

REVIEW

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Modulatory roles of baicalin, punicalagin, and naringenin in molecular pathways of metabolic syndrome

Varshini Bhavanandam Mahankali¹ and Supriya Velraja^{1*} 

Abstract

Background Metabolic syndrome is a prevailing health condition characterized by insulin resistance, atherogenic dyslipidemia, central obesity, and hypertension. The following factors are utilized to diagnose metabolic syndrome: blood pressure, high-density lipoprotein (HDL) levels, triglyceride levels, waist circumference, fasting glucose levels, and cholesterol levels. The etiology of the condition is primarily hereditary and/or acquired through lifestyle habits (such as high intake of processed foods, sedentary lifestyle, irregular meal patterns, and excessive calorie consumption) that leads to insulin resistance and thereby progressing to inflammation. Sedentary lifestyle, urbanization and dietary modifications are all the causative factors for the increasing incidence rate of Metabolic syndrome globally. The essential and primary source of treatments include healthy diet, exercise and symptomatic management.

Methods This narrative review was searched using the keywords—“metabolic syndrome, baicalin, punicalagin, naringenin” exclusively on scientific databases such as Google Scholar, Scopus and PubMed.

Discussion and conclusion Polyphenols have potent antioxidant qualities, therapeutic effects, and potential health advantages. These compounds can be utilized to treat metabolic syndrome because of their anti-inflammatory and free-radical scavenging qualities. This review paper discusses the promising potential of baicalin, punicalagin, and naringenin (including naringin) in alleviating metabolic syndrome. Baicalin, punicalagin, and naringenin are present in Chinese skullcap (*Scutellaria baicalensis*), pomegranate (*Punica granatum*) peel and citrus fruits, respectively. They target oxidative stress, inflammation, and insulin resistance through improvement in lipid metabolism, regulate glucose homeostasis, and mitigate cardiovascular risks, making them promising candidates for managing metabolic syndrome.

Keywords Metabolic syndrome, Baicalin, Punicalagin, Naringenin

Introduction

Metabolic syndrome (MetS) represents a collection of metabolic irregularities, which comprise insulin resistance (IR), atherogenic dyslipidemia, central obesity,

and hypertension. The development of MetS involves various genetic and acquired factors that are linked to IR and persistent low-grade inflammation. If not addressed, MetS is notably correlated with a heightened risk of progressing to diabetes and cardiovascular diseases (CVDs). The NCEP ATP III definition states that metabolic syndrome is present if three or more of the following five criteria are met: blood pressure greater than 130/85 mmHg, fasting triglyceride (TG) level greater than 150 mg/dl, fasting high-density lipoprotein (HDL) cholesterol level less than 40 mg/dl (for men) or

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50 mg/dl (for women), fasting blood sugar greater than 100 mg/dl, and waist circumference greater than 40 or 35 inches (for women) [1, 2].

Metabolic syndrome (MetS) is characterized by a group of metabolic irregularities, including insulin resistance, atherogenic dyslipidemia, central obesity, and hypertension. In 2009, Alberti et al. established a global definition of MetS, stating that the presence of three abnormal findings would indicate MetS. The International Diabetes Federation and the American Heart Association/National Heart, Lung, and Blood Institute identified risk factors such as elevated blood pressure, dyslipidemia (increased triglycerides and decreased high-density lipoprotein cholesterol), elevated fasting glucose, and central obesity [1].

Serum insulin level is not a part of diagnosis of MetS as its measurement is unwieldy with respect to population geographic. As a result waist circumference was included as it is co-related with IR [3].

Individuals with an “apple-shaped” body, characterized by central or abdominal visceral obesity, are at a higher risk of developing IR compared to those with a “pear-shaped” body, which is associated with subcutaneous fat accumulation. Nevertheless, waist circumference alone does not provide a definitive assessment of abdominal adiposity and should be evaluated in conjunction with body mass index (BMI) to effectively identify high-risk abdominal obesity [4].

The global prevalence of MetS extends from 12.5 to 31.4%. The Eastern Mediterranean Region and the Americas had a far higher prevalence, and it rose as nation's income level rose. Ethnic-specific central obesity was present in 45.1% of cases worldwide, systolic blood pressure (BP) ≥ 130 mmHg and/or diastolic BP ≥ 85 mmHg in 42.6% of cases, HDL cholesterol < 1.03 in men or < 1.29 in women in 40.2% of cases, serum triglycerides ≥ 1.7 mmol/L in 28.9% of cases, and fasting plasma glucose ≥ 5.6 mmol/L in 24.5% of cases [5]. Depending on the criterion used as well as the population's geographic location, environment, gender, age, race, and ethnicity, the prevalence of MetS varies significantly worldwide, ranging from less than 10% to 84%. According to estimates from the International Diabetes Federation (IDF), around 25% of adults worldwide have MetS (International Diabetes Federation IDF 2006) [6].

