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Review Article

Therapeutic potential of p-coumaric acid in metabolic syndrome: molecular mechanisms, preclinical evidence, and translational prospects

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Abstract

Objective: Metabolic syndrome (MetS) is a multifaceted condition characterized by interconnected risk factors such as hyperglycemia, dyslipidemia, insulin resistance, hypertension, and central obesity. These factors increase the risk of cardiovascular disorders and type 2 diabetes. Due to the limitations of current pharmacological treatments, plant-derived polyphenols are being investigated as potential multitarget therapeutic candidates. This review critically explores the pharmacological potential of p-coumaric acid (p-CA), an abundantly present dietary phenolic acid, in addressing MetS.

Materials and Methods: A literature search using PubMed, Scopus, and Web of Science identified studies that highlighted the therapeutic potential and targeted molecular pathways of p-coumaric acid in preclinical studies.

Results: Preclinical findings suggest that p-CA confers benefits through multiple mechanisms, such as reducing oxidative stress, inhibition of proinflammatory cytokines through NF-κB suppression, and improving insulin sensitivity through IRS-1/PI3K/Akt pathway, and regulating lipid metabolism through AMPK, PPARα, and SREBP-1c signaling. Collectively, these effects lead to better glucose tolerance, improved lipid profiles, and enhanced liver function in high-fat diet and diabetic animal models.

Conclusion: With its pleiotropic activities and favorable safety profile, p-CA shows promise as a nutraceutical candidate for the prevention and management of MetS. Nonetheless, clinical evidence remains insufficient. Future research should prioritize improving its bioavailability, defining optimal dosing strategies, and conducting rigorous clinical trials to confirm its therapeutic potential.

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Introduction

Metabolic syndrome (MetS) is a complex metabolic disorder that involves several interrelated risk factors including insulin resistance, dyslipidemia, hyperglycemia, central obesity, and high blood pressure (Fahed et al. 2022). The presence of any three of these conditions serves as a diagnostic criterion of MetS established by the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) and the International Diabetes Federation (IDF) (Nwankwo, Okamkpa and Danborno 2022). This complex overlapping of these factors remarkably enhances the chances of developing non-alcoholic fatty liver disease (NAFLD), type 2 diabetes mellitus (T2DM), and cardiovascular diseases (CVD). All of these factors are also the leading causes of mortality and morbidity. Generally, the South Asian population is known to have a high prevalence rate of diabetes, obesity, and hypertension, largely due to the dietary patterns and sedentary lifestyle (Pandit et al. 2012). In Pakistan, a prominent South Asian country, a study was recently conducted to estimate the prevalence of MetS by using two different methods, and prevalence was reported to range from 29 to 49% (Naveel et al. 2022). Whereas globally, after meeting the diagnostic criteria, the increasing burden of Mets is estimated to be one-quarter of the adult population. Nonetheless, the prevalence is increasing in both developed and developing nations, primarily due to higher calorie intake, inactive lifestyle, and the trend of urbanization (Saklayen 2018). Traditionally available pharmacological therapies including hypoglycemia drugs, hypotensive drugs, statins, and weight loss drugs, mainly focus on a single aspect of the syndrome instead of focusing core systemic imbalance (Lim and Eckel 2014). Furthermore, long-term usage of these drugs has been associated with side effects, poor patient compliance, and various other issues. These limitations have prompted an increased research interest in the exploration of safer and multifactorial therapeutic alternatives, particularly derived from natural sources.

In this context, polyphenols, which are naturally occurring compounds present in cereals, fruits, vegetables, and herbs, have gained great attention because of their broad spectrum of pharmacological activities (Mustafa et al. 2022). Among these polyphenols, p-coumaric acid (p-CA; 4-hydroxycinnamic acid; HCA) is commonly present in honey, whole grains, wine, tomatoes, and apples. Its reported therapeutic activities include antioxidant, antihyperglycemic, antihyperlipidemic, and anti-inflammatory properties (Zaman et al. 2023). Structurally, p-CA is composed of a hydroxylated aromatic ring along with a propenoic acid side chain, which plays a crucial role in its bioactivity and capability to influence key metabolic pathways (Pei et al. 2016). Although various preclinical studies have reported the benefits of p-CA in individual components of MetS, a comprehensive overview of its mechanisms and therapeutic significance in MetS is still lacking. To address this gap, this review critically evaluates the available evidence on the pharmacological effects of p-CA on MetS. Particularly, it focuses on its molecular pathways, cellular targets, biological activities, preclinical outcomes, and translational challenges to outline future directions. Furthermore, it addresses the following key aspects: how does p-CA concurrently regulate the core interconnected pathways driving Mets (AMPK, PI3K/Akt, NF-κB)? It further explores the strength and limitations of current preclinical evidence. Lastly, it looks into the definitive translational barriers, clinical gap, and future strategies to overcome these barriers and gaps. By critically evaluating these aspects, this review provides a unique integrated perspective on therapeutic potential of p-CA, via modulating cross-talk between different pathways and a forward-looking roadmap for clinical translation.

Methods and Materials

A literature search using PubMed, Scopus, and Web of Science identified studies that highlighted the therapeutic potential and targeted molecular pathways of p-CA in preclinical studies. We used following keywords: metabolic syndrome" OR "p-coumaric acid" OR "signaling pathway". Data inluded original preclinical studies, isolated treatments of p-coumaric acid and outcomes related to metabolic syndrome components.

Results

Sources and bioavailability of p-CA

Natural sources of p-CA

p-CA is a prominent hydroxycinnamic acid belonging to the class of phenolic compounds. It is ubiquitously distributed in the plant kingdom and commonly found in a wide variety of dietary sources. These include fruits (such as apples, pears, and grapes), vegetables (like peppers and onions), legumes, cereals (including rice, wheat, and corn), and derived products such as wine, vinegar, and honey (Figure 1) (Chen et al. 2024). It is also present in several medicinal plants and herbs traditionally used in natural therapies. It is synthesized through the shikimate pathway. The shikimate pathway plays a central role in the secondary metabolism of plants. Through chorismate, it results in the production of aromatic amino acids such as tyrosine and phenylalanine. Afterwards, the enzyme phenylalanine ammonia-lyase or tyrosine ammonia-lyase catalyzes the deamination process, which produces cinnamic acid (El-Seedi et al. 2012). Because of its abundant occurrence in the human diet, p-CA is known as one of the most commonly used phenolic acids.

