International Journal of Pharmacology

ISSN 1811-7775

science alert

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Asian Network for Scientific Information

OPEN ACCESS International Journal of Pharmacology

ISSN 1811-7775
DOI: 10.3923/ijp.2019.1.9

Review Article
Pharmacological Uses of *Ginkgo biloba* Extracts for Cardiovascular Disease and Coronary Heart Diseases

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Abstract

Globally the cardiovascular disease (CVDs) and coronary heart disease (CHD) are main cause of death. *Ginkgo biloba* is one of the oldest plants in the world, originating in China, science is known as the "living fossil". *Ginkgo biloba* leaves extract (GBLE) is a bioactive substance extracted from the *Ginkgo biloba*, the main active ingredients of *Ginkgo* flavonoids and ginkgolide compound, three or four, one of the most important *Ginkgo biloba* leaves extract is widely used as a drug or food additive in more than 130 countries. Thousands of years ago Asian and other region was use the traditional Chinese medicine (TCM), they verified some effective disorders. The medicinal uses of *Ginkgo biloba* have been widely used for various disease including cardiovascular disease and coronary heart disease. The properties of *Ginkgo* are mentioned here for example; improved blood flow, antioxidant, strengthens blood vessels, anti-inflammatory, relaxes the lungs, vasodilator and circulatory system tonic. *Ginkgo biloba* leaves extract also appears to have an anti-inflammatory impact that may make it useful in the future for situations like organ transplants and multiple sclerosis. However, due to the multi component of the herb, up to now the molecular mechanisms of action and signaling pathways leading to the therapeutic effects of GBLE remain, still, poorly understood.

Key words: *Ginkgo biloba*, cardiovascular disease, coronary heart disease, flavonoids

Received: October 05, 2017 **Accepted:** November 09, 2018 **Published:** December 15, 2018

Citation: Zhiming Shu, Akhtar Hussain Shar, Mohamed Shahen, He Wang, Mahmoud Alagawany, Mohamed E. Abd El-Hack, Shahmir Ali Kalhoro, Muhammad Rashid and Piar Ali Shar, 2019. Pharmacological uses of *Ginkgo biloba* extracts for cardiovascular disease and coronary heart diseases. Int. J. Pharmacol., 15: 1-9.

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

The cardiovascular disease (CVDs) and coronary heart disease (CHD) are first world's killer disease of human being in current years owing to the striking mortality and morbidity involved, the molecular mechanism is extremely remaining unclear and complex[1]. The uses of shrub *Ginkgo biloba* are also related with living fossils. The shrub *Ginkgo biloba* is a class of that 150 million years ago that researcher find the highest development during the Cretaceous and Jurassic historical period[2]. It was one of the greatest example of alive fossils. *Ginkgo biloba* leave extract is a gymnosperm; therefore, the seed of *Ginkgo biloba* are not cover an ovary wall. *Ginkgo biloba* is widely cultivated in many countries such as Argentina, North America, Asia and Europe[2]. The best source of medicine is seed of *Ginkgo biloba* through Chinese Traditional Medicines (TCM). Now a day's different observation is used for life the threating disease[3]. Currently, the extract of *Ginkgo biloba* in the method are folded shape medicine, the liquids solutions are can be obtained in America and Europe[4]. Cardiovascular and cerebrovascular disease is the main cause of death in the world. Accordingly, the advance approaches of innovative is not only reduce the high cost of prevention during treatment of these ailments but also minimalize the side effects of equivalent alternative and effective drugs is countless significance to health of public[5]. At present, it is mainly treated by Western medicine. In recent years, domestic and foreign researchers show that the GBLE has many advantages, such as multiple links, multiple targets, little adverse reaction and it has a good prospect of application[6]. In this study, the effect and mechanism of GBLE on prevention and treatment of cardiovascular and cerebrovascular diseases in recent years were reviewed to promote the application of GBLE in cardiovascular and cerebrovascular diseases. Although many CVDs are not fatal, they seriously disturb the individual's normal daily life and the related costs on health care systems are enormous[7]. For centuries, GBLE have been widely used in TCM for treating various medical conditions. In recent decades, a commercial standardized GBLE has been marketed as a therapeutic dietary supplement for counteracting a wide range of diseases and has demonstrated its neuroprotective and antioxidant properties, against a variety of cardiovascular and neurological disorders[8-10]. *Ginkgo* can overlap against platelet accumulation and such as individuals taking anticoagulants (blood thinners) or antithrombotic medicines, included aspirin should seek professional guidance. Due to the specific and potent antagonist activity against platelet activating factor (PAF), ginkgolides can improve the blood circulation; treat to thrombosis and illness of blood vessels of the heart and brain[11]. The chemical composition of *Ginkgo* leaves is very complex, so far found more than 170 compounds. *Ginkgo biloba* vinegar is the most active platelet activating factor A antagonist in nature. Currently, with the increased incidence of CVDs, more attention has been drawn to develop herbal drugs from traditional Chinese medicine (TCM), a whole medicinal system with clinical practice over thousands of years[12-17]. Through the synergistic effect of multi-ingredients, multitargets and multipath ways, TCM produces its efficacy in a holistic way with fewer side effects, showing a significant advantage over a single drug treatment, especially in treating chronic complex and multifactorial diseases[18]. A growing body of evidence supported by both experimental and clinical studies has highlighted the beneficial role of GBLEs on cognitive function, different types of cancer and especially the treatment of CVDs[19,20]. It has a strong effect on the cardiovascular system; this study will review the recent progress in the research of the relationship between *Ginkgo biloba* leaves extract and CVDs.