Metaflammation and chronic low-grade inflammatory states are frequently associated with metabolic alterations that are directly linked to the prevalence of CVD, including obesity, diabetes mellitus, and hypertension [7].

A rise in the levels of inflammation-promoting signaling molecules, primarily interleukin-1 β (IL-1 β), tumor necrosis factor- α (TNF- α) and IL-6, which

come from chronically inflamed adipose tissue and are linked to oxidative stress, is another characteristic of metaflammation. Oxidative stress results from post-translational changes of proteins, lipids, and DNA caused by an excess of reactive oxygen species, which overwhelms antioxidant mechanisms [8].

Hyperglycemia increases oxidative stress and generates advanced glycosylation end products (AGEs). Inflammation and oxidative stress contribute to cellular senescence and CVD [7].

The study conducted by Neeland et al. [9] aimed to provide clinicians, researchers, and policymakers a thorough understanding of the complex mechanisms, diagnostic difficulties, and changing management approaches of MetS in order to support integrated, patient-centered approaches to its prevention and treatment. It was concluded that sedentary lifestyle, urbanization and dietary modifications are all the causative factors for the increasing incidence rate of MetS globally. The essential and primary source of treatments include healthy diet, exercise and symptomatic management [9].

This review paper explores the mechanisms of action of baicalin, punicalagin, and naringenin in alleviating MetS.

Punicic acid, found in *Punica granatum L*, simultaneously activates PPAR α and PPAR γ , which boosts the metabolism and regulation of fatty acids while reducing inflammation. These actions may aid in addressing dyslipidemia, insulin resistance, and inflammation in adipose tissue [10]. Administering a methanol extract of the flowers orally at a dose of 500 mg/kg prevents the rise in plasma glucose levels caused by glucose loading in Zucker diabetic fatty rats [11].

Oral treatment of naringin at a dose of 50 mg/kg body weight for 56 days significantly reduced oxidative stress and enhanced cardiac antioxidant capacity in a 2016 animal study examining hyperglycemia-induced cardiac fibrosis. Treatment with naringin increased the activity of cytosolic superoxide dismutase (SOD, CuZn form) by around 65% while dramatically decreasing the activity of NADPH oxidase, a crucial enzyme that produces reactive oxygen species. Furthermore, it reduced the high levels of advanced oxidation protein products (AOPP) in cardiac tissue and plasma, which suggests a decrease in oxidative protein damage. These results imply that naringin slows the development of cardiac fibrosis in hyperglycemic circumstances via reducing oxidative stress-mediated heart damage [12].

Over the course of 8 weeks, oral baicalin (400 mg/kg) dramatically improved aberrant blood lipid profiles, increased insulin sensitivity, decreased hepatic fat deposition, and lowered body weight gain. With responsive metabolic pathways such as the citrate

cycle, alanine/aspartate/glutamate metabolism, glycerophospholipid metabolism, and aminoacyl-tRNA biosynthesis, BC therapy corrected changes in seven important metabolites brought on by HFD. According to gut microbiota studies, BC changed the intestinal microbial community's functional ability as well as its composition in MetS mice. These results point to the gut microbiota as a molecular target for BC's activity and imply that it has therapeutic potential for diet-induced MetS [13].

Pathophysiology of metabolic syndrome

Adipose tissue plays a major role in the development of central metabolic diseases. The primary pathophysiological attributes of MetS are visceral adipose tissue (VAT), IR, dyslipidemia, hypertension and endocrine mediation. Lately, atherothrombotic events, systemic inflammation, persistent oxidative stress, and endothelial dysfunction have also been identified as key pathogenic contributors. The complicated and multidimensional pathophysiology of MetS is created by the combination of the clinical variables, genetic

susceptibility, and traditional pathogenic factors [14]. The pathophysiology of MetS is depicted in Fig. 1