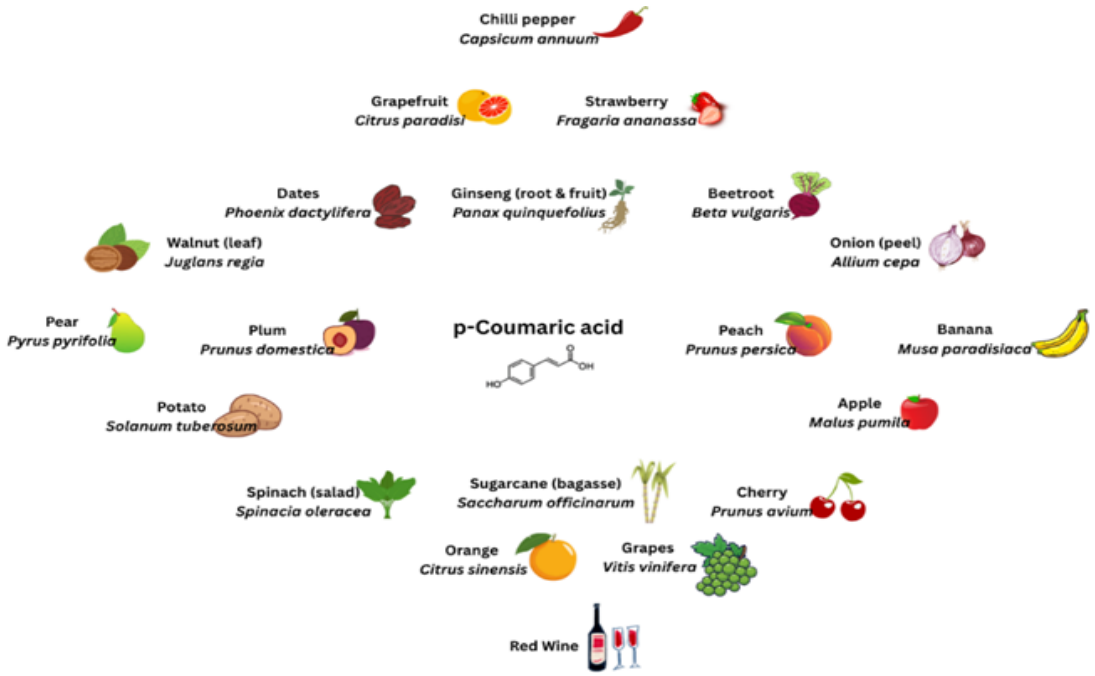

Figure 1. Natural sources of p-coumaric acid

Absorption, metabolism, and bioavailability

The absorption and bioavailability of pure cinnamic acids in humans have not been comprehensively explored, primarily due to differences in individual dietary patterns and the diverse food variety consumed. Studies suggest that dietary polyphenols, especially cinnamic acids, have limited intestinal absorption, with approximately 10% of absorption associated with their interaction with other compounds present in the plant cell wall. After intestinal absorption, these

polyphenols undergo microbial metabolism in the colon, resulting in the production of metabolites such as phenylpropionic and benzoic acids (Leonard et al. 2021). Most of the free cinnamic acids are absorbed intact through the gastrointestinal tract, while HCA esters and HCAs attached to carbohydrate chains are hydrolyzed by enzymes (Nguyen et al. 2021). The absorption rate and extent of HCAs generally depend on their structure after ingestion. Studies have shown that the absorption capacity of bound HCAs by specific enterocytes in the gastrointestinal wall is lower than their free forms (Rodriguez-Duran et al. 2014; Wang et al. 2023). The p-CA is rapidly absorbed after oral administration. After a dose of 100 μmol/kg, the reported t_{max} (time to reach maximum plasma levels) was 10 min (C_{max} = 165.7 μmol/L), (Konishi, Hitomi and Yoshioka 2004). While another study reported a faster increase (t_{max} = 3.72 min) (Meng et al. 2006). It is readily absorbed from the gastrointestinal tract in the free form. Approximately 57.8% of plasma p-CA stays in free form 10 min after administration, with 50% of free form remaining even after one hour (Konishi, Hitomi and Yoshioka 2004).

Pathophysiological basis of MetS

The MetS involves a cascade of metabolic disruptions that cluster together and significantly increase the risk of developing CVD, T2DM, and NAFLD (Chen and Pang 2021). Therefore, understanding the underlying pathophysiological mechanism is required to identify therapeutic targets and to evaluate the potential of compounds like p-CA.

Insulin resistance and hyperglycemia

Insulin resistance is the main pathophysiological mechanism involved in the progression of MetS. In this condition, insulin-responsive tissues such as skeletal muscle, liver, and adipose tissue become less sensitive to circulating insulin, which triggers a compensatory overproduction of insulin from pancreatic β-cells, resulting in hyperinsulinemia. Reduced insulin sensitivity causes impaired glucose uptake by skeletal muscle, resulting in hyperglycemia, which is further exacerbated by unchecked gluconeogenesis by the liver, ultimately leading to T2DM (Da Silva et al. 2020). Besides its effects on glucose metabolism, insulin resistance in adipose tissue increases lipolysis, generating free fatty acids that promote triglyceride synthesis in the liver, along with the formation of small, dense low-density lipoproteins(LDL-C) particles and a reduction in high-density lipoproteins (HDL) cholesterol, characteristic of atherogenic dyslipidemia (Fonseca 2005). The combined effect of hyperinsulinemia, hyperglycemia, and dyslipidemia promotes vascular resistance. This, in turn, not only disrupts nitric oxide (NO) regulated vasodilation but also augments sympathetic tone and sodium retention in the kidneys, ultimately resulting in hypertension. Adding to this burden, visceral adiposity further disturbs the systemic homeostasis by secreting proinflammatory cytokines and adipokines, generating a condition of chronic low-grade inflammation (Tylutka et al. 2023). Overall, these interconnected and overlapped abnormalities establish the clinical features of MetS and substantially increase the risk of CVD and renal complications.

