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Review Article

The therapeutic potential of Honeysuckle in cardiovascular disease: an anti-inflammatory intervention strategy

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Abstract: Honeysuckle is a conventional Chinese medicine with several therapeutic applications. With the advancement of modern scientific technologies, Honeysuckle's pharmacological effects and medicinal properties have been investigated more thoroughly. Studies demonstrate that the bioactive compounds in Honeysuckle possess anti-inflammatory effects via several mechanisms, protecting the cardiovascular system. This article provides a reference for the clinical use of Honeysuckle by reviewing research on the therapeutic impact of Honeysuckle and its active constituents on cardiovascular diseases, such as coronary atherosclerotic heart disease (CHD), myocardial ischemia-reperfusion (MI/R), acute myocardial infarction (AMI), hypertension, arrhythmia, and heart failure, through the inhibition of inflammatory responses.

Keywords: Honeysuckle, anti-inflammatory, cardiovascular disease, review

Introduction

Cardiovascular disease (CVD) is a prevalent chronic disease. In recent years, the prevalence of CVD has been rising each year. The World Health Organization (WHO) research indicates that CVD remains a primary cause of worldwide mortality, accounting for around 17.9 million deaths per year [1]. The inflammatory response is crucial in developing CVD, as an excessive inflammatory reaction will lead to dysfunction of vascular endothelial cells, atherosclerotic plaque, thrombosis, and other complications. Inflammatory biomarkers can predict CVD as an independent risk factor [2, 3]. However, there are disadvantages in traditional treatments, including low compliance and pharmaceutical side effects. Because of their ability to reduce inflammation, natural products have made strides in treating CVD. Therefore, one of the current research priorities is to find an herbal remedy that has anti-inflammatory properties that inhibit the progression of CVD. Si-Miao-Yong-An decoction, a traditional Chinese herbal formulation, has been employed to address cardiovascular issues due to its anti-inflammatory properties. Honeysuckle is the main component significantly contributing to these effects. Natural herbs, such as Honeysuckle, have demonstrated beneficial effects on the inflammatory response. The active compounds in Honeysuckle, including flavonoids, have shown anti-inflammatory and cardioprotective properties. This study compiled existing information regarding the role of Honeysuckle and its active components in CVD through anti-inflammatory mechanisms. It assessed their function as a benchmark for prospective clinical applications.

Inflammation and CVD

Recent data has demonstrated a robust association between inflammation and CVD, establishing inflammation as a critical focus in research on cardiovascular comorbidities [4]. Atherosclerotic CVD is one of the important causes of morbidity and death worldwide [5]. The in-

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flammatory response mechanism of atherosclerosis (AS) was initially discovered in the 1980s. In the late 1990s, Ross formally articulated it based on injury response theory. Numerous clinical and experimental studies have subsequently enhanced the inflammatory theory of AS, indicating that AS is characterized by low-grade inflammation [6, 7]. The CANTOS [8] and COLCOT [9] clinical trials have verified the inflammatory theory of AS and have identified the inhibition of the NOD-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome pathway as one of the anti-inflammatory therapeutic pathways for AS. Monocytes attracted to the injury site may evolve into pro-inflammatory macrophages, which can lead to CVD. At the molecular level, overactive inflammasomes play a vital role in the development and progress of some cardiovascular diseases.

Furthermore, because of the deposition of lipoproteins in the artery wall, inflammation is thought to substantially impact the onset and development of AS [10]. AS caused by an inflammatory state is also one of the risk factors for arrhythmia development [11]. Inflammation may accompany the formation and progression of plaques. Localized or systemic inflammation and recurrent infections may elevate the probability of plaque rupture before thrombosis. Macrophages and smooth muscle cells can secret inflammatory cytokines, including interleukin-6 (IL-6) and interleukin-1β (IL-1β) [12-14]. C-reactive protein (CRP) is a non-specific marker of inflammation, and its elevated levels are closely related to an increased risk of CVD. CRP is a downstream product of interleukin-1 (IL-1), linked to various inflammatory diseases and AS. Inflammatory CVD develops due to IL-1's stimulation of adhesion molecules and induction of monocyte chemoattractant protein-1 (MCP-1). By eliminating atherosclerotic plaques, MCP-1-recruited phagocytes can result in AMI. IL-1 also promotes the growth of vascular smooth muscle cells and the expression of IL-6 [15]. Therefore, inflammation and CVD are intimately associated.

