness.

Self-emulsifying drug delivery systems (SEDDS)

SEDDS represents a novel formulation technology using an isotropic blend of oils and surfactants with co-surfactants capable of forming small emulsion droplets automatically after mixing with aqueous gastrointestinal fluids [226, 227]. The attractiveness of self-emulsifying drug delivery systems in obesity management derives from their ability to increase solubility alongside improving both stability and bioavailability rates of drug substances that target metabolic pathways related to obesity [228]. Current therapeutic medications used to treat obesity encounter several problems since they dissolve poorly in water and show low bioavailability. The oil phase of SEDDS contains encapsulated hydrophobic drugs that enable quick passage through gastrointestinal tract fluids because they bridge liquid phases efficiently thereby enhancing both drug absorption and efficacy [229]. Controlled by surfactants along with co-surfactants the SEDDS system enables quick emulsification and maintains drug continuity through sustained dispersion to achieve consistent dosing outcomes and predictable drug effects [229]. Oral delivery using SEDDS systems acts as a practical method to distribute lipophilic compounds which target lipid metabolism while regulating appetite and absorbing fat. The combination of solubility and absorption barrier modification in SEDDS establishes this pharmaceutical approach as a strong solution for obesity drug delivery efficiency.

Table 6 provides a comparative analysis of the various lipid-based nanocarriers, highlighting their structural characteristics, advantages, and limitations. The table categorizes key nanocarriers, including liposomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), lipid micelles, exosomes, and self-emulsifying drug delivery systems (SEDDS). Each type is assessed based on its advantages over conventional formulations, its suitability for encapsulating natural compounds, and potential challenges in formulation and clinical application. By understanding the strengths and weaknesses of these systems, researchers can optimize their use in obesity therapy, paving the way for more effective and targeted treatment strategies.

Advantages of lipid-based nano-carriers in natural compound delivery

Lipid-based nanocarriers represent a notable development in drug delivery, owing to their capacity to carry bioactive molecules, especially natural products, to designated target locations. Nano-carriers, such as lipid nanoparticles (LNPs), liposomes, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs), provide numerous benefits for the delivery of natural compounds, including increased solubility and bioavailability, enhanced stability, and regulated release [34, 242–244].

Enhanced solubility and bioavailability

Natural chemicals, including polyphenols, flavonoids, alkaloids, terpenoids, and other plant-derived bioactives, often exhibit inadequate water solubility and diminished bioavailability. Lipid-based nano-carriers significantly enhance the solubility of hydrophobic substances by forming nanoscale structures that encapsulate bioactive molecules inside or on the lipid matrix's surface. Liposomes are spherical vesicles formed by lipid bilayers capable of encapsulating both hydrophilic and hydrophobic substances. Earlier reports have supported the role of lipid-based nano-carriers, including liposomes, enhance the solubility and bioavailability of plant-derived bioactives such as polyphenols, flavonoids, alkaloids, and terpenoids: Janet et al.[245], in their study explores the role of lipid-based nano-carriers in improving the solubility and bioavailability of poorly soluble bioactive compounds. The study highlighted how liposomes encapsulate both hydrophilic and hydrophobic molecules, thereby enhancing their stability and bioavailability. In another study by Hu et al. [246], this study evaluates the pharmacokinetics of liposome-encapsulated polyphenols and demonstrates a significant improvement in bioavailability compared to free-form compounds, and Pugazhendhi et al. [246], discussed nano-liposomes as efficient carriers for plant bioactives, including their ability to enhance solubility and control the release of bioactive molecules for better therapeutic effects.

Enhanced absorption and bioavailability

The solubility of bioactive natural chemicals is greatly increased using lipid-based nano-carriers, leading to enhanced absorption in the gastrointestinal (GI) tract. Liposomes replicate the natural processes of lipid digestion and absorption, enhancing the bioavailability of the substances. Moreover, these nano-carriers safeguard bioactive substances against enzymatic degradation in the gastrointestinal system, so averting premature breakdown prior to absorption, which further improves their bioavailability. The reports by Subramanian [247], and Liu et al. [248] highlighted the potential of lipid-based nanocarriers in improving the solubility and bioavailability of bioactive natural chemicals. These carriers facilitate enhanced absorption through solubilization in the intestinal milieu, intestinal

Table 6 Comparative analysis of lipid-based nano-delivery systems for obesity management: types, advantages, and limitations

