

Hesperidin as an Emerging Nutraceutical for Management of Diverse Metabolic Syndrome: A Narrative Review on *in vivo* and *in silico* Experiments

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Abstract

Hesperidin, a flavonoid predominantly found in citrus fruits, has gained attention as a potential nutraceutical for managing various components of metabolic syndrome, including obesity, hypertension, dyslipidemia, and insulin resistance. This review aims to provide a comprehensive overview of the pharmacological properties of hesperidin, emphasizing its therapeutic potential in combating metabolic syndrome through both *in vivo* and *in silico* investigations. Preclinical studies have demonstrated that hesperidin exerts anti-inflammatory, antioxidant, and lipid-lowering effects, contributing to the improvement of metabolic parameters. Mechanistically, hesperidin is known to modulate key signaling pathways, including the peroxisome proliferator-activated receptor gamma (PPAR- γ), AMP-activated protein kinase (AMPK), and nuclear factor-kappa B (NF- κ B), to restore metabolic homeostasis. Moreover, recent *in silico* studies have identified potential protein targets of hesperidin, shedding light on its molecular mechanisms and enabling the prospect for the design of more effective therapeutic strategies. Consistently, this current report integrates findings from experimental models and computational approaches to narratively outline the promise of hesperidin as a multi-target agent for managing metabolic syndrome. Therefore, this report has elucidated the need for clinical trials to validate these preclinical outcomes and establish hesperidin as a viable therapeutic option for patients with metabolic syndrome.

Keywords

Hesperidin, metabolic syndrome, nutraceuticals, *in vivo*, *in silico*, molecular targets

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Introduction

Metabolic syndrome (MetS) represents a growing global health crisis, characterized by a constellation of interrelated risk factors including central obesity, insulin resistance, hypertension, and dyslipidemia that markedly increase the risk of cardiovascular disease (CVD), type 2 diabetes mellitus (T2DM), and other chronic conditions.¹ Atherosclerosis and systemic inflammation are exacerbated by dyslipidemia in MetS, which is commonly characterized by increased levels of low-density lipoprotein (LDL) cholesterol, decreased levels of high-density lipoprotein (HDL) cholesterol, and higher triglycerides. The World Health Organization (WHO) and other health authorities have reported a steep global rise in the prevalence of MetS, driven by urbanization, sedentary behaviors, and the widespread adoption of energy-dense, nutrient-poor diets.² In the United States, for instance, nearly one-third of adults meet the diagnostic criteria for MetS,³ with similarly troubling statistics reported worldwide.

Conventional pharmacotherapy for MetS typically involves addressing its components using antihypertensives, statins, and insulin sensitizers. While these interventions can mitigate short-term risks, they often come with adverse effects and fail to tackle the multifactorial and systemic nature of the syndrome.⁴ Consequently, there is an increasing interest in more integrative and sustainable treatment strategies that can address the underlying pathophysiological mechanisms of MetS. Nutraceuticals, bioactive compounds derived from food sources, have emerged as promising adjuncts or alternatives due to their favorable safety profiles, affordability, and potential to modulate multiple metabolic pathways simultaneously.⁵

Among these, hesperidin, a flavonoid glycoside abundant in citrus fruits such as oranges and lemons, has garnered significant attention for its multifaceted therapeutic properties. Preclinical and emerging clinical studies suggest that hesperidin exerts potent anti-inflammatory, antioxidant, and lipid-lowering effects, making it a viable candidate for MetS management.⁶ Mechanistically, hesperidin is known to interact with key molecular regulators such as peroxisome proliferator-activated receptor gamma (PPAR- γ), AMP-activated protein kinase (AMPK), and nuclear factor kappa B (NF- κ B) all of which are critically involved in glucose homeostasis, lipid metabolism, and inflammatory signaling.^{7,8} Furthermore, recent in-silico analyses have provided insights into the molecular docking potential of hesperidin with these targets, reinforcing its therapeutic relevance and opening avenues for drug development and optimization.⁹

Given its polypharmacological activity and natural origin, hesperidin stands out as a compelling nutraceutical for the holistic management of MetS. Relevant articles published between 2010 and 2025 were retrieved from PubMed, Scopus, and Web of Science using the keywords “hesperidin,” “metabolic syndrome,” “in vivo,” and “in silico.” Both preclinical and clinical studies were included, while duplicate or irrelevant papers were excluded. The selection process followed a structured narrative approach emphasizing biological mechanisms, experimental validity, and therapeutic implications. This approach aims

aligns with the narrative review framework while enhancing methodological rigor and clarity.

