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Nanoformulated Phytochemicals in Obesity Therapy: Enhancing Bioavailability and Target Specificity of Natural Compounds

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ABSTRACT

Phytochemicals such as polyphenols, terpenoids and alkaloids show robust anti-obesity activity in vitro and in animal models through modulation of adipogenesis, lipolysis, thermogenesis, inflammation, insulin signaling and gut microbiota. However, their translation into effective human therapies is hampered by poor aqueous solubility, low oral bioavailability, rapid metabolism and limited tissue targeting. Nanotechnology-based delivery systems offer a rational solution by protecting phytochemicals from degradation, enhancing absorption, prolonging circulation and directing them to metabolically relevant tissues. This review summarizes the molecular mechanisms by which key phytochemicals exert anti-obesity effects, outlines pharmacokinetic barriers and describes major classes of nanocarriers, including lipid-based nanoparticles, nanoemulsions, polymeric systems, phytosomes and hybrid platforms. We discuss targeted and stimuli-responsive nanoformulations aimed at adipose tissue, liver and gut, and highlight preclinical evidence that nanoencapsulation enhances efficacy of curcumin, resveratrol, catechins, berberine and related compounds. Finally, we examine safety, quality, regulatory and equity challenges, and propose future directions for integrating nanoformulated phytochemicals into precision obesity therapy.

Keywords: Obesity; Phytochemicals; Nanocarriers; Bioavailability; Targeted therapy

INTRODUCTION

Obesity is a multifactorial, relapsing disease driven by chronic caloric excess, sedentary behaviour and genetic and environmental factors[1–3]. Conventional pharmacotherapy targets central appetite circuits, nutrient absorption, or incretin signaling but frequently encounters limited long-term efficacy, side effects or cost barriers. Against this backdrop, phytochemicals, bioactive molecules derived from plants, have attracted strong interest as complementary or alternative anti-obesity agents[4, 5].

Preclinical and emerging clinical data show that multiple classes of phytochemicals can modulate key pathways involved in energy balance and metabolic homeostasis. Polyphenols such as epigallocatechin-3-gallate (EGCG), resveratrol, quercetin, anthocyanins and ellagic acid reduce adipogenesis, enhance lipolysis, stimulate thermogenesis and improve insulin sensitivity in cell and animal models[6–9]. Alkaloids such as berberine and capsaicin, terpenoids such as curcumin and carotenoids like fucoxanthin similarly influence PPARγ, C/EBPα, AMPK, SIRT1 and UCP1 signaling, and can reshape gut microbiota composition in directions associated with leanness. Clinical studies, although heterogeneous, have reported modest but significant reductions in body weight, waist circumference and lipid parameters with selected phytochemicals including green tea catechins, resveratrol, berberine and garcinia-derived hydroxycitric acid[8, 10–12].

Despite this promise, translation has been disappointing. Many phytochemicals require gram-level daily doses in conventional formulations to achieve modest effects, and inter-individual variability in response is high. The core issue is pharmacokinetics. Polyphenols and related compounds often have low aqueous solubility, dissolve poorly in gastrointestinal fluids and undergo extensive first-pass metabolism and efflux, resulting in low systemic exposure and short half-lives[13, 14]. Curcumin is a classic example: although potent in vitro, it exhibits extremely low oral bioavailability due to poor solubility, rapid metabolism to glucuronides and sulfates and fast biliary excretion. Resveratrol, quercetin and many flavonoids share similar constraints[13].

Moreover, the tissues most relevant to obesity like adipose depots, liver, skeletal muscle, gut epithelium and brain, are not equally exposed to circulating phytochemicals. Conventional oral supplements distribute largely

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according to passive diffusion and systemic circulation, with no particular preference for adipose tissue or inflamed metabolic organs. Consequently, achieving therapeutic concentrations at target sites often necessitates high systemic doses, increasing the risk of off-target effects, drug–drug interactions and poor adherence[15].