Inflammation-associated mechanisms in CHD

CHD is associated with a complex inflammatory process influenced by multiple factors. CHD is strongly linked to AS, involving various inflammatory mediators such as CRP, IL-6, IL-1β, IL-1, interferon-γ (IFN-γ), P-selectin, and E-selectin, as well as numerous cell types, including macrophages, monocytes, vascular endothelial cells, vascular smooth muscle cells, and T-lymphoid cells [16]. The formation of NLRP3 inflammasomes in macrophages contributes significantly to AS pathogenesis. The classic inflammatory pathways of NLRP3/IL-1β/IL-6/hypersensitive C-reactive protein (hs-CRP) are widely recognized as contributors to increased risk of vascular AS [17]. Toll-like receptors (TLRs) signaling promotes inflammatory factor production through immune activation, and plays an important role in the onset and progression of CHD. Inhibition of TLRs can reduce the development of vascular inflammation and AS to a certain extent [18]. Toll-like receptor 4 (TLR4) binds to endogenous ligands during arterial injury, leading to activation of nuclear factor kappa-B (NF-κB) and its translocation to the nucleus to promote the transcription of inflammatory factors, which regulate macrophage polarization resulting in endothelial lipid deposition and induction of the inflammatory response in AS [19]. The c-Jun N-terminal kinase (JNK)/nuclear transcription factor activating protein-1 (AP1) signaling is associated with the occurrence and progression of AS. JNK can induce the expression of inflammatory factors downstream of c-JNK, resulting in an inflammatory reaction. The transcription factor AP1 can also promote the expression of inflammatory factors in AS lesions [20-22].

Inflammation-associated mechanisms in MI/R

MI/R induces an acute inflammatory response in which MI/R injury is associated with inflammasome activation, and NLRP3 is the initial receptor [23]. Reactive oxygen species (ROS) and pro-apoptotic signaling pathways also play a central role in the inflammatory phase, and white blood cells and mitochondria are also major participants in MI/R-associated inflammation [24]. TLR4 has been shown to activate the NLRP3 inflammasome through the NF-κB pathway [25], and the TLR4/NLRP3 axis is closely associated with both inflammation and programmed cell death in cardiomyocytes [26]. The inflammatory response in MI/R injury is mediated by the TLR4/MyD88/NF-κB pathway and the NLRP3 inflammasome, which leads to myocardial injury [27, 28].

Inflammation-associated mechanisms in AMI

AMI is associated with various inflammatory markers and cytokines, such as IL-1, IL-6, tumor

necrosis factor-α (TNF-α), CRP, increased serum levels of galectin-3 (Gal-3), and myeloperoxidase (MPO) [29, 30]. Genetic or pharmacological inhibition of the NLRP3 inflammasome and toll-like receptor 2 (TLR2) or TLR4 has been shown to reduce the infarct size in myocardial infarction (MI) [31, 32]. TLR2 and TLR4 can bind to MyD88, activate intracellular transduction pathways, promote the expression of pathways such as NF-κB and JNK, and participate in physiological processes such as apoptosis and the inflammatory response [33, 34]. Following AMI, cells within various myocardial components sustain damage or perish, initiating an acute pro-inflammatory response that releases numerous pro-inflammatory mediators, resulting in the recruitment of inflammatory cells to the infarcted region and intensifying the inflammatory response [35].

Inflammation-associated mechanisms in hypertension

The development of hypertension is associated with inflammation and the immune system. The triggering of an inflammatory response by the immune system can lead to an increase in blood pressure. Cells of the innate immune system can produce ROS, with long-term inflammation increasing the generation of ROS, affecting the endothelial regulation of vascular tension and structure. The persistence of inflammation reduces the bioavailability of nitric oxide (NO), affecting vascular dilation [36]. T cell effectors of the adaptive immune system play an important role in the vasoconstriction associated with hypertension, leading to elevated blood pressure and subsequent damage to target organs [37]. The PI3K/AKT signaling pathway can promote the contractions of vascular smooth muscle, increase vascular tension, and induce macrophage polarization, affecting the expression of pro-inflammatory factors [38]. The JAK/STAT pathway is involved in immune regulation and can modulate the expression of the pro-inflammatory factors IL-1β, IL-6, and TNF-α, thus stimulating the inflammatory process, and is closely associated with the development of hypertension [39, 40].

Inflammation-associated mechanisms in arrhythmia

Both atrial and ventricular arrhythmias are associated with inflammation [41]. The inflammatory response can promote electrical remodeling as well as remodeling of the atrial structure and changes in the conduction pathways within the atrium [42]. Arrhythmia is associated with multiple inflammatory biomarkers, including CRP, hs-CRP, TNF-α, and IL-6 [43]. Higher levels of CRP have been shown to be linked with reduced success in cardioversion and maintenance of the sinus rhythm and may increase the risk of atrial fibrillation recurrence after cardioversion [44]. TLR4/NF-κB can mediate the inflammatory response and influence the onset of atrial fibrillation by inhibiting the transcription of genes encoding Na^+ channels [45]. The activation of NLRP3 inflammasomes, downstream of TLR4/NF-κB, induces the upregulation of ultrarapid delayed rectifier K^+ channels, decreasing the myocardial static potential and shortening the duration of the action potential, resulting in cardiac electrical remodeling and arrhythmia [46].

