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Phytochemical based nanoformulations: an advanced strategy for the management of metabolic syndrome

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ABSTRACT

Metabolic syndrome (MetS), a silent epidemic condition is characterized by a cluster of metabolic dysfunctions, including hypertension, central obesity, insulin resistance and atherogenic dyslipidemia, which collectively increase the risk of type 2 diabetes mellitus and cardiovascular diseases. The rising global prevalence of MetS and its association with increased morbidity and mortality have made it a significant public health concern. The complex pathophysiology of MetS, driven by the intricate interplay of metabolic, hormonal and inflammatory pathways, often results in partial therapeutic efficacy, treatment resistance and challenges in achieving sustained disease control. Recently, phytochemicals which are the bioactive compounds derived from plants have gained considerable attention for their therapeutic potential in managing MetS owing to their diverse pharmacological properties, such as anti-inflammatory, antioxidant and hypoglycemic effects. Phytochemicals like curcumin, resveratrol and epigallocatechin gallate have demonstrated efficacy in ameliorating metabolic derangements associated with MetS. However, their clinical application is often limited by poor bioavailability, rapid metabolism and low solubility. To address these limitations, nanoformulations of phytochemicals have been developed, leveraging advancements in nanotechnology to enhance their stability, solubility and bioavailability. Encapsulation in nanosystems, such as liposomes, polymeric nanoparticles, nanoemulsions and solid lipid nanoparticles, enables sustained release, targeted delivery and improved therapeutic efficacy while minimizing adverse effects. These nanoformulations facilitate precise delivery of active moieties to specific tissues or cellular targets, thereby optimizing therapeutic outcomes. This review highlights the potential of application of nanoformulated phytochemicals in the management of MetS, emphasizing their pharmacokinetic improvements and therapeutic benefits.

Keywords: Nanoformulations, Phytochemicals, Metabolic syndrome, Drug delivery systems, Nanotechnology, Nanocarriers.

INTRODUCTION

Metabolic syndrome (MetS) is a major health challenge, characterized by interconnected metabolic dysfunctions including insulin resistance, central obesity, atherogenic dyslipidemia and hypertension. These disturbances form a complex pathophysiological network, significantly increasing the risk of type 2 diabetes (T2D) by fivefold and cardiovascular diseases (CVD) by twofold, highlighting MetS as a key contributor to global morbidity and mortality [1]. Its rising prevalence, driven by sedentary lifestyles, poor diet, physical inactivity and genetic predispositions, underscores the need for effective management strategies.

Phytochemicals have attracted considerable attention for their potential in the prevention and management of MetS. They exhibit diverse pharmacological activities including antioxidant, anti-inflammatory and anticancer effects [2]. Flavonoids like quercetin contribute to cardiovascular protection and may aid diabetes management by modulating molecular pathways [3]. Their multifaceted activities make phytochemicals promising agents for targeting the complex pathophysiology of MetS.

However, clinical application is limited by poor bioavailability, low solubility and instability. Curcumin exemplifies these challenges, as poor solubility and rapid degradation necessitate high doses for efficacy [4]. Similar limitations affect other phytochemicals, highlighting the need for innovative delivery approaches.

Nanotechnology has emerged as a promising tool for addressing these challenges. Nanoformulations-based delivery systems enhance solubility, stability and bioavailability, while enabling controlled and

targeted delivery These nanosystems improve permeability across biological barriers and improve their therapeutic efficacy [5]. The high surface area-to-volume ratio and customizable physical and chemical attributes to optimize drug loading and targeted delivery thereby broadening the scope of phytochemical applications in managing MetS [6].

This review explores the therapeutic potential of phytochemicals and their nanoformulations in MetS management, highlighting recent advances in nano formulation technologies and delivery strategies to improve health outcomes in this complex disorder.