Another layer of complexity is that phytochemicals frequently act on multiple pathways simultaneously, including antioxidant and anti-inflammatory mechanisms, modulation of adipokines and restructuring of the gut microbiome [16]. While this pleiotropy may be beneficial, it complicates dose–response relationships and makes it difficult to distinguish direct target effects from systemic spillover. Inter-individual differences in gut microbiota and phase II metabolism further amplify variability[17].

Nanotechnology offers a coherent strategy to address these limitations. Encapsulating phytochemicals within nanocarriers can increase apparent solubility, protect them from pH, light and enzymatic degradation, and promote transport across intestinal epithelium via transcellular, paracellular or lymphatic routes[18–20]. Lipid-based carriers, nanoemulsions, polymeric nanoparticles, solid lipid nanoparticles, nanostructured lipid carriers, dendrimers and phytosomes have all been investigated to enhance the bioavailability of dietary polyphenols and other plant-derived compounds.

Importantly, nanoformulation does more than passively improve exposure. Surface functionalization with targeting ligands, such as peptides or antibodies that recognize adipocyte or hepatic receptors, can increase accumulation in adipose tissue or liver, where anti-obesity effects are most needed[21]. Stimuli-responsive materials responsive to pH, enzymes or redox conditions can trigger controlled release in the gut, inflamed adipose tissue or diseased liver. In this way, nanocarriers can reshape the biodistribution and temporal profile of phytochemicals, increasing local concentrations at therapeutic sites while limiting systemic exposure[22–24].

Recent reviews synthesize growing evidence that nanoencapsulated phytochemicals exhibit superior anti-obesity activity compared with their free counterparts, including greater weight reduction, improved lipid profiles and enhanced insulin sensitivity in rodent models. Nanoformulated EGCG, curcumin, resveratrol, quercetin and berberine often demonstrate efficacy at doses where free compounds are ineffective, supporting the notion that nano-delivery can unlock latent therapeutic potential[25]. At the same time, nano-phytomedicine is not a panacea. Nanocarriers introduce new variables such as size, charge, composition, and stability that affect safety and regulatory pathways. Manufacturing complexity and costs must be considered, particularly if the goal is long-term therapy in large populations[26–29]. Nonetheless, the convergence of phytochemistry and nanotechnology holds real promise for more potent, targeted, and personalized obesity therapies that preserve the favorable safety profile and pleiotropic benefits of natural compounds while overcoming their pharmacokinetic handicaps.

The following sections dissect the molecular mechanisms of key anti-obesity phytochemicals, identify pharmacokinetic hurdles that nanoformulations aim to solve, describe major nanocarrier platforms and targeting strategies, and review preclinical and emerging clinical data on nanoformulated phytochemicals in obesity management.

2. Anti-Obesity Mechanisms of Key Phytochemicals

Phytochemicals exert anti-obesity effects through diverse, often overlapping molecular pathways. Polyphenols such as EGCG, resveratrol and quercetin inhibit adipogenesis by downregulating transcription factors PPARγ and C/EBPα, which are central to adipocyte differentiation[25, 30–32]. They also activate AMPK and SIRT1, promoting fatty acid oxidation, mitochondrial biogenesis and improved insulin signaling in the liver and skeletal muscle. Resveratrol and catechins further stimulate browning of white adipose tissue and increase UCP1 expression, enhancing thermogenesis and energy expenditure[33–35].

Curcumin, a diarylheptanoid from turmeric, combines anti-inflammatory and metabolic effects. It suppresses NF-κB and JNK signaling, reducing production of TNF-α, IL-6 and other cytokines that drive insulin resistance. Curcumin also modulates adipokines by lowering leptin and increasing adiponectin, and can inhibit adipocyte hypertrophy and macrophage infiltration into adipose tissue [13, 13, 36]. Fucoxanthin, a marine carotenoid, has been shown to reduce weight gain, stimulate thermogenesis through UCP1 upregulation in white adipose depots and improve lipid profiles in animal models.