Inflammation-associated mechanisms in heart failure

Inflammation is recognized as a major contributor to heart failure [47]. The levels of pro-inflammatory cytokines, such as TNF-α, IL-1, and IL-6, as well as those of CRP, are upregulated in heart failure and correlated with the severity of heart failure [48]. Among them, TNF-α is a typical pro-inflammatory cytokine that plays a key role in the pathological process of heart failure. It can induce myocardial cell hypertrophy, activate metalloproteinases (MMPs), and lead to myocardial fibrosis. Its level in the circulation is closely related to the degree of heart failure and is an independent predictor of mortality in patients with heart failure [49, 50]. The NLRP3 inflammasome can promote the progression of fibrosis by stimulating the production of IL-1β and interleukin-18 (IL-18) [51, 52]. The activation of TLR4/NF-κB signaling also induces the expression of pro-inflammatory cytokines and triggers immune cell infiltration and cardiac dysfunction after myocardial ischemia, thus exacerbating the development of heart failure [53]. The PI3K/AKT pathway can regulate myocardial cell apoptosis and promote macrophage polarization, thereby stimulating or inhibiting inflammatory responses, making it an important target for the treatment of heart failure [54].

Anti-inflammatory effects of active substances from Honeysuckle on CVD

Honeysuckle is a plant from the Lonicera family, primarily found in Asia, Europe, and North America. It possesses the properties of heat clearance, detoxification, and the dispersion of wind and heat. Honeysuckle is a plant used in both medicinal and culinary applications. It is frequently used in traditional Chinese medicine. It was initially described in Ge Hong's *Handbook of Prescriptions for Emergencies* during the Eastern Jin Dynasty and has been used clinically for over a thousand years. Honeysuckle was included in the *Chinese Pharmacopoeia* in 1995, and over 500 medicines containing Honeysuckle components are now used to treat various diseases. At first, Honeysuckle stems and leaves were used as medicinal components. All parts of Honeysuckle, especially the flower buds, were used in therapeutic therapy after the Ming Dynasty.

Honeysuckle is used in a wide range of medicinal formulations. Honeysuckle is used to prepare tea, beverages, wine, and various food products, which may possess preventive or therapeutic properties against diseases [55]. Throughout the COVID-19 pandemic, Honeysuckle was extensively utilized as a heat-clearing and detoxifying remedy in epidemic prevention and treatment, closely associated with its constituents and properties. Honeysuckle comprises several phytochemical constituents, primarily phenolic acids, volatile oils, saponins, and flavonoids. Honeysuckle, a traditional Chinese herbal remedy showing anti-inflammatory properties, contains active compounds that inhibit the release of inflammatory mediators, including CRP, INF-γ, IL-1β, IL-6, and TNF-α, thus reducing the initiation of inflammatory responses. It can inhibit the inflammatory response induced by oxidative stress, exert immunosuppressive effects through inhibiting pro-inflammatory cytokines, and demonstrate anti-inflammatory effects by blocking signaling pathways such as NF-κB, JNK, mitogen-activated protein kinase (MAPK), and TLR4. Inflammation and immunity are closely related at the organizational, cellular, and molecular levels. The exclusive use of anti-inflammatory, immunosuppressive, or immunomodulatory medications for disease treatment is inadequate. The active compounds in Honeysuckle demonstrate anti-inflammatory and immune-regulating properties, indicating substantial potential for application [56] (**Table 1**).

Chlorogenic acid (CGA)

CGA is the primary phenolic acid in Honeysuckle, classified in the extensive phenolic acid family, with the IUPAC designation 3-o-caffeoylquinic acid, as shown in **Figure 1A**. CGA protects vascular endothelial cells, thereby protecting cardiac cells from TNF-α caused injury by obstructing the NF-κB and JNK signaling pathways, it can also impede the inflammatory response induced by lipopolysaccharide (LPS) by attenuating the activation of the JNK/AP-1 and NF-κB signaling pathways [57]. Administering CGA in a rat model subjected to a high-fat diet can diminish left ventricular inflammatory cell infiltration and visceral fat [58]. In addition, CGA can also improve endothelial function through anti-inflammatory effects, and it can reduce TNF-α-induced protein expression of MCP-1, vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) [59].

Research has shown that the levels of IL-6, IL-1, and TNF-α in hypertensive patients are higher than those in normotensive individuals [36]. CGA can enhance vascular endothelial function by exerting antihypertensive effects through its anti-inflammatory properties [60]. Taking CGA in hypertensive patients can considerably reduce blood pressure and improve vascular inflammatory response, and there are no adverse responses [61]. Through the regulation of rein-angiotensin-aldosterone-system (RAAS), CGA can lower levels of TNF-α, IL-1β, and other inflammation-related indicators, improve vascular endothelial function and NO bioavailability, regulate the PI3K/AKT pathway, and thus exert antihypertensive effect [62-64]. CGA can significantly reduce the atherosclerotic lesion area in the aortic root of ApoE-/- mice, reducing inflammatory markers and thus playing the role of anti-atherosclerosis [65]. The anti-AS mechanism of CGA pertains to its suppression of inflammatory responses and lipid accumulation. CGA can significantly diminish the concentrations of IL-6, interleukin-8 (IL-8), TNF-α, MCP-1, and IFN-γ associated with the onset and progression of AS in the serum of ApoE-/- mice, elevate the levels of anti-inflammatory cytokines interleukin-4 (IL-4) and interleukin-10 (IL-10), enhance the expression of MAPK, inhibit the downstream activation of JNK, and lower

