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The Role of Natural Product-Derived Nanoparticles in Modulating Gut Microbiota in Obesity and Diabetes

Mugo Moses H.

School of Natural and Applied Sciences Kampala International University Uganda

ABSTRACT

Obesity and diabetes are major global health challenges with complex etiologies involving genetic, environmental, and metabolic factors. Recent research highlights the gut microbiota as a key player in metabolic regulation, and its dysbiosis is closely associated with the development of both obesity and diabetes. Natural products have long been used for their therapeutic properties, and recent advancements in nanotechnology have enabled the development of natural product-derived nanoparticles (NP-NPs) with enhanced bioavailability, stability, and targeted delivery. These NP-NPs exhibit remarkable potential in modulating gut microbiota composition and function, thereby offering promising therapeutic avenues for managing obesity and diabetes. This review explores the current state of knowledge on the role of NP-NPs in reshaping the gut microbiota, elucidating their mechanisms of action, preclinical and clinical evidence, and future perspectives in personalized medicine and metabolic disease treatment. The integration of nanotechnology with natural products offers a novel and synergistic strategy to combat metabolic disorders by targeting the gut microbiota–host metabolism axis.

Keywords: Natural product-derived nanoparticles; gut microbiota; obesity; diabetes; nanomedicine; metabolic disorders; microbiome modulation

INTRODUCTION

The increasing prevalence of obesity and type 2 diabetes mellitus (T2DM) continues to pose significant public health challenges, placing a considerable burden on global healthcare systems[1–4]. These metabolic disorders are not only linked to genetic and lifestyle factors but are also closely associated with the gut microbiota, a diverse and dynamic community of trillions of microorganisms inhabiting the gastrointestinal tract[5, 6]. Emerging evidence has underscored the critical role of the gut microbiome in modulating host metabolism, immune function, and energy homeostasis[7–9]. Dysbiosis, a disruption in the normal composition and function of gut microbiota, has been increasingly recognized as a major contributing factor to metabolic dysfunctions[9–11]. This imbalance can trigger a cascade of pathological processes, including chronic low-grade inflammation, insulin resistance, and lipid abnormalities, all of which are hallmarks of obesity and T2DM. As a result, strategies targeting the gut microbiome have gained traction as potential therapeutic approaches to mitigate the onset and progression of these metabolic syndromes[12, 13].

Natural products, particularly plant-derived compounds such as polyphenols, alkaloids, flavonoids, and terpenoids, have been widely explored for their beneficial effects in preventing and managing metabolic diseases[14, 15]. These bioactive molecules exert a variety of pharmacological effects, including antioxidant, anti-inflammatory, and antidiabetic actions, and have been shown to influence gut microbiota composition and function positively[16–19]. For instance, polyphenols can stimulate the growth of beneficial bacteria such as *Bifidobacterium* and *Lactobacillus*, while inhibiting pathogenic strains[20]. However, a major challenge limiting the clinical application of these compounds lies in their poor bioavailability, rapid degradation in the gastrointestinal tract, and limited systemic absorption. This results in insufficient concentrations reaching target tissues or interacting effectively with gut microbial populations[21]. Therefore, despite their promising therapeutic potential, the practical use of many natural products is hindered by these pharmacokinetic limitations.

To address these challenges, nanotechnology has emerged as a powerful tool for enhancing the efficacy and stability of natural compounds[22–25]. The development of natural product-derived nanoparticles (NP-NPs) represents a significant advancement in the delivery of bioactive agents for metabolic disease therapy[26]. These nanoparticles can encapsulate or be synthesized from natural products, thereby enhancing their solubility, protecting them from enzymatic degradation, and enabling controlled or targeted release within the gastrointestinal environment. NP-NPs can be engineered to interact directly with gut microbiota or intestinal

epithelial cells, modulating microbial balance and improving metabolic outcomes[23, 27, 28]. For example, curcumin-loaded nanoparticles have demonstrated enhanced anti-inflammatory and antidiabetic effects in animal models compared to free curcumin[29, 30]. Similarly, resveratrol and quercetin, when delivered via nanoformulations, exhibit improved bioavailability and greater efficacy in modulating glucose and lipid metabolism. As the field progresses, integrating nanotechnology with natural product pharmacology holds significant promise for developing next-generation therapeutics aimed at managing obesity, T2DM, and related metabolic disorders through precise gut microbiota modulation.