Presently, to uncover the action mechanisms of GBLE for treating CVDs, innovative systems pharmacology approach were performed (Fig. 1). First, the active ingredients of GBLEs with favorable pharmacokinetic properties were screened out

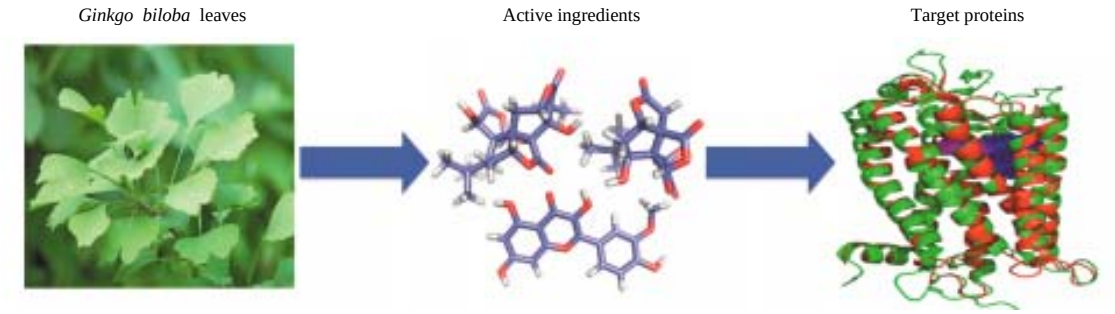
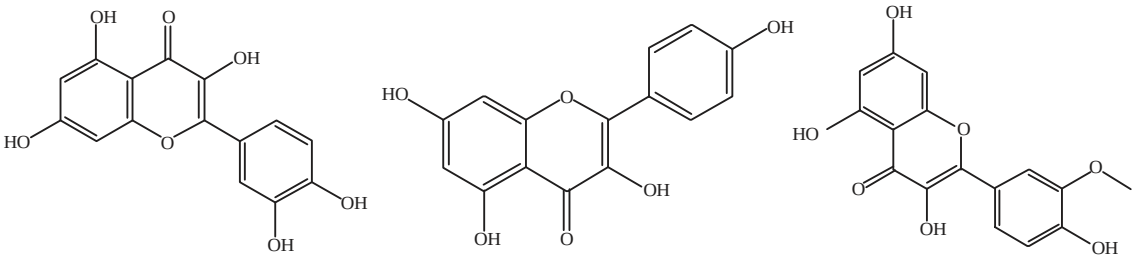
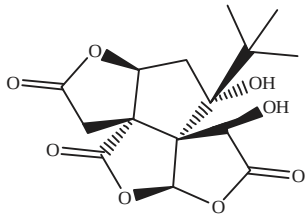
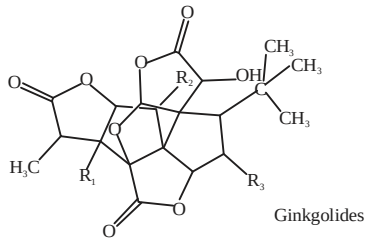