Table 1. Detailed information on bioactive ingredients targeting anti-inflammatory effects in Honeysuckle

No.	Active ingredients	Mechanism of action	Signaling pathways	Treatment disease	References
1	Chlorogenic acid	(1) Suppress inflammatory responses and lipid accumulation (2) Reduce IL-6, IL-8, TNF-α, MCP-1 and IFN-γ (3) Enhance the expression of MAPK	Inhibit the downstream activation of JNK	AS	[65, 66]
2	Chlorogenic acid	(1) Regulate RAAS (2) Increase NO bioavailability (3) Improve vascular endothelial function (4) Reduce IL-1β, TNF-α, etc.	Regulate PI3K/AKT signaling pathway	Hypertensive	[62-64]
3	Chlorogenic acid	(1) Reduce IL-1β, IL-6, TNF-α, and INF-γ (2) Increase IL-4 and IL-10 (3) Enhance antioxidant enzyme activity	Inhibit NF-κB and JNK signaling pathways	AMI	[57]
4	Chlorogenic acid	(1) Reduce the levels of inflammatory factors (2) Inhibit ROS production (3) Reduce ANP, BNP and β-MHC	Inhibit NF-κB and JNK signaling pathways	Heart failure	[68, 69]
5	Caffeic acid	(1) Inhibit the inflammatory response (2) Decrease TNF-α and IL-6, etc.	Inhibit NF-κB signaling pathway	AS	[82, 83]
6	Caffeic acid	(1) Increase NO release and the bioavailability of NO (2) Promote the generation and proliferation of endothelial cells (3) Inhibit leukocyte adhesion and endothelial cell apoptosis (4) Inhibit ROS production	Inhibit JAK/STAT and ERK1/2 signaling pathways	Hypertensive	[64, 72, 73]
7	Luteolin	(1) Reduce macrophage infiltration (2) Inhibit the expression of ICAM-1, VCAM-1, TNF-α and IL-6	Inhibit NF-κB, AKT signaling pathways	AS	[81]
8	Luteolin	(1) Reduce IL-1β, IL-18, and TNF-α (2) Downregulate the expression of TLR4, MyD88 and NF-κB	Regulate TLR4/NF-κB/NLRP3 and Sirt1/NLRP3/NF-κB signaling pathways	MI/R	[82-84]
9	Luteolin	(1) Inhibit ROS production (2) Suppress the activate antioxidant enzymes (3) Obstruct leukotriene production and release	Inhibit NF-κB, AKT and MAPK signaling pathways	Heart failure	[76, 77]
10	Quercetin	(1) Inhibit expression of ICAM-1 and VCAM-1 (2) Reduce IL-1 β and TNF-α (3) Inhibit the expression of TLRs (4) Inhibit endothelial leukocyte adhesion	Inhibit TLR/NF-κB signaling pathway	AS	[92, 93]
11	Quercetin	(1) Reduce IL-1β and TNF-α (2) Reduce the transcriptional activity of NF-κB	Inhibit NF-κB and AP-1 signaling pathways	CHD	[94-96]
12	Quercetin	(1) Inhibit ROS production (2) Reduce TNF-α, IL-6 and IL-1β (3) Increase IL-10 (4) Reduce CK and LDH	Inhibit TLR4/NLRP3 signaling pathway	MI/R	[99-101]
13	Quercetin	(1) Weaken the activation of NLRP3 inflammasomes (2) Inhibit the inward flow of Ca^{2+} and Na^{+} and the outward flow of K^{+} (3) Reduce IL-1β, IL-18, TNF-α, and IL-6 (4) Inhibit ROS production	Inhibit NF-κB signaling pathway	Arrhythmia	[99, 102]

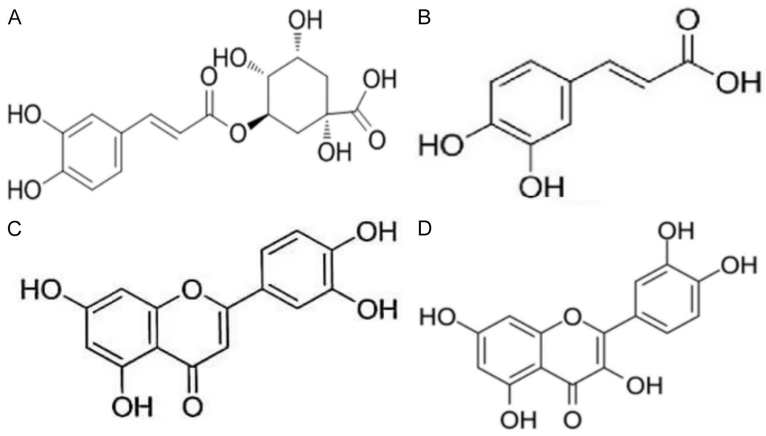

Figure 1. Chlorogenic acid (A), Caffeic acid (B), Luteolin (C), Quercetin (D).

