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# Nano-Enabled Phytotherapeutics for Obesity Management: Translating Preclinical Discoveries into Clinical Opportunities

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**ABSTRACT**

Obesity represents a major global public health challenge associated with long-term complications such as type 2 diabetes, cancer, cardiovascular diseases, and respiratory disorders, largely driven by modern lifestyles and unhealthy dietary patterns. Although conventional treatment strategies, including lifestyle modification, pharmacotherapy, and bariatric surgery, offer therapeutic benefits, they are often limited by adverse effects, long-term adherence, and inconsistent efficacy. While phytoconstituents are often considered to possess favourable safety profiles due to their natural origin and multitargeted mechanisms of action, it is important to recognize that they are not inherently devoid of toxicity. Rigorous toxicological evaluation is essential, particularly in the context of nano-enabled delivery systems, where alterations in pharmacokinetics, biodistribution, and cellular interactions may significantly influence their safety profile. However, their clinical translation is frequently hampered by poor aqueous solubility, low bioavailability, and rapid systemic clearance. Nanotechnology provides a promising approach to overcome these limitations by improving the pharmacokinetics, stability, and targeted delivery of bioactives. This review presents a comprehensive evaluation of herbal nanotherapeutics for obesity management, focusing on the design and application of diverse nanocarrier systems, including polymeric nanoparticles, nanoemulsions, liposomes, solid lipid nanoparticles, and micelles. Additionally, current challenges, regulatory considerations, and future perspectives are examined to guide the development of safe, effective, and patient-friendly herbal nanomedicines for obesity treatment.

**Key words:** Obesity, Nanomedicine, Phytoconstituents, Toxicity, Clinical Evidences

## INTRODUCTION

Obesity has emerged as a critical and escalating worldwide health issue, contributing substantially to the onset and progression of various chronic illnesses, including cardiovascular disorders, T2D, dyslipidemia, non-alcoholic fatty liver disease, and several forms of cancer. According to recent WHO estimates (2022), more than 1 billion people worldwide are living with obesity, including over 650 million adults and approximately 340 million children and adolescents aged 5–19 years (Islam et al., 2024). The prevalence continues to rise disproportionately across low- and middle-income countries, urban populations, and among women, highlighting significant demographic disparities. Since 1975, the prevalence of obesity has nearly tripled, positioning it among the leading causes of preventable mortality. Economically, the burden is equally alarming, with the global cost of obesity-related health conditions projected to reach $1.2 trillion annually by 2025, underscoring its profound impact on public health systems and global economies (Shende & Narvenker, 2021). Conventional strategies for managing obesity such as lifestyle modifications, pharmacotherapy, and bariatric surgery have achieved varying degrees of success.

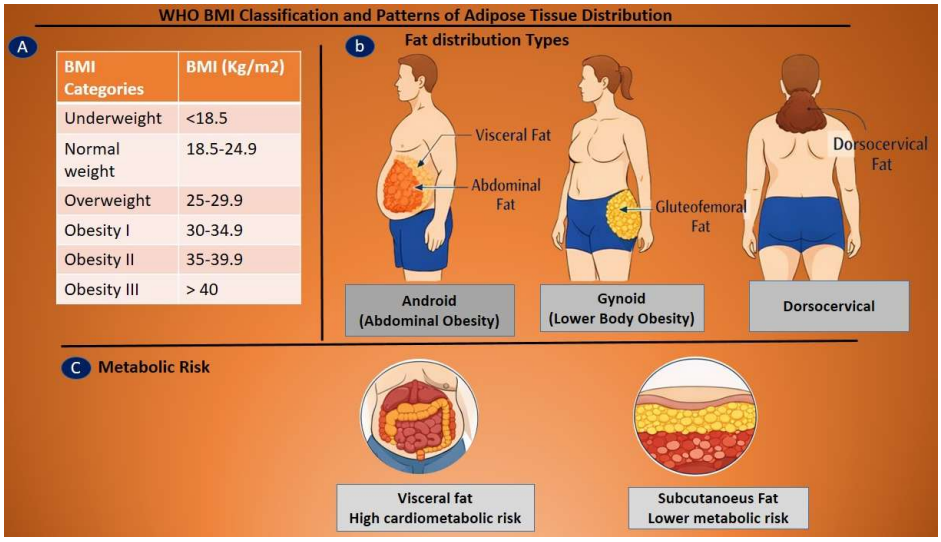


Figure 1. Classification of obesity as per WHO guidelines.

However, their long-term effectiveness is frequently hindered by challenges including weight regain, adverse side effects, poor patient compliance, and limited accessibility. These limitations have prompted growing interest in safer and more sustainable approaches, with natural products, especially those derived from medicinal plants, emerging as promising alternatives for long-term obesity management (Sood et al., 2025).

Herbal medicines and their bioactive Phytoconstituents, including polyphenols (PP), flavonoids, terpenoids, alkaloids, and saponins, have demonstrated notable potential in obesity management, supported by both experimental and clinical studies. These natural compounds exert diverse pharmacological effects, such as regulating lipid metabolism, suppressing appetite, inhibiting adipogenesis, enhancing energy expenditure (EE), and positively modulating gut microbiota (GM). However, despite their therapeutic promise, the clinical use of Phytoconstituents is hindered by various pharmacokinetic and physicochemical challenges. Many herbal compounds suffer from poor water solubility, low gastrointestinal absorption, instability under physiological conditions, and rapid systemic clearance. Together, these limitations result in poor BA, diminished therapeutic efficacy, and inconsistent clinical outcomes, restricting their broader adoption in conventional anti-obesity therapies (Rani et al., 2025).

Nanotechnology has emerged as a promising strategy to address the limitations of Phytoconstituents based therapies by enhancing their delivery and therapeutic efficacy. A range of nanoformulations, including polymeric NPs, lipid-based carriers, nanoemulsions, micelles, and liposomes, provide unique benefits. These include larger surface area, improved permeability and retention (EPR) effect, controlled and sustained release, protection from degradation, and TD to specific tissues or cellular sites. By harnessing these features, nanotechnology improves the pharmacokinetic behavior of phytochemicals and strengthens their anti-obesity activity even at lower doses, thereby reducing the risk of toxicity and side effects (Shree et al., 2023). The presented review seeks to deliver a comprehensive overview of recent developments in nanotechnology-based herbal and Phytoconstituents therapies for obesity management. It systematically explores the molecular mechanisms underlying the anti obesity effects of key phytochemicals, their incorporation into various nanocarriers (NCs) systems, and the supporting preclinical and clinical evidence. Additionally, the review highlights technological advancements that facilitate the formulation of these nano-based therapies. It also critically examines current limitations, regulatory hurdles, and the potential for future clinical application, offering valuable insights into the development of safe, effective, and user-friendly nanomedicines derived from natural sources (Figure 1).

**Biological Pathways Involved in the Anti-Obesity Activity of Phytoactives**

Numerous in vivo, in vitro, and clinical studies have been conducted to investigate the anti-obesity potential of Phytoconstituents. These studies have demonstrated that Phytoconstituents exert their effects through multiple mechanisms, either individually or in combination. The reported anti-obesogenic actions include inhibition of key enzymes, appetite suppression, stimulation of energy expenditure, suppression of adipocyte differentiation (AD), regulation of lipid metabolism, and modulation of the GM (Ohishi et al., 2021).

**Digestive enzyme inhibition**

Enzyme inhibition plays a key role in the anti-obesity effects of Phytoconstituents. By suppressing the activity of digestive enzymes (DE) such as amylase, lipase, and β-glucosidase, these compounds reduce the breakdown of fats and carbohydrates, thereby lowering overall energy intake. Among these, amylase and glucosidase are the primary enzymes involved in starch hydrolysis during carbohydrate digestion (Kumar & Alagawadi, 2013). Amylase acts on the glycosidic bonds in starch, breaking it down into oligosaccharides and maltose. These oligosaccharides are further hydrolyzed by glucosidase to produce glucose in the intestines, which is then transported into systemic circulation via glucose transporters. Elevated blood glucose levels trigger insulin secretion, facilitating glucose uptake from the bloodstream. Subsequently, glucose is metabolized through three primary pathways: glycolysis for energy production, glycogenesis in the liver and muscles for glycogen storage, and lipogenesis in the liver and adipose tissue (AT) for fat synthesis (Liu et al., 2020).

Lipase is the key enzyme responsible for breaking down dietary fats, including triglycerides (TGL) and phospholipids. In humans, lipases are classified into two types: pre-duodenal (gastric and lingual) and extra-duodenal (hepatic, pancreatic, lipoprotein, and endothelial). Among these, pancreatic lipase (PL) accounts for the hydrolysis of about 50–70% of dietary fats, while gastric lipase digests roughly 25–30% (Xian et al., 2025). Lingual lipase contributes only minimally. These enzymes break down fats into monoglycerides and fatty acids (FA), which form micellar complexes with bile salts and lysophosphatidic acid to facilitate absorption into enterocytes. Inside enterocytes, TGL are reassembled and stored in AT as energy reserves. When excess carbohydrates and fats are consumed beyond the body's energy needs, they are converted into fat and deposited in AT, contributing to obesity (Ai et al., 2024).

Inhibiting DE, particularly gastrointestinal lipase, represents an effective strategy for managing obesity. Phytoactives can act as reversible or irreversible inhibitors; the former bind weakly and compete with lipid substrates, while the latter form stable intermediates that permanently inactivate lipase. Several natural compounds have demonstrated strong PL inhibitory activity. For instance, ginkgetin, isoginkgetin, and bilobetin from *Ginkgo biloba* effectively dock into the catalytic cavity of PL, forming hydrogen bonds within its active site, and exhibit $IC_{50}$ values between 1.64 and 3.81 μg/mL. Similarly, methanolic extracts of muscadine grape (*Vitis rotundifolia*) fruit and skin, rich in cyanidin and cyanidin-3, showed inhibitory effects with $IC_{50}$ values of 11.15 and 16.90 μg/mL, respectively (Xian et al., 2025). Extracts from cloudberry, raspberry, and strawberry, containing ellagitannins and proanthocyanidins, also displayed significant inhibition, with an $IC_{50}$ of 5 μg/mL. Other studies have highlighted polyphenolic walnut extract, which demonstrated an $IC_{50}$ of 163 μg/mL in vitro and reduced body weight (BW) gain by 13.52% in obese mice after eight weeks of treatment. Likewise, galangin, a flavonol glycoside from *Alpinia*, showed an $IC_{50}$ of 48.20 μg/mL, and oral administration at 50 mg/kg over six weeks led to a 40% reduction in BW in female rats. Furthermore, compounds such as gallic acid, epigallocatechin, and epigallocatechin gallate (EGCG) exhibited inhibitory effects on PL, with $IC_{50}$ values of 387.2, 237.3, and 391.2 μM, respectively (Sandhu et al., 2020). The polyphenolic extract of *Terminalia paniculata*, containing ellagic acid, gallic acid, and quercetin, demonstrated strong enzyme inhibition, achieving 78% PL inhibition and 81% α-amylase inhibition at 250 μg/mL. Similarly, an extract of *Nelumbo nucifera* inhibited α-amylase, α-glucosidase, and PL in porcine models, with $IC_{50}$ values of 0.38 μg/mL for α-glucosidase and 0.2 μg/mL for PL, comparable to acarbose and orlistat, respectively. In another study, a novel flavanone from Ying De black tea inhibited α-glucosidase with an $IC_{50}$ of 10.2 μM, closely matching the $IC_{50}$ of acarbose (11.8 μM) (Trandafir et al., 2022).