Gut Microbiota and Its Role in Metabolic Disorders

The human gastrointestinal tract harbors a complex and dynamic population of microorganisms collectively referred to as the gut microbiota[20, 31, 32]. This microbial ecosystem is composed of bacteria, viruses, fungi, archaea, and protozoa, with bacteria being the most predominant. Among these, the most abundant bacterial phyla are Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria[33]. These microorganisms establish a symbiotic relationship with the host, playing a crucial role in various physiological processes. The gut microbiota contributes significantly to the digestion and fermentation of indigestible dietary components, production of short-chain fatty acids (SCFAs), synthesis of essential vitamins such as B and K, and regulation of the immune system. It also plays a critical role in maintaining the integrity of the intestinal barrier, thereby preventing the translocation of pathogens and toxins into systemic circulation[31, 34]. Recent research has increasingly implicated the gut microbiota in the pathogenesis of metabolic disorders, including obesity, type 2 diabetes mellitus (T2DM), and metabolic syndrome. Disruptions in the composition and function of gut microbiota—referred to as dysbiosis—have been linked to altered energy homeostasis, systemic inflammation, insulin resistance, and lipid dysregulation. Thus, understanding the interplay between the gut microbiota and host metabolism is essential for developing targeted microbiome-based therapies for metabolic diseases.

Composition and Function of Gut Microbiota

The gut microbiota is composed of trillions of microbial cells, with bacteria representing the majority. These microbes are predominantly classified into four major phyla: Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria. Firmicutes and Bacteroidetes alone constitute over 90% of the gut bacterial population[35, 36]. The composition of these microbial communities is highly individualized, influenced by factors such as diet, age, genetics, environment, and antibiotic use. Despite individual variability, a healthy gut microbiota maintains a balanced microbial diversity, which is critical for optimal host physiological function[37]. Functionally, the gut microbiota acts almost like a separate organ. It ferments dietary fibers to produce SCFAs, including acetate, propionate, and butyrate, which serve as energy sources for colonic epithelial cells and play key roles in regulating host metabolism and immune responses. The microbiota also assists in bile acid metabolism, cholesterol homeostasis, and the detoxification of xenobiotics[37]. Furthermore, it educates and modulates the host immune system, helping to distinguish between harmless antigens and harmful pathogens. Additionally, the microbiota influences the development of the gut-associated lymphoid tissue (GALT) and helps maintain mucosal immunity. Disruption in these microbial functions can predispose individuals to various metabolic disorders, reinforcing the significance of maintaining a healthy and diverse gut microbiota for metabolic health[38].

Gut Dysbiosis in Obesity and Diabetes

Gut dysbiosis refers to an imbalance in the composition and function of the gut microbiota, often characterized by reduced microbial diversity and a shift toward pathogenic microbial profiles[9, 33, 39]. In metabolic disorders such as obesity and type 2 diabetes mellitus (T2DM), gut dysbiosis is a recurring finding and has been extensively studied for its pathophysiological implications[40]. One of the most consistent microbial alterations observed in obese individuals is an increased Firmicutes to Bacteroidetes (F/B) ratio. This shift is thought to enhance the capacity of the microbiota to extract energy from the diet, thereby promoting fat storage and weight gain[40]. Moreover, obesity and T2DM are associated with a higher abundance of pro-inflammatory bacteria such as *Enterobacteriaceae* and *Ruminococcus gnavus*, and a decreased presence of beneficial microbes like *Akkermansia muciniphila* and *Faecalibacterium prausnitzii*[41]. These changes are accompanied by increased intestinal permeability, allowing endotoxins such as lipopolysaccharides (LPS) to enter the bloodstream, triggering low-grade systemic inflammation, an important factor in insulin resistance and metabolic dysfunction. Dysbiosis also impairs the production of SCFAs and disrupts bile acid signaling, further contributing to glucose intolerance and lipid abnormalities[41]. Understanding these microbial shifts offers potential therapeutic targets, such as prebiotics, probiotics, and fecal microbiota transplantation, for restoring microbial balance and improving metabolic outcomes in affected individuals.