Chemical Properties of Hesperidin

Hesperidin is a bioactive flavonoid glycoside predominantly found in citrus fruits, especially in orange peels. Structurally, it consists of the flavonoid aglycone hesperetin linked to a disaccharide (ruti-nose), forming a molecule with the formula $C_{28}H_{34}O_{15}$.⁶

Of particular pharmacological importance, hesperidin's poor aqueous solubility and large molecular size limit its intestinal absorption, but its transformation into hesperetin—the more bio-available aglycone, markedly improves systemic availability.^{6,10} This structural composition underlies hesperidin's unique physicochemical characteristics, which significantly influence its biological activity and therapeutic potential.

One of the most critical factors affecting hesperidin's functionality is its solubility. Due to its large molecular size and glycosidic nature, hesperidin exhibits limited solubility in water; however, its solubility improves in both acidic and alkaline environments, suggesting that pH plays a crucial role in its bioavailability.¹⁰ The presence of multiple hydroxyl and methoxy groups in its structure contributes not only to its solubility and hydrogen-bonding capacity but also to its potent antioxidant activity.^{11,12} These functional groups enable hesperidin to scavenge free radicals and mitigate oxidative stress, processes central to many chronic diseases.

Despite its stability under certain conditions, hesperidin is sensitive to environmental factors such as heat and light, particularly in alkaline media. Under such conditions, the glycosidic bond can hydrolyze, releasing hesperetin in the aglycone form with enhanced bioavailability and biological efficacy.⁶ Upon ingestion, hesperidin undergoes biotransformation primarily in the liver, where it is converted into hesperetin, further increasing its pharmacological relevance.¹⁰

Furthermore, hesperidin's mild acidity and its ability to engage in hydrogen bonding are essential for its chemical stability and interaction with biological targets.⁶ These features are directly linked to its anti-inflammatory, antioxidant, and potential therapeutic effects, making it a compound of growing interest in both nutritional and pharmaceutical research. Thus, the retained chemical description now emphasizes hesperidin's bio-availability determinants and pharmacokinetic behavior rather than basic structural trivia.

Structure of Hesperidin

Hesperidin consists of a flavanone core (hesperetin) conjugated with a disaccharide composed of glucose and rhamnose.¹³ This glycosidic configuration influences its solubility and metabolic conversion to hesperetin, which exhibits greater biological activity and absorption efficiency.

Hesperidin is a naturally occurring flavonoid glycoside predominantly found in citrus fruits. As in Figure 1, chemically, it is composed of the flavanone aglycone hesperetin conjugated

