

Herbal Remedies: A Potential Therapeutic Approach for Cardiovascular diseases

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Abstract

Herbal medicine and its derivatives have been utilized in clinical management since the dawn of civilization. These remedies have proven to offer comprehensive relief for individuals suffering from Cardiovascular Disease (CVD), which remains the leading cause of death worldwide. According to the World Health Organization (WHO), a staggering 17.9 million people, accounting for approximately 32% of global deaths, succumb to CVD annually. Clinical research has now firmly established the valuable efficacy of herbal medicine in treating this condition. This article delves into an in-depth examination of CVD, including its risk factors, associated treatments involving herbal remedies, and the phytopharmacological mechanisms behind the effectiveness of these herbal products.

Keywords: Civilization • Clinical management • Cardiovascular Disease (CVD) • World Health Organization (WHO) • Mortality • Herbal remedies • Phytopharmacological mechanism

Introduction

The Cardiovascular System (CVS) comprises the heart and the vasculature system, which forms a closed circulatory system. Positioned centrally within the thorax, the heart functions as a conductor, propelling blood through arteries that branch out into smaller arterioles and eventually reach the capillaries [1]. The Cardiovascular System (CVS) plays a vital role in regulating homeostasis and maintaining vital signs. Additionally, it aids in protection by carrying white blood cells that eliminate cellular debris and combat pathogens. Through continuous and controlled transportation, the CVS delivers essential substances such as nutrients, electrolytes, amino acids, enzymes, dissolved gases, and hormones to every tissue and cell, contributing significantly to functions such as respiration, metabolism, and immunity. Its remarkable capabilities have an astonishing impact on overall health and well-being [2,3].

Any abnormalities or conditions that impact the cardiovascular system (heart and blood vessels) can lead to the development of Cardiovascular Disease (CVD) [4,5]. CVD is not a singular disease, but rather a collection of various diseases and injuries that impact the cardiovascular system. It stands as the primary cause of morbidity and mortality worldwide, according to the World Health Organization (WHO). Globally, CVD remains the leading cause of death and is projected to continue in that position. In 2005, it was estimated that cardiovascular disease claimed the lives of 17 million individuals, accounting for 30% of global deaths. Among these cases, heart attacks were responsible for 7.2 million deaths, while strokes accounted for 5.7 million deaths. Approximately 80% of these fatalities occurred in low- and middle-income countries. If current trends persist, by 2030, it is estimated

that 23.6 million individuals will die from cardiovascular disease, primarily due to heart attacks and strokes [6].

Literature Review

Classification

Major cardiovascular disease includes

Coronary artery diseases or ischemic heart diseases or coronary heart diseases: Coronary artery blockage occurs when there is a buildup of atherosclerotic plaque within the arteries that supply blood to the heart. This plaque proliferation restricts the flow of blood and oxygen to the heart muscle, resulting in various complications such as angina, heart attack, heart failure, and cardiomyopathy. Angina refers to chest pain or discomfort caused by reduced blood flow to the heart. A heart attack, also known as myocardial infarction, transpires when the blood supply to a section of the heart muscle is abruptly blocked. Heart failure occurs when the heart is unable to pump blood efficiently, leading to fluid buildup and an inadequate supply of oxygen to the body's organs. Cardiomyopathy is a condition characterized by the weakening of the heart muscle, affecting its ability to pump blood effectively. These complications are direct consequences of the progressive narrowing and blockage of coronary arteries due to the proliferation of atherosclerotic plaques [7].

Angina: Angina, a condition characterized by insufficient supply of oxygen-rich blood to the heart muscles, can be classified into two types: "Stable" angina and "Unstable" angina. Stable angina is typically triggered by physical activity or stress, and its symptoms are consistently alleviated by rest. On the other hand, unstable angina occurs when there is hemodynamically unstable plaque and involves the presence of thrombosis. It can be triggered even when an individual is at rest or not very active [8,9].

Heart attack: Myocardial Infarction, commonly referred to as a heart attack, occurs when there is a sudden blockage in the blood vessel that supplies the heart. The term "Myo" signifies the muscle, "cardial" pertains to the heart, and "infarction" denotes the death of tissue resulting from inadequate blood supply. In the context of a heart attack, this blockage hinders the normal blood flow to the heart muscle, leading to tissue damage and potentially life-threatening consequences. Therefore, a myocardial infarction is a critical medical event characterized by the abrupt occlusion of a heart blood vessel, necessitating immediate medical attention and intervention [10-13].

Heart failure: Congestive heart disease and hypertension are conditions characterized by the progressive and chronic inability of the heart to effectively pump an adequate amount of blood to meet the body's oxygen and blood

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Received: 05 July 2023, Manuscript No. jnp-23-104967; **Editor Assigned:** 07 July 2023, PreQC No. 104967; **Reviewed:** 19 July 2023, QC No. Q-104967; **Revised:** 24 July 2023, Manuscript No. R-104967; **Published:** 01 August 2023, DOI: 10.37421/2472-0992.2023.9.252

requirements. As a result, the body's needs are not adequately met, leading to a range of symptoms and complications. These conditions are further classified into three distinct categories based on their specific characteristics and underlying causes. Proper management and treatment of congestive heart disease and hypertension are crucial to mitigate the risks associated with these conditions and improve the overall well-being of affected individuals. By addressing the underlying factors contributing to the inadequate pumping function of the heart and implementing appropriate medical interventions, it is possible to enhance the quality of life for those living with these conditions [10,11].

- **Right-sided heart failure:** When the right chamber, comprising the right auricle and right ventricle, loses its pumping capacity, blood begins to back up into other tissues, including the liver and abdomen. This, in turn, leads to hepatomegaly, which refers to the abnormal enlargement of the liver, and Ascites, a condition characterized by the accumulation of fluid in the abdominal cavity [14]. In such a case, your ankles, leg, and belly may swell [15].
- **Left-sided heart failure:** When the left ventricle, which is the heart's primary pumping power source, becomes progressively weakened and is unable to effectively pump blood, it leads to symptoms such as fatigue and the build-up of fluid in the lungs, resulting in pulmonary edema and shortness of breath [16-18].
- **Congestive Heart Failure (CHF):** In the chronic phase, both the left and right sides of the heart experience failure, resulting in the accumulation of fluid in the lungs known as pulmonary edema. This condition is subsequently followed by the accumulation of fluid in the liver and abdomen, causing peripheral edema [19].

Cardiomyopathy: Cardiomyopathy is a term used to describe abnormalities in the heart muscle, which can manifest as thickened, enlarged, or stiffened muscle tissue, leading to impaired blood pumping throughout the body. This condition has the potential to progress into heart failure, a serious medical condition. There are three distinct types of cardiomyopathies that have been identified. These include hypertrophic cardiomyopathy, where the heart muscle becomes abnormally thickened; dilated cardiomyopathy, characterized by the heart's chambers becoming enlarged and weakened; and restrictive cardiomyopathy, in which the heart muscle becomes stiff, impeding proper filling of the chambers. Understanding these different types of cardiomyopathies is crucial for accurate diagnosis and effective management of the condition [20].

- **Dilated cardiomyopathy:** Systolic heart failure occurs when the left ventricle, which is the heart's primary pumping chamber, undergoes a significant decrease in ejection fraction. This condition is characterized by the stretching, dilation, and weakening of the left ventricle, resulting in its inability to effectively pump blood throughout the body. As a

consequence, the heart's overall pumping capacity is compromised, leading to various symptoms and complications associated with heart failure [21].

