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Smart Nano-Delivery of Natural Compounds for Targeted Modulation of Gut Microbiota in Diabesity-Associated Cancer

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ABSTRACT

The global rise in diabesity, a sydemic of type 2 diabetes and obesity has been strongly linked to an increased risk of various cancers, collectively referred to as diabesity-associated cancers. Mounting evidence underscores the pivotal role of gut microbiota dysbiosis in mediating the inflammatory, metabolic, and oncogenic processes underpinning this comorbidity. Natural bioactive compounds, particularly polyphenols, alkaloids, and terpenoids, possess multifaceted therapeutic properties, including antioxidative, anti-inflammatory, anti-diabetic, and anticancer activities. However, their clinical translation is often hindered by poor bioavailability and non-specific targeting. Recent advancements in smart nanotechnology offer innovative strategies for overcoming these limitations by enabling controlled, site-specific delivery and enhanced stability of these compounds. This review explores the intersection of gut microbiota modulation, diabesity-driven carcinogenesis, and nanocarrier-based delivery of natural compounds. We examine various types of smart nanocarriers including polymeric nanoparticles, lipid-based nanocarriers, and stimuli-responsive systems and their potential in precision targeting of dysbiotic gut environments. The review further discusses challenges and future directions in developing gut microbiota-responsive nano delivery systems as next-generation interventions for diabesity-associated cancers.

Keywords: Diabesity, Gut Microbiota, Smart Nanocarriers, Natural Compounds, Cancer Therapy

INTRODUCTION

The global health landscape is increasingly burdened by the twin epidemics of obesity and type 2 diabetes mellitus (T2DM), a comorbid condition collectively referred to as diabesity[1, 2]. This term describes the pathophysiological interconnection between obesity and T2DM, which often coexist and share overlapping molecular and cellular mechanisms[3–5]. These include chronic low-grade inflammation, insulin resistance, mitochondrial dysfunction, dysregulated lipid metabolism, and heightened oxidative stress[6–8]. The growing prevalence of diabesity poses significant clinical and socioeconomic challenges worldwide, exacerbated by sedentary lifestyles, unhealthy diets, and genetic predispositions[9, 10].

Beyond the well-documented cardiovascular and metabolic complications of diabesity, there is a growing body of evidence linking this condition to an increased risk of several types of cancer. These include, but are not limited to, colorectal, breast, pancreatic, endometrial, and liver cancers, collectively referred to as *diabesity-associated cancers*[7, 11–13]. The association between diabesity and carcinogenesis is multifactorial and involves complex interactions between systemic metabolic derangements and local tissue environments. Key contributors to this oncogenic milieu include elevated insulin and insulin-like growth factor (IGF) levels, chronic inflammation, dyslipidemia, and alterations in adipokine signaling[14–16]. These factors collectively enhance cellular proliferation, inhibit apoptosis, and promote tumor growth and metastasis.

In recent years, the gut microbiota, the complex and dynamic community of trillions of microorganisms inhabiting the gastrointestinal tract has gained considerable attention as a critical regulator of metabolic health and disease[17–19]. This microbial ecosystem plays an essential role in nutrient absorption, immune system development, maintenance of gut barrier integrity, and modulation of inflammatory responses[19, 20]. In the context of diabesity, the gut microbiota undergoes significant alterations in composition and function, a state referred to as dysbiosis. Dysbiosis is characterized by a loss of microbial diversity, enrichment of pathogenic bacteria, and reduction in beneficial species such as *Bifidobacterium* and *Lactobacillus*[17].

Importantly, dysbiosis is not only implicated in the development of diabesity but is also increasingly recognized as a key player in the etiopathogenesis of cancer[21]. Mechanistically, an imbalanced gut microbiota can disrupt intestinal barrier integrity, leading to increased intestinal permeability (commonly known as “leaky gut”) and translocation of bacterial endotoxins such as lipopolysaccharide (LPS) into systemic circulation[19, 22]. This endotoxemia triggers chronic inflammation and immune dysregulation, creating a pro-carcinogenic environment. Additionally, certain microbial metabolites, such as secondary bile acids and trimethylamine-N-oxide (TMAO), have been shown to possess genotoxic and tumor-promoting properties, further establishing the link between gut microbiota, diabesity, and cancer[17, 23, 24].