Pathophysiology of Metabolic Syndrome

MetS represents a multifaceted cluster of interrelated metabolic abnormalities, primarily characterized by insulin resistance, central obesity, hypertension and dyslipidemia. Together, these factors substantially increase the risk of T2D and CVD. Insulin resistance, often aggravated by visceral fat accumulation, drives systemic metabolic disturbances, while hypertension and dyslipidemia create a pro-atherogenic environment that elevates cardiovascular risk. As illustrated in Figure 1, the interaction of these metabolic disturbances underpins the development and progression of MetS.

The etiology of MetS is multifactorial, involving genetic susceptibility, epigenetic regulation, environmental exposures and lifestyle factors. While inherited traits shape individual predisposition, poor diet and sedentary behavior remain the strongest external drivers of its global rise [7,8]. Epigenetic mechanisms, including DNA methylation and histone modifications, mediate long-term effects of environmental inputs and can even produce heritable metabolic changes [9,10]. Early-life exposures, such as maternal obesity and adverse intrauterine conditions, further heighten susceptibility to metabolic disturbances later in life [7,11].

Chronic insulin resistance contributes to hyperglycemia, impaired lipid metabolism and ectopic fat deposition in the liver and skeletal muscle. In muscle, accumulation of intramyocellular lipids disrupts mitochondrial function [12] while in the liver, steatosis progresses to non-alcoholic fatty liver disease (NAFLD) and in severe cases to NASH, fibrosis and hepatocellular carcinoma [13,14]. These interlinked metabolic impairments ultimately magnify cardiovascular and systemic risks.

Chronic low-grade inflammation, which arises primarily from dysfunctional adipose tissue is also a hallmark of MetS. Excess adiposity alters the secretion profile of adipokines, increasing pro-inflammatory mediators such as leptin, Tumor Necrosis Factor-alpha (TNF- α), Interleukin-6 (IL-6), resistin and chemerin, while reducing protective adipokines like adiponectin [15]. This persistent inflammatory state contributes to progressive metabolic dysfunction and cardiometabolic complications.

Gut microbiota dysbiosis further amplifies this inflammatory milieu. Alterations in microbial composition disrupt intestinal homeostasis, compromise the gut barrier and degrade the mucus layer, thereby facilitating the systemic translocation of bacterial products such as lipopolysaccharide (LPS) often referred to as "leaky gut" [16,17]. Reduced microbial production of short-chain fatty acids impairs gut integrity, energy metabolism and hormone secretion (Glucagon-Like Peptide-1, Peptide YY) which favors adiposity and insulin resistance [18,19]. Moreover, bacterial translocation into adipose tissue perpetuates systemic low-grade inflammation and metabolic disruption, as explained in Figure 2 [20]. Diets rich in fat and refined carbohydrates further aggravate dysbiosis and intestinal permeability, accelerating the pathogenesis of MetS [17].

Phytochemicals in treatment of MetS

The management of MetS has increasingly incorporated phytochemicals, which offer diverse mechanisms targeting multiple aspects of the syndrome while minimizing side effects. By modulating physiological processes, phytochemicals aim to improve metabolic control and reduce the risk of associated CVD and T2D.

Phytochemicals exert therapeutic effects in MetS through antioxidant, anti-inflammatory and hypoglycemic properties. Curcumin, derived from turmeric, enhances insulin sensitivity, regulates lipid metabolism and reduces systemic inflammation [21]. Catechin A, a curcuminoid, supports weight management and improves lipid profiles [22]. Allicin, from garlic, improves glucose homeostasis, activates brown adipose tissue and reduces oxidative stress and inflammation [23,24].

Quercetin, a flavonoid in onions, exhibits anti-hyperglycemic and anti-hyperlipidemic effects while improving vascular function [25,26]. Berberine regulates peroxisome proliferator-activated receptor gamma (PPAR γ) and adenosine monophosphate-activated protein kinase (AMPK) signaling, maintaining lipid and glucose homeostasis, enhancing insulin sensitivity and reducing inflammation [27,28]. Resveratrol mitigates adipose tissue inflammation, enhances antioxidant defenses and modulates pro-inflammatory cytokines via nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) and Toll-like receptor (TLR) pathways [29,30].

