Pharmacological effects of *Ginkgo biloba* and its active ingredients in the treatment of cardiovascular diseases

Mei-Juan Liao1,2,3, Qin Li1,2,3, Q-Yuan Luo4, Xing-Yi Chen1,3, Ji-Yu Chen1,2,*, Yan He1,2,2*

1Clinical Trials Center, The Affiliated Hospital of Guizhou Medical University, Guiyang 550000, China. 2Key Laboratory of Basic Pharmacology of Ministry of Education, Zunyi Medical University, Zunyi, Guizhou province, P.R. China. 3School of Pharmacy, Guizhou Medical University, Guiyang 550000, China. 4Basic Medical College of Guizhou Medical University, Guiyang 550000, China.

*These authors contributed equally to this work and are co-first authors for this paper.

**Correspondence to:** Yan He, Ji-Yu Chen. Clinical Trials Center, The Affiliated Hospital of Guizhou Medical University, No. 28 Guiyi street, Guiyang 550000, China. E-mail: Yanhe_submission@163.com; Jiuyu_Chen@foxmail.com.

**Author contributions**

He Y and Chen JY made the main themes of the study. Liao MJ and Li Q searched databases and selected articles, assessed papers for eligibility, read full texts, assessed their quality and drafted the manuscript. Chen JY and He XY reviewed the draft critically. Luo QY and Chen XY checked the English and produced Figures.

**Competing interests**

The authors declare no conflicts of interest.

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**Abbreviations**

CVDs, cardiovascular diseases; ROS, reactive oxygen species; GA, ginkgolide A; GB, ginkgolide B; GC, ginkgolide C; GLD, ginkgolide; Hcy, homocysteine; GBE, Ginkgo biloba extract; ICAM-1, intercellular cell adhesion molecule-1; GBLCG, Ginkgo biloba leaf constituent group; PAF, platelet aggregating factor; ER, endoplasmic reticulum; TG, triglyceride; TC, total cholesterol; OS, oxidative stress; A3, atherosclerosis; HUVECs, human umbilical vein endothelial cells; AIS, acute ischemic stroke; TGF-β 1, transforming growth factor β 1; GK, ginkgolide K; H/R, hypoxia/reoxygenation; HF, heart failure; DOX, doxorubicin; AIC, adriamycin-induced myocardial MI/R, myocardial ischemia-reperfusion injuries; I/R, ischemia/reperfusion; SNMI, Shuaxueing injection; GFGs, ginkgo flavonol glycosides; GGLs, ginkgolides G; HIF-1, Hypoxia inhibitory factor-1; 5-HT, 5-Hydroxytryptamine.

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**Keywords:** cardiovascular diseases; *Ginkgo biloba*; active ingredients; pharmacological effects

**Abstract**

Cardiovascular diseases (CVDs) are the leading cause of deaths among adult population in China, whose incidence and mortality rates continue rising with a trend towards younger ages. Although numerous drugs are used to prevent and treat CVDs, the long-term prognosis of patients with CVDs is still not very satisfactory. Therefore, there is an urgent need to explore new safe and effective drugs for CVDs in clinical practice. As a traditional medicine in China, *Ginkgo biloba* has a history of more than 2,000 years in clinical practice experience, meanwhile its therapeutic role in CVDs has been revealed in more and more clinical studies. As a living fossil of traditional Chinese medicine, *Ginkgo biloba*, a deciduous tree plant of the Ginkgo family and genus, contains active medicinal ingredients in its leaves, kernels, outer skins and roots. *Ginkgo biloba* leaves are the main medicinal part, which are mild in nature, sweet, bitter and astringent in taste. *Ginkgo biloba* activates the circulation of blood, relieves pains, and lowers lipids, which is mainly used to treat chest obstruction and heartaches, stroke hemiplegia, and asthma, as well as hyperlipidemia, etc. This paper aims to review the medicinal properties of *Ginkgo biloba* and its active ingredients in the treatment of CVDs, with emphasis on the antioxidant, apoptosis-inhibiting, anti-inflammatory mechanism and other mechanisms, so as to provide a scientific basis for their clinical application as well as further development and utilization.
Highlights
In this study, a comprehensive summary was provided on the pharmacological mechanisms of Ginkgo biloba leaves and their active ingredients in the treatment of cardiovascular diseases such as atherosclerosis, hypertension, hyperlipidemia, myocardial ischemia-reperfusion injury, myocardial infarction, arrhythmia, heart failure, and anthraclycine-induced cardiotoxicity. This provides new insights into the treatment of cardiovascular diseases using traditional Chinese medicine.

Medical history of objective
The leaves and fruits of Ginkgo biloba are considered to be of rich medicinal value, and have significant therapeutic effects in the prevention and treatment of cardiovascular diseases. According to Compendium of Materia Medica (Li Shizhen, 1578 C.E.), Ginkgo biloba has the effect of “benefiting the heart and lungs, relieving cough, and lowering phlegm”, and has been used to treat symptoms such as palpitations, chest tightness, and cough. Modern pharmacological studies have shown that ginkgo has a variety of pharmacological effects such as lowering blood pressure, lowering blood lipids, anti-platelet aggregation, antioxidant, anti-inflammatory and so on.

Background
Cardiovascular diseases (CVDs), known as the “first killer” of human health, are also a primary factor threatening people’s lives and health in China, with their incidence and mortality rates having increased recently. According to the China Cardiovascular Health and Disease Report 2020, the number of CVDs in China is estimated to be 330 million, ranking the first cause of death in urban and rural areas [1]. Although a large number of cardiovascular therapeutic drugs have been marketed, the safety and efficacy issues exposed during their long-term use have also received widespread attention [2]. Therefore, it is of great clinical importance to develop new effective drugs for the therapies and preventive treatment of cardiovascular disorders.

The pathogenesis of CVDs has been extensively explored in previous studies based on different molecular mechanisms, among which Oxidative Stress (OS) is closely related to the development of CVDs. The accumulation of reactive oxygen species (ROS) in the body can cause OS and trigger inflammation, both of which will promote the oxidation of oxidation of LDL, injuries of the endothelial function or apoptosis, the formation, and rupture of atherosclerotic plaques, the formation of atherosclerotic thrombosis as well as a series of pathological processes of CVDs.

Over the last few years, with the accumulation of clinical evidence and the continuous exploration of the pharmacological mechanisms of traditional Chinese medicines, research on traditional Chinese medicines for the prevention and treatment of CVDs has received extensive attention. Increasing evidence suggests that herbal medicines have great potential in complementary and alternative therapies for the primary and secondary prevention of CVDs, which also provides new directions for the development of cardiovascular therapeutic drugs [3]. Ginkgo biloba, a traditional Chinese medicine coming from a deciduous tree of the Ginkgo family, is commonly used as a botanical drug worldwide, and it is popular in China and the United States. Ginkgo biloba possesses a broad range of pharmacological effects, which receive considerable clinical usage for the treatment of neuroprotection, cardiovascular protection, and anti-inflammatory as well as anti-oxidant diseases. With the deepening of studies on the therapeutic effects of Ginkgo biloba and its active ingredients in the treatment of CVDs, the mechanism of its therapeutic effects is receiving increasing attention. This article reviews the research on the effects of Ginkgo biloba and its active ingredients on CVDs, elaborates on the specific mechanisms of their therapeutic effects, and discusses the research applications of Ginkgo biloba and its active ingredients to give a theory base for further clinical research and application.