Fig. 1: Chemical ingredients of *Ginkgo biloba* leaves







↵	R1↵	R2↵	R3↵
Ginkgolide A↵	OH↵	H↵	H↵
Ginkgolide B↵	OH↵	OH↵	H↵
Ginkgolide C↵	OH↵	OH↵	OH↵
Ginkgolide J↵	OH↵	H↵	OH↵
Ginkgolide M↵	H↵	OH↵	OH↵

Fig. 2: Structures of quercetin, kaempferol, isorhamnetin, bilobalide and ginkgolides

by a systems-ADME process. Second, multiple targets of these bioactive chemicals were determined and validated by a comprehensive method. Third, through the network analysis, the crucial disease-relevant biological pathways were captured and the multi mechanisms of GBLE were also interpreted. The systemic network was created for determining the interaction of cardiovascular for invention of gene are also subordinate with given phenotypic subsection in the PPI network[21].

Other uses: Other uses of GBLE is often recommended diabetes-related nerve system damage, poor blood circulation, allergies, depression, short-term memory loss, vertigo, headache, tinnitus, atherosclerosis, cochlear deafness, macular degeneration and diabetic retinopathy. One more usefulness for *Ginkgo biloba* is the medication of impotency. This current study gives us a new idea about the CVDs and CHD through the system pharmacological treatment in herbal medicine, it's also normal sighting of patent drug mixture that are the individually subtherapeutic[22].

Chemical ingredients of *Ginkgo biloba* leaves: The chemical ingredients are also checked in the extract of *Ginkgo biloba* leaves. The names and structures of ginkgolide's in GBLE are shown in Fig. 2. The both of bilobalide and ginkgolides are the main ingredients of *Ginkgo biloba* that display all biological and/or pharmacological activities of *Ginkgo biloba*. However, the fundamental mechanism of molecular are also interact with medicinal herbs during treating of such disease are still unclear[5]. The chemical abstracts service name of the isorhamnetin is 4H-1-benzopyran-4-one, trihydroxy-2-(4-hydroxy-3-methoxyphenyl-9CI). Kaempferol is a metabolite of quercetin and isorhamnetin is a metabolite of kaempferol. Commercial GBLE of the *Ginkgo* leaves are enriched water-acetone or water-ethanol of the *Ginkgo* leaves extract and are standardized on their flavonoid content or their tripotential one content[23]. The alkylbenzoic acids and alkylphenol acids actions against the allergic immunotoxin and other unwanted properties are completely remove from the *Ginkgo biloba* leaves extract[24]. The efficiency of *Ginkgo biloba* leaves extract is likely subsidized through the terpene ticlatones (ginkgolide's or bilobalide), glycosides flavonoid, its explanation for quantity and value of ingredient in the *Ginkgo biloba* leaves extract has never been[23]. Considerable of these ingredients produce mental altering effects and memory boosting, which are due to the neurogenesis-promoting