Berberine, an isoquinoline alkaloid, exerts multi-organ actions. It activates AMPK, downregulates lipogenic genes, enhances insulin receptor expression and modulates gut microbiota by enriching short-chain fatty acid–producing bacteria[37–39]. Clinically, berberine has demonstrated reductions in body weight, fasting glucose and triglycerides, although gastrointestinal side effects limit tolerability in some patients. Other phytochemicals, such as hydroxycitric acid from garcinia, anthocyanins from berries and various terpenoids, likewise influence appetite, lipid metabolism and inflammation[40]. An emerging theme is gut microbiota modulation. Many polyphenols undergo extensive biotransformation by intestinal microbes, producing metabolites that may be more bioactive than parent compounds. Conversely, polyphenols shape microbial composition, often increasing[41] Bacteroidetes, Akkermansia and other taxa are associated with improved metabolic health while

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reducing endotoxin-producing Proteobacteria. These reciprocal interactions help explain why phytochemicals can attenuate metabolic endotoxemia, strengthen intestinal barrier function and enhance GLP-1 secretion[41]. At the systems level, phytochemicals tend to have modest, multi-target effects rather than strong single-target actions. They partially suppress adipogenesis, modestly enhance thermogenesis, improve insulin sensitivity and reduce subclinical inflammation. In populations, such distributed effects may be beneficial because obesity is itself a systems-level disorder[42]. However, modest effect sizes in free form limit their standalone therapeutic value. Nanoformulation can amplify these mechanisms by increasing local concentrations at target tissues, synchronizing delivery of multiple phytochemicals or co-delivering phytochemicals with complementary agents such as omega-3 fatty acids, probiotics or conventional drugs. The mechanistic palette of phytochemicals thus provides a strong foundation on which nanotechnology can build more potent and targeted anti-obesity interventions[42].

3. Pharmacokinetic Barriers and the Rationale for Nanoencapsulation

The pharmacokinetic profile of most phytochemicals is dominated by poor absorption, extensive metabolism and rapid clearance. Many polyphenols and terpenoids are hydrophobic, leading to low dissolution in gastrointestinal fluids and limited permeation across the unstirred water layer adjacent to the intestinal epithelium[43]. Even when absorbed, they are subject to phase II metabolism in enterocytes and hepatocytes, yielding glucuronide and sulfate conjugates that differ in bioactivity and are readily excreted in bile or urine. The net result is low plasma exposure of the native compound and short systemic half-life[43].

Curcumin exemplifies this pattern: after oral dosing, only trace amounts of free curcumin appear in plasma, with most recovered as conjugated metabolites. Resveratrol and quercetin exhibit similar rapid conjugation and biliary excretion [36, 44, 45]. Berberine shows poor intestinal absorption and strong first-pass metabolism, which necessitates relatively high doses to achieve metabolic effects, at the cost of gastrointestinal adverse events. Additionally, efflux transporters such as P-glycoprotein and MRP2 can pump phytochemicals back into the intestinal lumen, further lowering net absorption[37, 46].

Nanoencapsulation addresses these issues through several mechanisms. First, reducing particle size to the nano-scale increases surface area and dissolution rate, improving apparent solubility of hydrophobic phytochemicals in gastrointestinal fluids[47]. Second, embedding phytochemicals in lipid matrices or surfactant-stabilized droplets facilitates incorporation into mixed micelles and chylomicrons, promoting lymphatic transport and partially bypassing hepatic first-pass metabolism. Third, encapsulation can shield phytochemicals from harsh gastric pH, light, and enzymatic degradation, preserving their chemical integrity until they reach absorptive sites[47].

Certain nanocarriers can modulate efflux pumps or tight junctions, enhancing transcellular or paracellular uptake. Polymeric nanoparticles and dendrimers can be engineered with mucoadhesive properties, increasing residence time in the small intestine and providing a depot from which phytochemicals slowly diffuse[48–50]. Phytosomes, complexes of phospholipids and phytochemicals, improve membrane permeability by presenting the compound in a more lipophilic, bilayer-compatible form.

Beyond oral absorption, nanoformulation influences distribution. Surface charge and composition determine interactions with plasma proteins and the mononuclear phagocyte system, shaping biodistribution to liver, spleen, adipose tissue or other organs. Ligand decoration can shift this balance toward specific cell types, such as adipocytes or hepatocytes expressing targeted receptors[51]. Controlled-release properties of nanocarriers allow sustained exposure at target sites, potentially enhancing chronic pathways such as adipogenesis inhibition or macrophage polarization in adipose tissue.