- **Hypertrophic cardiomyopathy:** In diastolic heart failure, there is a thickening of the heart muscle, particularly in the ventricles and ventricular septum. This condition is accompanied by changes in the mitral valve and increased stiffness of the left ventricle. These cellular changes ultimately lead to restricted filling of the ventricles with blood. As a consequence, there is a reduction in blood flow from the left ventricle to the aorta, impairing the delivery of oxygenated blood to organs, tissues, and cells throughout the body [22].
- **Restricted cardiomyopathy:** When the walls of the lower chambers of your heart, known as ventricles, lose their flexibility and become rigid or stiff, they face difficulty expanding adequately to accommodate the incoming blood. Consequently, the ventricles struggle to hold a sufficient amount of blood, resulting in an impaired pumping function of the heart. Over time, this inability to pump effectively leads to heart failure, where the heart is unable to fulfill its role in circulating blood throughout the body [23].

Aortic disease: Abnormal widening of the aorta, which is the primary blood vessel responsible for supplying blood to the body, can manifest as an aortic aneurysm. This condition presents as a balloon-like bulge in the aorta and can occur in various locations along the vessel. Aortic disease encompasses two main manifestations: plaque thrombosis and aortic dissection. Plaque thrombosis refers to the accumulation of plaque within the walls of the aorta, leading to the development of the disease. On the other hand, aortic dissection occurs when blood accumulates between the tunica layers of the aorta, causing further complications. These conditions highlight the importance of monitoring and managing the health of the aorta to prevent potential complications and ensure optimal blood flow throughout the body [24].

Peripheral vascular disease or peripheral arteries disease: Atherosclerotic plaques narrow or obstruct large arteries, primarily those supplying blood to peripheral areas outside of the heart and brain [24].

Stroke and Transient Ischemic Attack (TIA): Stroke can occur due to restricted oxygen-rich blood flow to a specific region of the brain, known as an ischemic stroke, or due to the disruption of a blood vessel, preventing blood flow to the brain, referred to as a hemorrhagic stroke, resulting in brain damage. The World Health Organization (WHO) identifies stroke as the fifth leading cause of death and disability in the United States. Meanwhile, a Transient Ischemic Attack (TIA) or mini-stroke resembles a stroke, but in this case, blood flow to the brain region is temporarily obstructed [25] (Figure 1).

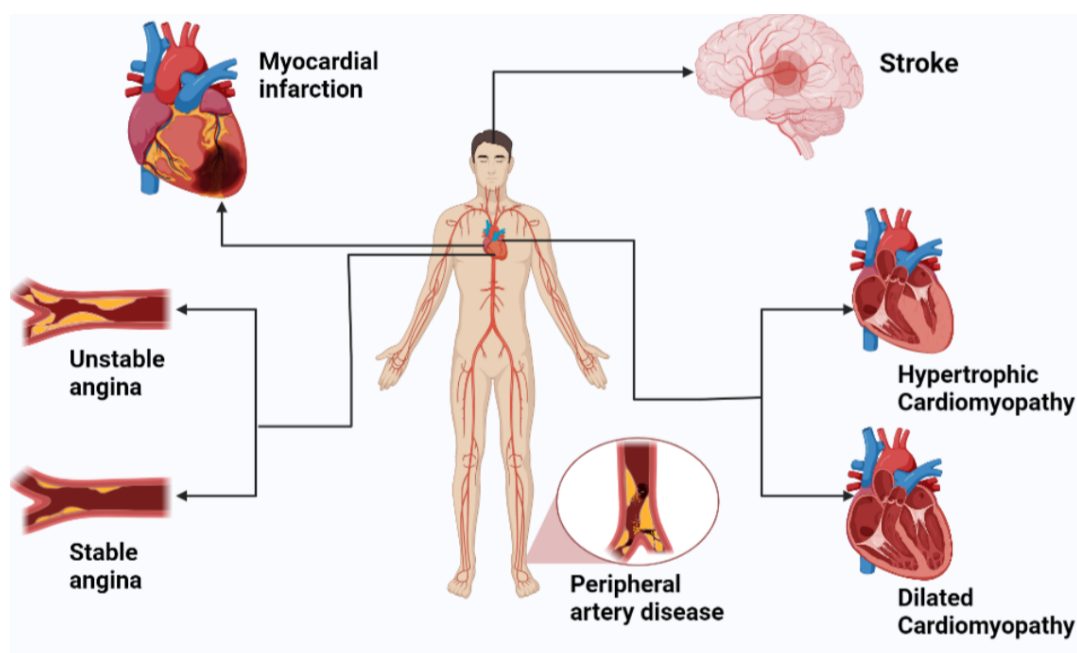


Figure 1. Illustrate the cardiovascular system (heart and vasculature system) of our body and also represent the various associated CVD.

The treatment goal of cardiovascular disease

Based on the provided information, it can be concluded that CVD is caused by vascular impairment, which arises from the formation of atherosclerotic plaque or thrombosis. Atherosclerosis, the condition in which fatty deposits accumulate in the walls of arteries, combines the terms "atheroma" and "sclerosis" to describe the stiffness of blood vessel walls [26,4]. Atherosclerosis is the buildup of lipids, cholesterol, and other materials in and on the walls of arteries, forming plaque.

This plaque may result in the:

- The stiffening of artery walls leads to hypertension.
- Stenosis results in the narrowing of blood vessels, causing a reduction in blood flow (e.g., angina).
- Plaque rupture produces something called a thrombus, which blocks a distal part of a blood vessel, leading to acute ischemia (for example, acute coronary syndrome) [27,30].

Our main treatment goal is to obtain relief from atherosclerotic plaque. In this section, we focus on plants and herbs for which there is evidence and value in the prevention, management, or treatment of CVD [4,5] (Figure 2).

G. lucidum

G. lucidum, also known as Lingzhi or Reishi, is a woody medicinal mushroom with various parts (mycelia, spores, and fruiting body) that are being utilized for their potential medicinal benefits. The name was originally proposed by Peter Adolf Karsten from Finland in the late 19th century. *G. lucidum* is native to Asia, specifically China, Japan, and Korea [27,29].

(In traditional Chinese medicine, *G. lucidum* is taken in the form of a decoction (mashed and boiled in water) or as tea and cookies. Commercially, *G. lucidum* is available as an extract in tablet, capsule, and powder forms [27,31]. There is no fixed dose available for *G. lucidum* it's going to lie between 1.5 to 9 grams of dried extract per day.

Phytoconstituent: A diverse array of bioactive constituents is found in *G. lucidum*, including polysaccharides, oxygenated triterpenoids, nucleosides, fatty acids, flavonoids, and steroids. Notably, *G. lucidum* is the exclusive source of ganoderic acids, a group of triterpenes carboxylic acids. These ganoderic acids exist in various forms, among which Ganoderic A, B, and C demonstrate a hypoglycemic effect. Additionally, Ganoderic F, B, D, H, K, S, and Y exhibit a hypotensive effect. Furthermore, triterpenoids possess antiplatelet aggregation, anti-androgenic, anti-histaminic, and anti-tumor effects [31].

Pharmacological action: Three peptides, namely QLVP, QDVP, and QLDL, referred to as ACE inhibitory peptides, possess the ability to inhibit the activity of ACE (Angiotensin-Converting Enzyme), which in turn leads to a reduction in blood pressure by inducing a vasodilatory effect. In addition, ganoderic acid exhibits beneficial effects by reducing atherosclerosis plaque in the bloodstream. This is achieved through the inhibition of cholesterol synthesis and its antioxidant

properties, as well as its ability to suppress the generation of free radicals, which are responsible for the formation of atherosclerosis plaques.

'*G. lucidum*: A Potent Medicinal Mushroom with Numerous Health Benefits', 2013 [32-34] (Figure 3).