S. no.	Lipid-based nanocarrier	Structural characteristics	Advantages over others	Advantages for natural compounds	Disadvantages/limitations	References
1	Liposomes	Spherical vesicles with a phospholipid bilayer	High biocompatibility, suitable for hydrophilic and hydrophobic drugs, enhances targeted delivery	Protects natural compounds like curcumin and catechins from degradation, improves bioavailability	Prone to instability and leakage, costly manufacturing, limited shelf life	[230, 231]
2	Solid lipid nanoparticles (SLNs)	Solid lipid core with a surfactant coating	Better stability than liposomes, controlled drug release, improved bioavailability of lipophilic drugs	Protects lipophilic compounds from degradation, enhances drug solubility	Low drug loading capacity, risk of drug expulsion during storage	[232, 233]
3	Nanostructured lipid carriers (NLCs)	Mixture of solid and liquid lipids forming an imperfect crystalline matrix	Higher drug loading than SLNs, better stability, prevents premature drug release	Suitable for phytochemicals with poor solubility, maintains active compounds' stability	Complexity in formulation, possible cytotoxicity at high concentrations	[234, 235]
4	Lipid micelles	Self-assembled amphiphilic lipids forming small spheres	Improves solubility of poorly water-soluble drugs, increases absorption	Enhances bioavailability of polyphenols and flavonoids	Limited drug payload, risk of instability in biological fluids	[236, 237]
5	Exosomes and biomimetic nanocarriers	Naturally derived extracellular vesicles or synthetic lipid bilayer nanocarriers	High biocompatibility, efficient cell uptake, minimal immunogenicity	Can carry anti-obesity drugs, enable targeted delivery to adipose tissue	Complex production process, regulatory hurdles for clinical use	[238, 239]
6	Self-emulsifying drug delivery systems (SEDDS)	Oil-based formulation forming fine emulsions in GI tract	Improves oral bioavailability, enhances stability of lipophilic drugs	Facilitates absorption of lipid-soluble phytochemicals like resveratrol and omega-3 fatty acids	Requires surfactants, risk of gastrointestinal irritation	[240, 241]

lymphatic transport, and modification of enterocyte-based transport [248]. They also protect bioactives from degradation by preserving their functional integrity. Lipid-based nanocarriers include liposomes and niosomes, solid lipid nanoparticles and nanostructured lipid carriers, and self-emulsifying drug delivery systems [248]. These carriers have shown clinical and pharmacokinetic improvements, such as increased bioavailability of compounds like curcumin, quercetin, and resveratrol. Lipid-based formulations also have potential for functional foods and pharmaceuticals, as they enable stable and effective delivery of poorly water-soluble compounds in food and medical applications.

Enhanced stability of bioactives

Lipid-based nano-carriers provide superior protection against environmental stressors like light, oxygen, and heat. Encapsulating these molecules inside lipid matrix protects them from external influences that may cause deterioration. Lipid nanoparticles serve as a protective barrier, preserving the integrity of encapsulated bioactives for extended durations. Liposomes can efficiently safeguard their contents from oxidation and hydrolysis by enclosing them inside an anhydrous lipid core, while solid lipid nanoparticles (SLNs) may inhibit oxidative degradation by offering a solid lipid matrix. Previously, some studies have reported the protective role of lipid-based nano-carriers against oxidation and hydrolysis: Viegas et al. [249], in their study, they reported the role of lipid-based nanocarriers in encapsulation and protection of bioactive compounds. This paper discusses how liposomes and solid lipid nanoparticles (SLNs) protect bioactives from oxidation and degradation. In another study by Nahum and Domb [250], Nanoencapsulation of food ingredients using lipid-based delivery systems" was reported. The study highlights how lipid nanoparticles (SLNs and nanostructured lipid carriers, NLCs) enhance the oxidative stability of encapsulated molecules. These provide strong evidence that lipid-based nano-carriers enhance the stability of encapsulated bioactives against oxidation, hydrolysis, and other degradative factors.

Improved shelf life and storage stability

Lipid-based nano-carriers augment the shelf life of natural bioactives by reducing degradation during storage. Stability studies of liposomal formulations by Pasarin et al. [251], and Rezagholizade-shirvan et al. [251] indicate that they may preserve the integrity of the encapsulated ingredient throughout prolonged storage, which is particularly advantageous in the creation of nutraceuticals and medicines derived from natural materials. This guarantees that the bioactive components maintain their potency and effectiveness throughout time.