Chronic inflammation

Chronic low-grade inflammation, another hallmark of MetS, is both a driver and a consequence of metabolic disruptions in MetS. As mentioned earlier, adipose tissue dysfunction triggers the secretion of adipokines and pro-inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and monocyte chemoattractant protein-1 (MCP-1). These mediators aggravate systemic insulin resistance and endothelial dysfunction (Montefusco et al. 2021). This inflammatory milieu activates innate

immune pathways of toll-like receptor (TLR) signaling and the Nod-like receptor pyrin domain containing 3 (NLRP3) inflammasome (Gora, Ciechanowska and Ladyzynski 2021), which further amplifies hyperglycemia, hypertension, and dyslipidemia, perpetuating a vicious cycle of cardiometabolic risk. This interaction highlights the cross-talk between metabolic and immune regulation.

Oxidative stress

Oxidative stress plays a pivotal role in the initiation and progression of metabolic syndrome by disrupting redox homeostasis and promoting cellular dysfunction (Irfan et al. 2024). Excess nutrient intake, insulin resistance, and dyslipidemia lead to mitochondrial overproduction of reactive oxygen species (ROS) which in turn, damage lipids, proteins, and DNA. In adipose tissue, oxidative stress amplifies inflammatory signaling and impairs adipokine secretion, thereby aggravating systemic insulin resistance (Ma et al. 2024). Similarly, endothelial oxidative stress reduces NO bioavailability, contributing to vascular dysfunction and hypertension. Moreover, ROS-mediated activation of stress-sensitive pathways, including nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and c-Jun N-terminal kinase (JNK), establishes a vicious cycle linking oxidative damage with chronic inflammation (Yu et al. 2024). Thus, oxidative stress is a critical target for therapeutic interventions.

Key molecular pathways

Multiple signaling pathways are implicated in the development and progression of MetS, including:

AMP-activated protein kinase (AMPK):

A central regulator of energy metabolism, AMPK activation improves glucose uptake, enhances fatty acid oxidation, and inhibits lipogenesis. AMPK functions as a cellular energy sensor and master regulator of metabolic homeostasis (Garcia and Shaw 2017). It is activated under conditions of energy stress, such as increased AMP/ATP and ADP/ATP ratios, where it restores balance by promoting catabolic pathways and inhibiting anabolic processes (Hardie, Ross and Hawley 2012). Upon activation, AMPK enhances glucose uptake in skeletal muscle through glucose transporter 4 (GLUT4) translocation, stimulates fatty acid oxidation by phosphorylating and inhibiting acetyl-CoA carboxylase (ACC), and suppresses lipogenesis via downregulation of sterol regulatory element-binding protein-1c (SREBP-1c) (Lin et al. 2021). In the liver, AMPK inhibits gluconeogenesis and cholesterol synthesis, thereby improving systemic insulin sensitivity (Johanns, Hue and Rider 2023). Beyond energy regulation, AMPK exerts antioxidant and anti-inflammatory effects by modulating signaling cascades such as NF-κB and Nrf2, linking it to the prevention of metabolic syndrome and its cardiovascular complications (Huang et al. 2024; Xu et al. 2024). Given its broad metabolic impact, AMPK is a promising therapeutic target for metabolic disorders.

Peroxisome proliferator-activated receptors (PPARs):

PPARs are ligand-activated nuclear receptors that play a pivotal role in lipid and glucose metabolism, energy homeostasis, and inflammation. There are three main isoforms, i.e. PPAR-α, PPAR-γ, and PPAR-δ/β, each with distinct tissue distribution and metabolic functions (Tyagi et al. 2011). PPAR-α, predominantly expressed in the liver, heart, and skeletal muscle, enhances fatty acid β-oxidation, reduces triglyceride accumulation, and improves lipid clearance (Luquet et al. 2005). PPAR-γ, highly expressed in adipose tissue, regulates adipogenesis, promotes insulin sensitivity, and modulates adipokine secretion. Its activation improves glucose uptake and reduces chronic inflammation by downregulating pro-inflammatory cytokines (Balistreri, Caruso and Candore

2010). PPAR-δ/β, expressed ubiquitously, enhances fatty acid utilization in skeletal muscle, improves mitochondrial biogenesis, and protects against obesity-induced insulin resistance (Kaur, Allahbadia and Singh 2021). Through transcriptional regulation of genes involved in lipid transport, storage, and oxidation, PPARs contribute to maintaining metabolic balance. Furthermore, they exert anti-inflammatory effects by antagonizing NF-κB signaling and reducing oxidative stress, linking them to the prevention of metabolic syndrome, T2DM, atherosclerosis, and CVD (Sharma et al. 2024).

NF-κB and MAPK pathways:

The NF-κB and MAPK signaling pathways play a central role in sustaining the observed chronic low-grade inflammation in MetS (Dąbek, Kułach and Gąsior 2010). Metabolic stressors such as oxidative stress, free fatty acids, and advanced glycation end-products (AGEs) activate the NF-κB pathway, leading to increased expression of pro-inflammatory cytokines (Liu et al. 2017). These inflammatory signals impair phosphorylation of insulin receptor substrate (IRS) and disturb the downstream PI3K/Akt signaling, ultimately promoting insulin resistance (Acosta-Martinez and Cabail 2022). Similarly, hyperglycemia, lipotoxicity, and oxidative stress activate MAPK pathways, including JNK, ERK, and p38 (Kaneto et al. 2005), which amplify transcription of inflammatory cytokines and induces serine phosphorylation of IRS proteins, further impairing insulin action (De Luca and Olefsky 2008). Moreover, the overlapped activation of NF-κB and MAPK not only targets adipose tissue and hepatic inflammation but also promotes endothelial dysfunction and increases cardiovascular complications. Collectively, these pathways represent the key therapeutic targets in MetS (Cucu 2022).

PI3K/Akt signaling

The phosphoinositide 3-kinase (PI3K)/Akt pathway is the primary intracellular signaling cascade that mediates insulin action and maintains metabolic homeostasis (Harmon, Lam and Glass 2011). Upon insulin binding, IRS proteins recruit and activate phosphatidylinositol 3-kinase (PI3K), leading to the generation of phosphatidylinositol 3,4,5-trisphosphate (PIP3) and subsequent phosphorylation of Akt (Kearney et al. 2021). Activated Akt facilitates the translocation of the glucose transporter GLUT4 to the plasma membrane in skeletal muscle and adipose tissue, thereby enhancing glucose uptake. Beyond glucose metabolism, Akt regulates glycogen synthesis via glycogen synthase kinase-3 (GSK-3) inhibition, suppresses gluconeogenesis in the liver, and promotes lipogenesis under anabolic conditions (Saltiel 2015; Sylow et al. 2021). Impairments in PI3K/Akt signaling, often due to chronic inflammation, lipotoxicity, or oxidative stress, contribute to insulin resistance, a central hallmark of metabolic syndrome. Dysregulation of this pathway not only disrupts glucose and lipid balance but also fosters endothelial dysfunction, further linking PI3K/Akt impairment to cardiovascular complications associated with metabolic syndrome (Ghafouri-Fard et al. 2022).