Natural Products and Gut Microbiota Modulation

Natural products, particularly those derived from plants, have garnered considerable interest for their prebiotic-like properties, which influence the gut microbiota in ways that promote health[15]. These compounds can selectively stimulate the growth of beneficial microorganisms such as *Bifidobacterium* and *Lactobacillus*, while suppressing pathogenic strains[42]. Polyphenols like curcumin and resveratrol, for example, not only alter the composition of the microbiota but also modulate its metabolic functions, leading to the production of short-chain fatty acids (SCFAs) that enhance gut health[42]. Flavonoids such as quercetin and catechins improve gut barrier function and prevent dysbiosis by supporting microbial diversity and maintaining mucosal integrity.

Additionally, alkaloids and terpenoids exert antimicrobial effects against harmful bacteria and help balance microbial communities[43]. These mechanisms collectively contribute to reduced inflammation, improved immune modulation, and better metabolic regulation, positioning natural products as promising agents in gut microbiome-targeted therapies. Despite these promising effects, the therapeutic efficacy of natural products is significantly hindered by several pharmacokinetic limitations. Many bioactive compounds suffer from poor bioavailability due to enzymatic degradation in the gastrointestinal tract and low solubility, leading to reduced concentrations reaching the colon, where most microbial interactions occur[43]. Furthermore, rapid metabolism and clearance from systemic circulation limit their biological activity duration, compromising their capacity to exert sustained prebiotic effects. For instance, polyphenols may be extensively metabolized before they reach target microbial populations, thus diminishing their influence on microbiota modulation. Such pharmacokinetic challenges underscore the importance of enhancing delivery methods, such as encapsulation technologies, co-administration with absorption enhancers, or structural modification of compounds to improve their stability and residence time in the gut environment. Without addressing these issues, the clinical translation of natural products as microbiota-targeted therapeutics remains constrained[43]. To harness the full potential of natural products as prebiotic-like agents, innovative strategies must be employed to overcome bioavailability and stability issues. Novel delivery platforms, including nanoparticle-based carriers and biodegradable polymer systems, offer promising solutions for protecting these compounds from premature degradation and ensuring targeted release in the colon. Moreover, fermentation of natural products by commensal bacteria may yield more bioactive metabolites with enhanced microbiota-modulating effects[44]. Future research should also focus on identifying synergistic combinations of natural products and conventional prebiotics to amplify health benefits. Precision nutrition approaches, supported by microbiome profiling, can help tailor interventions based on individual microbial signatures, increasing therapeutic efficacy[44]. Ultimately, integrating natural product-based strategies with advanced biotechnological and pharmaceutical innovations may pave the way for the development of next-generation prebiotics capable of modulating gut microbiota with improved consistency and clinical outcomes.

