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Role of Herbal Active Compound in Cardiac Failure Treatment

Jyotsna Upadhyay[1*], Amle Vandana Sonaji[2], Khonde Shital Trimbak[2], Chapke Seema Ganesh[3], Kisan Vivek Pawar[2], Anamika[1] and Roshan Kumar[1]

[1]Assistant Professor, Department of Pharmacy, Shree Dev Bhoomi Institute of Education Science and Technology, Dehradun, 248007, Dehradun, Uttarakhand, INDIA.

[2]Shri Bhairavnath Nisarg Mandal, S.R.T.M. University, Hingoli, Maharashtra, INDIA.

[3]Shri Bhairavnath Nisarg Mandal's Diploma in Pharmacy Institute, Hingoli, Maharashtra INDIA.

[*]Corresponding Author: upadhyayseena@yahoo.com

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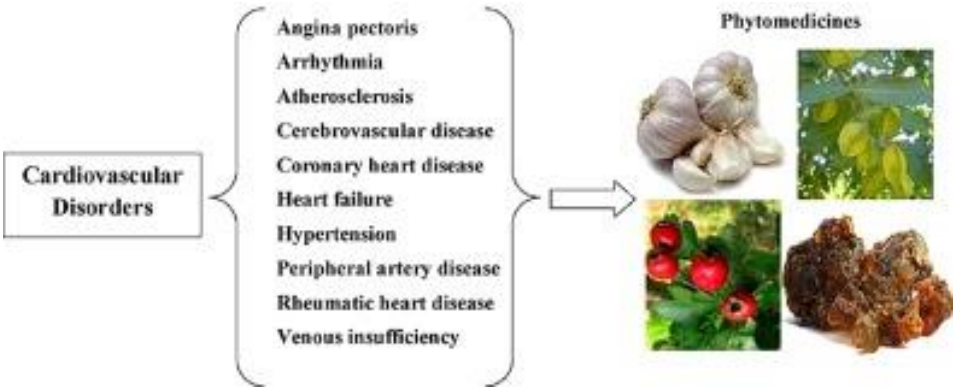
ABSTRACT

The prevalence of cardiovascular diseases (CVDs) is constantly rising, making them a major health burden. In terms of global mortality and morbidity, they are still at the top. An alternate method of treating many illnesses, including CVDs, is the use of medicinal herbs. There is a current, unprecedented push to include herbal remedies into contemporary healthcare systems. The widespread conviction in their safety and the fact that they offer more effective treatment at a lower cost than conventional modern medicines are two of the main factors propelling this movement. However, there has not been enough testing of the purported safety of herbal remedies. As a result, people need to know that medical herbs can be toxic, have possibly fatal side effects, and can interact negatively with other drugs. Experimental evidence suggests that medicinal herbs may be useful in the treatment of cardiovascular diseases (CVDs) due to their ability to inhibit multiple risk factors for these conditions. So, in order to successfully use herbs in CVD therapy, there have been numerous initiatives to transition medicinal herb research from the lab to the clinic. Presented below are cardiovascular diseases (CVDs) and the variables that put people at risk for developing them. Next, we provide a synopsis of herbal medicine's role in the treatment of disease, with a focus on cardiovascular diseases. In addition, information is compiled and examined about the ethnopharmacological therapeutic possibilities and medicinal qualities against cardiovascular diseases of four commonly used plants: ginseng, gingko biloba, ganoderma lucidum, and gymnostemma pentaphyllum. The use of these four plants in the treatment of cardiovascular diseases (CVDs) including myocardial infarction, hypertension, peripheral vascular disorders, coronary heart disease, cardiomyopathies, and dyslipidemias has been well examined. We are also making an effort to describe the current in vitro and in vivo investigations that have attempted to examine the cellular and molecular underpinnings of the four plants' cardio-protective effects. Lastly, we highlighted the effectiveness, safety, and toxicity of these four medicinal herbs by reviewing and reporting the results of current clinical trials.