Discussion

Cross-talk between these pathways

The pathogenesis of MetS involves a highly interconnected network of signaling pathways, where AMPK, PPARs, NF-κB/MAPK, and PI3K/Akt act in dynamic cross-talk rather than isolated mechanisms. Under basal conditions, AMPK functions as a central energy sensor, enhancing glucose uptake and fatty acid oxidation while suppressing lipogenesis (Garcia and Shaw 2017). This metabolic role synergizes with PPARs, particularly PPARα and PPARγ, which regulate lipid handling, adipogenesis, and insulin sensitivity

(Leonardini et al. 2009). However, in MetS, AMPK activity is impaired due to insulin resistance and nutrient excess, causing downregulation of PPARs, which results in increased lipid accumulation and dyslipidemia (Coughlan et al. 2013). Simultaneously, another significant hallmark of insulin resistance, the PI3K/Akt pathway, is impaired. It diminished further glucose uptake and disturbs the downstream metabolic regulation, contributing to more imbalance. Accompanying this are NF-κB and MAPK pathways, which secrete inflammatory cytokines and aggravate insulin resistance (Lathigara, Kaushal and Wilson 2023). More importantly, these pathways do not work independently i.e. downregulated AMPK signaling cannot effectively inhibit NF-κB/MAPK-driven inflammation (Xu et al. 2024), resulting in suppression of PI3K/Akt insulin signaling by NF-κB. Hence, the maladaptive cross-talk between these key molecular pathways drives the systemic glucolipid metabolic disturbance, low-grade inflammation, and oxidative stress, which are characteristics of MetS (Figure 2). This integrated disruption underscores the therapeutic rationale to target multiple pathways simultaneously, such as activation of AMPK enhances the PPAR signaling, restores the PI3K/Akt activity, and suppresses the NF-κB/MAPK pathways. Natural compounds that have the potential to target multiple pathways within this network, such as p-CA, offer strong therapeutic potential for the holistic management of MetS.

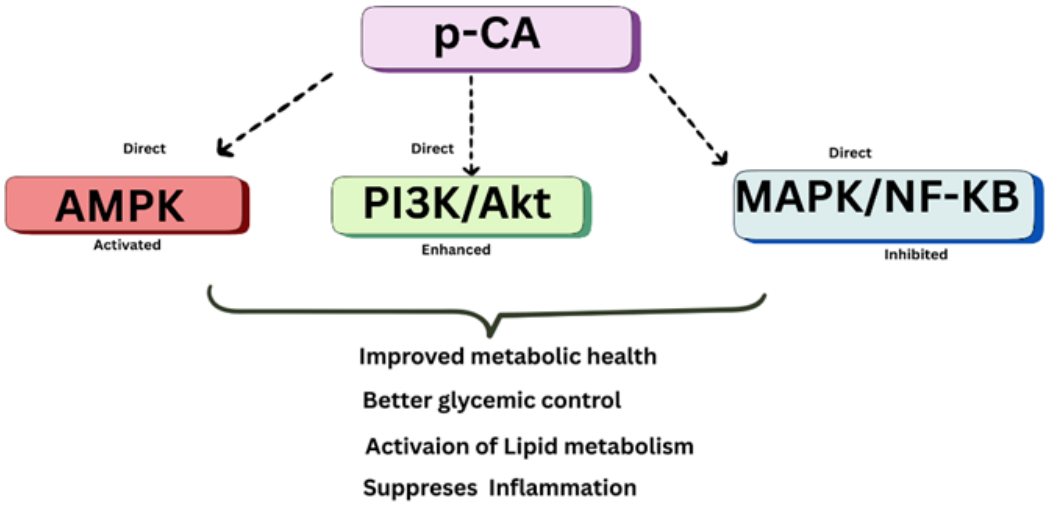

Figure 2. Illustrating cross-talk between key molecular pathways implicated in METs

Pharmacological effects of p-CA

Preclinical studies have demonstrated that p-CA exerts significant therapeutic effects against multiple components of metabolic syndrome through its pleiotropic actions. These effects are largely attributed to its antioxidant, anti-inflammatory, hypoglycemic, lipid-lowering, and organ-protective properties. The compound interacts with key molecular pathways involved in metabolic regulation, making it a promising candidate for the management of MetS (Table 1).

Antioxidant properties

The p-CA exerts potent antioxidant activity through multiple interlinked mechanisms that collectively reduce oxidative injury at cellular and molecular levels. First, p-CA directly scavenges a broad spectrum of ROS, including hydroxyl radicals, superoxide anions, hydrogen peroxide, and peroxynitrite, owing to its phenolic hydroxyl group, which donates hydrogen atoms or electrons to neutralize free radicals (Zeb 2020). In addition to radical quenching, hydroxycinnamic acids chelate redox-active transition metals such

as Fe^{2+} and Cu^{2+}, thereby attenuating reactions that otherwise accelerate ROS generation and oxidative chain reactions (Razzaghi-Asl et al. 2013). A particularly critical protective role of p-CA is observed in mitochondrial integrity. Mitochondria are primary sites of ROS generation, and oxidative stress often leads to mitochondrial dysfunction, loss of membrane potential, release of cytochrome c, and activation of apoptotic cascades (Nakamura, Nakamura and Yodoi 1997; Xie et al. 2011). Unlike single-target antioxidants, p-CA integrates chemical, enzymatic, and mitochondrial levels of defense, making it a strong candidate for nutraceutical or pharmacological interventions against oxidative stress–related diseases.

