



NANOTECHNOLOGY-ENABLED DELIVERY OF PHYTOCHEMICALS FOR METABOLIC DISORDERS: FROM MECHANISMS TO CLINICAL POTENTIAL

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ABSTRACT

Metabolic disorders, including type 2 diabetes mellitus, obesity, dyslipidemia, and cardiovascular diseases, represent a major global health challenge characterized by complex and interrelated pathophysiological mechanisms such as insulin resistance, chronic inflammation, oxidative stress, and impaired lipid metabolism. Phytochemicals derived from natural sources have gained considerable attention due to their multifaceted therapeutic properties, including antioxidant, anti-inflammatory, hypoglycemic, and lipid-lowering effects. However, their clinical application is often limited by poor solubility, low bioavailability, rapid metabolism, and lack of targeted delivery. Nanotechnology-enabled drug delivery systems have emerged as a promising strategy to overcome these limitations by enhancing the pharmacokinetic and pharmacodynamic profiles of phytochemicals. Preclinical studies have demonstrated significant improvements in glycemic control, lipid regulation, and reduction of oxidative stress and inflammation, while emerging clinical evidence supports their potential translational value. Despite these advancements, challenges related to large-scale manufacturing, regulatory approval, long-term safety, and cost-effectiveness remain critical considerations. Overall, nanotechnology-enabled delivery of phytochemicals represents a transformative approach in the management of metabolic disorders, offering enhanced efficacy, targeted action, and improved patient compliance, with significant potential for future clinical and industrial applications.

Keywords: Nanotechnology, Phytochemicals, Metabolic Disorders, Drug Delivery

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INTRODUCTION

Metabolic disorders, encompassing conditions such as obesity, type 2 diabetes mellitus, dyslipidemia, and cardiovascular diseases, represent a major global health burden driven by complex interactions between genetic, environmental, and lifestyle factors. These disorders are characterized by interconnected pathophysiological mechanisms, including insulin resistance, chronic low-

grade inflammation, oxidative stress, and impaired lipid metabolism, which collectively contribute to increased morbidity and mortality. Despite their potential, the clinical translation of phytochemicals remains limited due to inherent challenges such as poor aqueous solubility, low bioavailability, rapid metabolism, instability under physiological conditions, and lack of targeted delivery, which significantly reduce their therapeutic efficacy. (David, 2025) To overcome these limitations, nanotechnology has emerged as a transformative approach in drug delivery, offering innovative platforms to enhance the pharmacokinetic and pharmacodynamic profiles of phytochemicals. Nanotechnology-enabled delivery systems, including nanoemulsions, liposomes, solid lipid nanoparticles,

nanostructured lipid carriers, polymeric nanoparticles, and self-nanoemulsifying drug delivery systems (SNEDDS), facilitate improved solubility, protection from degradation, controlled release, and enhanced cellular uptake of bioactive compounds. These nanoscale carriers can also be engineered for site-specific targeting, thereby maximizing therapeutic outcomes while minimizing systemic side effects. Furthermore, nanocarriers can modulate biological barriers such as intestinal epithelium and hepatic first-pass metabolism, leading to increased systemic availability of phytochemicals. Advances in nanotechnology have also enabled the incorporation of multifunctional properties, such as stimuli-responsive release and co-delivery of multiple bioactive, which are particularly beneficial in addressing the multifactorial nature of metabolic disorders (Alghamdi et al., 2025).

