Exploring the potential of honokiol as a treatment for cardiovascular disease (Review)

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Abstract. Cardiovascular diseases (CVDs) remain a leading cause of global mortality. As the burden of these diseases continues to rise, the development of innovative therapeutic agents has become increasingly important. Honokiol, a bioactive compound extracted from the bark and leaves of particular Magnolia species, has garnered attention for its wide-ranging pharmacological effects, including anti-inflammatory, antioxidant, and vasodilatory properties. Emerging research suggests that honokiol holds significant promise as a therapeutic agent for managing CVDs. The present review provides a comprehensive overview of the bioactive properties, cardiovascular effects, mechanisms of action, and potential clinical utility of honokiol for the treatment of CVDs. Furthermore, challenges and future directions for the clinical translation of honokiol are discussed at length to provide additional context.

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1. Introduction

Cardiovascular disease (CVD) is the leading cause of global mortality, and its prevention and treatment thus represent a major public health challenge. The World Health Organization has estimated that ~17.9 million deaths worldwide were due to CVD in 2019, with 85% resulting from acute events such as myocardial infarction and stroke (1). Low- and middle-income countries account for three-quarters of global CVD-related mortality, with an estimated one-third of these deaths occurring in individuals <70 years of age (1). Pathologically, CVD encompasses a spectrum of noncommunicable diseases, including coronary artery disease, cerebrovascular disease, and peripheral arterial disease, which are driven primarily by modifiable risk factors such as unhealthy diet, a lack of physical activity, tobacco use, and obesity (1). Despite pharmacological advances, current interventions face significant limitations. For instance, while statins are effective for managing dyslipidemia, they carry risks of myotoxicity and rhabdomyolysis (2,3). Similarly, although dual antiplatelet therapy reduces mortality from myocardial infarction, it is associated with an increased risk of bleeding complications. These challenges are compounded by the multifactorial pathogenesis of CVD, necessitating therapeutic strategies that target multiple interconnected pathways, such as the use of anti-inflammatory, antioxidant, and cardioprotective agents (3). The effectiveness of conventional chemical agents is limited by their single-target mechanisms, potential for drug resistance, and risk of myotoxicity, while antiplatelet therapies are also linked to increased hemorrhagic risk (4). Within this context, natural products from traditional medicinal formulations have re-emerged as promising candidates for multimodal intervention.

Honokiol, a hydrophobic allyl biphenol compound isolated from the traditional Chinese herb *Magnolia officinalis*, represents a prime candidate in this quest (5). As one of the major bioactive components of *Magnolia officinalis*, its concentration serves as a key indicator for evaluating the quality of the herb (6). Beyond its established antimicrobial, antiviral, anticancer, anti-inflammatory, antioxidative, and anti-aging properties, honokiol has been found to have significant pharmacological effects on the cardiovascular system, including cardioprotection, enhancement of cardiac function,

vasodilation, and antihypertensive effects, inhibition of platelet aggregation, and anti-atherosclerotic properties (7-9). These multifaceted properties and effects on cardiovascular health suggest the potential of developing honokiol as a novel therapeutic agent, opening new avenues in the treatment of CVD. The present review focused on the functions and associated mechanisms of honokiol in CVD, with an anlysis of its clinical applications and challenges. The aim was to provide new directions for research on the use of honokiol in clinical practice.

2. Structure and function of honokiol

Honokiol, chemically designated as 3',5-di-2-propenyl-1,1'-biphenyl-2,4'-diol, has a molecular formula of $C_{18}H_{18}O_2$ and a molecular weight of 266.33 g/mol (Fig. 1). In appearance, this hydrophobic allyl biphenol compound is a white to off-white crystalline powder with a melting point of ~87.5˚C (8). While it has limited solubility in water, it is highly soluble in organic solvents such as ethanol, diethyl ether, and chloroform (8). The chemical structure of honokiol is characterized by the presence of two phenolic hydroxyls and two allyl groups. This distinctive configuration contributes to the variety of biological activities of the compound (8). The phenolic hydroxyl moieties act as hydrogen donors, conferring significant antioxidant activity and enabling the scavenging of excessive free oxygen radicals and thus reducing oxidative stress-mediated damage in cells and tissues (9). Concurrently, the allyl groups contribute to various chemical reactions involved in antibacterial, anti-inflammatory, and antitumor activities (9).

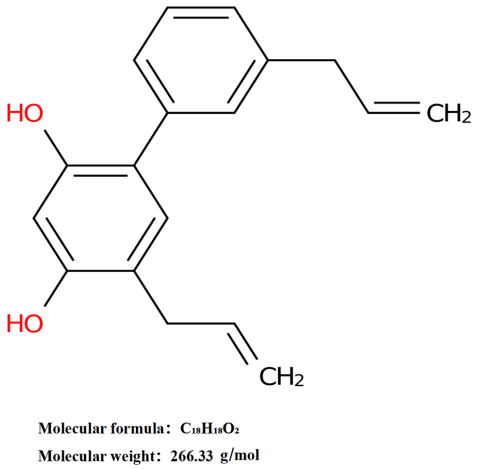

Figure 1. Structure of honokiol.