Chemical Composition
The chemical composition of Ginkgo biloba is complex, which mainly includes: starch, protein, amino acids, flavonoids, terpenoids, polyphenols, polysaccharides and trace elements. Among them, flavonoids and terpene lactones are the main active constituents of Ginkgo biloba. At present, more than 110 kinds of flavonoids in Ginkgo biloba have been reported, including monoalkanoflavones, flavonols, dihydroflavonols, diflavones, flavonoid glycosides, and catechins. According to their chemical types, terpene lactones can be divided into diterpene lactones, sesquiterpene lactones, and triterpenes, including ginkgolide A (GA), ginkgolide B (GB), ginkgolide C (GC) and Bilobalid etc. [4] (Figure 1).

Security
Recently, Ginkgo biloba and its active ingredients have been increasingly used worldwide as botanical dietary supplements, whose safety and efficacy are of increasing concern [5]. In order to assess the effectiveness and security of Ginkgo biloba and its active extracts, more and more basic and clinical studies are being conducted in different disease areas. The results of some clinical studies over time suggested that Ginkgo biloba and its active extracts were safe and well-tolerated [6]. However, it has been reported in some studies that the long-term consumption of large amounts of Ginkgo biloba extracts (GBE) by elderly people with diseases such as diabetes, hypertension, and rheumatism might have adverse effects in terms of interactions with drugs used for disease treatment [7]. Of course, more clinical trial data is required to systematically assess the safety risks in the clinical application of Ginkgo biloba and its active extracts.

Effects of Ginkgo biloba and its active ingredients on CVDs
CVDs refer to a group of cardiac and vascular diseases, mainly including angina pectoris, myocardial infarction, hypertensive heart disease, hyperlipidemia, strokes, heart failure, cardiomyopathy, endocarditis, arrhythmias, valvular heart disease, aortic diseases, peripheral arterial disease and other cardiovascular as well as circulatory diseases [8]. By summarizing the results of previous studies, we found that Ginkgo biloba and its active ingredients were significant in treating cardiovascular disorders, including hypertension, atherosclerosis, angina pectoris, and coronary heart disease (Figure 2).

Anti-atherosclerotic Effect
Atherosclerosis (AS) is the leading cause of death worldwide, and today, the high intensity of work often leads to disrupted circadian rhythms and irregular diets, which increase the risk of atherosclerotic CVDs [9]. The natural course of atherosclerosis begins in childhood with a long subclinical phase, and diagnosis usually occurs in advanced stages or after a cardiovascular event [10]. AS is also a prevalent type of cardiovascular disorders and a significant risk factor of a variety of diseases, which is a chronic vascular inflammatory lesion co-caused by a variety of factors such as lipid metabolism disorders, endothelial injuries, inflammatory responses and OS [11]. Ginkgo biloba and its active components can exert good anti-AS effects by modulating the AS pathological process from various key aspects (Figure 3).

Effects of Ginkgo biloba and its active ingredients on vascular endothelial cells. The homocysteine (Hcy) theory of AS was first proposed in 1969, and numerous subsequent clinically-relevant studies have confirmed that high Hcy is one of the most important independent high-risk factors for arteriosclerosis [12, 13]. During the metabolism of vascular endothelial cells, Hcy undergoes auto-oxidation, leading to the generation of strong oxidants that cause

Figure 2 Therapeutic effects of *Ginkgo biloba* and its extracts on cardiovascular diseases. GA, ginkgolide A; GB, ginkgolide B; GC, ginkgolide C; MI/RI, myocardial ischemia-reperfusion injuries.
structural and functional damage to the cells, and then the endothelial cell apoptosis occurs, which is also one of the main mechanisms of high Hcy leading to AS. Previous studies have shown that GA safeguards endothelial cells against Hcy-mediated injuries by restoring eNOS expression and inhibiting super oxide anion production based on a model of Hcy-induced endothelial cell dysfunction in porcine coronary arteries. Furthermore, these findings indicate that GA has almost no effect on healthy endothelial cells, reflecting its good safety profile [14].

At the same time, numerous previous studies have shown that endothelial dysfunction induced by ox-LDL activation of endothelial cells is also an important feature of the pathological changes of atherosclerosis [15]. The protection of GB in endothelial cells could be due to a decrease in the expression of lectin-like oxidized LOX-1 and an increase in that of Sirtuins1 in ox-LDL-stimulated endothelial cells through a pathway related to the inhibition of Akt activation [16]. It was found in an in vitro study that in ox-LDL-treated human umbilical vein endothelial cells (HUVECs) and a RAW246.7 mouse macrophage model, GB could be activated by targeting LOX-1, NOX-4, MCP-1, intercellular cell adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1, which were inflammatory cascade markers improving ox-LDL-induced endothelial dysfunction and thus exerting atheroprotective effects [17]. Li and colleagues discovered that treating HUVECs with ox-LDL led to a marked rise in the expression of ICAM-1, which was linked to the enhancement of iNOS phosphorylation and the relocalization of NF-κB to the nucleus. ICAM-1 is involved in the progression of atherosclerotic lesions, which contributes to inflammatory responses within vascular walls by increasing endothelial cell activation and enhancing atherosclerotic plaque formation directly contributing to the inflammatory responses within vessel walls. The addition of GB attenuates the expression of ox-LDL-induced ICAM-1 and the relocalization of NF-κB [18, 19]. In addition to this, it has also been shown that GB can inhibit the reduction of vascular endothelial cell permeability caused by ox-LDL stimulation, thereby improving vascular permeability and reducing inflammatory cell infiltration [20].

Endothelial cells are very sensitive, which may undergo phenotypic alterations in conditions with varying shear stresses, and these differences are linked to the adhesion of thrombocytes and monocytes to endothelial cells, a phenomenon associated with the development of chronic vascular inflammation and atherosclerosis. GB inhibits the adhesion of platelets and monocytes under conditions of varying shear stresses in laminar flow. In addition, the expression of vascular cell adhesion molecule-1, VE-cadherin, and CX34 in TNFa-treated HUVECs decreases with GB under laminar flow shear stresses, suggesting that GB may contribute to the treatment of atherosclerotic inflammation [21]. It has been indicated that the GB-induced inhibition of connexin expression is linked with the blockade of the PI3K/Akt signaling pathway [22]. CX43 is a connexin protein that has a direct association with the formation of atherosclerosis. The overall effect of CX43 on the involvement of lymphocytes in the development of atherosclerosis is complex; in general, it is involved in the activation and functions of numerous lymphocyte subtypes. Thus, depending on the activation degree of each type of cell, it may have both pro-atherosclerotic and anti-atherosclerotic functions [23]. EGb761 is often used for CVD prevention [24]. CX43-mediated gap junction communication plays a key role in atherosclerotic plaque formation. Meanwhile GBE may prevent the atherosclerosis progression by decreasing the expression of CX43 protein and exert anti-atherosclerotic effects by activating the NF-κB pathway, so as to induce the expression of endothelial HO-1, which plays a key role in preventing vascular inflammation [25–27]. GBE can not only induce the expression of HO-1 in endothelial cells but also clear ROS, thus exerting anti-atherosclerosis and anti-inflammatory effects [28].