the levels of IL-6, IL-1β, and TNF-α in LPS-induced RAW264.7 cells [65, 66]. CGA can significantly reduce the levels of IL-1β, IL-6, TNF-α, and INF-γ, increase the levels of IL-4 and IL-10, and enhance antioxidant enzyme activity in AMI model rats, thereby inhibiting cardiac dysfunction caused by an inflammatory response, reducing MI area, reducing myocardial injury and fibrosis degree, and improving survival rate after MI [67].

Studies indicate that in a mouse model of heart failure generated by transverse aortic constriction, CGA exhibits cardioprotective properties by reducing the levels of inflammatory factors and suppressing the activation of NF-κB and JNK signaling pathways, safeguarding myocardial cells from TNF-α-induced injury, and demonstrating anti-apoptotic activities. Furthermore, it suppresses isoproterenol-induced myocardial hypertrophy by obstructing the ROS and NF-κB pathway, resulting in reduced levels of hypertrophic markers atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and beta-myosin heavy chain (β-MHC), thus preventing and reversing myocardial hypertrophy, which is crucial for heart failure treatment [68, 69].

Caffeic acid (CA)

CA is one of the active components in Honeysuckle, with a structure as shown in **Figure 1B**. Moreover, widely found in numerous plants, it can protect the cardiovascular system through various mechanisms, including its anti-inflammatory and antioxidant capabilities. One of the primary mechanisms CA exerts therapeutic effects on CVD is its anti-inflammatory action. By diminishing leukocyte intrusion and suppressing the expression of inflammatory cytokines including serum IL-6, IL-8, and TNF-α, CA can have anti-inflammatory actions, thereby treating CVD [70].

CA has an antihypertensive solid effect and has been proven to have non-toxic side effects [71]. Fukuda et al. [72] reported that CA has a vasodilatory impact on aging and spontaneously hypertensive rats. CA can increase NO release, promote the generation and proliferation of endothelial cells, and inhibit leukocyte adhesion and endothelial cell apoptosis. Agunloye et al. [64] found that CA can actively regulate blood pressure in cyclosporin-induced hypertensive rats by increasing the bioavailability of NO. CA can have therapeutic effects on spontaneously hypertensive rats by suppressing the proliferation of smooth muscle cells, blocking the JAK/STAT and ERK1/2 signaling pathways, and inhibiting ROS production [73]. In vitro studies in human umbilical vein endothelial cells (HUVECs) have shown that CA (5-25 μM) significantly reduces TNF-α induced monocyte adhesion to HUVECs, as well as the expression of adhesion factors such as VCAM-1 and ICAM-1. CA can also directly inhibit NF-κB DNA binding activity in TNF-α induced HUVECs [74]. Sun et al. [75] showed that CA can reduce the area of atherosclerotic lesions in the whole aorta and aortic sinus of ApoE-/- mice by 50% compared with the normal saline control group. It is suggested that CA can serve as a preventive and therapeutic agent in AS by inhibiting the inflammatory response, as evidenced by its ability to reduce local inflammation and decrease TNF-α and IL-6.

Luteolin

Luteolin is a low-toxicity natural flavonoid compound, as shown in **Figure 1C**, which has been demonstrated to have protective effects against various cardiovascular diseases. Luteolin primarily exerts anti-inflammatory effects by inhibiting the expression of NO and inducible nitric oxide synthase (iNOS), eliminating ROS, sup-

pressing ROS production and the activation of antioxidant enzymes, obstructing leukotriene production and release, and diminishing the expression of pro-inflammatory cytokines through the inhibition of pathways such as NF-κB, AKT, and MAPK, ultimately reducing myocardial cell apoptosis and enhancing myocardial cell function [76, 77]. Luteolin demonstrates anti-inflammatory properties in *in vivo and in vitro* studies, mitigating inflammation induced by pro-inflammatory agents. Luteolin can diminish LPS-induced AKT phosphorylation, activate antioxidant enzymes, and inhibit the NF-κB pathway and the synthesis of pro-inflammatory mediators. Luteolin can also inhibit pro-inflammatory cytokines, such as IL-2, IL-6, IL-8, IL-1β, IFN-β, and TNF-α, and increase the anti-inflammatory factor IL-10 [78]. It was initially discovered by Wu et al. that luteolin dose-dependently suppresses the production of TNF-α and IL-6 in macrophages [79]. In SD rat bone marrow-derived macrophages, luteolin can limit the release of TNF-α, IL-8, IL-6, and granulocyte-macrophage colony-stimulating factor (GM-CSF) in addition to inhibiting the activation pathways of NF-κB, ERK1/2, and JNK1/2 [80].