Nanotechnology in Natural Product Delivery

Nanoparticle Systems for Natural Products

Nanoparticle-based delivery systems have revolutionized the application of natural products by significantly improving their bioavailability, solubility, and stability. Many bioactive compounds derived from natural sources suffer from poor physicochemical properties such as low aqueous solubility, chemical instability, and rapid degradation in the gastrointestinal tract[44, 45]. To address these challenges, various nanocarrier systems have been developed. Polymeric nanoparticles, such as those made from chitosan or poly(lactic-co-glycolic acid) (PLGA), provide biocompatibility and controlled drug release profiles. Lipid-based nanoparticles, including liposomes and solid lipid nanoparticles, encapsulate hydrophobic compounds effectively and protect them from enzymatic degradation[26, 46, 47]. Metallic nanoparticles, like gold and silver, offer unique optical and electronic properties useful in both therapeutic and diagnostic applications. Biogenic nanoparticles synthesized using plant extracts represent an eco-friendly alternative with added bioactivity. Collectively, these nanoparticle systems offer a promising platform for the efficient delivery of natural products, particularly in addressing complex diseases where conventional drug delivery fails.

Advantages of NP-NPs

Nanoformulated natural products (NP-NPs) offer a multitude of advantages over their unformulated counterparts, particularly in enhancing therapeutic outcomes and ensuring precise delivery. One of the most significant benefits is improved bioavailability[48], which ensures that higher concentrations of bioactive compounds reach the target site. NP-NPs also offer improved stability, preventing premature degradation of sensitive phytochemicals in the gastrointestinal tract. These systems enable controlled and sustained release, minimizing the frequency of administration and maintaining therapeutic concentrations over longer periods[49]. Moreover, NP-NPs can be engineered for targeted delivery, enabling the compounds to act precisely at the site of disease or within specific cellular compartments. Importantly, these nanoformulations protect natural products from gastric acidity and enzymatic degradation, thereby improving oral efficacy. Additionally, NP-NPs can be tailored to deliver bioactives directly to the gut microbiota, a key site of action in metabolic disorders. Altogether, these advantages make NP-NPs a promising strategy in natural product-based therapeutics[49].

Preclinical Evidence

Preclinical studies have demonstrated the potential of nanoformulated natural products (NP-NPs) in modulating gut microbiota and ameliorating obesity and diabetes-related metabolic disturbances[50]. For example, curcumin-loaded nanoparticles have shown promising effects in obese mice by improving insulin sensitivity, reducing systemic inflammation, and restoring gut microbial diversity. Similarly, nanoformulations of resveratrol have led to a significant increase in *Akkermansia muciniphila*, a beneficial bacterium known to strengthen the intestinal barrier and enhance metabolic health[51]. Berberine nanoparticles have also shown efficacy in diet-induced obesity models by reshaping the gut microbiome composition, reducing pro-inflammatory bacteria, and decreasing body weight gain and systemic inflammation[52]. These studies highlight that NP-NPs not only improve the pharmacokinetic profiles of natural compounds but also potentiate

their therapeutic effects via gut microbiota modulation. The ability to influence microbial ecology and host metabolism simultaneously positions NP-NPs as a novel strategy in the prevention and treatment of metabolic diseases.

Mechanisms of Action

The therapeutic efficacy of nanoformulated natural products (NP-NPs) in metabolic disorders such as obesity and diabetes is largely mediated through their multifaceted interactions with the gut microbiota[53]. One key mechanism involves microbiota-targeted delivery, where NP-NPs are engineered to resist upper gastrointestinal degradation and release their payload directly in the colon, thereby acting on specific microbial niches. Additionally, many NP-NPs exert prebiotic effects by promoting the growth of beneficial microbial species such as *Bifidobacterium* and *Lactobacillus*, which contribute to improved metabolic outcomes. These formulations also possess anti-inflammatory properties, helping to neutralize microbial endotoxins like lipopolysaccharides and reducing local and systemic inflammation[54]. Moreover, NP-NPs enhance gut barrier integrity by strengthening tight junctions between epithelial cells, thus preventing the translocation of harmful substances into circulation—a process known as metabolic endotoxemia. These mechanisms collectively underscore the therapeutic potential of NP-NPs as targeted tools to modulate the gut microbiome and improve host metabolic health.