Collectively, these improvements can increase the area under the curve for active phytochemical species by several-fold and extend their time above minimal effective concentrations. This pharmacokinetic enhancement is central to the observed superiority of nanoformulated phytochemicals in preclinical obesity models and underpins their potential as clinically relevant agents rather than merely nutraceutical adjuncts.

4. Nanocarrier Platforms for Anti-Obesity Phytochemicals

Multiple nanocarrier classes have been developed to deliver phytochemicals, each with distinct advantages and constraints for obesity therapy. Lipid-based systems are particularly prominent. Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) encapsulate hydrophobic phytochemicals within solid or mixed solid–liquid lipid cores stabilized by surfactants[19, 26, 52, 53]. They offer good biocompatibility, protect labile compounds and can be tailored for controlled release. Curcumin-, resveratrol- and EGCG-loaded SLNs and NLCs have shown improved bioavailability and superior anti-obesity effects in animal studies relative to free compounds.

Nanoemulsions, typically oil-in-water dispersions with droplet sizes below 200 nm, are attractive for oral delivery of lipophilic phytochemicals. They can be prepared using food-grade oils and surfactants, making them suitable for functional foods and nutraceuticals. Nanoemulsions enhance solubilization, digestion and absorption

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of phytochemicals and can be designed for rapid or sustained release[54]. For obesity, nanoemulsified green tea catechins, curcumin and carotenoids are being explored in beverages and dietary supplements.

Polymeric nanoparticles formed from biodegradable polymers such as PLGA, chitosan and alginate provide versatile platforms for encapsulating both hydrophilic and hydrophobic phytochemicals[49]. PLGA nanoparticles offer controlled release and protection against degradation, while chitosan imparts mucoadhesive and permeation-enhancing properties. Dendrimers, highly branched synthetic polymers, can host phytochemicals within internal cavities or on their surface, though toxicity and clearance issues require careful tuning[54].

Phytosomes represent a distinct approach in which phytochemicals form complexes with phospholipids, enhancing membrane permeability and bioavailability while maintaining a relatively simple composition[55]. Commercial phytosome formulations of silymarin, curcumin and green tea catechins have shown improved pharmacokinetics in humans, and similar strategies are now being applied to novel anti-obesity phytochemicals[55]. Hybrid nanocarriers combine features from multiple classes. For example, polymer–lipid hybrid nanoparticles integrate a polymeric core with a lipid shell, offering both structural stability and biomimetic interfaces. Surface modification with polyethylene glycol can prolong circulation, while attachment of targeting ligands supports tissue selectivity[56]. Inorganic carriers such as mesoporous silica and magnetic nanoparticles have also been explored for phytochemical delivery, often with an eye toward imaging or externally triggered release, although their long-term safety profile in chronic metabolic indications remains less well defined[56].

Selection of an appropriate carrier depends on the physicochemical properties of the phytochemical, the desired route of administration, target tissue and release kinetics. For obesity therapy, oral delivery remains a priority, favoring food-compatible lipids, polymers and surfactants. Nonetheless, parenteral or transdermal nanoformulations may be relevant where rapid onset or precise dosing is required, particularly when nano-phytochemicals are used as adjuncts to other pharmacotherapies.

5. Targeted and Stimuli-Responsive Nanoformulations for Metabolic Organs

Beyond generic bioavailability enhancement, nanocarriers can be engineered for organ- and cell-specific delivery of phytochemicals[57]. Adipose tissue is a prime target in obesity, as it is central to energy storage, adipokine secretion and inflammatory crosstalk. Nanoparticles decorated with peptides that recognize adipocyte or adipose vasculature markers can preferentially accumulate in white or brown fat depots, increasing local concentrations of anti-adipogenic or thermogenic phytochemicals[22, 23]. In principle, curcumin or resveratrol nanoparticles targeted to obese adipose tissue could more effectively suppress inflammation and promote browning than systemic administration of free compounds.