Lipid-based nano-carriers provide targeted and sustained release of natural bioactives, allowing for regulated delivery of the encapsulated molecules [252]. This is especially beneficial for administering bioactives in localised treatments for illnesses like cancer, inflammation, or infection. Lipid nanoparticles may be functionalised with ligands or antibodies on their surface that precisely recognise and bind to receptors on target cells. Lipid-based nano-carriers provide continuous and regulated release of natural chemicals, therefore extending their therapeutic efficacy and reducing adverse effects. Encapsulating these drugs in lipid-based carriers allows for regulated release over a prolonged duration. SLNs and NLCs are often formulated with a solid lipid matrix that gradually releases bioactive chemicals, ensuring a prolonged release profile. This method reduces the need for regular delivery, improves patient adherence, and sustains stable medication concentrations in the body. Lipid-based carriers may be engineered to release natural substances in response to particular stimuli, such as changes in pH or temperature, therefore improving the accuracy of medication delivery.

Advances in targeted delivery using lipid-based nano-carriers

Tissue-specific targeting, and Cellular uptake mechanisms are major strategies for targeted delivery in obesity therapy/ Nanotechnology stands as a promising strategy for obesity therapy through targeted tissue delivery to enhance both precision and outcomes and reduce adverse effects (Fig. 3). Lipid-based nanoparticles combined with polymeric nanoparticles receive equal consideration as adipose-specific ligands together with thermoresponsive nanoparticles beside lipophilic medicine delivery through microneedles for adipose tissue administration and nanocarrier-assisted gene delivery [34, 253]. The design of lipid-based nanoparticles allows scientists to create targeted delivery options for tissues that face obesity-related complications in adipose tissue and liver and muscle. The unique design of polymeric nanoparticles allows for delivering active substances that bind directly to tissue receptors. Medication delivery to adipose tissue becomes more targeted once nanoparticle platforms combine adipose-specific ligands [253, 254].

The body temperature sensitivity of thermoresponsive nanoparticles enables precise drug delivery into adipose tissue. Film-coated drug delivery systems encapsulate hydrophobic pharmaceutical agents to increase their stability and enhance their absorption and tissue retention properties [255]. The engineering of microneedles

