TMR

REVIEW

Traditional Medicine Research 2024;9(5):26. https://doi.org/10.53388/TMR20231022001

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

Mei-Juan Liao[1, 2, 3#], Qin Li[1, 2#], Qi-Yuan Luo[4], Xing-Yi Chen[1, 3], Ji-Yu Chen[1, 2*], Yan He[1, 2*]

[1]Clinical Trials Center, The Affiliated Hospital of Guizhou Medical University, Guiyang 550000, China. [2]Key Laboratory of Basic Pharmacology of Ministry of Education, Zunyi Medical University, Zunyi, Guizhou province, P.R. China. [3]School of Pharmacy, Guizhou Medical University, Guiyang 550000, China. [4]Basic 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; Jiyu_Chen@foxmail.com.

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.

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

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 Y reviewed the draft critically. Luo QY and Chen XY checked the English and produced Figures.

Competing interests

The authors declare no conflicts of interest.

Acknowledgments

This study was funded by the National Natural Science Foundation of China (82260096; 82300547), the Science and Technology Foundation of Basic Research Program of Guizhou Province ([2023] General 371; [2020]1Y381), the Administration of Traditional Chinese Medicine of Guizhou Province (QZYY-2018-130), the Cultivation Plan of the NSFC (National Natural Science Foundation of China) of Guizhou Medical University (21NSFCP13), the project of Key Laboratory of Basic Pharmacology of Ministry of Education, Zunyi Medicial University (No. qianjiaoheKYzi[2022]395, the Science and Technology Foundation of Health Commission of Guizhou Province (gzwkj2022-221).

Peer review information

Traditional Medicine Research thanks Wang Zhen and other anonymous reviewers for their contribution to the peer review of this paper.

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; AS, 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/RI, myocardial ischemia-reperfusion injuries; I/R, ischemia/reperfusion; SXNI, Shuxuening injection; GFGs, ginkgo flavonol glycosides; GGs, ginkgolides G; HIF-1, Hypoxia inhibitory factor-1; 5-HT, 5-Hydroxytryptamine.

Citation

Liao MJ, Li Q, Luo QY, Chen XY, Chen JY, He Y. Pharmacological effects of *Ginkgo biloba* and its active ingredients in the treatment of cardiovascular diseases. *Tradit Med Res*. 2024;9(5):26. doi: 10.53388/TMR20231022001.

Executive editor: Xi-Yue Liu.

Received: 23 October 2023; **Accepted:** 10 January 2024; **Available online:** 12 January 2024.

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 anthracycline-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 monoflavones, flavonols, dihydroflavones, 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

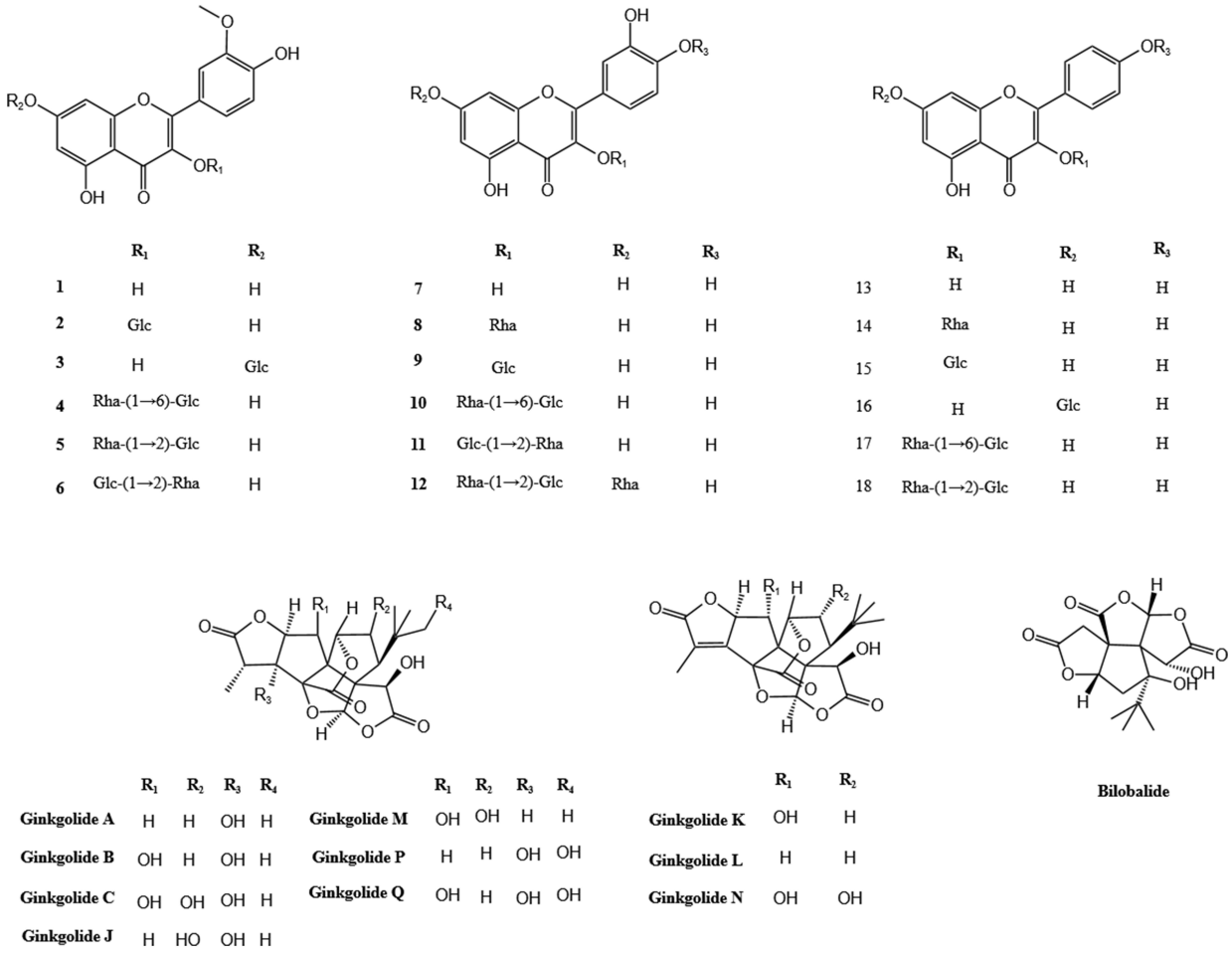
CVDs refer to a group of cardiac and vascular diseases, mainly including angina pectoris, myocardial infarction, hypertensive heart disease, hyperlipidemia, strokes, heart failure, cardiomyopathy, endocarditis, arrhythmias, valvular heart disease, aortic diseases, peripheral arterial disease and other 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

Traditional Medicine Research 2024;9(5):26. https://doi.org/10.53388/TMR20231022001



	R_1	R_2
1	H	H
2	Glc	H
3	H	Glc
4	Rha-(1→6)-Glc	H
5	Rha-(1→2)-Glc	H
6	Glc-(1→2)-Rha	H

	R_1	R_2	R_3
7	H	H	H
8	Rha	H	H
9	Glc	H	H
10	Rha-(1→6)-Glc	H	H
11	Glc-(1→2)-Rha	H	H
12	Rha-(1→2)-Glc	Rha	H

	R_1	R_2	R_3
13	H	H	H
14	Rha	H	H
15	Glc	H	H
16	H	Glc	H
17	Rha-(1→6)-Glc	H	H
18	Rha-(1→2)-Glc	H	H

	R_1	R_2	R_3	R_4
Ginkgolide A	H	H	OH	H
Ginkgolide B	OH	H	OH	H
Ginkgolide C	OH	OH	OH	H
Ginkgolide J	H	HO	OH	H

	R_1	R_2	R_3	R_4
Ginkgolide M	OH	OH	H	H
Ginkgolide P	H	H	OH	OH
Ginkgolide Q	OH	H	OH	OH

	R_1	R_2
Ginkgolide K	OH	H
Ginkgolide L	H	H
Ginkgolide N	OH	OH

Bilobalide

Figure 1 Representative flavonoids and terpene lactones from *Ginkgo biloba*. Reproduced with permission. Liu L, Wang Y, Zhang J, Wang S. Advances in the chemical constituents and chemical analysis of Ginkgo biloba leaf, extract, and phytopharmaceuticals. *J Pharm Biomed Anal.* 2021;193:113704. Copyright © 2020 Published by Elsevier.

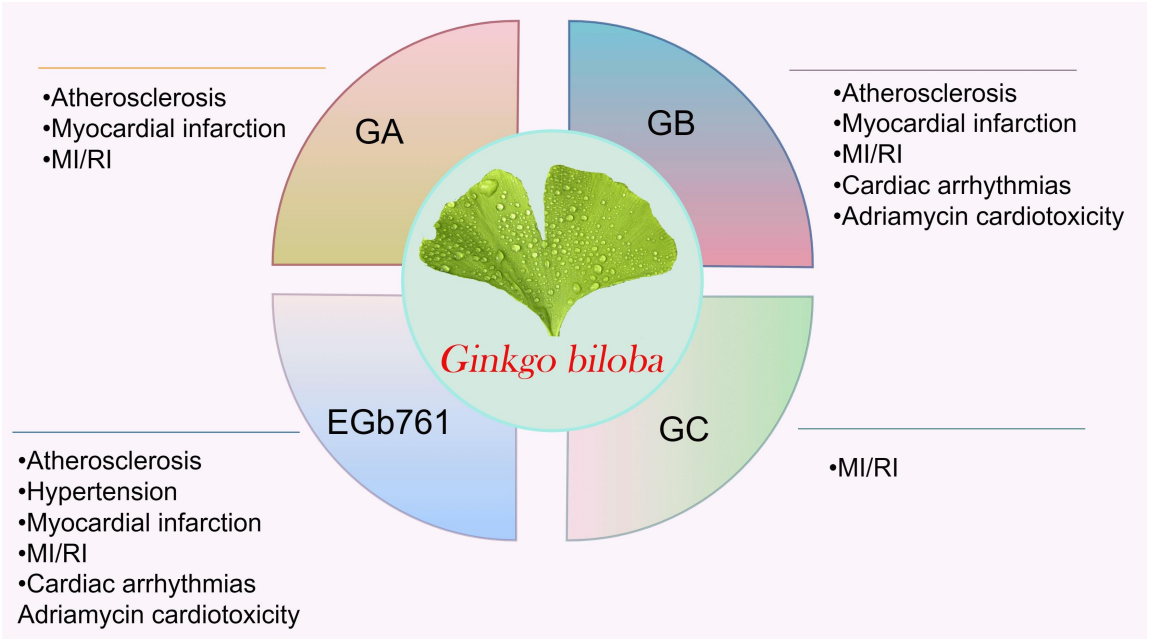


Figure 2 Therapeutic effects of *Ginkgo biloba* and its extracts on cardiovascular diseases. GA, ginkgolide A; GB, ginkgolide B; GC, ginkgolide C; MI/RI, myocardial ischemia-reperfusion injuries.