Given the central role of the gut microbiota in modulating host metabolism and carcinogenesis, strategies aimed at modulating microbial composition and activity have garnered significant interest. Among these, the use of natural compounds derived from medicinal plants, marine organisms, and dietary sources has emerged as a promising avenue[25]. These bioactive compounds including polyphenols, flavonoids, alkaloids, terpenoids, and polysaccharides exhibit a wide range of biological activities such as anti-inflammatory, antioxidant, anti-diabetic, and anti-cancer effects. Importantly, many of these natural agents exert their effects, at least in part, through modulation of the gut microbiota, restoring microbial balance and enhancing gut barrier function[25]. However, the therapeutic potential of natural compounds is often hampered by pharmacokinetic limitations, including poor solubility, instability in the gastrointestinal tract, rapid metabolism, and low bioavailability[26, 27]. These challenges hinder their effective delivery to target tissues, including the gut, and limit their clinical application.

To overcome these obstacles, nanotechnology-based drug delivery systems have been developed as innovative platforms for enhancing the efficacy and targeted delivery of natural bioactives[28, 29]. Nanocarriers such as liposomes, solid lipid nanoparticles, polymeric nanoparticles, dendrimers, and nanoemulsions offer several advantages, including improved solubility and stability, sustained and controlled release, protection from enzymatic degradation, and the ability to target specific tissues or microbial populations in the gut[30, 31]. Moreover, these smart delivery systems can be engineered to respond to specific physiological triggers such as pH, temperature, or enzymatic activity thereby ensuring precise and efficient drug release[32].

In the context of diabesity-associated cancers, nanotechnology-enhanced delivery of natural compounds represents a multifaceted therapeutic strategy[31]. By simultaneously targeting metabolic dysfunction, modulating gut microbiota, and exerting anti-tumor effects, these integrated approaches hold promise for breaking the pathological nexus between diabesity and cancer. Furthermore, ongoing advances in personalized nanomedicine and microbiome profiling are likely to pave the way for more tailored interventions, optimizing therapeutic outcomes and minimizing adverse effects.

In sum, the intersection of diabesity, gut microbiota dysbiosis, and cancer represents a complex yet targetable axis in modern biomedicine. Leveraging the synergistic potential of natural bioactives and nanotechnology offers a novel and promising approach to mitigate the burden of diabesity-associated malignancies, ultimately contributing to more effective and holistic patient care.

2. Diabesity and Its Link to Cancer: A Microbiota-Mediated Perspective

2.1 Pathophysiological Intersections of Diabesity and Cancer

Diabesity, the coexistence of type 2 diabetes and obesity, promotes a metabolic milieu that significantly increases cancer risk. One of the central features of this environment is hyperinsulinemia, which results from insulin resistance and increased pancreatic beta-cell activity[11, 33]. Elevated insulin levels enhance the bioavailability of insulin-like growth factor-1 (IGF-1), a potent mitogen. IGF-1 activates the PI3K/Akt and MAPK signaling pathways, driving uncontrolled cellular proliferation and survival[34]. This state suppresses apoptosis, a natural cell-death mechanism, thereby facilitating the survival of genetically unstable or transformed cells. The combined mitogenic and anti-apoptotic signals create conditions favorable to early tumor development and progression. Moreover, insulin and IGF-1 upregulate the expression of vascular endothelial growth factor (VEGF), promoting angiogenesis that supplies nutrients and oxygen to emerging tumors[34].

In addition to hormonal disturbances, diabesity is characterized by adipokine dysregulation, wherein the secretion patterns of bioactive molecules from adipose tissue are significantly altered[35]. Leptin, often elevated in obesity, acts as a growth factor and supports cancer cell proliferation, migration, and angiogenesis[36, 37]. Conversely, adiponectin a protective adipokine with anti-inflammatory and anti-proliferative properties is markedly reduced. The imbalance between pro- and anti-tumorigenic adipokines disrupts cellular homeostasis, tipping the scale toward malignancy[35]. Additionally, excess adiposity contributes to hypoxic conditions within adipose tissue, further stimulating the production of reactive oxygen species (ROS) and other signaling molecules that promote mutagenesis and genomic instability. This complex network of hormonal and molecular disruptions underscores the intricate relationship between diabesity and cancer pathogenesis[35].