Inflammatory responses are thought to significantly influence the formation and progression of AS, in addition to the accumulation of lipoproteins in the artery wall [10]. In ApoE-/- mice, luteolin may significantly reduce AS caused by a high-fat diet by lowering macrophage infiltration and mRNA expression of TNF-α, IL-6, ICAM-1, and VCAM-1 [81]. The pathways and complex interactions of inflammation play a crucial role in the process of MI/R injury. Luteolin can protect against MI/R injury via the TLR4/NF-κB/NLRP3 inflammasome pathway. Moreover, luteolin can significantly downregulate the expression of MyD88, NF-κB, and TLR4 while decreasing the serum levels of IL-1β, IL-18, and TNF-α in MI/R model rats and the supernatant of H9c2 cells [82, 83]. This might be connected to the potent cardioprotective effect of luteolin on MI/R damage. By controlling the Siti1/NLRP3/NF-κB inflammasome pathway, significantly reducing leukocyte infiltration, and upregulating the expression of several upstream binding factors, luteolin can also reduce inflammatory damage in rats following MI/R [84]. The above research indicates that luteolin can strengthen the contraction of myocardial cells, improve cardiac function, and reduce the infarct size.

The restricted oral bioavailability of flavonoids is typically attributed to first-pass metabolism in the liver and intestines. The limited therapeutic application of luteolin is due to its low bioavailability and inadequate water solubility. The use of preparation technologies, including particulate drug delivery systems, solid dispersions, inclusion complexes, phospholipid complexes, and hydrogels, can enhance the bioavailability of luteolin. The bioavailability of luteolin can be up to ten times higher than that of the original drugs, which offers essential support for further studies [85].

Quercetin

Quercetin is a flavonoid compound and one of the active ingredients in Honeysuckle, as shown in **Figure 1D**. Quercetin has anti-inflammatory, anti-atherosclerotic, and anti-proliferative effects [86, 87]. Quercetin has good pharmacokinetic characteristics. According to a network pharmacology study, quercetin interacts with 12 Kyoto Encyclopedia of Genes and Genomes (KEGG) signaling pathways and 47 targets associated with CVD, which may result in synergistic therapeutic effects. Quercetin prevents and treats CVD by systematically and thoroughly regulating numerous signaling pathways, including TNF-α, MAPK, IL-17, and PI3K/AKT pathways associated with inflammation [88]. Quercetin reduces inflammatory reactions, cellular apoptosis, and ROS production brought on by LPS. This has been associated with the activation of caspase-3 and NF-κB, which PI3K/AKT controls. ROS and TLRs can activate the PI3K/AKT signaling pathway [89, 90]. Quercetin can also weaken the activation of NLRP3 inflammasomes, thereby playing a protective role in the cardiovascular system [91]. Quercetin can inhibit the occurrence and development of AS by reducing inflammatory reactions [92, 93]. Quercetin can inhibit the TLR/NF-κB signaling pathway in endothelial cells, thereby inhibiting endothelial leukocyte adhesion induced by oxidized low-density lipoprotein (ox-LDL) and alleviating inflammation of AS [93]. Quercetin can inhibit the expression of TLRs and the levels of TNF-α and IL-1β in rats with AS, and can inhibit the formation of atherosclerotic plaques and significantly lower serum levels of IL-1β and TNF-α by reducing the transcriptional activity of NF-κB in individuals with CHD, thereby safeguarding cardiovascular health [94-96].

Inflammation is intricately linked to myocardial infarction/reperfusion damage. While inflammation is initiated during myocardial ischemia, restoring oxygen supply and blood flow enhances inflammatory signaling pathways [97, 98]. An essential component of the MI/R inflammatory phase is ROS and pro-apoptotic signaling pathways [24]. Quercetin can reduce ROS production, alleviate MI/R injury, decrease MI area, and improve cardiac function in MI/R mice [99]. Quercetin can reduce myocardial injury markers such as creatine kinase (CK) and lactate dehydrogenase (LDH), raise IL-10, and suppress TNF-α, IL-6, and IL-1β production to lessen MI/R injury [100, 101]. Quercetin can exert anti arrhythmic effects by inhibiting the inward flow of Ca^{2+} and Na^{+}, inhibiting the outward flow of K^{+}, suppressing ROS generation, weakening the activation of NLRP3 inflammasome, inhibiting the NF-κB pathway and inflammatory cytokines such as IL-1β, IL-18, TNF-α, and IL-6 [99, 102].

Quercetin is absorbed throughout the intestines of rats [103], and the total oral bioavailability of quercetin in ileostomy patients is 24% [104]. The oral bioavailability of total quercetin was 59.1% after oral administration of quercetin in rats [105]. The T1/2 of total quercetin in the human body is highly protracted, with a distribution T1/2 of 3.8 hours and an elimination T1/2 of 16.8 hours [106]. Current studies demonstrate that quercetin nanoparticle formulations and oligoglycoside derivatives significantly improve the bioavailability of quercetin, indicating substantial application potential [107, 108].