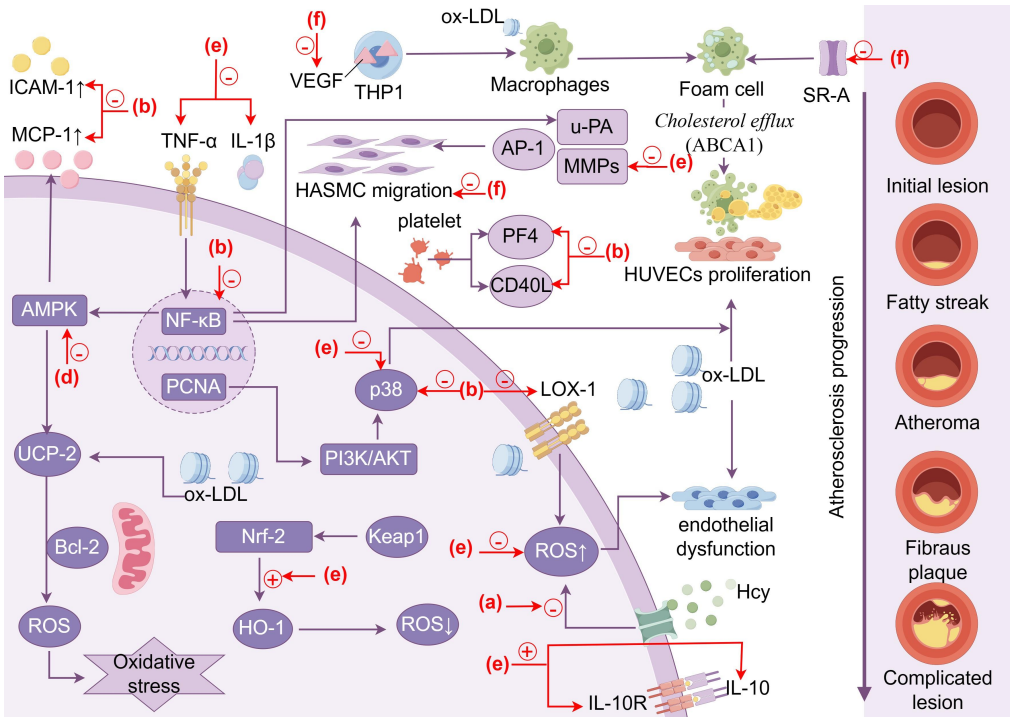


Figure 3 Mechanisms of *Ginkgo biloba* and its extracts in the treatment of atherosclerosis. *Ginkgo biloba* and its extracts affect multiple pathways that form atherosclerosis. (a) Ginkgolide A. (b) Ginkgolide B. (c) Ginkgolide C. (d) Ginkgolide G. (e) Ginkgo Biloba Extract. (f) Ginkgo Biloba Extract EGB761. ⊕, promote;⊖, inhibite. HUVECs, human umbilical vein endothelial cells; HASMC, human aortic smooth muscle cells; ROS, reactive oxygen species.

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 IκB 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-calmodulin, and Cx43 in TNF*α*-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 Nrf-2 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 cell 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 PF4 and CD40L in thrombin-activated platelets, which is able to partially reduce the level of ATP release and Ca^{2+} 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 cysteinase 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

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

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 liptein cholesterol.

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 liptein 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 doses, TG, TC, and low-density lipoprotein cholesterol were also significantly reduced while significantly elevating the level of high density liptein 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 hypolipidaemic effects of *Ginkgo biloba* are further supported by these findings.

Therapeutic effects on hypertension

Hypertension is one of the risk factors of CVDs globally, and arterial hypertension is a major risk factor of CVDs, with poorly-controlled hypertension further contributing to strokes, ischaemic 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 hypertensive disease prevention and treatment 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 amlodipine benzenesulfonate 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 antithrombotic 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

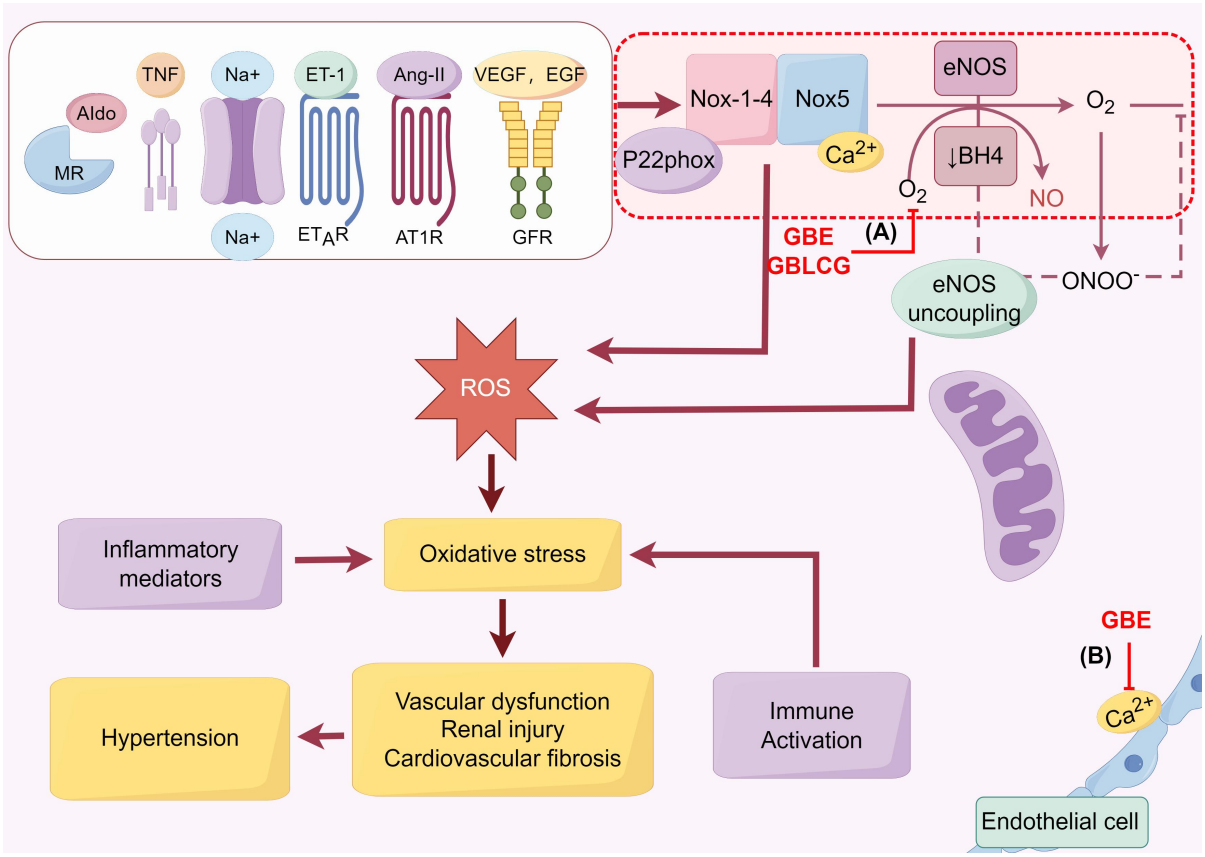


Figure 4 Mechanisms of *Ginkgo biloba* and its extracts in the treatment of hypertension. *Ginkgo biloba* and its extracts inhibit several processes involved in the development of dynamic hypertension. (A) GBE and GBLCG reduce Oxidative Stress by ameliorating endothelial NO pathway dysfunction. (B) GBE increases Ca^{2+} levels in endothelial cells, thereby reducing systolic blood pressure. GBE, *Ginkgo biloba* extract; GBLCG, *Ginkgo biloba* leaf constituent group; ROS, reactive oxygen species.

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, EGb761 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 EGb 761, 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].

GBE 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

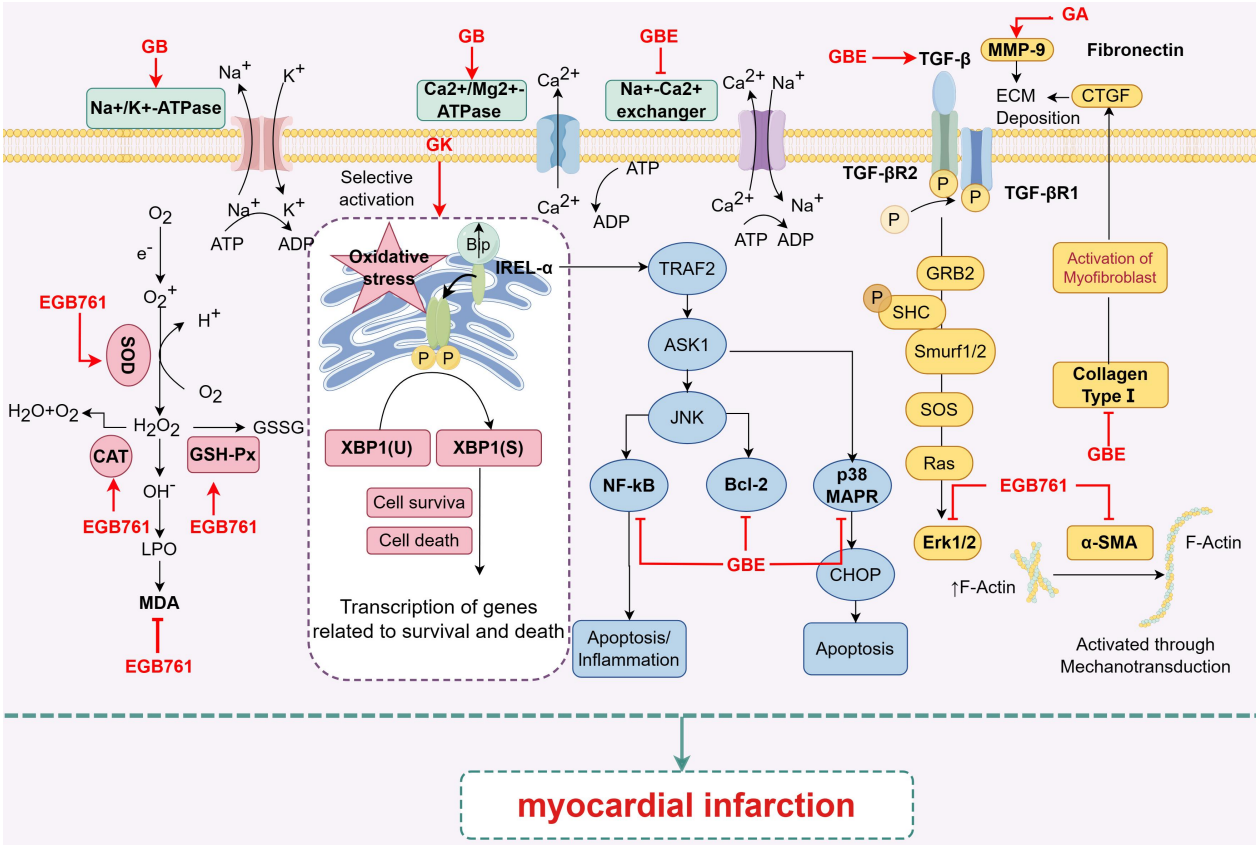


Figure 5 Mechanism of ginkgo biloba and its extracts in the treatment of myocardial infarction. *Ginkgo biloba* and its extracts inhibit several processes that cause myocardial infarction, including Oxidative Stress, fibrosis, and inflammation in cardiomyocytes, in addition to acting on the associated ion pumps. GA, ginkgolide A; GB, ginkgolide B; GBE, *Ginkgo biloba* extract; ECM, extracellular matrix; GSSG, Guanosine-2',3'-cyclic Monophosphate; LPO, lipid peroxidat; MDA, malondialdehyde; CTGF, connective tissue growth factor.