Foxglove (*D. purpurea*)

Foxglove is a herbaceous biennial plant, or shrub, that belongs to the family of cardiac glycosides. It is predominantly found in Europe, Western Asia, and Northwestern Africa, specifically in the Mediterranean region. The plant acquired its name from Anglo-Saxon origins, where it was referred to as "foxes glofa," meaning "the glove of the fox." This name was given due to the resemblance of the flower's shape to the finger of a glove. The medicinal properties of foxglove were extensively researched and validated by a scientist named William Withering. He successfully treated a patient suffering from dropsy (edema) caused by coronary failure using foxglove extract [35,36].

Leaves of foxgloves are used for his or her medicinal benefits. Tincture B.P -5 to 15 drops, infusion B.P -2 to 4 drachms, powder leaves -½ to 2 grains, fluid extract -1 to three drops, and Solid extract USP -1 by 8 grains are used.

Its dose size isn't fixed may vary from person to person or their diseased condition. Currently, approximately 1.7 million patients in the U.S. are receiving digoxin for the treatment of heart failure and atrial fibrillation, conditions for which the leaves of foxgloves are utilized due to their medicinal benefits [36].

Phytoconstituent: The compounds Digitalis, Digitoxin, and Digoxin are potent cardioactive substances that have been commonly used to treat irregular heart rhythms and, in some cases, congestive heart failure. A recent clinical study has demonstrated that digitalis exhibits the ability to specifically target cancer cells and restrict their growth, suggesting its potential for cancer treatment. However, the therapeutic value of these compounds is limited due to their narrow therapeutic index, necessitating careful dosage adjustment for each patient. An excessively high dose can lead to cardiac arrest, which is why consumption of the foxglove plant (a source of these compounds) is poisonous [35].

The pharmacological action: Digitalis, a potent compound found in the dried leaves of common foxglove, can act as a strong inhibitor of the alpha subunit of the sodium and potassium ATPase pump (Na⁺/K⁺ ATPase). This inhibition subsequently hampers the function of the sodium/calcium (Na⁺/Ca²⁺) exchanger pump, resulting in an increased concentration of calcium ions within the cells. This leads to enhanced contractile protein activity, causing smooth contraction, vasoconstriction, and increased force of myocardial contraction. Consequently, the heart muscle is strengthened. The inhibitory effect on the Na⁺/K⁺ pump may also enhance baroreceptor sensitivity in patients with heart failure [35,36] (Figure 4).

G. biloba

G. biloba is an herbaceous medicinal plant commonly known as ginkgo. It has existed on Earth for over 200 million years. In traditional Chinese medicine,

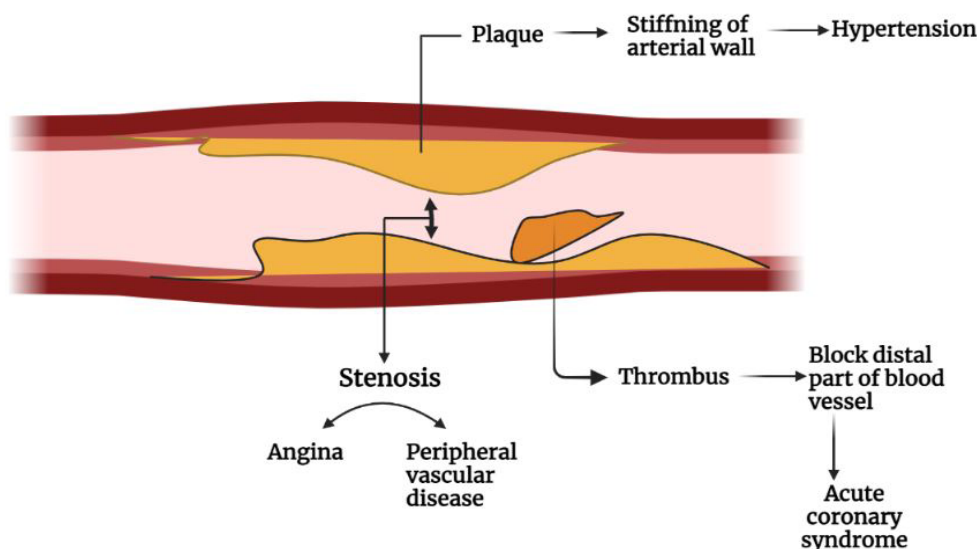


Figure 2. Illustrate the plaque formation and associated disease with it.

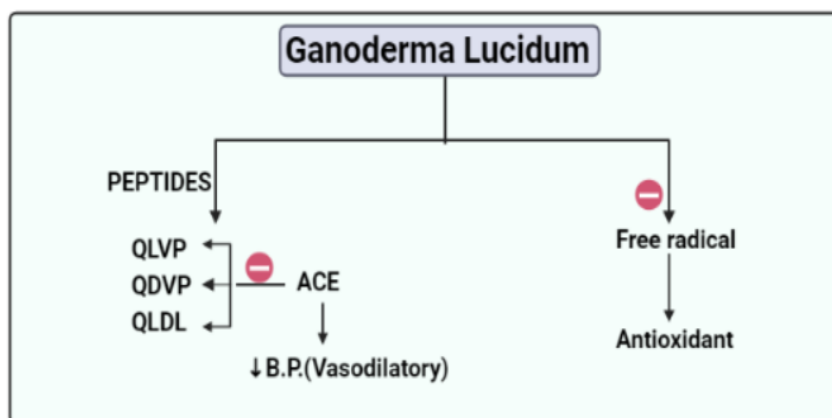


Figure 3. Illustration of pharmacological mechanism of *Ganoderma Lucidum*.

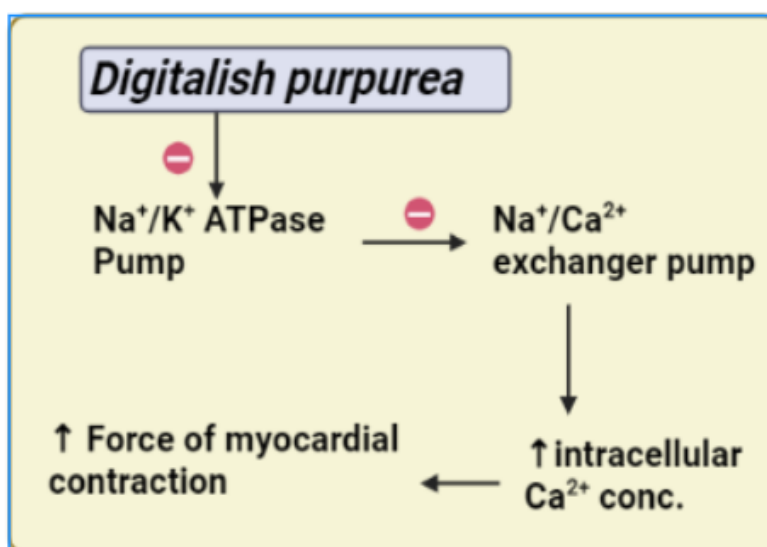


Figure 4. Illustration of pharmacological mechanism of *D.purpurea*.

ginkgo is considered to have a combination of flavors, including fat, sweet, bitter, and astringent. It belongs to the family Ginkgoaceae and is indigenous to China and Japan. Ginkgo is also cultivated for ornamental purposes in various temperate regions [37].

Ginkgo leaf extract has been utilized for its medicinal benefits, and it is commercially available in the forms of capsules, gels, and liquid extracts. The recommended daily dosage varies depending on various factors, but generally, a mean dose of 160 mg per day is suggested for peripheral vascular disease [38,39].

Phytoconstituent: The main bioactive constituents of ginkgo are flavonoids (ginkgo flavone glycosides), terpenoids (ginkgolides and bilobalide), flavones, and organic acids. Ginkgolides are unique to ginkgo and are categorized into types A, B, C, J, or M. They are responsible for improving circulatory flow without affecting blood pressure. Flavonoids, on the other hand, reduce capillary permeability, fragility, and act as free radical scavengers [40].