Clinical trial study on Honeysuckle-related Chinese medicine prescription

Traditional Chinese medicine is usually used in clinical practice in the form of prescriptions to play a better role. Many traditional Chinese medicine prescriptions containing Honeysuckle have significant therapeutic effects on CVD, such as Si-Miao-Yong-An decoction, conventional Chinese patent medicines such as Qidongyixin oral liquid, Mailuoning, Tongsaimai Tablet, and other antipyretic toxic Chinese medicine prescriptions often reduce the incidence of angina pectoris and adverse cardiovascular events by inhibiting inflammatory reaction, anti-AS, and stabilizing plaque.

Si-Miao-Yong-An decoction often plays a role in treating CVD by reducing inflammation. Clinical studies have shown that Si-Miao-Yong-An decoction can significantly reduce the level of serum hs-CRP in acute coronary syndrome (ACS) patients and improve the onset of angina pectoris in ACS patients [109]. Si-Miao-Yong-An acts more effectively than atorvastatin calcium tablets alone, a decoction mixed with atorvastatin calcium tablets in the treatment of AS and can help to transition unstable plaque to stable plaque, lower the level of hs-CRP and ease inflammation [110]. Qidongyixin oral liquid can significantly reduce the levels of inflammatory indicators hs-CRP, IL-6, and TNF-α in patients with acute MI, improve the cardiac function of patients, and reduce the incidence of adverse cardiovascular events [111]. Following four weeks of treatment with Tongsaimai tablets in patients with CHD, levels of CRP and endothelin (ET) diminished, and dyslipidemia improved, demonstrating substantial changes relative to the control group [112]. Mailuoning helps to reduce inflammation and stabilize plaque. Mailuoning and Lipitor used together significantly lower the serum hs-CRP level in ACS patients, and the results are better than those from Lipitor alone [113].

Discussion

Studies have shown that Honeysuckle alcohol extract can reduce the release of inflammatory mediators and cytokines such as IL-1, IL-6, and TNF-α [114]. The aqueous Honeysuckle extract can downregulate the mRNA and protein expression levels of inflammatory cells through the TLR4/NF-κB signaling pathway [115]. The decoction of Honeysuckle improves the activity of superoxide dismutase (SOD) in myocardial tissue, lowers levels of malondialdehyde (MDA), mitigates oxidative damage, decreases inflammatory factors like IL-6 and TNF-α in myocardial cells, and lowers levels of myocardial enzymes like LDH, CK, and serum CK-MB, all of which protect the heart. The particular mechanism might entail the suppression of NF-κB and caspase-3 expression [116]. Prior clinical studies have demonstrated that following two months of quercetin administration, patients showed enhancements in left ventricular systolic performance and left ventricular ejection fraction (EF). Chekalina et al. performed clinical research with 85 patients suffering from CHD, demonstrating that quercetin can influence

central hemodynamic parameters in stable CHD patients and improve myocardial ischemia. This indicates that quercetin possesses a cardioprotective effect in individuals with CHD [117].

Currently, in addition to the four active substances of Honeysuckle, namely CGA, CA, luteolin, and quercetin, which have been widely reported, organic acids such as ferulic acid, flavonoids such as kaempferol and cynaroside have been shown to have anti-inflammatory effects. Ferulic acid inhibits cyclooxygenase-2 (COX-2), prostaglandin E2 (PGE2), and TNF-α, improving endothelial function *in vivo* and *in vitro* [118, 119]. Clinical studies have also shown that ferulic acid can effectively alleviate angina attacks in patients with CHD angina pectoris [120]. Ferulic acid can significantly reduce the inflammatory markers hs-CRP and TNF-α in subjects, and supplementing with ferulic acid can improve patients' blood lipid status and inflammation [121].

In cells untreated and treated with kaempferol, pathway analysis of differentially expressed genes (DEG) indicates that kaempferol exhibits anti-inflammatory and anti-atherosclerotic properties in atherosclerotic cell models. In cells treated with kaempferol, the expression of MCP-1 diminished by 73.7-fold, while the expression of ICAM-1 decreased by 2.5-fold [122]. Moreover, research has shown that kaempferol can inhibit the activation of AKT and NF-κB in LPS and adenosine triphosphate (ATP)-induced cardiac fibroblasts and significantly inhibit the release of IL-6, IL-18, IL-1β, and TNF-α, thereby alleviating the inflammatory response of cardiac fibroblasts [123]. Cynaroside is a flavonoid found in Honeysuckle, and it has been demonstrated to possess potential biological effects in modulating inflammation and inhibiting azithromycin-induced cardiomyocyte pyroptosis [124].

