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# Combating the Diabesity-Cancer Axis with Green Nanomedicine: Role of Polyphenols, Flavonoids, and Alkaloids

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## ABSTRACT

The coexistence of obesity and type 2 diabetes, termed *diabesity*, is a growing global health crisis with strong correlations to the initiation and progression of various cancers. Chronic inflammation, oxidative stress, hyperinsulinemia, and altered adipokine signaling link diabesity to tumorigenesis. Conventional therapeutic strategies face significant challenges, including limited efficacy, side effects, and poor bioavailability of phytotherapeutic agents. Green nanomedicine, which utilizes eco-friendly synthesis methods for nanoparticles loaded with bioactive phytochemicals, offers a promising solution. This review explores the potential of polyphenols, flavonoids, and alkaloids natural compounds with well-documented antioxidant, anti-inflammatory, anti-obesity, and anti-cancer properties when formulated using green nanotechnology. The integration of these phytochemicals into nanoparticles enhances their bioavailability, target specificity, and therapeutic outcomes against the diabesity-cancer axis. We highlight current research, mechanisms of action, challenges, and future directions for leveraging green nanomedicine in combating this interconnected triad of metabolic and oncologic diseases.

**Keywords:** Diabesity, Green nanomedicine, Polyphenols, Flavonoids, Alkaloids

## INTRODUCTION

The global prevalence of *diabesity* a synergistic and pathophysiologically interlinked manifestation of obesity and type 2 diabetes mellitus (T2DM) has escalated into a major public health crisis, reaching epidemic proportions[1, 2]. Diabesity is not only a dual metabolic disorder but also a critical risk factor for numerous chronic diseases, particularly certain types of cancer[3]. Alarmingly, individuals affected by diabesity face an increased incidence of malignancies, including but not limited to breast, liver, colorectal, and pancreatic cancers. This association is underpinned by a complex and intertwined network of pathological processes, including chronic low-grade inflammation, insulin resistance, hormonal dysregulation, dyslipidemia, and oxidative stress[4–6]. Together, these factors create a pro-tumorigenic environment that promotes both metabolic dysfunction and cancer initiation, progression, and metastasis[7, 8].

The pathological crosstalk between these processes illustrates a biological continuum that simultaneously drives the onset of diabesity and enhances the susceptibility to cancer[9–12]. Chronic inflammation, for example, contributes to insulin resistance and promotes oncogenic signaling through inflammatory cytokines like TNF-α, IL-6, and CRP. Insulin resistance, in turn, leads to hyperinsulinemia and increased levels of insulin-like growth factor-1 (IGF-1), which can act as potent mitogens for cancer cells[3, 13, 14]. Moreover, the adipose tissue in obese individuals becomes a source of pro-inflammatory adipokines and free fatty acids, further exacerbating systemic inflammation and oxidative stress. These shared molecular pathways offer a compelling rationale for integrated therapeutic strategies targeting both diabesity and cancer concurrently[15–17].

Despite advancements in pharmacotherapy, the current pharmacological interventions for managing diabesity and associated cancers remain suboptimal. Conventional drugs often suffer from multiple limitations, including poor long-term efficacy, adverse side effects, drug resistance, and low patient compliance[18]. The frequent need for polypharmacy in treating comorbid conditions like obesity, diabetes, and cancer further complicates therapeutic regimens, increasing the risk of toxicity and drug-drug interactions. Moreover, these synthetic agents typically address symptoms rather than targeting the root causes or the interconnected molecular pathways that drive these complex diseases[19].

In response to these challenges, there has been growing interest in exploring natural bioactive compounds, particularly phytochemicals, as alternative or adjunct therapeutic agents. Phytochemicals such as polyphenols (e.g., resveratrol, curcumin, and epigallocatechin gallate), flavonoids (e.g., quercetin, kaempferol), and alkaloids (e.g., berberine, capsaicin) have demonstrated remarkable bioactivity in preclinical and clinical studies. These compounds exhibit multifaceted mechanisms of action, including anti-inflammatory, antioxidant, anti-proliferative, and insulin-sensitizing properties[20]. Their ability to modulate multiple molecular targets makes them especially suitable for addressing the multifactorial nature of diabesity and its associated cancers.