The liver is another critical site, given its role in de novo lipogenesis, VLDL production and insulin clearance. Targeting ligands such as galactose or N-acetylgalactosamine exploit the asialoglycoprotein receptor on hepatocytes to deliver phytochemicals that modulate lipid metabolism and inflammation. Nanoencapsulated silymarin, curcumin and resveratrol have shown improved efficacy in models of non-alcoholic fatty liver disease, suggesting that similar strategies could benefit obesity patients with fatty liver[58]. The gut offers unique opportunities for local action. Oral nanoformulations can be designed to release phytochemicals primarily in the small intestine or colon using pH- and enzyme-responsive coatings[2, 59]. There, they can interact directly with the gut epithelium and microbiota, modulating barrier integrity, incretin release and microbial composition. For example, nanoencapsulated polyphenols that are stable in the upper GI tract but release in the colon may preferentially act on microbial targets, reshaping communities toward metabolically favorable configurations.

Stimuli-responsive nano-systems add temporal precision. Materials that respond to redox state, pH or enzymes enriched in inflamed adipose or fatty liver can trigger the release of phytochemicals only within diseased tissues[22]. External stimuli such as near-infrared light or magnetic fields may be used to activate photothermal or magnetothermal nanoparticles loaded with phytochemicals, creating local microenvironmental changes and controlled drug release. Although most work in this area remains preclinical, it offers intriguing possibilities for on-demand modulation of energy expenditure or inflammation[24]. Finally, combination nanoformulations that co-deliver phytochemicals with conventional anti-obesity drugs or metabolic hormones may enhance efficacy and reduce dose requirements for synthetic agents[60]. For instance, a nanocarrier could simultaneously deliver berberine and a low-dose GLP-1 receptor agonist to the liver and intestine, leveraging complementary mechanisms while minimizing systemic exposure. Such integrated designs align with emerging precision medicine strategies that seek to align pharmacologic profiles with individual metabolic phenotypes.

6. Preclinical and Emerging Clinical Evidence for Nanoformulated Phytochemicals

A growing body of preclinical data supports the superiority of nanoformulated phytochemicals over conventional preparations in obesity models[61]. Nanoencapsulated EGCG has shown enhanced suppression of weight gain, adipocyte hypertrophy and hepatic steatosis at lower doses than free EGCG, consistent with improved bioavailability and tissue distribution[61]. Curcumin-loaded nanoparticles and nanoemulsions have

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demonstrated greater reductions in body weight, adipose inflammation, insulin resistance and serum lipids compared with equivalent doses of free curcumin in high-fat diet–induced obese rodents[62].
Resveratrol nanoparticles have improved oral absorption and enhanced anti-adipogenic, anti-inflammatory and insulin-sensitizing effects in animal studies[33]. Berberine-loaded liposomes and polymeric nanoparticles increase intestinal absorption, plasma exposure and metabolic benefits, including reductions in fasting glucose, triglycerides and visceral fat mass, while potentially reducing gastrointestinal intolerance by limiting free berberine in the lumen[63]. Polyphenol-loaded nanoemulsions and SLNs, including combinations of catechins, quercetin and anthocyanins, have similarly produced stronger anti-obesity and anti-diabetic effects in rodent models than unformulated mixtures.

Clinical evidence remains relatively limited but is emerging. Some studies have reported improved pharmacokinetic profiles and greater reductions in liver fat, oxidative stress markers and metabolic parameters with nanoformulated curcumin and silymarin compared to standard preparations, primarily in NAFLD and metabolic syndrome rather than obesity per se[64]. Nano-phytosome formulations of green tea catechins have shown higher plasma levels and enhanced effects on antioxidant status and lipid profiles in humans, suggesting potential for weight management, although dedicated obesity trials are still sparse[64]. Translating preclinical successes to humans faces several obstacles. Doses, treatment durations and formulations vary widely across studies, complicating comparisons. Many trials are small, short and focused on surrogate markers rather than clinically meaningful endpoints such as sustained weight loss or reduced incidence of diabetes. Inter-individual variability in gut microbiota and metabolic status may influence response to nanoformulated phytochemicals, implying that patient stratification will be important in future trials[65].
Nevertheless, the convergence of evidence suggests that nanoformulation consistently enhances exposure and, in many cases, therapeutic effects of phytochemicals. As newer formulations progress to phase I and II studies with standardized endpoints, a clearer picture will emerge regarding their role as standalone agents, adjuncts to standard drugs or components of multi-modal lifestyle and pharmacologic interventions.