Sulforaphane, from cruciferous vegetables, activates the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway, reducing oxidative stress and improving glucose metabolism, while modulating bile acid and fatty acid metabolism to alleviate metabolic-associated fatty liver disease [31,32]. Gingerol, particularly 6-gingerol, enhances mitochondrial function and inhibits triglyceride biosynthesis, thereby reducing cardiovascular risks [33-35].

Epigallocatechin gallate (EGCG), from green tea, inhibits adipogenesis, promotes adipocyte browning and improves energy metabolism, providing protection against T2D and cardiovascular complications [36,37]. Caffeine enhances insulin sensitivity and lipid profiles via gut microbiota and bile acid modulation [38]. Monacolin K, from red yeast rice, inhibits HMG-CoA reductase, reducing low-density lipoprotein (LDL) and triglycerides while increasing HDL. It also activates Sirtuin 1 (SIRT1) and AMPK pathways, promoting lipid catabolism and glucose regulation in MetS patients [39,40].

Limitations of Phytochemicals

Phytochemicals hold considerable therapeutic potential for managing MetS; however, their clinical application is limited by poor absorption, low solubility, environmental instability and extensive first-pass metabolism, all of which reduce bioavailability. Moreover, the lack of targeted delivery systems further compromises efficacy, while variability in bioactive concentrations, potential drug interactions and safety concerns at high doses present additional challenges. Overcoming these limitations requires advanced delivery systems, optimized formulations and standardized extraction techniques to enhance both therapeutic effectiveness and profiles.

A major challenge is poor water solubility, which restricts absorption and systemic availability, particularly for compounds such as curcumin [41], naringenin [42] and quercetin [43]. Poor chemical stability and rapid metabolic transformation further reduce efficacy, as seen with resveratrol [44], naringenin [42] and quercetin [43] which exhibit oral bioavailability below 5%.

Stability concerns also affect several phytochemicals. Compounds such as allicin [45], EGCG [46] and sulforaphane [47,48] are prone to degradation under heat, pH variations and oxidation. Addressing these issues through innovative drug delivery systems is essential to enhance bioavailability, stability and overall therapeutic potential,

thereby realizing the full clinical utility of phytochemicals in managing MetS.

Nanoformulations of Phytochemicals

Phytochemicals such as curcumin, quercetin, berberine, allicin and sulforaphane are widely recognized for their therapeutic potential, yet their clinical use remains restricted by poor solubility, low bioavailability and instability. To address these challenges, nanoformulation technologies including solid lipid nanoparticles (SLNs), liposomes, niosomes and polymeric nanoparticles (PNPs) have emerged as effective strategies. These carriers improve solubility, stability and absorption, while also enabling controlled and sustained release. By enhancing pharmacokinetics and facilitating targeted delivery, nanoformulations hold promise in managing MetS-related conditions such as diabetes, dyslipidemia, obesity and fatty liver, as highlighted in Figure 3.

Nano-based systems offer unique advantages owing to their high surface area, ability to cross biological barriers and potential for sustained release. Among them, nanoemulsions form stable dispersions that improve solubility, absorption and biological activities, while nanoemulsions extend these benefits to topical, oral and ocular applications [49,50]. Lipid-based systems such as phytosomes and SLNs further enhance stability and uptake; phytosomes achieve this by binding bioactives to phospholipids, whereas SLNs encapsulate hydrophobic compounds for controlled release and scalability [51,52].

Other versatile systems include self-nanoemulsifying drug delivery systems (SNEDDS), which form oil-in-water emulsions in gastrointestinal fluids to enhance absorption and reduce toxicity [53]. PNPs protect sensitive compounds and ensure targeted, controlled release [54] while nanogels combine hydrogel and nanoemulsion properties to provide high permeability, sustained release and non-invasive delivery [50].

More advanced carriers such as dendrimers and nanosponges further expand the scope of phytochemical delivery. Dendrimers, with their branched architecture, enhance solubility, stability and targeted release [55]. Nanosponges, often cyclodextrin-based, encapsulate hydrophobic compounds like curcumin and resveratrol in stable, cross-linked networks, offering improved therapeutic efficacy and safety [56,57].