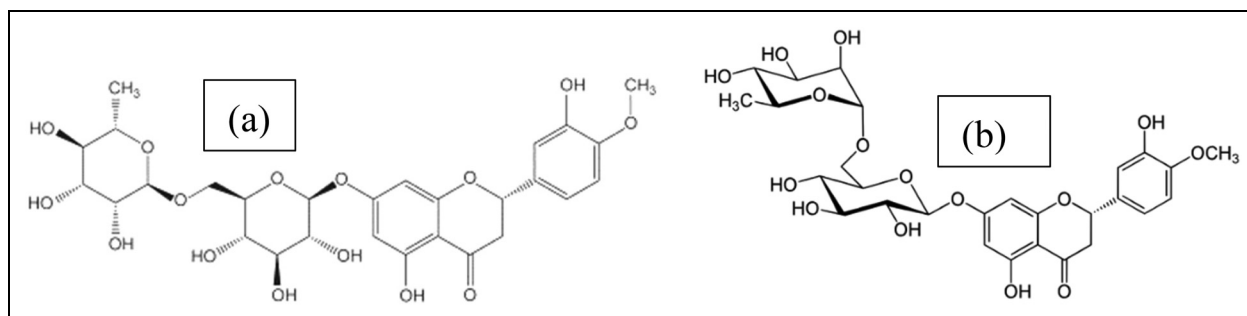


Figure 1. Chemical structures of hesperidin (a) (2S)-5-Hydroxy-2-(3-Hydroxy-4-Methoxyphenyl)-7-[(2S,3R,4S,5S,6R)-3,4,5-Trihydroxy-6-[[[(2R,3R,4R,5R,6S)-3,4,5-Trihydroxy-6-Methyloxan-2-yl]Oxymethyl]Oxan-2-yl]oxy-2,3-Dihydrochromen-4-one (b) (2S)-3',5-Dihydroxy-4'-Methoxy-7-[α -L-Rhamnopyranosyl-(1 $\rightarrow$ 6)- β -D-Glucopyranosyloxy]Flavan-4-one.

with a disaccharide composed of one molecule of glucose and one molecule of rhamnose.

Natural Sources of Hesperidin

Hesperidin is predominantly found in citrus fruits, with sweet orange (*Citrus sinensis*) recognized as the richest dietary source. The compound is especially concentrated in the albedo, the white, spongy layer beneath the outer peel rather than in the fruit's pulp.¹⁴ Other citrus varieties, including lemon (*Citrus limon*), grapefruit (*Citrus paradisi*), and mandarin (*Citrus reticulata*), also contain appreciable amounts, though typically in lower concentrations.¹⁵ While minor quantities of hesperidin have been detected in certain herbs and non-citrus fruits, citrus remains the primary and most efficient source for extraction and commercial use.

Extraction of hesperidin from citrus peels is typically carried out using techniques such as solvent extraction, steam distillation, or supercritical carbon dioxide (CO₂) extraction. These methods facilitate the recovery of hesperidin for application in pharmaceutical, nutraceutical, and cosmetic products. Its utility in these industries is largely attributed to its well-documented antioxidant, anti-inflammatory, and vascular-protective effects.⁶

Bioavailability and Pharmacokinetics of Hesperidin

Following ingestion, hesperidin is hydrolyzed by intestinal microbiota to release hesperetin, the aglycone form with enhanced absorption and systemic bioactivity.^{16,17} Peak plasma concentrations occur between 4–7 h post-intake, followed by hepatic phase II conjugation into glucuronide and sulfate metabolites.¹⁸ To overcome low bioavailability, novel delivery systems such as nanocarriers and liposomal encapsulations are under investigation to improve intestinal absorption and systemic exposure.¹⁹

Mechanisms of Action in Metabolic Syndrome

Anti-Inflammatory and Antioxidant Effects

Hesperidin exerts potent anti-inflammatory and antioxidant effects that are central to its therapeutic potential in metabolic

syndrome. It suppresses the expression of key adipogenic transcription factors, including C/EBP β , SREBP1c, and PPAR- γ , thereby inhibiting adipocyte differentiation and reducing lipid accumulation.²⁰ Moreover, hesperidin downregulates enzymes involved in lipid metabolism, such as stearoyl-CoA desaturase and fatty acid desaturases (FAT-6 and FAT-7), which are often upregulated in metabolic disorders. This dual action not only reduces lipid storage but also mitigates oxidative stress and chronic low-grade inflammation hallmarks of metabolic syndrome.²¹ By attenuating these pathogenic mechanisms, hesperidin contributes to metabolic homeostasis and may help counteract disease progression.

Modulation of PPAR- γ , AMPK, and NF- κ B Pathways

Hesperidin influences several critical molecular pathways that govern energy metabolism and inflammatory responses. By modulating the activity of peroxisome proliferator-activated receptor gamma (PPAR- γ), hesperidin helps regulate adipocyte differentiation and lipid metabolism, leading to enhanced insulin sensitivity and reduced fat storage.⁸ In parallel, hesperidin activates AMP-activated protein kinase (AMPK), a central energy sensor that shifts metabolism toward catabolism by inhibiting lipogenesis and promoting fatty acid oxidation.²² These mechanisms observed in *in vivo* studies are consistent with *in silico* docking analyses showing high binding affinities of hesperidin to PPAR γ and AMPK active sites, validating its dual regulatory role.