Phytonutrients: pathway of action

A broad class of phytonutrients known as polyphenols (PPs) have phenolic rings with two or more hydroxyl groups. Along with documented clinical research, they have potent antioxidant qualities, a variety of therapeutic effects (anti-inflammatory, anti-obesity, anti-diabetic, cardioprotective, and hepatoprotective effects), and potential health advantages both in vivo and in vitro. These compounds can be utilized to treat a variety of illnesses linked to MetS because of their anti-inflammatory and free-radical scavenging qualities [15]. Because of their established anti-inflammatory, antioxidant, and insulin-sensitizing qualities—all of which are crucial for MetS—baicalin, punicalagin, and naringenin were chosen. Additionally, they are readily available and useful for dietary-based preventive or adjunctive strategies against MetS because they are naturally present in foods and kitchen ingredients that are frequently consumed, such as naringenin in citrus

Pathophysiology of MetS

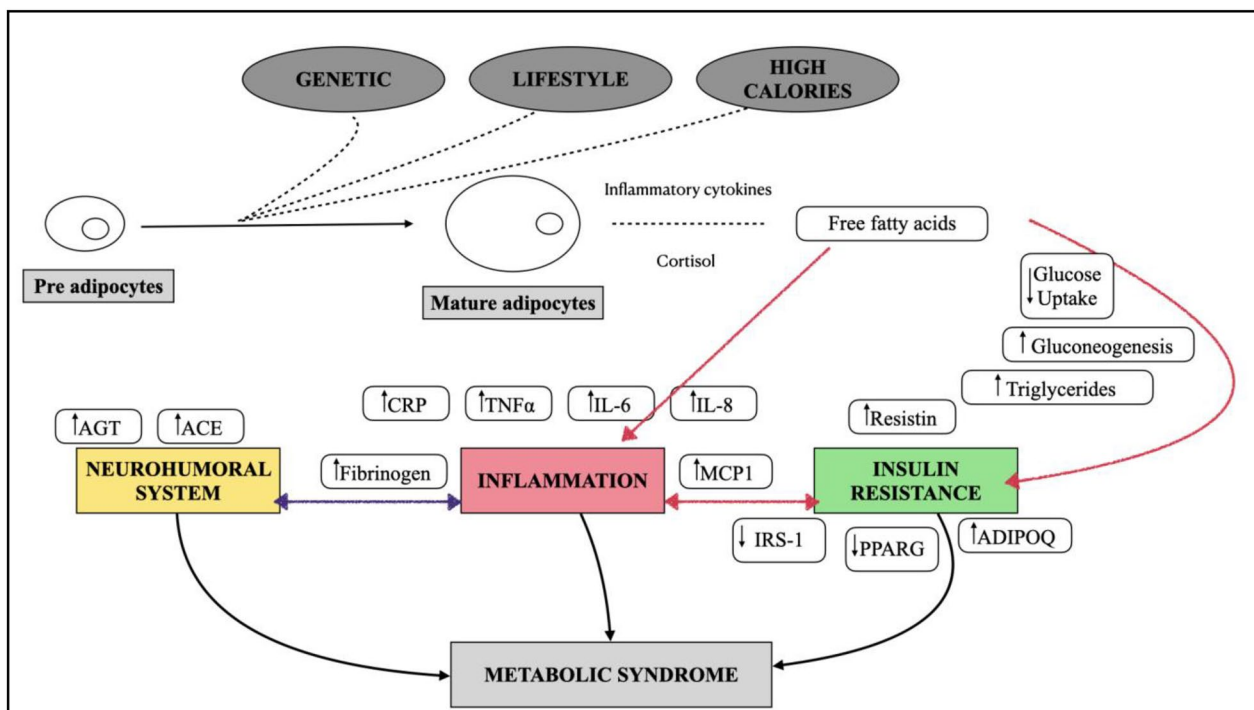


Fig. 1 Genetic predisposition, unhealthy lifestyle and a high calorie diet leads to the differentiation from pre-adipocytes to mature adipocytes thereby releasing free fatty acid release in the blood. As a result, increased CRP (C-reactive protein), TNF- α , IL-6 (interleukin-6), IL-8 (interleukin-8), MCP-1 (monocyte chemoattractant protein-1) and Fibrinogen provokes inflammation. Inflammation triggers neurohumoral system through up regulating AGT (angiotensinogen) and ACE (angiotensin-converting enzyme) as well as IR through up regulating Resistin, ADIPOQ (adiponectin) and down regulating IRS-1 (insulin receptor substrate 1) and PPARG (peroxisome proliferator-activated receptor gamma)

fruits, punicalagin in pomegranates, and baicalin in *Scutellaria baicalensis* (used in herbal teas).