However, despite their promising therapeutic potential, the clinical application of many phytochemicals remains limited due to their poor solubility, low stability under physiological conditions, rapid metabolism, and limited bioavailability. These pharmacokinetic limitations have prompted the scientific community to investigate novel delivery systems that can enhance the therapeutic performance of natural compounds.

Nanotechnology has emerged as a transformative platform in modern medicine, offering innovative solutions for drug delivery, diagnostics, and therapeutic monitoring. By manipulating materials at the nanoscale, nanotechnology allows for the development of carriers such as liposomes, solid lipid nanoparticles, dendrimers, and polymeric micelles that can encapsulate phytochemicals and improve their solubility, stability, and controlled release[21, 22]. When these nanotechnological approaches are integrated with environmentally sustainable ("green") principles—such as the use of plant-derived reducing agents or eco-friendly solvents—the resulting *green nanomedicine* offers a cutting-edge, biocompatible, and sustainable solution for therapeutic development[23–25].

Green nanomedicine represents an advanced frontier in the application of natural compounds for managing chronic diseases[26]. By leveraging the principles of green chemistry and nanoscience, researchers have developed nanoparticles that not only enhance the therapeutic index of phytochemicals but also minimize toxicity and environmental impact. For instance, green-synthesized gold and silver nanoparticles have been shown to deliver curcumin and quercetin with improved bioavailability and targeted anti-cancer effects. Similarly, polymeric nanoparticles loaded with resveratrol or berberine have demonstrated enhanced efficacy in models of insulin resistance and obesity-associated cancers[27, 28]. This integrative approach holds immense potential in bridging the gap between traditional herbal medicine and modern pharmacotherapy. By enabling the efficient delivery of phytochemicals to target tissues, green nanomedicine can modulate key signaling pathways involved in the diabesity-cancer axis, thereby offering a more holistic, multifactorial intervention. Furthermore, such strategies align with the global shift towards personalized and precision medicine, offering tailored treatments with reduced side effects. In sum, the escalating burden of diabesity and its oncogenic complications underscores the urgent need for innovative and integrative treatment modalities. Green nanomedicine, through the synergistic application of phytochemicals and eco-friendly nanotechnology, offers a promising and sustainable therapeutic avenue. Future research should focus on clinical translation, regulatory standardization, and long-term safety evaluations to fully harness its potential in combating the dual threats of metabolic dysfunction and cancer.

## The Diabesity-Cancer Axis: Mechanistic Insights

### Chronic Inflammation and Oxidative Stress

Low-grade chronic inflammation and oxidative stress are pivotal mechanisms that underlie both obesity and type 2 diabetes mellitus (T2DM), often referred to collectively as "diabesity." In this pathological state, there is persistent activation of the immune system and elevated levels of reactive oxygen species (ROS), which together create a pro-oxidative and pro-inflammatory microenvironment[7, 29, 30]. This environment promotes DNA damage, impairs DNA repair mechanisms, and fosters genomic instability—key events in the initiation and progression of various cancers. Adipose tissue, particularly visceral fat, acts as an active endocrine organ by releasing numerous pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and C-reactive protein (CRP). These cytokines not only sustain systemic inflammation but also contribute to insulin resistance and metabolic dysfunction[29, 31]. Furthermore, oxidative stress arising from mitochondrial dysfunction and excess nutrient supply exacerbates inflammation through activation of transcription factors like NF-κB and AP-1. These, in turn, upregulate inflammatory gene expression and promote carcinogenic signaling pathways[4, 32]. Thus, the synergistic impact of chronic inflammation and oxidative stress not only accelerates the metabolic complications of diabesity but also serves as a critical link between metabolic disorders and oncogenesis by altering the tissue microenvironment to favor tumorigenesis.