Anti-inflammatory effects

The p-CA exhibits potent anti-inflammatory activity through an integrated network of molecular pathways that disrupt chronic inflammatory signaling common in metabolic syndrome and related disorders. At the cellular level, it attenuates activation of redox-sensitive transcription factors such as NF-κB and activator protein-1 (AP-1) by inhibiting upstream IKK and MAPK signaling cascades (e.g. JNK, p38, and ERK), thereby reducing transcription of pro-inflammatory cytokines including TNF-α, IL-6, and MCP-1 (Sabitha et al. 2019; Zhao et al. 2016). The attenuation of IKK and MAPK signaling by p-CA is due to its indirect antioxidant activity. By neutralizing reactive free radicals and reducing cellular oxidative stress, it mitigates the redox-sensitive activation of these upstream kinases. Although the direct interaction with IKK or MAPK has not been yet explored, current evidence suggests that antioxidant activity of p-CA is an indirect mechanism through neutralizing oxidative signals which trigger activation of IKK or MAPK (Peng et al. 2018). Consequently, this suppression of cytokine secretion mitigates macrophage infiltration and adipose tissue inflammation, which are central contributors to systemic insulin resistance (Kang et al. 2016). Parallel to its effects on cytokine signaling, p-CA modulates the balance of eicosanoid metabolism by downregulating cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) (Zhao et al. 2016), resulting in decreased production of prostaglandins and NO, key mediators of vascular inflammation and oxidative damage. In endothelial cells, these actions help preserve NO bioavailability, maintain vasodilatory function, and prevent leukocyte adhesion. Furthermore, p-CA enhances anti-inflammatory regulatory mechanisms by activating Nrf2, which not only boosts antioxidant defenses but also induces expression of anti-inflammatory mediators like heme oxygenase-1 (HO-1). This dual antioxidant/anti-inflammatory function is reinforced by inhibition of inflammasome activation (e.g. NLRP3), reducing secretion of IL-1β and IL-18, central cytokines in metabolic inflammation. Importantly, p-CA anti-inflammatory actions are complemented by its metabolic effects, by improving insulin sensitivity and lipid metabolism via AMPK and PPAR activation, it indirectly reduces metabolic stress that often perpetuates inflammation (Yoon et al. 2013). Collectively, these activities position p-CA as a multi-targeted anti-inflammatory agent capable of modulating key pathways in immune regulation, redox balance, and metabolic signaling, thereby offering therapeutic promise in conditions like metabolic syndrome, diabetes, and related cardiovascular and neuroinflammatory disorders.

Antidiabetic and insulin-sensitizing effects

The p-CA exerts significant antidiabetic effects through multiple interrelated molecular mechanisms that target glucose homeostasis, insulin signaling, and pancreatic β-cell protection. One of its primary actions lies in improving insulin sensitivity by enhancing the PI3K/Akt

signaling cascade (Liu and Li 2021), which facilitates GLUT4 translocation to the plasma membrane, thereby promoting glucose uptake in skeletal muscle and adipose tissue. By attenuating oxidative stress, p-CA preserves insulin receptor integrity and prevents serine phosphorylation of IRS-1, a modification typically induced by ROS and inflammatory mediators that leads to insulin resistance (Nie and Cooper 2021). Additionally, it helps maintain pancreatic β-cell viability by reducing ROS accumulation and suppressing apoptotic pathways such as caspase activation, thereby sustaining endogenous insulin secretion (Peng et al. 2018). It also possesses strong inhibitory potential of key carbohydrate-metabolizing enzymes such as α-amylase and α-glucosidase, allowing p-CA to control glycemic levels by delaying carbohydrate breakdown and intestinal absorption, ultimately lowering postprandial glucose spikes (Huang et al. 2023). Besides its glycemic regulation, it modulates the adipokine secretion through downregulation of leptin and upregulation of adiponectin. It generates a metabolic-friendly environment to restore insulin sensitivity (Alam et al. 2016). It also controls the unchecked gluconeogenesis in the liver by targeting and downregulating critical enzymes responsible for glucose output, i.e. phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (Yoon and Jung 2025). Moreover, the anti-inflammatory properties of p-CA synergize with its antihyperglycemic properties to restore impaired insulin receptor signaling. Overall, these multifaceted effects of p-CA make it a promising nutraceutical agent to exert control over multiple pathophysiological aspects of MetS. These aspects are illustrated in the Figure 3, showing molecular targets of p-CA.

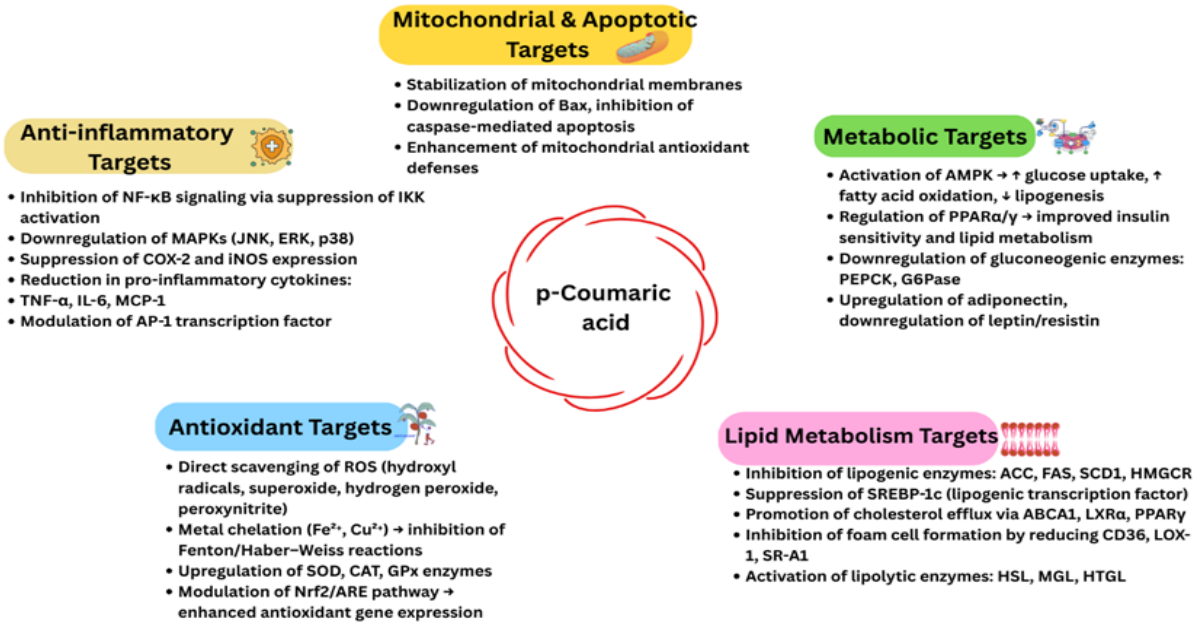

Figure 3. Exhibiting molecular targets of p-coumaric acid

Lipid-modulating and anti-obesity effects

The p-CA exerts hypolipidemic effects through a coordinated regulation of metabolic enzymes and molecular pathways. For instance, in animal models of hyperlipidemia and NAFLD, it has been reported to upregulate the expression levels and functioning of hepatic lipolytic enzymes such as monoacylglycerol lipase (MGL), hormone-sensitive lipase (HSL), and hepatic triglyceride lipase (HTGL).