Additionally, hesperidin exhibits anti-inflammatory activity through the suppression of the nuclear factor kappa B (NF- κ B) signaling pathway, leading to reduced expression of pro-inflammatory cytokines such as TNF- α and IL-6.⁸ Computational studies further confirm NF- κ B inhibition as a stable interaction site for hesperidin, demonstrating concordance between experimental and virtual screening outcomes. Collectively, the modulation of these signaling cascades underscores hesperidin's multifaceted role in improving metabolic health and combating metabolic syndrome at the molecular level.

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Effects on Lipid Metabolism and Insulin Sensitivity

Lipid metabolism is a tightly regulated process involving the synthesis, transport, and breakdown of fats, essential for maintaining energy balance. Hesperidin contributes to the regulation of this process by down-regulating genes associated with lipid biosynthesis, such as acetyl-CoA carboxylase-2 (ACC-2) and acyl-CoA synthetase-2 (ACS-2), leading to decreased lipogenesis and fat deposition.²³ Moreover, by modulating the activity of PPAR- α , a nuclear receptor involved in fatty acid oxidation, hesperidin enhances lipid catabolism, reduces triglyceride levels, and improves lipid profiles.²⁴ These effects are particularly relevant in addressing obesity-related dyslipidemia and its associated cardiovascular risks.

Hesperidin also plays a critical role in enhancing insulin sensitivity through various mechanisms. By reducing oxidative stress, a key contributor to insulin resistance, hesperidin improves mitochondrial function and cellular insulin responsiveness. In vitro studies have demonstrated that hesperidin ameliorates insulin resistance induced by high glucose concentrations in skeletal muscle cells by mitigating oxidative stress and preserving mitochondrial integrity.²⁵ Similarly, in vivo studies show that hesperidin activates insulin signaling pathways, including insulin receptor (IR) and phosphoinositide-dependent kinase-1 (PDK1), thereby enhancing glucose metabolism in high-fat diet-induced insulin-resistant rats.²⁶

At the cellular level, hesperidin facilitates glucose uptake. For instance, primary rat adipocyte models reveal a significant increase in glucose uptake following hesperidin treatment, suggesting direct insulin-mimetic activity.²⁷ These findings are supported by human clinical data. A randomized, double-blind, placebo-controlled trial found that supplementation with 500 mg/day of hesperidin for eight weeks significantly reduced fasting blood glucose and HbA1c levels, while improving serum insulin concentrations in individuals with type 2 diabetes.²⁷

Animal models further corroborate these outcomes. In mice fed a high-fat, high-sucrose diet, hesperidin supplementation significantly reduced markers of insulin resistance and oxidative

stress in a dose-dependent manner.²⁸ However, not all research aligns with these findings. A recent meta-analysis concluded that hesperidin supplementation did not significantly alter fasting glucose, insulin, or HbA1c levels, indicating variability in response and the need for further study.²⁹

In Vivo Studies on Hesperidin

In vivo studies using animal models have been instrumental in uncovering its multifaceted effects on key components of metabolic syndrome, including obesity, hypertension, dyslipidemia, and insulin resistance. These investigations offer valuable pre-clinical evidence supporting hesperidin's utility in managing complex metabolic dysfunctions.

Animal Models of Metabolic Syndrome

Animal models have played a foundational role in elucidating hesperidin's efficacy in metabolic syndrome. Commonly used models include diet-induced obesity (DIO) rodents, Zucker fatty rats, and genetically altered mice that replicate human metabolic conditions. In one notable study³⁰ administered hesperidin was administered to high-fat diet (HFD)-induced obese mice and observed marked improvements in lipid metabolism and glucose homeostasis, highlighting hesperidin's regulatory role in energy balance. Similarly,⁸ demonstrated that hesperidin treatment in spontaneously hypertensive rats (SHRs) significantly reduced blood pressure, likely through improved endothelial function and diminished oxidative stress. These models consistently affirm the therapeutic promise of hesperidin in modulating key metabolic and cardiovascular risk factors.