### Hyperinsulinemia and IGF Signaling

In the context of diabesity, insulin resistance is a central feature that leads to a compensatory increase in insulin production—a condition termed hyperinsulinemia[33]. Chronic hyperinsulinemia not only reflects the metabolic derangements of obesity and type 2 diabetes but also has significant implications for cancer development. One of the key pathways affected by elevated insulin levels is the insulin-like growth factor (IGF) signaling axis, particularly through insulin-like growth factor-1 (IGF-1). IGF-1 is a potent mitogenic and anti-apoptotic molecule that promotes cellular proliferation and survival[34]. In hyperinsulinemic states, bioavailable IGF-1 increases due to reduced levels of IGF-binding proteins, enhancing the activation of the IGF-1 receptor (IGF-1R) on various cells, including pre-malignant and malignant cells. This activation triggers downstream signaling cascades such as the PI3K/Akt and MAPK pathways, which further stimulate cell cycle

progression, inhibit apoptosis, and support angiogenesis and metastasis[34, 35]. As a result, tissues exposed to high insulin and IGF-1 levels are more susceptible to neoplastic transformation. Moreover, insulin itself may act as a growth factor by directly interacting with insulin receptors on cancer cells[36]. Hence, hyperinsulinemia and augmented IGF signaling represent critical oncogenic drivers that connect the metabolic dysregulation of diabesity to increased cancer risk.

### Dysregulated Adipokines and Hormonal Imbalance

Adipose tissue, once regarded merely as a fat storage depot, is now recognized as a highly active endocrine organ that secretes a variety of bioactive molecules known as adipokines[37, 38]. In diabesity, the function of adipose tissue becomes dysregulated, leading to an imbalance in adipokine production that significantly impacts metabolic homeostasis and cancer risk. Two key adipokines, leptin and adiponectin, exhibit opposing roles in inflammation and carcinogenesis. In obese individuals, leptin levels are typically elevated. Leptin promotes angiogenesis, cellular proliferation, and migration through activation of signaling pathways such as JAK/STAT3, MAPK, and PI3K/Akt, thereby fostering tumor development[39]. Additionally, leptin can enhance inflammatory responses and stimulate the production of other cytokines, reinforcing a pro-carcinogenic environment. In contrast, adiponectin—usually decreased in obesity and T2DM—exerts anti-inflammatory, anti-proliferative, and insulin-sensitizing effects[39]. Low adiponectin levels remove this protective barrier, facilitating tumorigenesis. Furthermore, diabesity is associated with other hormonal imbalances, such as increased estrogen production from aromatase activity in adipose tissue, which may contribute to hormone-sensitive cancers like breast and endometrial cancer[40–42]. Overall, the dysregulation of adipokines and related hormonal disturbances in diabesity creates a milieu conducive to malignancy by disrupting normal cellular signaling, immunity, and metabolic regulation.

## Phytochemicals as Therapeutic Agents in Diabesity and Cancer

### Polyphenols

Polyphenols are a diverse group of naturally occurring compounds found abundantly in fruits, vegetables, tea, coffee, and wine[43, 44]. Notable polyphenols such as resveratrol (found in grapes), curcumin (from turmeric), and epigallocatechin gallate (EGCG, present in green tea) have gained significant attention for their wide range of health-promoting properties[20]. These compounds exhibit strong antioxidant capabilities by neutralizing free radicals and preventing oxidative damage to cellular components such as DNA, proteins, and lipids. Additionally, polyphenols have anti-inflammatory effects through the suppression of pro-inflammatory cytokines and inhibition of critical signaling pathways such as nuclear factor-kappa B (NF-κB) and signal transducer and activator of transcription 3 (STAT3)[45]. Curcumin, in particular, has been shown to downregulate both NF-κB and STAT3, which are often implicated in chronic inflammation, cancer progression, and metabolic diseases[46, 47]. Moreover, polyphenols have insulin-sensitizing effects, making them valuable in managing type 2 diabetes and metabolic syndrome. However, despite their potential, the clinical translation of polyphenols is hindered by poor bioavailability due to low solubility, rapid metabolism, and limited systemic absorption. Ongoing research focuses on enhancing their bioefficacy through novel delivery systems, such as nanoparticles, liposomes, and conjugation with bioenhancers, to unlock their full therapeutic potential in chronic disease management.

