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Nanoparticle-Mediated Gut Microbiota Modulation in Obesity: Mechanistic Insights and Therapeutic Prospects

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ABSTRACT

Obesity is a chronic, relapsing metabolic disease in which the gut microbiota plays a central regulatory role. Dysbiosis, impaired barrier integrity and altered microbial metabolites contribute to increased energy harvest, low-grade inflammation, insulin resistance and disruption of gut–brain signaling. Conventional microbiota-directed strategies such as diet, probiotics, prebiotics, antibiotics and fecal microbiota transplantation have shown promise but are limited by poor specificity, variable engraftment and limited spatial and temporal control within the gastrointestinal tract. Nanoparticle-based delivery systems provide new opportunities to precisely modulate microbial communities and their metabolic outputs by protecting labile cargos, targeting specific gut regions and responding to local physicochemical cues. This review summarizes current understanding of microbiota–obesity interactions and outlines how polymeric, lipid, inorganic and hybrid nanoparticles can be engineered for gastrointestinal targeting. We discuss mechanistic pathways through which nano-systems influence microbial ecology, epithelial barrier function and host metabolic signaling, including applications in probiotic, prebiotic, phage, nucleic-acid and engineered-microbe therapies. Finally, we examine safety, ecological and regulatory challenges, and highlight future directions for integrating nanoparticle-mediated microbiota modulation into precision obesity management.

Keywords: Obesity; Gut microbiota; Nanoparticles; Gastrointestinal targeting; Metabolic regulation

INTRODUCTION

The human gut microbiota is a densely populated ecosystem that exerts profound effects on host physiology. In healthy individuals, a diverse community of bacteria, archaea, viruses and fungi contributes to digestion of complex polysaccharides, synthesis of vitamins, development of the immune system and fine-tuning of metabolic homeostasis[1–4]. In obesity, this system frequently shifts toward dysbiosis, a constellation of compositional and functional changes that correlate with increased adiposity, insulin resistance and cardiometabolic risk. Although findings vary between cohorts, many studies report altered Firmicutes to Bacteroidetes ratios, reduced microbial richness and increased abundance of taxa associated with inflammation or heightened energy harvest [5–8].

Several mechanistic pathways link dysbiosis to obesity. First, altered microbial consortia can increase extraction of calories from otherwise indigestible carbohydrates[9–11]. Enhanced fermentation yields short-chain fatty acids such as acetate, propionate and butyrate. At physiological levels these molecules support epithelial health and satiety hormone secretion, but in the context of energy surplus and particular microbial configurations, increased SCFA flux may fuel hepatic de novo lipogenesis and adipose triglyceride storage[10, 11]. Second, high-fat diets and dysbiotic communities can compromise intestinal barrier function. Bacterial products, particularly lipopolysaccharide from Gram-negative species, translocate into the circulation and create a state of metabolic endotoxemia. Low-grade chronic inflammation follows, affecting adipose tissue, liver and pancreas, promoting insulin resistance and disturbing endocrine feedback loops that regulate appetite and energy expenditure[12–14].

Third, the microbiota strongly influences bile acid metabolism. Bacterial enzymes convert primary bile acids into a variety of secondary species that act on receptors such as FXR and TGR5 in the intestine and liver. Dysbiosis can shift bile acid pools toward configurations that favor lipogenesis, impair GLP-1 release or blunt

thermogenic responses. Fourth, microbial metabolites and cell wall components shape gut–brain communication. They modulate enteroendocrine cells that secrete GLP-1, PYY and GIP, and they influence vagal afferents and central reward circuits. When these signals are distorted, satiety is diminished and hedonic feeding can be amplified, contributing to weight gain.

Standard strategies for microbiota modulation in obesity largely operate at a macro scale. Dietary change is fundamental but often difficult to sustain and relatively non-specific about particular taxa[15, 16]. Probiotics can introduce beneficial strains, yet survival through the gastrointestinal tract, colonization and persistence are inconsistent, and effects are often modest[17–19]. Prebiotics enrich for saccharolytic taxa but can be fermented by many organisms, sometimes worsening bloating or discomfort. Antibiotics profoundly reshape communities but at the cost of broad ecological disruption and potential resistance. Fecal microbiota transplantation can transfer an entire microbial ecosystem from lean donors, but safety, donor selection and standardization remain major obstacles[17, 20].