Baicalin

Scutellaria baicalensis (Baikal skullcap or Chinese skullcap) contains a polyphenolic substance called baicalin, a significant bioactive flavonoid that is used extensively in ancient Chinese medicine to treat bacterial and viral infections, inflammation, hypertension, and CVD. Additionally, both by itself and in conjunction with other herbs, *S. baicalensis* exhibits promise in reducing hyperglycemia and avoiding dyslipidemia in rats with STZ-induced diabetes. The extracts reduced the plasma triglycerides and total cholesterol in rats given a high-fat diet, according to studies using an experimental model. In addition, *S. baicalensis* lowers human plasma triglyceride levels [16–18] (Fig. 2). Oren-gedoku-to (Huanglian-Jie-Du-Tang, OGT) is a traditional Kampo remedy utilized in Japan for the treatment of cerebrovascular conditions, high blood pressure, gastritis, and liver ailments. Baicalin is a flavonoid found in *S. baicalensis*, one of OGT's core ingredients. This research examined whether consuming

OGT extract (TJ-15) could impact fatty acid metabolism and modify plasma concentrations of typical antioxidant molecules like albumin, uric acid, and bilirubin. The results indicate that TJ-15 might aid in stroke prevention by improving microcirculation (function of small blood vessels), possibly through beneficial changes in lipid and protein metabolism, as well as enhancing antioxidant levels [19].

Baicalin inhibited the transcription of the lipogenic genes peroxisome proliferator-activated receptor γ (PPAR γ) and CCAAT-enhancer binding protein α (C/EBP α) in 3T3-L1 pre-adipocytes. This is due to its effect on the activation of Adenosine Monophosphate-Activated Protein Kinase (AMPK) pathway. When AMPK is activated, it signals the cell to decrease fat storage capacity and enhance fat catabolism [20].

Baicalin also relieved dyslipidemia in rats given a high-fat diet by increasing the expression of the lipolytic agent peroxisome proliferator-activated receptor α (PPAR α) and its target gene carnitine palmitoyltransferases-1 (CPT-1) in the carotid artery. Baicalin has been proven to PPAR α activation leading to up regulation of CPT-1,