Zarie et al. screened ethanolic extracts from over 100 plants for anti-obesity potential. *Physalis minima* (62.5%) and *Terminalia chebula* (59.1%) showed the highest yields, while *Bistorta polygonum* had the strongest antioxidant activity

(IC50 = 1.43 ppm) and *Semecarpus anacardium* the highest phenolic content (54.21 mg GAE/g). Enzyme inhibition assays revealed strong effects, with *Ginkgo biloba* inhibiting PL (81.48%), *Cinnamomum cassia* inhibiting α-amylase (78.44%), and *Punica granatum* inhibiting α-glucosidase (101.55%). Extracts from *S. anacardium*, *M. fragrans*, *C. cassia*, *R. coriaria*, and *E. sinica* inhibited all three enzymes, making them promising candidates for obesity therapy. Many of these plants are part of the human diet, suggesting potential as safe, natural anti-obesity remedies (Zarei et al., 2025). Furthermore, Gudasi et al. explored the anti-obesity potential of *Ailanthus excelsa* Roxb. using in vitro enzyme assays, network pharmacology, and molecular docking. The hydroalcoholic extract and its fractions inhibited porcine PL, HMG-CoA reductase, α-glucosidase, and α-amylase, with the ethyl acetate fraction showing the strongest effects (IC50: 56.25–125.93 μg/mL). Isoquercetin exhibited high binding affinities to all four enzymes (−7.11 to −10.41). PPI and cluster analyses identified central obesity-related targets, including ADIPOQ, PPARA, PPARG, AKT1, and MTOR, linked to key metabolic pathways. Overall, *A. excelsa* demonstrated significant enzyme inhibition and strong metabolite–target interactions, supporting its potential as a therapeutic candidate for obesity management (Gudasi et al., 2025).

**Appetite Suppression**

Appetite regulation through hormonal and neurological pathways plays a crucial role in controlling obesity. Hormones such as serotonin, dopamine, and histamine are closely associated with appetite modulation. The hypothalamus is central to this process, integrating signals from the brainstem and other regulatory systems to detect peripheral metabolic cues and adjust feeding behavior accordingly. AT also contributes by producing bioactive adipokines, including adiponectin and leptin, which are essential for maintaining energy balance and glucose homeostasis. Leptin, a cytokine whose secretion correlates with body fat mass, acts on receptors in the CNS, particularly within the hypothalamus, to regulate the brain-gut axis. Activation of these receptors reduces food intake and promotes EE. Insulin, secreted by the pancreas, similarly signals the CNS to regulate long-term energy balance and suppress appetite (V. Kumar et al., 2022).

Insulin and leptin signaling play a central role in suppressing energy intake by communicating with the hypothalamus, which integrates various neurotransmitters and neuropeptides to maintain energy homeostasis. Adiponectin, an adipokine, further supports this regulation by enhancing insulin sensitivity, promoting glucose uptake in skeletal muscle and liver, reducing FA flux to the liver, and increasing FA oxidation through activation of AMP-activated protein kinase (AMPK), a key cellular energy sensor that regulates lipid metabolism and energy homeostasis. This inhibits the acetyl-CoA carboxylase (ACC) and lowers malonyl-CoA levels. Appetite is also regulated by intestinal hormones such as cholecystokinin, GLP-1, peptide YY, and pancreatic polypeptide, which send satiety signals to the brain. In parallel, antagonism of melanin concentrating hormone (MCH), an endogenous appetite stimulant, reduces food intake and BW. Phytoactives can modulate these pathways by targeting MCH receptors, inhibiting hunger signals, or reducing appetite-related hormone production. Examples include extracts from tea plants, Indian cactus, bitter orange, and Hoodia gordonii, the latter of which has been shown to increase ATP levels in hypothalamic neurons, contributing to hunger suppression and reduced food consumption (Malik et al., 2024; Stuby et al., 2019).

Several studies have demonstrated the anti-obesity effects of polyphenolic extracts in both humans and animal models. For instance, administration of polyphenolic extracts from *Hibiscus sabdariffa* and *Lippia citriodora* to obese individuals over two months resulted in significant reductions in BW (up to 3.48 kg) along with decreased hunger and appetite. These effects were attributed to modulation of intestinal peptide production, AMPK activation, and regulation of adipohormones. Similarly, epigallocatechin gallate (EGCG) from green tea extract (GTE) suppressed ghrelin secretion and increased adiponectin levels, leading to significant reductions in BW, total cholesterol (TC), and low-density lipoprotein (LDL) levels in overweight and obese women after 12 weeks of supplementation at 856.8 mg/day. Polyphenolic aqueous extracts from *Carum carvi* L. also reduced hunger, decreased carbohydrate intake by 8.7%, and improved anthropometric parameters such as waist circumference and waist-to-hip ratio in obese women over a three-month period. In animal studies, oral administration of anthocyanins from *Glycine max* (L.) seed coat significantly limited weight gain and food intake in male Sprague Dawley rats (SDR) over 40 days, primarily by modulating neuropeptide Y and hypothalamic γ-aminobutyric acid (GABA)

receptor activity. Collectively, these findings highlight the potential of phytoactives as effective anti-obesity agents through appetite suppression and energy balance regulation (Deswal et al., 2024; Lacatusu et al., 2019).

**Stimulation of energy expenditure**

Total daily EE is influenced by basal metabolic rate (BMR), the thermic effect of food, physical activity, and thermogenesis, which generates heat to maintain body temperature. In mammals, AT exists primarily as white adipose tissue (WAT) and brown adipose tissue (BAT). BAT plays a crucial role in controlling adiposity by dissipating energy through non-shivering thermogenesis. This process is regulated by uncoupling protein 1 (UCP1), which disrupts the proton gradient, reducing ATP production while generating heat. BAT activity is stimulated by dietary intake and other physiological conditions via sympathetic pathways, primarily through β3-adrenoreceptors. UCP3, a homolog of UCP1, is also involved in thermogenesis and is modulated by thyroid hormones, leptin, and β3-adrenergic agonists, contributing to potential anti-obesity effects.Thus, activating BAT and modulating UCP function represents a physiological strategy for controlling obesity. Phytoactives can act as thermogenic agents, enhancing EE and regulating gene expression and physiological functions within AT(El-Menshawe et al., 2018).

Curcumin and quercetin, resveratrol and gallic acid, which controls the thermogenesis of AMPK, sirtuins, proliferator activated receptor gamma coactivator 1-α (PGC-1α), catechol-O-methyl transferases and sympate nervous system (SNS) respectively. The Epigall ocatechin-3-gallate (EGCG), derived from GTE to promote thermogenesis and energy loss. Administering 1% EGCG for 4 weeks in high-fat diet (HFD) based on lard in mice, enhancing the expression of the UCP1 PGC-1α gene. The effect of EGCG in the HFD induced obese mice, results to decrease a blood glucose (BG) and TGL over the HFD group of mice only. In addition, this supplementation also significantly reduces the weight of perirenal WAT (pWAT), epididymal WAT (eWAT), and subcutaneous WAT (sWAT) respectively over the HFD group**.** This effect is mediated by promoting thermogenesis, enhancing FA oxidation, reducing lipid deposition in adipose tissues, and improving glucose and lipid metabolism. EGCG activates pathways such as AMPK and increases the expression of thermogenic genes which collectively counteract the weight gain associated with HFD. Apart from this, the histological examination revealed the adipose cell size reduction in WAT and inhibition in lipid droplets deposition in BAT**.** Furthermore, no major difference was reported among the NCD group and the NCD+EGCG mice group. Thus, the result concludes that EGCG treatment notably decreases the lipid deposition in AT and resisted obesity caused by HFD. The polyphenolic extract of mango (gallo tannin derivative), shows an improvement of the expression of thermogenesis, results to suppress the adipogenesis and improved thermogenesis in 3T3-L1 adipocytes. Another example which is the use of resveratrol (RV) inhibits the BW gain in grey mouse lemur with enhancement in EE and also reduces energy intake by 13%. In addition, *in vivo* investigation in the rhesus monkey ascribed decrease in adipocyte size and increased SIRT1 expression in visceral white AT (WAT). Another study revealed the cyanidin and malvidin, which is obtained from the fermented black carrot. Further, its 2% intake into female rats for up to 12 weeks, results to enhance EE (Goktas et al., 2020).

**Suppression of adipocyte differentiation**

Adipocytes, the primary cellular component of AT, play a central role in maintaining energy and lipid homeostasis. Excess energy derived from food is stored as TGL in both white and brown adipose tissue (WAT and BAT), with BAT utilizing some of this energy for thermogenesis. Adipocytes originate from mesenchymal precursor cells, which differentiate into preadipocytes and subsequently mature into functional adipocytes. However, excessive adipogenesis and uncontrolled differentiation of adipocytes lead to abnormal fat accumulation, contributing to obesity (Dinda & Dinda, 2022).