Role of Natural Products in Metabolic Disorders

Natural products have long been recognized as a valuable source of therapeutic agents in the management of metabolic disorders, offering a diverse array of bioactive compounds with multifaceted pharmacological activities. Metabolic disorders, including type 2 diabetes mellitus, obesity, dyslipidemia, and cardiovascular diseases, are characterized by complex pathophysiological mechanisms such as insulin resistance, chronic inflammation, oxidative stress, and altered lipid metabolism. In this context, natural products derived from plants, marine sources, and microorganisms have gained significant attention due to their ability to target multiple pathways simultaneously, thereby providing a holistic approach to disease management. Phytochemicals such as polyphenols, flavonoids, alkaloids, terpenoids, saponins, and glycosides have been extensively studied for their beneficial effects in regulating glucose homeostasis, improving insulin sensitivity, modulating lipid profiles, and reducing inflammatory responses (Al Bayati, 2025). For instance, compounds like curcumin, resveratrol, quercetin, and Berberine have demonstrated significant antidiabetic and cardio protective properties through mechanisms involving activation of AMP-activated protein kinase (AMPK), modulation of peroxisome proliferator-activated receptors (PPARs), inhibition of inflammatory cytokines, and enhancement of antioxidant defense systems. Additionally, natural products have shown potential in regulating angiogenesis and energy metabolism, thereby contributing to weight management and prevention of obesity-related complications. Unlike conventional synthetic drugs, which often target a single pathway and may be associated with adverse effects, natural products offer a safer profile with synergistic actions, making them suitable for long-term use in chronic conditions. Moreover, traditional medicinal systems such as Ayurveda and Traditional Chinese

Medicine have long utilized natural products for metabolic health, providing a rich foundation for modern drug discovery and development (Sharma et al., 2025).

Dyslipidemia and Lipid Metabolism Disorders

Dyslipidemia and lipid metabolism disorders are central components of metabolic syndrome and are strongly associated with an increased risk of cardiovascular diseases, including atherosclerosis, coronary artery disease, and stroke. Additionally, insulin resistance promotes the formation of small dense LDL particles, which are highly atherogenic due to their increased susceptibility to oxidation and enhanced ability to penetrate the arterial wall. Oxidized LDL further triggers endothelial dysfunction and inflammatory responses, accelerating plaque formation and vascular damage (Merolla et al., 2025). Lipid metabolism disorders are also influenced by genetic factors, dietary habits, sedentary lifestyle, and hormonal imbalances, which collectively exacerbate the dyslipidemia profile. Adipose tissue dysfunction plays a crucial role in this process by releasing excess free fatty acids into the circulation, which are taken up by the liver and contribute to hepatic steatosis and dysregulated lipoprotein production. Moreover, chronic low-grade inflammation associated with obesity further disrupts lipid metabolism by altering the expression of key enzymes and transcription factors, such as sterol regulatory element-binding proteins (SREBPs) and peroxisome proliferator-activated receptors (PPARs), which regulate lipid synthesis and oxidation. Hormonal regulators, including insulin, leptin, and adiponectin, also influence lipid metabolism, and their dysregulation contributes to metabolic imbalance. Clinically, dyslipidemia is managed through lifestyle modifications, including dietary interventions, physical activity, and pharmacological therapies such as statins, fibrates, and cholesterol absorption inhibitors. However, these treatments may be associated with adverse effects and may not fully address the multifactorial nature of lipid disorders. Consequently, there is growing interest in alternative and complementary approaches, including natural products and advanced drug delivery systems, to improve lipid profiles and reduce cardiovascular risk (Li et al., 2023).

Role of Adipokines and Hormonal Imbalance

Adipocytes and hormonal imbalance play a central role in the development and progression of metabolic disorders, particularly within the context of obesity and metabolic syndrome. Adipose tissue is now recognized not merely as an energy storage organ but as an active endocrine organ that secretes a variety of bioactive molecules known as adipokines, which regulate metabolic homeostasis, inflammation, insulin sensitivity, and energy balance. Key adipokines include leptin, adiponectin, resistin, visfatin, and inflammatory

cytokines such as tumor necrosis factor- α (TNF- α) and interleukin-6 (IL-6). Under normal physiological conditions, these adipocytes maintain a balanced metabolic state; however, in obesity and related disorders, adipose tissue undergoes hypertrophy and dysfunction, leading to altered secretion profiles that contribute to metabolic dysregulation. Leptin, primarily involved in appetite suppression and energy expenditure, is often elevated in obese individuals, yet paradoxically, leptin resistance develops, impairing its regulatory function.(Xie & Li, 2023) In contrast, adiponectin, which enhances insulin sensitivity and exhibits anti-inflammatory and anti-Atherogenicity properties, is significantly reduced in individuals with metabolic syndrome, thereby exacerbating insulin resistance and cardiovascular risk. Additionally, increased levels of pro-inflammatory adipocytes such as TNF- α and IL-6 promote chronic low-grade inflammation, which interferes with insulin signaling pathways and contributes to the development of type 2 diabetes mellitus. Hormonal imbalance further complicates this scenario, involving disruptions in insulin, glucagon, cortisol, and other endocrine regulators that are critical for maintaining glucose and lipid homeostasis. Insulin resistance, a hallmark of metabolic disorders, leads to compensatory hyperinsulinemia, which not only affects glucose uptake but also alters lipid metabolism, promoting hepatic lipogenesis and dyslipidemia. Cortisol, a stress hormone, when chronically elevated, contributes to central obesity, increased gluconeogenesis, and insulin resistance. Furthermore, imbalances in gut hormones such as ghrelin and incretins (GLP-1 and GIP) influence appetite regulation, glucose metabolism, and energy balance, thereby playing a significant role in metabolic disease progression(Choi et al., 2020).