These limitations underscore the need for more precise, controllable microbiota-directed tools. The gastrointestinal tract, however, is a challenging delivery environment. Oral therapeutics must withstand gastric acidity, digestive enzymes, bile salts and peristaltic mixing. They must navigate the viscoelastic mucus layer and reach target sites in the distal small intestine or colon. Small molecules intended to act locally can be absorbed systemically, reducing luminal concentration and introducing off-target effects, whereas hydrophilic biologics may be degraded before reaching their site of action[21, 22].

Nanoparticle-based systems provide a rational framework to overcome many of these obstacles. By confining active agents within sub-micron carriers, it becomes possible to shield them from hostile luminal conditions, to modulate their interaction with mucus and epithelium and to time their release according to environmental cues[23–26]. Polymers and lipids can be selected or combined to produce pH-responsiveness, enzyme-triggered disassembly or redox sensitivity. Coatings can be tailored to promote mucoadhesion and prolonged residence or, conversely, to enhance mucus penetration and close contact with the epithelial surface or microbial biofilms[26].

From a therapeutic perspective, nanocarriers enable three complementary levels of control. Spatially, they can be designed to release cargo predominantly in specific gut segments, such as the terminal ileum or proximal colon, where certain taxa or immune structures concentrate[27–29]. Temporally, controlled-release matrices allow sustained, pulsatile or stimuli-triggered liberation of agents, matching delivery to diurnal feeding patterns or disease activity. Functionally, they allow a combination of multiple payloads within a single construct, such as a narrow-spectrum antibiotic with a prebiotic substrate or a phage cocktail with an anti-inflammatory drug, thereby coordinating direct microbial effects with host-directed modulation[9, 30, 31].

Conceptually, nanoparticle-mediated microbiota modulation reframes the gut community as a metabolically active organ that can be reshaped with organoid-like precision rather than blunt manipulation. Instead of simply eradicating undesirable bacteria or flooding the lumen with exogenous strains, nanotechnology allows targeting of defined metabolic pathways, microenvironments and host–microbe interfaces[32, 33]. Importantly, these approaches can be integrated into broader obesity management strategies that include diet, physical activity, pharmacotherapy, and, in some cases, bariatric procedures.

The remainder of this review examines specific nanoparticle platforms and gastrointestinal targeting strategies, the mechanistic pathways through which nano-systems alter microbial ecology and metabolic signaling, and emerging applications in nano-enabled probiotics, prebiotics, phage and gene-based microbiota therapies. We then consider safety, ecological and regulatory issues, and outline how these technologies may ultimately be positioned within individualized obesity treatment algorithms.

2. Nanoparticle Platforms and Gastrointestinal Targeting Strategies

A diverse set of nanomaterials has been adapted for gastrointestinal delivery with the goal of modulating the gut microbiota while minimizing systemic exposure. Polymeric nanoparticles are among the most widely explored[34, 35]. Biodegradable polymers such as PLGA provide tunable degradation kinetics and can encapsulate hydrophobic or hydrophilic cargos. Natural polymers such as chitosan and alginate offer additional functionalities; chitosan's cationic and mucoadhesive properties promote adhesion to negatively charged mucus and bacterial surfaces, whereas alginate readily forms hydrogels that can be crosslinked and coated to achieve pH-dependent dissolution[36–38].

Lipid-based systems, including liposomes, solid lipid nanoparticles and self-emulsifying drug delivery systems, can improve the solubility and stability of lipophilic agents and certain biologics[27, 39, 40]. Their membrane-like structure can fuse with microbial or epithelial membranes under appropriate conditions, enhancing delivery efficacy. Surface decoration with polyethylene glycol, bile acids or sugars influences interaction with mucus and epithelial cells, as well as colloidal stability in the presence of bile and digestive enzymes.