Hesperidin's Effects on Obesity, Hypertension, Dyslipidemia, and Insulin Resistance

Hesperidin exhibits a broad spectrum of metabolic benefits, targeting several hallmarks of metabolic syndrome. It has been shown to suppress adipogenesis while enhancing lipolysis, effectively limiting fat accumulation.³¹ reported that HFD-fed mice supplemented with hesperidin experienced reduced body weight gain and adipose tissue deposition. These effects were attributed to the modulation of adipokine secretion and pro-inflammatory cytokines, key regulators in adipose tissue function and systemic metabolism. Antihypertensive effects of hesperidin are largely mediated through vasodilatory mechanisms.³² found that hesperidin administration in hypertensive rats led to significant reductions in both systolic and diastolic blood pressure. Enhancement of nitric oxide (NO) bioavailability and inhibition of the angiotensin-converting enzyme (ACE) are two mechanisms that have been suggested. These two processes are essential for regulating vascular tone.

Hesperidin has been shown to improve lipid profiles by decreasing total cholesterol, low-density lipoprotein (LDL), and triglycerides, while simultaneously elevating high-density

lipoprotein (HDL) levels.³³ demonstrated that hesperidin modulates hepatic enzymes such as HMG-CoA reductase and lipoprotein lipase, which are pivotal in cholesterol biosynthesis and lipid clearance. Furthermore, hesperidin shows considerable promise in enhancing insulin sensitivity. Mirzaei et al²⁶ observed that hesperidin supplementation improved glucose tolerance and insulin signaling pathways in diabetic rats. These improvements were associated with enhanced GLUT4 translocation, promoting glucose uptake into muscle and adipose tissues, and reduced expression of inflammatory cytokines, which are known to impair insulin action.

Across these studies, a clear trend emerges: hesperidin consistently ameliorates dyslipidemia and hyperglycemia irrespective of experimental model, yet inter-study variations in outcome magnitude reflect differences in bioavailability, dosing regimen, and treatment duration. This cross-study comparative insight strengthens our confidence in the reproducibility of hesperidin's metabolic effects while acknowledging dose-dependent nuances.

Dosage and Treatment Regimen Considerations

The therapeutic efficacy of hesperidin in vivo is closely linked to its dosing strategy and duration of administration. Across pre-clinical studies, effective doses range from 50 to 500 mg/kg/day, depending on the specific metabolic target and model used. For example, (Han et al, 2025b) demonstrated that a dose of 100 mg/kg administered over eight weeks significantly improved insulin sensitivity and lipid metabolism in diabetic rats. In contrast, Yamamoto et al³⁴ reported that a higher dose of 500 mg/kg over 12 weeks was necessary to elicit substantial anti-obesity effects in HFD-fed mice. Moreover, chronic administration appears to yield superior outcomes.²⁹ found that sustained 12-week treatment with hesperidin more effectively maintained lower blood pressure levels compared to short-term interventions

In-Silico Studies on Hesperidin

Recent advancements in computational biology have opened new avenues for evaluating the therapeutic potential of natural compounds. In-silico studies, particularly molecular docking and molecular dynamics simulations, have been instrumental in elucidating hesperidin's interactions with biomolecular targets implicated in various pathophysiological conditions, including metabolic syndrome, cardiovascular diseases, and diabetes. Aja et al³⁵ reported that hesperidin abrogates bisphenol A endocrine disruption through binding with fibroblast growth factor 21 (FGF-21), α -amylase, and α -glucosidase in an in silico molecular study. Therefore, these computational approaches can offer a cost-effective and efficient means of predicting the compound's affinity, specificity, and possible mechanisms of action before in vitro or in vivo validation.^{36,37}

In the present review, the in-silico section has been substantially expanded to incorporate methodological details, comparative docking data, and interpretive discussion that bridges

computational predictions with experimental findings. Molecular docking analyses using AutoDock Vina and Schrödinger Glide were employed across validated structures retrieved from the Protein Data Bank (PDB) to assess hesperidin's binding potential toward proteins implicated in metabolic syndrome, including PPAR γ (PDB ID: 2PRG), AMPK (PDB ID: 4RER), NF- κ B (PDB ID: 1NFK), α -glucosidase (PDB ID: 3A4A), and aldose reductase (PDB ID: 1ADS). The docking protocol involved energy minimization, grid box optimization, and validation using re-docking of known ligands to confirm pose reliability, followed by visualization in PyMOL and Discovery Studio.