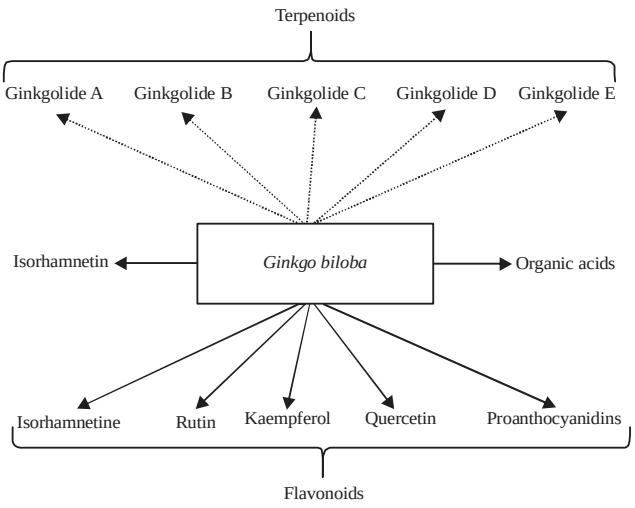


Fig. 3: Chemical constitute of EGB 761

properties and antioxidant of flavanol's of *Ginkgo biloba*[24]. The bioavailability of EGB 761 has been elaborated in the human and rats. Oral administration or injections of acute and subacute doses of EGB 761 in distribution of *Ginkgo* components in distinct tissues and plasma follows linear pharmacokinetics in rat and human[25,26]. It is not only inhibits PLA[27], produces antioxidant and anti-inflammatory effects[28-30], modulates gene expression[31] and promotes memory[32], however also produces multiple effects on the apoptotic pathway and on mitochondrial function and[33,34], through the stabilization of mitochondrial membrane potential are improvement of energy metabolism, upregulation of anti-apoptotic Bcl-2 protein and downregulation of pro-apoptotic Bax protein, suppression of cytochrome C release, decrease of caspase 9, caspase 3 activity after oxidative stress and decrease of apoptotic cell death[33].

Flavonoids: *Ginkgo biloba* flavonoids is low molecular weight compounds, which can be divided into two kinds of the compounds, such as flavonoids and catechins with the 36 compounds (Fig. 3). The quality control of GBLE mainly detected the content of these two flavonoids. Flavonoids is a class of polyphenolic compounds universally existing in the plant kingdom, including flavanol glycosides and aglycones are getting increasing attention for their antioxidant, improved cardiovascular well-being and anticancer activities[35]. Pharmacokinetic studies have shown that many flavonoids are poorly absorbed leading to a low OB[36]. Furthermore, 18 targets are commonly modulated flavonoids and TTLs exhibiting a similar therapeutic mechanism of these two major groups of constituents of GBLE. For examples, such of the compounds are ginkgolide B quercetin are sharing seven protein targets and it has been reported with both compounds can be show their neuroprotective properties by blockage of the early signaling cascades leading to a β toxicity[37,38].

Coronary heart disease: In the absence of myocardial anoxia increased the free oxygen radical, low density lipoprotein, increased susceptibility to C oxidation, decreased antioxidant function, leading to CHD patients with ODLL and MDA were significantly elevated in X Vitamin C Content Apparent descent. As all know, after the ischemia massive production of excitatory amino acids are mainly glutamate study in the microglia activation and an inflammatory response, leading to an increased degree of ischemic damages[39]. Scientists continue to survey the significance of prevention and therapy for stroke patients attributed to GABL. It is supposed that preventing blood coagulate from developing and increasing blood flow to the brain, *Ginkgo biloba* may aid stop strokes from occurring. It is also supposed that the herb prohibits damage to the free radicals of brain cells after a stroke. The main component of GBLE flavonoids could inhibit with lipid peroxidation and oxidative modification of DLL superoxide anion radical scavenging in patients with LDLM and decreased significantly the content of vitamin C increased high significantly to achieve the therapeutic effect of CHD. In this review article, authors mention interpret the fundamental mechanism of important kinds of CHD through the linking of targets, drugs and disease to find the compound-target-disease relationship for restructuring of the biological and expressive networks based on systems pharmacological method[40].

Coronary heart disease: Coronary artery disease is caused by coronary artery atherosclerosis, inflammation or embolism. In recent years, the prevalence of CHD increased year by year seriously endangering the health of patients. The research group using ultrasound, coronary angiography, coronary endothelium-dependent vasodilatation, plasma nitric oxide (NO), endothelin (ET), detection of angina symptoms, ECG and other methods, the EGB 761 study on patients with CHD including the elderly and postmenopausal in women. The GBLE are also increased NO, ET and ET ratio in patients with CHD and the increase of LAD blood flow was significantly correlated with the changes of NO and ET[41]. The total effective rate of the left ventricular systolic and diastolic meaning of the left ventricular expulsion portion[42]. The early diastolic phase and the late diastolic filling ratio were significantly improved[42].