Upregulation of these enzymes results in the breakdown of cholesterol esters and triglycerides (Yuan et al. 2023). Concurrently, it activates AMPK, which facilitates lipolysis and inhibits lipogenesis (Wang et al. 2025), and stimulates fatty acid oxidation via upregulating carnitine palmitoyltransferase-1 (CPT1) and acyl-CoA synthetase long-chain family member 1 (ACSL1) (Liao et al. 2023). In other animal models of fructose-induced dyslipidemia, p-CA restored lipid levels by downregulation of lipogenic enzymes and transcription factors such as ACC, fatty acid synthase (FAS), stearoyl-CoA desaturase 1 (SCD1), and sterol regulatory element-binding protein 1c (SREBP-1c). At same time, it also suppressed cholesterol synthesis by HMG-CoA reductase (HMGCR) and its regulator of transcription SREBP-2 (Yoon and Jung 2025). Eventually, p-CA facilitates cholesterol efflux and regulates foam cell formation by increasing the expression of PPARγ, liver X receptor alpha (LXRα), and ATP-binding cassette transporter A1 (ABCA1) while decreasing the scavenger receptors lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1), scavenger receptor class A type I (SR-A1), and cluster of differentiation 36 (CD36) (Moon and Yun 2024). Collectively, these actions regulate lipid metabolism by decreasing its synthesis and storage, increasing lipolysis and fatty acid oxidation, and enhancing cholesterol clearance and making p-CA a favorable candidate to mitigate hyperlipidemia.

Safety in humans and dietary exposure

As a naturally occurring component of many foods, humans are regularly exposed to p-CA through diet, often without adverse effects. The estimated daily intake from a polyphenol-rich diet is considered to be within the safe range. It is generally recognized as safe (GRAS) when consumed as part of food or natural extracts. No significant adverse events have been reported in the limited human studies or trials involving polyphenol mixtures containing p-CA (Heleno et al. 2015). It demonstrates an excellent safety profile in preclinical studies, with low acute and chronic toxicity, no genotoxicity, and broad tolerability (Devi et al. 2022; Nishi et al. 2018). Its natural dietary presence further supports its potential as a safe therapeutic agent. Nevertheless, future studies in humans are essential to confirm long-term safety, define optimal dosage ranges, and assess possible drug interactions in clinical settings.

Clinical evidence and translational gaps

Although a growing body of preclinical studies has established the therapeutic potential of p-CA in models of metabolic syndrome and its components, clinical validation in humans remains extremely limited. Bridging the gap between animal research and clinical application is crucial to unlock its potential as a nutraceutical or adjunctive therapy for metabolic disorders. To date, no large-scale clinical trials have been published that directly evaluate the effects of isolated p-CA in patients with metabolic syndrome. However, some indirect evidence exists: Human dietary studies involving polyphenol-rich foods (e.g. whole grains, red wine, fruits, and vegetables) suggest improvements in insulin sensitivity, lipid profiles, and blood pressure, benefits likely attributable in part to p-CA and related compounds (Hanhineva et al. 2010). Small-scale pharmacokinetic studies have demonstrated that p-CA is absorbed and detectable in human plasma after consumption of foods like wine, honey, or cereal bran, supporting its bioavailability (Kim et al. 2020).

A major limitation of the current evidence base is its predominant reliance on preclinical models, including *in vitro* experiments and rodent studies (Table 2).

Table 1. Showing the pharmacological properties of p-CA, its effect of cellular machinery through different metabolic pathways.

Sr. No	Pharmacological property	Effect on cellular machinery	Pathway	Reference
1	Antioxidant	Scavenges reactive oxygen species (ROS). Prevents metal-catalyzed free radical propagation. Enhances endogenous antioxidant defense systems. Upregulates the activity and expression of antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx)	Nrf2/Keap1 signaling pathway	(Razzaghi-Asl et al. 2013; Zeb 2020)
2	Anti inflammatory	Activation of redox-sensitive transcription factors. Reduces transcription of pro-inflammatory cytokines including TNF-α, IL-6, and MCP-1. Mitigates macrophage infiltration and adipose tissue inflammation. Induces expression of anti-inflammatory mediators	MAPK signaling cascades. PPAR associated pathway	(Kang et al. 2016; Sabitha et al. 2019; Zhao et al. 2016)
3	Anti diabetic	Improves insulin sensitivity in skeletal muscle and adipose tissue. Preserves insulin receptor integrity and prevents serine phosphorylation of IRS-1. Maintains pancreatic β-cell viability. Inhibit key digestive enzymes and reduces postprandial glucose spikes.	PI3K/Akt signaling cascade NF-κB signaling	(Alam et al. 2016; Nie and Cooper 2021; Peng et al. 2018)
4	Anti-Obesity	Prevents fat accumulation. Enhances expression and activity of hepatic lipolytic enzymes. Promotes the breakdown of triglycerides and cholesterol esters. Downregulates lipogenic enzymes and transcription factors. Facilitates cholesterol efflux and counters foam cell formation.	AMPK pathway PPARα and PPARγ pathways	(Liao et al. 2023; Wang et al. 2025; Yuan et al. 2023)

Table 2. Summarizing preclinical evidence of p-CA in different models of MetS.