Properties of Baicalin

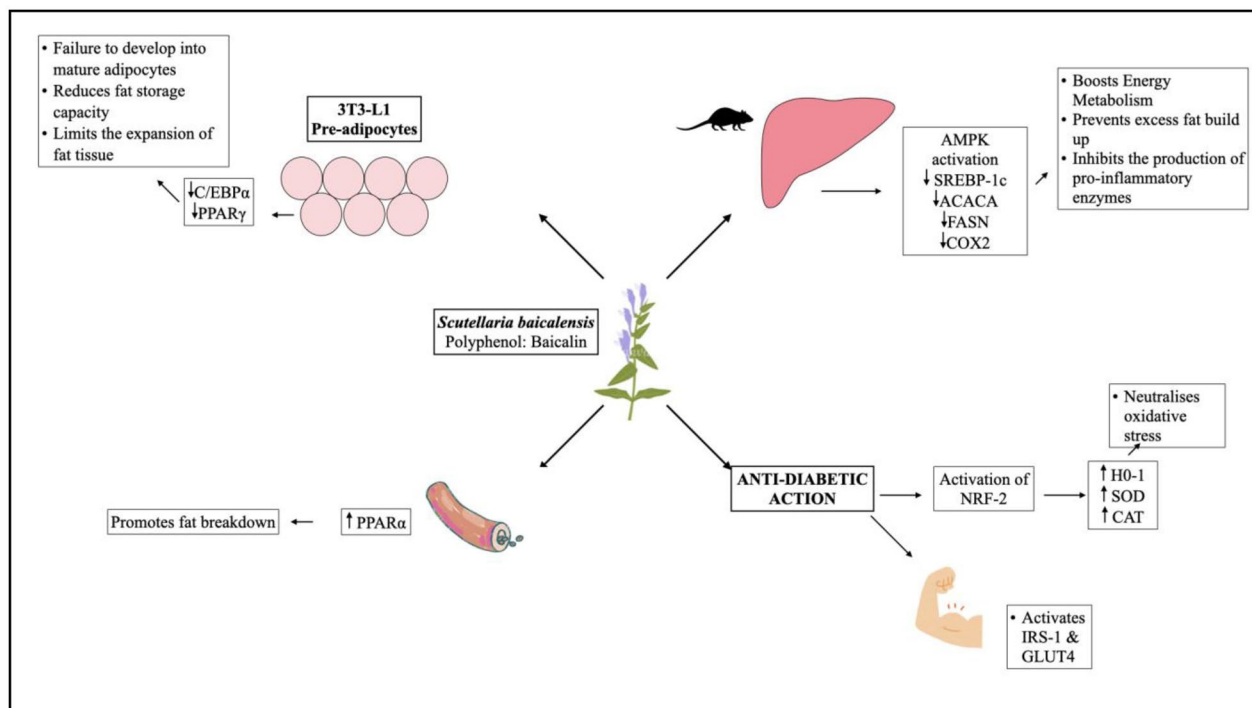


Fig. 2 Baicalin plays a protective role in alleviating MetS through various metabolic pathways. It reduces the fat storage capacity and expansion of fat tissue through down regulating CCAAT-enhancer binding protein α (C/EBP α) and peroxisome proliferator-activated receptor γ (PPAR γ). Promotes fat catabolism by up regulating peroxisome proliferator-activated receptor α (PPAR α). Improves energy metabolism through activating Adenosine Monophosphate-Activated Protein Kinase (AMPK) pathway. Activation of NRF2, insulin receptor substrate 1 (IRS-1) and glucose transporter 4 (GLUT4) and up regulation of heme oxygenase 1 (HO-1), superoxide dismutase (SOD), and catalase (CAT) regulates blood glucose level

an essential enzyme involved in mitochondrial fatty acid transport and β -oxidation, thereby promoting the catabolism of triglyceride and LDL levels [21].

Guo et al. [18] outlined that baicalin enhanced AMPK phosphorylation and down regulated sterol regulatory element-binding protein 1c (SREBP-1c) and its target enzymes, acetyl-CoA carboxylase alpha (ACACA) and fatty acid synthase (FASN). This ameliorated metabolic health and attenuated hepatic steatosis in high-fat diet (HFD) rats [18].

Baicalin also helps in managing diabetes and its complications by enhancing antioxidant activity, insulin signaling, and glucose metabolism. In human umbilical vein endothelial cells susceptible to high glucose levels, baicalin stimulates NRF2, increasing heme oxygenase 1 (HO-1), superoxide dismutase (SOD), and catalase (CAT), thereby protecting blood vessels from damage in diabetic patients. In skeletal muscle cells, baicalin enhances insulin sensitivity by activating IRS-1 and glucose transporter 4 (GLUT4), leading to improved glucose uptake. This is facilitated through the activation of AMPK, PI3K/AKT, and MAPK/ERK signaling pathways [22].

In animal study, baicalin was shown to reverse high-fat diet (HFD)-induced hyperglycemia and IR by activating the AKT/AS160/GLUT4 and MAPK/PPAR γ coactivator 1 α (PGC-1 α)/GLUT4 pathways, which promote glucose transport and utilization, improving overall glucose homeostasis. Zhang et al. [21] concludes that the complete benefits of baicalin on MetS will only be revealed through clinical trials including people with NAFLD or diabetes, despite the fact that it has lipid-lowering and anti-inflammatory effects in circulating systems.

Punicalagin

Punicalagin (PUN) is an ellagitannin present in pomegranate (*Punica granatum*) peel. It is a polyphenol that has been proven to have anti-inflammatory properties, as well as hepatoprotective, anti-atherosclerotic, chemopreventive, and antiproliferative properties against tumor cells [23, 24].

It suppresses inflammation by blocking the NF- κ B and MAPK signaling pathways, which lowers the production of pro-inflammatory cytokines in LPS-stimulated macrophages, such as TNF- α , IL-1 β , and IL-6. PUN's immunosuppressive effects are aided by its suppression of NFAT activation, which also prevents T cell proliferation and IL-2 production. By diminishing the expression of anti-apoptotic proteins (Bcl-2, Bcl-XL) and flaring up pro-apoptotic markers (Bax), it induces autophagy through the AMPK-p27 signaling pathway and encourages apoptosis in cancer cells. PUN has shown

antibacterial, antiviral, antioxidant, hepatoprotective, anti-diabetic, and anti-obesity.

Properties, including the regulation of genes linked to glucose and fatty acid metabolism and the inhibition of lipid formation. It has the potential to treat chronic illnesses and enhance general health due to its varied pharmacological activities [25].