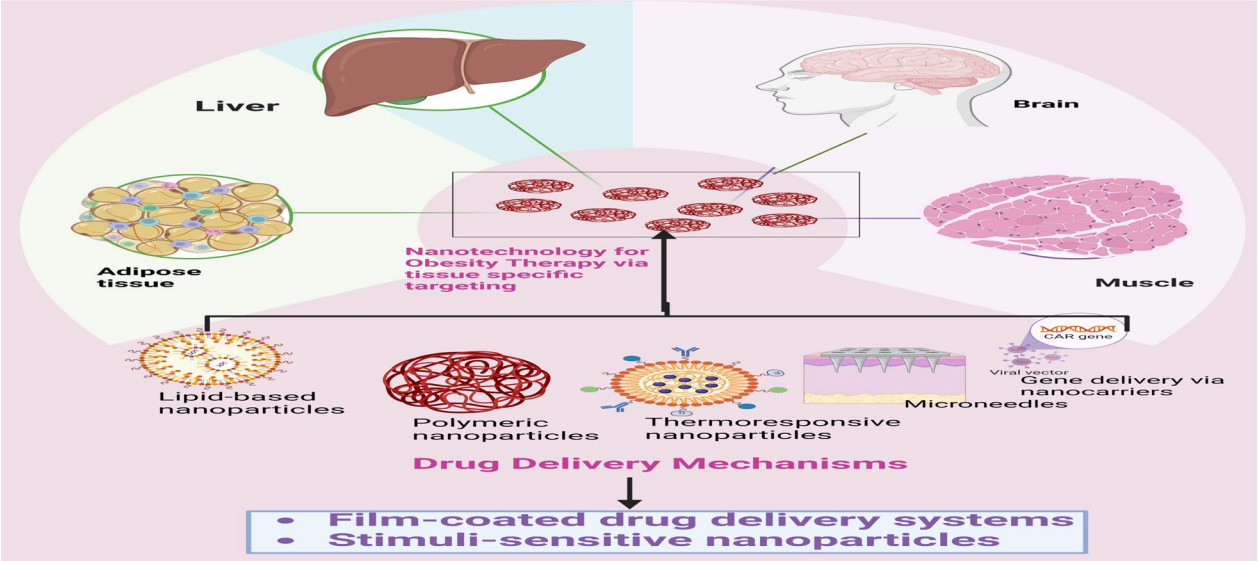


Fig. 3 Strategies for tissues targeted delivery Using Nanotechnolgy in obesity therapy. (Created in https://BioRender.com). This Figure illustrates cutting-edge strategies that leverage nanotechnology to achieve tissue-specific drug delivery in obesity treatment. The figure demonstrates how lipid-based and polymeric nanoparticles can be engineered with adipose-specific ligands to ensure targeted delivery to adipose tissue, liver, or muscle. It also shows how thermos-responsive nanoparticles can be triggered by body temperature to release their therapeutic contents precisely within adipose tissue. Additionally, the use of microneedle systems is presented as a non-invasive method to deliver anti-obesity agents transdermally, enhancing drug retention and minimizing discomfort. Gene delivery applications using nanocarriers such as siRNA-loaded nanoparticles—are depicted for their ability to modulate obesity-related genes at the molecular level. Furthermore, the figure outlines dual-delivery platforms that co-administer appetite suppressants and anti-inflammatory agents for synergistic therapeutic effects. Finally, stimuli-responsive nanoparticles are highlighted for their ability to release drugs selectively in response to environmental changes such as pH, temperature, or enzymatic activity, offering precise and personalized therapeutic outcomes in obesity management

involves limiting penetration to the epidermis only allowing for targeted medication administration while enhancing both patient comfort and reducing procedure aggression [256]. Nanocarriers help neuro-direct delivery to specific brain locations responsible for controlling hunger together with metabolism [257]. Dual therapy delivered through nanotechnology-based encapsulation improves the delivery of weight-loss medicines and appetite-suppressant compounds simultaneously for heightened treatment outcomes [257]. Stimuli-sensitive nanoparticles automatically release their therapeutic content when activated by specific pH environments, enabling them to reach targeted body areas including stomach tissues and adipocytes [258].

Advances in intelligent nanoplatforms for adipose tissue remodelling manipulate nanomaterials to manage adipogenesis as they explore potential ways to address metabolic dysfunctions through specific modification of adipose tissue gene expression patterns [34, 259]. Nanotechnology-based tissue-specific delivery for obesity treatment shows great promise to boost both treatment efficiency and safety while providing patients with targeted and personalized therapy options.

Researchers have used receptor-mediated endocytosis (RME) as an emerging approach to optimize the exact targeting capacity of anti-obesity pharmaceuticals while enhancing their performance [260, 261]. According to these studies, RME enables drug molecules to selectively bind to specific cell surface receptors, triggering internalization into target cells and reducing off-target effects. Scientists have stated that this mechanism enhances drug bioavailability and ensures that therapeutic agents reach their intended site of action with greater specificity. Moreover, experts have noted that RME-based drug delivery can overcome biological barriers, minimize systemic toxicity, and improve the pharmacokinetic profile of anti-obesity agents [112, 260]. Recent advancements have also demonstrated that functionalizing nanoparticles with ligand-based targeting strategies further refines drug delivery through RME [112, 262].

Cellular receptor mediated endocytosis (RME) serves as a mechanism to transport particular molecules into cells through surface receptor-mediated binding events. Selective cell surface receptor detection enables cellular regulation of substance entry including hormones and growth factors and nutrients and drugs [263]. Through receptor-mediated endocytosis therapeutic agents can be transported directly to their intended cells which results in lower side effects and stronger drug effects in obesity

treatment. The RME process involves the following steps: A sequential process takes place including ligand binding followed by clathrin-coated vesicle formation leading to endosomal internalization and uncoating then trafficking before ligand action or degradation occurs [264]. Common cellular receptors involved in RME mechanisms related to obesity comprise insulin receptor (IR), leptin receptor (Ob-R), fatty acid receptors (FFARs), scavenger receptors (SRs) and CD36 (Fatty acid translocase) alongside adiponectin receptors (AdipoR1 and AdipoR2) and endothelial receptors (e.g. VEGF receptors) [265].

Advantages of RME for obesity therapy include [266, 267]

RME structures enable pharmacological compounds to bind with specific receptors that permit desired drugs to reach their target tissues with minimal unintended consequences. Drugs can penetrate cell membranes more efficiently when using receptor-mediated processes which enhances both tool availability in the body as well as therapeutic results. Drugs that were previously eliminated before reaching their target site benefit from this delivery approach which ensures safe arrival.

Database-guided drug delivery through RME functions to protect target cells from dangerous systemic side effects. Drugs with harmful side effects benefit remarkably when they receive precise targeted treatment. By targeting specific receptors that participate in obesity-related pathways the therapeutic agents maintain their ability to impact molecular mechanisms of obesity including fat accumulation and insulin resistance and inflammatory processes. New treatment enhancements become possible through this method of delivery. Medical scientists can use RME to penetrate biological barriers including the blood–brain barrier for drug distribution when treating central regulations of appetite and energy expenditure.

