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Bioactive Natural Products in the Nano Era: A Multi-Target Approach to Combat Diabesity and Associated Cancer Risks

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ABSTRACT

The global surge in diabesity, a pathological convergence of obesity and type 2 diabetes has become a major public health concern, further exacerbated by its association with increased cancer risks. Current monotherapeutic strategies often fall short in addressing the multifactorial nature of these interconnected conditions. Natural bioactive compounds have emerged as promising multi-target therapeutics due to their antioxidant, anti-inflammatory, anti-obesogenic, and anti-cancer properties. However, their clinical translation is hindered by issues such as poor solubility, low bioavailability, and rapid metabolism. Recent advancements in nanotechnology offer a transformative platform to overcome these limitations by enhancing delivery efficiency, stability, and targeted action of these bioactives. This review presents a comprehensive analysis of the molecular mechanisms by which bioactive natural products particularly polyphenols, alkaloids, terpenoids, and flavonoids modulate diabesity and its oncogenic sequelae. It also explores cutting-edge nanocarrier systems such as liposomes, polymeric nanoparticles, dendrimers, and nanoemulsions that have been engineered for effective delivery. The review further underscores the promise of nanoformulated botanicals in reshaping therapeutic paradigms through a multi-target approach aimed at metabolic, inflammatory, and oncogenic signaling pathways. Integrating natural product pharmacology with nanomedicine opens new frontiers in combating diabesity and its malignant complications.

Keywords Diabesity, Cancer, Natural Products, Nanotechnology, Polyphenols, Nanoformulations, Multi-target Therapy, Obesity, Type 2 Diabetes, Nanomedicine

INTRODUCTION

The co-occurrence of obesity and type 2 diabetes mellitus (T2DM), collectively termed diabesity, has emerged as a formidable challenge to global health systems[1, 2]. According to the World Health Organization (WHO), the prevalence of obesity has nearly tripled since 1975, with over 650 million adults affected in 2022. Concurrently, over 537 million individuals are living with diabetes, predominantly T2DM, with projections reaching 783 million by 2045[3–5]. Diabesity not only significantly reduces quality of life but also acts as a potent risk factor for multiple types of cancers, including colorectal, breast, endometrial, liver, and pancreatic cancers[6–9]. The pathophysiological interplay between insulin resistance, chronic inflammation, altered adipokine profiles, and oxidative stress fosters a pro-oncogenic environment, underscoring the need for integrated therapeutic strategies[4].

Traditional pharmacological interventions for obesity, T2DM, and cancer often adopt a single-target approach, addressing one aspect of the disease pathology. However, diabesity and its associated cancer risks involve complex, overlapping pathways that span metabolic dysregulation, mitochondrial dysfunction, chronic inflammation, and aberrant cell signaling. Consequently, there is an increasing interest in multi-target therapies that can holistically modulate these interconnected pathways[1, 10, 11]. Among such interventions, bioactive natural products have garnered significant attention due to their wide range of pharmacological effects and historical use in ethnomedicine[6, 12, 13].

Natural compounds such as polyphenols (e.g., resveratrol, curcumin, and quercetin), terpenoids (e.g., ursolic acid and limonene), alkaloids (e.g., berberine), and flavonoids (e.g., catechins and apigenin) exhibit potent anti-inflammatory, antioxidant, insulin-sensitizing, and anti-proliferative properties[12, 14–17]. Preclinical studies have shown their ability to modulate several molecular targets, including AMP-activated protein kinase (AMPK), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), mammalian target of