AD is regulated by multiple transcription factors that play a critical role in obesity management. Key regulators of adipocyte development include peroxisome proliferator-activated receptors (PPARs), CCAAT/enhancer-binding proteins (C/EBPs), and sterol regulatory element-binding proteins (SREBPs). FA synthase (FAS) is also essential for adipogenesis, and its inhibition significantly reduces ATformation. Phytoactives such as resveratrol, curcumin, genistein, and EGCG can inhibit one or multiple stages of adipogenesis, affecting preadipocyte proliferation, differentiation, and maturation. For example, hydroxylated polymethoxy flavones from orange peels inhibit AD in 3T3-L1 adipocytes by modulating adipocyte-specific transcriptional regulators. Similarly, quercetin administration in

F344 male rats suppresses adipogenesis by downregulating adipogenic marker transcription in muscle progenitor cells. Aqueous extracts of *Hibiscus sabdariffa* have also been shown to reduce AD in 3T3-L1 preadipocytes through modulation of key transcription factors. Collectively, these findings indicate that phytoactives can target multiple steps of adipocyte differentiation, making them promising anti-obesity agents (Lai et al., 2013).

**Regulation of lipid metabolism**

Lipid metabolism involves a complex network of enzymatic and hormonal pathways responsible for the synthesis, storage, and degradation of TGL. Further, they are categorized into cholesterol metabolism, FA metabolism and TGL. Human cholesterol is either obtained from the diet or synthesized by the liver, and its levels are regulated through physiological processes involving synthesis, absorption, transport, and excretion. Bio-precursors for cholesterol are acetyl-coenzyme A (acetyl-coA), that is controlled by the receptor SREBP-1a, SREBP, LDL and HMG-CoA. While SREBP-1c has been activated due to endoplasmic reticulum stress, which improves lipogens gene transcription, especially with FAS and stearoyl CoA desaturase. In lipid synthesis pathways, AMPK is prime regulator of lipid synthesis pathways that may reduce the FA synthesis by acted on SREBP-1c and FA synthase. Moreover, AMPK activation results to induce of FA oxidation in the liver and inhibits biogenesis of cholesterol. In the similar manner, carnitine palmitoyl transferase 1A, which increases the FA oxidation and reduce the levels of hepatic TGL. PPAR-α, that can control cholesterol and lipid metabolism break-down. Therefore, it concludes the regulation of these factors which may affect the lipid metabolism and impart the desirable effects in management of obesity (Taghipour et al., 2019).

Extracts of *Hibiscus sabdariffa* exert anti-obesity effects by enhancing lipid metabolism. Polyphenolic extracts of *Hibiscus sabdariffa* and *Lippia citriodora*, when included in dietary supplements for overweight and obese individuals, significantly reduced BW, abdominal fat, and overall body fat, while also lowering TC and LDL levels. In animal studies, PP from blueberries downregulated the expression of SREBP-1 and FA synthase (FAS) while upregulating CPT-1 and PPAR-α. They also promoted AMPK phosphorylation, an effect similarly observed with phenolic compounds such as quercetin, resveratrol, curcumin, and EGCG. Likewise, GTE containing PP reduced cholesterol, TGL, LDL, and insulin levels in high-fat diet (HFD) mice. Polyphenolic extracts from *Solanum nigrum*, administered to HFD-fed mice for 10 weeks, enhanced lipolysis through activation of CPT-1 and PPAR-α while suppressing FAS to inhibit lipogenesis. Additionally, anthocyanins such as malvidin and cyanidin from black carrot extract significantly reduced BW gain by 32.83% and LDL cholesterol by 29.58% in ovariectomized female rats compared to controls [89]. The extract containing resveratrol which is obtained from the seed of Melinjo. It is administered in healthy young male for 14 days, results to enhance the adiponectin level. In addition, this adiponectin also suppressing the lipogenesis and enhance β oxidation, where it exerted as anti-obesity action. In a another study a significant reduction in body fat was reported, along with improvements in HDL cholesterol and serum adiponectin levels, following six weeks of supplementation with 5g of anthocyanin-rich pulp of *Euterpe edulis* Mart in obese patients (Hu et al., 2022).

**Modulation of gut microbiota**

The GM is a complex bacterial ecosystem residing in the gastrointestinal tract (GIT), with approximately 90% composed of Bacteroidetes and Firmicutes. Other phyla, including Actinobacteria, Proteobacteria, and Verrucomicrobia, are also present and implicated in various health outcomes. Diet plays a critical role in shaping GM composition: high-fat and high-carbohydrate diets promote the growth of Firmicutes, whereas low-fat diets favor Bacteroidetes. Obesity is often associated with high-fat diets and reduced microbial diversity. The GM can influence obesity by enhancing energy extraction through prebiotics, modulating FA oxidation, reducing bile acid production, and promoting satiety. Conversely, high-fat diets decrease short-chain FA (SCFA) production while increasing levels of lipopolysaccharides (LPS) and branched-chain amino acids (BCAAs), contributing to metabolic disturbances (Shi et al., 2014). In addition, all this causes fats to be stored and creates obesity. The addition of phytoactives to the diet leads to microbial diversity in the intestines and produces metabolites that assist regulate obesity. Researchers reported the use of qurecetin and resveratrol in the HFD fed rats, results to lower the Firmicutes-to-Bacteroidetes (F/B) ratio.

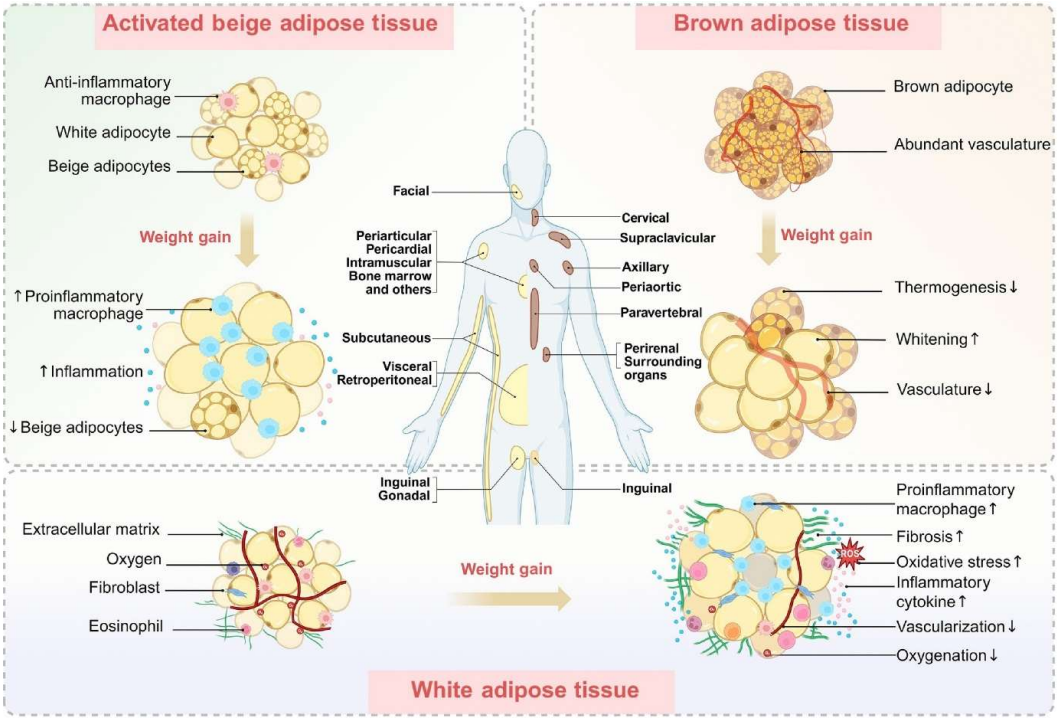


Figure 2: Pathological changes in adipose tissues during obesity. Reproduced with permission from Wang (et al., 2025)

Furthermore, a major decrease in BW, dimension of adipocytes after the 10 weeks of treatment was reported. In alternative research, the usage of EGCG in HFD bone mice is significantly reduced, and bacteroidetes are significantly improved, resulting in a lower firmicutes/bacteroidetes ratio of HFD throughout 8 weeks of treatment. In the same way, the use of polyphenolic extract of blueberry, which may alter the gut microbiodata and concurrently decrease the BW gain in mice. Therefore, from the above discussion, it concludes that the phyto actives from various sources have ability to modulating the gut microbiodata, which may result to better approach in the management of obesity (Zhou et al., 2017).

Collectively, these biological pathways highlight the significant therapeutic potential of phytoconstituents in obesity management through multi-targeted mechanisms. However, despite these promising effects, the clinical translation of compounds such as epigallocatechin gallate (EGCG) and resveratrol remains substantially limited due to their poor aqueous solubility, low gastrointestinal absorption, rapid metabolism, and overall low bioavailability. These pharmacokinetic constraints often result in suboptimal therapeutic outcomes and inconsistent efficacy in vivo. Therefore, to fully harness the anti-obesity potential of these bioactives, advanced delivery strategies are essential. In this context, nano-enabled approaches offer a rational and necessary solution by enhancing stability, improving bioavailability, enabling targeted delivery, and ensuring sustained therapeutic action, thereby bridging the gap between preclinical promise and clinical applicability (Figure 2).

**Phyto-actives in obesity treatment**

**Polyphenols**

Polyphenols (PP), a diverse class of plant-derived secondary metabolites, are well known for their bioactive properties and health-promoting effects. Dietary inclusion of PP has been associated with multiple benefits related to obesity. Their anti-obesity effects involve several mechanisms, either individually or in combination, including inhibition of key enzymes, suppression of AD, regulation of lipid metabolism, appetite suppression, enhancement of EE, and modulation of GM.

In vitro studies have provided supporting evidence for these effects. For example, catechins from GTE were shown to reduce lipid deposition by inhibiting the differentiation of 3T3-L1 preadipocytes into adipocytes. Epigallocatechin gallate (EGCG) further promoted the browning of white WAT into BAT and improved glucose homeostasis in 3T3-L1 cells by restoring redox balance and alleviating mitochondrial dysfunction. In human studies, daily intake of GTE containing 583 mg of catechins over 12 weeks significantly reduced AT mass, BW, and serum LDL-C levels. Additionally, GTE supplementation decreased lipid accumulation by inhibiting AD and promoting WAT browning (Pastor-Villaescusa et al., 2018).

Furthermore, Tung and his team mates investigated the browning effect of curcumin on 3T3-L1 adipocytes following treatment with 20 μM curcumin. The results showed an upregulation of brown fat-specific markers, including FGF21, and Tbx1, indicating the transformation of WAT into beige adipocytes. Curcumin also decreased TGL levels in these BAT by enhancing the expression of mitochondrial proteins CPT-1 and cytochrome C, thereby promoting fat oxidation. Additionally, curcumin increased the phosphorylation of ACC, the pAMPK/AMPK ratio, and HSL expression, which collectively facilitated lipolysis and inhibited FA synthesis (Tian et al., 2024) (Table I).

