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Exploring the Pharmacology of *Ginkgo biloba*: A Solution for Cardiovascular Diseases

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ABSTRACT

Cardiovascular diseases are a leading cause of global mortality, necessitating the exploration of safe and effective treatments. *Ginkgo biloba*, an ancient medicinal plant, has gained attention for its potential in managing cardiovascular health. This review explores the pharmacological mechanisms of *Ginkgo biloba*, focusing on its cardiovascular benefits. This review aims to understand the pharmacological mechanisms of *Ginkgo biloba* in addressing cardiovascular diseases. The method used in this review was a systematic review conducted through the PRISMA guidelines. *Ginkgo biloba* contains bioactive compounds, including flavonoids, terpenoids, and polysaccharides, that exhibit anti-diabetic, anti-inflammatory, anti-fatty liver hemorrhagic syndrome, anti-oxidant, anti-depressant, and anti-cancer. In conclusion, *Ginkgo biloba* offers a promising therapeutic solution for cardiovascular desease.

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1. INTRODUCTION

Ginkgo biloba is one of the herbal plants that has been used in traditional medicine for thousands of years, especially in Asia. This plant is known for its ability to improve blood circulation and provide benefits for cardiovascular health. *Ginkgo biloba* can inhibit and induce metabolic enzymes and transporters, indicating the possibility of interactions that may affect the effectiveness or safety of other medications for certain conditions when used simultaneously [1]. Various modern studies show that *Ginkgo biloba* extract can help improve blood flow, reduce inflammation, and protect heart cells from damage due to oxidative stress. *Ginkgo biloba* can enhance heart perfusion and reduce the risk of coronary artery disease by inhibiting platelet aggregation and increasing nitric oxide (NO) production in the body [2].

Heart disease remains one of the leading causes of death worldwide, making it crucial to explore effective and safe therapies. In this context, *Ginkgo biloba* emerges as a promising alternative. *Ginkgo biloba* extract not only improves vascular function but also has protective effects against heart dysfunction induced by stress factors, such as hypertension [3]. By understanding the mechanisms of *Ginkgo biloba*, we can better appreciate its therapeutic potential in the management of cardiovascular diseases.

2. METHOD

This research method was conducted through a systematic search of the PubMed and Google Scholar databases. The keywords used in the search were "Pharmacological properties of *Ginkgo biloba*," "Mechanisms of *Ginkgo biloba* in cardiovascular diseases," and "*Ginkgo biloba*."

The inclusion criteria were research articles discussing the activity of *Ginkgo biloba* in improving blood circulation and addressing heart disease.

A total of 121 articles were initially identified, followed by a selection process involving accessible articles with full text, excluding review articles. Data collection for this analysis was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, as illustrated in Figure 1. The studies included in this review primarily focus on the pharmacological properties of *Ginkgo biloba* and its mechanisms in supporting cardiovascular health. The findings from these studies will be summarized in Table 1, presenting the key results from each relevant study and explaining the primary effects of *Ginkgo biloba* on heart and vascular health.

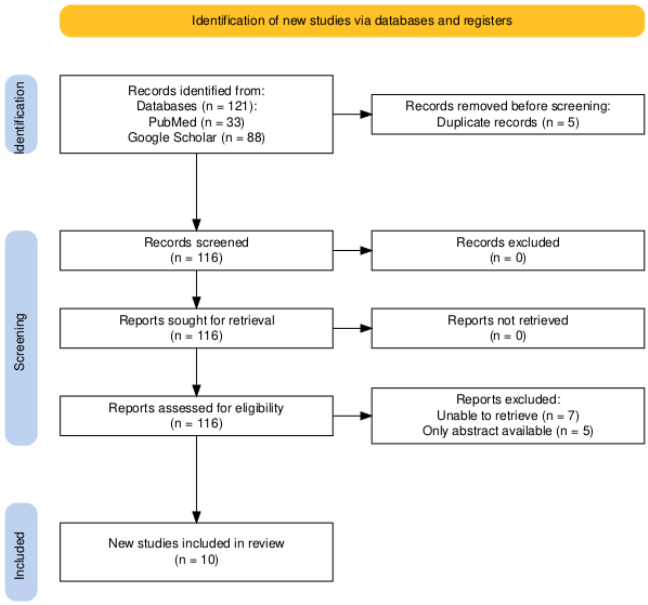

Figure 1. PRISMA Flowchart for the Review Methodology

3. RESULTS AND DISCUSSION

Below is a table containing the article titles, research findings, and publication years arranged in ascending order:

Table 1. Identification of *Ginkgo biloba*

Year	Article Title	Highlight
2019	[4]	*Ginkgo biloba* extract (GBE) acts through the mTOR and NF-κB pathways to reduce atherosclerosis by decreasing plaque size and lipid deposition while suppressing the expression of CD68, MMP2, and MMP9. Both GBE and rapamycin inhibit the upregulation of mTOR and SQSTM1/p62 in the aortas of diabetic rats, demonstrating protective effects in this condition. Additionally, GBE reduces markers of endoplasmic reticulum stress (ERS), serum lipid levels, blood glucose, and inflammatory cytokines in diabetic rats.
2021	[5]	*Ginkgo biloba* extract 80 (GBE80) provides protective benefits against myocardial injury resulting from acute myocardial infarction (AMI) in aged rats. By activating the AKT/GSK3β/β-catenin signaling pathway, GBE80 mitigates oxidative stress and prevents apoptosis in cardiac muscle cells. After seven days of GBE80 treatment, a notable decrease in infarct size and protection from H2O2-induced toxicity were observed, with no adverse effects on healthy cardiac cells.
2022	[6]	*Ginkgo biloba* reduces urea, glucose, FT3, and TSH levels while increasing platelet counts in rats experiencing ischemic stroke. However, it also causes negative changes in thyroid function and increases triglyceride levels in control groups.
2022	[7]	*Ginkgo biloba* leaf extract (GBE) protects the heart and brain in rats fed a high-fat diet and exposed to chronic stress by reducing inflammation, oxidative stress, and depressive behaviors. GBE also increases helper T lymphocytes and anti-inflammatory cytokines such as IL-37 and IL-38. This protection occurs primarily through the inhibition of the NF-κB pathway, reducing inflammatory proteins in the brain and heart.

2022	[8]	*Ginkgo biloba provides cardioprotective benefits in rats under hypoxic and hypothyroid stress by lowering blood glucose, reducing oxidative stress, and suppressing inflammatory mediators in the serum and aorta. While it does not alter thyroid hormone levels (T3 and T4), it helps stabilize TSH levels and improves vascular function. This effect is achieved through the regulation of the endothelin-1/nitric oxide signaling pathways, making Ginkgo biloba a potential vasodilator for conditions of hypoxic hypothyroidism.*
2023	[9]	*Ginkgo biloba* exerts protective effects by suppressing the inflammatory and apoptotic pathways induced by cyclosporine A. The extract enhances the activity of antioxidant enzymes such as catalase, superoxide dismutase, and glutathione, while reducing biomarkers of oxidative damage and inflammation like MDA, IL-6, TNF-α, and caspase-3. Additionally, *Ginkgo biloba* improves vascular tone and regulates thebalance between vasoconstriction and vasodilation by influencing the nitric oxide and endothelin-I signaling pathways, which also aids in normalizing Na-K ATPase activity, contributing to enhanced structural and histological integrity.
2023	[10]	*Ginkgo biloba* Dropping Pills (GBDP) significantly reduce the frequency of angina attacks and improve depressive symptoms in patients, thus enhancing their overall quality of life. The pharmacological effects of GBDP involve the mechanism of nitric oxide release from the endothelium, which helps improve coronary blood flow. Additionally, GBDP also provides antidepressant effects that support the patients' mental well-being.
2023	[11]	Alkaline Phosphatase (ALP), Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Lactic Dehydrogenase (LDH), and Creatine Kinase-MB (CK-MB) are important indicators related to heart damage, especially in the case of myocardial infarction. Both water-based and alcohol-based *Ginkgo biloba* extracts show good inhibitory effects on the LDH and CK-MB enzymes. This suggests that *Ginkgo biloba* can help reduce heart damage by lowering the activity of these enzymes, which are elevated due to heart injury.
2023	[12]	*Ginkgo biloba* extract can improve blood biochemical indicators in laying hens experiencing fatigue syndrome due to a high-fat diet. Additionally, this extract enhances antioxidant activity in the liver and serum by increasing levels of glutathione, superoxide dismutase, total antioxidant capacity, and glutathione peroxidase, while reducing malondialdehyde. *Ginkgo biloba* extract also lowers the expression of genes associated with lipid synthesis and inflammation, as well as improves the composition of disrupted gut microbiota, particularly by increasing the number of Megasphaera in the cecum. disrupted by a high-fat diet, especially by increasing the number of Megasphaera in the cecum.
2024	[13]	Treatment with *Ginkgo biloba*, both in the form of extract and capsules, significantly reduced serum glucose levels, VLDL, LDL, as well as the enzymes ALP, AST, and ALT. Additionally, this treatment increased HDL, insulin levels, body weight, food intake, and food efficiency. Ginkgo capsules showed the best results in lowering blood sugar levels, followed by a combination of extract and capsules.