Phytochemicals with Antidiabetic Potential

Phytochemicals with antidiabetic potential have emerged as promising therapeutic agents in the management of type 2 diabetes mellitus and associated metabolic disorders, owing to their ability to modulate multiple biochemical and molecular pathways involved in glucose homeostasis. Additionally, phytochemicals play a crucial role in regulating key signaling pathways such as AMP-activated protein kinase (AMPK), peroxisome proliferator-activated receptors (PPARs), and phosphoinositide 3-kinase/protein kinase B (PI3K/Akt), which are essential for maintaining glucose and lipid metabolism.(Firdous et al., 2025) The antioxidant properties of these compounds help mitigate oxidative stress, a major contributor to β -cell dysfunction and insulin resistance, while their anti-inflammatory effects reduce the production of pro-inflammatory cytokines that interfere with insulin signaling. Furthermore, phytochemicals have been shown to protect pancreatic β -cells from apoptosis, enhance glucose uptake in skeletal

muscle and adipose tissue, and modulate hepatic gluconeogenesis, thereby contributing to overall glycemic control. Some compounds, such as berberine, have also demonstrated the ability to alter gut microbiota composition, which plays a significant role in metabolic regulation and insulin sensitivity. Despite their therapeutic potential, the clinical application of phytochemicals is often limited by factors such as poor aqueous solubility, low bioavailability, rapid metabolism, and instability under physiological conditions. These limitations necessitate the development of advanced delivery systems to enhance their pharmacokinetic and pharmacodynamics profiles(Dutta, 2023).

Mechanisms of Action of Nano formulated Natural Products

The mechanisms of action of Nano formulated natural products in the management of metabolic disorders are multifaceted and involve both enhanced delivery characteristics and improved biological interactions at the cellular and molecular levels. Nano formulations, including lipid-based nanoparticles, polymeric carriers, Nano emulsions, and self-nanoemulsifying drug delivery systems, significantly enhance the therapeutic performance of natural bioactive compounds by overcoming inherent limitations such as poor solubility, low bioavailability, and rapid metabolic degradation. One of the primary mechanisms is the improvement in cellular uptake and permeability, as nanoscale carriers facilitate transcellular and paracellular transport across biological membranes, including the intestinal epithelium, thereby increasing systemic absorption. These systems also enable targeted delivery to specific tissues such as the liver, adipose tissue, and pancreas, which are key organs involved in metabolic regulation. Surface modification of nanoparticles with ligands or polymers further enhances receptor-mediated uptake, allowing precise targeting of diseased tissues.(Patel et al., 2024) At the molecular level, Nano formulated phytochemicals effectively modulate critical metabolic signaling pathways, including AMP-activated protein kinase (AMPK), peroxisome proliferator-activated receptors (PPARs), and the PI3K/Akt pathway, leading to improved insulin sensitivity, enhanced glucose uptake, and regulation of lipid metabolism. Additionally, Nano formulations provide sustained and controlled release of bioactive compounds, maintaining therapeutic concentrations over extended periods and reducing dosing frequency. Another important mechanism involves the protection of phytochemicals from enzymatic degradation and harsh gastrointestinal conditions, thereby preserving their structural integrity and pharmacological activity. Nano formulated natural products also exhibit enhanced antioxidant and anti-inflammatory effects by efficiently scavenging reactive oxygen species and inhibiting pro-inflammatory cytokines such as TNF- α and IL-6, which

are key contributors to insulin resistance and metabolic dysfunction. Furthermore, these systems can modulate gut microbiota composition, promoting beneficial microbial populations that influence metabolic pathways and energy homeostasis (Adetunji et al., 2021).