**Epigallocatechin Gallate (EGCG)**

Enhanced EE through increased thermogenesis has been observed in male C57BL/6J mice with diet-induced obesity, where the phytonutrient EGCG exhibited significant effects on blood glucose (BG) and TGL levels. These effects were attributed to reduced lipid accumulation in AT and inhibition of body fat gain. EGCG, the primary catechin in GTE, is associated with multiple health benefits, particularly reductions in BW and AT mass. Its ability to activate AMPK in skeletal muscle, liver, and WAT, along with decreased caloric intake, likely contributes to its effect on lowering BW. Additionally, EGCG significantly improves epididymal fat mass and blood lipid profiles, including TGL, total cholesterol, high-density lipoprotein cholesterol (HDL-C), and LDL cholesterol (LDL-C) (Wilasrusmee et al., 2024).

An in vitro study involving *E. coli* and *C. elegans* strains fed with an OP50 diet demonstrated EGCG's potential to regulate body fat content. EGCG suppressed adipogenesis, leading to reduced fat accumulation in *C. elegans*, as indicated by the downregulation of the ATGL-1 gene expression after treatment. In overweight mice fed a high-calorie diet, EGCG was found to reduce body fat by decreasing calorie intake and enhancing FA lipolysis and oxidation both in vivo and in vitro. Additionally, a clinical trial involving 15 women with central obesity showed that EGCG supplementation contributed to the regulation of plasma cholesterol and TGL levels. Additionally, in a group of 102 women with a BMI of 27 $kg/m^2$ and a WC of 80 cm, a 12-week EGCG treatment led to major decreases in BW, BMI, and WC (R. Yan & Cao, 2025). Despite these potent anti-obesity effects, the clinical application of EGCG is limited by its poor stability, low oral bioavailability, and rapid systemic clearance, thereby necessitating nano-enabled delivery systems to enhance its therapeutic efficacy.

**Gallic Acid**

Gallic acid (GA), chemically known as 3,4,5-trihydroxybenzoic acid, is a naturally occurring phenolic compound commonly found in fruits, vegetables, GTE, and fruit juices. It contributes to energy balance and overall physiological homeostasis. GA exerts anti-obesity effects by inhibiting lipogenesis, the metabolic process that converts carbohydrates into fat, thereby reducing fat accumulation. Additionally, GA modulates thermogenic gene expression in interscapular BAT and activates the AMPK/SIRT1/PGC-1α pathway, promoting beneficial metabolic effects. In vitro studies using murine 3T3-L1 preadipocytes and RAW 264 macrophages demonstrated that GA treatment significantly reduced adipocyte size, an important factor as adipocyte hypertrophy is associated with AT inflammation and metabolic disorders (MD) (Jian et al., 2025).

In reported in vivo studies on obesity in male C57BL/6 mice, GA treatment led to a major reduction in fat accumulation and AT content by enhancing lipolysis. At the same time, it suppressed the expression of fatty acid synthase (FAS), a key enzyme involved in lipogenesis, thereby inhibiting fat synthesis. This dual action contributed to improved lipid degradation and a reduction in overall fat and calorie storage. Obese individuals who took capsules consisting 200 mg of GA and 50 mg of a Chinese herbal decoction three times daily for 24 weeks did not show any weight loss or reduction in food consumption, mainly because adequate serum concentrations were not achieved (Sousa et al., 2024).

Table I. Common medicinal plants and herbs used in obesity management, highlighting their major bioactive constituents, mechanisms of action, and their reported effects.

| Plant/Herb | Key Bioactive Compounds | Mechanism of Action | Reported effect | Reference |
|---|---|---|---|---|
| *Camellia sinensis* (Green tea) | EGCG, catechins | ↑Thermogenesis, ↓ adipogenesis, AMPK activation | Reduced body weight, lipid levels | (Chilakala et al., 2023) |
| *Curcuma longa* (Turmeric) | Curcumin | Inhibits adipogenesis, ↑ lipid metabolism, anti-inflammatory | Reduced fat accumulation | (Lee et al., 2023) |
| *Garcinia cambogia* | Hydroxycitric acid (HCA) | Inhibits ATP-citrate lyase, suppresses lipogenesis | ↓ appetite, ↓ fat synthesis | (Kang et al., 2023) |
| *Hibiscus sabdariffa* | Polyphenols, anthocyanins | Regulates lipid metabolism, reduces adipogenesis | ↓ body weight, ↓ LDL | (Dilokthornsakul et al., 2024) |
| *Citrus aurantium* (Bitter orange) | Synephrine | Appetite suppression, β-adrenergic stimulation | ↑ fat oxidation | (Lin et al., 2023) |
| *Nelumbo nucifera* (Lotus) | Flavonoids, alkaloids | Inhibits lipase and carbohydrate-digesting enzymes | ↓ fat absorption | (H. Huang et al., 2024) |
| *Vitis vinifera* (Grape) | Resveratrol | Activates SIRT1/AMPK, enhances fat oxidation | ↓ adipocyte size, ↓ BW | (Mohamed et al., 2024) |
| *Capsicum annuum* (Red pepper) | Capsaicin | Enhances thermogenesis, increases energy expenditure | ↓ fat mass, ↑ metabolism | Oh, M-J et al., 2023 |

However, the clinical translation of gallic acid is constrained by its limited bioavailability and rapid metabolism, highlighting the need for nano-based delivery approaches to improve its pharmacokinetic profile and therapeutic potential.

**Quercetin and Resveratrol**

Quercetin exhibits anti-obesity effects by acting through the mitogen-activated protein kinase (MAPK) and AMPK1 signaling pathways. Quercetin demonstrates anti-obesity effects by modulating the MAPK and AMPK1 signaling pathways. Similarly, resveratrol a phytoalexin found in the skin and grape seeds and present in red wine has shown potential in in vivo studies to protect against diet-induced obesity and MD such as insulin resistance and hepatic steatosis. The anti-obesity effects of the combined treatment with resveratrol and quercetin (CQR) are associated with reduced BW gain, smaller adipocyte size, decreased AT mass, and improved serum lipid profiles. These effects are largely attributed to CQR's anti-inflammatory properties, through that it modulates adipokine secretion and activates the AMPK1/Sirtuin 1 (AMPK1/SIRT1) signaling pathway. Together, these actions enhance energy metabolism, suppress adipogenesis, and alleviate obesity-related inflammation, making the combination more effective than either compound alone. Overall, these findings suggest that CQR has the potential to alleviate HFD induced obesity and inflammation (Lu et al., 2025).

In an *in vitro* study using human SGBS adipocytes, adipogenesis was inhibited through downregulation of key adipogenic genes, including PPARγ and C/EBPα. Levels of adipokines such as ANGPTL4, PAI-1, and adipsin,

Table II. Investigations on Phytoconstituents based therapies for the diagnosis of Obesity.

| Phyto-actives | Type of Study | Sources | Mechanism of Action | Outcomes | Limitations | Reference |
|---|---|---|---|---|---|---|
| Polyphenolic extract | *In vitro* | Cloudberry | It shows anti-obesity action via inhibition of PL | Extract containing phenolic compound found porcine PL inhibition with $EC_{50}$ at the concentration of 5 µg phenols/ mL. | In vitro only; lacks in vivo/clinical validation and BA data | (Ohishi et al., 2021) |
| Galangin | *In vivo* | *Alipinia galangal* Willd | It shows anti-obesity action via inhibition of PL | Galagin extract containing different concentrations incubated for 30 minutes, found IC50 at the 48.20 mg/ mL and revealed PL inhibition | High concentrations required; single animal model; no human studies | (Kumar & Alagawadi, 2013) |
| Flavonoids | *In vitro* | *Nelumbo nucifera* | It exerted anti-obesity action via inhibition of porcine PL α-glucosidase and α- amylase | The *in vitro* study at the concentration used 0.1 g/ ml extract for 5 min, 20 min, found significant inhibition of porcine PL, α-glucosidase and α- amylase with $IC_{50}$. | High concentrations required; single animal model; no human studies | (Liu et al., 2020) |
| Flavanones | *In vitro* | Ying De black tea | It shows anti-obesity action via inhibitory action of α-glucosidase | The *in vitro* study revealed significant inhibition of α-glucosidase with $IC_{50}$ value of 10.2 µg/mL at the 6 different concentration. | In vitro only; does not account for metabolism or systemic effects | (Zhou et al., 2017) |
| Hydroxylated polymethoxyflavones (HPMFs) | *In vitro* | Citrus peel | It found anti-obesity action via inhibition of adipogenesis by interfered with adipocyte specific transcriptional regulators and other signals pathways. | The in vitro studies on 3T3-L1 cells for the duration of 8 days, it found significant inhibition of lipid accumulation in adipocytes | Limited to cell line; unclear translation to humans; no pharmacokinetic data | (Lai et al., 2013) |
| Polyphneolic extract | *In vivo* | Walnut | Anti-obesity action exerted by significant inhibition of PL | Oral administration of 200 µg/ g of BW in obese mice for 8 weeks, results to significantly decrease the BW gain by 13.52%. | Animal study only; small sample size; dose relevance to humans uncertain | (Shi et al., 2014) |
| Cyanidin and Malvidin | *In vivo* | Fermented black carrot | Anti-obesity effect exerted by stimulation of EE and modulation of lipid metabolism | It found higher reduction in BW gain in ovariectomized female Sprague–Dawley rats by 32.83%, TGL by 24.4% and LDL by 29.58% over the control. | Ovariectomized rat model only; species differences; limited duration | (Park et al., 2015) |

Table II. Investigations on Phytoconstituents based therapies for the diagnosis of Obesity.