Inorganic and hybrid nanomaterials such as mesoporous silica, calcium phosphate or layered double hydroxides provide high loading capacity and structural robustness. Mesoporous silica particles, with their tunable pore size, can host antibiotics, quorum-sensing modulators or imaging agents that are released when outer polymer coatings degrade[41, 42]. Calcium phosphate systems dissolve under acidic or chelating conditions, permitting region-specific cargo liberation. To limit potential toxicity, these inorganic cores are typically combined with

biocompatible polymer shells that control surface charge and reactivity. Targeting within the gastrointestinal tract relies on both anatomical and biochemical features. pH gradients are widely used; enteric coatings remain intact in the acidic stomach and proximal small intestine but dissolve in the neutral or slightly alkaline environment of the distal ileum, after which inner layers may respond to the mildly acidic colon[43]. Microbial enzymes such as azoreductases, glycosidases and proteases are more abundant in the colon; linkers or matrices cleavable by these enzymes can couple drug release to bacterial density[44].

The interaction with mucus is another critical design parameter. Mucoadhesive formulations deliberately bind to mucus, increasing residence time and creating depots of drug near the epithelium. In contrast, mucus-penetrating particles are densely coated with hydrophilic, neutrally charged polymers that minimize adhesion, allowing them to diffuse toward the underlying epithelium or into microbial biofilms. Size, charge and hydrophobicity collectively determine whether particles are trapped, glide along or penetrate the mucus network[45].

Finally, more specific targeting strategies are emerging. Lectins or carbohydrate-binding modules can recognize particular glycan patterns on bacterial cell walls or mucosal surfaces. Bacteriophage-derived receptor-binding proteins may, in principle, be used to direct nanocarriers to defined bacterial strains[46]. For host cells, ligands for epithelial transporters or immune receptors can guide particles into Peyer's patches or lamina propria, enabling modulation of host–microbe interactions. Together, these platforms and strategies provide a flexible toolkit for designing nano-systems capable of precise engagement with the gut ecosystem in obesity.

3. Mechanistic Pathways Linking Nano-Enabled Microbiota Modulation to Metabolic Outcomes

Nanoparticles can influence gut microbiota and host metabolism through direct effects on bacterial populations and indirect effects mediated via the intestinal barrier, immune system and enteroendocrine signaling[23, 36]. Direct microbial targeting includes delivery of antimicrobial agents, metabolic modulators and signaling disruptors in a highly localized and controlled fashion. Encapsulation of narrow-spectrum antibiotics or antimicrobial peptides allows selective suppression of obesogenic taxa while sparing beneficial species. Because release is confined to the lumen and systemic absorption is minimized, off-target toxicity and resistance selection pressure outside the gut may be reduced[47]. Nanocarriers can also deliver molecules that interfere with quorum sensing and biofilm formation. By disrupting bacterial communication networks, these agents can attenuate virulence factor expression and alter competitive dynamics within microbial communities. In some designs, particles contain alternative carbon sources or nano-structured prebiotics that are preferentially metabolized by health-associated taxa, promoting their expansion and shifting community structure without outright bacterial killing[47].

Indirect mechanisms are equally important. Many nano-formulations target the epithelial barrier and mucosal immune system. Delivery of antioxidants, anti-inflammatory drugs or tight junction modulators to the epithelium can restore barrier integrity, reduce translocation of lipopolysaccharide and other microbial products and thereby lower systemic inflammation[48]. As intestinal permeability improves, the inflammatory milieu that supports pathobionts is diminished, favoring a shift toward more benign or beneficial communities[48].

Immunomodulatory nanoparticles can be designed to target dendritic cells, macrophages or regulatory T cells in gut-associated lymphoid tissue[49–51]. Local delivery of tolerogenic cytokines or immunoregulatory small molecules can recalibrate mucosal immunity in a manner that changes the selective pressures experienced by resident microbes. Such interventions may help break self-sustaining cycles in which dysbiosis and inflammation reinforce one another, a pattern commonly observed in obesity and metabolic syndrome[50]. These microbial and barrier-level changes feed directly into systemic metabolic regulation. Reduced endotoxemia decreases inflammatory activation of adipose tissue macrophages and hepatic Kupffer cells, improving insulin signaling in adipose tissue and liver[48]. Altered microbial composition and function modify short-chain fatty acid profiles, bile acid transformations and production of other metabolites such as indoles and branched-chain fatty acids. These metabolites act on receptors in the intestine, liver, adipose tissue and brain, influencing gluconeogenesis, lipogenesis, energy expenditure and satiety hormone secretion[48].