Anti-inflammatory and Antioxidant Mechanisms

Anti-inflammatory and antioxidant mechanisms play a pivotal role in the therapeutic efficacy of natural products and their Nano formulations in the management of metabolic disorders, as chronic low-grade inflammation and oxidative stress are fundamental drivers of disease progression. (Jomova et al., 2024) Concurrently, natural products exert anti-inflammatory effects by inhibiting the activation of NF- κ B and suppressing the production of pro-inflammatory mediators, thereby reducing tissue inflammation and improving insulin signaling. Nano formulations further enhance these effects by improving the stability, bioavailability, and targeted delivery of phytochemicals, ensuring higher intracellular concentrations at sites of inflammation and oxidative damage. For instance, Nano encapsulation protects sensitive compounds from degradation and facilitates sustained release, leading to prolonged antioxidant and anti-inflammatory activity. Additionally, nano-sized carriers improve cellular uptake, allowing efficient interaction with intracellular signaling pathways and organelles such as mitochondria, where oxidative stress is prominently generated. These systems also reduce systemic toxicity and enhance therapeutic specificity, thereby minimizing off-target effects. By attenuating oxidative stress and inflammatory responses, Nano formulated natural products help restore metabolic balance, improve insulin sensitivity, and prevent complications such as endothelial dysfunction and atherosclerosis (Aundhia et al., 2024).

Pharmacokinetics and Pharmacodynamics

Pharmacokinetics and pharmacodynamics are critical determinants of the therapeutic efficacy of Nano formulated natural products in the management of metabolic disorders, as they govern the absorption, distribution, metabolism, excretion, and biological effects of bioactive compounds. Traditional phytochemicals often exhibit poor pharmacokinetic profiles characterized by low aqueous solubility, limited intestinal permeability, rapid first-pass metabolism, and short systemic half-life, which significantly compromise their clinical utility. Nanotechnology-based delivery systems address these limitations by enhancing the bioavailability and stability of phytochemicals through improved solubilization and protection from enzymatic degradation. Nano formulations such as lipid nanoparticles, polymeric nanoparticles, liposomes, and Nano emulsions facilitate enhanced absorption via transcellular and paracellular pathways, as well as through lymphatic transport, thereby

bypassing hepatic first-pass metabolism (Nouri et al., 2020). This leads to increased plasma concentration and prolonged circulation time of the active compounds. Additionally, the small particle size and large surface area of nanocarriers enable better tissue distribution and cellular uptake, ensuring higher drug accumulation in target organs such as the liver, pancreas, and adipose tissue, which are central to metabolic regulation. From a pharmacodynamic perspective, nanoformulated natural products exhibit enhanced therapeutic activity due to sustained and controlled drug release, which maintains optimal drug levels over extended periods and reduces dosing frequency. These systems also enable targeted delivery through surface modification with ligands, allowing receptor-mediated uptake and improved specificity toward diseased tissues. As a result, the interaction of phytochemicals with molecular targets such as AMP-activated protein kinase (AMPK), peroxisome proliferator-activated receptors (PPARs), and insulin signaling pathways is significantly amplified, leading to improved glucose uptake, lipid metabolism, and anti-inflammatory responses. Furthermore, nanoformulations can reduce systemic toxicity and adverse effects by minimizing off-target distribution and ensuring localized drug action (Paul, 2025).

Preclinical Studies and Experimental Evidence

Preclinical studies and experimental evidence provide a crucial foundation for understanding the efficacy, safety, and mechanistic pathways of Nano formulated natural products in the management of metabolic disorders. Similarly, berberine-loaded nanoparticles have demonstrated improved glucose uptake and enhanced insulin signaling in adipocyte and muscle cell lines (Kambale et al., 2022). In vivo studies further validate these findings, using well-established animal models such as high-fat diet-induced obese mice, streptozotocin-induced diabetic rats, and genetic models of metabolic syndrome. These studies consistently report that Nano formulated natural products result in better glycemic control, reduced body weight gain, improved lipid profiles, and decreased systemic inflammation compared to conventional formulations. Toxicological evaluations in preclinical models also indicate that these Nano formulations are generally well-tolerated, with reduced systemic toxicity and minimal adverse effects when compared to higher doses of free phytochemicals (Ahmed et al., 2021). Furthermore, advanced imaging and bio distribution studies have confirmed targeted delivery and accumulation of Nano carriers in metabolically active tissues, supporting their role in site-specific therapy. Emerging evidence also highlights the potential of multifunctional Nano carriers capable of co-delivering multiple bioactive compounds or combining natural products with conventional drugs, resulting in synergistic effects. Despite these promising