The pharmacological action: The therapeutic effects of ginkgo are primarily attributed to its constituents, flavonoids and terpenoids. *G. biloba* Extract (GBE) has been found to exhibit antihypertensive effects by blocking the activity of Angiotensin-Converting Enzyme (ACE).

GBE also possesses antioxidant properties as it inhibits the generation of free radicals. Free radicals are responsible for various cardiovascular events such as the formation of atherosclerotic plaques and vascular injuries. GBE reduces the activity of enzymes involved in the breakdown of atherosclerotic plaques, such as MMP-1, particularly in oxidized Low-Density Lipoprotein (LDL) or "bad cholesterol," and in human coronary smooth muscle fibers induced by 4-hydroxynonenal.

One of the components of ginkgo, ginkgolide B, is responsible for dysfunctional endothelin regulation by inhibiting the production of Monocyte Chemoattractant Protein-1 (MCP-1) and intracellular adhesive molecule-1 (ICAM-1). It also reduces the expression of various inflammatory cytokines. Increased levels of ICAM-1 and MCP-1 are associated with inflammation, dyslipidemia, and various cardiovascular events. Another constituent, ginkgolide C, reduces adipogenesis (formation of fat cells) and enhances lipolysis (breakdown of fats), leading to a suppression of lipid accumulation.

Please note that the revised sentence provides a clearer and more concise explanation of the various effects of ginkgo biloba extract, focusing on the specific mechanisms and their implications in cardiovascular health [38,39,37] (Figure 5).

Astragalus (*A. membranaceus*)

Astragalus, also known as Huang qi or milk vetch, is a medicinal Chinese herb derived primarily from beans or legumes. It belongs to the Leguminosae family and is found in Asia, Europe, and North America. In traditional Chinese medicine, it is used to treat various disorders, primarily as a lung tonic and for its immunomodulatory activity. Recent *in vitro* and *in vivo* experimental data have provided evidence of its significant role in treating various cardiovascular diseases [41].

The dried root and stem extract of astragalus is commonly used in formulations. The typical daily dose of astragalus powder ranges from 4 to 7 grams, which may vary depending on factors such as the user's health, age, and other conditions [42].

Phytoconstituent: The main constituents of *A. membranaceus* include polysaccharides, triterpenoids (such as Astragaloside), isoflavones (including Kumatakenin), calycosin, glycosides, and malonates. Among them, Astragaloside

IV is considered the most bioactive ingredient found in Astragalus. It has been extracted, isolated, and patented under the name TA-65.

Polysaccharides exhibit potent anti-inflammatory activities and can effectively reduce blood cholesterol levels. Flavonoids act as cardioprotective agents, while Astragaloside IV provides protection against ischemic and hypoxic myocardial cell injury by improving contractility and diastolic dysfunction. Additionally, it aids in regulating blood sugar and blood lipid levels [43].

The pharmacological action: Astragaloside-IV (AS-IV) is a compound found in *A. membranaceus* and is known for its diverse range of functions. It has been observed to inhibit cardiac hypertrophy induced by isoproterenol and appears to reverse myocardial dysfunction caused by Angiotensin-II in vascular smooth muscle cells. AS-IV also exhibits antioxidant effects by inhibiting the generation of free radicals during myocardial ischemic reperfusion and reducing oxidative stress markers such as Malondialdehyde (MDA), while maintaining the activity of Superoxide Dismutase (SOD).

Furthermore, AS-IV has been shown to have a positive inotropic effect, enhancing myocardial contractility and improving ventricular ejection in patients with congestive heart failure [42,41,44,45] (Figure 6).

Hawthorn (*C. oxycantha*)

Hawthorn (*C. oxycantha*), also known as haw, may-bush, or white horn, is a woody spiny shrub and tree that belongs to the Rosaceae family. It is native to temperate regions in Asia, Europe, and North America and is characterized by its bright green leaves, white flowers, and red berries.

The leaves, flowers, and fruit of *C. oxycantha* (also known as *C. pinnatifida* or Shanghai) have been used for their therapeutic purposes. Commercially, hawthorn is available in various forms such as oral capsules, tablets, dried leaves or flower infusions, liquid extracts, and tinctures.

The recommended dosage of hawthorn may vary from 160 mg to 900 mg, taken two to three times a day. This dosage is approved for functional class II anti-arrhythmia treatment, and it is equivalent to 30 to 168.7 mg of procyanidins or 3.5 mg to 19.8 mg of flavonoids per dose [43,46].

Phytoconstituent: The hawthorn fruit contains bioactive constituents such as oligomeric pyocyanin, triterpenoids, flavonoids, and catechins. These compounds have been associated with various health benefits, including the alleviation of digestive disorders, reduction of blood cholesterol levels, positive inotropic effects (improving heart muscle contraction), vasodilatory properties, and anti-hyperlipidemic actions [43].

The pharmacological action:

The various pharmacological mechanism of hawthorn includes:

The pharmacological mechanisms of hawthorn include the following:

Positive inotropic effect: Hawthorn has been observed to increase the contractility of myocardial muscle by influencing the Na⁺/K⁺ ATPase pump and enhancing calcium (Ca²⁺) transport in cardiomyocytes.

Anti-arrhythmic effect: Hawthorn exhibits an anti-arrhythmic effect by blocking potassium channels, leading to the prolongation of the duration of action potential.

Vasodilatory effect: Hawthorn has shown vasodilatory effects in both coronary and peripheral vessels. This effect is attributed to the influence of endothelial Nitric Oxide Synthase (eNOS), resulting in increased nitric oxide levels. Additionally, hawthorn has an inhibitory action on Angiotensin-Converting Enzyme (ACE).

Hypolipidemic action: Hawthorn demonstrates a hypolipidemic action by inhibiting cholesterol synthesis within the liver and lipid absorption in the intestine.

Antioxidant effect: Hawthorn exhibits antioxidant effects by inhibiting the formation of thromboxane, thereby preventing stenosis [47] (Figure 7).

Ginseng (*Panax Species*)

Ginseng is a highly regarded medicinal herb that has been used in East Asian countries for thousands of years. It is commonly referred to as "man root" due to its root resembling the shape of a human. The most widely used species of Ginseng include Korean red ginseng (*P. ginseng*), Chinese Ginseng (*Panax*