Implications of Ginkgo biloba and its active ingredients on foam cells and adipocytes. In addition, ox-LDL damage to vascular endothelial cells will lead to the adhesion of monocytes in peripheral blood in terms of endothelial injuries, in which foam cells are formed through the phagocytosis of ox-LDL in plasma and progressively develop into atherosclerotic plaques, with intra-plaque haemorrhage as a driver of atherosclerotic progression [29]. It is known that macrophage foaminess is another important risk factor in the development of atherosclerosis. It has been reported that EgB761 can inhibit monocyte/macrophage-derived foam cell formation by
downregulating the production of ox-LDL-induced vascular endothelial growth factor in THP1 monocytes, and in vitro cellular models can be exerted to inhibit pharmacological effects during AS development based on an in vitro model [30]. In addition, EGb761 can increase the protein stability of ATP-binding cassette transporter A1 by downregulating the expression of class A scavenger receptor, thereby reducing cholesterol uptake and increasing cholesterol efflux meanwhile ultimately reducing macrophage cholesterol accumulation caused by ox-LDL induction, thus inhibiting foam cell formation and exerting anti-AS effects [31]. In addition, GBE has been shown to have anti-atherosclerosis properties by inhibiting the production of pro-inflammatory factors IL-1β and TNF-α through ox-LDL-stimulated U937 foam cells while upregulating the expression of anti-inflammatory factors interleukin-10 and interleukin-10 receptor [32].

Obesity is related to an increased prevalence of chronic diseases including CVDs, meanwhile adipocyte proliferation and lipid accumulation are major contributors to overweight. Ginkgolide G increases the decomposition of fat and inhibits its formation in adipocytes through the activation of the AMPK pathway [33]. Gautam, J et al. isolated bone marrow cells for a study on the effect of Egb 761 on adipocytes, who found that through a treatment of high-cholesterol-diet-fed animals with EGB 761, the total cholesterol (TC) level significantly decreased compared to the high-cholesterol-diet high-cholesterol-diet-fed group (control group). Bone marrow cells induced to become lipid differentiated in the presence of EGB 761 showed a reduction in adipogenesis [34].

Implications of Ginkgo biloba and its active ingredients on platelets. GB is known to be a platelet-activating factor inhibitor (PAF), and PAF plays an important role in the development of atherosclerosis [35, 36]. GB makes atherosclerosis attenuate in ApoE-/- mice while inhibiting platelet release by inhibiting the PI3K/Akt pathway of thrombin- and collagen-activated platelets [37]. In addition, GB ameliorates atherosclerosis in ApoE-/- mice induced by high-fat diets by modulating the intestinal flora, which significantly reduces high-fat-diet-induced AS by increasing the relative abundance of lactobacillus and decreasing the relative abundance of helicobacter, but the exact mechanism still needs further investigation [38]. In fresh human platelets, GB is found to effectively inhibit the expression of FF4 and CD40L in thrombin-activated platelets, which is able to partially reduce the level of ATP release and Ca2+ outflow through a mechanism that may be related to the phosphorylation inhibition of Syk- and p38 MAPK [39]. With the inhibition of p38 MAPK in vivo, the number and functional activity of angiogenic cells increases while reducing the progression of atherosclerotic disease [40].

Implications of Ginkgo biloba and its active ingredients on smooth muscle cells. Smooth muscle cells, as multipotent cells, are the most important components of atherosclerotic lesions, whose migration and proliferation are among the causes of atherosclerosis. In a study conducted based on an in vitro model and a type 2 diabetic rat model, EGB761 was shown to reduce the proliferation and migration of vascular smooth muscle cells and exert anti-AS effects. In addition, it was also found in this study that kaempferol and quercetin, the major subcomponents of EGB761, could also exert anti-AS effects by reducing the migration of vascular smooth muscle cells and increasing the cytokine activity [41]. MMPs are known to cause unstable and ruptured atherosclerotic plaques [42]. GBE inhibits the production of ox-LDL-induced MMP-1, which may be achieved by inhibiting PDGFR-β activation in human coronary smooth muscle cells [43].

Therapeutic effect on hyperlipidemia

Hyperlipidemia is known as a major risk factor in the development of CVDs as well as an independent and important risk factor of AS, whose main disease feature is abnormal lipid metabolism, and the TC level is one of the most frequently requested laboratory tests on primary care as part of lipid profile screening, which is designed to identify people at increased cardiovascular risks [44, 45]. In recent years, with the improvement of life quality and changes in lifestyle habits, the number of people suffering hyperlipidemia and the resulting deaths have been increasing worldwide, causing a great burden of diseases [46]. Currently, the main therapeutic measures for hyperlipidemia include dietary control, the maintenance of exercise, and pharmacological treatment. Clinically, synthetic lipid-lowering drugs, represented by atorvastatin, niacin, and ezetimibe, are the first-line treatment for hyperlipidemia. However, the application of natural lipid-lowering drugs for the prevention and treatment of hyperlipidemia as well as its complications seems to be an urgent clinical problem due to the limitations caused by side effects and contraindications associated with the long-term use of synthetic lipid-lowering drugs [47]. A number of studies have confirmed the therapeutic effect of ginkgo and its active extracts on hyperlipidaemia (Table 1).

Table 1 Summary of effects of Ginkgo biloba and its active ingredients on hyperlipidemia

<table>
<thead>
<tr>
<th>References</th>
<th>Type</th>
<th>Subjects</th>
<th>Active ingredient</th>
<th>Target or Pathways</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>[49]</td>
<td>In vivo</td>
<td>Sprague-Dawley rats</td>
<td>GBE</td>
<td>/</td>
<td>TG↓ TC↓ LDL-C↓ MDA↓ HDL-C↑</td>
</tr>
<tr>
<td>[50]</td>
<td>In vivo</td>
<td>Male Spague-Dawley rats</td>
<td>GBE</td>
<td>/</td>
<td>TG↓ TC↓ LDL-C↓ HDL-C↑</td>
</tr>
<tr>
<td>[51]</td>
<td>In vivo</td>
<td>Sprague-Dawley rats</td>
<td>GBE</td>
<td>HL LPL</td>
<td>FBA excretion↑ Blood lipid level↓ Liver lipid content↓ Adipocyte volume↓ Plasma statin exposure↑</td>
</tr>
<tr>
<td>[52]</td>
<td>In vivo</td>
<td>Male Spague-Dawley rats</td>
<td>GBE</td>
<td>/</td>
<td>TC↓ TG↓</td>
</tr>
<tr>
<td>[53]</td>
<td>In vivo</td>
<td>Patients</td>
<td>Ginkgo biloba</td>
<td>/</td>
<td></td>
</tr>
<tr>
<td>[55]</td>
<td>In vitro</td>
<td>PL solution</td>
<td>Iotinkgetin</td>
<td>Lipid absorption↓ Ginkgetin</td>
<td></td>
</tr>
</tbody>
</table>

GBE, Ginkgo biloba extract; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; MDA, malondialdehyde; FBA, fecal bile acid; HDL-C, high density lipoprotein cholesterol.