rapamycin (mTOR), and peroxisome proliferator-activated receptors (PPARs), among others[18]. These multi-target effects make them ideal candidates for addressing the multifactorial nature of diabesity and its malignant progression.
Despite their promising bioactivity, many of these natural compounds suffer from poor aqueous solubility, instability under physiological conditions, rapid hepatic metabolism, and limited systemic availability, thereby restricting their clinical efficacy. Herein lies the transformative potential of nanotechnology[19, 20]. The advent of nanomedicine has revolutionized drug delivery systems by enabling precise targeting, controlled release, improved solubility, and enhanced bioavailability. Nanoformulations such as liposomes, solid lipid nanoparticles (SLNs), polymeric nanoparticles, micelles, and nanoemulsions are being increasingly explored to improve the pharmacokinetics and pharmacodynamics of natural bioactives[21–24].
For instance, curcumin-loaded nanoparticles have demonstrated superior anti-diabetic and anti-cancer efficacy compared to free curcumin due to enhanced cellular uptake and sustained release[25]. Similarly, quercetin nanoemulsions have shown improved adipocyte differentiation control and insulin sensitivity[26]. These nanoscale delivery vehicles can also be engineered with surface ligands for targeted delivery to adipose tissue, pancreatic islets, or tumor microenvironments, thereby minimizing off-target effects and toxicity[27]. Moreover, emerging research is exploring stimuli-responsive nanocarriers that release bioactives in response to specific physiological conditions such as pH, temperature, or redox gradients commonly found in inflamed or cancerous tissues[28]. This smart delivery approach enhances therapeutic specificity while reducing systemic side effects. Additionally, co-delivery systems encapsulating multiple bioactive compounds or combining natural products with conventional drugs are being investigated for synergistic benefits[26].
Integrating bioactive natural products with nanotechnology not only improves their pharmacological performance but also aligns with the growing demand for personalized and precision medicine [29–31]. This fusion represents a paradigm shift in treating chronic, multifactorial diseases like diabesity and cancer, offering a sustainable, non-toxic, and holistic therapeutic strategy. However, despite promising preclinical data, clinical translation remains limited, primarily due to regulatory hurdles, scalability challenges, and the need for long-term safety evaluations. This review provides a detailed synthesis of the current understanding of how bioactive natural products act on multiple molecular targets in diabesity and related cancers. It also explores the nano-enabled advancements that have elevated their potential as therapeutic agents in the modern pharmaceutical landscape. Special emphasis is placed on nanoformulation design, delivery strategies, preclinical outcomes, and the translational challenges ahead. By highlighting the synergistic interface of natural pharmacology and nanotechnology, this review aims to pave the way for innovative, effective, and safer interventions for diabesity and its oncogenic complications.

Mechanisms of Diabesity and Its Oncogenic Link

Diabesity, a portmanteau of diabetes and obesity, signifies a complex and interdependent pathological state where obesity and type 2 diabetes mellitus (T2DM) coexist**[1, 2]**. This condition has gained increasing recognition due to its profound public health implications and its emerging association with oncogenesis**[32, 33]**. At the heart of diabesity lies a constellation of interconnected molecular and physiological mechanisms that drive systemic metabolic dysregulation and create a permissive environment for carcinogenesis**[34]**. One of the hallmark features of diabesity is chronic low-grade inflammation, which originates from the hypertrophy and hyperplasia of adipose tissue. As adipocytes enlarge, they undergo hypoxia and necrosis, triggering the recruitment of immune cells, particularly macrophages. These infiltrating immune cells, along with stressed adipocytes, secrete pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and monocyte chemoattractant protein-1 (MCP-1)**[4, 16]**. These inflammatory mediators impair insulin receptor signaling by promoting serine phosphorylation of insulin receptor substrates (IRS), leading to insulin resistance, a core component of T2DM.
Simultaneously, dysregulated lipid metabolism contributes to metabolic toxicity. An overabundance of circulating free fatty acids (FFAs) due to lipolysis in insulin-resistant adipose tissue accumulates in non-adipose tissues, including the liver and skeletal muscle[35]. This lipotoxicity leads to mitochondrial dysfunction and the overproduction of reactive oxygen species (ROS), which damage cellular components such as DNA, proteins, and lipids. Moreover, ROS contribute to insulin resistance and promote oxidative stress, further exacerbating the inflammatory state.
Another central player is hyperinsulinemia, a compensatory response to insulin resistance. Elevated insulin levels not only disrupt normal metabolic processes but also engage mitogenic pathways such as PI3K/Akt/mTOR and Ras/Raf/MEK/ERK, which stimulate cellular proliferation, inhibit apoptosis, and increase protein synthesis[36–38]. These signaling cascades are pivotal in cancer biology, indicating a direct mechanistic link between diabesity and tumorigenesis. The oncogenic link of diabesity extends beyond insulin and inflammatory signaling. Adipokines, bioactive molecules secreted by adipose tissue, play significant roles[39]. For example, leptin, which is elevated in obesity, promotes angiogenesis, cell proliferation, and migration by activating pathways like JAK/STAT and MAPK. In contrast, adiponectin, an anti-inflammatory