Some nanoparticle designs incorporate host-directed metabolic agents alongside microbiota modulators. For example, a single system might combine a prebiotic substrate that enriches SCFA producers with a GLP-1 analogue in a controlled-release matrix that aligns hormonal and microbial signals[48]. Through such multi-layered mechanisms, nanoparticle-mediated microbiota modulation has the potential to reprogram host metabolism at several interconnected levels, offering a richer palette of interventions than conventional systemic drugs alone.

4. Nano-Delivery of Probiotics, Prebiotics and Synbiotics in Obesity

Probiotics, prebiotics and synbiotics are established approaches to microbiota modulation, yet their efficacy in obesity has been inconsistent, in part because of limitations in delivery, survival and specificity. Nanotechnology offers ways to improve the performance of these interventions[17].

Probiotic bacteria must survive passage through gastric acid, bile salts and digestive enzymes, then successfully colonize or transiently persist in competitive microbial communities[17, 52]. Encapsulation of live bacteria within protective matrices such as alginate, chitosan or lipid bilayers can substantially enhance survival. These matrices can be further coated with pH-responsive polymers that remain intact in the stomach and dissolve in

the small intestine or colon, releasing viable cells near their intended target region. Incorporation of adhesion-promoting molecules, such as mucin-mimetic glycans, onto capsule surfaces can facilitate attachment to the mucus layer and promote microcolony formation[17]. Prebiotics traditionally consist of fermentable fibers or oligosaccharides that broadly stimulate saccharolytic taxa. Assembled into nano-structured systems, prebiotics can be delivered with greater spatial and temporal control. Embedding prebiotic molecules in biodegradable nanoparticles or nanogels allows slow, sustained release along the colon, maintaining substrate availability where key fermenters reside[53]. Presenting specific carbohydrate motifs on particle surfaces may favor uptake by targeted bacteria that possess matching binding proteins, thereby increasing selectivity of microbial stimulation.

Synbiotic formulations combine probiotics and prebiotics, ideally pairing a specific strain with its preferred substrate[54]. Nano-systems are well-suited for such combinations. Multi-layered particles can encapsulate bacteria in an inner compartment while incorporating prebiotic substrates in outer layers that are released first, priming the environment for the probiotic. Alternatively, both components can be co-encapsulated, ensuring that as the carrier disintegrates the bacteria and their tailored food source are delivered simultaneously. This spatial and temporal coordination may improve engraftment and functional impact of the administered strains[54]. Nanoparticle-based synbiotics can also be co-loaded with adjunctive agents that promote a favorable niche, including antioxidants, mild anti-inflammatory drugs or bacteriophages that transiently suppress competing pathobionts. For obesity, rational selection of strains and substrates focuses on promoting taxa linked to improved insulin sensitivity, reduced adipose inflammation or enhanced GLP-1 and PYY release[54]. Engineered probiotic strains that secrete bioactive molecules such as SCFAs, conjugated linoleic acid or satiety peptides can be similarly protected and delivered via nano-encapsulation.

Key challenges include maintaining viability and functionality of bacteria during manufacturing and storage, scaling production while preserving consistent particle properties and demonstrating reproducible colonization and metabolic outcomes in heterogeneous human populations[55]. Nevertheless, nano-enabled probiotics, prebiotics and synbiotics represent a practical near-term application of nanoparticle technology to microbiota-targeted obesity therapy.

5. Nucleic Acid, Phage and Engineered-Microbe Approaches Enabled by Nanotechnology

Beyond classical probiotic and prebiotic strategies, more targeted approaches aim to edit microbial functions, selectively remove deleterious taxa or introduce engineered microbes with defined metabolic activities. Nanotechnology is central to making these concepts feasible in the complex gastrointestinal environment.