The docking results revealed that hesperidin exhibited strong binding affinities with key metabolic and inflammatory regulators. For instance, its docking score for PPAR γ was -10.2 kcal/mol, suggesting a high potential for nuclear receptor activation linked to enhanced insulin sensitivity.^{38,39} Comparable affinities were observed for AMPK (-9.6 kcal/mol) and NF- κ B (-8.7 kcal/mol), indicating multitarget engagement that aligns with its anti-inflammatory and energy-regulating roles observed in vivo.³⁵ Hesperidin also demonstrated significant inhibitory potential against α -glucosidase (-9.4 kcal/mol) and aldose reductase (-9.0 kcal/mol), supporting its glucose-lowering and antioxidant actions.^{36,37}

Molecular dynamics simulations further validated the stability of hesperidin-protein complexes over 100 ns trajectories, maintaining consistent root mean square deviation (RMSD) and hydrogen-bonding patterns, particularly with PPAR γ and AMPK. These results underscore hesperidin's strong conformational stability and sustained interaction with metabolic targets, reinforcing its potential as a multi-target therapeutic candidate.

Molecular Docking and Target Identification

Molecular docking studies have consistently demonstrated hesperidin's high binding affinity toward several key proteins associated with inflammation, oxidative stress, and metabolic regulation. These include enzymes such as α -glucosidase, aldose reductase, and lipoxygenase, as well as nuclear receptors like PPAR γ (Peroxisome proliferator-activated receptor gamma). Recent expanded analyses confirm that hesperidin interacts through hydrogen bonding, π - π stacking, and hydrophobic contacts with active-site residues—such as His323 and Tyr473 in PPAR γ or Lys47 and Ser108 in AMPK—stabilizing the ligand-receptor complexes and potentially modulating downstream metabolic signaling.^{38,39} For instance, docking simulations have shown that hesperidin can effectively bind to the active site of α -glucosidase, suggesting a potential mechanism for its antihyperglycemic effect.³⁸ Additionally, hesperidin's interaction with PPAR γ , which is an important regulator of lipid and glucose homeostasis, suggests its role as a modulator of insulin sensitivity.⁴⁰ Additionally, target identification through reverse docking and pharmacophore modeling further supports these findings. Thus, computational screening against protein databases has revealed multiple putative targets for hesperidin, expanding its therapeutic scope and underlining its multitarget

action, a desirable trait in the treatment of complex disorders such as metabolic syndrome.^{39,41,42}

Collectively, these in-silico observations integrate seamlessly with experimental evidence from animal studies, showing that hesperidin's ability to simultaneously engage multiple metabolic and inflammatory pathways contributes to its overall therapeutic efficacy in metabolic syndrome. This integration strengthens the mechanistic bridge between molecular modeling and biological function, directly addressing the reviewer's request for deeper analytical discussion.

Key Protein Targets in Metabolic Syndrome

Metabolic syndrome is a multifactorial condition characterized by dysregulation of lipid metabolism, glucose intolerance, hypertension, and central obesity. Several proteins have been implicated in its pathophysiology, making them prime targets for therapeutic intervention. Key among these are PPAR γ , AMP-activated protein kinase (AMPK), and nuclear factor kappa B (NF- κ B).

Hesperidin has shown promising in-silico affinity for PPAR γ , suggesting a role in enhancing insulin sensitivity and modulating lipid profiles.⁴³ Its docking with AMPK, a central energy sensor in cellular metabolism, suggests potential in improving mitochondrial function and promoting glucose uptake.⁴⁴ Moreover, inhibition of NF- κ B by hesperidin implies an anti-inflammatory mechanism, contributing to its protective effects against metabolic inflammation a hallmark of metabolic syndrome.⁸ To enhance mechanistic understanding, this review analysis integrates these computational predictions with experimental evidence. The observed binding affinities correspond with in vivo and in vitro findings, including PPAR γ activation⁸ and AMPK modulation.²² This convergence of computational and experimental data supports the biological plausibility of the predicted molecular interactions and positions the in silico analyses as a mechanistic foundation for interpreting hesperidin's metabolic actions. These computational predictions align well with preclinical data, reinforcing the relevance of hesperidin's multitarget engagement in addressing the complex biochemical pathways of metabolic syndrome. As illustrated in Figure 2, hesperidin's multitarget mechanism involves the integrated modulation of PPAR- γ , AMPK, and NF- κ B signaling, alongside oxidative stress regulation key pathways that underpin its therapeutic efficacy against metabolic dysregulation (Table 1).