| Phyto-actives | Type of Study | Sources | Mechanism of Action | Outcomes | Limitations | Reference |
|---|---|---|---|---|---|---|
| EGCG | *In vivo* | Green tea | Anti-obesity effect exerted by stimulation of EE and modulation of lipid metabolism | It found significant reduction in BW gain, TGL level and reduced lipid accumulation in adipose tissue of male C57BL/6J mice. | Dose used higher than normal human intake; interspecies variation | (Dalvi et al., 2017) |
| Purified polyphenol extract | *In vitro, In vivo* | Blueberry | Anti-obesity effect exerted by regulation of lipid metabolism and gut microbiodata | It showed significant reduction of BW gain, along with it reduces TGL, LDL and leptin in male C57BL/6J mice. | Mostly animal/cell data; GM findings may not directly extrapolate to humans | (Jiao et al., 2019) |
| Polyphenol extract | *In vitro, In vivo* | Green Tea | Anti-obesity action received by regulation of lipid metabolism | Oral administration of polyphenolic extract in C57BL/6J mice, it received significant reduction in total cholesterol, TGL and LDL | Lack of human trials; controlled environment may not reflect real dietary intake | (Pérez-Torres et al., 2021) |
| Extract containing quercetin, catechin, rutin, epicatechin, epigallocatechin gallate and gallic acid. | *In vivo* | *Solanum nigrum* | Anti-obesity action received by lipolysis, reduction in BW and body fat. | The oral administration of an extract at the dose range of 0.5-2% in male C57BL/6 mice for the duration of 10 weeks, results to regulate lipid metabolism by enhancing the lipolysis via activation of PPAR-α and CPT-1 and suppresses the FAS to inhibit lipogenesis. | Animal model; long-term safety and human applicability not tested | (Peng et al., 2020) |
| Anthocyanins | *In vitro, In vivo* | Glycine max (L.) Merr. seed coat | It showed anti-obesity action via reduction in food intake and regulation of neuropeptide Y and γ amino butyric acid receptor in hypothalamus | Administration of 6 mg/kg and 24 mg/kg of extract through oral route in male Sprague–Dawley rats for up to the duration of 40 days, results to significant downregulation in the BW gain by 15.76% and concurrently lowers the food intake by 19.10% over the control groups. | Rodent-specific neuroregulation; human CNS response may differ | (Badshah et al., 2013) |

Table II. Investigations on Phytoconstituents based therapies for the diagnosis of Obesity.

| Phyto-actives | Type of Study | Sources | Mechanism of Action | Outcomes | Limitations | Reference |
|---|---|---|---|---|---|---|
| **Clinical Investigations** | | | | | | |
| EGCG | Clinical | Green tea | It showed anti-obesity action via suppressing the regulation of ghrelin secretion and adiponectin levels. | It is administered in obese and overweight individuals, received significant decrease in BW by 1.43%, total cholesterol level by 7.49% and LDL by 10.10% | Modest effects; short-term; interindividual variability not addressed | (Chen et al., 2016) |
| Polyphenolic extract containing 3.5% anthocyanins and 15% verbascoside | Clinical | *Hibiscus sabdariffa* (HS) and *Lippia citriodora* (LC) | It acts as anti-obesity action via suppression of appetite through regulation of resistin, leptin, ghrelin and glucagon-like peptide-1 levels | Administration of 500 mg of LC (35%) and HS (65%) by oral route for the duration of 60 days in obese and overweight individuals, results to significant reduction in BW and decrease in hunger and appetite | Short duration (60 days); small sample size; no long-term safety data | (Boix-Castejón et al., 2018) |
| Extract contains 90% of total polyphenols as catechin | Clinical | Red orange, grapefruit, sweet orange and guarana | It acts as antiobesity action by appetite suppression through controlling the ghrelin secretion and adiponectin levels. | Intake of two capsule containing 450 mg of dry extract per day in overweight individuals for the duration of 12 weeks, results to significant reduction in BW and abdominal body fat over the placebo. | Proprietary extract; small cohort; unclear reproducibility | (Kazemipoor et al., 2016) |
| Resveratrol | Clinical | *Gnetum gnemon* L. seed | It shows anti-obesity action by regulation of lipid metabolism | Oral intake of 150-300 mg of resveratrol in healthy young male for the duration of 14 days, results to adiponectin level. | Very short duration (14 days); small sample size; limited to healthy males | (Oniki et al., 2020) |
| Anthocyanins | Clinical | Blueberry | It shows anti-obesity action by regulating the lipid metabolism | Administration of anthocyanins in overweight/obese adult individuals for the treatment duration of 12 weeks, after all found reduction in bodyweight by 11.34%, body fat by 20.89%, and total cholesterol in 14.75% from the baseline. | Study design details limited; sample size unclear; need replication | (Jiao et al., 2019) |

as well as glycolytic enzymes PFKP, ENO2, and PFKFB4 factors associated with obesity and AT dysfunction were also reduced. In an in vivo study with male Wistar rats with diet-induced obesity, modulation of the GM resulted in significant decreases in BW gain, visceral AT mass, and adipocyte size. Additionally, a clinical trial involving 11 obese but otherwise healthy men demonstrated that downregulation of genes related to Wnt signaling, intercellular junctions, angiogenesis, Notch signaling, and G protein-coupled receptors, alongside upregulation of cell cycle regulatory pathways, contributed to reductions in adipocyte size and improved adipogenesis (Wang et al., 2024). Despite their promising pharmacological activities, both quercetin and resveratrol suffer from poor aqueous solubility, low bioavailability, and rapid metabolic degradation, which significantly limit their clinical efficacy and underscore the importance of nano-enabled delivery strategies (Table II).

**Nanosystems in obesity treatment**

Despite the promising anti-obesity potential of phytoconstituents, their clinical translation through conventional formulations remains limited due to poor aqueous solubility, low bioavailability, rapid metabolism, and lack of tissue-specific targeting. These limitations often result in inconsistent therapeutic outcomes and necessitate higher doses, increasing the risk of adverse effects. In this context, nano-enabled delivery systems represent a significant advancement by enhancing solubility, protecting bioactives from degradation, and improving absorption and pharmacokinetic profiles. Furthermore, nanocarriers enable controlled release and targeted delivery to metabolically active tissues such as adipose tissue, thereby improving therapeutic efficiency while minimizing systemic exposure. Thus, the shift from traditional formulations to nano-enabled approaches is not merely technological but essential for achieving effective and clinically translatable obesity management.

Nanotherapy, a subset of therapeutics, utilizes nanotechnology in drug delivery systems (DDS) to enable TD to specific sites while minimizing the required dosage. Over the decade, nanotechnology has significantly transformed drug administration by improving therapeutic efficacy through its nanoscale size (1–100 nm) and precise targeting capabilities. The integration of nanotechnology with herbal medicine, referred to as herbal nanotherapeutics, has improved the efficacy of active herbal compounds in treating various conditions, including diabetes, cancer, and hypertension. The physicochemical limitations of natural compounds such as poor water solubility, low gastrointestinal absorption, rapid metabolism, and instability under physiological conditions can be effectively addressed through advanced nanotechnology-based delivery systems. Strategies such as encapsulating bioactives in liposomes, SLNs, nanoemulsions, polymeric NPs, phytosomes, and micelles enhance solubility, protect compounds from enzymatic or pH-mediated degradation, and facilitate controlled or sustained release. Surface modification of NCs with ligands enables TD to specific tissues, while size reduction improves permeability and retention at desired sites. These approaches not only improve pharmacokinetics and BA but also reduce the required therapeutic dose, minimizing potential toxicity. Collectively, such NCs systems significantly amplify the therapeutic efficacy of natural compounds by ensuring greater stability, efficient absorption, and precise site-specific action. This fusion of nanotechnology and traditional herbal knowledge has propelled advancements in medicine by enhancing the stability of herbal formulations, boosting their therapeutic effectiveness, and enabling targeted drug delivery (DD) (Patias et al., 2024).

**Liposomes**

Liposomes are lipid-based DDS composed of hydrophilic (HPL) heads and hydrophobic (HPb) tails, enabling them to carry both HPL and lipophilic compounds. HPL drugs are encapsulated within the aqueous core, while lipophilic drugs are embedded in the lipid bilayer. The use of liposomes as NCs for herbal medicines has been shown to improve the stability and tolerability of Phytoconstituents while reducing their toxicity. For example, Lacatusu et al. demonstrated the effectiveness of liposomes in delivering capsaicin, an anti-obesity compound from red pepper extract. This liposomal system improved gastric tolerability and enhanced TD to AT. In an in vivo study, Albino Swiss mice fed a high-fat diet (HFD) for three weeks showed a 15% reduction in BW after treatment with capsaicin-loaded liposomes compared to controls. Liposomes are particularly suitable for capsaicin due to its lipophilic nature, as the lipid bilayer enhances its solubility, stability, and targeted delivery to adipose tissue. Supporting these findings, Joo et al. administered capsaicin at 10 mg/kg to Sprague-Dawley rats, revealing that its

anti-obesity effects were mediated through downregulation of Hsp27 and Steap3 proteins, along with upregulation of the olfactory receptor Olr1434 in obese WAT (Song et al., 2024).

A study demonstrated that resveratrol acts as a potent anti-obesity agent, primarily through promoting the browning of WAT. However, another clinical study using traditional resveratrol formulations also reported effective anti-obesity effects but encountered limitations, including poor solubility, low stability, and reduced BA. To enhance the therapeutic potential of resveratrol as an anti-obesity agent, Zu et al. encapsulated it in lipid NCs, aiming to improve its pharmacological activity and chemical stability. This approach is justified by the poor aqueous solubility and instability of resveratrol, where lipid-based carriers improve its bioavailability and protect it from degradation. The anti-obesity effect of resveratrol was confirmed through a study using 3T3-L1 white adipocyte cell models, which investigated its ability to induce the browning of WAT (Lu et al., 2024).

Silibinin, also known as silybin, is the primary active component of silymarin, a standardized extract from milk thistle seeds commonly used in managing chronic liver conditions associated with obesity. Its clinical application, however, is limited by low solubility and poor BA. To address these limitations, Chen et al. developed a lipid-based NCs system for oral delivery of silibinin, which increased its BA by 2.9-fold and significantly enhanced its therapeutic efficacy. In preclinical studies, administration of silibinin-loaded lipid NCs at 300 mg/kg to male SDR resulted in a marked reduction in collagen production and lipid droplet formation, demonstrating potent anti-obesity effects (Liu et al., 2023).