Pharmacological analyses of honokiol have demonstrated its wide range of biological activities (9). Honokiol has antimicrobial properties, inhibiting the growth of various pathogenic microorganisms, including *Staphylococcus aureus, Escherichia coli*, and *Candida albicans*. Its antimicrobial effects primarily involve the disruption of the cell membrane of the microorganism and interference with transport and energy functions, thereby reducing both antimicrobial and bactericidal/fungicidal effects (10). In terms of its anti-inflammatory properties, honokiol can inhibit the production of inflammatory mediators such as tumor necrosis factor-alpha (TNF-α) and interleukin (IL)-6 (11). It also regulates inflammation-related signaling pathways, including that of nuclear factor kappa B (NF-κB) and reduces inflammatory cell infiltration, thus inducing anti-inflammatory effects (12). As an effective antioxidant, honokiol can scavenge and eliminate free radicals, such as superoxide anions and hydroxyl radicals, directly, and can also upregulate the activities of intracellular antioxidant enzymes, including superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px), thereby enhancing the antioxidant defense mechanisms of the body (13). Furthermore, honokiol has a variety of other biological activities, including antitumor, antiviral, anti-anxiety, and sleep-promoting effects (8,9,14,15).

These biological activities are potentially linked to pharmacological effects on the cardiovascular system. Inflammation and oxidative stress play pivotal roles in the onset and progression of CVD (16,17). For instance, the formation of atherosclerotic plaques is closely associated with inflammatory cell infiltration and the production of oxidized low-density lipoproteins (18). The anti-inflammatory and antioxidant activities of honokiol can mitigate damage to vascular endothelial cells, suppress inflammatory responses, and reduce lipid oxidation, thereby exerting a protective effect on the cardiovascular system. Additionally, honokiol can block calcium channels, and can thus modulate calcium ion concentrations in cardiomyocytes (19) and vascular smooth muscle cells (20), influencing both the contractile and diastolic functions of the heart, as well as vascular tension. These findings provide a theoretical basis for its application in the treatment of CVD.

3. Biological activity of honokiol

Honokiol exhibits a broad spectrum of biological activities relevant to the therapeutic management of CVDs (21) (Fig. 2). These activities including antioxidant, anti-inflammatory, vasodilatory, anti-thrombotic, anti-platelet, and cardioprotective effects, highlight the value of studying honokiol to develop improved strategies for managing CVDs.

Antioxidant activity. A key attribute of honokiol is its potent antioxidant capacity. Oxidative stress, caused by the loss of appropriate balance between reactive oxygen species (ROS) and antioxidant defense systems, is a major contributor to the onset of CVDs such as atherosclerosis (22), myocardial infarction (23), and heart failure (24). Honokiol exhibits potent antioxidant activity through its ability to scavenge both ROS and reactive nitrogen species (RNS), including superoxide anions (O_2^-), hydroxyl radicals (·OH), and peroxynitrites ($ONOO^-$). Its unique ortho-dihydroxy structural motif enables the efficient capture of free radicals (2.5 radicals per molecule), thereby disrupting lipid peroxidation. In a linoleic acid emulsion model, honokiol was found to block lipid peroxidation 15-20% more effectively than under control conditions, attributed to its ability to stabilize lipid membranes and suppress free radical propagation. This mechanism reduces the amount of oxidative damage to cellular organelles, extracellular matrices, and genomic DNA, as evidenced by decreased levels of malondialdehyde (MDA) and 8-hydroxy-2'-deoxyguanosine adducts in treated samples (25). It can help to scavenge free radicals, including superoxide anions and hydroxyl radicals, and it