adipokine with insulin-sensitizing effects, is typically reduced in obese individuals. Its deficiency removes a critical inhibitory signal against tumor progression and insulin resistance[4, 40]. The imbalance in adipokines creates a microenvironment conducive to tumor growth and metastasis.
Moreover, diabesity-associated hyperglycemia contributes to the generation of advanced glycation end-products (AGEs), which interact with their receptor (RAGE) on cells to promote inflammation and oxidative stress[41, 42]. AGEs also induce endothelial dysfunction and may facilitate cancer cell adhesion and invasion. Genomic instability, a defining feature of cancer, is promoted by ROS-induced DNA damage and impaired DNA repair mechanisms in the diabesity state.
Recent studies have demonstrated that individuals with diabesity exhibit increased risk for a range of cancers, including colorectal, pancreatic, breast, liver, and endometrial cancers[43]. These observations are supported by epidemiological data linking increased body mass index (BMI), insulin resistance, and hyperinsulinemia with higher cancer incidence and mortality[8].
From a therapeutic perspective, understanding these mechanisms underscores the importance of integrated strategies that address both metabolic and oncogenic processes. Lifestyle interventions such as diet and exercise can reduce adiposity, improve insulin sensitivity, and suppress inflammation. Pharmacological agents like metformin, which activates AMP-activated protein kinase (AMPK), can inhibit mTOR signaling and decrease hepatic glucose production while exhibiting potential anti-cancer effects[44]. In sum, diabesity represents a pathological nexus where metabolic dysregulation, chronic inflammation, hormonal imbalances, and oxidative stress converge to promote oncogenesis. The oncogenic potential of diabesity is not merely a secondary consequence of metabolic disease but is driven by overlapping molecular pathways that fuel both metabolic dysfunction and tumor progression. Addressing diabesity from a molecular and systemic level is critical for curbing both the diabetes epidemic and the rising tide of obesity-associated cancers.

Bioactive Natural Compounds: Sources and Molecular Targets

Natural bioactive compounds, derived from plants, microbes, marine organisms, and other natural sources, have gained significant attention in recent years as potential therapeutics for complex metabolic and oncological disorders[12, 45]. Their diverse chemical structures and ability to interact with multiple biological targets make them ideal candidates for the management of diabesity and its associated cancer risk[44]. These compounds encompass a wide array of chemical classes, including polyphenols, flavonoids, alkaloids, terpenoids, lignans, and saponins. Many of these bioactives modulate critical signaling pathways involved in glucose and lipid metabolism, inflammation, oxidative stress, and cell cycle regulation, making them effective in both preventing and treating diabesity and related malignancies[12]. For example, curcumin, a polyphenol from turmeric (*Curcuma longa*), exhibits potent anti-inflammatory and antioxidant properties[12]. It activates AMP-activated protein kinase (AMPK), which enhances insulin sensitivity, promotes lipid oxidation, and inhibits lipogenesis. Curcumin also downregulates nuclear factor-kappa B (NF-κB), a transcription factor involved in inflammatory gene expression. Additionally, curcumin has been shown to inhibit the PI3K/Akt/mTOR pathway, thereby exerting anti-proliferative effects on various cancer cell lines[20, 46, 47].
Resveratrol, found in grapes and red wine, exhibits similar pleiotropic effects. It not only activates AMPK and sirtuin-1 (SIRT1) but also modulates peroxisome proliferator-activated receptors (PPARs), particularly PPAR-γ, which plays a vital role in adipogenesis, lipid metabolism, and insulin sensitivity[48–50]. Resveratrol also exhibits anti-cancer effects through its inhibition of cyclooxygenase-2 (COX-2), induction of apoptosis, and suppression of angiogenesis via vascular endothelial growth factor (VEGF) inhibition[48]. Flavonoids such as quercetin, luteolin, and epigallocatechin gallate (EGCG)—the latter abundant in green tea—possess anti-diabetic and anti-cancer properties[51, 52]. EGCG, for instance, inhibits adipocyte differentiation, enhances insulin sensitivity, and reduces oxidative stress. It also induces apoptosis and cell cycle arrest in cancer cells by modulating Bcl-2 family proteins, caspases, and p53 signaling. Quercetin suppresses tumor growth and metastasis by inhibiting matrix metalloproteinases (MMPs) and NF-κB activity[16, 26].
Another notable compound is berberine, an isoquinoline alkaloid found in *Berberis* species. Berberine improves glucose metabolism by activating AMPK and reducing insulin resistance. It exhibits anti-proliferative effects in cancer cells by downregulating c-Myc, cyclin D1, and Bcl-2, while upregulating p21 and p53, thus restoring the balance between oncogenes and tumor suppressors[53, 54].
Saponins and terpenoids, derived from herbs like ginseng and licorice, also demonstrate multi-targeted mechanisms[55, 56]. These compounds can inhibit lipogenesis, suppress inflammatory cytokine production, and promote mitochondrial biogenesis. They exert anti-cancer effects through cytotoxicity, inhibition of angiogenesis, and modulation of the tumor microenvironment[55]. The therapeutic efficacy of these bioactives is not limited to isolated compound activity but also involves synergistic interactions when used in combinations or as part of whole plant extracts. This synergy enhances bioavailability and target modulation while minimizing toxicity. Moreover, these compounds often act on epigenetic regulators, such as histone deacetylases (HDACs) and DNA methyltransferases (DNMTs), offering potential for long-term modulation of gene expression associated with diabesity and cancer[57]. In sum, bioactive natural compounds represent a promising frontier

in combating the dual burden of diabesity and cancer. Their ability to modulate multiple biochemical pathways, exert anti-inflammatory and antioxidant effects, and regulate metabolic and oncogenic processes underscores their potential as part of integrated therapeutic strategies. Continued research into their molecular mechanisms, pharmacokinetics, and synergistic potential will pave the way for their incorporation into evidence-based clinical practice.