GRAPHICAL ABSTRACT



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I. INTRODUCTION

Heart failure is a growing and significant issue in healthcare systems and people's lives globally. The illness in question is multifaceted and diverse, resulting in a diminished quality of life for individuals affected by it and imposing a significant economic cost on society as a whole. This narrative review explores the significant subject of "Advancements in Heart Failure Management," with a specific emphasis on novel therapies that have the potential to transform the treatment of heart failure. This narrative review holds significance in acknowledging heart failure as a prominent public health concern that necessitates innovative solutions. Furthermore, it provides a critical assessment of novel therapeutic approaches. To understand the importance of advancements in heart failure treatment, it is necessary to comprehend the magnitude and severity of the issue. Heart failure affects around 64 million individuals worldwide. Another issue of worry is the increasing prevalence of this disease. The increasing prevalence of heart failure cases can be attributed to factors such as an ageing population and the presence of cardiovascular risk factors such diabetes, obesity, and high blood pressure [1]. Heart failure incurs significant economic burden, with annual healthcare expenditures amounting to billions of dollars [2]. Heart failure not only has financial implications, but it also significantly diminishes the quality of life for those affected. The manifestation of symptoms such as difficulty breathing, persistent tiredness, and reduced ability to engage in physical activity are indicative of this condition. The combined impact of these symptoms results in a significant decrease in the average duration of life [3]. Advancements in both theoretical understanding and practical application have brought about a significant transformation in the management of heart failure over the past few decades. Historically, the primary method of managing heart failure has been through the use of pharmaceutical treatment, which involves the use of diuretics, beta-blockers, angiotensin receptor blockers (ARBs), and angiotensin-converting enzyme (ACE) inhibitors. The primary objectives of these drugs [4] are to decrease fluid retention and enhance heart function. In addition, implantable cardioverter-defibrillators (ICDs) and cardiac resynchronization treatment (CRT) have become essential instruments in combating heart failure, demonstrating significant reductions in mortality and hospitalisations for specific groups of patients [5,6]. Individuals suffering from end-stage heart failure, who persistently experience symptoms and have compromised cardiac function, have a critical opportunity to undergo a heart transplant, which has traditionally been regarded as the most effective treatment choice [7]. However, the limited availability of donor organs hinders the potential use. Despite major therapeutic improvements, heart failure continues to pose significant hurdles. Despite the utilisation of optimal treatments, it is crucial to acknowledge that certain individuals may not exhibit a favourable response, and the progression of the disease is expected to persist. Adverse reactions, pharmacological sensitivities, and non-compliance with complex prescription schedules can complicate the management of medical conditions [8]. There is a significant lack of supplementary and alternative approaches in the heart failure treatment industry. There is an urgent requirement to promptly develop novel therapeutic strategies in response to the increasing prevalence of heart failure and the constraints of present therapies. Emerging treatments encompass several innovative approaches such as regenerative medicine, precision medicine, device-based therapy, advanced pharmacological agents, and other novel methods. The key objectives of these developing drugs are to enhance the targeting of the fundamental processes of heart failure, improve patient outcomes, and optimise the quality of life. This comprehensive study examines the potential of these novel drugs to significantly transform the treatment of heart failure. This study seeks to contribute to the existing knowledge on heart failure by closely examining recent advancements and their potential implications for the future. Ultimately, our goal is to foster additional innovation and progress in the sector. The primary objective of this research is to analyse and examine the efficacy and mechanisms of novel drugs used in the therapy of heart failure, as well as to compare their effectiveness with existing treatment modalities. We will conduct a comprehensive assessment of all developing medicines, considering their merits and drawbacks. Thoroughly evaluating different treatment strategies can considerably help medical practitioners and academics, enabling them to make informed judgements on how to integrate these methods into clinical practice. Lastly, the narrative review will propose potential avenues for future research and advancement in the field of heart failure management. An effective method to foster a culture of ongoing innovation and guide future research endeavours is to pinpoint areas that necessitate more investigation. This narrative review aims to provide a thorough examination of recent advancements that could potentially transform the treatment of heart failure, a prevalent global health issue. The focus will be on exploring several innovative medicines.