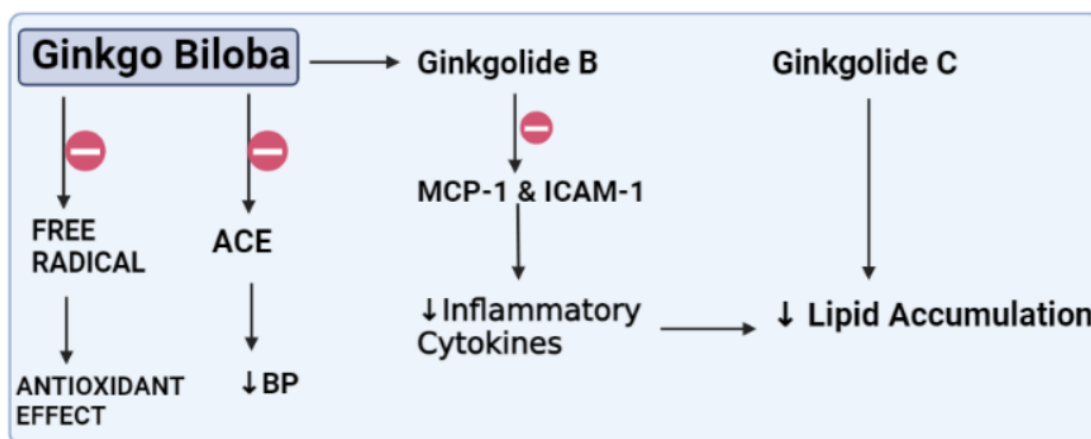


Figure 5. Illustration of pharmacological action of *G. biloba*

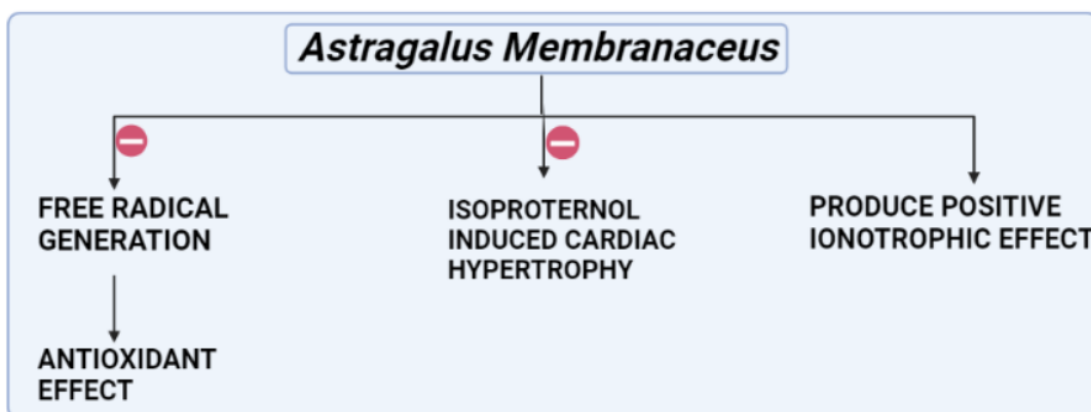


Figure 6. Illustration of pharmacological mechanism of *A. membranaceus*.

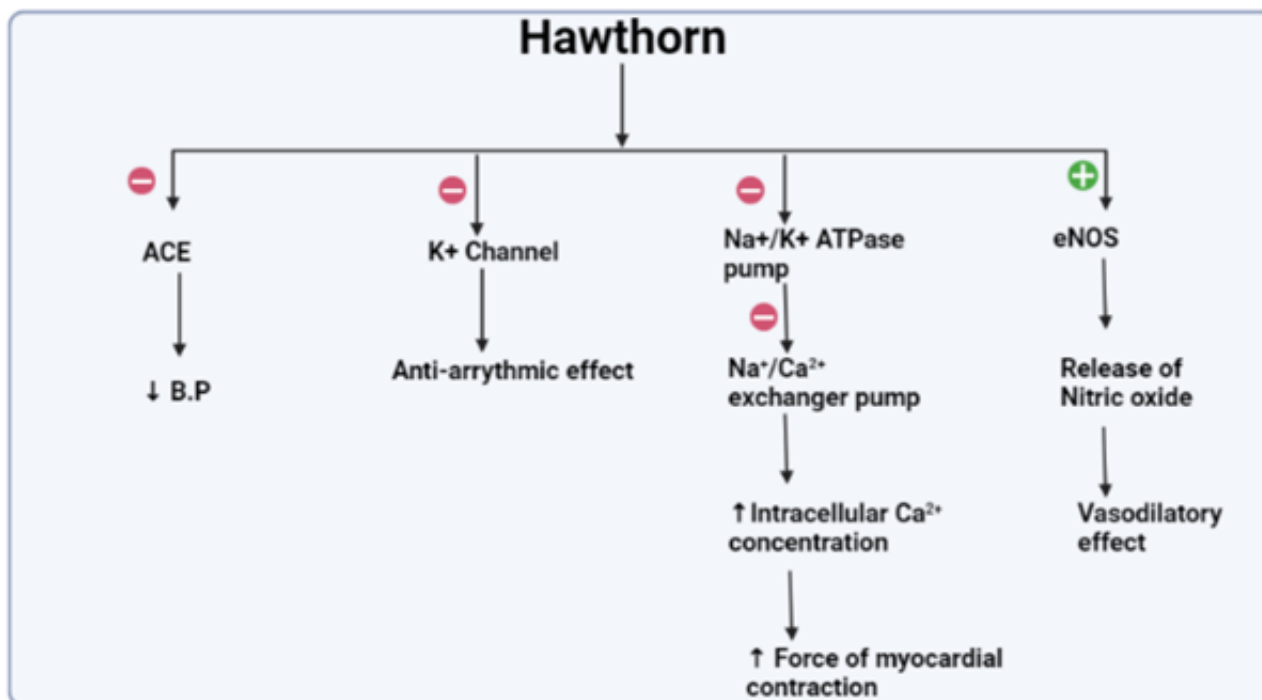


Figure 7. Illustration of pharmacological mechanism of Hawthorn.

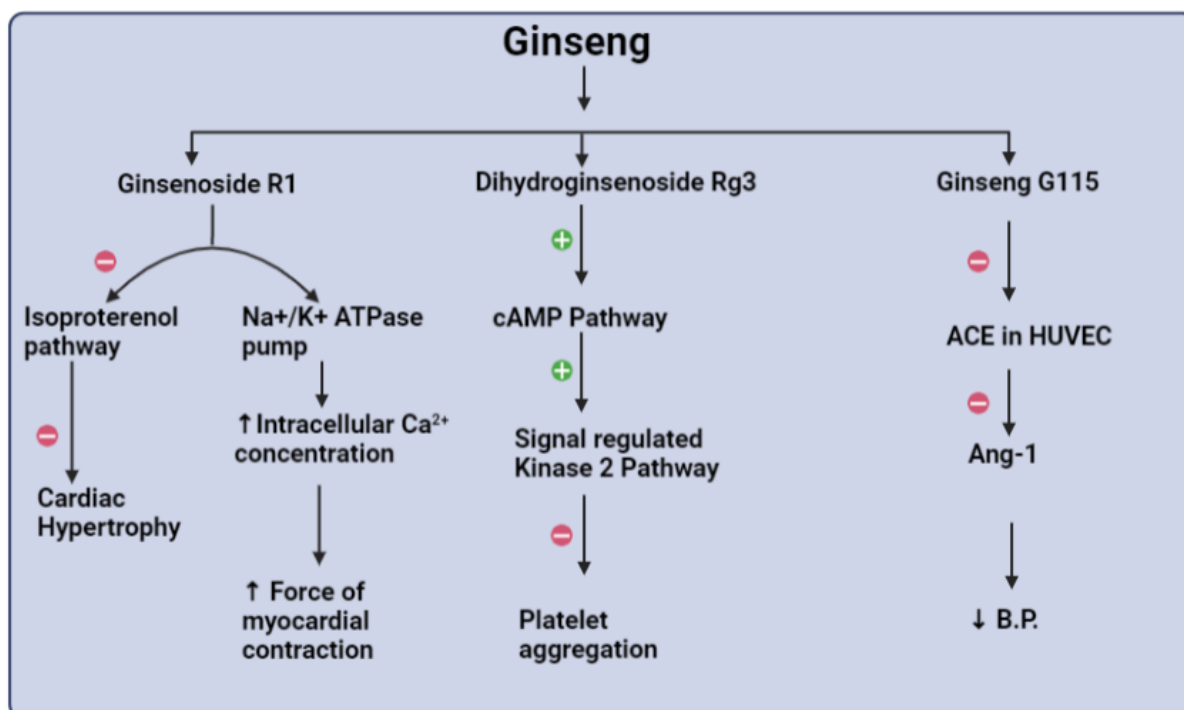


Figure 8. Illustration of pharmacological mechanism of Ginseng.