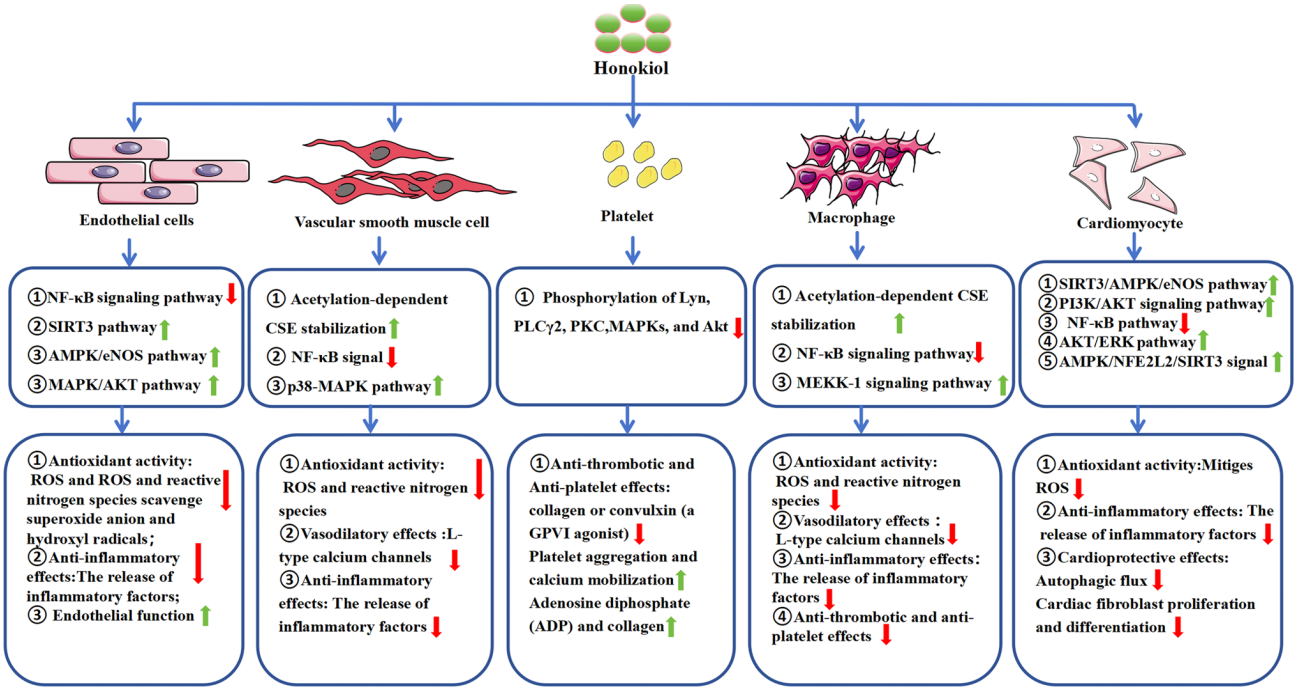

Figure 2. Biological activities of honokiol. NF-κB, Nuclear factor kappa-B; SIRT3, sirtuin 3; AMPK, adenosine 5'-monophosphate-activated protein kinase; eNOS, endothelial nitric oxide synthase; CSE, cystathionine γ lyase; MAPK, mitogen-activated protein kinase; PLCγ2, phospholipase C γ2; PKC, protein kinase C; AKT, protein kinase B; MEKK-1, mitogen-activated protein kinase kinase 1; ERK, extracellular regulated protein kinases; NFE2L2, nuclear factor erythroid-derived 2-like 2.

suppresses the biogenesis of ROS within cells (22). Moreover, honokiol was found to preserve mitochondrial function by inhibiting Fe(III)-adenosine diphosphate (ADP)/NADPH- and Fe(III)-ADP/NADH-induced lipid peroxidation, thereby sustaining the activities of respiratory enzymes and maintaining mitochondrial redox homeostasis. Honokiol treatment was observed to significantly reduce MDA levels in myocardial mitochondria in spontaneously hypertensive rat models while simultaneously increasing plasma nitrite/nitrate (NO_2^-/NO_3^-) levels, ultimately improving nitric oxide (NO) metabolism (13). In a model of sodium fluoride (NaF)-induced neurotoxicity, activation of the AMPK/PGC-1α/SIRT3 signaling axis restored the activity of SOD2, mitochondrial DNA transcription, and ATP synthesis, thereby reversing synaptic damage and cognitive deficits (26); these effects were mediated by honokiol activation of the AMPK/NFE2L2/SIRT3 signaling pathway, promoting AMPK phosphorylation and nuclear translocation of nuclear factor erythroid 2-related factor 2 (Nrf2) (22). This process led to an upregulation of sirtuin 3 (SIRT3) expression, thereby enhancing the activities of mitochondrial manganese superoxide dismutase (MnSOD) and catalase (CAT) and thus reducing ROS accumulation. Concurrently, the Keap1/Nrf2/ARE axis was found to promote the expression of the antioxidant enzyme glutathione (GSH), resulting in further reductions in both ROS accumulation and apoptosis (27). These data collectively demonstrate that honokiol enhances the activity of antioxidant enzymes such as SOD and CAT, strengthening the ability of the body to defend against oxidative stress. Consistent with these findings, it is reasonable to infer that these properties are particularly valuable in combating oxidative damage associated with endothelial dysfunction, plaque formation, and myocardial injury.

Anti-inflammatory effects. Chronic inflammation plays a central role in various cardiovascular conditions, including atherosclerosis, hypertension, and heart failure (28-30). Honokiol has been demonstrated to effectively inhibit pro-inflammatory signaling pathways such as the NF-κB (31), mitogen-activated protein kinase (MAPK) (32), and silent information regulator SIRT3 (33) pathways. By suppressing NF-κB activation, honokiol can reduce the expression of inflammatory cytokines and mediators such as TNF-α, IL-6, IL-1β, inducible NO synthase (iNOS), cyclooxygenase-2 (COX2), vascular cell adhesion molecule 1, and intercellular adhesion molecule-1, all of which are pivotal in vascular inflammation and atherosclerosis (34). Additionally, honokiol has been shown to inhibit inflammatory enzymes, including COX2 and NOS, further mitigating inflammatory responses (35).