Another hallmark of diabesity is chronic low-grade inflammation, which plays a pivotal role in carcinogenesis[38]. Adipose tissue in obese individuals is infiltrated by immune cells, particularly macrophages, which secrete pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β. These cytokines activate transcription factors like NF-κB and STAT3, which regulate genes involved in inflammation, proliferation, and survival[6]. This sustained inflammatory response fosters an environment conducive to tumor initiation and progression. Furthermore, chronic inflammation impairs immune surveillance by disrupting the function of natural killer cells and cytotoxic T lymphocytes, enabling malignant cells to evade immune detection[33, 39].

Together, hyperinsulinemia, adipokine imbalance, and persistent inflammation constitute a pathophysiological triad that connects diabesity with increased susceptibility to various cancers, including those of the colon, pancreas, breast, and liver.

2.2 Role of Gut Microbiota in Diabesity-Associated Carcinogenesis

The gut microbiota, a diverse ecosystem of microorganisms residing in the gastrointestinal tract, plays a crucial role in metabolic health and disease progression. In individuals with diabesity, microbial diversity is often reduced, and pathogenic taxa are enriched—a condition known as gut dysbiosis[21, 40]. One key mechanism by which dysbiosis contributes to cancer development is through increased intestinal permeability, also referred to as "leaky gut." This condition permits the translocation of bacterial endotoxins such as lipopolysaccharides (LPS) into the bloodstream, activating the innate immune system. The ensuing systemic inflammation is a critical driver of insulin resistance and creates a pro-inflammatory milieu conducive to carcinogenesis[41]. The chronic stimulation of immune pathways results in oxidative stress, DNA damage, and alterations in tumor suppressor gene expression, laying the foundation for cancer initiation.

Another important pathway involves altered bile acid metabolism driven by gut microbiota imbalance. In healthy individuals, primary bile acids are converted into secondary bile acids by gut bacteria, which play a role in lipid digestion and modulate metabolic signaling pathways[42]. However, in dysbiosis, this conversion becomes dysregulated. Accumulation of toxic secondary bile acids, such as deoxycholic acid (DCA), has been implicated in colorectal cancer due to its genotoxic effects[42]. These bile acids also interfere with nuclear receptors like FXR and TGR5, which regulate inflammation, glucose homeostasis, and cell proliferation. Disruption of these signaling cascades contributes to metabolic derangements and promotes tumorigenesis, especially in the gastrointestinal tract[42]. This highlights the importance of microbial composition in maintaining bile acid balance and intestinal health.

Additionally, microbial metabolites such as short-chain fatty acids (SCFAs) and secondary bile acids influence gene expression and immune responses[43]. SCFAs like butyrate, propionate, and acetate are produced through the fermentation of dietary fibers by commensal bacteria and exert anti-inflammatory and anti-carcinogenic effects. Butyrate, in particular, serves as an energy source for colonocytes and acts as a histone deacetylase (HDAC) inhibitor, thereby modulating epigenetic expression of genes involved in apoptosis and tumor suppression[43]. However, a decline in butyrate-producing bacteria due to dysbiosis reduces these protective effects. Conversely, the overproduction of carcinogenic metabolites from protein fermentation and bile acid transformation exacerbates the risk of neoplastic transformation. Therefore, restoring a healthy gut microbiome through diet, probiotics, and prebiotics offers a promising strategy to prevent or mitigate diabesity-associated cancer development.

3.1 Categories and Sources of Natural Compounds for Gut Microbiota Modulation

Natural compounds capable of modulating gut microbiota composition and activity are increasingly recognized as valuable tools in managing diabesity and related cancers. Among these, polyphenols, a diverse class of phytochemicals found in fruits, vegetables, tea, coffee, and wine exhibit strong antioxidant, anti-inflammatory, and prebiotic properties. Examples include curcumin, resveratrol, and epigallocatechin gallate (EGCG)[44, 45]. These compounds can increase the abundance of beneficial bacteria such as *Lactobacillus* and *Bifidobacterium*, while suppressing the growth of pathogenic species. Moreover, polyphenols influence microbial metabolite production, enhancing levels of short-chain fatty acids and reducing genotoxic by-products[25]. These effects translate into improved insulin sensitivity, reduced systemic inflammation, and decreased risk of carcinogenesis, making polyphenols powerful agents in the modulation of metabolic and immune pathways via the gut microbiome.