The present study demonstrates that Honeysuckle and its active constituents can reduce the concentrations of inflammatory factors IL-1β, IL-6, IL-8, IL-18, TNF-α, MCP-1, and IFN-γ, while increasing the levels of anti-inflammatory factors IL-10 and IL-4, etc. They downregulate the mRNA and protein expression levels of inflammatory cells, reduce macrophage infiltration, inhibit leukocyte adhesion, regulate RAAS, increase NO levels and NO bioavailability, inhibit ROS production, inhibit ICAM-1 and VCAM-1 expression, improve vascular endothelial function, and exert therapeutic effects on CVD by regulating inflammatory signaling pathways such as TLR/NF-κB, NLRP3/NF-κB, TLR4/MyD88/NF-κB, PI3K/AKT, TLR4/NLRP3, JNK, etc.

The onset and progression of CVD are tightly linked to the inflammatory response. As a strong anti-inflammatory agent, Honeysuckle is a traditional Chinese medicine that may be used to both prevent and treat CVD. Although Honeysuckle's anti-inflammatory properties are beneficial in treating CVD, numerous challenges must be addressed. First, current research focuses on a few components, such as flavonoids, and ignores other potential bioactive components, which may limit the disclosure of the full pharmacological effects of Honeysuckle. Second, the oral bioavailability of Honeysuckle is a crucial issue. As a traditional Chinese medicine, Honeysuckle is mainly administered orally; however, the low oral bioavailability of its flavonoids and organic acids restricts its therapeutic effects. Furthermore, current research into the anti-inflammatory properties of Honeysuckle concerning CVD predominantly emphasizes animal model studies and *in vitro* cellular tests, with a notable deficiency of adequate clinical trials to substantiate its therapeutic efficacy in people through inhibiting the inflammatory response. Therefore, this review mainly provides evidence for the anti-inflammatory treatment of CVD with Honeysuckle through animal studies and cellular tests, lacking clinical research evidence. Moreover, there are many active ingredients in Honeysuckle. This review only summarizes some common active ingredients that exert therapeutic effects on CVD through anti-inflammatory mechanisms, and the mechanism of action of Honeysuckle is not fully revealed.

Comprehensive studies on the active ingredients of Honeysuckle are necessary to clarify its pharmacological effects, evaluate its interactions with microorganisms in clinical trials, and determine its metabolic benefits. Meanwhile, developing innovative dosage forms or delivery mechanisms to improve bioavailability can help establish favorable conditions for employing Honeysuckle as a natural medicinal agent or functional food to prevent CVD. Improving bioavailability is a key link to promoting the trans-

formation of Honeysuckle into modern drugs and realizing its anti-inflammatory therapeutic potential for CVD. The active compound in Honeysuckle has been extensively validated in fundamental research for its anti-inflammatory properties for CVD and has demonstrated considerable therapeutic potential. As a result, additional high-quality clinical trials should be undertaken, and long-term follow-up assessments should be implemented to furnish robust evidence supporting the widespread clinical application of Honeysuckle in the anti-inflammatory treatment of CVD.

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Disclosure of conflict of interest

None.

Abbreviations

ACS, acute coronary syndrome; AMI, acute myocardial infarction; ANP, atrial natriuretic peptide; AP1, nuclear transcription factor activating protein-1; AS, atherosclerosis; ATP, adenosine triphosphate; BNP, brain natriuretic peptide; CA, caffeic acid; CGA, chlorogenic acid; CHD, coronary atherosclerotic heart disease; CK, creatine kinase; COX-2, cyclooxygenase-2; CRP, C-reactive protein; CVD, cardiovascular disease; DEG, differentially expressed genes; EF, ejection fraction; ET, endothelin; Gal-3, galectin-3; GM-CSF, granulocyte-macrophage colony-stimulating factor; hs-CRP, hypersensitive C-reactive protein; HUVECs, human umbilical vein endothelial cells; ICAM-1, intercellular adhesion molecule-1; IFN-γ, interferon-γ; IL-1, interleukin-1; IL-1β, interleukin-1β; IL-4, interleukin-4; IL-6, interleukin-6; IL-8, interleukin-8; IL-10, interleukin-10; IL-18, interleukin-18; iNOS, inducible nitric oxide synthase; JNK, c-Jun N-terminal kinase; KEGG, Kyoto Encyclopedia of Genes and Genomes; LDH, lactate dehydrogenase; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; MCP-1, monocyte chemoattractant protein-1; MDA, malondialdehyde; MI, myocardial infarction; MI/R, myocardial ischemia-reperfusion; MMPs, metalloproteinases; MPO, myeloperoxidase; NF-κB, nuclear factor kappa-B; NLRP3, NOD-like receptor family pyrin domain-containing 3; NO, nitric oxide; PGE2, prostaglandin E2; RAAS, rein-angiotensin-aldosterone-system; ROS, reactive oxygen species; SOD, superoxide dismutase; TLR2, toll-like receptor 2; TLR4, toll-like receptor 4; TLRs, toll-like receptors; TNF-α, tumor necrosis factor-α; VCAM-1, vascular cell adhesion molecule-1; β-MHC, beta-myosin heavy chain.

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