Bcl-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^+-Ca^{2+} 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 Ca^{2+}/Mg^{2+}-ATPase activity of myocardial tissues, thus regulating intra- and extracellular ion homeostasis, especially Ca^{2+} 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 hemopoiesis 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

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*, Bilobalide, 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/RI [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/RI 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/RI 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 GB 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/RI 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 I/R-induced 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/RI by enhancing the A20-dependent NF-κB signalling pathway, thus ameliorating inflammatory injuries caused by MI/RI both in vivo and in vitro [106].

In addition to the active components in *Ginkgo biloba* mentioned above, EGb761, which contains terpenoid and flavonoid components, has also been reported to have significant cardioprotective effects against myocardial I/R injuries [107]. It was found in a study that the synergistic effects of flavonoid glycosides and terpenoids might contribute to the cardioprotective effects of EGb761 by inhibiting cytochrome c release and caspase activation during MI/RI 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; EGb761 was able to significantly reduce serum cTnI concentration during reperfusion while significantly reducing infarct sizes; EGb761 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 Ca^{2+}-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 Ca^{2+} overload, thus playing a protective role in MI/RI [116].

GC also ameliorates the symptoms of I/R injuries, which is demonstrated by the decrease in infarction area, the prevention of myofibrillar degeneration, and the reversal of mitochondrial dysfunction; GC benefits MI/RI 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 sequelae 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

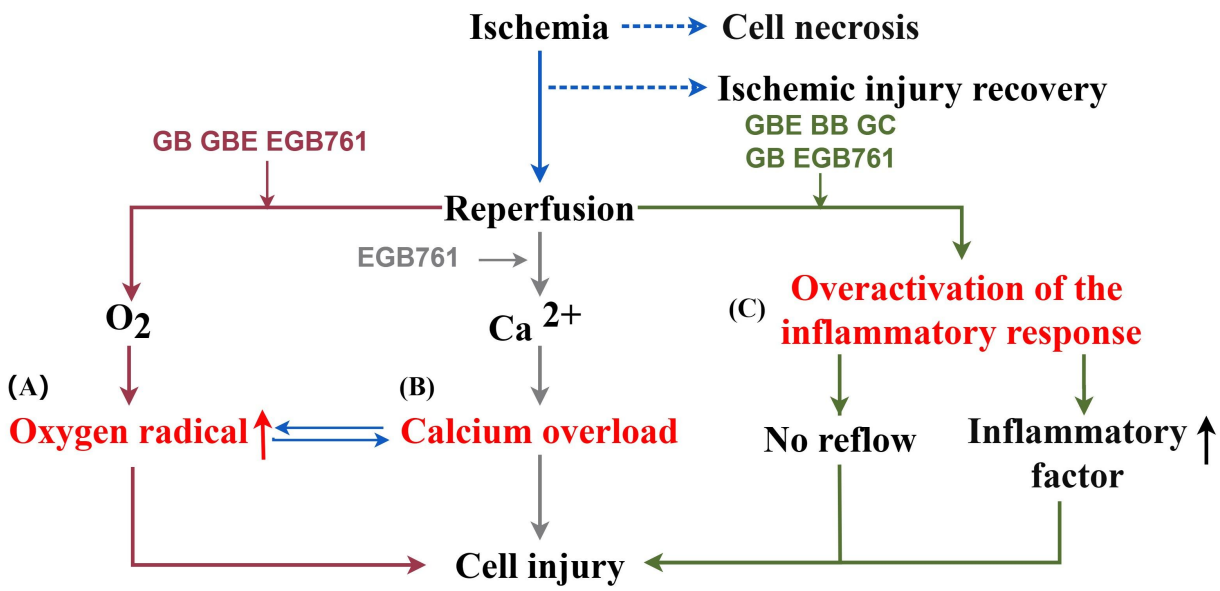


Figure 6 Mechanisms of *Ginkgo biloba* and its extracts in the treatment of myocardial ischemia-reperfusion injury. Ginkgo and its extracts inhibit multiple aspects of myocardial ischaemia-reperfusion injury process. (A) GB, GBE and EGB761 can reduce the production of oxygen free radicals. (B) EGB761 attenuates mitochondrial Ca^{2+} 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.

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, GBE50 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 Ca^{2+}, 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 gastrin promotes positive energy metabolism, and GBE improves cardiac function and energy metabolism in rats with HF by increasing gastrin 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

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. Isoginkgo 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 restoring 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, isorhamnetin, and sesquiterpenes were the key constituents of FG in the treatment of AIC and that STAT3 might be a key target [161].

Among them, isorhamnetin, a rich flavonol glycoside in herbal medicinal plants such as *Ginkgo biloba*, has significant cardioprotective effects on the heart [162, 163]. Isorhamnetin is 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 therapeutical effects of GA, GB, and isorhamnetin as well as their cooperative effects on the PI3K-AKT and NF- κ B 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 transmitral 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 (Ca^{2+}) 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 adjuvant 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 CVDs such as atherosclerosis, hypertension, hyperlipidemia and myocardial ischemia-reperfusion injury arrhythmias (Figure 7). Also, through a large number of previous basic clinical studies, the good efficacy,

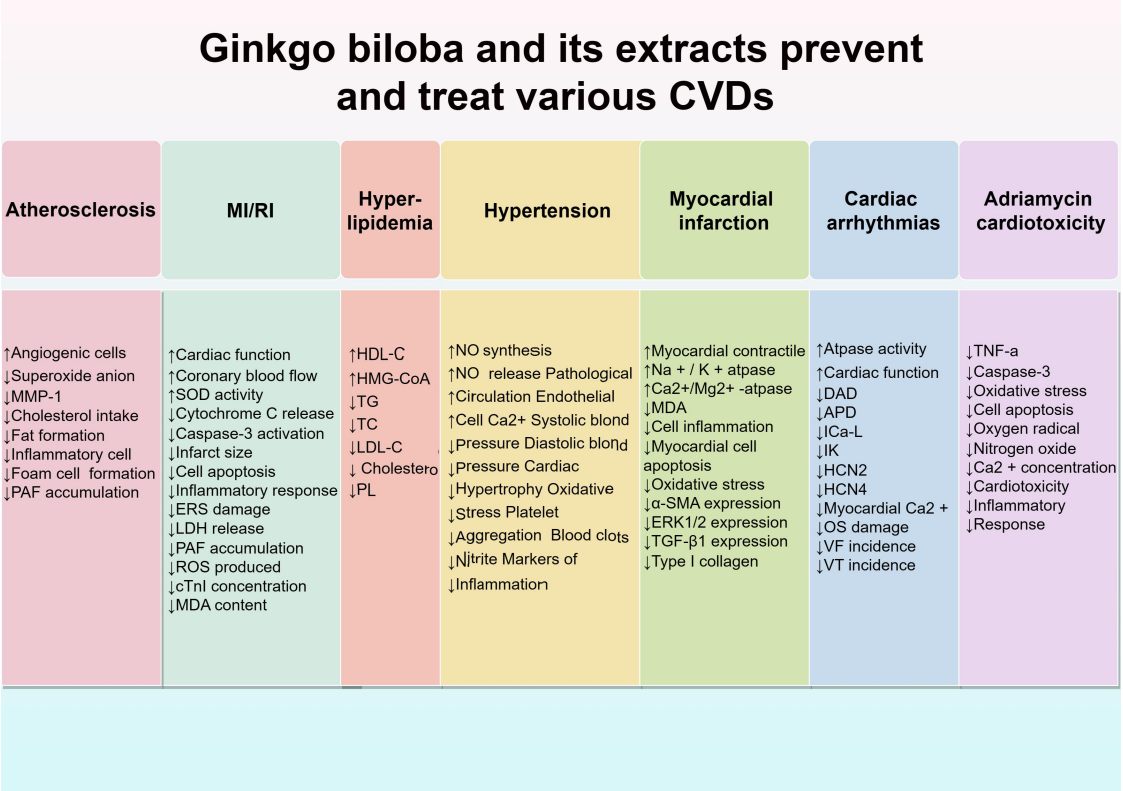


Figure 7 Mechanisms of ginkgo and its extracts in the treatment of various cardiovascular diseases. PAF, platelet aggregating factor; ERS, endoplasmic reticulum stress; ROS, reactive oxygen species; MDA, malondialdehyde; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; DAD, delayed after 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.

References

1. writing committee of the report on cardiovascular health and diseases in china. Report on Cardiovascular Health and Diseases in China 2021: An Updated Summary. *Biomed Environ Sci.* 2022;35(7):573–603. Available at: http://doi.org/10.3967/bes2022.079
2. Björnsson ES. Hepatotoxicity of statins and other lipid-lowering agents. *Liver Int.* 2016;37(2):173–178. Available at: http://doi.org/10.1111/liv.13308
3. Hao P, Jiang F, Cheng J, Ma L, Zhang Y, Zhao Y. Traditional Chinese Medicine for Cardiovascular Disease. *J Am Coll Cardiol.* 2017;69(24):2952–2966. Available at: http://doi.org/10.1016/j.jacc.2017.04.041
4. Liu L, Wang Y, Zhang J, Wang S. Advances in the chemical constituents and chemical analysis of Ginkgo biloba leaf, extract, and phytopharmaceuticals. *J Pharm Biomed Anal.* 2021;193:113704. Available at: http://doi.org/10.1016/j.jpba.2020.113704
5. Diamond BJ, Bailey MR. Ginkgo biloba: indications, mechanisms, and safety. *Psychiatr Clin North Am.* 2013;36(1):73–83. Available at: http://doi.org/10.1016/j.psc.2012.12.006
6. Eisvand F, Razavi BM, Hosseinzadeh H. The effects of Ginkgo biloba on metabolic syndrome: A review. *Phytother Res.* 2020;34(8):1798–1811. Available at: http://doi.org/10.1002/ptr.6646
7. Unger M. Pharmacokinetic drug interactions involving Ginkgo biloba. *Drug Metab Rev.* 2013;45(3):353–385. Available at: http://doi.org/10.3109/03602532.2013.815200
8. Leong DP, Joseph PG, McKee M, et al. Reducing the Global Burden of Cardiovascular Disease, Part 2: Prevention and Treatment of Cardiovascular Disease. *Circ Res.* 2017;121(6):695–710. Available at: http://doi.org/10.1161/CIRCRESAHA.117.311849
9. In Het Panhuis Wietse, Schönke Milena, Modder Melanie, et al. Time-restricted feeding attenuates hypercholesterolaemia and atherosclerosis development during circadian disturbance in APOE*3-Leiden.CETP mice. *EBioMedicine.* 2023;93:104680. Available at: http://doi.org/10.1016/j.ebiom.2023.104680
10. Núñez E, Fuster V, Gómez-Serrano M, et al. Unbiased plasma proteomics discovery of biomarkers for improved detection of subclinical atherosclerosis. *EBioMedicine.* 2022;76:103874. Available at: http://doi.org/10.1016/j.ebiom.2022.103874
11. Soppert J, Lehrke M, Marx N, Jankowski J, Noels H. Lipoproteins and lipids in cardiovascular disease: from mechanistic insights to therapeutic targeting. *Adv Drug Delivery. Rev* 2020;159:4–33. Available at: http://doi.org/10.1016/j.addr.2020.07.019
12. McCully KS. Vascular pathology of homocysteinemia: implications for the pathogenesis of arteriosclerosis. *Am J Pathol.* 1969;56(1):111–128. Available at:

https://pubmed.ncbi.nlm.nih.gov/5792556/
13. McCully KS. Hyperhomocysteinemia and arteriosclerosis: historical perspectives. *Clin Chem Lab Med.* 2005;43(10):980–986. Available at: http://doi.org/10.1515/CCLM.2005.172
14. Zhou W, Chai H, Courson A, et al. Ginkgolide A attenuates homocysteine-induced endothelial dysfunction in porcine coronary arteries. *J Vasc Surg.* 2006;44(4):853–862. Available at: http://doi.org/10.1016/j.jvs.2006.06.012
15. Kattoor AJ, Kanuri SH, Mehta JL. Role of Ox-LDL and LOX-1 in Atherogenesis. *Curr Med Chem.* 2019;26(9):1693–1700. Available at: http://doi.org/10.2174/0929867325666180508100950
16. Ma Lina, Liu Xueqing, Zhao Yanyang, Chen Beidong, Li Xingguang, Qi Ruomei. Ginkgolide B reduces LOX-1 expression by inhibiting Akt phosphorylation and increasing Sirt1 expression in oxidized LDL-stimulated human umbilical vein endothelial cells. *PLoS One.* 2013;8(9):e74769. Available at: http://doi.org/10.1371/journal.pone.0074769
17. Feng Z, Yang X, Zhang L, et al. Ginkgolide B ameliorates oxidized low-density lipoprotein-induced endothelial dysfunction via modulating Lectin-like ox-LDL-receptor-1 and NADPH oxidase 4 expression and inflammatory cascades. *Phytother Res.* 2018;32(12):2417–2427. Available at: http://doi.org/10.1002/ptr.6177
18. Li R, Chen B, Wu W, Bao L, Li J, Qi R. Ginkgolide B Suppresses Intercellular Adhesion Molecule-1 Expression via Blocking Nuclear Factor-κB Activation in Human Vascular Endothelial Cells Stimulated by Oxidized Low-Density Lipoprotein. *J Pharmacol Sci.* 2009;110(3):362–369. Available at: http://doi.org/10.1254/jphs.08275FP
19. Lawson C, Wolf S. ICAM-1 signaling in endothelial cells. *Pharm Rep.* 2009;61(1):22–32. Available at: http://doi.org/10.1016/S1734-1140(09)70004-0
20. Liu XQ, Chen BD, Bao Li, Wu W, Sun WJ, Qi RM. Effect of ginkgolide B on junctional proteins in oxidized LDL-stimulated human umbilical vein endothelial cells.. *Chin Pharmacol Bull.* 2014;30(05):646–651. (Chinese) Available at: https://www.cnki.net/KCMS/detail/detail.aspx?dbcode=CJFD&dbname=CJFD2014&filename=YAOL201405014&uniplatform=OVERSEA&v=uimDDrSgOiI3OV0TCpknz3srAyJmlbZidXnZxwj4-3rv3W7tpvYIPOBjXkwQTEnG
21. Zhang M, Sun J, Chen B, et al. Ginkgolide B inhibits platelet and monocyte adhesion in TNF*α*-treated HUVECs under laminar shear stress. *BMC Complement Altern Med.* 2018;18(1):220. Available at: http://doi.org/10.1186/s12906-018-2284-8
22. Liu X, Sun W, Zhao Y, et al. Ginkgolide B Inhibits JAM-A, Cx43, and VE-Cadherin Expression and Reduces Monocyte Transmigration in Oxidized LDL-Stimulated Human Umbilical Vein Endothelial Cells. *Oxid Med Cell Longev.* 2015;2015:907926. Available at: http://doi.org/10.1155/2015/907926
23. Pfenniger A, Chanson M, Kwak BR. Connexins in atherosclerosis. *Biochim Biophys Acta.* 2013;1828(1):157–166. Available at: http://doi.org/10.1016/j.bbamem.2012.05.011
24. Zhou W, Chai H, Lin PH, Lumsden AB, Yao Q, Chen C. Clinical Use and Molecular Mechanisms of Action of Extract of Ginkgo biloba Leaves in Cardiovascular Diseases. *Cardiovasc Drug Rev.* 2004;22(4):309–319. Available at: http://doi.org/10.1111/j.1527-3466.2004.tb00148.x
25. Kwak BR, Veillard N, Pelli G, et al. Reduced Connexin43 Expression Inhibits Atherosclerotic Lesion Formation in Low-Density Lipoprotein Receptor–Deficient Mice. *Circulation.* 2003;107(7):1033–1039. Available at: http://doi.org/10.1161/01.CIR.0000051364.70064.D1
26. Wei JM, Wang X, Gong H, Shi YJ, Zou Y. Experimental research Ginkgo suppresses atherosclerosis through downregulating the expression of connexin 43 in rabbits. *Arch Med Sci.* 2013;9(2):340–346. Available at: http://doi.org/10.5114/aoms.2013.34416
27. Araujo JA, Zhang M, Yin F. Heme Oxygenase-1, Oxidation, Inflammation, and Atherosclerosis. *Front Pharmacol.* 2012;3:119. Available at: http://doi.org/10.3389/fphar.2012.00119
28. Chen JS, Huang PH, Wang CH, et al. Nrf-2 mediated heme oxygenase-1 expression, an antioxidant-independent mechanism, contributes to anti-atherogenesis and vascular protective effects of Ginkgo biloba extract. *Atherosclerosis.* 2011;214(2):301–309. Available at: http://doi.org/10.1016/j.atherosclerosis.2010.11.010
29. Tong W, Zhang Y, Hui H, et al. Sensitive magnetic particle imaging of haemoglobin degradation for the detection and monitoring of intraplaque haemorrhage in atherosclerosis. *EBioMedicine.* 2023;90:104509. Available at: http://doi.org/10.1016/j.ebiom.2023.104509
30. Liu HJ, Wang XL, Zhang L, et al. Inhibitions of vascular endothelial growth factor expression and foam cell formation by EGb 761, a special extract of Ginkgo biloba, in oxidatively modified low-density lipoprotein-induced human THP-1 monocytes cells. *Phytomedicine.* 2009;16(2–3):138–145. Available at: http://doi.org/10.1016/j.phymed.2008.11.003
31. Tsai JY, Su KH, Shyue SK, et al. EGb761 ameliorates the formation of foam cells by regulating the expression of SR-A and ABCA1: role of haem oxygenase-1. *Cardiovasc Res.* 2010;88(3):415–423. Available at: http://doi.org/10.1093/cvr/cvq226
32. Jiao YB, Rui YC, Yang PY, Li TJ, Qiu Y. Effects of Ginkgo biloba extract on expressions of IL-1beta, TNF-alpha, and IL-10 in U937 foam cells. *Yao Xue Xue Bao.* 2007;42(9):930–934. Available at: https://pubmed.ncbi.nlm.nih.gov/18050733/
33. Bu S, Yuan CY, Xue Q, Chen Y, Cao F. Bilobalide Suppresses Adipogenesis in 3T3-L1 Adipocytes via the AMPK Signaling Pathway. *Molecules.* 2019;24(19):3503. Available at: http://doi.org/10.3390/molecules24193503
34. Gautam J, Kushwaha P, Swarnkar G, et al. EGb 761 promotes osteoblastogenesis, lowers bone marrow adipogenesis and atherosclerotic plaque formation. *Phytomedicine.* 2012;19(12):1134–1142. Available at: http://doi.org/10.1016/j.phymed.2012.07.005
35. Brochériou I, Stengel D, Mattsson-Hultén L, et al. Expression of Platelet-Activating Factor Receptor in Human Carotid Atherosclerotic Plaques. *Circulation.* 2000;102(21):2569–2575. Available at: http://doi.org/10.1161/01.CIR.102.21.2569
36. Koch E. Inhibition of platelet activating factor (PAF)-induced aggregation of human thrombocytes by ginkgolides: considerations on possible bleeding complications after oral intake of Ginkgo biloba extracts. *Phytomedicine.* 2005;12(1–2):10–16. Available at: http://doi.org/10.1016/j.phymed.2004.02.002
37. Liu XY, Zhao GX, Yan Y, Bao L, Chen BD, Qi RM. Ginkgolide B reduces atherogenesis and vascular inflammation in ApoE(-/-) mice. *PLoS One.* 2012;7(5):e36237. Available at: http://doi.org/10.1371/journal.pone.0036237
38. Lv Z, Shan X, Tu Q, Wang J, Chen J, Yang Y. Ginkgolide B treatment regulated intestinal flora to improve high-fat diet induced atherosclerosis in $ApoE^{-/-}$ mice. *Biomed Pharmacother.* 2021;134:111100. Available at: http://doi.org/10.1016/j.biopha.2020.111100
39. Liu X, Yan Y, Bao L, Chen B, Zhao Y, Qi R. Ginkgolide B inhibits platelet release by blocking Syk and p38 MAPK phosphorylation in thrombin-stimulated platelets. *Thromb Res.* 2014;134(5):1066–1073. Available at: http://doi.org/10.1016/j.thromres.2014.08.025