Punicalagin reduces inflammation and lipid production in the adipocytes of obese mice given a high-fat diet. Punicalagin not only activates NRF2 signaling but also efficiently suppresses the expression of NF- κ B and cytokines linked to inflammation, including IL-1 β , TNF- α , MCP-1, IL-6, and NLR family pyrin domain-containing 3 (NLRP3) [26]. Through the activation of PGC-1 α and the NRF2 cascade, punicalagin has been shown to influence oxidative stress and mitochondrial biogenesis for the liver and heart. Punicalagin additionally enhance the expression of adiponectin's liver receptor ADIPOR2 and adiponectin production [21].

Punicalagin has been shown to reduce kidney and liver damage in diabetic mice by inhibiting the high mobility group box 1 (HMGB1)/TLR4/NF- κ B pathway, which is involved in gluconeogenesis and the inflammatory response, and by activating PI3K/AKT signaling. It also reduced the expression of the gasdermin D (GSDMD) and pyroptosis-related factors caspase 1, as well as the pro-inflammatory proteins IL-1 β and NLRP3, which improves the renal interstitial hyperplasia and glomerular hypertrophy of diabetic mice [27].

According to a study conducted by Quirós-Fernández et al. [28], punicalagin and hydroxytyrosol supplementation significantly enhanced the early atherosclerosis indicators involved in the asymptomatic phase in an adult population with atherosclerosis. In summary, the prehypertension and hypertension subgroups showed lower systolic and diastolic blood pressure as well as serum oxidized LDL following a 20-week medication combination [28] (Fig. 3).

Naringenin

The primary sources of naringenin (naringin is the glycosylated form of naringenin) (4',5,7-trihydroxyflavonone) in large concentrations are citrus fruits and tomatoes. Because of its antioxidant and anti-inflammatory properties, naringenin offers a number of benefits, including cardioprotective, anti-diabetic, antimicrobial, anticancer anti-obesity, immunomodulator, gastroprotective, nephroprotective, and neuroprotective effects [29].

In rats administered with a high-sucrose diet, naringenin may enhance the expression of hepatic PPAR α and PGC-1 α . This ultimately reduced the amount of TG and TC in plasma and liver by promoting the