3.1. Cardiovascular Diseases

Cardiovascular disease is a term used to describe various disorders that affect the heart and blood vessels. This condition includes coronary artery disease, cerebrovascular disease, hypertension, and peripheral vascular disease. In addition, cardiovascular disease also encompasses other health issues, such as rheumatic heart disease caused by rheumatic infection and congenital heart disease due to structural heart abnormalities present from birth [14].

Cardiovascular disease is the leading cause of death worldwide. In 2004, approximately 17.1 million people died from this disease, with 7.2 million of those deaths attributed to coronary heart disease and 5.7 million to stroke. In Indonesia, cardiovascular diseases account for more than 30% of deaths across all ages, with the breakdown of deaths as follows: 15.4% due to stroke, 6.8% due to hypertension, 5.1% due to coronary heart disease, and 4.6% due to heart disease. Patients with cardiovascular diseases need to manage their quality of life, including physical function, physical roles, pain management, emotional health, and social support [15].

Medications commonly prescribed to patients with cardiovascular diseases include antiplatelet drugs, statins, β-blockers, and renin-angiotensin system inhibitors [16]. In addition, cardiovascular diseases can also be treated with various bioactive compounds from *Ginkgo biloba*. *Ginkgo biloba* can enhance blood circulation, regulate blood lipid levels, and protect against ischemic damage. This makes it a valuable therapeutic option for various cardiovascular conditions [17].

3.2. *Ginkgo biloba*

Ginkgo biloba is an ancient plant native to China [18] and is known for its wide range of health benefits for living organisms, containing various bioactive components that make it a chemically diverse plant. The drying process of *Ginkgo biloba* using infrared methods has been shown to enhance its potent antioxidant activity and increase the bioactive compound content within it [19]. This plant possesses various medicinal and pharmacological properties, including its ability as an anticancer, antidemensia, antidiabetic, antiobesity, antilipidemic, antimicrobial, antioxidant, lipid peroxidation inhibitor, antiplatelet, anti-inflammatory, hepatoprotective, antidepressant, anti-aging, immunomodulatory, antihypertensive, and neuroprotective agent [20, 21, 22].

.*Ginkgo biloba* has become one of the most popular herbal medicines in the world due to its wide range of applications, fast onset of action, reliable efficacy, low toxicity, and easy accessibility. Although *Ginkgo biloba* is known as one of the most popular and classic herbal medicines, its extract has various pharmacological actions depending on its chemical components, including flavonoids, terpenoids, and polysaccharides. Biloba and ginkgolides in *Ginkgo biloba*

extract play a crucial role in maintaining the effectiveness and consistency of the extract due to its unique chemical composition [23]. To analyze these components, High-Performance Liquid Chromatography (HPLC) is commonly used to separate compounds based on their interactions with the column and the mobile phase liquid. Detection is carried out using methods such as Refractive Index Detection (RI), Evaporative Light Scattering Detection (ELSD), or Mass Spectrometry (MS). Various extraction techniques have been developed to enhance the purity and active compound content of *Ginkgo biloba* extract, such as supercritical carbon dioxide extraction and ionic liquid extraction. Synthesis and biosynthesis can also serve as efficient alternatives to produce specific compounds from *Ginkgo biloba* in a more controlled and efficient manner [24].

Ginkgo biloba is widely used in the treatment of cardiovascular diseases due to its definite curative effects, minimal side effects, availability in various forms (liquid or pill), and its safe and practical usage. The most significant risk factor for cardiovascular diseases is regulating glucose levels to slow the progression of diabetes and reduce mortality rates from cardiovascular diseases [25]. It is established that administering *Ginkgo biloba* in capsule form at a dosage of 4.68 mg per day can lead to a reduction in blood glucose levels [13].

3.3. Pharmacological Properties and Mechanisms of *Ginkgo biloba* in Managing Cardiovascular Diseases

Below are the pharmacological properties and mechanisms of *Ginkgo biloba* in managing cardiovascular diseases

3.3.1. Anti-Diabetic Properties

Diabetes mellitus is one of the leading causes of cardiovascular disease [26]. Approximately 50% of diabetic patients are at risk for non-fatal cardiovascular events [5]. One approach to address this is by modulating the pathology of Endoplasmic Reticulum Stress (ER Stress), which can enhance the autophagy process. Autophagy plays a crucial role in cell maintenance by ensuring the removal of damaged components and the recycling of their building blocks [28]. Research conducted on ApoE-/- mice induced with streptozotocin (STZ) showed that *Ginkgo biloba* leaf extract could mitigate atherosclerosis through the mTOR and NF-κB signaling pathways [4].