**Solid lipid nanoparticles (SLN)**

SLNs are lipid monolayer carrier systems with a solid lipid core, widely used in DD due to their stability, non-toxicity, cost-effectiveness, and suitability for large-scale production. SLNs are used to encapsulate poorly water-soluble Phytoconstituents derived from medicinal plants, aiming to enhance their stability and BA, reduce toxicity, and enable targeted and controlled release of the bioactives. In a study conducted by Ezhilarasi et al. SLNs were formulated with hydroxycitric acid (HCA), resulting in improved BA compared to unencapsulated HCA. Hydroxycitric acid, a powerful ATP-citrate lyase inhibitor derived from the Garcinia cambogia plant, is commonly used as an anti-obesity agent. SLNs are particularly advantageous for such compounds as they provide a solid lipid matrix that enhances stability, controls drug release, and improves bioavailability of poorly soluble phytoconstituents. The enhanced BA was demonstrated in a preclinical study using Wistar rats, which showed a major increase in Cmax compared to the untrapped form. The SLN formulation of HCA not only boosted its pharmacological effectiveness and enabled TD to AT but also minimized related side effects, such as testicular atrophy and liver toxicity (Uti et al., 2025).

Ding et al. successfully formulated SLNs to enhance the therapeutic potential of fucoxanthin against obesity and its related metabolic disturbances. The selection of SLNs for fucoxanthin is appropriate due to its lipophilic and oxidation-sensitive nature, where the solid lipid core offers protection from degradation and enhances systemic availability. In their study, high-fat diet (HFD)-induced obese mice were treated with either free fucoxanthin, lyophilized SLNs (L-SLN), or dispersed SLNs (D-SLN) loaded with fucoxanthin. Among these, D-SLN exhibited the most pronounced anti-obesity effect, leading to a 29.94% reduction in BW gain and a 61.80% decrease in fat mass compared to the HFD control group ($p < 0.05$). These benefits were accompanied by significant improvements in key metabolic parameters, including fasting blood glucose, liver enzyme activity, lipid profile, and inflammatory biomarkers such as leptin and monocyte chemoattractant protein-1 (MCP-1). Histopathological analysis further validated these outcomes, revealing markedly reduced hepatic lipid droplet accumulation and improved adipocyte as well as testicular morphology. Collectively, these findings highlight the promise of fucoxanthin-loaded SLNs, particularly the D-SLN formulation, in advancing fucoxanthin toward clinical development as an effective anti-obesity agent (Al Massadi et al., 2025).

Furthermore, Uner et al. developed SLNs loaded with caffeine (CF), chlorogenic acid (CLA), and their combination (CF + CLA), leveraging the advantages of SLNs as cost-effective, stable, and tissue TD systems. A central composite design model was employed to optimize the formulations, while UHPLC enabled precise quantification of CF and CLA content. The SLNs were prepared via high-pressure homogenization (HPH) using Compritol® 888 ATO as the solid lipid and poloxamer® 407 as the surfactant. The optimized NPs, with an average

size of 110.2 ± 0.1 nm, were characterized and subsequently tested for anti-adipogenic activity using 3T3-F442A cell lines. Further mechanistic insights were obtained through rt-PCR and ELISA analyses of adipogenic markers. Notably, the CF (1 mM) + CLA (0.5 mM) co-loaded SLN formulation demonstrated significant efficacy in suppressing adipogenesis via the PPAR-γ/C/EBP-α signaling pathways. In comparison to regular coffee extract, this optimized SLN formulation exhibited 45.8% greater effectiveness in inhibiting AD ($p < 0.05$). These findings underscore the potential of CF + CLA-loaded SLNs as a promising strategy for obesity management (Uner & Macit Celebi, 2023).

**Phytosomal nanocarrier**

Phytosomes are lipid-based NCs systems synthesized through the complexation of bioactive Phytoconstituents with a lipid layer. In phytosomes, chemical bonds between the herbal extract's active components and the lipid matrix enhance the chemical stability of otherwise highly degradable compounds, improve BA, and enhance therapeutic efficacy. The combination of a soluble herbal extract with a lipophilic outer layer allows phytosomes to offer superior absorption, increased BA, and more targeted action compared to traditional herbal extract formulations (Ortega-Pérez et al., 2023).

Menshawe et al. developed a nano soybean phytosome grafted thermogel with anti-obesity properties. Derived from *Glycine max* of the Fabaceae family, soybean exhibits anto-obesity effects due to its active Phytoconstituents, including proteins, saponins, and phosphatidylcholine. In a preclinical study involving 21 male Albino rats, topical application of a 2.5% phytosomal soybean formulation to the abdominal area resulted in a weight gain significantly lower than the control group's 51.020 ± 4.78%, along with reduced lipid levels. The nanosized phytosomes enhanced skin permeation and introduced an innovative topical approach for obesity management (Razzak et al., 2023).

Razzak et al. investigated whether supplementation with a phytosomal formulation of curcumin could reduce adiposity indices and soluble vascular cell adhesion molecule-1 (sVCAM-1) levels in high-fat diet (HFD)-fed rats. Seventeen male rats were assigned to three groups: normal diet (ND), HFD, and HFD supplemented with phytosomal curcumin (HFD-C). Anthropometric parameters were recorded weekly for 20 weeks, after which sVCAM-1 levels were assessed using one-way ANOVA followed by Tukey's post-hoc analysis. As expected, the HFD group exhibited the highest anthropometric values. While no significant differences were observed between the HFD and HFD-C groups for raw measures, analysis of changes from baseline revealed significant reductions in BW gain and abdominal circumference in the HFD-C group compared to HFD alone. Moreover, sVCAM-1 levels were significantly lower in the HFD-C group, indicating attenuation of obesity-associated endothelial dysfunction. These findings highlight its potential as a complementary therapeutic strategy to counteract dyslipidemia and obesity-related cardiovascular complications (Abdul Razzak et al., 2024).

**Magnetic and Polymeric nanoparticles**

NPs, typically measuring between 1 to 100 nm, are extensively utilized in DDS due to their exceptionally small size and ability to provide targeted action. Various types of NPs such as polymeric, metallic, and magnetic NPs are employed to develop efficient and effective DD platforms. Encapsulating herbal medicines within nanoparticulate systems enhances the therapeutic efficacy of Phytoconstituents while minimizing their associated toxicities. Notably, NPs exhibit a strong ability to deliver plant- and herb-derived anti-obesity bioactive compounds to targeted sites. Among these, metal NPs such as silver, gold, and palladium have shown promise in obesity treatment by enabling precise and targeted DD (Mohaghegh et al., 2024; Salih et al., 2025).

In passive targeting, metal NPs coated with bioactive compounds tend to accumulate in fat-storing tissues, delivering targeted therapeutic effects. In contrast, active targeting utilizes specific ligand-receptor interactions and cellular recognition to facilitate precise binding between carrier NPs and target cells, allowing for the intracellular delivery of anti-obesity bioactive agents. Researchers are actively developing nanoparticulate delivery systems for herbal drugs as a safer and more effective alternative for obesity treatment. Nallamuthu et al. developed chitosan NPs for the TD of chlorogenic acid, a phenolic compound found in various fruits such as apples, plums, and berries, as well as vegetables like sweet potatoes, lettuce, and spinach. The anti-obesity potential of chlorogenic acid was demonstrated by Cho et al. who reported a 16% reduction in BW, a 46% decrease in AT weight, along with significant reductions in plasma leptin, insulin levels and visceral fat mass (Choi et al., 2024).

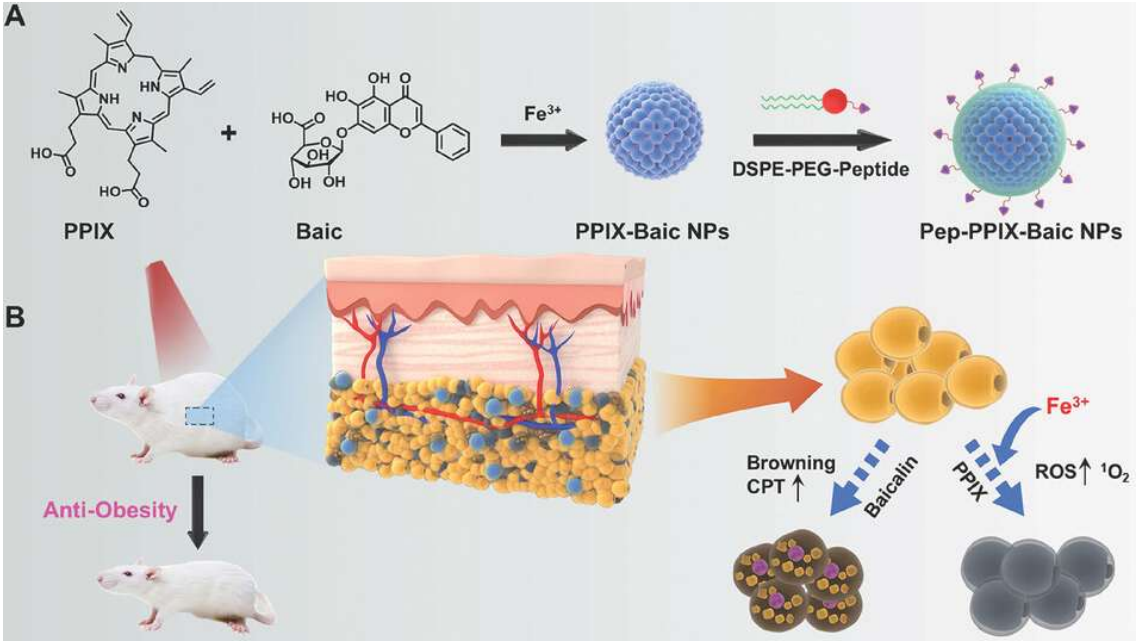


Figure 3. Hybrid Nanoparticles for Synergistic Photodynamic Therapy and Browning Induction in Obesity Treatment. Reproduced with permission from Ma, et al. (2024).

Similarly, Reshma et al. investigated the anti-obesity potential of bioengineered silver NPs (AgNPs) in high-fat diet (HFD)-induced obese albino rats. The AgNPs were synthesized using methanolic pulp extract of *Persea americana* and subsequently characterized through phytochemical analysis, UV–vis spectroscopy, FTIR, SEM, and XRD. Phytochemical screening confirmed the presence of tannins, flavonoids, steroids, saponins, carbohydrates, alkaloids, phenols, and glycosides. The formation of AgNPs was evidenced by a UV–vis absorption peak at 402 nm, while FTIR analysis revealed functional groups corresponding to hydroxyl and amide stretches, indicating their role in NPs capping and stabilization. XRD confirmed the crystalline nature of the AgNPs, and SEM analysis showed predominantly spherical morphology. In vivo evaluation demonstrated that AgNP supplementation improved serum lipid profiles, restored biochemical parameters, and reduced hepatocyte degradation in obese rats, as confirmed by histopathological examination. Collectively, these findings highlight that AgNPs derived from *Persea americana* extract exhibit significant anti-obesity effects and may represent a promising nanotherapeutic approach for obesity management.