Anti-thrombotic and anti-platelet effects. Platelet aggregation and thrombus formation are both central to the pathophysiology of stroke, myocardial infarction, and other facets of ischemic heart disease. Honokiol has been demonstrated to inhibit both of these processes (36). It is capable of suppressing platelet aggregation and the formation of thromboxane A2, which mediates vasoconstriction and platelet function (37). Honokiol was observed to selectively inhibit platelet aggregation and calcium mobilization induced by collagen or convulxin [a glycoprotein VI (GPVI) agonist], preventing the phosphorylation of Lyn, phosholipase C γ2, protein kinase C, MAPKs, and AKT following convulxin stimulation, reducing binding of an anti-GPVI antibody (FITC-JAQ1) to human platelets, and significantly prolonging closure time in human whole-blood assays while increasing the occlusion time in murine models of thrombotic platelet thrombosis. These findings demonstrate the

potential of honokiol as a novel anti-platelet and anti-thrombotic agent (38). Experimental studies have shown that honokiol can prevent platelet aggregation by reducing numerous agonists, such as ADP and collagen, emphasizing its potential utility as a therapeutic agent for limiting the incidence of thrombosis-related cardiovascular episodes (36).

Vasodilatory effects and protection of endothelial function. The maintenance of optimal blood pressure and organ perfusion hinges on the effective regulation of vascular tonus (39). Honokiol has been been shown to enhance vascular function through a variety of mechanisms, suggesting a promising avenue for the management of hypertension and ischemic heart disease. By stimulating the release of NO from endothelial cells, honokiol promotes vasodilation, as NO is a potent vasodilator that increases cyclic guanosine monophosphate levels and blocks L-type calcium channels, inhibiting calcium ion influx and relaxing vascular smooth muscle, thereby reducing vascular resistance and lowering blood pressure (40). Furthermore, honokiol has been demonstrated to enhance endothelial relaxation by activation of SIRT3, particularly under conditions of severe inflammation. As a specific activator of SIRT3, honokiol was shown to promote the SIRT3-dependent AMPK/eNOS pathway, restoring phosphorylation of eNOS at the Ser1177 site (41). This process not only induced NO generation but also improved endothelium-dependent vasodilation, ultimately restoring microcirculatory homeostasis (41).

In addition, honokiol mitigated reduced vasodilation in the aorta and mesenteric arteries, thereby improving endothelium-dependent vasodilation in a rat model of type 2 diabetes. Specifically, honokiol maintained the ratio of phosphorylated to total eNOS and increased the expression of CD31, which is typically reduced in diabetic rats. These findings suggest that honokiol may prevent diabetes-induced atherosclerosis by protecting the vascular endothelium and activating SIRT3, thereby enhancing the overall health and function of the endothelium (42). Honokiol has also been found to play a significant role in the regulation of vascular tonus, improvements in endothelial function, and the prevention of vascular dysfunction through multiple mechanisms. Activation of SIRT3 was shown to promote the generation of NO, and this, together with the inhibition of inflammation and oxidative stress, collectively improve vascular function and endothelial health (42). This multifaceted approach offers new strategies and hope for the treatment of CVD, highlighting the potential of honokiol as a valuable therapeutic agent.

Cardioprotective effects. Honokiol exhibits significant cardioprotective effects, particularly in ischemic heart diseases such as myocardial infarction and reperfusion injury (43). Its multifaceted mechanisms, including the reduction of oxidative stress, inflammation, and apoptosis, contribute to its efficacy in minimizing myocardial damage (44,45).

Experimental studies have demonstrated that honokiol reduces infarct size, prevents cardiomyocyte apoptosis, and improves cardiac function post-ischemia (44,45). These effects are mediated primarily through the activation of survival signaling pathways, inhibition of apoptotic cascades, and enhancement of mitochondrial function. Honokiol achieves these benefits by boosting autophagic flux and modulating the PI3K/AKT signaling pathway (44). Additionally, it has been shown to reduce the levels of cardiac fibrosis following ischemia, thereby preserving myocardial structure and function (45).

The cardioprotective effects of honokiol are further substantiated by its ability to promote the expression of the cardiac protective protein uncoupling protein 3 (UCP3), as well as its maintenance of the mitochondrial membrane potential. These effects reduce the production and accumulation of ROS following myocardial infarction, thereby mitigating myocardial fibrosis and improving heart failure outcomes (24). Honokiol was also found to block agonist-induced and pressure overload-mediated cardiac hypertrophy in mice, and these anti-hypertrophic effects were observed to be dependent on the activation of SIRT3 (46). By enhancing the expression and activity of SIRT3, honokiol treatment resulted in reduced acetylation of SIRT3 substrates in the mitochondria, such as MnSOD and oligomycin sensitivity conferring protein (47). This resulted in enhanced mitochondrial respiration and reduced ROS synthesis in wild-type, but not in SIRT3-knockout, cells. Moreover, honokiol inhibited the proliferation of cardiac fibroblasts and their differentiation into myofibroblasts in a SIRT3-dependent manner (47).

In summary, the comprehensive cardioprotective functions of honokiol suggest its potential as a promising therapeutic candidate for ischemic heart diseases. Its ability to reduce oxidative stress, inflammation, and apoptosis, while enhancing mitochondrial function and autophagy, underscores its potential in mitigating myocardial damage and improving cardiac outcomes. The activation of SIRT3 and modulation of the PI3K/AKT pathway further consolidate its role in preventing cardiac hypertrophy and fibrosis.

4. Research progress of honokiol in cardiovascular diseases

Honokiol has garnered increasing attention in cardiovascular medicine due to its diverse pharmacological properties. This section offers an overview of the most up-to-date findings discussing the benefits of honokiol in different cardiovascular conditions (Fig. 3).