Properties of Punicalagin

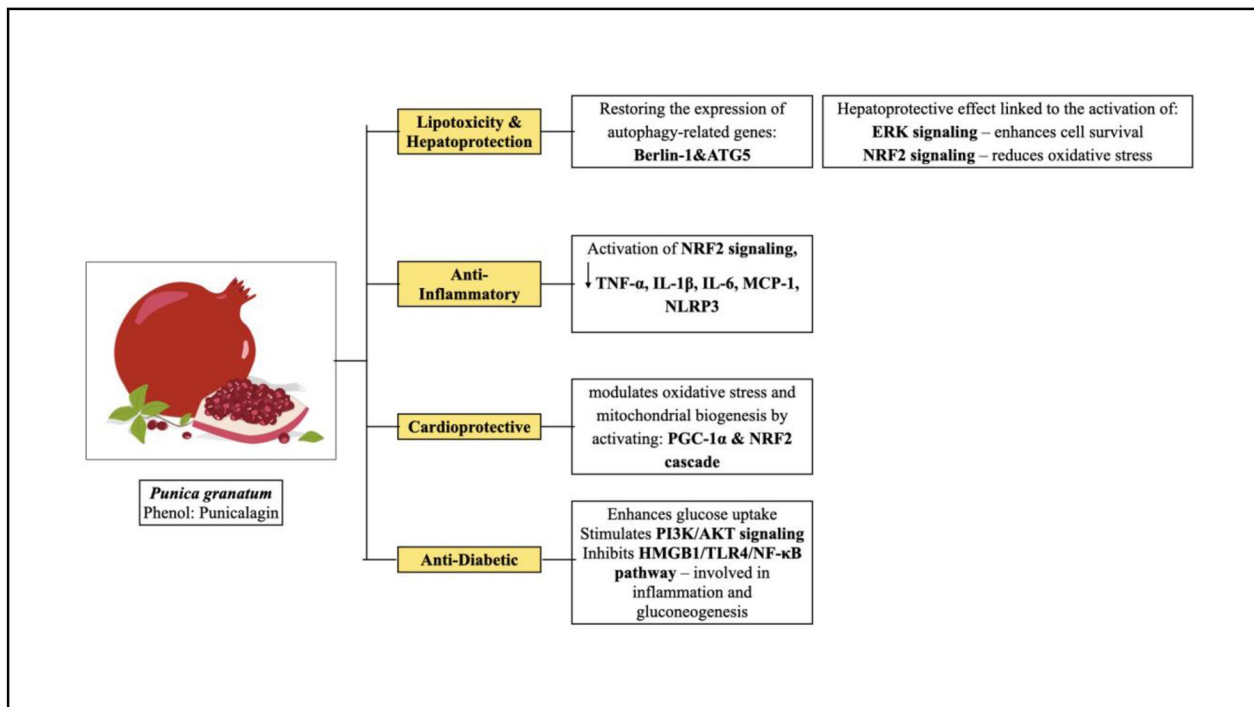


Fig. 3 Punicalagin restores lipotoxicity and hepatoprotection through Berlin-1, Autophagy-Related Gene 5 (ATG5), Nuclear Factor Erythroid 2-Related Factor (NRF) and Extracellular signal-Regulated Kinase (ERK) signaling. Possesses anti-inflammatory activity through down regulating IL-1β, TNF-α, MCP-1, IL-6 and NLR family pyrin domain-containing 3 (NLRP3). It modulates oxidative stress thereby showing cardioprotective properties through activation of Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) and the NRF2 (Nuclear Factor Erythroid 2-Related Factor 2) cascade. It is also known to be an anti-diabetic agent through stimulating glucose uptake via phosphatidylinositol 3-kinase (PI3K) and protein kinase B (AKT) signaling and inhibiting high mobility group box 1 (HMGB1)/TLR4/NF-κB pathway

transcriptions of downstream fatty acid oxidation genes such CPT-1, uncoupling protein 1 (UCP1), uncoupling protein 2 (UCP2), apolipoprotein A-I (APOA-I), and acyl-CoA oxidase (ACOX) [30].

Naringin has been proven to have a protective role in decelerating the progression of atherosclerosis. It reduces the activity of enzyme acetyl-CoA acetyltransferase (ACAT) which plays a major role in the formation of cholesterol esters, and downregulate the expression of pro-inflammatory cytokines such as MCP-1 and vascular cell adhesion molecule 1 (VCAM-1) [31].

Further, naringin inhibits vascular smooth muscle cell (VSMC) proliferation and the inflammatory response, thereby decelerating the development of atherosclerosis. Research stimulates that naringenin prevents TNF-α-induced VSMC migration and proliferation by amplifying the expression and activity of heme oxygenase-1 (HO-1). Through NRF2 activation, naringenin increases HO-1 levels, which lowers reactive oxygen species (ROS) production and reduces white blood cell recruitment. Furthermore, naringenin suppresses the NF-κB signaling

pathway in macrophages, thereby decreasing the production of inflammatory cytokines such as IL-33, TNF-α, IL-1β, and IL-6 [21] (Fig. 4).

Conclusion

Inflammation, oxidative stress, and impaired glucose and lipid metabolism are caused by genetic susceptibility, unhealthy lifestyle choices, and excessive caloric consumption. Targeting these underlying systems is necessary to restore metabolic equilibrium. Notably, phytonutrients including baicalin, punicalagin, and naringenin exhibit strong therapeutic promise in modifying these pathways.

Baicalin plays a critical role in enhancing metabolic health through various signaling pathways. Moreover, it suppresses the production of inflammatory cytokines. Baicalin reduces serum glucose and triglyceride levels, averts fat accumulation in the liver, enhances insulin sensitivity, and lowers oxidative stress and overall inflammation.