However, several challenges need to be addressed [268]: Researchers need to invest deeply into understanding receptor biology to develop drugs that will exclusively target overexpressed receptors yet preserve normal physiological activities. Internalized drugs require proper cellular routing to achieve therapeutic outcomes within their proper intracellular compartments. An improper drug routing system could result in damaged or unproductive drug effects. The effectiveness of receptor-targeted therapies becomes limited when cells reduce receptor expression levels or create resistance mechanisms during prolonged treatment. The optimization of delivery vehicles including nanoparticles and liposomes remains essential to achieve efficient therapeutic agent transport while minimizing adverse immune system effects.

Receptor-mediated endocytosis demonstrates excellent potential to become a key method for targeted drug delivery treatment of obesity. This approach enables increased therapeutic drug performance through its ability to target specific receptors found on chosen cells combined with enhanced bioavailability and efficacy and reduced systemic toxicity. The complete success of RME therapy for obesity treatment and related metabolic disorders requires overcoming three primary barriers including receptor selectivity and intracellular trafficking and resistance development.

Functional modifications of lipid-based nano-carriers for obesity management

Nanotechnology advances have led laboratories to develop lipid-based nanocarriers that improve drug delivery targets alongside increasing bioavailability and decreasing adverse effects. The modified nanocarriers achieve enhanced effectiveness for obesity treatments through functionalization methodologies. This section focuses on two key strategies for functionalizing lipid-based nano-carriers: Scientific modifications that strengthen delivery system surface properties involve both ligand attachment protocols and responsive triggering protocols.

Surface functionalization with ligands

Surface functionalisation involves altering the surfaces of nanocarriers with particular ligands, like peptides, antibodies, or small molecules, to facilitate targeted distribution and enhance therapeutic efficacy. Surface functionalisation is especially advantageous in obesity therapy, since it improves the distribution of anti-obesity drugs to target organs such as adipose tissue, liver, or the hypothalamus. Ligand-based targeting enhances specificity, reduces off-target effects, and augments therapeutic effectiveness [269, 270].

Peptide ligands are extensively used owing to their diminutive size, biocompatibility, and capacity to selectively target certain cell receptors [271, 272]. Examples include RGD peptides that specifically target integrins in adipose tissue, and GLP-1 analogues that modulate appetite and energy expenditure. Monoclonal antibodies may be attached to lipid-based nanocarriers to identify particular antigens on target cells, including anti-CD36 antibodies, antibodies against obesity hormone receptors, and tiny chemicals such as folic acid or hyaluronic acid.

Two methods for ligand attachment include covalent conjugation, which guarantees stable ligand attachment and minimises the risk of premature detachment, and non-covalent binding, which adsorbs ligands onto the nanocarrier surface via hydrophobic or electrostatic

interactions [273]. Click Chemistry is an exceptionally efficient, bioorthogonal method used to conjugate ligands to lipid nanocarriers while preserving their functional characteristics [274].

Obesity management applications including the targeting of adipose tissue, hypothalamic intervention, and the promotion of thermogenesis. Surface functionalisation may augment the distribution of anti-obesity drugs, diminish off-target effects, and promote medication effectiveness.

Use of stimuli-responsive systems

Lipid-based nanocarriers that respond to stimuli are engineered to react to certain environmental triggers, such pH, temperature, enzymes, or redox potential, facilitating regulated and localised medication release. These mechanisms are essential in obesity therapy by delivering medications to variable settings such as inflammatory adipose tissue, acidic endosomes, or metabolically active brown adipose tissue [275, 276].

There are three categories of stimuli-responsive systems: pH-responsive systems that release pharmaceuticals at acidic pH levels, temperature-responsive systems that release medications in reaction to temperature variations, and enzyme-responsive systems, together with redox-responsive systems [277, 278]. These systems may be engineered to provide anti-inflammatory drugs to inflamed adipose tissue, thermogenic agents to brown adipose tissue, lipase inhibitors to diminish fat absorption, and antioxidants to mitigate oxidative stress in obesity-related inflammation.