High glucose levels accelerate the formation of atherosclerotic plaques, characterized by increased plaques in the lumen, lipid accumulation, and intima, as well as a reduction in collagen area within the plaques. This condition also increases the expression of CD68, MMP2, and MMP9 in atherosclerotic plaques and affects the expression of Endoplasmic Reticulum Stress markers such as p-JNK, CHOP, and Caspase-12 [4]. ER Stress caused by high glucose levels can activate NF-κB via the IRE1α and PERK signaling pathways, which promotes macrophage adhesion to the vessel wall and accelerates the atherosclerosis process. This activation also leads to increased inflammatory cytokine production, Reactive Oxygen Species (ROS) formation, and creates a positive feedback loop that exacerbates inflammation by triggering the release of more inflammatory cytokines [4]. *Ginkgo biloba* extract can stabilize atherosclerotic plaques by reducing plaque/lumen area and lipid accumulation in plaques/intima, through the inhibition of SQSTM1/p62 expression in ApoE-/- diabetic mice. This effect is achieved by inhibiting the mTOR and NF-κB signaling pathways, which in turn reduces the expression of Endoplasmic Reticulum Stress markers such as p-JNK, CHOP, and Caspase-12. Additionally, this inhibition also alleviates inflammation by lowering the levels of cytokines such as IL-1, IL-6, TNF-α, and iNOS. Inhibition of SQSTM1/p62 expression indicates autophagy protection, which plays an important role in preventing the development of diabetic atherosclerosis [4].

3.3.2. Anti-Inflammatory Properties

Ginkgo biloba leaf extract demonstrates significant anti-inflammatory effects [40]. This extract is capable of alleviating heart inflammation induced by a High-Fat Diet (HFD) and Chronic Unpredictable Mild Stress (UCMS). It works by suppressing the inflammatory response through the upregulation of peripheral anti-inflammatory cytokines such as IL-37 and IL-38, while simultaneously reducing the expression of pro-inflammatory cytokines like IL-1β in heart tissue, by inhibiting the NF-κB signaling pathway. This inhibition decreases the expression of P-IκB-α and P-P65, thereby reducing the activity of the inflammatory pathway within the tissue. HFD and UCMS can increase oxidative stress, which damages endothelial cells and triggers inflammation. *Ginkgo biloba* extract helps reduce ROS (Reactive Oxygen Species) formation, thereby preventing inflammation in tissues [7].

3.3.3. *Anti-Fatty Liver Hemorrhagic Syndrome (FLHS)*

Ginkgo biloba extract has been shown to reduce fat accumulation in the liver of obese rats. This extract works by lowering the expression of genes involved in the formation of new fats in the body, such as FAS (Fatty Acid Synthase), SREBP-1c (Sterol Regulatory Element-Binding Protein 1c), GPAT (Glycerol-3-Phosphate Acyltransferase), PPARγ (Peroxisome Proliferator-Activated Receptor Gamma), LXRα (Liver X Receptor Alpha), SCD1 (Stearoyl-CoA Desaturase 1), and ChREBP1 (Carbohydrate Response Element Binding Protein 1). *Ginkgo biloba* extract also reduces liver enzyme levels of ALT (Alanine Aminotransferase), AST (Aspartate Aminotransferase), and ALP (Alkaline Phosphatase) to repair liver damage. Additionally, *Ginkgo biloba* extract can regulate the gut microbiota of chickens fed a high-fat diet (HFD) by increasing Megasphaera bacteria, which activate SCFA (Short-Chain Fatty Acids) for lipid metabolism, reduce inflammation, and decrease ROS (Reactive Oxygen Species) formation. Furthermore, GBLP-3 (*Ginkgo biloba* Leaf Polysaccharide-3) and P-GBLP-3 (phosphorylated-GBLP-3) isolated from *Ginkgo biloba* leaves can also inhibit hydroxyl radicals, DPPH radicals, and lipid peroxidation in a dose-dependent manner [30].

3.3.4. *Antioxidant Properties*

Ginkgo biloba can reduce oxidative stress, inflammation, and improve vascular function in hypothyroid rats with oxygen deficiency by modulating the ET-1/NO (Endothelin-1) pathway. In hypothyroid conditions, endothelial function is impaired. In this condition, ET-1 (Endothelin-1) levels increase, disrupting the balance between vasoconstriction and vasodilation, which worsens vascular dysfunction. *Ginkgo biloba* helps to lower ET-1 (Endothelin-1) levels and increase Nitric Oxide (NO) production to restore the balance between vasoconstriction and vasodilation, as well as improve blood flow and vascular function. Nitric oxide (NO) acts as a vasodilator that helps relax blood vessels and increase blood flow [8].