40. Seeger FH, Sedding D, Langheinrich AC, Haendeler J, Zeiher AM, Dimmeler S. Inhibition of the p38 MAP kinase in vivo improves number and functional activity of vasculogenic cells and reduces atherosclerotic disease progression. *Basic Res Cardiol.* 2009;105(3):389–397. Available at: http://doi.org/10.1007/s00395-009-0072-9
41. Lim Soo, Yoon Ji Won, Kang Seon Mee, et al. EGb761, a Ginkgo biloba extract, is effective against atherosclerosis in vitro, and in a rat model of type 2 diabetes. *PLoS One.* 2011;6(6):e20301. Available at: http://doi.org/10.1371/journal.pone.0020301
42. Newby AC. Dual Role of Matrix Metalloproteinases (Matrixins) in Intimal Thickening and Atherosclerotic Plaque Rupture. *Physiol Rev.* 2005;85(1):1–31. Available at: http://doi.org/10.1152/physrev.00048.2003
43. Akiba Satoshi, Yamaguchi Hidenori, Kumazawa Satomi, Oka Mayuko, Sato Takashi. Suppression of oxidized LDL-induced PDGF receptor beta activation by ginkgo biloba extract reduces MMP-1 production in coronary smooth muscle cells. *J Atheroscler Thromb.* 2007;14(5):219–225. Available at: http://doi.org/10.5551/jat.e516
44. Stewart J, McCallin T, Martinez J, Chacko S, Yusuf S. Hyperlipidemia. *Pediatr Rev.* 2020;41(8):393–402. Available at: http://doi.org/10.1542/pir.2019-0053
45. Meeks KAC, Bentley AR, Agyemang C, et al. Ancestral and environmental patterns in the association between triglycerides and other cardiometabolic risk factors. *EBioMedicine.* 2023;91:104548. Available at: http://doi.org/10.1016/j.ebiom.2023.104548
46. Chew Nicholas W S, Ng Cheng Han, Tan Darren Jun Hao, et al. The global burden of metabolic disease: Data from 2000 to 2019. *Cell Metab.* 2023;35(3):414–428.e3. Available at: http://doi.org/10.1016/j.cmet.2023.02.003
47. El-Tantawy WH, Temraz A. Natural products for controlling hyperlipidemia: review. *Arch Physiol Biochem.* 2018;125(2):128–135. Available at: http://doi.org/10.1080/13813455.2018.1441315
48. Yao P, Song F, Li K, et al. Ginkgo bilobaExtract Prevents Ethanol Induced Dyslipidemia. *Am J Chin Med.* 2007;35(04):643–652. Available at: http://doi.org/10.1142/S0192415X07005132
49. Xu MC, Cheng XM, Ma LL. Study on effective dosages of ginkgo leaf extracts on regulating blood lipid of hyperlipidemia rats. *Chinese Traditional and Herbal Drugs.* 2021;52(02):454–458. (Chinese) Available at: https://www.cnki.net/KCMS/detail/detail.aspx?dbcode=CJFD&dbname=CJFDLAST2021&filename=ZCYO202102019&uniplatform=OVERSEA&v=Sss_mGh-o6v2WTBtH_UAV5DQdLHi1BSD8HP1U3iOtS4_MW0Nm1MxOfU9XgSRlJJO
50. Zhang Q, Wang G, A J, et al. Application of GC/MS-based metabonomic profiling in studying the lipid-regulating effects of Ginkgo biloba extract on diet-induced hyperlipidemia in rats. *Acta Pharmacol Sin.* 2009;30(12):1674–1687. Available at: http://doi.org/10.1038/aps.2009.173
51. Wang Q, Liu Z, Wang R, et al. Effect of Ginkgo biloba extract on pharmacology and pharmacokinetics of atorvastatin in rats with hyperlipidaemia. *Food Funct.* 2023;14(7):3051–3066. Available at: http://doi.org/10.1039/D2FO03238D
52. Al-Zakaria SA, Thanon IA-J, Saadallah LM. Effect of Ginkgo biloba on lipid profile in hypertensive patients on Valsartan monotherapy. *Ann Coll Med Mosul.* 2018;40(2):29–33. Available at: http://doi.org/10.33899/mmed.2018.160002
53. Šamec Dunja, Karalija Erna, Dahija Sabina, Hassan Sherif T S. Biflavonoids: Important Contributions to the Health Benefits of Ginkgo (*Ginkgo biloba* L.). *Plants* (*Basel*). 2022;11(10):1381. Available at: http://doi.org/10.3390/plants11101381
54. Liu PK, Weng ZM, Ge GB, et al. Biflavones from Ginkgo biloba as novel pancreatic lipase inhibitors: Inhibition potentials and mechanism. *Int J Biol Macromol.* 2018;118(Pt B):2216–2223. Available at: http://doi.org/10.1016/j.ijbiomac.2018.07.085
55. Mills KT, Stefanescu A, He J. The global epidemiology of hypertension. *Nat Rev Nephrol.* 2020;16(4):223–237. Available at: http://doi.org/10.1038/s41581-019-0244-2
56. Zhou B, Perel P, Mensah GA, Ezzati M. Global epidemiology, health burden and effective interventions for elevated blood pressure and hypertension. *Nat Rev Cardiol.* 2021;18(11):785–802. Available at: http://doi.org/10.1038/s41569-021-00559-8
57. Reel PS, Reel S, van Kralingen JC, et al. Machine learning for classification of hypertension subtypes using multi-omics: A multi-centre, retrospective, data-driven study. *EBioMedicine.* 2022;84:104276. Available at: http://doi.org/10.1016/j.ebiom.2022.104276
58. Louca P, Tran TQB, Toit C du, et al. Machine learning integration of multimodal data identifies key features of blood pressure regulation. *EBioMedicine.* 2022;84:104243. Available at: http://doi.org/10.1016/j.ebiom.2022.104243
59. Husain S, Andrews NP, Mulcahy D, Panza JA, Quyyumi AA. Aspirin Improves Endothelial Dysfunction in Atherosclerosis. *Circulation.* 1998;97(8):716–720. Available at: http://doi.org/10.1161/01.CIR.97.8.716
60. Zhang J, Ma YL. Observation on the Efficacy of Ginkgo Ketone Ester Drop Pill in Improving Hypertension Combined with Carotid Atherosclerotic Plaque. *Emerg Med Int.* 2022;2022:8650537. Available at: http://doi.org/10.1155/2022/8650537
61. Kubota Y, Tanaka N, Kagota S, et al. Effects of Ginkgo biloba Extract Feeding on Salt-Induced Hypertensive Dahl Rats. *Biol Pharm Bull.* 2006;29(2):266–269. Available at: http://doi.org/10.1248/bpb.29.266
62. Kubota Y, Tanaka N, Kagota S, et al. Effects of Ginkgo biloba extract on blood pressure and vascular endothelial response by acetylcholine in spontaneously hypertensive rats. *J Pharm Pharmacol.* 2006;58(2):243–249. Available at: http://doi.org/10.1211/jpp.58.2.0012
63. Umegaki K, Shinozuka K, Watarai K, et al. Ginkgo Biloba Extract Attenuates The Development Of Hypertension In Deoxycorticosterone Acetate-Salt Hypertensive Rats. *Clin Exp Pharma Physio.* 2000;27(4):277–282. Available at: http://doi.org/10.1046/j.1440-1681.2000.03236.x
64. Abdel-Zaher AO, Farghaly HSM, El-Refaiy AEM, Abd-Eldayem AM. Protective effect of the standardized leaf extract of Ginkgo biloba (EGb761) against hypertension-induced renal injury in rats. *Clin Exp Hypertens.* 2018;40(8):703–714. Available at: http://doi.org/10.1080/10641963.2018.1425421
65. Abdel-Zaher AO, Farghaly HSM, El-Refaiy AEM, Abd-Eldayem AM. Protective effect of the standardized extract of ginkgo biloba (EGb761) against hypertension with hypercholesterolemia-induced renal injury in rats: Insights in the underlying mechanisms. *Biomed Pharmacother.* 2017;95:944–955. Available at: http://doi.org/10.1016/j.biopha.2017.08.078
66. Mansour SM, Bahgat AK, El-Khatib AS, Khayyal MT. Ginkgo biloba extract (EGb 761) normalizes hypertension in 2K, 1C hypertensive rats: Role of antioxidant mechanisms, ACE inhibiting activity and improvement of endothelial dysfunction. *Phytomedicine.* 2011;18(8–9):641–647. Available at: http://doi.org/10.1016/j.phymed.2011.01.014
67. Liang H, Yuan X, Sun C, et al. Preparation of a new component group of Ginkgo biloba leaves and investigation of the antihypertensive effects in spontaneously hypertensive rats. *Biomed Pharmacother.* 2022;149:112805. Available at:

http://doi.org/10.1016/j.biopha.2022.112805
68. Zhang J, Fu S, Liu S, Mao T, Xiu R. The therapeutic effect of Ginkgo biloba extract in SHR rats and its possible mechanisms based on cerebral microvascular flow and vasomotion. *Clin Hemorheol Microcirc.* 2000;23(2–4):133–138. Available at: https://pubmed.ncbi.nlm.nih.gov/11321432/
69. Owolabi Mayowa O, Thrift Amanda G, Mahal Ajay, et al. Correction to Lancet Public Health 2022;7:e74–85. *Lancet Public Health.* 2022;7(1):e14. Available at: http://doi.org/10.1016/S2468-2667(21)00281-4
70. Tsao Connie W, Aday Aaron W, Almarzooq Zaid I, et al. Correction to: Heart Disease and Stroke Statistics-2023 Update: A Report From the American Heart Association. *Circulation.* 2023;147(8):e622. Available at: http://doi.org/10.1161/CIR.0000000000001137
71. Webb AJS, Werring DJ. New Insights Into Cerebrovascular Pathophysiology and Hypertension. *Stroke.* 2022;53(4):1054–1064. Available at: http://doi.org/10.1161/STROKEAHA.121.035850
72. Sasaki Y, Noguchi T, Yamamoto E, et al. Effects of Ginkgo biloba extract (EGb 761) on cerebral thrombosis and blood pressure in stroke-prone spontaneously hypertensive rats. *Clin Exp Pharma Physio.* 2002;29(11):963–967. Available at: http://doi.org/10.1046/j.1440-1681.2002.03761.x
73. Buus SMØ, Schmitz ML, Cordsen P, Johnsen SP, Andersen G, Simonsen CZ. Socioeconomic Inequalities in Reperfusion Therapy for Acute Ischemic Stroke. *Stroke.* 2022;53(7):2307–2016. Available at: http://doi.org/10.1161/STROKEAHA.121.037687
74. Choi JH, Poli S, Chen M, et al. Selective Brain Hypothermia in Acute Ischemic Stroke: Reperfusion Without Reperfusion Injury. *Front Neurol.* 2020;11:594289. Available at: http://doi.org/10.3389/fneur.2020.594289
75. Saleem S, Zhuang H, Biswal S, Christen Y, Doré S. Ginkgo Biloba Extract Neuroprotective Action Is Dependent on Heme Oxygenase 1 in Ischemic Reperfusion Brain Injury. *Stroke.* 2008;39(12):3389–3396. Available at: http://doi.org/10.1161/STROKEAHA.108.523480
76. Clark WM, Rinker LG, Lessov NS, Lowery SL, Cipolla MJ. Efficacy of Antioxidant Therapies in Transient Focal Ischemia in Mice. *Stroke.* 2001;32(4):1000–1004. Available at: http://doi.org/10.1161/01.STR.32.4.1000
77. Dong Y, Zhang J, Wang Y, et al. Effect of Ginkgolide in Ischemic Stroke patients with large Artery Atherosclerosis: Results from a randomized trial. *CNS Neurosci Ther.* 2021;27(12):1561–1569. Available at: http://doi.org/10.1111/cns.13742
78. Hayward CJ, Batty JA, Westhead DR, et al. Disease trajectories following myocardial infarction: insights from process mining of 145 million hospitalisation episodes. *EBioMedicine.* 2023;96:104792. Available at: http://doi.org/10.1016/j.ebiom.2023.104792
79. Shi H, Huang Z, Xu T, Sun A, Ge J. New diagnostic and therapeutic strategies for myocardial infarction via nanomaterials. *EBioMedicine.* 2022;78:103968. Available at: http://doi.org/10.1016/j.ebiom.2022.103968
80. Sagris Marios, Antonopoulos Alexios S, Theofilis Panagiotis, et al. Risk factors profile of young and older patients with myocardial infarction. *Cardiovasc Res.* 2022;118(10):2281–2292. Available at: http://doi.org/10.1093/cvr/cvab264
81. Zhang Q, Wang L, Wang S, et al. Signaling pathways and targeted therapy for myocardial infarction. *Signal Transduct Target Ther.* 2022;7(1):78. Available at: http://doi.org/10.1038/s41392-022-00925-z
82. Liu YL, Zhou Y, Sun L, et al. Protective effects of Gingko biloba extract 761 on myocardial infarction via improving the viability of implanted mesenchymal stem cells in the rat heart. *Mol Med Rep.* 2014;9(4):1112–1120. Available at: http://doi.org/10.3892/mmr.2014.1959
83. Li Y, Zhang Y, Wen M, et al. Ginkgo biloba extract prevents acute myocardial infarction and suppresses the inflammation- and apoptosis-regulating p38 mitogen-activated protein kinases, nuclear factor-κB and B-cell lymphoma 2 signaling pathways. *Mol Med Rep.* 2017;16(3):3657–3663. Available at: http://doi.org/10.3892/mmr.2017.6999
84. Liu AH, Bao YM, Wang XY, Zhang ZX. Cardio-Protection by Ginkgo biloba Extract 50 in Rats with Acute Myocardial Infarction is Related to Na^+–Ca^{2+} Exchanger. *Am J Chin Med.* 2013;41(4):789–800. Available at: http://doi.org/10.1142/S0192415X13500535
85. LI Y, Zhang QY, Luo LY, Tan J, Qian BY, Zhang JC. Effects of Ginkgo Biloba Extract on Transforming Growth Factor Beta 1 after Acute Cardiac Infarction in Rats. *BMC Complement Altern Med.* 2016;34(12):2945–2947. (Chinese) Available at: http://doi.org/10.13193/j.issn.1673-7717.2016.12.035
86. Zhou CX, Li X, Shu JL, Xu L. Effects of Ginkgolide B on Energy Metabolism in Rats with Myocardial Ischemia/Reperfusion Injury. *Laboratory Animal Science.* 2018;35(05):7–10. (Chinese) Available at: https://www.cnki.net/KCMS/detail/detail.aspx?dbcode=CJFD&dbname=CJFDLAST2018&filename=SYDG201805002&uniplatform=OVERSEA&v=F5xMS1F2o0Lpg0asunLmbRj7fg6zbV3wFLv_frVEq2eeUDiMv60bK6-Jrusb3VRw
87. Zhao K, Li Y, Zhou Z, et al. Ginkgolide A alleviates cardiac remodeling in mice with myocardial infarction via binding to matrix metalloproteinase-9 to attenuate inflammation. *Eur J Pharmacol.* 2022;923:174932. Available at: http://doi.org/10.1016/j.ejphar.2022.174932
88. Liu M, Chen Z, Chen L. Endoplasmic reticulum stress: a novel mechanism and therapeutic target for cardiovascular diseases. *Acta Pharmacol Sin.* 2016;37(4):425–443. Available at: http://doi.org/10.1038/aps.2015.145
89. Wang S, Wang Z, Fan Q, et al. Ginkgolide K protects the heart against endoplasmic reticulum stress injury by activating the inositol-requiring enzyme 1α/X box-binding protein-1 pathway. *Br J Pharmacol.* 2016;173(15):2402–2418. Available at: http://doi.org/10.1111/bph.13516
90. Lan C, Chen C, Qu S, et al. Inhibition of DYRK1A, via histone modification, promotes cardiomyocyte cell cycle activation and cardiac repair after myocardial infarction. *EBioMedicine.* 2022;82:104139. Available at: http://doi.org/10.1016/j.ebiom.2022.104139
91. Wang S, Hu S, Luo X, et al. Prevalence and prognostic significance of DNMT3A- and TET2- clonal haematopoiesis-driver mutations in patients presenting with ST-segment elevation myocardial infarction. *EBioMedicine.* 2022;78:103964. Available at: http://doi.org/10.1016/j.ebiom.2022.103964
92. Peng JF, Salami OM, Lei C, Ni D, Habimana O, Yi GH. Targeted mitochondrial drugs for treatment of myocardial ischaemia-reperfusion injury. *J Drug Target.* 2022;30(8):833–844. Available at: http://doi.org/10.1080/1061186X.2022.2085728
93. Moens AL, Claeys MJ, Timmermans JP, Vrints CJ. Myocardial ischemia/reperfusion-injury, a clinical view on a complex pathophysiological process. *Int J Cardiol.* 2005;100(2):179–190. Available at: http://doi.org/10.1016/j.ijcard.2004.04.013
94. Guillon J M, Rochette L, Baranes J. Effects of Ginkgo biloba extract on 2 models of experimental myocardial ischemia. *Presse Med.* 1986;15(31):1516–1519. Available at: https://doi.org/10.1007/978-3-642-73686-5_17
95. Qiao ZY, Huang JH, Ma JW, et al. Ginkgo biloba extract reducing myocardium cells apoptosis by regulating apoptotic related proteins expression in myocardium tissues. *Mol Biol Rep.* 2013;41(1):347–353. Available at: http://doi.org/10.1007/s11033-013-2868-9