Functional lipids are often included into these systems, including pH-sensitive lipids that destabilise under acidic conditions and thermosensitive lipids that experience phase changes at designated temperatures. Multistimuli-responsive devices may be engineered to react to many stimuli, offering enhanced regulation of medication release. Surface coatings may augment stability and mitigate premature medication release [279]. Applications in obesity treatment include regulated appetite suppression, focused thermogenesis, inflammation reduction, and oxidative stress alleviation. pH-sensitive nanocarriers may transport appetite suppressants straight to the acidic areas of the brain, while temperature-responsive carriers can convey thermogenic drugs to brown adipose tissue. Redox-responsive carriers may transport antioxidants to diminish reactive oxygen species (ROS) in adipose tissue.

Precision therapeutics in obesity management

Role of precision medicine in obesity treatment

Precision medicine represents a disruptive therapeutic strategy for obesity treatment which uses individual patient characteristics to craft personalized prevention approaches together with therapeutic strategies [280]. By categorizing obesity using distinct phenotypes this approach provides therapeutics that address individual characteristics of specific patient groups. Mathematical epidemiology studies four essential factors for obesity development: genetic vulnerability in combination with environmental conditions together with epigenetic transformations along with gastrointestinal microbial activity [281]. Precision medicine employs genomics proteomics metabolomics and microbiomics to establish individualized treatment methods. The precision approach leverages genomic discoveries alongside polygenic risk scores and genetic and environmental interaction data and pharmacogenomics and metabolicomics approaches for modifying the microbiome along with life choices together with wearable techoology and digital health systems [282, 283].

The approach of precision medicine helps both medical drugs and alternative therapeutic procedures deliver better results during obesity care. Drug therapies and pharmacogenomics paired with dietary adjustments and surgical options and behavioral therapy make up pharmacological approaches [283]. Medical precision advances through technological development including artificial intelligence and machine learning alongside omics integration and telemedicine and biobanks and big data solutions. The implementation of precision medicine encounters several obstacles which include ethical difficulties and equity matters and restrictions in access along with data protection concerns together with obesity treatment complexity and delayed therapeutic results and the absence of standardized processes for adopting precision medicine in clinical settings. Future approaches in obesity management include both artificial intelligence systems and targeted treatment development and precision-based community prevention strategies [283].

Precision medicine represents a ground-breaking method of handling obesity care through its ability to handle patients' diverse medical profiles. This new model takes advantage of genomic and metabolomic as well as microbiomic and digital health advances to deliver personalized effective interventions. Research combined with technological innovation creates promising opportunities for precision medicine integration into standard obesity treatment practices which should enhance patient success rates and lower obesity's global impact.

Integration of lipid-based nano-carriers in precision therapeutics

The use of lipid-based nano-carriers represents groundbreaking technology for therapeutic obesity management through precision delivery [284]. The carriers enable precise targeted drug delivery while providing better systemic drug access and synergistic administration of multiple therapeutic components. The potential increases markedly when lipid-based nano-carriers team up with personalized medicine methods that analyze both genetic data and metabolic processes to create customized interventions [285]. Lipid-based nano-carriers form the foundation of tailored drug products that match obesity treatment approaches to a patient's specific profile. The method delivers maximum therapeutic benefit by reducing undesired effects. The strategy delivers several critical benefits such as optimal drug delivery and increased bioavailability together with tissue-specific targeting and extended dose control with reduced unwanted drug interactions.

Precision and Therapy Efficacy in obesity treatment is enhanced through the combination of lipid-based nano-carriers and genetic and metabolic profiling approaches. Through siRNA or mRNA or CRISPR/Cas9 nucleate acid therapies loaded onto lipid carrier's genetic profiles enable precise targeting of obesity-associated genes [286]. Drug optimization by metabolic profiling uses released drugs that specifically act on metabolic pathways detected within individual patient profiles. Combination drug therapy achieves multifactorial targets when distinct therapeutic substances are administrated through co-delivery strategies reproducing synergistic actions. Lipid nanoparticles enable symbiotic drug delivery of GLP-1 analogs with anti-inflammatory agents to manage both appetite control and inflammatory processes. The delivery of AMPK activators together with leptin mimetics in nanostructured lipid carriers (NLCs) leads to simultaneous thermogenic effect and satiety regulation [287, 288].

The challenges of pharmacogenomics in drug response can be overcome through optimized therapeutic delivery strategies which minimize drug response variability. Lipid-based formulations enhance drug delivery to patients who have polymorphisms in their CYP450 enzymes because these formulations avoid excess hepatic metabolic breakdown [289, 290].