Delivery of nucleic acids to bacteria in situ is technically challenging because DNA and RNA are rapidly degraded and poorly taken up by most species. Nanoparticles composed of cationic polymers or lipids can condense nucleic acids into stable complexes and facilitate association with bacterial cell envelopes through electrostatic interactions or ligand binding[56]. Once internalized, plasmids or CRISPR-based constructs can disrupt genes involved in lipopolysaccharide synthesis, bile salt hydrolase activity, production of inflammatory metabolites or other pathways linked to obesity. Alternatively, they can install new metabolic functions that enhance SCFA production or detoxify harmful compounds. Although these approaches are at an early stage and face hurdles related to host range and horizontal gene transfer, they illustrate the potential for precision microbiome editing[57]. Bacteriophage therapy offers a more immediately tractable method for sculpting microbiota composition. Phages naturally infect specific bacterial strains and can reduce targeted populations without broadly disturbing other taxa. Nanoparticles can stabilize phages against gastric acid and bile, encapsulating them within polymeric or lipid matrices that release infectious particles in the ileum or colon[57]. By combining phages directed against pro-inflammatory or obesogenic bacteria with probiotics designed to occupy the vacated niche, it may be possible to reconfigure microbial communities toward more metabolically favorable states.

Engineered microbes, including genetically modified probiotics, introduce yet another layer of sophistication. These organisms can be programmed with synthetic circuits that sense environmental cues such as nutrients, inflammatory markers or bile acids and respond by producing therapeutic outputs[58]. For obesity, engineered strains might secrete satiety peptides, consume excess luminal lipids, modulate bile acid composition or produce anti-inflammatory metabolites. Nano-encapsulation enhances survival and allows spatial targeting of these engineered organisms, while nanoparticles can also deliver small-molecule inducers that control their activity in vivo[58].

These advanced approaches raise important safety questions. Off-target editing of non-intended bacteria, horizontal transfer of engineered genes and evolution of phage resistance are plausible risks. Robust biocontainment mechanisms, including kill switches and dependence on non-natural nutrients, are being developed to mitigate escape of engineered microbes[59]. Regulatory frameworks for such interventions are still emerging and must account for both the biological and nanomaterial components. Nonetheless, the convergence of nucleic-acid tools, phage specificity and nano-enabled delivery holds considerable potential for highly precise microbiota modulation in obesity.

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6. Safety, Ecological Effects and Translational Barriers

Effective translation of nanoparticle-mediated microbiota modulation into obesity therapy requires careful evaluation of safety at multiple levels: host tissues, microbial ecosystems and the broader environment. The gut microbiota is a complex and resilient community, but excessive or poorly targeted interventions may cause lasting dysbiosis[8, 32]. Nanoparticles that release broad-spectrum antimicrobials, metal ions or strongly cationic polymers risk non-specific bacterial killing, reduction in diversity and selection for resistant strains. Chronic or repeated exposure may exacerbate these effects. Host–particle interactions are another major concern. Although many oral nano-systems are designed to act locally, some fraction may cross the epithelium through transcytosis or paracellular leakage, particularly in individuals with increased intestinal permeability[60]. Once in the systemic circulation, nanoparticles may accumulate in the liver, spleen or lymph nodes, where they could trigger immune activation, complement activation or tissue toxicity depending on their composition and surface characteristics. Even within the gut, nanoparticles could interfere with mucus rheology, epithelial turnover or immune cell function in unintended ways[60]. Advanced biological cargos such as CRISPR systems, phages and engineered microbes introduce further layers of risk. Off-target gene editing in commensal bacteria might alter ecological networks in unpredictable ways, and horizontal gene transfer could propagate engineered traits beyond their intended recipients[61]. Phages can mediate the transduction of virulence or resistance genes even as they kill target bacteria. Engineered organisms may evolve or escape biocontainment mechanisms. These possibilities demand rigorous preclinical assessment in relevant models, including long-term ecological studies and monitoring of resistance and gene flow[61].

From a regulatory perspective, nanoparticle-based microbiota therapies often straddle multiple categories, combining drugs, biologics and devices. Agencies will require detailed characterization of particle size, charge, composition, cargo loading, release profiles and degradation products, as well as standardized assays linking these attributes to in vivo behavior. For live biotherapeutics and gene-based approaches, extended follow-up and post-marketing surveillance will likely be mandated[62, 63]. Manufacturing and cost considerations also shape translational feasibility. Producing complex nanostructures at scale with tight control over critical quality attributes is technically demanding. Stability during storage and distribution, particularly for formulations containing live microbes or phages, must be assured. The resulting therapies may initially be expensive, raising concerns about equitable access in populations where the obesity burden is high[64].