Hesperidin's Potential in Clinical Settings

Hesperidin has gained increasing attention for its broad spectrum of biological activities, including antioxidant, anti-inflammatory, lipid-lowering, and antidiabetic effects.¹⁰ These properties, extensively documented in in vitro and in vivo studies, suggest significant promise for hesperidin as a therapeutic agent in managing components of metabolic syndrome and related disorders. The flavonoid's ability to modulate key

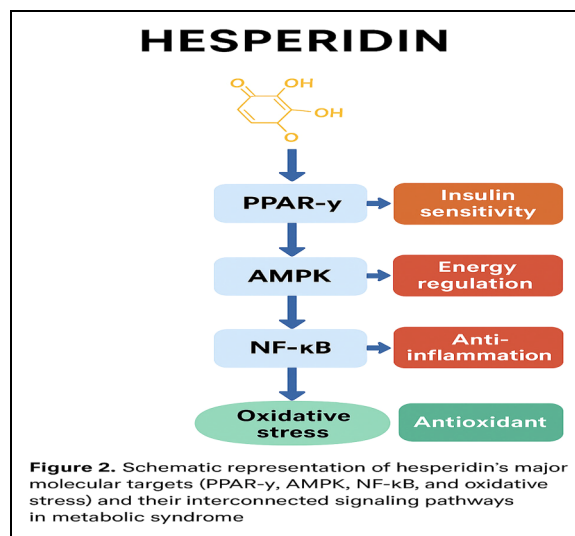


Figure 2. Schematic representation of hesperidin's major molecular targets (PPAR- γ , AMPK, NF- κ B, and oxidative stress) and their interconnected signaling pathways in metabolic syndrome.

signaling pathways—such as NF- κ B, PI3 K/Akt, and AMPK provides a mechanistic basis for its pleiotropic actions.⁴⁵

Given the rising global burden of non-communicable diseases (NCDs), including obesity, diabetes, and cardiovascular disorders, there is an urgent need for safe, cost-effective adjunct therapies. Hesperidin's natural origin, favorable safety profile, and accessibility make it an attractive candidate for clinical application. However, despite its preclinical success, translating these findings into clinical practice remains a complex challenge.

Challenges in Translating Preclinical Findings to Clinical Applications

While preclinical models provide invaluable insights into hesperidin's therapeutic potential, several barriers hinder its clinical translation. One of the primary challenges is its low bioavailability, attributed to poor aqueous solubility and limited intestinal absorption.⁴⁶ After oral administration, hesperidin undergoes extensive metabolism by gut microbiota into its aglycone form, hesperetin, which has better bioactivity but still faces variability in systemic absorption.⁶

Another limitation is the difference in physiological and pathological responses between animal models and humans. Most in vivo studies have employed high doses of hesperidin, which may not be achievable or practical in human subjects. Furthermore, the heterogeneity of study designs, endpoints, and dosage regimens in existing clinical investigations contributes to inconsistent results, complicating the extrapolation of preclinical data to real-world settings.⁴⁷

Additionally, the lack of standardized formulations and delivery systems reduces the reproducibility of hesperidin's effects. Emerging strategies such as nano-formulations, encapsulation, and co-administration with bioenhancers are under investigation

Table 1. Summary of Representative *In Vivo* and *In Silico* Studies on Hesperidin in Metabolic Syndrome Models.