Alkaloids, particularly berberine, derived from plants like *Berberis vulgaris*, also show promise in gut microbiota modulation[46, 47]. Berberine exerts antimicrobial activity against harmful bacteria while promoting beneficial strains, thereby rebalancing microbial communities in individuals with metabolic disorders[47]. It also influences bile acid metabolism and SCFA production, which are critical in controlling lipid and glucose homeostasis. Additionally, berberine has demonstrated significant anti-cancer properties, including inhibition of tumor proliferation and angiogenesis. By targeting the gut-liver axis, it contributes to both metabolic and immune system regulation, highlighting its dual functionality in diabesity and cancer management. Its ability to regulate microbial gene expression and suppress endotoxemia further supports its use as a therapeutic compound[48].

Other classes of natural bioactives include terpenoids and polysaccharides. Terpenoids like ursolic acid, found in apples and rosemary, possess anti-inflammatory and anti-tumor activities. Ursolic acid has been shown to modulate gut microbiota composition by increasing microbial diversity and promoting the growth of SCFA-producing bacteria[49]. This contributes to better gut barrier integrity and reduced systemic inflammation. On the other hand, polysaccharides such as inulin, a prebiotic fiber from chicory root and Jerusalem artichokes, serve as substrates for microbial fermentation[49]. Inulin selectively promotes the growth of beneficial microbes, enhances SCFA production, and modulates host immune responses[49]. Through these mechanisms, natural compounds not only support microbial balance but also exert systemic effects that mitigate the pathophysiological link between diabesity and cancer, offering a promising adjunct to dietary and pharmacological interventions.

3.2 Mechanisms of Action

These bioactive compounds, often derived from dietary sources or microbial metabolites, promote gut health through a multifaceted set of mechanisms. One critical function is the enhancement of beneficial gut microbiota, such as *Lactobacillus* and *Bifidobacterium* species[50]. These probiotic organisms play vital roles in maintaining homeostasis by producing antimicrobial substances, regulating pH, and competing for adhesion sites, thereby limiting colonization by pathogens[50]. The promotion of these commensals leads to improved digestion, enhanced immune regulation, and better metabolic outcomes. Furthermore, these beneficial bacteria can influence host gene expression and signaling pathways that maintain mucosal integrity and anti-inflammatory balance[50].

Another significant mechanism is the suppression of pathobionts like *Clostridium difficile*, which are normally present in low numbers but can cause disease when dysbiosis occurs[51]. These compounds also stimulate the production of short-chain fatty acids (SCFAs), such as butyrate, propionate, and acetate, which have potent anti-inflammatory properties. SCFAs serve as energy sources for colonocytes, reinforce tight junction protein expression, and modulate immune responses to prevent chronic inflammation[51]. Additionally, the restoration of gut barrier integrity is essential in preventing microbial translocation and systemic inflammation. Despite these therapeutic potentials, the clinical translation of such compounds faces challenges due to poor stability, limited absorption, and rapid metabolism—issues that advanced drug delivery systems aim to overcome.

4. Smart Nano-Delivery Systems: A Paradigm Shift

4.1 Overview of Smart Nanocarriers

Smart nano-delivery systems represent a transformative approach to overcoming pharmacokinetic limitations associated with bioactive compounds[52]. These nanocarriers are designed to release their payload in response to specific physiological triggers such as pH changes, redox gradients, enzymatic activity, or microbial-derived metabolites—ensuring site-specific and time-controlled delivery[53, 54]. Polymeric nanoparticles, often made from biodegradable materials like PLGA, are widely employed for their customizable release profiles and biocompatibility. Lipid-based carriers, including liposomes and solid lipid nanoparticles, offer enhanced encapsulation of hydrophobic compounds and improved mucosal permeability[31]. Similarly, mesoporous silica nanoparticles provide high surface area and tunable pore sizes, allowing for efficient loading and sustained release of various therapeutic agents[55].

Stimuli-responsive hydrogels further add to the versatility of smart nanocarriers[56]. These hydrogels can swell or degrade in response to environmental changes, enabling the release of encapsulated compounds specifically at sites of inflammation or microbial imbalance[57]. The integration of these technologies helps in overcoming the instability of bioactives in the harsh gastrointestinal environment and minimizes off-target effects, thereby enhancing therapeutic efficacy and patient compliance[58]. Moreover, these systems offer the potential for co-delivery of synergistic agents, opening avenues for combination therapy. As a result, smart nanocarriers represent a promising frontier in microbiome-targeted therapy, particularly for managing complex gastrointestinal disorders.