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As a common dietary supplement, GBE has been reported to have good lipid-regulating effects. In a rat model of ethanol-induced hyperlipidemia, the level of alcoholic lipid peroxidation and restored triglyceride (TG), total cholesterol, low-density lipoprotein cholesterol, malondialdehyde and high density liprotein cholesterol was significantly improved with GBE, resulting in beneficial effects on the lipid profile of the rats [48]. In addition, through GBE interventions of different densities, TG, TC and low-density lipoprotein cholesterol were also significantly reduced while significantly elevating the level of high density lipoprotein cholesterol, thus exerting hypolipidemic effects [49]. In addition, using metabolomics-related research techniques, GBE has been found to have several hypolipidemic effects on dietary hyperlipidemia, including limiting cholesterol absorption, inhibiting the inactivation of HMG-CoA and favouring the regulation of essential fatty acids, among others [50]. Recently, it has also been shown that, in addition to demonstrating good hypolipidemic effects on a rat model of hyperlipidemia, GBE also improved the pharmacokinetics of atorvastatin when combined with atorvastatin while showing a potential protective effect on atorvastatin-induced hepatic injuries [51]. This suggests that GBE has a positive synergistic effect as a dietary supplement to statins on the treatment of dyslipidemia, which is beneficial for its clinical application and also provides new ideas for the selection of therapeutic agents for hyperlipidemia treatment. Similarly, Al-Zakaria, S. A. et al. monitored the lipid profile of hypertensive patients with Ginkgo biloba as an add-on therapy of valsartan monotherapy and found that after the Ginkgo biloba treatment, a significant reduction was shown in serum TC and TGs, whereas there were no significant changes in LDL, VLDL, HDL or the atherogenic index [52]. Therefore, Ginkgo biloba and its extracts can be considered as natural, effective and relatively-safe lipid-lowering drugs.

GBE is frequently used to treat hyperlipidemia. However, the bioactive ingredients in Ginkgo biloba leaves, or their potential mechanisms are not completely elucidated [53]. The inhibitory potential of major biflavonoids in Ginkgo biloba on PL was investigated in a study, which was a critical target in the regulation of lipid metabolism. The findings definitively proved that all tested biflavonoids in Ginkgo biloba, specifically isoginkgetin, leucovorin and ginkgetin, showed a high to intermediate inhibition of PL. Further studies on inhibition kinetic analyses and docking simulations show that isoginkgetin, bilobalamin, and ginkgetin are effective PL inhibitors that can strongly interact with the catalytic triad of PL through hydrogen bonding [54]. The hypolipidemic effects of Ginkgo biloba are further supported by these findings.

Therapeutic effects on hypertension
Hypertension is one of the risk factors of CVs globally, and arterial hypertension is a major risk factor of CVDs, with poorly-controlled hypertension further contributing to strokes, ischemic heart disease, as well as other vascular and kidney diseases [55–57]. The prevention and treatment of hypertension have become a major concern in public health which has received increasing attention.

Effects of Ginkgo biloba and its active ingredients on endothelial dysfunction.
Blood pressure is a complex polygenic multifactorial trait determined by the interaction of multiple genetic, molecular, and physiological pathways [58]. It is well known that endothelial dysfunction is also closely related to the pathogenesis of hypertension, targeting which has become disease preventive intervention is an effective intervention. At the same time, endothelial dysfunction is closely related to the progression of atherosclerosis, and through the treatment of carotid atherosclerotic plaques with ginkgolide drops combined with hypertension drugs, blood pressure, blood lipids, and vascular endothelial function of patients can be improved [59, 60].

According to previous studies, GBE significantly reduces systolic blood pressure, improves endothelial NO pathway dysfunction, and enhances the diastolic responses of acetylcholine to aortic vascularity in a high-salt-induced Dahl salt-sensitive rat hypertension model, thus exerting a protective effect on blood pressure in high-salt-induced Dahl hypertensive rats [61]. In addition, it has also been shown that GBE may exert a protective effect on spontaneously-hypertensive rat models by increasing the intracellular calcium level in endothelial cells and improving acetylcholine-induced diastolic effects on vascular endothelial cells, thereby reducing the systolic blood pressure of spontaneously hypertensive rats [62]. Blood pressure exhibits a distinct circadian rhythm, and GBE has a significant antihypertensive impact throughout the daytime period in rats; nevertheless, this impact is not found in rats with normal blood pressure. These results suggest that GBE has an antihypertensive effect that is time-dependent [63].

The Role of Ginkgo biloba and its active ingredients in OS. OS and related oxidative damage resulting in vascular endothelial injuries are also key aspects in the pathogenesis of hypertension, and Ginkgo biloba as well as its extracts can reduce blood pressure by inhibiting the occurrence of OS (Figure 4).

In L-nitro arginine methyl ester-induced hypertension rat models, with a daily oral administration of 100 mg/Kg EGB761 for 4 weeks, the systolic, diastolic and mean arterial blood pressure of L-nitro arginine methyl ester-induced hypertensive rats was significantly reduced, together with a reduced level of OS, nitrite and inflammatory markers in renal tissues, suggesting that EGB761 had good antihypertensive effects and protection against hypertension-induced renal injuries [64]. Similarly, in a rat model of hypertension with hypercholesterolemia, blood pressure in the model group was significantly reduced with 100 mg/kg EGB761 administered daily for 5 weeks while exerting an antihypertensive effect [65]. In addition, in a “two kidneys, one clip” renal hypertension rat model, a dose-dependent decrease in systolic blood pressure was found after a continuous oral administration with EGB761 of different doses for four weeks, whose hypotensive effect might be related to the inhibition of angiotensin-converting enzyme activity, the maintenance of cellular antioxidant capacity and the inhibition of vascular effects on vasoconstrictors while maintaining vascular activity on endothelium-dependent as well as non-dependent vasodilators [66]. A study was conducted to prepare a Ginkgo biloba leaf constituent group (GBLCG) consisting of high-purity flavonoid glycosides and terpene lactones in Ginkgo biloba to investigate its therapeutic effects on hypertension. The results showed that the GBLCG had better antihypertensive activity than the GBE group, where cardiac hypertrophy was improved better than the amloidpine benzene sulfonate group in a rat model of spontaneous hypertension. Therefore, GBLCG has the potential to reduce blood pressure and improve cardiac hypertrophy. This may occur through the promotion of NO synthesis and release from endothelial cells, the reduction of OS, the inhibition of platelet aggregation, and the promotion of lesions [67]. The vasorelaxation of cerebral microvessels was severely inhibited in hypertensive rats, and through treatment with EGb761, vasorelaxation was stimulated, which might increase cerebral blood perfusion by driving blood flow in a wave-like fashion [68].

Effect of Ginkgo biloba and its active extracts on strokes. A “stroke” is also known as a “cerebrovascular accident”, which is an acute CVD, including ischemic and hemorrhagic strokes. Strokes are the second leading cause of death and the third leading cause of disabilities globally [69]. The 2023 update of stroke statistics of the American Heart Association shows that ischemic strokes account for the highest proportion of all strokes, accounting for 87%; the second is cerebral hemorrhage, which accounts for 10% [70]. High blood pressure is closely related to the occurrence of strokes, and a survey indicates that more than 50% of ischemic strokes and 70% of hemorrhagic strokes are associated with high blood pressure as well as its consequences [71].