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II. METHODOLOGY

For this review, we conducted a comprehensive search of the existing literature to gather information on the bioactive constituents found in medicinal plants and their impact on oxidative stress. The Institute for Scientific Information (ISI) Web of Knowledge, MEDLINE, PubMed, Scopus, Google Scholar, and the China National Knowledge Infrastructure (CNKI) databases were queried using pertinent keywords and phrases such as "natural drugs and oxidative stress", "natural active ingredients and oxidative stress", "traditional Chinese medicine and oxidative stress", "phytochemistry/medicinal plant extracts and oxidative stress", "medicinal plants and cardiovascular diseases", and "natural active ingredients and cardiovascular diseases". We deliberately chose authentic articles from the search results that specifically mention natural medicines or their active ingredients and their impact on oxidative stress or cardiovascular diseases (CVDs). The primary factors we considered when selecting our search criteria were as follows:

Natural antioxidant for treatment of Various Cardiovascular disease

In order to reduce the amount of oxidative damage that occurs in cardiovascular tissue, an increasing number of medicinal herbs are starting to be used as natural antioxidants in clinical settings [32]. It is possible to extract the antioxidant activity of active components from a wide variety of medicinal plants [33, 34]. Polysaccharides, flavonoids, and phenols are only few of the compounds that are found in traditional Chinese medicine. Treatment for cardiovascular disease in the modern day includes the use of natural medicine as an essential component. Within free radicals, there exist electrons that are not paired, and these electrons have a tendency to couple. The domino effect is caused by the combination of free radicals, which results in the production of even more radical chemicals. Traditional Chinese medicine contains active compounds that have the ability to counteract this domino effect through both their direct and indirect effects. In addition to their ability to modulate oxidative stress, these components are known to reduce lipid peroxidation and the formation of free radicals, boost radical scavenging, improve the activity of antioxidant enzymes, and raise the anti-inflammatory response [35]. When compared to synthetic antioxidants, the safety profile of natural medicinal plants that include antioxidant properties is greater. This is due to the fact that natural antioxidants have a lower toxicity level. Because of these advantages, it is possible that medicinal plants that contain antioxidants could one day be used to treat cardiovascular disease by concentrating on oxidative stress.

Coronary Atherosclerotic Heart Disease

Coronary atherosclerotic heart disease (CHD) is generally caused by a narrowing or blockage of the coronary artery [36, 37]. This is the primary cause of the condition. Insufficiency of oxygen and oxygen supply to the heart is caused by arterial stenosis or occlusion [38, 39]. This disorder is characterised by the development of atherosclerotic plaques that are packed with lipids and are located underneath the tunica intima of the great and medium arteries. Damage induced by lipid peroxidation, which can be brought on by a number of different coronary heart disease risk factors [40, 41], might hasten the progression of atherosclerosis. During the early stages of atherosclerosis, a decrease in blood flow can have a number of repercussions, including a decrease in endogenous ATP levels, activation of AMPK, inhibition of mTOR, and increased reactive oxygen species (ROS), which can lead to oxidative stress. There is a possibility that an excessive amount of reactive oxygen species (ROS) could be the cause of dysfunction in endothelial and smooth muscle cells. Atherosclerosis and coronary heart disease (CHD) can advance more rapidly as a result of its propensity to activate inflammatory signalling and mitochondria-mediated apoptosis in cardiomyocytes [42]. Alterations in the number of reactive oxygen species (ROS) can react to the binding of extracellular signals to receptors on the surface of cells, and these changes can operate as second messengers. Through the Ca2+ signal transduction pathway, the mitogen-activated protein kinase signalling pathway, and the protein kinase B signalling route, reactive oxygen species (ROS) are responsible for regulating the transmission of signals from cardiomyocytes [43, 44]. Recent research in the field of pharmacology has shown that various Chinese herbal extracts possess antioxidant characteristics, which indicates that they have the potential to be an effective treatment for coronary heart disease.

Ginsenosides

There is a class of bioactive components known as ginsenosides that are produced by plants belonging to the genus Panax. These ginsenosides are non-toxic and possess antioxidant characteristics [45, 46]. In addition to their antioxidant properties, Rb1, Rg1, and Rg2 are ginsenosides that protect the myocardium from free radicals, improve myocardial ischemia and hypoxia, reduce intracellular calcium overload, and have been shown to have antioxidant effects [19, 47]. It has been demonstrated beyond a reasonable doubt that the ginsenosides Rb1, Rg1, and Rg2 have the ability to prevent coronary heart disease. Apoptosis in cardiomyocytes can be reduced by ginsenoside Rb1, which also decreases oxidative stress, upregulates mTOR signalling, and inhibits the expression of genes that cause apoptosis, Bax and Fas, respectively [48]. Ginsenoside Rb1 is a compound that has been shown to have these properties. More recent studies have demonstrated that Rb1 is responsible for activating the PI3K/Akt/Nrf2 signalling pathway. This, in turn, leads to an increase in the activity of antioxidant enzymes and a reduction in the damage that is caused by free radicals to