96. Bao Y, Liu AH, Zhang ZX, Li Y, Wang XY. Effects of Ginkgo biloba extract 50 preconditioning on contents of inflammation-related cytokines in myocardium of rats with ischemia-reperfusion injury. *J Chin Integr Med.* 2010;8(4):373–378. (Chinese) Available at: https://www.cnki.net/KCMS/detail/detail.aspx?dbcode=CJFD&dbname=CJFD2010&filename=XBZX201004019&uniplatform=OVERSEA&v=vXTw9c59g8fDLj-hJSJTp9c-fAXOpK_O79J6L0r6Jhz0b-qQ5WuQ6YmAmghQaszp
97. Liu YQ, Liu H, Han PL, Zhou CY, Cui QT. Protective effect of bilobalide on myocardial ischemia/reperfusion injury of rats via anti-inflammation and anti-oxidation. *Chin J Pharmacol Toxicol.* 2019;33(04):241–249. (Chinese) Available at: https://www.cnki.net/KCMS/detail/detail.aspx?dbcode=CJFD&dbname=CJFDLAST2019&filename=YLBS201904001&uniplatform=OVERSEA&v=4LYvE3nkWKPpMqPAuxSjclddOHHM4B1frfSSH0Uv3dd4kT0wzleXzI0BhebOxf7y
98. Lyu M, Cui Y, Zhao T, et al. Tnfrsf12a-Mediated Atherosclerosis Signaling and Inflammatory Response as a Common Protection Mechanism of Shuxuening Injection Against Both Myocardial and Cerebral Ischemia-Reperfusion Injuries. *Front Pharmacol.* 2018;9:312. Available at: http://doi.org/10.3389/fphar.2018.00312
99. Wang R, Wang M, Zhou J, et al. Shuxuening injection protects against myocardial ischemia-reperfusion injury through reducing OS, inflammation and thrombosis. *Ann Transl Med.* 2019;7(20):562–562. Available at: http://doi.org/10.21037/atm.2019.09.40
100. Xiao G, Lyu M, Wang Y, et al. Ginkgo Flavonol Glycosides or Ginkgolides Tend to Differentially Protect Myocardial or Cerebral Ischemia–Reperfusion Injury via Regulation of TWEAK-Fn14 Signaling in Heart and Brain. *Front Pharmacol.* 2019;10:735. Available at: http://doi.org/10.3389/fphar.2019.00735
101. Zhu PC, Tong Q, Zhuang Z, et al. Ginkgolide B for Myocardial Ischemia/Reperfusion Injury: A Preclinical Systematic Review and Meta-Analysis. *Front Physiol.* 2019;10:1292. Available at: http://doi.org/10.3389/fphys.2019.01292
102. Hao Y, Sun Y, Xu C, et al. Improvement of Contractile Function in Isolated Cardiomyocytes From Ischemia-Reperfusion Rats by Ginkgolide B Pretreatment. *J Cardiovasc Pharmacol.* 2009;54(1):3–9. Available at: http://doi.org/10.1097/FJC.0b013e3181a91410
103. Hao YL, Yang Y, Wu JX, et al. Improvement of contractile function of isolated hearts with ischemia-reperfusion injury of aged rats by ginkgolide B post-treatment. *Chin J New Drugs.* 2016;25(23):2707–2713. (Chinese) Available at: https://www.cnki.net/KCMS/detail/detail.aspx?dbcode=CJFD&dbname=CJFDLAST2017&filename=ZXYZ201623013&uniplatform=OVERSEA&v=RCpzyYUIyHmA0fgJ9TkebxywXhEhVYXK17L1nCYGbPQIUCVRI7Nd2S4sBdgO1pRy
104. Liu J, Wu P, Xu Z, Zhang J, Liu J, Yang Z. Ginkgolide B inhibits hydrogen peroxide-induced apoptosis and attenuates cytotoxicity via activating the PI3K/Akt/mTOR signaling pathway in H9c2 cells. *Mol Med Rep.* 2020;22(1):310–316. Available at: http://doi.org/10.3892/mmr.2020.11099
105. Pei HX, Hua R, Guan CX, Fang X. Ginkgolide B Reduces the Degradation of Membrane Phospholipids to Prevent Ischemia/Reperfusion Myocardial Injury in Rats. *Pharmacology.* 2015;96(5–6):233–239. Available at: http://doi.org/10.1159/000438945
106. Zhang R, Xu L, Zhang D, et al. Cardioprotection of Ginkgolide B on Myocardial Ischemia/Reperfusion-Induced Inflammatory Injury via Regulation of A20-NF-κB Pathway. *Front Immunol.* 2018;9:2844. Available at: http://doi.org/10.3389/fimmu.2018.02844
107. Liebgott T, Miollan M, Berchadsky Y, Drieu K, Culcasi M, Pietri S. Complementary cardioprotective effects of flavonoid metabolites and terpenoid constituents of Ginkgo biloba extract (EGb 761) during ischemia and reperfusion. *Basic Res Cardiol.* 2000;95(5):368–377. Available at: http://doi.org/10.1007/s003950070035
108. Shen J, Lee W, Gu Y, Tong Y, Fung PC, Tong L. Ginkgo biloba extract (EGb761) inhibits mitochondria-dependent caspase pathway and prevents apoptosis in hypoxia-reoxygenated cardiomyocytes. *Chin Med.* 2011;6(1):8. Available at: http://doi.org/10.1186/1749-8546-6-8
109. Tang Y, Zhou G, Yao L, et al. Protective effect of Ginkgo bilobaleaves extract, EGb761, on myocardium injury in ischemia reperfusion ratsviaregulation of TLR-4/NF-κB signaling pathway. *Oncotarget.* 2017;8(49):86671–86680. Available at: http://doi.org/10.18632/oncotarget.21372
110. Chen XJ, Ren SM, Dong JZ, Qiu CG, Chen YW, Tao HL. Ginkgo biloba extract-761 protects myocardium by regulating Akt/Nrf2 signal pathway. *Drug Des Devel Ther.* 2019;13:647–655. Available at: http://doi.org/10.2147/DDDT.S191537
111. Zhang C, Wang DF, Zhang Z, Han D, Yang K. EGb 761 Protects Cardiac Microvascular Endothelial Cells against Hypoxia/Reoxygenation Injury and Exerts Inhibitory Effect on the ATM Pathway. *J Microbiol Biotechnol.* 2017;27(3):584–590. Available at: http://doi.org/10.4014/jmb.1611.11024
112. Ran K, Yang DL, Chang YT, et al. Ginkgo biloba extract postconditioning reduces myocardial ischemia reperfusion injury. *Genet Mol Res.* 2014;13(2):2703–2708. Available at: http://doi.org/10.4238/2014.April.8.14
113. Shen J, Wang J, Zhao B, Hou J, Gao T, Xin W. Effects of EGb 761 on nitric oxide and oxygen free radicals, myocardial damage and arrhythmia in ischemia-reperfusion injury in vivo. *Biochim Biophys Acta.* 1998;1406(3):228–236. Available at: http://doi.org/10.1016/S0925-4439(98)00007-6
114. Hao YL, Yang Y, Wu JX, et al. Improvement of contractile function of isolated hearts with ischemia-reperfusion injury of aged rats by ginkgolide B post-treatment. *Chin J New Drugs.* 2016;25(23):2707–2713. (Chinese) Available at: https://www.cnki.net/KCMS/detail/detail.aspx?dbcode=CJFD&dbname=CJFDLAST2017&filename=ZXYZ201623013&uniplatform=OVERSEA&v=RCpzyYUIyHmA0fgJ9TkebxywXhEhVYXK17L1nCYGbPQIUCVRI7Nd2Xsz5HbeeBi_
115. Pietri S, Maurelli E, Drieu K, Culcasi M. Cardioprotective and Anti-oxidant Effects of the Terpenoid Constituents ofGinkgo bilobaExtract (EGb 761). *J Mol Cell Cardiol.* 1997;29(2):733–742. Available at: http://doi.org/10.1006/jmcc.1996.0316
116. Li T, Zhang Y, Tian J, Yang L, Wang J. Ginkgo biloba Pretreatment Attenuates Myocardial Ischemia-Reperfusion Injury via mitoBKCa. *Am J Chin Med.* 2019;47(05):1057–1073. Available at: http://doi.org/10.1142/S0192415X1950054X
117. Zhang R, Han D, Li Z, et al. Ginkgolide C Alleviates Myocardial Ischemia/Reperfusion-Induced Inflammatory Injury via Inhibition of CD40-NF-κB Pathway. *Front Pharmacol.* 2018;9:109. Available at: http://doi.org/10.3389/fphar.2018.00109
118. Zhou X, Wang HY, Wu B, et al. Ginkgolide K attenuates neuronal injury after ischemic stroke by inhibiting mitochondrial fission and GSK-3β-dependent increases in mitochondrial membrane permeability. *Oncotarget.* 2017;8(27):44682–44693. Available at: http://doi.org/10.18632/oncotarget.17967
119. Barrett PM, Komatireddy R, Haaser S, et al. Comparison of 24-hour Holter monitoring with 14-day novel adhesive patch electrocardiographic monitoring. *Am J Med.* 2014;127(1):95.e11–95.e17. Available at: http://doi.org/10.1016/j.amjmed.2013.10.003

120. Hammerer-Lercher A, Namdar M, Vuilleumier N. Emerging biomarkers for cardiac arrhythmias. *Clin Biochem.* 2020;75:1–6. Available at: http://doi.org/10.1016/j.clinbiochem.2019.11.012
121. Wang X, Zhang Z, Liu A. Effect of GBE50 on experimental arrhythmias. *China J Chin Mater Med.* 2010;35(2):199–203. (Chinese) Available at: https://www.cnki.net/KCMS/detail/detail.aspx?dbcode=CJFD&dbname=CJFD2010&filename=ZGZY201002023&uniplatform=OVERSEA&v=Sa11XfkwukjoldBaOTveTHfLA5znhQbCR9kh6dGzBLznipdjz1IWE61hGW36GzOD
122. Zhao X, Yao H, Yin HL, et al. Ginkgo biloba Extract and Ginkgolide Antiarrhythmic Potential by Targeting hERG and ICa-L Channel. *J Pharmacol Sci.* 2013;123(4):318–327. Available at: http://doi.org/10.1254/jphs.13118FP
123. Haines DD, Bak I, Ferdinandy P, et al. Cardioprotective Effects of the Calcineurin Inhibitor FK506 and the PAF Receptor Antagonist and Free Radical Scavenger, EGb 761, in Isolated Ischemic/Reperfused Rat Hearts. *J Cardiovasc Pharmacol.* 2000;35(1):37–44. Available at: http://doi.org/10.1097/00005344-200001000-00005
124. Chen H, Chen Y, Yang J, Wu P, Wang X, Huang C. Effect of Ginkgo biloba extract on pacemaker channels encoded by HCN gene. *Herz.* 2020;46(3):255–261. Available at: http://doi.org/10.1007/s00059-020-04933-z
125. Chai LN, Du R, Zhang YY. Effects and Mechnism of Ginkgolide B on Myocardial Arrhythmia Induced by Myocardial Ischemia - reperfusion. *JETCM.* 2018;27(4):619–621+636. (Chinese) Available at: http://doi.org/10.3969/j.issn.1004-745X.2018.04.016
126. Koltai M, Tosaki A, Hosford D, Braquet P. Ginkgolide B protects isolated hearts against arrhythmias induced by ischemia but not reperfusion. *Eur J Pharmacol.* 1989;164(2):293–302. Available at: http://doi.org/10.1016/0014-2999(89)90470-6
127. Cianfrocca Cinzia, Pelliccia Francesco, Auriti Antonio, Santini Massimo. Ginkgo biloba-induced frequent ventricular arrhythmia.. *Ital Heart J.* 2002;3(11):689–691. Available at: https://pubmed.ncbi.nlm.nih.gov/12506530/
128. Pocock SJ, Wang D, Pfeffer MA, et al. Predictors of mortality and morbidity in patients with chronic heart failure. *Eur Heart J.* 2005;27(1):65–75. Available at: http://doi.org/10.1093/eurheartj/ehi555
129. Di Palo KE, Barone NJ. Hypertension and Heart Failure. *Heart Failure Clinics.* 2020;16(1):99–106. Available at: http://doi.org/10.1016/j.hfc.2019.09.001
130. Pagliaro BR, Cannata F, Stefanini GG, Bolognese L. Myocardial ischemia and coronary disease in heart failure. *Heart Fail Rev.* 2019;25(1):53–65. Available at: http://doi.org/10.1007/s10741-019-09831-z
131. Wang Y, Li Y, Zhang W, Yuan Z, Lv S, Zhang J. NLRP3 Inflammasome: a Novel Insight into Heart Failure. *J Cardiovasc Transl Res.* 2022;16(1):166–176. Available at: http://doi.org/10.1007/s12265-022-10286-1
132. van der Pol A, van Gilst WH, Voors AA, van der Meer P. Treating OS in heart failure: past, present and future. *European J of Heart Fail.* 2018;21(4):425–435. Available at: http://doi.org/10.1002/ejhf.1320
133. Aimo A, Castiglione V, Borrelli C, et al. OS and inflammation in the evolution of heart failure: From pathophysiology to therapeutic strategies. *Eur J Prev Cardiolog.* 2019;27(5):494–510. Available at: http://doi.org/10.1177/2047487319870344
134. Aktaa S, Batra G, Cleland JGF, et al. Data standards for heart failure: the European Unified Registries for Heart Care Evaluation and Randomized Trials (EuroHeart). *Eur Heart J.* 2022;43(23):2185–2195. Available at: http://doi.org/10.1093/eurheartj/ehac151
135. Strassheim D, Dempsey EC, Gerasimovskaya E, Stenmark K, Karoor V. Role of Inflammatory Cell Subtypes in Heart Failure. *J Immunol Res.* 2019;2019:2164017. Available at: http://doi.org/10.1155/2019/2164017
136. Shirazi LF, Bissett J, Romeo F, Mehta JL. Role of Inflammation in Heart Failure. *Curr Atheroscler Rep.* 2017;19(6):27. Available at: http://doi.org/10.1007/s11883-017-0660-3
137. Li Y, Xu C, Wang H. Systems pharmacology reveals the multi-level synergetic mechanism of action of Ginkgo biloba L. leaves for cardiomyopathy treatment. *J Ethnopharmacol.* 2021;264:113279. Available at: http://doi.org/10.1016/j.jep.2020.113279
138. Kim YA, Cho H, Lee N, et al. Doxorubicin-induced heart failure in cancer patients: A cohort study based on the Korean National Health Insurance Database. *Cancer Med.* 2018;7(12):6084–6092. Available at: http://doi.org/10.1002/cam4.1886
139. Xu Z, Wu W, Lan T, Zhang X. Protective effects of extract of Ginkgo biloba on adriamycin-induced heart failure and its mechanism: role of ghrelin peptide. *Zhongguo Zhong Yao Za Zhi.* 2009;34(21):2786–2789. Available at: https://pubmed.ncbi.nlm.nih.gov/20209916/
140. Zhang Z, Song Y, Zhang X, et al. Optimized new Shengmai powder ameliorates myocardial fibrosis in rats with heart failure by inhibition of the MAPK signaling pathway. *J Ethnopharmacol.* 2024;319:117210. Available at: http://doi.org/10.1016/j.jep.2023.117210
141. Bakhshi H, Michelhaugh SA, Bruce SA, et al. Association between proteomic biomarkers and myocardial fibrosis measured by MRI: the multi-ethnic study of atherosclerosis. *EBioMedicine.* 2023;90:104490. Available at: http://doi.org/10.1016/j.ebiom.2023.104490
142. Tan X, Xian W, Chen Y, et al. Exploring the therapeutic mechanism of quercetin for heart failure based on network pharmacology and molecular docking. *Nan Fang Yi Ke Da Xue Xue Bao.* 2021;41(8):1198–1206. (Chinese) Available at: http://doi.org/10.12122/j.issn.1673-4254.2021.08.11
143. Warbrick I, Rabkin SW. Hypoxia-inducible factor 1-alpha (HIF-1α) as a factor mediating the relationship between obesity and heart failure with preserved ejection fraction. *Obes Rev.* 2019;20(5):701–712. Available at: http://doi.org/10.1111/obr.12828
144. Liang T, Wei C, Lu S, et al. Ginaton injection alleviates cisplatin-induced renal interstitial fibrosis in rats via inhibition of apoptosis through regulation of the p38MAPK/TGF-β1 and p38MAPK/HIF-1α pathways. *Biomed Rep.* 2021;14(4):38. Available at: http://doi.org/10.3892/br.2021.1414
145. Wang W, Ma K, Liu J, Li F. Ginkgo biloba extract may alleviate viral myocarditis by suppression of S100A4 and MMP-3. *J Med Virol.* 2019;91(12):2083–2092. Available at: http://doi.org/10.1002/jmv.25558
146. Selim AM, Sarswat N, Kelesidis I, Iqbal M, Chandra R, Zolty R. Plasma Serotonin in Heart Failure: Possible Marker and Potential Treatment Target. *Heart Lung Circ.* 2017;26(5):442–449. Available at: http://doi.org/10.1016/j.hlc.2016.08.003
147. Liu MY, Zhang LJ. Role of Ginkgo biloba extract in regulating 5-hydroxytrytamine and its receptor in heart failure mice. *Zhonghua Yi Xue Za Zhi.* 2018;98(25):2024–2029. (Chinese) Available at: http://doi.org/10.3760/cma.j.issn.0376-2491.2018.25.012
148. Zhang L, Liu J, Ge Y, Liu M. Ginkgo biloba Extract Reduces Hippocampus Inflammatory Responses, Improves Cardiac Functions And Depressive Behaviors In A Heart Failure Mouse Model. *Neuropsychiatr Dis Treat.* 2019;15:3041–3050. Available at: http://doi.org/10.2147/NDT.S229296