Studies have shown that with the use of EGB 761, blood pressure can be lowered, and the systolic blood pressure of untreated stroke-prone spontaneously hypertensive rats increases with age, with the use of EGB 761 in which can blood pressure be lowered with strong antihypertensive and antioxidant effects [72]. The most appropriate treatment for acute strokes is to dredge the blocked arteries immediately, and reperfusion therapy (thrombolysis) is crucial for the recovery after ischemic strokes. Although the problem
of ischemia can be solved through reperfusion, it may aggravate the injuries caused by ischemia, which may lead to the progression of infarction, intracranial hemorrhage, and poor prognosis [73, 74]. Gb761 can be used to significantly improve the neurobehavioral function and infarct size of rats after cerebral ischemia reperfusion. Without affecting physiological parameters, Gb761 can play a protective role in cerebral ischemia reperfusion injuries through the stimulation of Nrf2-antioxidant/ electrophilic response elements and the increase of the HO-1 level [75]. Similarly, pretreatment of a focal central nervous system reperfusion model with GBE and another antioxidant resulted in a relative reduction of 35% to 40% in lesion size within 24h [76]. However, GBE of higher doses may increase the risk of haemorrhagic transformation after strokes, so considerations on the dose should be taken into account when using GBE. As a PAF antagonist, ginkgolide (GLD) can be used to slightly reduce the accumulation of PAF after ischemic strokes, which can reduce their recurrence within 72h after the onset of an acute ischemic stroke (AIS) in patients with intracranial artery stenosis, and GLD may be an alternative treatment for patients with AISs and intracranial artery stenosis [77]. To sum up, high blood pressure is an important cause of strokes, and *Ginkgo biloba* extracts can not only reduce blood pressure but also serve as drugs for preventive treatment to reduce the damaging effects of strokes.

The above studies have fully proved that *Ginkgo biloba* and its extracts have a comprehensive and multi-pathway protective effect on various types of hypertension and hypertension-induced strokes suffered by animals, but its application in the actual clinical prevention and treatment of hypertension needs to be evaluated through more clinical studies with sufficient sample size.

**Protective effect on myocardial infarction**

To date, knowledge of the risks caused by diseases following MI has been limited, while the number of MI survivors has increased dramatically in recent decades [78]. MI is a CVD mainly caused by the interruption of blood supply due to lesions in coronary arteries, resulting in ischemia and hypoxia of some cardiomyocytes, which in turn leads to their necrosis. MI will lead to insufficient perfusion of blood to vital organs, which can cause fatal injuries to patients [79]. Increasing age, hypertension, increased LDL, high cholesterol and fat, obesity, hyperglycemia as well as chronic kidney diseases are all risk factors for MI [80]. The signaling pathways involved in the pathology of MI that have been reported are key pathways involved in inflammatory responses (e.g., the NLRP3/caspase-1 and TLR4/MyD88/NF-κB signaling pathway), oxidative-stress- and apoptosis-related pathways (e.g., the Notch and Nrf2/HO-1 signaling pathway) and myocardial-fibrosis-related pathways (TGF-β/SMADs and the Wnt/β-catenin signaling pathway), among others [81]. These signaling pathways are key to the development of MI, and it is currently a relatively popular research direction to find new therapeutic strategies for MI by targeting them. *Ginkgo biloba* and its active extracts can act on multiple pathways to exert therapeutic effects on MI (Figure 5). Focusing on the above key signaling pathways, we found that previous studies showed that in rat models of MI, with the increase of intervention time of Gb761, its ability to reduce malondialdehyde content and increase the activity of antioxidant enzymes SOD, CAT and GSH PX gradually increased, it could also improve the survival and differentiation of transplanted mesenchymal stem cells, reduce the inflammation and OS in the microenvironment of infarcted myocardium, and then exert protective effect on rats with MI [82].

*Ginkgo* has also been shown to protect against MI in previous studies. Li, Y et al. showed that GBE inhibited the p38 MAPK, NF-κB and...
Bel-2 pathway, thereby suppressing the inflammation and apoptosis of cardiomyocytes after MI exerted a protective effect in mice with acute MI [83]. In addition to anti-inflammatory and anti-apoptotic effects, GBE also prevents myocardial ischemic injuries by inhibiting the abnormal expression of the Na⁺/Ca²⁺ exchanger, restoring the myocardial myofiber deformation in MI regions and promoting the recovery of myocardial contractile function [84]. Furthermore, GBE may also play a corresponding protective role by inhibiting the expression of transforming growth factor β1 (TGF-β1), an important signaling pathway activator of myocardial fibrosis that inhibits the expression of type I collagen and improves MI-induced ventricular remodeling [85].

In addition, ginkgolides showed their therapeutic potential in MI. GB has been reported to significantly increase the Na⁺/K⁺-ATPase and Ca²⁺/Mg²⁺-ATPase activity of myocardial tissues, thus regulating intra- and extracellular ion homeostasis, especially Ca²⁺ homeostasis, to improve energy metabolism disorders of myocardial tissues, thus exerting a protective effect on rats with MI [86]. It has also been concluded that GA treatment alleviates cardiac insufficiencies and fibrosis in mice with MI and also reduces inflammation, together with cardiac dysfunction and remodeling, by binding to MMP-9. Thus, GA is a potential drug for cardiac remodeling therapy [87]. Endoplasmic reticulum (ER) stress is related to the progression of a multitude of illnesses, and the goal of targeting ER stress has become a novel treatment method for CVDs [88]. ginkgolide K (GK) markedly reduces ER stress-induced cell deaths, and in mice with ischemic injuries, GK reduces the size of infarcts, relieves the heart function impairments and improves ER dilation. GK is able to limit ER stress injuries and ameliorate ER stress for the treatment of CVDs through the selective activation of the IRE1α/XBP1 pathway [89].

Although an adult mammalian heart can only be moderately renewed through cardiomyocyte proliferation, facilitating this process is considered a promising therapeutic strategy for repairing cardiac damage, but little has been written about the ability of Ginkgo biloba or its active extracts to promote cardiomyocyte proliferation, which may be a new direction of research [90]. Clonal hematopoiesis driven by mutations of DNMT3A or TET2 has recently been identified as a new risk factor of CVDs, which may enhance inflammatory responses and thus accelerate the progression of the diseases. The full pharmacological effects of Ginkgo biloba or its active extracts are not yet known, which, could possibly be used to treat MI caused by these mutations, need to be experimentally explored [91].

**Protective effect on myocardial ischemia-reperfusion injuries**

Acute myocardial infarction is a type of CVD that threatens human life, and by timely restoring blood flow myocardial cell injuries and necrosis caused by myocardial ischemia be alleviated, but the recovery process of blood flow after myocardial ischemia can further cause myocardial cell damage [92]. Various clinical features of such injuries include myocardial necrosis, arrhythmias, myocardial stunning and endothelial as well as microvascular dysfunction, which include no reflow phenomenon [93]. Therefore, it is essential to actively explore effective interventions for myocardial ischemia-reperfusion injuries (MI/RI) or develop drugs with potential therapeutic effects.

The potential therapeutic effects of natural plants, drugs, and compounds on MI/RI have received much attention in the past few years. In as early as 1986, the protective effect of GBE on MI/RI was found by J M Guillon using two different in vitro ischemia-reperfusion models (rat and guinea pig heart) [94]. Subsequently, numerous ex vivo and in vivo studies have also shown that GBE can exert some protective effects against MI/RI through various action mechanisms. Zeng Yong Qiao et al. found that in a rat ischemia/reperfusion (I/R) model, GBE inhibited IR-induced apoptosis by inhibiting the release of cytochrome C and blocking the activation of caspase 3, through which myocardial infarct size was also significantly reduced, thus exerting a
The protective effect on myocardial I/R injuries in rats [95]. In addition, GBE ameliorates myocardial inflammatory responses caused by I/R. It is shown that GBE modulates inflammatory responses after I/R injuries by decreasing the expression of the pro-inflammatory factors TNF-α and interleukin 6 while increasing the expression of the anti-inflammatory factors interleukin 4 and interleukin 10 for regulation [96]. Similar to GBE, another active ingredient in Ginkgo biloba, Bilenol, also attenuates inflammatory responses in the myocardial tissues of I/R model rats through a similar anti-inflammatory response [97].