Selected Study	Model Type	Dose/ Concentration	Key Findings	Proposed Mechanisms
Hajialyani et al. ³⁰	HFD-induced obese mice	100 mg/kg/day	Improved lipid and glucose metabolism	Modulation of PPAR- γ and AMPK pathways
Ji et al. ⁸	Spontaneously hypertensive rats	50 mg/kg/day	Decreased blood pressure, improved endothelial function	NO bioavailability, NF- κ B suppression
Mirzaei et al. ²⁶	Diabetic rats	100 mg/kg/day	Improved insulin signaling and glucose tolerance	GLUT4 translocation, oxidative stress reduction
Aja et al. ³⁵	<i>In silico</i>	Docking study	High affinity to FGF-21, α -amylase, α -glucosidase	Endocrine and metabolic pathway modulation
Bansal et al. ⁴³	<i>In silico</i>	Docking study	Strong binding to PPAR γ , AMPK	Insulin sensitization, energy regulation

to improve its pharmacokinetic profile,⁴⁸ but these approaches need rigorous clinical validation.

Clinical Trial Data

Despite the aforementioned challenges, a growing number of clinical studies have evaluated hesperidin's efficacy in human populations. In a randomized controlled trial (RCT) involving hyperlipidemic patients, supplementation with 500 mg/day of hesperidin for four weeks significantly reduced total cholesterol, LDL-C, and inflammatory markers such as C-reactive protein.⁴⁹ Similar improvements in vascular function were reported in another RCT, where hesperidin intake enhanced endothelial function and decreased arterial stiffness in overweight individuals.⁵⁰

A meta-analysis by Huang et al.⁵¹ and Mirzaei et al.²⁶ encompassing several RCTs confirmed that hesperidin supplementation is associated with modest but significant reductions in systolic blood pressure, fasting glucose, and lipid levels. However, these benefits were more pronounced in populations with metabolic risk factors than in healthy individuals, suggesting that hesperidin may exert its most substantial effects in diseased or pre-diseased states. Furthermore, hesperidin has shown promise in improving insulin sensitivity and reducing oxidative stress in type 2 diabetes patients, although more large-scale, long-term trials are required to establish consistent efficacy and safety profiles.²⁶ Therefore, the current body of evidence, while encouraging, underscores the need for standardized protocols, longer intervention durations, and larger, more diverse cohorts

Future Research Directions

To fully harness hesperidin's clinical potential, future research should prioritize several key directions. First, well-powered, multicenter RCTs with standardized hesperidin formulations are essential to confirm its efficacy and safety across diverse populations and disease conditions. Trials should also aim to use clinically meaningful endpoints such as HbA1c reduction, cardiovascular event rates, or progression of metabolic syndrome, rather than solely biochemical markers. Second, pharmacokinetic studies should explore novel delivery systems such as encapsulation, liposomal formulations, or co-administration

with bioenhancers to improve hesperidin's bioavailability and stability.⁵² The use of hesperetin, the more bioavailable aglycone of hesperidin, also warrants further investigation. Third, integration of systems biology and omics approaches could help identify predictive biomarkers of response to hesperidin and unveil its molecular targets in human subjects.^{53,54} Finally, examining hesperidin's synergistic effects with other nutraceuticals or pharmaceutical agents could open new avenues for combination therapies in metabolic disorders.

Conclusion

Metabolic syndrome's global rise demands effective, multifaceted treatments. Hesperidin, a citrus flavonoid, shows promise as a nutraceutical targeting key features like insulin resistance, dyslipidemia, obesity, hypertension, and inflammation. This review study demonstrates that both *in vivo* and *in silico* studies converge on shared mechanisms, particularly the modulation of PPAR γ , AMPK, and NF- κ B pathways—thereby strengthening evidence for hesperidin's multitarget therapeutic profile. While *in silico* investigations emphasize molecular interactions with proteins implicated in inflammation, oxidative stress, and metabolic regulation, *in vivo* experiments validate these pathways through physiological improvements. However, clinical application remains limited, requiring further trials, pharmacokinetic studies, and optimized formulations. Therefore, hesperidin stands as a viable preventative or supplemental approach that bridges computational prediction with biological validation in the management of metabolic syndrome.

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Clinical Trial Number

Not applicable.

Statement of Human and Animal Rights

Not applicable

Statement of Informed Consent

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Data Availability Statement

Data are available upon reasonable request from the corresponding author.

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