Nanomaterials in Metabolic Syndrome

Nanoformulations of bioactive compounds have emerged as a pioneering strategy to enhance the therapeutic efficacy of natural compounds in managing MetS, a complex condition characterized by obesity, hypertension, dyslipidemia and insulin resistance. MetS poses a significant global health burden, contributing to the rising prevalence of CVD, T2D and NAFLD [58]. Despite the pharmacological potential of bioactives such as curcumin, EGCG, resveratrol and berberine, their clinical application is limited by poor bioavailability, low aqueous solubility and chemical instability [4]. Nanoformulations offer solutions through enhanced surface area-to-volume ratio, targeted delivery, sustained and controlled release and improved bioavailability, thereby optimizing pharmacokinetic and pharmacodynamic properties for effective MetS management [5,49]. Curcumin, a polyphenol from *Curcuma longa*, exhibits anti-inflammatory and antioxidant properties but suffers from poor pharmacokinetics. Turmeric derived nanovesicles enhancing lipolysis and inhibiting lipogenesis [59]. PLGA nanoparticles improve cardiovascular function and normalize blood pressure in diet-induced MetS models at lower doses than unformulated curcumin [60], while SNEDDS enhance curcumin bioavailability, improving lipid profile modulation in diabetic models [5].

EGCG, a potent antioxidant from *Camellia sinensis*, benefits from liposomal and metal-based nanoparticles, enhancing its bioavailability

and antioxidative property. These formulations mitigate oxidative stress, improve cardiovascular outcomes via Nrf2/HO-1 activation and regulate intercellular adhesion molecule-1 (ICAM-1) [61]. Resveratrol, encapsulated in oxidized starch-lysozyme nanocarriers, targets the liver, reduces triglyceride accumulation and improves insulin sensitivity through the AMPK/SIRT1/ Sterol regulatory element-binding protein-1c (SREBP-1c) pathway [62]. Nanoemulsions, liposomes and starch-based nanoparticles further enhance resveratrol's solubility, stability and bioavailability [63].

Ginsenosides from *Panax ginseng* formulated in SNEDDS and liposomes improve solubility and bioavailability while modulating phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) and AMPK-c-Jun N-terminal kinase (JNK) signaling pathways to regulate glucose homeostasis and lipid metabolism [64]. Quercetin, with antioxidant and anti-inflammatory effects, has been incorporated into SNEDDS and iron oxide nanoparticles, improving solubility, bioavailability, cardiovascular function and glycemic control [25,65].

Overall, nanoformulations represent a transformative advancement in MetS management. By improving bioavailability, stability and targeted delivery, nanotechnology overcomes limitations of conventional formulations and amplifies therapeutic efficacy. Nanovesicles, nanoparticles, nanoemulsions and liposomal carriers optimize pharmacokinetic and pharmacodynamic profiles, promoting improved lipid profile modulation, glucose homeostasis, oxidative stress reduction and cardiovascular health. As research in this field progresses, the development of innovative nanoformulations hold significant promise for advancing MetS therapeutics and enabling new clinical interventions in this multifactorial disorder.

Limitation of Nanoformulation

Nanoformulations of phytochemicals enhance stability, bioavailability and pharmacokinetics, offering promising strategies for managing MetS. However, clinical translation faces challenges including low absorption rates due to their large molecular sizes, which significantly reduces their therapeutic efficacy. Although nanotechnological approaches like polymeric and solid lipid nanoparticles have improved solubility and enabled controlled release, challenges such as potential toxicity, physicochemical instability and large-scale production constraints persist [66,67].

Nanoemulsions, solid lipid nanoparticles and SNEDDS have shown to improve therapeutic efficacy of compounds like curcumin, resveratrol and quercetin. However, comprehensive toxicity evaluations and clinical trials are essential to ensure their long-term safety and efficacy. Additionally, the preparation methods, choice of polymers and synthesis techniques significantly influence the physicochemical properties and therapeutic outcomes of nanoformulations, thereby necessitating rigorous standardization and validation [68,69].