Human Studies

Clinical evidence regarding the use of nanoparticle-formulated polyphenols is still in its early stages, but emerging trials show promising results. Initial studies suggest that these advanced formulations may significantly improve glycemic control in patients by enhancing the bioavailability and targeted delivery of polyphenols, which are known for their antioxidant and anti-inflammatory properties[55, 56]. Additionally, there is evidence indicating a positive modulation of the gut microbiota, which plays a critical role in metabolic health and glucose regulation. Despite these encouraging findings, important challenges remain. The safety profile of nanoparticle-formulated polyphenols needs a comprehensive assessment, especially concerning potential toxicity and immune responses over prolonged use[56, 57]. Furthermore, the feasibility of large-scale production and cost-effectiveness must be addressed to ensure accessibility. Lastly, long-term clinical outcomes and possible side effects are yet to be fully understood, making further rigorous and well-designed studies essential before these formulations can be widely recommended in clinical practice.

Challenges and Future Directions

Safety and Regulatory Issues: The safety profile of nanoparticles (NPs), particularly metallic or non-biodegradable types, remains a significant concern in biomedical applications. These materials may accumulate in tissues, triggering toxicity through oxidative stress, inflammation, or unintended interactions with biological systems. Their persistence and potential to cross biological barriers necessitate rigorous toxicological assessments to ensure patient safety. Furthermore, natural product-based nanoformulations face unique regulatory challenges. Unlike conventional drugs, these formulations often combine complex bioactive compounds with nanoscale carriers, complicating standardization, quality control, and reproducibility. Regulatory agencies require comprehensive data on physicochemical characteristics, pharmacokinetics, and long-term effects before approval. The lack of standardized guidelines for nanomedicines, coupled with varying national regulations, further delays clinical translation. Addressing these issues demands collaborative efforts to establish clear frameworks and robust testing protocols, balancing innovation with patient safety and facilitating smoother pathways for regulatory approval.

Personalized Therapy: Personalized therapy leveraging nanoparticles (NPs) must account for the inherent variability in individual microbiomes, which profoundly influence therapeutic outcomes. Microbiome composition varies widely across populations and can modulate drug metabolism, immune responses, and disease susceptibility. This variability means that a one-size-fits-all nanoformulation may yield inconsistent results or adverse effects. Therefore, tailored NP-based interventions that consider each patient's unique microbiome profile are essential to maximize efficacy and minimize risks. The integration of multi-omics technologies—genomics, transcriptomics, proteomics, and metabolomics—offers a comprehensive understanding of individual biological contexts. By analyzing this rich data, clinicians and researchers can design personalized NP therapies that precisely target dysregulated pathways or microbial populations. This systems biology approach not only refines patient stratification but also paves the way for adaptive, dynamic nanoformulations responsive to evolving disease states, ultimately advancing precision medicine.

Translational Research: Translational research in nanoparticle-based therapies faces the critical challenge of bridging the gap between promising preclinical findings and effective clinical applications. While numerous NP formulations demonstrate potent effects in vitro or in animal models, many fail to replicate these results in humans due to biological complexity and variability. Addressing this requires the development of advanced nano-delivery systems capable of precise, context-sensitive action. Smart nanoparticles that respond dynamically to specific microbial or metabolic cues represent a frontier in this field. These systems can release therapeutic agents in response to localized signals such as pH changes, enzyme activity, or microbial metabolites, enhancing specificity and reducing side effects. Furthermore, close collaboration between basic scientists, clinicians, and regulatory bodies is essential to streamline the translation process. Rigorous clinical trial design,

real-time monitoring, and adaptive strategies will accelerate the integration of nanoformulations into standard care, improving patient outcomes through innovative, responsive nanomedicine platforms.

CONCLUSION

Natural product-derived nanoparticles represent a frontier in metabolic disease management by synergizing traditional medicine with modern nanotechnology. Their ability to modulate gut microbiota offers a promising strategy to combat obesity and diabetes through targeted, microbiota-centric therapies. Further interdisciplinary research is essential to fully harness their therapeutic potential and translate findings into clinical success.

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