7. Safety, Regulatory and Translational Considerations

While phytochemicals are often perceived as inherently safe, nanoformulation introduces new safety and regulatory considerations. Nanocarrier components like lipids, surfactants, polymers and inorganic materials must be biocompatible, non-immunogenic and suitable for chronic administration in largely ambulatory populations. Food-grade lipids and emulsifiers offer a favorable starting point for oral nanoemulsions and SLNs, but polymeric and inorganic carriers may require more extensive toxicological evaluation[66]. Key issues include potential accumulation of non-biodegradable materials, interactions with the immune system and off-target organ deposition, particularly in liver and spleen. For obesity therapy, where treatment may be long-term or even lifelong, subtle toxicity that would be acceptable in oncology is not tolerable. Thus, safety margins must be high, and benefit–risk assessments must consider that modest weight loss is the likely effect size[67].
Regulatory agencies increasingly view nanoformulated phytochemicals not as simple dietary supplements but as complex medicinal products, especially when claims involve disease treatment rather than general wellness[68]. This entails stringent requirements for characterization of nanocarriers (size distribution, morphology, surface charge, composition, drug loading and release profiles) and robust demonstration of batch-to-batch consistency. Novel excipients or carrier architectures may require full toxicology packages. In some jurisdictions, nanoformulated phytochemicals may be regulated as combination products if they merge food and drug characteristics[68].
Manufacturing scalability and cost are further challenges. Techniques such as high-pressure homogenization, microfluidization and nanoprecipitation can be scaled industrially, but maintaining narrow particle size distributions and stable encapsulation during storage is non-trivial[69]. Cold-chain requirements or short shelf life would limit access in low-resource settings, where obesity prevalence is rising rapidly. Ensuring that nano-phytomedicines are affordable and accessible, rather than boutique products for high-income consumers, is essential if they are to make a meaningful public health impact[69].
Finally, there are conceptual and ethical questions. Marketing of nanoformulated "natural" products can blur boundaries between nutraceuticals and drugs, risking overstatement of efficacy or under-communication of potential risks. Transparent labeling, evidence-based claims and post-marketing surveillance will be needed to maintain trust. Equity considerations are central: advanced nanoformulations should not divert attention from structural determinants of obesity or crowd out investment in basic lifestyle and environmental interventions.
Addressing these issues requires collaboration between formulation scientists, clinicians, regulators, industry and public health experts. If navigated thoughtfully, nanoformulated phytochemicals could bring together the evolutionary familiarity and multi-target benefits of plant-derived compounds with the precision and potency of modern drug delivery science, enriching the therapeutic toolbox for obesity management.

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CONCLUSION

Nanoformulated phytochemicals represent a promising frontier in obesity therapy, aiming to transform broadly effective but pharmacokinetically limited natural compounds into potent, targeted interventions. By enhancing solubility, stability, absorption and tissue specificity, nanocarriers amplify the anti-adipogenic, thermogenic, insulin-sensitizing and anti-inflammatory actions of polyphenols, terpenoids, alkaloids and related molecules. Preclinical data consistently show superior metabolic outcomes with nanoencapsulated phytochemicals compared with free forms, and early clinical studies suggest improved pharmacokinetics and organ-protective effects, particularly in metabolic liver disease. Significant challenges remain in ensuring long-term safety, scalable and cost-effective manufacturing, rigorous clinical validation and equitable access. Nevertheless, as nanotechnology, phytochemistry and precision medicine continue to converge, nanoformulated phytochemicals are well positioned to complement lifestyle interventions and conventional drugs, offering individualized, multi-target approaches to the prevention and treatment of obesity and its cardiometabolic complications.

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