Case studies and clinical applications

Liraglutide for obesit

Liraglutide demonstrates successful weight control as a GLP-1 receptor agonist. Pharmacokinetic properties of liraglutide improve significantly when doctors encapsulate it inside liposomes because the system combats degradation and extends its therapeutic window thus increasing weight management performance [291, 292]. The use of liposomal formulations leads to a higher rate of patient adherence while lowering treatment side effects more effectively than established medicine products.

siRNA-LNPs for lipid dysregulation

Clinical research demonstrated promise for lipid nanoparticles carrying ANGPTL3 siRNA which reduce plasma lipid levels through their regulatory role in metabolic pathways [293, 294]. The system demonstrates significant potential in dyslipidemia management for obese patients by blocking lipid regulatory pathways and restoring normal lipid distribution.

Omega-3 nanoemulsions in inflammation control

Nanoemulsions containing omega-3 fatty acids show anti-inflammatory benefits for obese patients through their ability to modulate adipose tissue macrophages and decrease overall inflammation and enhance insulin sensitivity [295, 296]. The delivery system based on nanoemulsions enables optimized bioavailability along with superior therapeutic effectiveness.

Polymeric nanoparticles for leptin delivery

Major controller of hunger and metabolic actions during weight management becomes limited by leptin resistance experienced in obese individuals. Lab-made polymeric nanoparticles that slowly deliver leptin through the bloodstream now demonstrate capabilities for barrier evasion and boosted brain access while leading to better regulation of energy balance systems [296].

Exosome-based delivery of therapeutics

Researchers investigate stem cell-derived exosomes to transport both anti-inflammatory cytokines and small molecules that help prevent inflammation caused by obesity [297, 298]. The natural nanocarriers have shown both targeted delivery and reduced immunogenic effects that demonstrate promise for future clinical implementations.

Gold nanoparticles for adipose tissue thermogenesis

Vital research shows gold nanoparticles could encourage thermogenic effects in adipose tissue by activating β-adrenergic receptors. Scientists created a new method that boosts calorie consumption while suppressing fat storage among obese patients [299, 300].

Lipid-based drug delivery for bariatric surgery support

Drug delivery systems based on lipids improve the absorption of nutrients and vitamins for patients who require bariatric surgery treatments [301]. The formulations help post-surgical patients who experience malabsorption problems by improving their nutritional health while aiding weight management for the long term [302].

Safety, toxicity, and regulatory considerations

Scientists have developed lipid-based nano-carriers for drug delivery because the obesity increase in recent years made traditional treatments insufficient. These delivery systems demonstrate dual advantages for optimizing drug treatment outcomes and reducing harmful side effects. Safety along with toxicity assessment and regulatory approval status constitutes essential elements for translating this technology into clinical practice.

Bioavailability becomes optimal and autoimmune reactions minimal through the application of lipid-based nano-carriers because these delivery systems exhibit three main safety attributes [303]: biocompatibility combined with biodegradability and targeted delivery capability. Safety issues stem from the size dependent toxicity together with surface modification challenges and variability in lipid materials [304]. The improvement of lipid-based nano-carriers safety relies on biochemical lipid optimization along with natural lipid selection and extensive preclinical research procedures. To obtain obesity management safety of lipid-based nano-carriers toxicological evaluations and risk assessments must be performed as fundamental steps. Key toxicological assessments consist of acute and chronic tests alongside genomictoxicity and carcinogenicity investigations and immunotoxicology investigation and pharmacokinetic/biodistribution research combined with risk assessment approaches [304]. Hazard identification pairs with dose–response assessment alongside exposure assessment and risk characterization to manage toxicological risks and builds advanced formulation techniques to optimize surface functionalization and develop safety biomarkers for early toxicity detection during clinical trials.

Safety evaluations along with tests for both quality and efficacy form the basis of regulatory standards which monitor lipid-based nano-carriers. The FDA together with EMA and WHO establish developmental and commercialization regulations for nano-pharmaceuticals through their established guidelines. The regulatory requirements for human medical care products include several components which encompass preclinical data based evaluations in addition to Good Manufacturing Practices (GMP) regulatory enforcement while also requiring clinical trial requirements and product characterization protocols alongside establishment of quality control measures. Standardized guidelines for lipid-based nano-carriers remain underdeveloped while regulatory requirements between countries differ and knowledge about both long-term biochemical transformations and bioaccumulation effects remains limited. Through the work of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and public–private partnerships the development and regulatory approval of lipid-based nano-carriers proceeds faster.

Safety testing combined with toxicity analysis and regulatory requirements prove essential for making lipid-based nano-carriers applicable in obesity therapy. Urgent toxicological evaluations and regulatory framework compliance remain essential because these systems demonstrate promising therapeutic potential. Further joint efforts between academia researchers and industry actors and regulatory organizations will have to develop safe clinical procedures for lipid-based nano-carriers to transform obesity treatment approaches.