In addition to this, the currently widely-used GBE preparation, Shuxuening injection (SXNI), was reported to greatly enhance heart functionality after I/R injuries in mice, increase coronary blood flow, and reduce myocardial infarct size; meanwhile, the heart effectively protected through Shuxuening injection was further revealed in this study based on a transcriptome sequencing analysis. It was further revealed in the study through a transcriptome sequencing analysis of the heart that an important target for the effective protection of cardiac I/R injuries using Shuxuening injection might be the tumor necrosis factor receptor superfamily member 12A, which also provided new insights into the clinical application of active ingredients in Ginkgo biloba to MI/R [98]. SXNI can reduce the area of myocardial infarction caused by the ligation of the left anterior descending coronary artery, lowering the myocardial enzyme level and improving myocardial pathological injuries; the myocardial protective mechanism of SXNI is closely related to maintaining the balance of oxidative and antioxidant systems, reducing OS and ER stress injuries, inhibiting excessive inflammatory factor responses, improving platelet functions as well as inhibiting thrombosis [99]. Xiao et al. reported that ginkgo flavonol glycosides (GFGs) and ginkgolides G (GGs) derived from SXNI could offer varied benefits in protecting against MI/R and cerebral/reperfusion injuries. Specifically, GFGs tend to be protective against myocardial injuries, and GGs tend to ameliorate cerebral injuries; moreover, GFGs could attenuate I/R injuries in mice with MI/R by down-regulating the TWEAK-Fn14 axis, while GGs could up-regulate the signaling pathway to protect the brain of mice with cerebral/reperfusion injuries from I/R injuries [100].

It has been found in previous studies that the possible mechanisms of cardioprotective effects of GBE are mainly related to anti-inflammatory, antioxidant, anti-apoptotic and improved energy metabolism, and that through GB interventions, myocardial infarct size and the expression of infarct-related markers after I/R could be significantly reduced [101]. In an isolated I/R model of male SD rats, GB was reported to improve the cardiac left ventricular function and reduce infarct size after I/R, together with a reduction in the release of lactate dehydrogenase and an improvement of the cardiomyocyte contractile function in rats by increasing the expression of B-cell lymphoma 2 (Bcl-2) protein, decreasing the expression of Bax protein as well as regulating cardiomyocyte apoptosis, thus exerting a corresponding protective effect [102]. In another study, it was found that GB could be treated to enhance the contraction amplitude of I/R-damaged cardiomyocytes in elderly SD rats and induce the PI3K/Akt signaling pathway to improve the cardiac function of elderly rats with I/R impairments [103]. GB also protects cardiac cells from peroxide-induced cytotoxicity and apoptosis, and in hydrogen-peroxide-treated H9c2 cells, GB up-regulates the expression level of the anti-apoptotic protein Bcl-2 and down-regulates that of the pro-apoptotic proteins cleaved caspase-3 and Bax; furthermore, GB inhibits hydrogen peroxide induced by activating the PI3K/Akt/mTOR pathway in the apoptosis in H9c2 cells [104]. PAF is crucial to maintaining the structural integrity of cell membranes and contributes to the development of MI/R injuries, and it has been demonstrated that PAF production is increased in cultured hypoxic cardiomyocytes, whereas GB reduces PAF-induced cellular injuries. Meanwhile, GB, a PAF antagonist, has a protective effect against myocardial dysfunction and membrane phospholipid degradation [105]. Zinc finger protein A20 plays a crucial role in various inflammatory diseases, and GB can provide protection against MI/R by enhancing the A20-dependent NF-κB signalling pathway, thus ameliorating inflammatory injuries caused by MI/R both in vivo and in vitro [106].

In addition to the active components in Ginkgo biloba mentioned above, EGb761, which contains terpenoid and flavonoid compounds, has also been reported to have significant cardioprotective effects against myocardial I/R injuries [107]. It was found in a study that the cardioprotective effects of flavonoid glycosides and terpenoids might contribute to the cardioprotective effects of GBS/761 by inhibiting cytochrome c release and caspase activation during MI/R injuries while preventing cell deaths [108]. In addition, through EGb 761 pretreatment, the myocardium may be protected from I/R injuries through the reduction of OS, the inhibition of the in vivo inflammatory cascade, and the inhibition of the TLR4/NF-κB pathway [109]. EGb 761 may also protect the myocardium by inhibiting cardiomyocyte apoptosis through the activation of the Akt/Nrf2 pathway, meanwhile increasing HO-1 expression [110]. A study based on an in vitro hypoxia/ reoxygenation (H/R) model of microvascular endothelial cells showed that EGb761 inhibited ROS production while increasing SOD activity, which was able to dose-dependently inhibit p53 and Bax expression, thereby reducing cell deaths and apoptosis and thus protecting myocardial endothelial cells from H/R injuries [111]. Ran, K. et al. also found that post-treatment with GBE could exert cardioprotective effects by decreasing the generation of oxygen free radicals and increasing the antioxidant capacity of cardiomyocytes; GBE761 was able to significantly reduce serum cTnI concentration during reperfusion while significantly reducing infarct sizes; GBE761 could make SOD activity increase with a significantly reduced malondialdehyde content [112]. EGb761 can also inhibit oxygen free radicals induced by lipid peroxidation in rat I/R injuries by regulating the level of nitric oxide, which plays a cardiovascular protective role [113]. In addition, EGb761 can also exert cardioprotective effects on I/R rats by regulating the I/R-induced nuclear translocation of NF-κB, scavenging free radicals and reducing ROS production [114]. A significant anti-ischemic effect can be observed after the administration of EGb 761 and GA, suggesting an improved recovery of the myocardial function. The perfusion of pre- and post-ischemic hearts with GA and GB results in a significant improvement of all hemodynamic parameters. Interestingly, their cardioprotective effect appears to inhibit the formation of free radicals rather than directly scavenging them [115]. In addition, EGb761 can also activate mitochondrial large conductance Ca2+-activated K+ channels, inhibit mitochondrial breakage, restore mitochondrial membrane potential, reduce the production of superoxide, and inhibit the occurrence of cell apoptosis from reducing H/R-induced myocardial mitochondrial Ca2+ overload, thus playing a protective role in MI/R [116].

GB also ameliorates the symptoms of I/R injuries, which is demonstrated by the decrease in infarct area, the prevention of myofibrillar degeneration, and the reversal of mitochondrial dysfunction; GC benefits MI/R injuries by inhibiting inflammation, which may involve the suppression of the CD40-NF-κB pathway and the expression of downstream inflammatory cytokines [117]. GK has a dual function after I/R injuries in that it inhibits mitochondrial fission through the phosphorylation of Drp1 phosphorylation and attenuates the mPTP opening of neurons in a GSK-3β-dependent manner, whereas Drp1 and GSK-3β appear to be crucial elements in mPTP opening following brain I/R injuries, so that with the use of GK, the sequence of AIS may be significantly attenuated [118].