Safety and toxicity concerns are critical in nanoformulations, particularly due to the unique physicochemical properties, such as size and surface charge, which influence their biological interactions and toxicity profiles. While natural polymers like chitosan show promise in mitigating these adverse effects, their systemic impacts and biocompatibility require thorough investigation. Even though several studies have demonstrated the efficacy of nanoformulations in reducing MetS markers of insulin resistance and oxidative stress, further research is necessary to confirm their long-term safety and minimize potential cytotoxicity [5].

Scalability and regulatory hurdles further complicate the application of these nanoformulations. Large scale production is constrained by financial and technical challenges, as well as the need to maintain stability and bioactivity during manufacturing. Regulatory agencies, including the Food and Drug Administration (FDA), require extensive data on biocompatibility, stability and clinical efficacy, which can be resource intensive and time consuming to generate [70]. Despite these

limitations, nanoformulations hold significant potential in addressing insulin resistance, oxidative stress and chronic inflammation and

overcoming these barriers is crucial for their therapeutic translation.

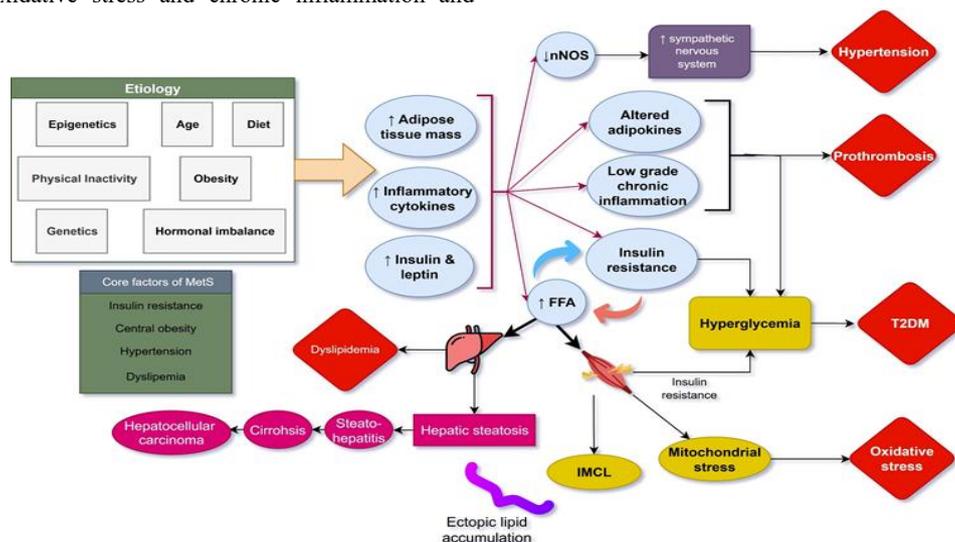


Figure 1: Overview of the pathophysiology of metabolic syndrome (MetS). **Abbreviations:** FFA – Free Fatty Acids; ins – inducible Nitric Oxide Synthase; T2DM – Type 2 Diabetes Mellitus; IMCL – Intramyocellular Lipid