results, challenges remain in translating preclinical findings to clinical applications due to differences in physiology, dosage scaling, and long-term safety considerations. Nonetheless, the growing body of experimental evidence strongly supports the potential of Nano formulated natural products as effective therapeutic strategies for metabolic disorders, providing a solid platform for further clinical investigation and drug development(Zubair et al., 2025).

Industrial and Commercial Potential

The industrial and commercial potential of Nano formulated natural products for metabolic disorders is rapidly expanding, driven by increasing global demand for effective, safe, and innovative therapeutic solutions that integrate natural bioactive with advanced drug delivery technologies. The growing prevalence of metabolic syndrome, diabetes, obesity, and cardiovascular diseases has created a substantial market opportunity for pharmaceutical, nutraceutical, and biotechnology industries to develop next-generation products with enhanced efficacy and patient compliance. Nano formulations such as Nano emulsions, solid lipid nanoparticles, nanostructured lipid carriers, liposomes, and polymeric nanoparticles offer significant advantages in improving the solubility, stability, and bioavailability of phytochemicals, thereby increasing their commercial viability. These technologies enable the transformation of traditional herbal products into scientifically validated, high-performance formulations that meet modern regulatory and quality standards(Patel et al., 2024). Intellectual property protection through patents for novel nanoformulations and delivery systems further enhances commercial prospects and encourages investment in research and development.(Patil & Baheti, 2025) The rise of personalized medicine and digital health technologies also presents new opportunities for tailoring nanoformulated therapies to individual metabolic profiles, thereby improving treatment outcomes. However, several challenges must be addressed to fully realize the commercial potential of these technologies, including high development costs, regulatory complexities, and the need for comprehensive safety and toxicity evaluations. Regulatory agencies such as the FDA and EMA are continuously evolving guidelines for

nanomedicine, requiring robust characterization, stability studies, and clinical validation. Market acceptance also depends on consumer awareness, trust in nanotechnology, and clear labeling of nano-based products. Despite these challenges, the convergence of nanotechnology and natural product research represents a promising frontier with significant industrial impact, offering innovative, market-ready solutions for managing metabolic disorders and contributing to the advancement of global healthcare and wellness industries(Radhakrishnan et al., 2022).

CONCLUSION

The nanotechnology-enabled delivery of phytochemicals represents a transformative and highly promising approach in the management of metabolic disorders, effectively bridging the gap between traditional natural therapeutics and modern pharmaceutical innovation. Metabolic disorders such as type 2 diabetes mellitus, obesity, dyslipidemia, and cardiovascular diseases are multifactorial in nature, involving complex interactions among metabolic, inflammatory, and hormonal pathways, which often limit the effectiveness of single-target therapies. Phytochemicals derived from natural sources offer a broad spectrum of biological activities, including antioxidant, anti-inflammatory, hypoglycemic, and lipid-lowering effects, making them ideal candidates for addressing these complex disease mechanisms. However, their clinical translation has historically been hindered by significant pharmacokinetic challenges such as poor aqueous solubility, low bioavailability, rapid metabolism, and instability under physiological conditions. At the molecular level, Nano formulated phytochemicals effectively modulate key signaling pathways, including AMP-activated protein kinase (AMPK), peroxisome proliferator-activated receptors (PPARs), and PI3K/Akt pathways, leading to improved insulin sensitivity, regulation of lipid metabolism, and attenuation of inflammatory responses. Furthermore, the integration of multifunctional and stimuli-responsive Nano carriers has opened new avenues for precision medicine, allowing for site-specific and condition-triggered drug release, which is particularly advantageous in managing chronic metabolic conditions.

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