Noto-Ginseng), and Japanese Ginseng (*Panax Japonicas*). The term "Panax" is derived from the Latin word "Panacea," which signifies the use of herbs for treating a wide range of conditions. In traditional Chinese medicine, both *P. ginseng* and *P. noto-ginseng* are employed for promoting homeostasis and treating patients with coronary artery disease [48,49].

Ginseng root, leaves, and berry extract has been used consistently due to its potential benefits such as anti-obesity, insulin sensitization, anti-hypertensive, and anti-hyperlipidemic properties. Currently, Ginseng is available in both liquid forms, such as oil extract or tea, as well as solid forms like tablets, capsules, or dried roots. It is generally recommended to take 1 to 2 grams of Ginseng root extract, 3 to 4 times a day, for a period of 3 to 4 weeks. However, it is important

to consult with your healthcare provider before taking Ginseng to ensure it is suitable for your individual health needs.

Phytoconstituent: More than 300 bioactive compounds have been identified in ginseng. Among them, ginsenosides, which are triterpene saponins, are frequently recognized for their potent therapeutic effects when extracted from ginseng. The commonly used ginsenosides include Rb1, Rg1, Rg3, Re, and Rd. These ginsenosides have demonstrated various beneficial actions such as anti-hypertensive, insulin sensitizing, and anti-hyperlipidemic effects [39].

The pharmacological action: Ginseng exhibits antihypertensive effects through various mechanisms. One of these mechanisms involves stimulating the secretion of Nitric Oxide (NO) from endothelial cells through the endothelial

Nitric Oxide Synthase (eNOS) pathway. This helps in relaxing the blood vessels and reducing blood pressure. Ginseng also inhibits the voltage-gated calcium ion channels present in vascular smooth muscle fibers, further contributing to the relaxation of blood vessels.

Ginsenoside Rb1, a component of ginseng, has been found to inhibit cardiac hypertrophy, which is the enlargement of the heart muscle. It is believed that the sugar position of ginsenoside Rb1 may act as a blocker of the sodium-potassium ATPase pump, leading to an increase in the force of contraction of the heart muscle.

Dihydro-Ginsenoside Rg3 has been observed to effectively inhibit platelet aggregation, which is the clumping together of blood platelets. This is achieved by rectifying downstream intracellular signaling pathways involving cyclic Adenosine Monophosphate (cAMP) and the Extracellular signal-Regulated Kinase-2 (ERK-2) pathways.

In addition, the ginseng extract known as G115 has demonstrated antihypertensive effects by inhibiting the activity of Angiotensin-Converting Enzyme (ACE) in Human Umbilical Vein Endothelial Cells (HUVECs) and reducing angiotensin-1-induced contraction in bovine mesenteric arteries [40] (Figure 8).

Garlic (*A. sativum*)

Garlic (*A. sativum*) is a highly aromatic herb belonging to the Allium family, Liliaceae. Commonly known as "stinking rose" in Chinese (dasuan) and "Knoblauch" in German, garlic is native to central Asia but widely cultivated and used in Italy and southern France [50].

Garlic, scientifically known as *A. sativum*, is recognized for its diverse properties in combating various cardiovascular conditions such as hypertension, inflammation, oxidative stress, and hyperlipidemia. Both raw garlic and its aqueous extract are utilized for their therapeutic benefits. According to a study, the effectiveness of aged garlic extract ranging from 600 mg to 1500mg was found to be comparable to the blood pressure medication atenolol when used over a 24-week period. Additionally, patients treated with 900mg of standardized garlic powder demonstrated a reduction of 9-18% in plaque volume, a decrease of 4% in Low-Density Lipoprotein (LDL) cholesterol (known as "bad" cholesterol), and an increase of 8% in High-Density Lipoprotein (HDL) cholesterol (known as "good" cholesterol) [20].

Phytoconstituent: Allicin is the primary bioactive compound found in garlic and is responsible for its characteristic odor. It is formed through the action of an enzyme called alliinase, which is activated when raw garlic is crushed. However, allicin becomes inactivated when the temperature exceeds 60°C. In addition to

allicin, other important sulfur-containing compounds present in garlic include allyl methyl thiosulfate, 1-propenyl allyl thiosulfate, and γ -L-glutamyl-S-alkyl-cysteine [48].

The pharmacological action: Extracted water, chloroform, or methanol from the drug inhibit platelet aggregation induced by ADP-Arachidonic Acid-Epinephrine and thrombin [49].

Garlic extract and juice have been found to exhibit antihyperlipidemic activity by increasing Tissue Plasminogen Activator (TPA) activity, which in turn reduces blood cholesterol levels by enhancing fibrinolytic activity [50] (Figure 9).

Guggul (commiphora mukul)

Guggul is an oleogum resin obtained from the Mukul Commiphora Myrrha tree, also known as Commiphora Mukul. Its Sanskrit name is Guggulu, which means "to guard against disease." Guggul is commonly referred to as gum guggul and guggulipid. It is native to India, Central Asia, and North Africa. In the Ayurvedic system of medicine, Guggul is used to balance the doshas and alleviate blockages in the channels [51].

Guggul can be used internally, topically as a salve or paste, and possibly as a gargle. However, there are no specific recommended guidelines for the proper use of guggul. Generally, doses ranging from 400 mg to 100 mg are considered safe [52].

Phytoconstituent: Gum guggul is a natural resin composed of various components. It consists of 29.3% gum, 0.6% essential oil, 61% resin, and 6.1% water. The most prominent steroidal components isolated from the crude extract are Guggulsterone E and Z. The resin fraction of guggul is responsible for its biological activity and constitutes 45% of the resin, while the remaining 55% is composed of insoluble carbohydrate gum, which is reported to have no therapeutic effects [53,51,52].

The pharmacological action: Guggulsterone exhibits antihyperlipidemic effects by inhibiting the oxidation of LDL (Low-Density Lipoprotein) and increasing the uptake of LDL cholesterol from the bloodstream into the liver, resulting in a decrease in LDL concentration.

Both E and Z Guggulsterone also function as antagonists of FXR (Farnesoid X Receptor), a type of nuclear hormone receptor, and BAR (Bile Acid Receptor), a steroid receptor. Additionally, they inhibit the activity of cholesterol 7- α hydroxylase (CYP7A1), an enzyme that plays a crucial role in the classical pathway of bile acid synthesis within the liver. This inhibition leads to a reduction in serum cholesterol levels.