In another study, Alsenousy et al. explored the anti-obesity potential of superparamagnetic iron oxide NPs (SPIONs) in a high-fat diet (HFD)-induced rat model of obesity, comparing their effects with the conventional anti-obesity drug orlistat. Obese rats received daily orlistat an d/or weekly SPIONs administration for eight weeks. At the end of the treatment period, blood samples were collected for biochemical analysis, and the animals were sacrificed to harvest WAT and BAT for evaluating thermogenic gene expression and mitochondrial DNA copy number (mtDNA-CN). The findings revealed, for the first time, that SPIONs significantly attenuated weight gain, hyperglycemia, dyslipidemia, and abnormal adipokine levels (adiponectin and leptin) in obese rats. At the molecular level, SPIONs markedly restored the dysregulated expression and protein content of inflammatory markers, while also improving mitochondrial biogenesis and functional parameters in both WAT and BAT. Collectively, these results demonstrate that SPIONs exert a potent anti-obesity effect by promoting WAT browning and enhancing BAT activation, positioning them as a novel nanotechnology-based strategy for obesity management (Alsenousy et al., 2022) (Figure 3).

**Micelles**

Micelles are aggregates of surfactant molecules consisting of HPL heads and HPb tails. Nanosized micelles are utilized in DDS to transport poorly soluble drugs, particularly bioactive compounds and Phytoconstituents that face challenges related to stability and poor solubility. The encapsulation of these poorly soluble compounds into nanosized micelles markedly enhances their solubility and BA. The encapsulation of poorly soluble phytoconstituents into micelles significantly enhances their aqueous solubility and stability. This is achieved through the formation of nanosized aggregates above the critical micelle concentration (CMC), where hydrophobic cores entrap lipophilic compounds while hydrophilic shells ensure dispersion in biological fluids (Cao et al., 2024; Zhao et al., 2019).

Similarly, in another study Zhang et al. illustrated the effectiveness of micellar NPs in treating obesity using curcumin-loaded polymeric micelles. Polymeric micelles are ideal for curcumin due to their ability to encapsulate hydrophobic compounds within their core, significantly improving aqueous solubility and bioavailability. Curcumin, a natural anti-obesity compound with poor water solubility, was encapsulated in nanosized micelles to enhance its BA and therapeutic efficacy. In a HFD induced obese mouse model, treatment with curcumin micelles majorly decreased BW gain, lowered cholesterol and TGL levels, enhanced insulin sensitivity, and reduced fat accumulation in WAT. The micellar formulation also downregulated inflammatory markers and activated the AMPK signaling pathway, promoting FA oxidation and suppressing fat synthesis. This study highlights the potential of micellar NPs as an effective delivery system for poorly soluble herbal compounds in the management of obesity (Ouyang et al., 2024). Furthermore, Niu et al. developed a combination therapy using celastrol (CLT) and phenformin (PHE) encapsulated within chondroitin sulfate-derived micelles for the management of obesity. In this approach, CLT was incorporated into 4-aminophenylboronic acid pinacol ester-modified chondroitin sulfate micelles (CS-PBE/CLT), while PHE was delivered through a chondroitin sulfate–phenformin conjugate micelle (CS-PHE).

These dual micellar systems were designed to actively target adipose tissues via CD44-mediated pathways. Mechanistic investigations revealed that the treatment markedly reduced inflammation and lipid accumulation, as evidenced by protein quantification and Oil Red O staining. In preliminary in vivo experiments, H&E staining, immunohistochemical analyses, insulin tolerance tests, and glucose tolerance tests demonstrated that the combined administration of CS-PBE/CLT and CS-PHE micelles not only decreased BW, WAT mass, and liver mass in high-fat diet–fed mice but also improved systemic glucose homeostasis. Collectively, these findings highlight the therapeutic potential of this dual micelle-based strategy as a promising alternative to current interventions for diet-induced obesity (Niu et al., 2024).

**Gold nanoparticles**

Gold NPs (AuNPs) have gained attention as promising NCs for obesity treatment owing to their biocompatibility, nanoscale size, and potential for functionalization to achieve TD. Their surface properties allow for effective transport of bioactive compounds directly to AT, enhancing therapeutic outcomes while minimizing systemic side effects. AuNPs can passively accumulate in fat deposits and can also be actively directed through ligand-mediated targeting (Ding et al., 2024).

Preclinical studies have shown that AuNPs conjugated with herbal extracts or synthetic compounds can decrease lipid deposition, inhibit AD, and promote lipolysis. For example, AuNPs synthesized using *Camellia sinensis* and *Citrus limon* extracts have demonstrated anti-obesity effects in 3T3-L1 cell lines by activating AMPK and suppressing PPARγ. In animal models, treatment with functionalized AuNPs has led to reduced BW gain, lower fat mass, improved lipid profiles, and increased insulin sensitivity (Yan et al., 2023). Ajayi et al. reported the biosynthesis of AuNPs (CFL-AuNPs) using an aqueous extract of *Cassia fistula* leaves (CFLE) for the management of obesity. The phytosynthesis was confirmed by the characteristic color change from colorless to wine red and a UV–visible absorption peak at 560 nm, with FTIR analysis indicating the involvement of phenolic, amine, and carbonyl groups in NPs stabilization. Morphological analysis revealed anisotropic particles with predominantly spherical and irregular shapes. Importantly, CFL-AuNPs demonstrated strong anti-obesity potential through PL inhibition, achieving 88.93 ± 0.81% activity with an $IC_{50}$ of 121.38 μg/mL, which was comparable to the standard drug Orlistat (89.46 ± 0.50%, $IC_{50}$ 120.51 μg/mL). These findings suggest that CFL-AuNPs may serve as an effective natural nanotherapeutic for obesity management (Ajayi et al., 2023).

Table 3: Comparative overview of nanocarrier systems used for the delivery of anti-obesity phytochemicals.

| Nanoparticle | Phytochemical | Mechanism | Composition | Effect | Reference |
|---|---|---|---|---|---|
| Liposome | Curcumin | Enhanced lipid metabolism, adipogenesis inhibition | Phosphatidylcholine, cholesterol | Reduced BW, improved lipid profile | (Kasprzak-Drozd et al., 2022) |
| SLNs | Berberine | Sustained release, thermogenesis enhancement | Glyceryl monostearate + surfactant | Decreased fat accumulation, improved insulin sensitivity | (Xue et al., 2015) |
| NLCs | Resveratrol | Increased stability, enhanced adipose targeting | Lipid blend + surfactant | Reduced visceral fat, improved lipid profile | (Nayak et al., 2024) |
| Polymeric NPs | EGCG | Controlled release, adipogenesis inhibition | PLGA-based | Lower BW gain, enhanced thermogenesis | (Huang et al., 2019) |
| Nanoemulsions | Curcumin | Improved solubility and BA | Oil-in-water emulsion | Increased fat metabolism, reduced lipid accumulation | (Agame-Lagunes et al., 2021) |
| Micelles | Resveratrol | Enhanced oral BA, adipose targeting | PEG-PLA micelles | Reduced weight gain, improved lipid profile | (Joseph et al., 2022) |

Despite their potential, issues like long-term toxicity, bioaccumulation, and regulatory hurdles must be resolved before they can be used in clinical settings. However, advancements in green synthesis and surface modification have improved the safety and targeting efficiency of AuNPs. Overall, gold NPs hold significant promise for developing safe and effective obesity therapies, especially when combined with plant-derived bioactives or pharmacological agents (Abel et al., 2023) (Table III).

**Toxicity**

Herbal nanotherapeutics offer considerable promise for obesity management, yet their safety profile remains a critical challenge. The incorporation of phytochemicals into NCs systems can significantly alter their pharmacokinetics, tissue distribution, and cellular uptake, potentially leading to unexpected toxicological effects. These effects may arise from the nanomaterials themselves, the phytochemicals, or complex interactions between the two at cellular and molecular levels. NPs, due to their high surface-area-to-volume ratio, exhibit enhanced chemical reactivity, which can contribute to adverse outcomes such as oxidative stress, inflammation, and cytotoxicity. For example, cationic polymers or surfactants in certain formulations may compromise cell membrane integrity or impair mitochondrial function. Non-biodegradable or slowly degrading NPs, including AuNPs, may accumulate in organs such as the liver, spleen, and kidneys, raising concerns regarding long-term organ-specific toxicity. Histopathological alterations and immune reactions have also been reported with certain lipid-based and polymeric NPs, often influenced by particle size, surface charge, composition, and the route of administration.

In a systematic analysis conducted by Mazzanti et al., nineteen cases of hepatotoxicity associated with the consumption of herbal products containing green tea (GT) were identified. The majority of affected individuals were women (16 out of 19), and in most cases the liver injury was classified as hepatocellular (16 out of 19). Causality assessment indicated a probable association in eight cases and a possible association in eleven cases. Seven patients had consumed

preparations containing only GT, while twelve cases involved multicomponent (MC) formulations. The hepatotoxic reactions linked to GT generally exhibited a long latency period (179.1 ± 58.95 days), but all cases resolved, with an average recovery time of 64.6 ± 17.78 days (Mazzanti et al., 2015). Similarly, in another study Navarro et al. investigated the potential toxicity of catechin-containing compounds. Their analysis revealed that 29 out of 73 herbal dietary supplements (HDS) (39.7%) contained catechins, despite not listing GTE or its components on the label. Among patients with confirmed hepatotoxicity, no statistically significant association was observed between catechin presence or dosage and liver injury causality, severity, or pattern. Catechin concentrations were generally low across most products, although levels tended to be higher in supplements marketed for weight loss. Considering that hepatotoxicity has been observed with conventional green tea extract formulations, the enhanced bioavailability and reduced first-pass metabolism associated with nano-enabled systems may lead to increased hepatic accumulation, thereby potentially exacerbating liver injury. This highlights the critical need for integrated toxicological assessment and dose standardization in nanoformulated phytotherapeutics (Navarro et al., 2013).