Ginkgo biloba leaf extract contains terpenoids and glycosides that play a role in reducing oxidative stress. The polysaccharides in *Ginkgo biloba* leaves have antioxidant potential in food processing [6]. *Ginkgo biloba* has been shown to reduce urea, glucose, and TSH (Thyroid Stimulating Hormone) levels in ischemic stroke rats after 3 months of administration. The flavonoids in *Ginkgo biloba* are responsible for its antioxidant action and lipid-lowering effects, although there were no significant changes in triglyceride levels in the treated rats. *Ginkgo biloba* also protects β-islet cell function and improves metabolic homeostasis [6]. Additionally, *Ginkgo biloba* has been shown to increase antioxidant enzyme levels such as SOD (Superoxide Dismutase), CAT (Catalase), and GSH (Glutathione), thereby preventing damage from free radicals and reducing malondialdehyde levels, which are indicators of lipid peroxidation [9].

GBE80 (Ginkgo biloba Extract 80) provides direct protection against cardiomyocyte injury induced by H2O2 at a concentration of 0.03%, which causes oxidative stress in these heart cells. A decrease in phosphorylated (p) AKT, pGSK3β, and β-catenin levels occurs when cardiomyocytes are exposed to H2O2, and GBE80 is utilized to activate the AKT/GSK3β/β-catenin signaling pathway in heart cells. In the acute myocardial infarction (AMI) model in elderly rats, GBE80 effectively reduces infarct size and apoptosis in myocardial tissue, thereby protecting the structure. The protective mechanism of GBE80 is associated with the activation of the AKT/GSK3β/β-catenin pathway, which accelerates myocardial tissue recovery, without exhibiting cytotoxic effects on cardiomyocytes at doses between 0–500 µg/ml, making it a potential alternative for clinical AMI treatment using Ginkgo biloba extract [5].

3.3.5. Antidepressant Properties

Patients with coronary heart disease often experience symptoms of depression. *Ginkgo biloba* plays a role in reducing the frequency of angina through vasodilation and enhancing the effects of venlafaxine. Vasodilation occurs through the mechanism of Nitric Oxide (NO), which is derived from the endothelium to increase blood flow [10]. Venlafaxine works by increasing serotonin and norepinephrine in the brain to stabilize mood and reduce symptoms of depression [32].

3.3.6. Anti-Cancer Properties

Ginkgo biloba combats cancer by stimulating the apoptosis of cancer cells, inhibiting cell proliferation, invasion, and migration, as well as exhibiting anti-inflammatory and antioxidant properties [33]. In patients with myocarditis, *Ginkgo biloba* leaf extract works by inhibiting the activity of the enzymes LDH (Lactate Dehydrogenase) and CK-MB (Creatine Kinase-MB) through a non-competitive inhibition mechanism. In this mechanism, the extract's inhibitor does not compete with the substrate for binding to the active site of the enzyme, but instead binds to an allosteric site. This changes the shape of the enzyme, disrupting its function as a catalyst. Water extract has been shown to inhibit both LDH and CK-MB, while alcohol extract only inhibits LDH. This inhibition

significantly reduces enzyme activity, even if substrate concentration increases, because the inhibitor's binding to the enzyme is independent of the amount of substrate. As a result, metabolic activities involving LDH and CK-MB, such as energy production and heart muscle function, can be affected. Inhibition of LDH and CK-MB has the potential to be an effective therapeutic approach for certain medical conditions, such as cancer. However, this inhibition must be used with caution to avoid harmful side effects, such as energy disruption in healthy tissues [28].

4. CONCLUSION

Cardiovascular disease is a leading cause of death worldwide, including in Indonesia, encompassing conditions such as coronary artery disease, stroke, and hypertension. One potential treatment is the use of *Ginkgo biloba* extract, which contains bioactive compounds like flavonoids, terpenoids, and polysaccharides known for their antioxidant, anti-inflammatory, and cardiovascular protective effects. *Ginkgo biloba* has been shown to effectively control blood sugar levels, prevent inflammation, and improve blood vessel function, all of which contribute to reducing the risk of cardiovascular complications. With its proven benefits and safety, *Ginkgo biloba* can serve as an adjunct therapy to support the comprehensive management of cardiovascular disease.

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