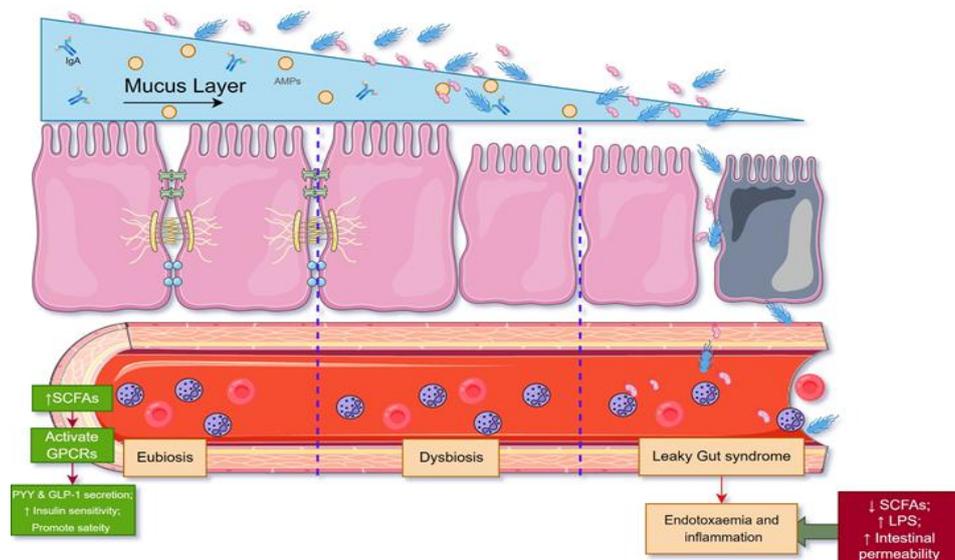


Figure 2: Dysbiosis and their impact on metabolic dysfunction. **Abbreviations:** SCFAs – Short-Chain Fatty Acids; GPCRs – G Protein-Coupled Receptors; PYY – Peptide YY; GLP-1 – Glucagon-Like Peptide-1; IgA – Immunoglobulin A; AMPs – Antimicrobial Peptides; LPS – Lipopolysaccharides

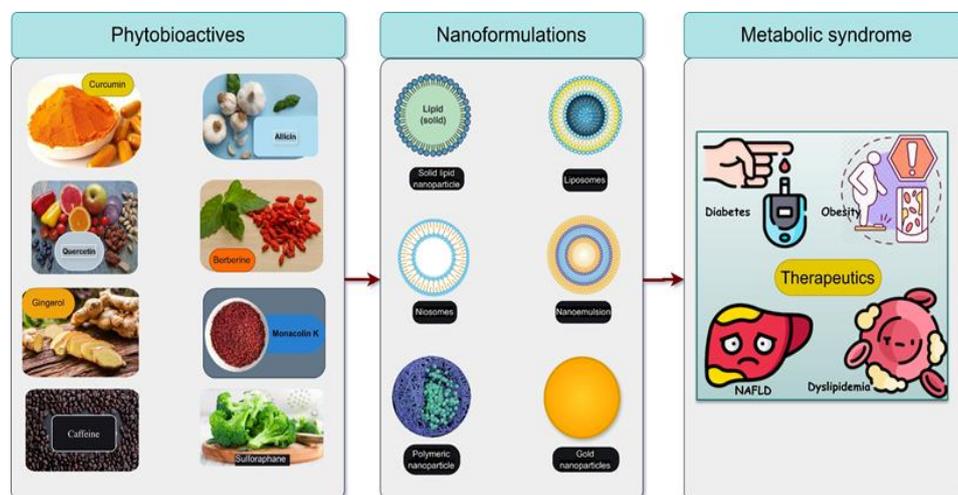


Figure 3: Therapeutic strategy of phytochemicals and its nanoformulation in metabolic syndrome and its associated disorders

CONCLUSION

Nanoformulations of phytochemicals marks a paradigmatic shift in MetS management, circumventing the key limitations of conventional therapies, such as poor bioavailability, rapid degradation and limited therapeutic efficacy. By leveraging advanced nanotechnology, these formulations enhance the solubility, stability and targeted delivery of bioactive compounds, thereby amplifying their therapeutic potential. Preclinical studies using nanoparticles, liposomes, nanoemulsions and solid lipid nanoparticles have demonstrated that targeted drug delivery leads to improved pharmacokinetics, sustained drug release and reduced side effects compared to traditional approaches. However, translating these advancements into clinical practice faces challenges due to concerns regarding toxicity, scalability and regulatory compliance. Overcoming these hurdles requires innovative strategies, biocompatible materials and rigorous clinical evaluations. Continued research efforts focusing on personalized medicine and scalable production strategies will be crucial in transforming these promising nanoformulations into clinically viable therapies, ultimately enhancing patient outcomes and mitigating the global burden of MetS.

Conflict of interest

The authors declared no conflict of interest.

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