Furthermore, Abdelhalim et al. demonstrated that intraperitoneal administration of AuNPs could induce hepatotoxicity, manifested by hepatic inflammatory damage, lipid peroxidation, and oxidative stress in vivo. This toxic response was evidenced by a significant elevation in serum liver function markers, including ALT, ALP, GGT, and total protein, along with an increase in the hepatic lipid peroxidation biomarker MDA. Concurrently, a marked depletion in the antioxidant biomarker GSH was observed. Notably, treatment with various natural antioxidants effectively mitigated these alterations by reducing serum liver function markers and MDA levels, while restoring tissue GSH content (Abdelhalim et al., 2018).

The phytochemical component of these formulations is not without risk. While naturally derived, compounds such as curcumin, EGCG, or resveratrol may exert toxic effects at high doses or with prolonged exposure. When incorporated into NCs, these phytochemicals may achieve higher local concentrations or enhanced cellular uptake, potentially amplifying hepatotoxicity, nephrotoxicity, or pro-oxidant effects. For instance, curcumin-loaded micelles or polymeric NPs, though improving solubility and BA, may increase intracellular accumulation and associated cytotoxicity. Similarly, concentrated EGCG or resveratrol delivered via NCs may exhibit enhanced pro-oxidant activity at the cellular level. Inorganic NPs, particularly gold or AgNPs, present additional concerns due to their slow clearance and potential for chronic tissue exposure and bioaccumulation.

Regulatory frameworks for herbal nanomedicines face unique challenges because these products combine bioactive herbal compounds with nanomaterials. Agencies such as the EMA and FDA emphasize comprehensive characterization of nanomaterials, including their physicochemical properties, reproducibility in manufacturing, and overall biocompatibility. However, combination products necessitate additional scrutiny due to complex pharmacokinetics, altered bio-distribution, and potential interactions with biological systems that may not occur with conventional herbal extracts. Dose standardization, batch-to-batch reproducibility, and chronic toxicity evaluation are particularly critical to mitigate safety risks. Regulatory guidance increasingly calls for thorough in vitro and in vivo toxicity assessments, including cytotoxicity, hemocompatibility, oxidative stress, and immunogenicity studies, complemented by advanced imaging and biodistribution analyses. Designing biodegradable, non-immunogenic NCs and establishing validated protocols for comprehensive safety evaluation are essential to ensure the safe translation of these combination products. Only through such rigorous toxicological assessment can the clinical potential of herbal nanomedicines for obesity be reliably and safely realized.

Importantly, the toxicity of herbal nanotherapeutics should not be viewed as a simple sum of "herbal" and "nanomaterial" effects, but rather as a dynamic interaction between the two. Nanocarriers can significantly alter the pharmacokinetics and biodistribution of phytoconstituents, potentially exacerbating their inherent toxicities. For instance, compounds such as green tea extract (GTE), which are associated with hepatotoxicity at higher doses, may exhibit enhanced hepatic exposure when delivered via nanocarriers due to improved bioavailability and protection from pre-systemic metabolism. By partially bypassing first-pass metabolism and facilitating increased cellular uptake, nanoformulations can lead to higher intracellular

concentrations, thereby amplifying pro-oxidant or cytotoxic effects. Furthermore, targeted or passive accumulation of nanoparticles in organs such as the liver may intensify organ-specific toxicity. Therefore, the safety evaluation of herbal nanomedicines must consider these synergistic interactions, emphasizing the need for integrated toxicological assessments that account for both the carrier system and the bioactive compound.

**Barriers to Herbal Nanoformulation**

Despite encouraging preclinical evidence, the successful translation of herbal nanoformulations from bench to bedside faces several formidable challenges. A major barrier lies in the inherent complexity of characterization. Nano-herbal systems are multi-component in nature, comprising diverse phytochemicals encapsulated in carriers with variable size, surface charge, morphology, and stability. Subtle variations in preparation methods can significantly alter their physicochemical and biological properties, making comprehensive characterization essential yet technically demanding. Advanced analytical tools such as dynamic light scattering, Nanoparticle tracking analysis (NTA), cryo-TEM, and mass spectrometry can help establish reproducible profiles, but standardization across laboratories remains limited, hindering regulatory confidence and clinical comparability (Zhao et al., 2024).

Another significant challenge is batch-to-batch variation. Herbal extracts inherently contain multiple active and inactive constituents, and their composition may vary depending on factors such as plant source, harvesting season, and extraction methods. When combined with the sensitivity of NCs synthesis to process parameters, this variability can compromise product consistency, efficacy, and safety. Solutions may include the adoption of standardized phytochemical fingerprints, validated manufacturing protocols, and robust quality control assays to ensure reproducibility at both laboratory and industrial scales. Cost and scalability also pose obstacles. Many nanoformulation methods, including high-pressure homogenization, microfluidics, and solvent evaporation, are resource-intensive and difficult to scale up without altering product characteristics. The expense associated with specialized raw materials, processing equipment, and quality assurance adds further barriers to widespread clinical adoption. Addressing these concerns will require investment in scalable, cost-efficient manufacturing technologies and industry–academic partnerships to streamline technology transfer (Uddandrao et al., 2023).

Regulatory ambiguity is perhaps the most persistent hurdle. Herbal nanoformulations straddle two domains phytomedicine and nanomedicine creating uncertainties in classification, approval pathways, and post-marketing surveillance. Current regulatory frameworks, such as those of the EMA and FDA, provide guidance for nanomaterials and botanical drugs separately, but clear guidelines for hybrid products remain underdeveloped. This ambiguity complicates the design of preclinical studies and clinical trials. Proactive engagement with regulators, early submission of investigational dossiers, and harmonization of global regulatory standards will be critical to clarify approval processes. Conclusively, translating herbal nanoformulations into clinical practice requires overcoming challenges in characterization, reproducibility, scalability, cost, and regulation. Progress will depend on the establishment of standardized analytical methods, validated manufacturing protocols, scalable production strategies, and harmonized regulatory frameworks. Addressing these barriers systematically will accelerate the safe and effective integration of nano-enabled herbal therapeutics into obesity management and beyond (Wang et al., 2025).

**Future Perspective**

The field of nano-enabled herbal therapeutics for obesity is rapidly evolving, yet several critical directions must be pursued to ensure meaningful translation into practice. A key priority is the rational integration of phytoactives with suitable NCs systems. Phytochemicals such as curcumin, EGCG, resveratrol, and berberine have consistently demonstrated anti-obesity potential in preclinical models, and their encapsulation in liposomes, micelles, solid lipid NPs, and polymeric carriers offers opportunities to enhance solubility, stability, and targeted BA. Comparative studies that systematically evaluate these pairings will be essential to identify formulations with the greatest therapeutic index while minimizing off-target effects.

Equally important is the establishment of a comprehensive toxicological framework. While NCs can improve the pharmacokinetics of phytochemicals, they may also modify biodistribution and cellular uptake in ways that introduce new safety concerns. For instance, concentrated curcumin in micellar systems raises

questions regarding hepatotoxicity, and the persistence of AuNPs highlights the need to understand long-term organ accumulation and clearance. Similarly, enhanced intracellular delivery of EGCG or resveratrol may amplify pro-oxidant effects. Importantly, increased bioavailability does not necessarily correlate with improved therapeutic outcomes, as exceeding the optimal concentration threshold may shift these compounds from antioxidant to pro-oxidant behavior, thereby increasing the risk of cytotoxicity.

As the field moves closer to clinical application, careful attention must also be given to early-phase trial design. Herbal nanoformulations intended for first-in-human testing should be supported by extensive preclinical safety data and preferably utilize biodegradable and metabolizable carriers rather than persistent inorganic platforms. Clinical studies should incorporate careful dose escalation, pharmacokinetic profiling, and biomarker-driven endpoints to capture both safety and early efficacy in obese populations.

Another major challenge is the translation of laboratory-scale formulations into reproducible, clinically compliant products. Scaling up under Good Manufacturing Practice (GMP) conditions requires strict control over parameters such as particle size, loading efficiency, and long-term stability. The development of robust, standardized production methods and harmonized characterization protocols will be critical to ensure regulatory acceptance. Regulatory agencies will also need to adapt existing frameworks to address the unique complexities of combination products that merge herbal bioactives with nanotechnology, demanding closer alignment between researchers, industry stakeholders, and regulators.

Taken together, the future of nano-enabled herbal therapeutics lies in a multidisciplinary approach that unites advances in phytochemistry, nanotechnology, toxicology, clinical sciences, and regulatory science. Addressing these challenges will not only accelerate the safe translation of such interventions for obesity but also provide a model for extending their application to other chronic MD.

## CONCLUSION

The integration of phytochemicals with advanced nanocarrier systems represents a transformative strategy to overcome the pharmacokinetic and therapeutic limitations of conventional anti-obesity approaches. Bioactive compounds such as curcumin, resveratrol, EGCG, and berberine have demonstrated significant potential in modulating lipid metabolism, adipogenesis, thermogenesis, and appetite regulation; however, their clinical applicability is substantially limited by poor aqueous solubility, low oral bioavailability, chemical instability, and rapid systemic clearance. Nano-enabled DDS including polymeric NPs, SLNs, nanostructured lipid carriers, liposomes, nanoemulsions, and micelles offer effective solutions by enhancing solubility, stability, bioavailability, and targeted delivery, while enabling controlled and sustained release. These advancements not only improve therapeutic efficacy but also reduce systemic toxicity and dose-related adverse effects.

Preclinical studies consistently demonstrate superior anti-obesity outcomes of nanoformulations compared to free compounds, often at reduced doses, highlighting their translational potential. Nevertheless, despite these promising developments, clinical translation remains limited due to challenges such as scalable manufacturing, batch-to-batch reproducibility, long-term safety concerns, and regulatory complexities. Variability in global regulatory frameworks further complicates widespread adoption, underscoring the need for harmonized guidelines, standardized characterization, and rigorous quality control. Moving forward, well-designed and adequately powered clinical trials, along with comprehensive toxicological assessments, will be essential to validate safety and efficacy in humans. Interdisciplinary collaboration among nanotechnologists, pharmacologists, clinicians, and regulatory authorities will be critical to bridge the gap between experimental success and clinical implementation. With continued innovation and coordinated efforts, nano-enabled phytotherapeutics hold substantial promise for advancing obesity management into a safer, more effective, and sustainable therapeutic paradigm.

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## CONFLICT OF INTEREST

There is no conflict of interest and disclosures associated with the manuscript.

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