### Flavonoids

Flavonoids are a subclass of polyphenols widely distributed in plant-based foods, including onions, apples, berries, and citrus fruits[48, 49]. Prominent flavonoids such as quercetin, kaempferol, and luteolin possess a broad spectrum of biological activities, making them key candidates in the prevention and management of metabolic and neoplastic disorders[20]. These compounds exhibit potent antioxidant and anti-inflammatory effects by scavenging reactive oxygen species (ROS) and inhibiting the expression of pro-inflammatory enzymes like cyclooxygenase (COX) and inducible nitric oxide synthase (iNOS)[50, 51]. In metabolic diseases, flavonoids play a regulatory role in glucose metabolism, enhance insulin sensitivity, and inhibit lipid accumulation by modulating pathways such as AMPK and PPARγ[51]. Quercetin, for example, not only regulates metabolic parameters but also exhibits anticancer effects by inducing apoptosis, inhibiting metastasis, and disrupting angiogenesis in various cancer cell lines[52, 53]. Additionally, flavonoids have been shown to arrest cancer cell cycles at specific checkpoints and modulate critical signaling pathways involved in tumorigenesis. Despite their promising pharmacological profile, flavonoids face limitations regarding solubility, metabolic stability, and bioavailability under physiological conditions[54, 55]. Strategies such as structural modification, formulation in nanoemulsions, and co-administration with absorption enhancers are being explored to overcome these barriers and enhance their effectiveness in clinical applications.

### Alkaloids

Alkaloids are nitrogen-containing secondary metabolites derived from a variety of plant species, known for their diverse pharmacological properties.[56] Common alkaloids such as berberine (from *Berberis* species), piperine (from black pepper), and sanguinarine (from *Sanguinaria canadensis*) have demonstrated remarkable potential in managing obesity, type 2 diabetes, and cancer. Berberine, for instance, exerts anti-diabetic effects by activating AMP-activated protein kinase (AMPK), a key regulator of energy metabolism that enhances glucose uptake and reduces hepatic gluconeogenesis[57]. Piperine not only improves lipid metabolism and insulin sensitivity but also enhances the bioavailability of other bioactive compounds by inhibiting drug-metabolizing enzymes like

CYP3A4[57]. Sanguinarine has shown efficacy in inducing apoptosis, modulating autophagy, and causing cell cycle arrest in various cancer models. Collectively, these alkaloids inhibit the growth and proliferation of cancer cells by interfering with critical molecular pathways involved in cell survival and proliferation[58]. Moreover, their anti-inflammatory and antioxidant properties further contribute to their therapeutic effects. However, challenges such as dose-dependent toxicity, limited solubility, and variable absorption rates remain key obstacles to their clinical use. Advances in medicinal chemistry and drug delivery systems are being applied to improve their pharmacokinetic properties, making alkaloids promising candidates for the development of novel therapeutic agents targeting metabolic and oncological disorders.

## Green Nanomedicine: A Game-Changer for Phytochemical Delivery

**Green nanomedicine** refers to the sustainable and environmentally friendly synthesis of nanoparticles using biological sources such as plant extracts, bacteria, fungi, and other microorganisms[59]. This eco-conscious approach eliminates the need for toxic chemicals traditionally used in nanoparticle production, reducing environmental pollution and potential human toxicity. By utilizing natural biomolecules as reducing and stabilizing agents, green nanomedicine produces nanoparticles that are not only highly stable and functional but also inherently biocompatible[60]. These nanoparticles are particularly well-suited for drug delivery applications due to their ability to improve the pharmacokinetic properties of therapeutic compounds. Furthermore, green-synthesized nanoparticles often exhibit intrinsic biological activities, such as antioxidant or antimicrobial properties, adding further therapeutic value[60]. The integration of green nanotechnology in medicine represents a significant advancement in nanoscience, merging nanotechnology with principles of green chemistry and biotechnology. This field is paving the way for safer, more effective, and sustainable therapeutic interventions, especially in the treatment of chronic and complex diseases[60].

**Advantages of Green Nanomedicine** are numerous and contribute significantly to its growing popularity in pharmaceutical research[61]. One of the foremost benefits is enhanced bioavailability. Encapsulating bioactive compounds within nanoparticles improves their water solubility, facilitates efficient absorption across biological membranes, and extends their systemic circulation time[61]. This ensures that drugs remain in the body longer and reach therapeutic levels more effectively. Another critical advantage is targeted delivery. By functionalizing the surface of nanoparticles with ligands or antibodies, these carriers can home in on specific tissues such as tumors or sites of inflammation, thereby minimizing damage to healthy tissues and reducing side effects[61]. Additionally, green nanoparticles can be engineered for controlled or sustained drug release, allowing for consistent therapeutic effects and reduced dosing frequency, improving patient compliance. Biocompatibility is also a hallmark of green nanomedicine, as natural sources like plants avoid harmful byproducts typically associated with synthetic chemicals. This makes green nanomedicine an attractive and safer alternative for clinical use.