Furthermore, Guggulsterone exhibits antioxidant and anti-inflammatory

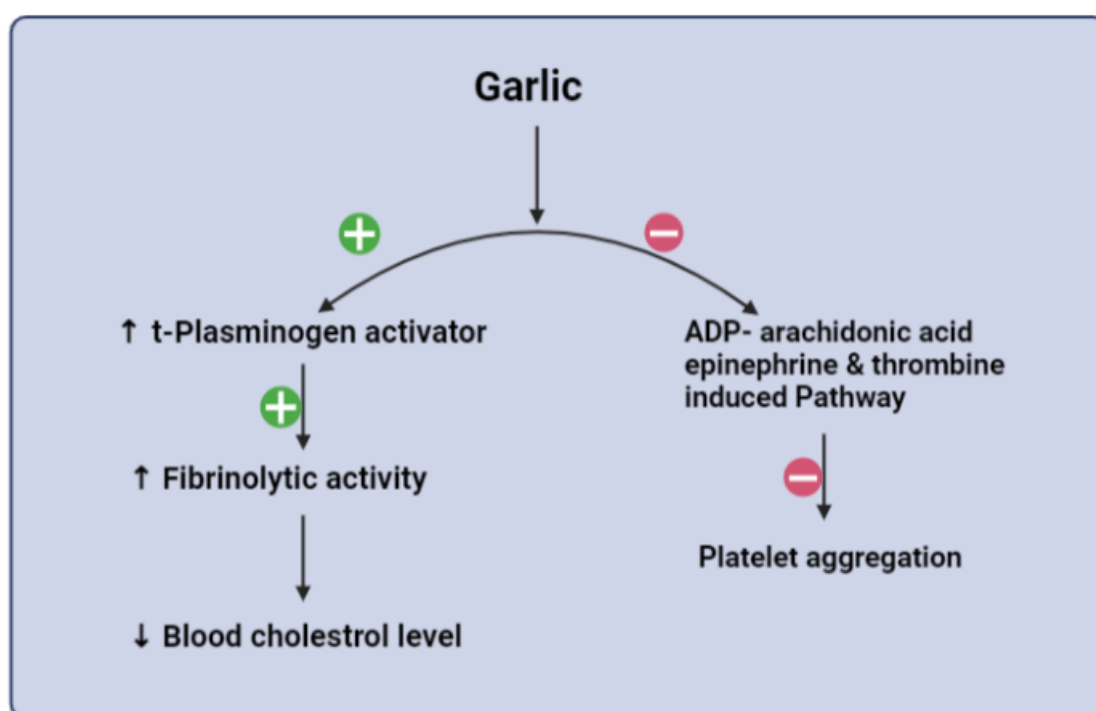


Figure 9. Illustration of pharmacological mechanism of Garlic.

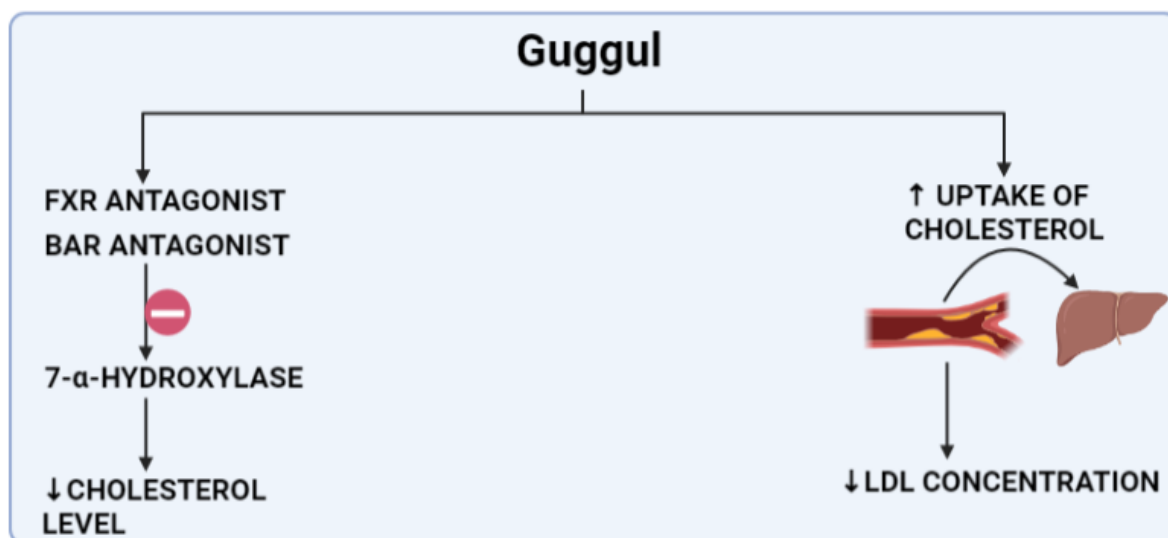


Figure 10. Illustration of pharmacological mechanism of Guggul.

Table 1. Medicinal plants and their ethnopharmacological uses.

S. No.	Scientific Name	Biological Source	Major Phytoconstituent	Part Used	Ethnopharmacological Uses	References
1.	<i>G. lucidum</i>	<i>G. lucidum</i> (curtis), also known as Reishi in Japan and Ling Zhi in China, belongs to the family Ganodermataae	Polysaccharides and triterpenoids are the major bioactive compounds in <i>G. lucidum</i> .	<i>G. lucidum</i> is available in various forms such as tablets, capsules, and powder. The fruiting body of <i>G. lucidum</i> is the part that is used for medicinal purposes.	<i>G. lucidum</i> has been used in traditional Chinese medicine for centuries. It is believed to have many health benefits including anti-inflammatory, antioxidant, and anticancer properties. It has also been used to treat liver diseases, hypertension, hyperlipidemia, and other ailments.	Klupp NL, et al. [32] Dan P and Aktif S [29]
2.	<i>D. purpurea</i>	Digitalis (Foxglove) is made up of the dried leaves of <i>D. purpurea</i> Linn, which belongs to the Scrophulariaceae family.	<i>D. purpurea</i> contains cardiac glycosides (Digitalis, Digitoxin, Digoxin), volatile oil, fatty matter, starch, gum and sugars.	The leaves of <i>D. purpurea</i> and Extract (Tincture, fluid and solid extract) are used for medicinal purposes.	<i>D. purpurea</i> is used in congestive heart failure, atrial fibrillation.	Kreis W [36] and GheorghiaeM, et al. [59]
3.	<i>G. biloba</i>	The Ginkgo leaf originated from the dioecious tree <i>G. biloba</i> , which is a member of the Ginkgoaceae family.	Ginkgolides	The leaves of <i>G. biloba</i> and Extract (Capsule, gel and liquid extract) are used for medicinal purposes.	<i>G. biloba</i> Show anti-hypertensive and Anti-oxidant effect.	Suleymanoa ZN [38] Li W, et al [39] Sun M, et al [37]
4.	<i>A. membranaceus</i>	<i>A. membranaceus</i> , commonly known as Mongolian milkvetch consist of dried root, belonging to family Leguminosae	Astragaloside IV	The dried of <i>A. membranaceus</i> and stem_Extract are used for medicinal purposes	<i>A. membranaceus</i> show positive Inotropic as well as anti-oxidant effect which is used in myocardial infarction.	Wang J, et al. [41] Liu P, et al. [42] Ny V, et al. [45]
5.	<i>C. oxycantha</i>	Hawthorn (<i>C. oxycantha</i>) is a woody spiny shrub and tree belonging to the family Rosaceae. It is also known to as haw, may-bush or white horn	The major phytoconstituents present in <i>C. oxycantha</i> are flavonoids, oligomeric procyanidins, cardiotionic amines, tripterpenes and purine derivatives	The leaves, flowers, and fruit of <i>C. oxycantha</i> are used for medicinal purposes. They can be consumed in various forms such as oral capsules, tablets, dried leaves or flower infusion, liquid extract, and tincture.	Hawthorn (<i>C. oxycantha</i>) has been used for various medicinal purposes such as treating cardiovascular diseases (Show Positive inotropic effect Anti-arrhythmic. hypolipidemic action), gastrointestinal ailments, and anxiety. It is also used to regulate blood pressure and reduce pain in the head and joint pains.	Wang J, et al. [47]
6.	Ginseng (Panax Species)	It is made up of the dried roots of <i>P. ginseng</i> C.A. Mey as well as other Panax species, including those in the Araliaceae family such as <i>P. japonicus</i> (Japanese Ginseng), <i>P. quinquefolius</i> (American Ginseng), <i>P. trifolius</i> (Dwarf Ginseng), and <i>P. vietnamensis</i> (Vietnamese Ginseng).	The major phytoconstituents present in <i>P. ginseng</i> are ginsenosides (Rb1, Rg1, Rg3, Re, and Rd) which are saponins of the glycosides group that are abundant in roots, leaves, stem, and fruits of the plant.	The root, berry, and leaves of the plant can be used for medicinal purposes. They can be consumed in various forms such as liquid form (oil extract or tea) or in solid form such as tablets, capsules, or dried roots.	<i>P. ginseng</i> is used in hypertension, Cardiac hypertrophy.	Kim JH [40]