Arrhythmia: Arrhythmia is an important group of diseases in the CVDs, Western medicine in the antiarrhythmic drugs almost all have adverse reactions to arrhythmia and GBLE adverse reactions. The Schlomka was identified three important characteristics of the cardiac arrhythmias such as (location, force and type) and inferred that a mechanically induced coronary vasospasm might be responsible for the various arrhythmias encountered with chest influence[43]. The EGB 761 can increase the barium chloride induced ventricular tachycardia, ventricular tachycardia, ventricular fibrillation, arrest and it has the effect of antiarrhythmic. At the same time, the whole animal GBLE leads to aconitine and ouabain arrhythmia also inhibited GBLE by inhibiting delayed after depolarizations, triggered activity and antiarrhythmic effect.

Diabetic cardiomyopathy: Diabetic cardiomyopathy is caused by diabetic microvascular disease and myocardial metabolic disorders caused by myocardial necrosis. The diabetic cardiomyopathy rats by intraperitoneal injection of GBLE in stratiotes induced the rat left ventricular end diastolic volume, stroke volume and insulin levels were significantly increased, while the left ventricular weight and blood glucose concentrations significantly reduce. This study indicated that GBLE could improve the cardiac function in the diabetic cardiomyopathy rats, the effect of GBLE on the prevention and treatment of cerebrovascular diseases.

Dementia: The arrival of the aging population dementia will bring a heavy burden on society. Therefore, it is a great significance to effectively delay and prevent dementia. The dementia studies have shown that GBLE is safe and effective in the treatment of dementia and can significantly improve the patient's cognitive function and social activities[44]. This reviewed the treatment of patients with mild to moderate dementia in the treatment of EGB[45]. The reviewed the possible mechanisms of GBLE in the treatment of Parkinson's disease, such as reducing monoamine oxidase activity, preventing the damage of nigrostriatal neurons and the toxicity[46]. In addition, the treatment of GBLE with 30 days in the aged rats could increase the number of times of crossing the Morris water maze and reduce the malondialdehyde (malondialdehyde) MDA level, indicating that GBLE improves the cognitive function in aged rats by reducing oxidative damage[47].

Cerebral infarction: Cerebral infarction is a common cerebrovascular disease, how to prevent and cure effectively is an important subject of medical research. At the present, GBLE has been used in the treatment of cerebral infarction and has good effect. The effects of GBLE on acute cerebral infarction in rats treated with thread embolism method were studied[48]. The study showed that GBLE could decrease the apoptosis of brain cells and protect the brain. Some researchers were observed 42 total numbers in the previous study based on the infarct size and neurological score of the 1232 animals[49].

Anti-inflammatory response: The anti-inflammatory response is well known that the pathological basis of cardiovascular and cerebrovascular disease is atherosclerosis modern medical technology has confirmed that the atherosclerosis is an inflammatory reaction in the intima. This review article is also suggested that the systems pharmacology combined the strategy for standard development of drug for composite disease associate[50].

The GBLE can reduce the level of inflammatory factors in acute coronary syndrome patients, such as tumor necrosis factor alpha (tumor necrosis factor-TNF-α), interleukin 6 (IL-6), matrix metalloproteinase 9 and reduce inflammatory reaction of atherosclerosis. Furthermore, some disorders of gastrointestinal may be increase patients risk of cardiovascular disease as well as[50].

The previous study of anti-apoptosis showed that apoptosis was involved in the pathological process of cardiovascular and cerebrovascular diseases, among which the Bcl2 protein family and Caspase family were studied. There are many members of the Bcl2 family, which have different functions and the anti-apoptotic genes are mainly Bcl2, while the main apoptosis promoting genes. Caspase is recognized

as an essential gene in the process of apoptosis and Caspase3 is thought to be a powerful executor of apoptosis. The GBLE could significantly inhibit the increase of Bax and Caspase3 expression induced by ischemia reperfusion in rat model of myocardial ischemia and reperfusion[51]. In diabetic cardiomyopathy and acute cerebral infarction rats, GBLE could increase Bcl2, decrease the expression of Caspase3 and decrease the apoptosis. In addition, GBLE could inhibit the neuronal apoptosis induced by cerebral ischemia and reperfusion and the recovery of motor function in rats[52].