149. Ahmed Z, Tang WHW. Pharmacologic Strategies to Target OS in Heart Failure. *Curr Heart Fail Rep.* 2012;9(1):14–22. Available at: http://doi.org/10.1007/s11897-011-0081-5
150. Wu X, Huang J, Tang J, et al. Isoginkgetin, a bioactive constituent from Ginkgo Biloba, protects against obesity-induced cardiomyopathy via enhancing Nrf2/ARE signaling. *Redox Biology*. 2022;57:102485. Available at: http://doi.org/10.1016/j.redox.2022.102485
151. Monserrat-Mesquida M, Quetglas-Llabrés M, Bouzas C, et al. Peripheral Blood Mononuclear Cells OS and Plasma Inflammatory Biomarkers in Adults with Normal Weight, Overweight and Obesity. *Antioxidants* (*Basel*). 2021;10(5):813. Available at: http://doi.org/10.3390/antiox10050813
152. Sharma A, Parikh M, Shah H, Gandhi T. Modulation of Nrf2 by quercetin in doxorubicin-treated rats. *Heliyon.* 2020;6(4):e03803. Available at: http://doi.org/10.1016/j.heliyon.2020.e03803
153. El-Boghdady, N. A. Increased cardiac endothelin-1 and nitric oxide in adriamycin-induced acute cardiotoxicity: protective effect of Ginkgo biloba extract. *Indian J Biochem Biophys.* 2013;50(3):202–209. Available at: https://pubmed.ncbi.nlm.nih.gov/23898483/
154. Zhang H, Li Y-J, Yang R. Tissue Doppler imaging observation on effect of long-term use of gingko biloba tablet on left ventricular function in patients with chronic heart failure. *Zhongguo Zhong Xi Yi Jie He Za Zhi.* 2010;30(5):478–481. Available at: https://pubmed.ncbi.nlm.nih.gov/20681276/
155. Kondratiuk VE, Synytsia YP. Effect of quercetin on the echocardiographic parameters of left ventricular diastolic function in patients with gout and essential hypertension. *Wiad Lek*. 2018;71(8):1554–1559. Available at: https://pubmed.ncbi.nlm.nih.gov/30684340/
156. Chang X, Zhang T, Wang J, et al. SIRT5-Related Desuccinylation Modification Contributes to Quercetin-Induced Protection against Heart Failure and High-Glucose-Prompted Cardiomyocytes Injured through Regulation of Mitochondrial Quality Surveillance. *Oxid Med Cell Longev*. 2021;2021:5876841. Available at: http://doi.org/10.1155/2021/5876841
157. Zhuang L, Zong X, Yang Q, Fan Q, Tao R. Interleukin-34-NF- κ B signaling aggravates myocardial ischemic/reperfusion injury by facilitating macrophage recruitment and polarization. *EBioMedicine.* 2023;95:104744. Available at: http://doi.org/10.1016/j.ebiom.2023.104744
158. Rong Y, Geng Z, Lau BH . Ginkgo biloba attenuates OS in macrophages and endothelial cells. *Free Radical Biol Med.* 1996;20(1):121–127. Available at: http://doi.org/10.1016/0891-5849(95)02016-0
159. Du Y, Han J, Zhang H, Xu J, Jiang L, Ge W. Kaempferol Prevents Against Ang II-induced Cardiac Remodeling Through Attenuating Ang II-induced Inflammation and OS. *J Cardiovasc Pharmacol.* 2019;74(4):326–335. Available at: http://doi.org/10.1097/FJC.0000000000000713
160. Naidu MU, Kumar KV, Mohan IK, Sundaram C, Singh S. Protective effect of Gingko biloba extract against doxorubicin-induced cardiotoxicity in mice. *Indian J Exp Biol.* 2002;40(8):894–900. Available at: https://pubmed.ncbi.nlm.nih.gov/12597018/
161. Sun X, Zhu Y, Li F, Li M, Wan G. Cardioprotective Mechanism and Active Compounds of Folium Ginkgo on Adriamycin-Induced Cardiotoxicity: A Network Pharmacology Study. *Comput Math Methods Med.* 2022;2022:4338260. Available at: http://doi.org/10.1155/2022/4338260
162. Chen Z, Sun J, Chen H, et al. Comparative pharmacokinetics and bioavailability studies of quercetin, kaempferol and isorhamnetin after oral administration of Ginkgo biloba extracts, Ginkgo biloba extract phospholipid complexes and Ginkgo biloba extract solid dispersions in rats. *Fitoterapia.* 2010;81(8):1045–1052. Available at: http://doi.org/10.1016/j.fitote.2010.06.028
163. Xu Y, Tang C, Tan S, Duan J, Tian H, Yang Y. Cardioprotective effect of isorhamnetin against myocardial ischemia reperfusion (I/R) injury in isolated rat heart through attenuation of apoptosis. *J Cell Mol Med.* 2020;24(11):6253–6262. Available at: http://doi.org/10.1111/jcmm.15267
164. Sun J, Sun G, Meng X, et al. Isorhamnetin protects against doxorubicin-induced cardiotoxicity in vivo and in vitro. *PLoS One.* 2013;8(5):e64526. Available at: http://doi.org/10.1371/journal.pone.0064526
165. Li Y, Xu C, Wang H, et al. Systems pharmacology reveals the multi-level synergetic mechanism of action of Ginkgo biloba L. leaves for cardiomyopathy treatment. *J Ethnopharmacol.* 2021;264:113279. Available at: http://doi.org/10.1016/j.jep.2020.113279
166. Liu TJ, Yeh YC, Ting CT, et al. Ginkgo biloba extract 761 reduces doxorubicin-induced apoptotic damage in rat hearts and neonatal cardiomyocytes. *Cardiovasc Res.* 2008;80(2):227–235. Available at: http://doi.org/10.1093/cvr/cvn192
167. Boghdady NAE. Antioxidant and antiapoptotic effects of proanthocyanidin and ginkgo biloba extract against doxorubicin-induced cardiac injury in rats. *Cell Biochem Funct.* 2012;31(4):344–351. Available at: http://doi.org/10.1002/cbf.2907
168. Yi SY, Nan KJ, Chen SJ. Effect of extract of Ginkgo biloba on doxorubicin-associated cardiotoxicity in patients with breast cancer. *Zhongguo Zhong Xi Yi Jie He Za Zhi.* 2008;28(1):68–70. Available at: https://pubmed.ncbi.nlm.nih.gov/18418975/
169. El-Boghdady, N. A. Increased cardiac endothelin-1 and nitric oxide in adriamycin-induced acute cardiotoxicity: protective effect of Ginkgo biloba extract. *Indian J Biochem Biophys.* 2013;50(3):202–209. Available at: https://pubmed.ncbi.nlm.nih.gov/23898483/
170. Gao J, Chen T, Zhao D, Zheng J, Liu Z. Ginkgolide B Exerts Cardioprotective Properties against Doxorubicin-Induced Cardiotoxicity by Regulating Reactive Oxygen Species, Akt and Calcium Signaling Pathways In Vitro and In Vivo. *PLoS One.* 2016;11(12):e0168219. Available at: http://doi.org/10.1371/journal.pone.0168219
171. Jasim ST, Al-Kuraishy HM, Al-Gareeb AI. Gingko Biloba protects cardiomyocytes against acute doxorubicin induced cardiotoxicity by suppressing OS. *J Pak Med Assoc.* 2019;69(Suppl 3)(8):S103–S107. Available at: https://pubmed.ncbi.nlm.nih.gov/31603888/
172. Wang Y, Zhao R, Wu C, et al. Activation of the sirtuin silent information regulator 1 pathway inhibits pathological myocardial remodeling. *Front Pharmacol.* 2023;14:1111320. Available at: http://doi.org/10.3389/fphar.2023.1111320
173. Jiang Q, Lu M, Li J, Zhu Z. Ginkgolide B Protects Cardiomyocytes from Angiotensin II-Induced Hypertrophy via Regulation of Autophagy through SIRT1-FoxO1. *Cardiovasc Ther.* 2021;2021:5554569. Available at: http://doi.org/10.1155/2021/5554569
174. Yan W, Xuan C, Xuan L, Xu R, Wang J. BN52021 protects rat cardiomyocyte from doxorubicin induced cardiotoxicity. *Int J Clin Exp Pathol.* 2015;8(2):1719–1724. Available at: https://pubmed.ncbi.nlm.nih.gov/25973059/