7.	<i>A. Sativum</i>	Garlic is known by various names such as Lasan, Stinking Rose Dasuan, and (Hindi). It belongs to the Liliaceae family and produces a ripe bulb known as "knoblauch" in German.	Garlic contains more than 200 chemical compounds with multiple properties. It is 65% water, 28% carbohydrates, 2.3% organosulfur compounds (Allicin), 2% proteins, 1.2 % free amino-acids, and 1.5% fiber	The part used for garlic is raw garlic and the extract used can be water, chloroform, or methanol extract.	Garlic has been shown to exert anti-platelet aggregation effect and antihyperlipidemic activity.	Banerjee SK and Maulik SK [50]
8.	<i>C. mukul</i>	Guggal, also known as Guggulu (Sanskrit), is a gum resin made by slicing the bark of <i>C. mukul</i> (H. and S.) Engl, a member of the Burseraceae family.	Guggulsterone E and Z are the major active constituents of Guggul. The ester soluble fraction of Guggul natural resin is 45%.	The gum resin of <i>C. mukul</i> is used for medicinal purposes	<i>C. mukul</i> has antihyperlipidemic, antioxidant and anti-inflammatory effect.	Deng R [53]
9.	<i>I. racemosa</i>	<i>I. racemosa</i> Hook, commonly known as Pushkarmool consists of dried root of <i>I. racemosa</i> Hook. Belonging to family Asteraceae	<i>I. racemosa</i> Hook contains Alantolactone, Dihydroisoalantolactone, neo-Alantolactone, Isoalantolactone, inunolise, sesquiterpene, inunolide-germacranolide, B-sitosterol, D-mannitol, sesquiterpene, Dihydroinunolide lactone- inunol, Alantodiene etc	The root of <i>I. racemosa</i> Hook is used in Ayurvedic and folk medicine. The roots are extracted using ethanol in the Soxhlet apparatus. The extract can be either hydroalcoholic or petroleum.	<i>I. racemosa</i> Hook root extract has been shown to have a cardio protective effect. It has also been shown to have a negative chronotropic effect and positive inotropic effect on isolated frog heart with petroleum ether extract. The extract has also been shown to improve antioxidant status, haemodynamic and left ventricular contractile function subsequent to suppression of oxidative stress	Chabukswar AR, et al. [54]
10.	<i>T. arjuna</i>	<i>T. arjuna</i> is a plant that belongs to the Combretaceae family. It is made up of dried stem bark.	Arjunin, arjunic acid, Arjunetin, arjunoside I, Arjunolone, arjunone, Pyrocatechols and punicallin are some of the major phytochemicals present in <i>T. arjuna</i> .	The bark stem is commonly used for medicinal purposes. The leaves, root, fruit and seed are also used. The extract can be aqueous or alcoholic.	<i>T. arjuna</i> has anti-atherogenic and hypolipidemic properties. It also reduces atherogenic index. The bark stem of arjuna possesses diuretic, inotropic, and chronotropic properties.	Dwivedi S and Chopra D [57] Kaur N, et al. [61] Khaliq F and Fahim M [62]
11.	<i>G. pentaphyllum</i>	<i>G. pentaphyllum</i> , commonly known as jiaogulan, is a dioecious, herbaceous climbing vine of the family Cucurbitaceae (cucumber or gourd family) widely distributed in South and East Asia as well as New Guinea	<i>G. pentaphyllum</i> contains Gynostemma (polysaccharide), water-soluble amino acids, and flavonoids.	The leaves and root of <i>G. pentaphyllum</i> are used to make an extract containing 85% gypenosides. The aqueous extract of the whole plant has been shown to have antioxidant and anti-inflammatory effects.	<i>G. pentaphyllum</i> has been shown to lower serum cholesterol, triglycerides, and LDL while raising HDL levels. It also has anti-hypertensive effects.	Tanner MA, et al. [65]
12.	<i>A. betulina</i>	<i>A. betulina</i> herba consists of the fresh or dried leaves and smaller stalks and belongs to the family Rutaceae.	Diosmin, menthol, and diosphenol are all major compounds present in <i>A. betulina</i> .	The leaves and stem of the plant are used, and an aqueous extract is made from them.	The plant has been used to treat angina pectoris and hypertension.	Huisamen B, et al. [60]
13.	Cranberries (<i>V. macrocarpon</i>)	Cranberries are a group of evergreen dwarf shrubs or trailing vines in the subgenus <i>Oxycoccus</i> of the genus <i>Vaccinium</i> .	Cranberries contain flavonoids such as anthocyanins, flavonols, and flavan3-ols as well as benzoic, hydroxycinnamic, and ellagic acids.	Cranberries are used in their entirety, including the fruit and juice.	These compounds can help increase LDL's oxidation resistance, lower blood pressure and prevent platelet aggregation	Dohadwala MM, et al. [56] McKay DL and Blumberg JB [63]
14.	European elderberry (<i>S. nigra</i> L.)	<i>S. nigra</i> is a species complex of flowering plants in the family Adoxaceae that is native to most of Europe.	Quercetin and rutin are flavonoids found in <i>S. nigra</i> . Additionally, the hemagglutinin protein <i>S. nigra</i> agglutinin III (SNA-III), cyanogenic glycosides like sambunigrin, viburnic acid, and vitamins A and C are also present in <i>S. nigra</i> .	Ripe fruit or berries of <i>S. nigra</i> is commonly used.	Reduce risk factors for heart disease in postmenopausal women	Schmitzer V, et al. [64]
15.	Goldenseal (<i>H. canadensis</i>)	Goldenseal (<i>H. canadensis</i>) is a perennial herb and a member of the buttercup family Ranunculaceae.	Isoquinoline alkaloids, including hydrastine, berberine, and canadine, are compounds found in Goldenseal (<i>H. canadensis</i>).	He roots, stems, leaves, flowers, and fruits of Goldenseal all possess distinct characteristics and are utilized in different applications.	Goldenseal (<i>H. canadensis</i>) exhibits an antiarrhythmic effect, stimulates cardiac contractibility, and has potential anti-hypertensive properties.	Asmi S and Lakshmi T [55]

effects by impeding the formation of harmful free radicals that contribute to the development of atherosclerosis [53-66] (Figure 10).

Conclusion

Cardiovascular Diseases (CVDs) are a leading cause of morbidity and

mortality worldwide, and their prevalence continues to increase. This has created a significant market demand for novel, safe, effective, and affordable therapeutic options. Various herbal plants have been traditionally used and recent evidence from *in vitro* and *in vivo* clinical studies on experimental animals suggests that they can modulate key cellular, molecular, and pharmacological mechanisms involved in CVD pathogenesis and pathophysiology. However, it is important to note that while these herbal remedies have shown promising therapeutic effects and improvements in CVD related conditions, their clear clinical advantages have not been fully established. Safety concerns have also been raised regarding the toxicity of certain plants, such as ginkgo biloba. Therefore, further investigation, including larger clinical trials, is necessary to examine the role of different medicinal plants and their underlying processes in relation to CVDs. Long-term clinical investigations should prioritize the assessment of safety and toxicity associated with these natural medicines.

Acknowledgment

We are thankful to Bio Render for providing the platform to create professional science figures.

Conflict of Interest

All authors have none to declare.

Funding

None.

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How to cite this article: Kushwah, Prashant Singh and Mehak Agrawal. "Herbal Remedies: A Potential Therapeutic Approach for Cardiovascular diseases." *J Pharmacogn Nat Prod* 9 (2023): 252.