Regulation of blood lipids: Regulation of blood lipids are prevention and treatment of atherosclerosis dyslipidemia is a major factor in the pathogenesis of atherosclerosis, atherosclerosis is the leading cause of cardiovascular and cerebrovascular diseases, is the pathological basis of their disease. Researchers show that GBLE and *Ginkgo* flavonoids can reduce serum total cholesterol, triglyceride, low-density lipoprotein levels, increase the level of high density lipoprotein, reduce vascular endothelial cell disintegration and atherosclerotic plaque formation. GBLE can improve the level of blood lipid in the patient observed with coronary disease and inhibit progression of atherosclerosis. After treatment with for patients with metabolic syndrome, the degree of atherosclerosis and the markers of oxidative stress were improved after GBLE treatment[53].

Medicinal and pharmacological applications of *Ginkgo biloba*: The pharmacological Treatment through *Ginkgo biloba* leaves extract can be sketched with Chinese traditional medicines during 2800 years before. The modern Chinese traditional medicines, fruit and leaves are yet suggested for the treatment of lung, asthma and Heart disease problem. The uses of boiled *Ginkgo biloba* leave method for inflammations of disease. *Ginkgo biloba* leaves extract are also use for hazard conditions of disease then may have poor movements as a common indication, such as vertigo, tinnitus and inner ear hearing loss[54]. *Ginkgo biloba* leaves extract (GBLE) is a popular dietary supplement taken by the public to enhance memory[55-57]. *Ginkgo biloba* is widely used for its reputed effectiveness in CNS disorders[58]. The pharmacological studies by Alzheimer and Krieglstein[33] supported the therapeutic use of *Ginkgo biloba* extract for Alzheimer's disease. The EGB 761 showed that the neuroprotective properties in Alzheimer's disease through its antioxidant aptitude and self-consciousness of Abita-induced harmfulness and death of cell[59-65]. As reported, GBLE is widely prescribed in the treatment of cognitive deficits including Alzheimer's disease[66]. GBLE can ameliorate learning and memory deficit induced by $AlCl_3$[67]. The improvements of *Ginkgo biloba* leaves extract are also globally present in blood flow, protect against hypoxia, inhibit platelets aggregations, improve the blood rheology and reduce the capillary penetrability[68]. So, the planed of *Ginkgo biloba* leaves extract is to treat also periphery-vascular disease and cerebrocardiovascular disease problems. The *Ginkgo biloba* leaves and *Ginkgo* flavonoid are showed the defending properties on central nerve system and cardiovascular disease are medically treatment of cardiovascular disease[69]. Some of points are under below:

- Refining system of brain: For example; depression, mental clarity, memory losses and Alzheimer's
- Establishment of cardiovascular disease and cerebrovascular disease system are through embarrassment of blood flow, oxygen system and platelets aggregations
- Defusing the able activists are that depreciate the nerves system, rush aging and damage the cellular health
- Steadying the cellular energy production with higher absorption of glucose, ATP, lower level of lactate and creatinine phosphate
- Some keys are mention like inflammation, allergies, migraine, asthma and suppressing hemorrhoids

CONCLUSION

Ginkgo biloba leaves extract (GBLE) prevention and treatment of cardiovascular and cerebrovascular diseases have the advantages of multiple links, multiple targets and more likely to promote the body to restore the overall dynamic balance. GBLE has a wide range of efficacy, less adverse reactions and broad application prospects. At present, the mechanism of *Ginkgo biloba* leaves extract on prevention and treatment of cardiovascular and cerebrovascular diseases at home and abroad. However, the composition of GBLE is complex and the prevention and treatment of cardiovascular and cerebrovascular diseases need to be further systematic and comprehensive study.

SIGNIFICANCE STATEMENT

This study shows that the *Ginkgo biloba* leaves extract is applied to the cardiovascular disease (CVDs) and coronary heart disease (CHD). Currently, the CVDs and CHD is big challenge for the human health and the researchers are also consideration to find effectiveness drug through the pharmacological methods for harmful problems of disease in the world.

ACKNOWLEDGMENTS

All the authors of the manuscript are immensely grateful to their respective universities and institutes for their technical assistance and valuable support in the completion of this research project.

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