Challenges and future directions

Challenges in developing lipid-based nano-carriers for obesity management

The encapsulation properties together with distribution efficiency of bioactive compounds makes lipid-based nanocarriers consisting of liposomes and solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) highly beneficial for obesity treatment. Lipid-based nanocarriers present various formulation difficulties involving material options together with encapsulation effectiveness and stability challenges and targeted drug delivery capabilities and toxicity evaluations and limits obstacles in scale-up production.

The process of selecting materials presents complex challenges because it requires specific assessments of the stability and compatibility between medicinal compounds and appropriate lipids and surfactants while guaranteeing biocompatibility. The extensive challenges for encapsulation efficiency exist for both hydrophilic and hydrophobic molecules while finding appropriate equilibrium between payload stability and release kinetics proves difficult. Physical instability mechanisms such as lipid oxidation together with aggregation and precipitation diminish the usable lifetime of nano-carriers. The technical difficulties of controlled release accompany the complex work necessary for targeting specific metabolic streams or adipose tissue cells through functionalisation approaches.

The development of industrial-scale manufacturing faces key limitations because of difficulties related to repeatable production procedures as well as complex

process equipment together with investment expenses and regulatory constraints along with challenges in stabilising methods scalability. Large-scale production faces multiple hurdles in sustaining uniform nano-carrier dimensions and dispersity metrics and drug loading precision levels despite rising expenses from specialized materials and equipment and monitoring procedures that increase commercialization barriers most strongly in low-resource settings. The ongoing development of regulatory frameworks for nano-pharmaceuticals continues alongside the need for extensive and costly research to demonstrate both safety and effectiveness and repeated clinical utility of lipid-based nano-carriers.

Future research directions

The design of innovative nano-carriers through hybrid lipid-polymer nano-carriers and stimuli-responsive systems achieves multiple improvements including stable payload delivery and controlled drug release with targeted drug delivery. The use of custom-made lipid blends in NLC systems improves both drug incorporation rates and their stability properties. Biodegradable and natural lipids derived from renewable natural lipids carry dual benefits of biocompatibility and reduced toxicity.

Antitobesity phytochemicals such as polyphenols, flavonoids, and alkaloids show improved distribution after encapsulation in lipid-based nanocarriers which increase accessibility while targeting specific areas. Nanocarriers enable improvement of stability and effectiveness by encapsulating marine-derived substances such as algae and sponges. The use of synergistic formulations creates a single nano-carrier system which combines several natural compounds to achieve enhanced therapeutic outcomes through synergistic interactions.

The field of nano-formulation design uses artificial intelligence and bioinformatics tools to drive optimization while conducting lipid-drug compatibility screenings through virtual models and performing predictive toxicity simulations alongside in silico release pattern assessments to enable custom nano-developments. Obesity treatment could undergo a fundamental transformation through novel treatment approaches that give both safer results with enhanced effectiveness and precise therapeutic intervention capabilities. Lipid-based nano-carriers hold great promise for obesity treatment by handling current challenges and leveraging future developments.

Conclusion

Lipid-based nano-carriers hold immense promise in advancing anti-obesity therapy by addressing challenges such as poor bioavailability, instability, and lack of targeted delivery for natural compounds. The nano-delivery systems comprising liposomes solid lipid nanoparticles and nanostructured lipid carriers improve bioactive agent delivery through enhanced solubility and stability with targeted distribution for better therapeutic results. These delivery systems now enable precision therapeutic treatments that represent a game-changing avenue for individualized and efficient obesity management.

Precise delivery strategies represent a key development because obesity therapy requires individualized medical solutions. Through smart tissue-targeting mechanisms and stimulus-triggered activation lipid-based nano-carriers optimize drug delivery to their site of action while lowering side effects and toxicities throughout the body. The discovery of these solutions creates opportunities to develop precision therapeutic methods which integrate genetic and metabolic signatures alongside microbiomic data for customized intervention strategies.

Achieving the most potent clinical applications of lipid-based nano-carriers depends on researchers working jointly with clinicians and policymakers. Strategies for resolving scalability issues and addressing regulatory requirements and security matters in lipid-based nano-carriers require joint initiatives with innovative research methods. Interdisciplinary collaboration will speed up lipid-based nano-carrier transition from research laboratories to clinical settings thereby providing new hope to treat obesity alongside its health complications.

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