Honokiol in atherosclerosis. Atherosclerosis is characterized by chronic inflammation, oxidative stress, and endothelial dysfunction, with honokiol providing a means of targeting all of these deleterious features (48). Research indicates that honokiol can limit plaque formation, reduce arterial inflammation, and enhance endothelial function (11). Zhu *et al* observed that honokiol regulated proliferation and migration in rat aortic smooth muscle cells induced by TNF-α. This involved blocking the activation of NF-κB through suppression of the ERK signaling pathway (34). Preclinical investigations using animal models (such as $ApoE^{-/-}$ mice) have demonstrated marked reductions in atherosclerotic plaque size together with improved arterial function, attributed to the antioxidant and anti-inflammatory properties of honokiol (22).

Honokiol in hypertension. Hypertension management is vital for reducing cardiovascular morbidity and mortality. Preclinical studies have shown that honokiol effectively decreases both systolic and diastolic blood pressure (39,40). In spontaneously hypertensive rats, oral administration

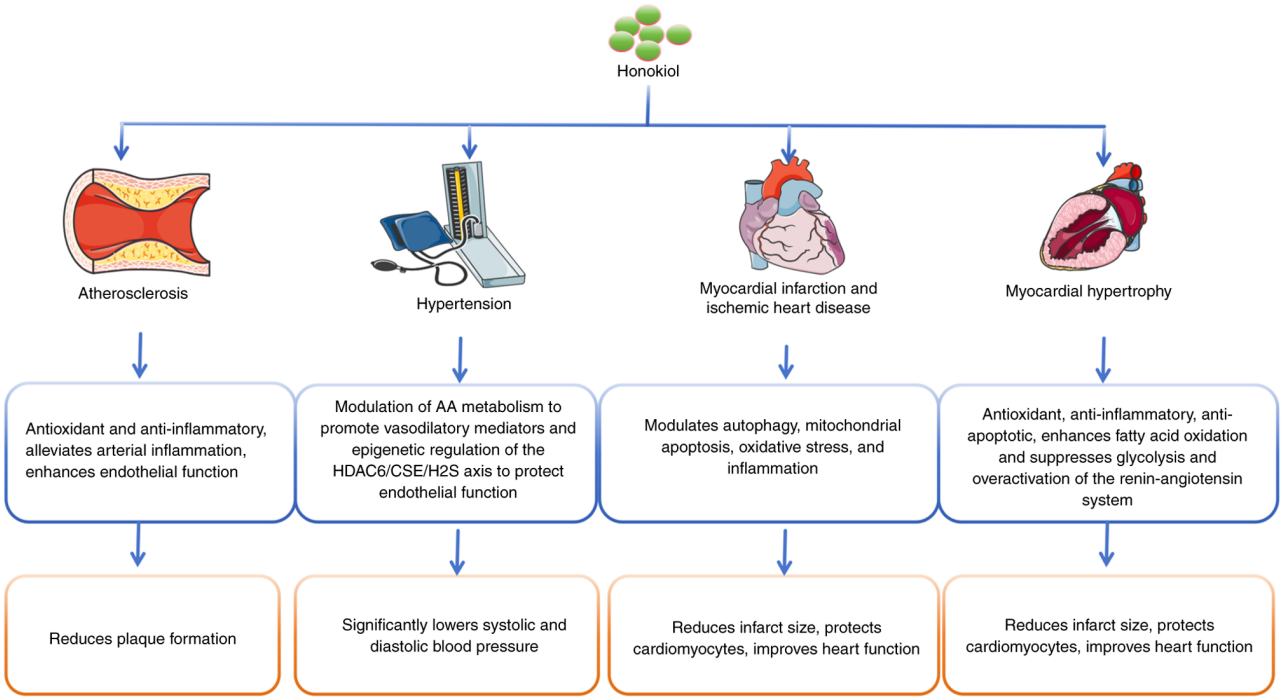

Figure 3. Research progress on honokiol in cardiovascular diseases. HDAC6, histone deacetylase 6; CSE, cystathionine γ lyase; H2S, Hydrogen sulfide.

of honokiol (30 mg/kg/day) significantly reduced systolic blood pressure by 28% over 4 weeks by the reprogramming of arachidonic acid (AA) metabolism. This involved the downregulation of COX-2 and 5-lipoxygenase (LOX), critical enzymes in pro-inflammatory eicosanoid biosynthesis, while upregulating the expression of 12/15-LOX leading to increased production of the vasoprotective metabolite lipoxin A4. Concurrently, honokiol suppressed leukotriene B4 generation, thereby reducing inflammatory vasoconstriction (39).

In a complementary study using angiotensin II (Ang II)-induced hypertensive mice, honokiol (10 mg/kg/day) was observed to attenuate systolic hypertension by 22% through a novel epigenetic mechanism. Honokiol was found to inhibit histone deacetylase 6 (HDAC6)-mediated ubiquitination and proteasomal degradation of cystathionine γ-lyase (CSE), rate-limiting enzymes in the biosynthesis of hydrogen sulfide (H_2S). Increased CSE activity restored H_2S bioavailability, which in turn preserved the phosphorylation of eNOS and reduced oxidative stress, thereby ameliorating endothelial dysfunction (40).