4.2 Functionalization and Targeting Strategies

The success of smart nano-delivery systems is significantly amplified by strategic surface functionalization, which allows for precise targeting of disease-relevant sites within the gastrointestinal tract[59]. By modifying the surface of nanocarriers with specific ligands such as antibodies, peptides, lectins, or microbial-responsive molecules, researchers can achieve targeted delivery to dysbiotic niches where pathogenic microorganisms dominate[59]. For instance, lectins can bind to specific carbohydrate residues on microbial cell walls, directing nanoparticles toward harmful bacteria while sparing beneficial flora[60]. Similarly, antibody-conjugated carriers can identify and accumulate in inflamed regions of the intestinal mucosa, enhancing site-specific drug accumulation and reducing systemic exposure[60].

In addition to targeting microbial imbalances, functionalized nanocarriers can also be directed toward tumor microenvironments in gastrointestinal cancers. These regions often exhibit unique biochemical signatures such as acidic pH, hypoxia, and elevated levels of specific enzymes or cytokines. Functionalized carriers can respond to these cues to release anticancer agents selectively within the tumor milieu, minimizing damage to healthy tissues[61]. This approach is not only applicable in oncology but also in treating inflammatory bowel disease, where localization to inflamed tissue is essential. The continued development of ligand-functionalized nanocarriers promises improved treatment specificity, reduced side effects, and the potential for personalized therapeutic interventions based on a patient's unique microbial or disease profile.

5. Application of Smart Nano-Delivery in Diabesity-Associated Cancer

Smart nano-delivery systems represent a cutting-edge advancement in improving the therapeutic potential of natural compounds for managing diabesity-associated cancers[62]. These nanocarriers enhance the bioavailability and stability of bioactive agents by encapsulating them in protective matrices. Such encapsulation guards the compounds against enzymatic degradation in the gastrointestinal tract, improves their solubility, and ensures efficient absorption.[63] This targeted approach ensures that therapeutic molecules reach systemic circulation in optimal concentrations, overcoming major pharmacokinetic challenges associated with natural compounds.

Moreover, these smart nanocarriers can be engineered to respond selectively to specific signals within the dysbiotic gut environment[64]. For instance, microbial enzymes like azoreductase and β-glucuronidase, which are overexpressed in the altered microbiota of diabesity patients, can trigger the release of encapsulated compounds at precise locations. This targeted delivery can restore gut microbiota balance, reduce chronic inflammation, and suppress key oncogenic signaling pathways along the gut-cancer axis. Collectively, such synergistic modulation enhances the therapeutic impact of natural compounds and presents a promising strategy for integrative management of diabesity-associated malignancies.

6. Challenges and Future Directions

Despite the promising capabilities of smart nanocarriers, their clinical application in diabesity-associated cancers is still constrained by safety and regulatory concerns. The potential toxicity, immunogenic responses, and long-term health impacts of nanomaterials remain largely understudied, warranting rigorous toxicological evaluations. Regulatory bodies must establish comprehensive guidelines to assess the biocompatibility and safety of these systems, ensuring they do not pose additional risks to patients already burdened with metabolic and oncologic conditions.

Looking forward, personalized nano-interventions tailored to individual microbiota profiles may provide more precise and effective therapies. Integration of nano-delivery platforms with multi-omics approaches, including genomics, metabolomics, and microbiomics, could unravel novel biomarkers and therapeutic targets for early and accurate intervention. However, translational gaps persist, as most findings are still limited to preclinical models. To fully realize the potential of smart nanodelivery in clinical practice, well-designed human trials and robust clinical validation are urgently needed to bridge this divide.

CONCLUSION

Smart nano-delivery systems present a novel frontier in harnessing natural compounds for gut microbiota modulation in diabesity-associated cancer. By overcoming bioavailability limitations and enabling targeted, controlled release, these systems have the potential to transform preventive and therapeutic strategies at the intersection of metabolic and oncological disorders. Continued interdisciplinary research integrating nanotechnology, microbiology, oncology, and systems biology will be critical to realizing their full clinical impact.

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