Nanotechnology in Natural Product Delivery

Nanotechnology-based delivery systems offer a transformative approach to overcome these limitations by enhancing the solubility, stability, and targeted delivery of bioactive compounds[29, 31]. Nanoscale carriers such as liposomes, solid lipid nanoparticles (SLNs), and polymeric nanoparticles can encapsulate natural products, protecting them from enzymatic degradation and facilitating controlled release[19]. These systems improve cellular uptake and extend the circulation time of therapeutic agents, leading to enhanced therapeutic efficacy and reduced systemic toxicity.

For instance, polymeric nanoparticles composed of biodegradable polymers like PLGA have been successfully employed to deliver compounds such as berberine, improving glycemic control and exhibiting anti-cancer properties in preclinical models. Liposomes have been used to encapsulate hydrophobic compounds like curcumin, significantly increasing their bioavailability and anti-inflammatory activity[29, 31]. Solid lipid nanoparticles loaded with resveratrol and EGCG demonstrate improved antioxidant and anti-diabetic effects. The versatility of nanocarriers allows for functionalization with targeting ligands, which can direct the payload to specific tissues, thereby enhancing therapeutic precision. These advancements highlight the potential of nanotechnology in optimizing the pharmacological benefits of natural bioactive compounds.

Nanoformulated Natural Products: Preclinical and Clinical Insights

Nanoformulated natural products have shown promising results in both preclinical and early-phase clinical studies[58]. These formulations enhance the bioavailability and therapeutic action of natural compounds, enabling more effective intervention in diabesity and its associated cancers. Nano-curcumin, for instance, has demonstrated improved pharmacokinetics and superior anti-diabetic and anti-obesity effects by modulating insulin sensitivity and reducing hepatic lipogenesis[31]. It also exhibits potent anti-tumor properties by suppressing angiogenesis and promoting cancer cell apoptosis. Similarly, quercetin nanoparticles show increased cellular uptake and prolonged circulation, resulting in better metabolic control and reduced tumor growth in animal models.

Berberine-loaded nanoparticles have been evaluated for their ability to enhance oral bioavailability, and studies have shown significant reductions in fasting glucose, HbA1c, and body weight, alongside anti-tumor effects in xenograft models[59]. Resveratrol-loaded SLNs improve antioxidant defense mechanisms and decrease insulin resistance, while also exhibiting cytotoxic effects against breast and colon cancer cell lines[60]. These formulations demonstrate that nanocarriers can effectively harness the therapeutic potential of natural compounds, providing a multifaceted strategy to address diabesity and its oncogenic risks. Continued investigation and validation in large-scale human trials are essential for transitioning these innovations into mainstream clinical practice.

Challenges and Future Prospects

Despite the promising potential of nanoformulated natural products, several challenges must be addressed to facilitate their clinical translation. Regulatory frameworks are still evolving to accommodate the unique characteristics of nanomedicines, including their safety profiles, manufacturing processes, and standardization. Long-term toxicity studies and pharmacovigilance are critical to ensure these formulations' safety. Furthermore, variability in the composition of natural products due to differences in cultivation, harvesting, and processing can affect reproducibility and efficacy, necessitating stringent quality control measures.

Another critical challenge is understanding the interaction between nanocarriers and biological systems, including their biodistribution, cellular uptake mechanisms, and immunogenic potential. Future research should aim to develop stimuli-responsive and co-delivery systems capable of targeting multiple disease pathways simultaneously. Integration of high-throughput screening, omics technologies, and artificial intelligence can accelerate the discovery and optimization of nanoformulated therapeutics. Collaborative efforts involving pharmacologists, nanotechnologists, clinicians, and regulatory agencies will be essential in translating these innovations from the laboratory to the clinic, ultimately improving patient outcomes in diabesity and cancer.

CONCLUSION

The convergence of natural bioactive compounds and nanotechnology presents a promising multi-targeted therapeutic approach to tackle the global burden of diabesity and its associated cancer risks. By enhancing delivery, bioavailability, and therapeutic efficacy, nanoformulations offer a revolutionary paradigm in managing complex metabolic and oncogenic disorders. The synergy between these two domains enables interventions that are both effective and sustainable, minimizing adverse effects and maximizing patient benefits. However, the successful implementation of this strategy requires overcoming several scientific and regulatory challenges. Future advancements should focus on improving formulation stability, achieving precise targeting, and ensuring safety through rigorous preclinical and clinical evaluations. As research in this field advances, nano-enabled natural therapeutics hold the potential to become a cornerstone in the integrated management of diabesity and cancer, ushering in a new era of personalized and precision medicine.

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