Collectively, these findings demonstrate that honokiol exerts antihypertensive effects through several pathways, namely, the modulation of AA metabolism to promote vasodilatory mediators and epigenetic regulation of the HDAC6/CSE/H_2S axis to protect endothelial function. These complementary mechanisms highlight the potential of honokiol as a multi-target therapeutic agent for hypertension, with implications for both blood pressure control and vascular protection.

Honokiol in myocardial infarction and ischemic heart disease. The cardioprotective properties of honokiol have been extensively explored in both acute and chronic myocardial infarction contexts. A study by Liu *et al* (24) investigated the therapeutic potential of honokiol in ameliorating heart failure following myocardial infarction. Using a mouse model of myocardial infarction, it was demonstrated that honokiol treatment led to a marked improvement in cardiac function, as evidenced by an increased ejection fraction and reduced left ventricular dilation. Mechanistically, honokiol upregulated the expression of UCP3, leading to reduced ROS generation and thus preventing oxidative stress (24). This effect was associated with preserved mitochondrial integrity and enhanced antioxidant capacity in cardiomyocytes. Furthermore, honokiol treatment reduced the levels of pro-inflammatory cytokines (such as TNF-α and IL-6) and inhibited apoptosis-related pathways, contributing to reduced myocardial fibrosis and cardiomyocyte death (24). The study highlighted UCP3-mediated ROS inhibition as a critical mechanism underlying the cardioprotective effects of honokiol, suggesting its potential as a therapeutic agent for heart failure after myocardial infarction.

In addition to its role in myocardial infarction, honokiol also has cardioprotective effects in ischemic heart disease. Tan *et al* (43) reported that honokiol treatment ameliorated myocardial ischemia/reperfusion injury by increasing autophagic flux and reducing ROS production. These protective effects were linked to the suppression of oxidative stress-related pathways (including NF-κB), coupled with the preservation of mitochondrial function via inhibition of mitochondrial permeability transition pore (mPTP) opening. Furthermore, honokiol alleviated myocardial ischemia/reperfusion injury by activating the PI3K/AKT signaling pathway, which inhibits mitochondrial apoptosis. Specifically, phosphorylation of downstream targets (such as GSK-3β) suppressed mPTP opening, thereby reducing cardiomyocyte apoptosis and improving the recovery of cardiac function (44). Moreover, Wang *et al* (45) described the dual actions of honokiol in cardioprotection as i) antioxidant effects induced by reducing lipid peroxidation markers (such as

MDA) and ROS generation, and ii) anti-inflammatory effects induced by downregulation of pro-inflammatory cytokines (including TNF-α and IL-6). Additionally, honokiol may enhance myocardial tolerance to hypoxia by improving both microcirculation and energy metabolism (45). Collectively, these studies underscore the multifaceted role of honokiol in myocardial ischemia/reperfusion injury through the modulation of autophagy, mitochondrial apoptosis, oxidative stress, and inflammation, offering a promising therapeutic avenue for ischemic heart disease.

Honokiol in myocardial hypertrophy. Recent research has demonstrated that honokiol can effectively mitigate Ang II-induced cardiac hypertrophy by disrupting the nuclear receptor 77 (Nur77)-liver kinase B1 (LKB1) complex and activating the AMPK pathway (49). Under Ang II stimulation, Nur77 binds to LKB1, leading to its sequestration in the nucleus and impairment of its cytoplasmic role as an upstream activator of AMPKα, a critical regulator of energy homeostasis and suppressor of hypertrophy. Honokiol promotes the dissociation of the Nur77-LKB1 complex, facilitating LKB1 translocation to the cytoplasm, where it phosphorylates AMPKα at Thr172 (49). Activated AMPKα inhibits mTOR/p70S6K signaling, which is a key driver of protein synthesis and cardiomyocyte growth, while restoring metabolic balance by enhancing fatty acid oxidation and suppressing glycolysis.

Furthermore, honokiol has also been found to exhibit multi-target anti-hypertrophic effects by attenuating Ang II-induced activation of the NF-κB and MAPK pathways, reducing the levels of inflammatory cytokines (such as TNF-α) and oxidative stress (40,50). It also downregulates the levels of angiotensin-converting enzyme and the Ang II receptor type 1 receptor, thereby suppressing overactivation of the renin-angiotensin system. *In vivo* studies using Ang II-infused mice revealed that honokiol could significantly reduce the thickness of the left ventricular wall, the cross-sectional area of cardiomyocytes, and the levels of fibrosis markers such as collagen deposition. *In vitro* experiments with neonatal cardiomyocytes confirmed that honokiol reversed Ang II-induced hypertrophy, an effect abolished by AMPK inhibition or LKB1 knockdown, underscoring the centrality of this pathway (49).

These findings highlight the potential of honokiol as a dual-target agent that disrupts pathological protein interactions (Nur77-LKB1) and restores AMPK-mediated metabolic regulation. In contrast to conventional therapies that primarily lower blood pressure, honokiol specifically addresses maladaptive cardiac remodeling without compromising hemodynamics, offering a safer profile. These findings indicate the advantages of the clinical translation of natural compounds targeting energy-sensitive pathways in CVD.