**Nanocarrier platforms** are at the core of green nanomedicine, providing the structural basis for the delivery of bioactive compounds. Polymeric nanoparticles, particularly those made from biodegradable polymers like poly(lactic-co-glycolic acid) (PLGA), have gained popularity for encapsulating plant-derived compounds such as flavonoids and polyphenols[62, 63]. These nanoparticles protect the encapsulated drug from degradation and allow for sustained release. Lipid-based nanocarriers, including liposomes and solid lipid nanoparticles, are especially effective for delivering hydrophobic phytochemicals, improving their solubility and stability. These carriers also exhibit good biocompatibility and can be functionalized for targeted therapy[63, 64]. Metallic nanoparticles, such as those composed of silver or gold, are increasingly being synthesized through green methods using plant extracts. These nanoparticles not only serve as delivery vehicles but also exhibit intrinsic therapeutic properties, such as anticancer, antimicrobial, and anti-inflammatory effects, enhancing their clinical utility[61]. Collectively, these nanocarriers highlight the versatility and effectiveness of green nanomedicine platforms in delivering a broad range of therapeutics.

**Case Studies of Green Nanomedicine in Diabesity-Associated Cancers**

| Phytochemical | Nanocarrier | Target | Outcome |
|---|---|---|---|
| Curcumin | Gold nanoparticles (green synthesized) | Breast cancer in diabetic model | Enhanced apoptosis, reduced tumor size |
| Quercetin | Chitosan nanoparticles | Colorectal cancer | Improved bioavailability, suppressed tumor growth |
| Berberine | Lipid nanoparticles | Liver cancer in obese mice | Improved insulin sensitivity, reduced tumor proliferation |

## Challenges and Future Perspectives

Despite the promising strides in green nanotechnology for cancer treatment, several critical challenges must be addressed to ensure its clinical applicability. One major issue is the lack of standardization in green synthesis protocols, leading to inconsistencies in nanoparticle size, shape, and functionality. This variability poses significant barriers to reproducibility and scalability, which are essential for large-scale manufacturing and regulatory approval. Additionally, while preliminary studies highlight the therapeutic potential of green-synthesized nanoparticles, comprehensive toxicity profiling remains underexplored. Understanding their long-term effects on cellular systems and organs is vital to mitigate potential risks and ensure patient safety.

Regulatory frameworks also present substantial hurdles. The absence of harmonized global regulations and guidelines specific to nanophytomedicines has delayed their transition from laboratory research to clinical practice. This regulatory ambiguity not only affects approval timelines but also impacts investor confidence and industrial interest. Moreover, the need for personalized nanomedicine platforms is increasingly evident. Cancer is a highly heterogeneous disease, and tailoring nanoparticle-based therapies to individual patients' metabolic and oncogenic profiles could significantly enhance treatment outcomes while minimizing side effects. However, developing such precision-based approaches requires robust diagnostic tools and interdisciplinary collaboration. Future research must prioritize clinical trials to validate the safety and therapeutic efficacy of these nanoparticles in human subjects. Such studies will help bridge the gap between bench and bedside. Additionally, integrating artificial intelligence (AI) and machine learning algorithms into nanoparticle design could revolutionize the optimization process, enabling predictive modeling for improved functionality and targeting. Exploring the potential of combining green nanomedicine with conventional chemotherapy or immunotherapy may also yield synergistic effects, enhancing overall treatment efficacy. Addressing these challenges through collaborative, multidisciplinary efforts will be key to unlocking the full potential of green nanotechnology in personalized cancer therapy.

## CONCLUSION

The intricate link between diabesity and cancer necessitates innovative therapeutic strategies that can simultaneously target metabolic and oncogenic pathways. Green nanomedicine offers a revolutionary approach to enhance the therapeutic potential of phytochemicals like polyphenols, flavonoids, and alkaloids. By improving bioavailability, targeting capability, and safety profiles, this strategy holds great promise in disrupting the diabesity-cancer axis. Continued interdisciplinary research is essential to translate these findings into tangible clinical outcomes, offering hope for more effective and sustainable management of this global health challenge.

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