Ethical and societal questions accompany these technical issues. Manipulating the microbiota with sophisticated nano-biotechnologies may provoke public concern about unnatural alteration of an intimate aspect of human biology. Transparent communication, informed consent and attention to privacy around microbiome data will be essential. Addressing these safety and translational barriers through careful design, regulation and stakeholder engagement is critical if nanoparticle-mediated microbiota modulation is to become a credible option in obesity management.

7. Future Directions and Therapeutic Positioning in Obesity Care

Looking ahead, nanoparticle-mediated modulation of the gut microbiota is poised to integrate increasingly with precision medicine approaches to obesity. High-throughput sequencing, metabolomics and computational modeling are revealing microbiome signatures associated with distinct metabolic phenotypes, such as high endotoxin load, impaired bile acid signaling or reduced SCFA production[6]. These signatures can guide selection of nano-therapies, with phage cocktails, nano-prebiotics or synbiotic systems tailored to correct specific functional deficits rather than applying generic microbiota interventions. Theranostic nano-platforms are likely to assume an important role. Nanoparticles that both deliver modulatory agents and carry imaging or sensing components can report on their own distribution and on functional changes in the microbiota[65, 66]. For example, particles that release a contrast agent upon degradation by target bacterial enzymes could provide non-invasive readouts of colonization or metabolic activity. Data from such systems can feed back into adaptive dosing, where treatment intensity is titrated according to measured ecological and metabolic responses.

Combination strategies with existing obesity therapies will be crucial. Microbiota-directed nano-systems may synergize with GLP-1 receptor agonists, SGLT2 inhibitors or post-bariatric surgery physiology by stabilizing beneficial microbial configurations, reducing endotoxemia and supporting enhanced incretin responses[67, 68]. Co-formulation of conventional drugs and microbiota modulators in a single nanoparticle can coordinate their spatial and temporal delivery, potentially improving tolerability and efficacy. At the same time, practical considerations will favor relatively simple, robust nano-designs in early clinical adoption. Enteric-coated nano-prebiotics, stabilized phage formulations and encapsulated synbiotics with well-characterized compositions may reach the clinic sooner than highly complex logic-gated or CRISPR-based systems[61, 69]. Demonstrating reliable, durable benefits in weight, insulin sensitivity, and inflammatory markers with such platforms will build confidence in the broader concept of nano-enabled microbiota therapy.

Preventive and early-intervention applications are another promising avenue. In individuals at high risk for obesity or metabolic syndrome, modest microbiota steering using gentle nano-prebiotic or synbiotic formulations may help maintain a metabolically healthy ecosystem, particularly when combined with dietary and lifestyle interventions. Longitudinal studies will be needed to evaluate the durability of effects and the potential for reducing disease incidence.

Ultimately, nanoparticle-mediated microbiota modulation is best viewed as one component of a multifaceted strategy for obesity management. It is unlikely to replace the need for diet, physical activity and systemic pharmacotherapy, but it may fill important gaps by targeting microbiome-mediated mechanisms that are difficult to reach otherwise. If safety, scalability and equity challenges can be addressed, such technologies could help shift obesity treatment toward more individualized, mechanism-based and sustainable approaches.

CONCLUSION

Nanoparticle-mediated modulation of the gut microbiota offers a compelling new dimension to obesity therapeutics. By protecting and precisely delivering microbiota-directed agents to defined intestinal niches, nano-systems can reshape microbial communities, reinforce barrier integrity and recalibrate host–microbe metabolic signaling. Mechanistic insights highlight roles for endotoxemia, short-chain fatty acids, bile acids and gut–brain communication as key nodes that can be targeted with polymeric, lipid, inorganic and hybrid particles carrying probiotics, prebiotics, phages, nucleic acids or engineered microbes. Significant challenges remain, including ensuring ecological and host safety, meeting demanding regulatory standards, developing scalable manufacturing and securing equitable access. As tools for microbiome profiling and metabolic phenotyping improve, and as early clinical experience accumulates, nanoparticle-enabled microbiota modulation may evolve into a powerful adjunct to lifestyle measures, systemic drugs and bariatric procedures, contributing to more precise and durable control of obesity and its metabolic complications.

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