5. Prospects of honokiol in cardiovascular diseases

Honokiol has emerged as a promising therapeutic agent for CVD due to its diverse pharmacological properties. Its ability to exert anti-inflammatory, antioxidant, and cytoprotective effects makes it a versatile candidate for the management of various CVD-related pathologies. A key advantage of honokiol is its cardioprotective ability, particularly in the alleviation of myocardial ischemia/reperfusion injury. By activating the Nrf2/HO-1 pathway, honokiol promotes cellular resistance to oxidative stress, a critical contributor to both atherosclerosis and heart failure (26,27). Additionally, its anti-atherogenic effects, such as the alleviation of endothelial dysfunction, inhibition of low-density lipoprotein (LDL) oxidation, and the prevention of foam cell formation, highlight its potential in slowing plaque progression (11,48).

Honokiol also has vasoprotective benefits, primarily through its upregulation of eNOS, which promotes vasodilation and improves blood pressure regulation (39-42). This mechanism is particularly relevant for patients with hypertension and those with metabolic disorders, where endothelial dysfunction is prevalent. Furthermore, honokiol exhibits anti-arrhythmic properties through its ability to modulate cardiac ion channels, thereby stabilizing electrical activity and reducing the risk of ventricular arrhythmias (45). Its anti-fibrotic effects further aid in the prevention of adverse myocardial remodeling, making it a potential therapeutic option for atrial fibrillation and post-infarction complications. Another notable feature is the anti-thrombotic activity of honokiol, associated with suppression of platelet aggregation without increasing the risk of bleeding, a significant advantage over traditional antiplatelet drugs (36-38). Its dual role in mitigating inflammation (via NF-κB and NLRP3 inflammasome inhibition) (51,52) and enhancing metabolic homeostasis (via AMPK/SIRT1 activation) further underscores its potential in treating complex CVDs (13). Given its multi-targeted mechanisms and natural origin, honokiol holds promise as a complementary or alternative therapy for CVDs, particularly in patients with multifactorial conditions.

A 2022 patent (patent no. CN114588136A) described the preparation of honokiol-based medications for the treatment of myocardial infarction (53). In mice, honokiol use was found to significantly improve cardiac function for 4 consecutive weeks (Table I) (53). When honokiol was used in ischemic models, it was found that the levels of lactate dehydrogenase increased while apoptosis decreased. This suggests that honokiol may be effective for treating ischemia-related injury (Table I) (53). Moreover, a traditional Chinese medicinal formulation consisting of honokiol, pachymic acid, and 10-dehydroxygingerdione has been widely utilized in the treatment of cardiovascular and cerebrovascular diseases (Table I) (54). Additionally, Li *et al* (55) synthesized a novel compound through the cyclization of metformin with honokiol (Table I), which showed significant efficacy in combating CVD. Notably, it exhibited superior anti-inflammatory effects in mouse models of early atherosclerosis when compared to honokiol or metformin individually, indicating enhanced efficacy and reduced toxicity (55). One patent describes a class of honokiol derivatives or salts containing C2 and C4'-phenol hydroxy substitutions for the prevention and/or treatment of CVD (Table I) (56). In rat models, these derivatives demonstrated significant cardioprotective effects against stress-induced cardiomyopathy-related behaviors (Table I) (56). Recently, derivatives of honokiol that incorporate amine groups on the aromatic ring have been utilized in the formulation of drugs related to resistance to myocardial ischemia, as well as in the composition of myocardial protective medications (Table I) (57). In rat models of myocardial

Table I. Patents related to enhancing the therapeutic efficacy of honokiol in the treatment of cardiovascular diseases.

Patent number	Patent title	Main findings	(Refs.)
CN114588136A	Application of honokiol in preparation of medicine for treating myocardial infarction	Improves heart function, reduces far-end myocardial fibrosis of an infarction region and myocardial cell apoptosis of an infarction marginal region.	(53)
CN109045045A	A kind of active ingredient of Chinese herbs composition for treating cardiovascular and cerebrovascular disease	This composition can treat cardiovascular and cerebrovascular diseases, it can markedly reduce the levels of TC, TG and LDL-C, and increase the level of HDL-C.	(54)
CN108033927A	A kind of compound and its preparation method and application	It exhibits beneficial effects in anti-inflammatory, hypoglycemic, lipid-lowering, antitumor, antibacterial, and cardio- and cerebrovascular disease-related activities.	(55)
CN109771431A	The new application of honokiol derivative	Preventing and/or treating cardiovascular and cerebrovascular diseases.	(56)
CN115581690A	Application of magnolol or aromatic ring amino substituted derivative of honokiol in preparation of anti-myocardial ischemia drugs and pharmaceutical composition	Myocardial infarct size, serum CK-MB and LDH levels were significantly decreased.	(57)

TC, total cholesterol; TG, triglyceride; LDL-C, low density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; CK-MB, serum creatine kinase muscle-brain fraction; LDH, lactate dehydrogenase.

ischemia-reperfusion, the administration of compound 16 (1,500 μg/kg, delivered in two intravenous doses) notably decreased the size of the myocardial infarcts and lowered the levels of serum creatine kinase muscle-brain fraction and lactate dehydrogenase (Table I) (57). In conclusion, honokiol holds promising prospects for application in the prevention and treatment of CVD.