Study Model	p-CA Dose & Duration	Key Outcomes	Proposed Mechanisms	Critical Appraisal / Limitations	Reference
High fat diet (HFD)-induced obesity (Mice)	100 mg/kg/day, 8 weeks	↓ Body weight, improved glucose tolerance, ↓ triglycerides.	Activation of AMPK; ↑ PPARα.	Single high dose used; lack of dose-response data. Physiological relevance of dose to human intake is unclear.	(Yoon et al. 2021)
Streptozotocin (STZ)-induced diabetic rats	50 mg/kg/day, 6 weeks	↓ Hyperglycemia, ↑ insulin.	↓ α-amylase activity; antioxidant effect.	STZ model is primarily β-cell destructive, not fully representative of T2DM insulin resistance. Limited investigation of long-term safety.	(Abdel-Moneim et al. 2017; Amalan et al. 2016)
Fructose-induced MetS (Hamsters)	50 mg/kg/day, 8 weeks	Improved dyslipidemia, ↓ hepatic steatosis.	Inhibition of SREBP-1c; ↓ HMGCR.	Study focused on lipid metabolism; limited data on glucose homeostasis and inflammation.	(Yoon and Jung 2025)
NAFLD models (Mice)	25mg/kg/day, 12 weeks	Reduced liver triglycerides, improved ALT/AST.	↑ Fatty acid oxidation (CPT1); ↓ NF-κB.	Comprehensive histological analysis (e.g., NAS score) was not performed. Mechanism suggested but not directly proven *in vivo*.	(Yoon et al. 2021; Yuan et al. 2023)
Isoproterenol-induced myocardial infarction rats	8 mg/kg/day, 1 week	Normalized ECG changes, restore heart rate	↓ Oxidative stress; ↑ NO bioavailability.	Demonstrates cardioprotection in an acute pharmacological injury model, which may not translate to chronic metabolic syndrome-related cardiac remodeling.	(Roy and Prince 2013)
Fructose induced dyslipidemia and hypertension in rats	100 mg/kg/day 2 weeks	Reduced atherogenic index, Restored blood pressure	↓ Dyslipidemia, ↓MDA, ↑SOD/glutathione	Shows robust lipid-lowering and hepatoprotective effects via key lipogenic pathways. However, there is lack of comparative efficacy against standard lipid-lowering agents.	(Mohammed, Khowailed and Abdelhakam 2021)

Abbreviations: high fat diet= HFD, streptozotocin=STZ, ; type 2 diabetes mellitus=T2DM=, non-alcoholic fatty liver disease activity score=NAS; AMP activated protein kinases=AMPK, Peroxisome Proliferator-Activated Receptor Alpha=PPARα, Sterol Regulatory Element-Binding Protein 1c= SREBP-1c, 3-Hydroxy-3-Methylglutaryl-CoA Reductase= HMGCR, Carnitine Palmitoyltransferase 1= CPT1, Nuclear Factor kappa-light-chain-enhancer of activated B cells=NF-Kb, Nitric oxide=NO, malondialdehyde=MDA, superoxide dismutase=SOD, Alanine Transaminase= ALT, Aspartate Transaminase= AST, electrocardiogram=ECG.

While these systems are indispensable for unraveling mechanistic pathways and providing initial proof-of-concept, their translational value is constrained. Rodents differ significantly from humans in cardiac physiology, immune regulation, metabolism, and drug biotransformation. For example, differences in heart rate, ion channel distribution, and metabolic enzyme activity can lead to therapeutic responses in rodents that are not faithfully replicated in humans. Moreover, the controlled environments of animal models do not account for the complexity of human disease, which is shaped by genetic heterogeneity, comorbidities, diet, lifestyle, and environmental exposures. Thus, while preclinical findings are encouraging, they should be interpreted with caution and not overstated as evidence of clinical efficacy. Rigorous validation in well-designed human studies remains essential before therapeutic translation.

Although preclinical data strongly support the therapeutic potential of natural polyphenols, clinical evidence remains sparse and underdeveloped. One reason for this gap is the pharmacokinetic complexity of polyphenols: most compounds undergo rapid metabolism and conjugation in the liver, resulting in poor bioavailability and transient plasma levels. In addition, considerable inter-individual variability in absorption, distribution, and clearance complicates dose optimization. The gut microbiome further influences polyphenol metabolism, producing bioactive metabolites that vary widely between individuals, making it difficult to predict therapeutic outcomes. These factors, coupled with challenges in standardizing botanical preparations and ensuring consistent dosing, often contribute to the failure of polyphenols to translate successfully from promising preclinical findings to robust clinical efficacy. Therefore, well-designed clinical trials that integrate pharmacokinetic profiling, personalized approaches, and microbiome considerations are needed to clarify their true therapeutic value.

Key translational barriers, strategies to bridge the gap and future directions

Firstly, gut microbiome-mediated metabolism plays a pivotal role in modulating the bioactivity of dietary polyphenols. A substantial portion of ingested polyphenols bypasses absorption in the small intestine and reaches the colon, where microbial enzymes, including glucosidases, reductases, and dehydroxylases, transform them into simpler, more absorbable metabolites, many of which exhibit unique and often enhanced biological functions compared to their parent compounds (Stevens and Maier 2016). In this context, various bacterial species have been identified as key catabolizers, capable of hydrolyzing glycosylated polyphenols into bioactive aglycones (Hu et al. 2024). Moreover, the inter-individual variability in gut microbial composition leads to distinct “polyphenol metabotypes,” which significantly influence the formation and systemic availability of these metabolites, thereby affecting the magnitude and variability of health outcomes observed across individuals (Tomás-Barberán, Selma and Espín 2016). Inter-individual variability in polyphenol absorption is influenced by a complex interplay of physiological, genetic, and environmental factors, which often results in heterogeneous plasma and tissue levels and complicates dose standardization in clinical settings (Morand 2024). Furthermore, studies have reported that phenolic acid bioavailability is affected by food matrix, chemical form, phase II metabolism, and transporter-mediated uptake, all of which vary among individuals (Eseberri et al. 2022). Collectively, these factors underscore why understanding and managing inter-individual variability is critical for designing robust clinical studies and developing personalized nutritional or therapeutic strategies. Lastly, achieving pharmacologically relevant plasma

concentrations of polyphenols directly from diet poses significant challenges. In vitro and animal studies commonly employ micromolar to millimolar concentrations that are rarely attainable in human circulation following standard dietary intake. Rapid metabolism and systemic clearance further limit exposure. Compounding these limitations, the majority of ingested polyphenols exhibit poor solubility, low intestinal permeability, and are selectively conjugated or metabolized even before absorption (Enaru et al. 2021). These factors contribute to the discrepancy between robust preclinical efficacy and the modest or inconsistent results observed in human trials. To translate the promising preclinical findings into clinical applications, the following strategies are recommended, as illustrated in Figure 4. To overcome the significant limitations of p-CA bioavailability, advanced formulation strategies are needed. Future studies should prioritize the development of nanocarriers such as liposomes and polymeric nanoparticles, self-emulsifying drug delivery systems (SEDDS), and prodrug approaches. These technologies can enhance the solubility, protect p-CA from rapid metabolism, and promote targeted delivery to specific tissues, thereby increasing the likelihood of achieving therapeutic concentrations in humans.