In conclusion, Ginkgo biloba and its extracts can inhibit the cellular damage induced by OS, calcium overload and the over-activation of inflammatory responses during myocardial ischemia reperfusion, thus exerting a protective effect on cardiomyocytes (Figure 6).

Therapeutic effect on cardiac arrhythmias

Arrhythmias are a very important group of CVDs, often accompanied by high morbidity and mortality [119]. Current research suggests that inflammation, fibrosis, and autoimmunity are involved in the main pathophysiological processes of arrhythmias. For the treatment of the
arrhythmias, pharmacological therapies remain the main clinical treatment strategies at present [120]. Reviewing previous studies, we found that the effects of *Ginkgo biloba* and its active extracts on arrhythmias were somewhat controversial. It has been found that in rat models of arrhythmias caused by aconitine and ouabain, GB50 can play an antiarrhythmic role by inhibiting delay after depolarization and triggering activities induced by ouabain and high calcium [121]. The present study substantiates that both GBE and GLD shorten the action potential duration and that GLD is more potent; they also both block ICa-L and IK currents, but GLD has a stronger inhibition effect on ICa-L than GBE. [122]. GBE and GLD may be used to treat and prevent ischemic arrhythmias. Combination therapies with the calcineurin inhibitor FK506 and EGB761 have been shown to synergistically improve the cardiac function after ischemia while decreasing the incidence of reperfusion-induced ventricular fibrillation and ventricular tachycardia, which can be achieved through the co-administration of GLD to achieve a sub-toxic dose of FK506, thereby preventing the development of cardiac hypertrophy [123]. Using the African clawed toad oocyte voltage-clamp technique, Hui Chen et al. found that GBE was able to inhibit HCN2 and HCN4 in a concentration-dependent manner in vitro, with a particularly-pronounced inhibitory effect on HCN4. This might also be the main action mechanism of GBE to exert antiarrhythmic effects in vitro [124].

In addition, through a rat I/R arrhythmia model, researchers found that GB could protect against arrhythmias in rats by ameliorating OS injuries, decreasing the concentration of myocardial tissue Ca2+, and increasing ATPase activity [125]. The antiarrhythmic effects of GB may be linked to inhibiting the rise of slow calcium influx caused by PAF in cardiomyocytes and, similar to the mechanism of the effect of existing antiarrhythmic drugs, GB may be able to prevent reentry mechanisms involved in the development of arrhythmias caused by cardiac ischemia [126].

However, there is also a case report on a patient who experienced frequent arrhythmic symptoms for a short period of time after taking *Ginkgo biloba*, which were relieved after he stopped taking it [127]. Therefore, more in-depth studies on the effects of *Ginkgo biloba* and its active ingredients on arrhythmias are needed to elucidate their pharmacological effects on arrhythmias.

**Therapeutic effects on heart failure**

Heart failure (HF) is a disease with impaired cardiac function, which is the end result of several cardiac diseases with high morbidity and mortality, and its path mechanisms are multifaceted [128]. Hypertension and coronary artery disease are the causes of HF, the damage to the myocardium caused by which can lead to the development of HF; coronary artery disease is considered to be a major risk factor in the development of HF, and prolonged hypertension leads to cardiac remodeling of the left ventricle, resulting in hypertensive heart disease, which ultimately manifests as HF [129, 130]. Inflammation may cause direct damage to cardiomyocytes, which has a significant impact on the onset, development, and prognosis of HF [131]. OS plays an important role in the development of HF, whose main cause is cardiac mitochondrial dysfunction, which in turn can have deleterious effects on cellular components, including the mitochondria themselves, thus creating a vicious cycle. OS can also contribute to myocardial tissue damage and inflammation, which can lead to the worsening of HF [132, 133].

Inflammation is known to be a cause of HF, and although some inflammation is necessary for injury repair, prolonged inflammation leads to myocardial remodeling and cardiomyocyte apoptosis while inducing inflammatory cell infiltration and fibrosis, which further damage the myocardium, thus leading to the development of HF [134–136]. Doxorubicin (DOX), a typical anticancer drug, can lead to cardiomyopathy and HF, and using a *Ginkgo biloba* treatment, DOX-induced inflammatory cell infiltration and cardiac injuries can be significantly reduced, with active compounds of *Ginkgo biloba* showing synergistic therapeutic effects by acting on multiple targets, thus modulating multiple pathways mainly involved in the pro-survival, anti-apoptotic and anti-inflammatory processes [137, 138].

Myocardial energy dysfunction is an important cause of DOX-induced HF, whereas gastric promotes positive energy metabolism, and GBE improves cardiac function and energy metabolism in rats with HF by increasing gastric expression and production [139]. Myocardial fibrosis is an important structural abnormality before the appearance of HF symptoms, and the MAPK signaling pathway is a key driver of myocardial fibrosis in patients with HF. Isorhamnetin, kaempferol, and quercetin inhibit myocardial fibrosis through the MAPK signaling pathway, thereby delaying HF [140, 141]. Quercetin may also inhibit apoptosis by modulating the AKT1-eNOS-MMP9 pathway, thereby ameliorating the pathophysiological changes of HF [142]. Hypoxia inhibitory factor-1 (HIF-1) is a heterodimer mainly composed of two

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**Figure 6 Mechanisms of *Ginkgo biloba* and its extracts in the treatment of myocardial ischemia-reperfusion injury.** *Ginkgo* and its extracts inhibit multiple aspects of myocardial ischaemia-reperfusion injury process. (A) GB, GBE and EGB761 can reduce the production of oxygen free radicals. (B) EGB761 attenuates mitochondrial Ca2+ overload in cardiomyocytes. (C) GBE, BB, GC, GB and EGB761 inhibit hyperactivation of inflammatory responses. GB, ginkgolide B; GC, ginkgolide C; BB, Bilobalide; GBE, *Ginkgo biloba* extract.

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subunits, HIF-1α and HIF-1β. An increased expression of HIF-1α promotes the formation of collagen fibers, which leads to fibrosis, and HIF-1α may be a key factor contributing to ejection-fraction-preserved HF [143]. It has been found that GBE can down-regulate the p38MAPK/HIF-1α signaling pathway to inhibit apoptosis, which may have a protective effect on HF [144]. In addition, GBE can ameliorate myocardial injuries by inhibiting MMP-3, thereby reducing myocardial fibrosis [145]. 5-Hydroxytryptamine (5-HT) is a marker of decompensation in patients with chronic heart failure, and the higher the level of 5-HT is, the more severe the symptoms of HF and systolic dysfunction will be [146]. Mice with HF showed significant changes in receptors 5-HT and 5-HT(2A) after treatment with GBE, suggesting that GBE might have a mitigating effect on HF symptoms [147]. Zhang, L. et al. found that GBE reduced the level of TNF-α, IL-1β and 5-HT, which also blocked the release of 5-HT in the peripheral blood [148].