6. Challenges in the clinical application of honokiol

Despite the therapeutic promise of honokiol, there are several barriers that impede the clinical adoption of honokiol in the treatment of CVD.

Limited bioavailability and pharmacokinetic constraints. One of the primary obstacles is the poor water solubility of honokiol, which restricts its oral absorption and systemic bioavailability. In CVDs, where sustained therapeutic levels are crucial, the rapid metabolism and short half-life of honokiol further diminish its efficacy. Research has indicated that honokiol undergoes extensive hepatic glucuronidation, leading to rapid clearance and suboptimal plasma concentrations (52). While the use of nanoparticle-based delivery systems and lipid formulations has been explored to enhance bioavailability, their scalability, stability, and cost-effectiveness remain unresolved issues for clinical use.

Insufficient clinical evidence in human CVD. Despite compelling preclinical data showing the ability of honokiol to reduce oxidative stress, inhibit vascular smooth muscle proliferation, and improve endothelial function, there are few clinical trials on its use in humans. Most studies have been conducted in cultured cells or animal models, which may not accurately reflect human pathophysiology (22-24). For instance, while honokiol has shown potential in reducing myocardial infarction size in rodents, its effects in human ischemic heart disease remain unverified. Additionally, there have been no systematic evaluations of optimal dosing, long-term safety, and potential interactions with standard cardiovascular medications (such as statins and antiplatelet drugs).

Mechanistic complexity and off-target effects. Honokiol modulates multiple signaling pathways relevant to CVDs, including the NF-κB, SIRT3, and PI3K/Akt pathways, which contribute to its anti-inflammatory and vasoprotective effects (42,58). However, this pleiotropic activity raises concerns about potential unintended effects, such as excessive modulation of blood pressure or interference with coagulation pathways. For example, the antiplatelet properties of honokiol could theoretically increase the risk of bleeding when used in combination with aspirin or clopidogrel. Further research is required to delineate its precise mechanisms and identify potential adverse interactions in patients with complex comorbidities.

Standardization and formulation challenges. The lack of standardized honokiol extracts complicates the reproducibility of clinical studies. Variations in purity, extraction methods, and chemical composition in preparations from different sources can lead to inconsistent therapeutic outcomes. Moreover, the development of a stable, scalable, and patient-friendly formulation (such as oral tablets or injectables) for CVD management

remains a hurdle. While intravenous administration may bypass absorption issues, it introduces practical limitations for chronic use in outpatient settings.

Regulatory and commercial hurdles. As a natural product, honokiol faces regulatory ambiguities in terms of intellectual property and drug approval. Unlike synthetic drugs, its natural origin complicates its protection by patents, discouraging pharmaceutical investment. Additionally, competition with unregulated dietary supplements, which often lack rigorous quality control, undermines incentives for its clinical development. To overcome these barriers, collaborative efforts between academia, industry, and regulatory agencies are essential to establish standardized protocols and secure funding for large-scale trials.

7. Conclusion and outlook

Honokiol has demonstrated significant therapeutic potential in the treatment of CVD through its multifaceted mechanisms. It exerts cardioprotective effects by modulating calcium channels, suppressing Ang II-induced myocardial hypertrophy, and reducing ventricular remodeling. Its anti-inflammatory and antioxidant properties are mediated through inhibition of NF-κB signaling and enhancement of SOD/GSH-Px enzyme activities, effectively mitigating oxidative stress in atherosclerosis and myocardial ischemia. Furthermore, honokiol can ameliorate metabolic dysregulation by lowering blood glucose and lipid levels while inhibiting oxidized LDL formation, thereby preventing diabetic cardiovascular complications. Additional benefits include antiplatelet aggregation and vasodilation, highlighting its utility in thrombosis prevention. Despite these benefits, its translation to clinical use faces challenges. Specifically, its hydrophobicity limits oral bioavailability, necessitating advanced delivery systems such as lipid-based nanoparticles, its multi-target interactions with pathways, such as the Nrf2-SLC7A11-GSH and MAPK pathways, require precise mechanistic elucidation to minimize off-target effects, and the lack of robust clinical trials hinders validation of safety and efficacy in humans. Future efforts should prioritize the development of innovative formulations (such as polymer-stabilized nanosuspensions), mechanistic exploration using single-cell and organoid models to map spatiotemporal regulatory networks in myocardial fibrosis, and investigation of combination therapies with statins or immunomodulators to enhance synergistic effects. Expanding its application to pulmonary hypertension and arrhythmia could further broaden its therapeutic scope. With interdisciplinary collaboration and evidence-based validation, honokiol is poised to emerge as a precision treatment in CVD management, bridging the gap between traditional medicine and modern pharmacotherapy.

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Authors' contributions

YZ and ZL contributed to the conception and design of the review, and the literature collection. XL prepared the draft of the manuscript. All authors contributed to manuscript revision, and read and approved the final version of the manuscript. Data authentication is not applicable.

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Competing interests

The authors declare that they have no competing interests.

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