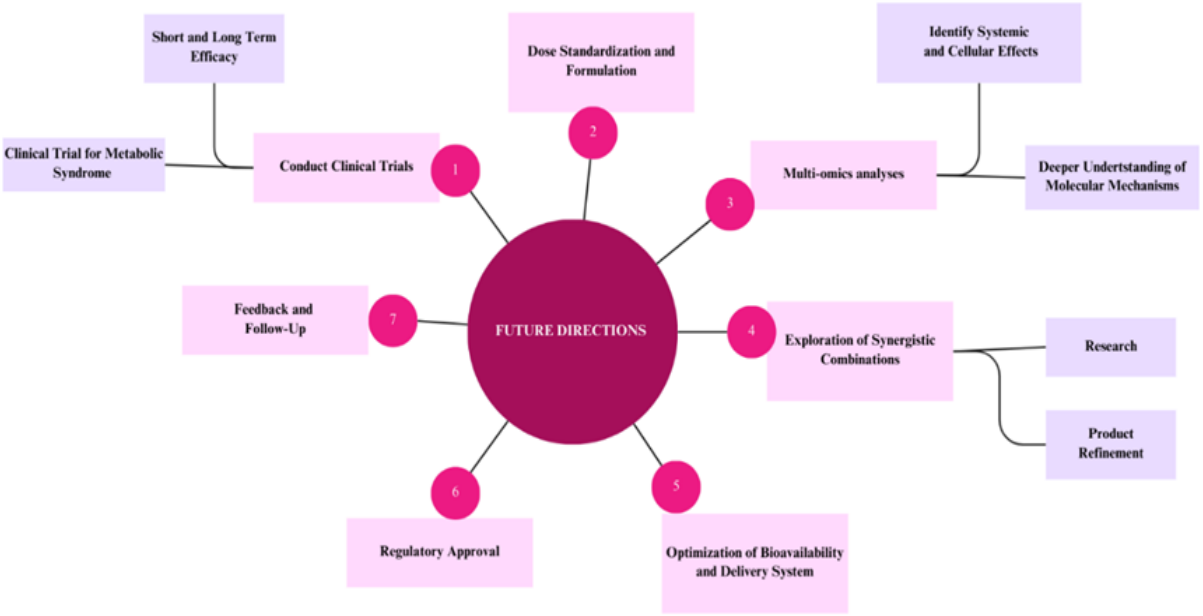

Figure 4. Illustrate the strategies to fill the existing research gaps of p-CA

Advanced formulation strategies to enhance bioavailability

It is paramount to overcome pharmacokinetic limitations to translate the promising preclinical efficacy of p-CA into clinical success. Advanced formulation strategies are actively being explored to increase their stability, solubility, and targeted delivery. Nanocarrier systems include the encapsulation of p-CA within lipid-based (liposomes and solid lipid nanoparticles) or polymer-based (chitosan nanocarriers) nanoparticles offer various advantages. These systems protect premature metabolic degradation of p-CA, increase its intestinal permeability through different uptake mechanisms, and facilitate sustained release, prolonging its circulation time (Nabih et al. 2025). In addition, surface functionalization of nanocarriers permits active targeting to specific tissues, including inflamed endothelium or adipose tissues, which are particularly relevant for Mets. Another approach is the conjugation

and prodrug approach. It involves chemically modifying p-CA to form conjugates or a prodrug is a strategic method to alter its physicochemical properties. Conjugation with amino acids, sugars, or other biocompatible molecules can significantly improve water solubility and membrane permeability (Pei et al. 2016). Prodrugs, inactive derivatives designed to release the active p-CA upon enzymatic cleavage *in vivo*, can enhance absorption and reduce first-pass metabolism, thereby increasing the systemic availability of the active compound. Lastly, complexation and co-administration approaches are also being explored. Formulating p-CA as an inclusion complexes with cyclodextrins can enhance its aqueous solubility and dissolution rate. Additionally, co-administration with bioavailability enhancers such as piperine or within a synergistic phytochemical mixture from its natural sources can inhibit its metabolic enzymes (glucuronidases) and improve net absorption (Meng et al. 2025). The implementation of these advanced delivery systems represents a critical frontier in p-CA research. Future preclinical studies must prioritize evaluating these formulated p-CA formulations in established Mets models. Success in these models would provide a compelling rationale for investing in the complex but necessary development of human-grade formulations, consequently bridging the gap between *in vivo* proof-of-concept and tangible clinical benefit.

p-Coumaric acid exhibits diverse biological effects, making it a promising and safe nutraceutical candidate for managing metabolic syndrome. Nevertheless, its clinical potential is limited by low bioavailability and the scarcity of well-designed human studies. To fully unlock its therapeutic benefits, advanced formulation strategies and comprehensive large-scale trials are crucial.

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Conflicts of interest

The Authors declare no conflict of interest.

Author contribution statement

L.N. conceived the idea and prepared original draft, R.N. reviewed editing, S.B. curated the data, Q.A. helped in diagrams and tables, S.I. prepared final draft.

CRediT

L.N. conceptualization and original draft, R.N. Review editing, S.B. Data curation, S.I. Final draft, Q.A. Diagram preparation, S.T. Proofreading

Declaration

We have not used any AI tools to prepare this review.

Statement of novelty

While p-Coumaric Acid individual benefits are known, this review provides a novel critical analysis of its therapeutic potential to combat the complex pathology of Metabolic Syndrome. We uniquely highlight the disconnect between robust preclinical data and the absence of human trials, proposing essential future directions to translate this promising phenolic acid from the lab to the clinic.

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