Properties of Naringenin

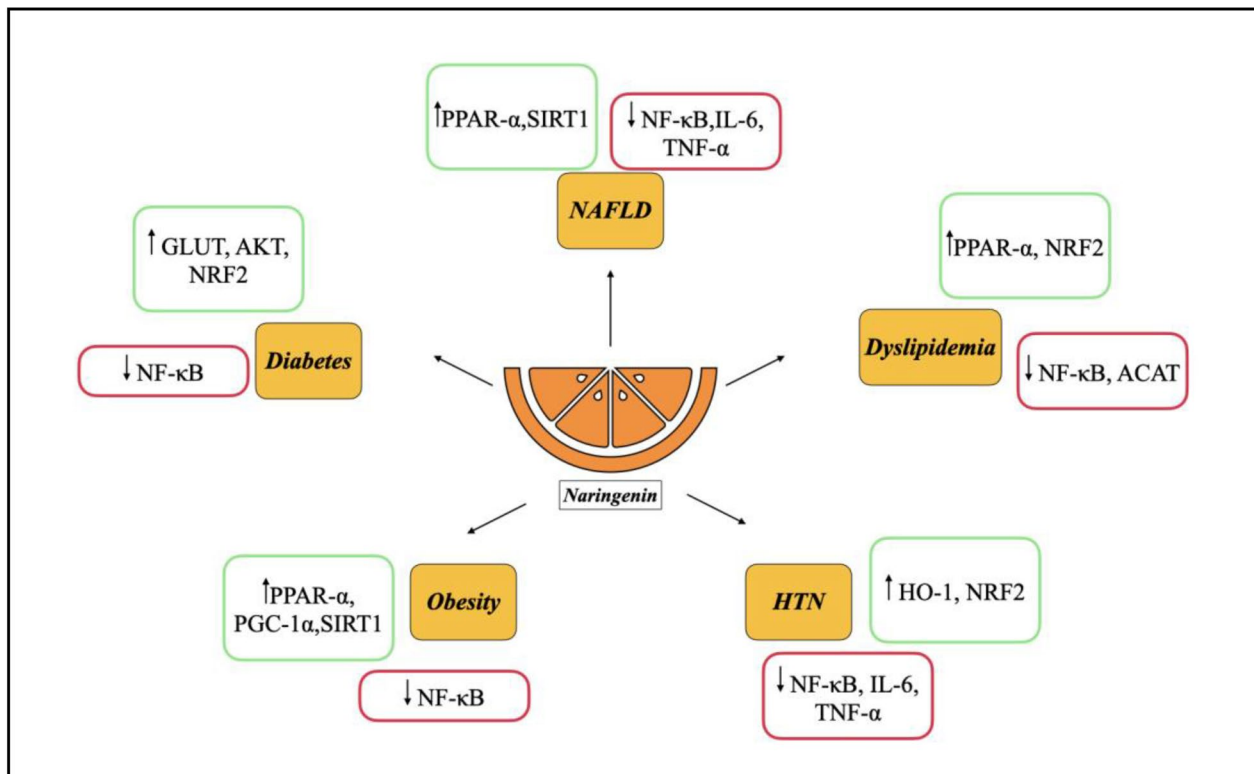


Fig. 4 Naringenin, a powerful phenolic compound possesses a multifactorial trait in alleviating non-alcoholic fatty liver disease, obesity, diabetes, hypertension and dyslipidemia through up regulating *PPAR-α* peroxisome proliferator-activated receptor alpha, *SIRT1* sirtuin 1, *PGC-1α* peroxisome proliferator-activated receptor gamma coactivator 1-alpha, *GLUT4* glucose transporter type 4, *PI3K/AKT* phosphoinositide 3-kinase/protein kinase B, *NRF2* nuclear factor erythroid 2-related factor 2v, *HO-1* heme oxygenase 1 and down regulating, *NF-κB* nuclear factor kappa-light-chain-enhancer of activated B cells, *ACAT* acetyl-CoA acetyltransferase, *TNF-α*, *IL-6* interleukin 6

Punicalagin underpins mitochondrial function and decreases oxidative damage by activating the NRF2, PGC-1α, and PI3K/AKT pathways, thereby restoring metabolic balance. It decreases inflammation and gluconeogenesis. Altogether, it contributes to improved insulin sensitivity, reduced lipotoxicity, and enhanced glucose and lipid metabolism.

Naringenin stimulates the NRF2 and HO-1 pathways, which reduces oxidative stress and inflammation. It also reduces the pro-inflammatory cytokines like TNF-α, IL-1β, and IL-6 production. By ameliorating glucose uptake, reducing triglyceride levels and systemic inflammation, naringenin augments vascular health and attenuates MetS.

The multi-faceted effects of baicalin, punicalagin, and naringenin on oxidative stress, inflammation, insulin signaling, and lipid metabolism reinstates metabolic homeostasis. Cooperatively, their effects exhibit their promise as therapeutic and natural instrument for the management of MetS.

Acknowledgements

The authors thank Sri Ramachandra Institute of Higher Education and Research (DU) for their support.

Author contributions

Varshini M B and Dr V Supriya have contributed to the design, concept, and manuscript preparation. Varshini M B drafted the manuscript and worked on the illustrations. Dr V Supriya supervised the work, reviewed, edited and finalized the manuscript.

Funding

No funding was received for this review article.

Data availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

All authors offer their consent toward publication.

Competing interests

The authors declare that they have no competing interests.

Received: 2 April 2025 Accepted: 18 September 2025

Published online: 08 October 2025

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