OS is an important pathophysiological pathway in the development and progression of HF [149]. Excessive OS refers to a feature of obesity-induced metabolic cardiomyopathy, which is a major cause of HF among obese patients. Isoflavonoids in Ginkgo flavonoids are bioactive biflavonoids isolated from the medicinal plant Ginkgo biloba, which attenuate obesity-induced OS and cardiomyocyte damage through the activation of Nrf2 [150, 151]. Quercetin has also been found to possibly protect against DOX-induced cardiomyopathy by increasing Nrf2 expression to improve antioxidant defenses while restraining biochemical and histological abnormalities [152]. Similarly, EGb761 is also protective against DOX-induced acute cardiotoxicity, and such a protective effect appears to be mediated by the modulation of inflammatory and vasoactive mediators as well as the inhibition of membrane lipid peroxidation [153]. The vast majority of HF begins with left HF, and through the long-term administration of Ginkgo biloba, the left ventricular function of patients with chronic heart failure is significantly improved [134, 154]. It was found in one study that through continuous treatment with quercetin for 12 months, the echocardiographic parameters of left ventricular diastolic function were improved [155]. In addition, quercetin helps maintain mitochondrial homeostasis, which may protect cardiomyocytes under inflammatory conditions, thereby reducing the incidence of HF [156]. Macrophage infiltration and polarization are integral to the progression of HF and cardiac fibrosis after IR, and Ginkgo biloba attenuates OS in macrophages as well as endothelial cells [157, 158]. Kaempferol has both anti-inflammatory and antioxidant properties, which prevents angiotensin II-induced cardiac fibrosis and dysfunctions [159].

Ginkgo biloba and its active extracts can act on multiple targets and have multiple effects, such as volatile anti-inflammatory and antioxidant effects, which can exert therapeutic and protective effects on HF, and some of them can be used as complementary therapies for the treatment of HF. However, there is limited research made by pharmacists on the interaction between Ginkgo biloba and its active extracts or drugs. Whether will the combination of drugs have adverse effects on patients’ bodies? This is a matter of concern.

**Protective effect against cardiotoxicity of doxorubicin**

DOX is a widely-used anti-tumor drug in the clinical treatment of malignant tumors, breast cancer, and non-Hodgkin’s lymphoma, whose use is limited by cumulative doses due to severe cardiotoxicity. GBE has a good cardioprotective effect against cardiotoxicity induced by DOX induction, thus GBE serves as a possible cardioprotectant for patients with chronic DOX-induced cardiac toxicity [160]. Studies based on a network pharmacology approach have shown that the possible mechanisms of Ginkgo biloba against Adriamycin-induced myocardial (AIC) were multi-component, multi-target, and multi-pathway. It was found that quercetin, lignans, kaempferol, isorhametin, and sesquiterpenes were the key constituents of FG in the treatment of AIC, and that STAT3 might be a key target [161].

Among them, isorhametin, a rich flavonol glycoside in herbal medicinal plants such as Ginkgo biloba, has significant cardioprotective effects on the heart [162, 163]. Isoflavonoids are typically cardioprotective against AIC both in vivo and in vitro, and such protection is associated with the inhibition of OS as well as subsequent mitochondria-dependent apoptotic and MAPK signaling pathways [164]. Furthermore, a research study validates an DOX-induced myocardial injury model to verify the therapeutic effects of GA, GB, and isorhametin as well as their cooperative effects on the PI3K-AKT and NF-κB signaling pathway in vitro, and finding that Ginkgo can exert a multi-pathway treatment effect on cardiomyopathy by acting on multiple targets regulating the pro-survival, anti-apoptotic and anti-inflammatory processes [165].

DOX impairs cardiomyocyte viability in part through the activation of p53-mediated mitochondria-dependent apoptotic signaling, meanwhile EGb761 effectively and broadly counteracts such effect of DOX, potentially protecting the heart from the severe toxicity of DOX [166]. Through EGb761 treatment, the markedly-elevated level of tumor necrosis factor-alpha and caspase-3 in the heart of DOX-intoxicated rats was ameliorated, and the protective effects of EGb761 against DOX-induced cardiac injuries might be related to antioxidant, anti-inflammatory and anti-apoptotic properties [167]. A clinical trial included 60 patients with stage IV breast cancer, who were randomly divided into two groups. The control group received chemotherapy with a 4-cycle PA regimen only; the treatment group received Egb761 on top of what was received by the control group. The results revealed that the incidence of electrocardiogram abnormalities in the treatment group was lower than that in the control group; myocardial enzyme profile parameters differed significantly between both groups. A study made by ultrasono-cardiogram revealed marked distinctions between the two groups in patients’ left ventricular diastolic and systolic diameters, along with early and late diastolic peak transmural flow velocity ratios and the fractional shortening rate. However, the ejection fraction was not significantly different. Therefore, EGb761 is an ideally-suited drug to prevent and attenuate DOX-induced acute cardiotoxicity, which also helps to attenuate chronic cardiotoxicity [168]. In addition, EGb761 scavenges oxygen radicals and nitrogen oxides, prevents pathological ET-1 and TNF-α elevation, and protects cardiac endothelial cells, thereby attenuating AIC. EGb761 can serve as an adjunct medication to mitigate the severe and possibly-deadly complications of DOX; nevertheless, the interaction of Egb761 with DOX needs to be tested through adequate clinical trials, and further studies are needed to determine whether EGb761 interferes with the antitumor properties of DOX [169].

GB may have cardioprotective effects by regulating ROS, Akt, and calcium pathways. Through the co-administration of GB with DOX during chemotherapy, the cardiotoxic side effects of DOX can be prevented [170]. In AIC suffered by rats, GB has a significant cardioprotective effect by attenuating OS [171]. Through the activation of SIRT1, myocardial remodeling can be ameliorated or prevented, and the progression of HF is delayed, whereas GB regulates autophagy via SIRT1-FoxO1 to protect cardiomyocytes from angiotensin II-induced hypertrophy [172, 173]. A study showed the pretreatment of H9c2 cardiomyocytes with a reduced GB (Ca2+) concentration and phosphorylated P38 MAPK expression to protect H9c2 cardiomyocytes against DOX-induced cell deaths, in which GB was effective for decreasing the toxicity of DOX to cells [174]. In the future, physicians may use GB as a cardioprotective adjunct to mitigate AIC.

**Summary**

Ginkgo biloba has a lengthy history of both medicinal and edible values, and with the continuous development of modern biotechnology, its rich pharmacological activities are gradually recognized. Modern pharmacological studies have also verified the broad application prospects of Ginkgo biloba and its active ingredients, which have a good efficacy in the treatment of cardiovascular diseases, atherosclerosis, hypertension, hyperlipidemia and myocardial ischemia-reperfusion injury arrhythmias (Figure 7). Also, through a large number of previous basic clinical studies, the good efficacy,
Ginkgo biloba and its extracts prevent and treat various CVDs

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Figure 7 Mechanisms of ginkgo and its extracts in the treatment of various cardiovascular diseases. PAF, platelet aggregating factor; ERS, endoplasmic reticulum stress; ROS, reactive oxygen species; MDA, malondialdehyde; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; DAD, delayed after depolarization; APD, action potential duration; ICA-L, L-type calcium channel; OS, oxidative stress; VF, ventricular fibrillation; VT, ventricular tachycardia.

Safety, tolerability and affordable formulation process of Ginkgo biloba have been demonstrated, together with its ability to provide a relatively safe, affordable and effective treatment option for some CVDs. With the increasing pursuit of healthy living, the widespread use of dietary supplements, and the deepening research on the pharmacological action mechanisms of Ginkgo biloba as well as its active ingredients, more medicinal values of Ginkgo biloba products will be developed and disclosed in an explosive manner. This also means that in the future, whether Ginkgo biloba or its active ingredients are used as pharmaceutical preparations as a supplementary treatment of clinical diagnosis and treatment or as dietary supplements or health products for daily health maintenance, they will bring profound significance to human health.

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review

Traditional Medicine Research


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