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the myocardium [49, 50]. Ginsenoside Rg2 has the potential to alleviate myocardial ischemia, hypoxia, and oxidative stress injury in rats [51]. This is accomplished via altering the activities of serum creatine kinase (CK), lactate dehydrogenase (LDH), lipid peroxides (LPOs), superoxide dismutase (SOD), and glutathione peroxidase (GPX). Other findings linked with ginsenoside Rg2 included a reduction in the amount of oxidative stress that was present in human epidermal keratinocytes [52]. Ginsenoside Rg1 may play a role in antioxidant defence by increasing signalling along the AMPK/Nrf2/HO-1 pathway. This is one of the proposed functions of This compound. In addition to this, it demonstrated protecting effects against heart failure that was caused by STZ [53]. Using the Nrf2/ARE signalling pathway, another research discovered that Rg1 improved cell survival, increased the expression of antioxidant proteins, and reduced the amount of reactive oxygen species (ROS) and cell death [54]. As a result, it would appear that Rg1 may be able to maintain the survival of cardiomyocytes by reducing oxidative stress.

Delphinidin-3-glucoside

The bioflavonoid delphinidin-3-glucoside (DPg) has potent antioxidant properties. DPg has the potential to reduce oxidative stress-induced damage, NF-κB p65 activity, ROS generation, p38 MAPK phosphorylation, and caspase-3 expression in response to oxidised low-density lipoprotein (oxLDL) [55]. Researchers also found that DPg protected HUVECs against oxLDL-induced oxidative stress by inducing autophagy via the AMPK/SIRT1 signalling pathway [56].

Total Flavonoids of Matsuba

Pine needles are a natural source of matsuba total flavonoids. Antioxidant, anti-inflammatory, and antibacterial properties are found in it [57, 58]. By decreasing malondialdehyde (MDA) levels and increasing SOD, GSH-PX, and CAT activities, matsuba's total flavonoids can reduce oxidative stress. Also, matsuba's total flavonoids can suppress LDL oxidative modification, eliminate O2 and H2O2 radicals directly, prevent free radical-induced oxidative stress chain reactions, and prevent the development of harmful compounds such copolyludiene and LPO [17]. This suggests that matsuba's total flavonoids could be an effective treatment for coronary heart disease.

Ischemia-Reperfusion Injury

Reoxygenating tissues that had their oxygen supply momentarily cut off causes a rise in reactive oxygen species (ROS) and oxidative stress, which in turn damages the mitochondrial ultrastructure and their metabolism [59]. It is now considered a key component in determining the outcome and chance of survival for cardiovascular disease patients. The synthesis of xanthine oxidase, the neutrophil respiratory burst, the mitochondrial single-electron reduction, the autoxidation of catecholamines, and intracellular Ca2+ overload are the primary causes of the an increase in ROS [60]. Myocardial cell death, inflammatory responses, and abnormalities in energy metabolism can be directly caused by an overabundance of reactive oxygen species (ROS) in the myocardial ischemia region [61]. Several studies have demonstrated that the active components of different CHMs can regulate oxidative stress and protect cardiac cells from ischemia-reperfusion injury.

Orientin

Natural plant extracts contain the flavonoid component known as orientationin. In addition to its antioxidant and anticancer effects, orientin aids in heart remodelling and protects against myocardial ischemia-reperfusion injury by bolstering antioxidant defences [62]. Reducing levels of ROS and inhibiting the oxLDL-induced increase in TNF-α, IL-6, and IL-1β, orientin has been demonstrated to have certain effects in research [63]. Orientin preserves the structural integrity of RBCs, decreases oxidative stress, and increases the activity of antioxidant enzymes, all of which protect RBCs from oxidative damage [18]. Research has also shown that orientin maintains autophagic equilibrium and regulates apoptosis through AMPK, Akt, mTOR, and Bcl-2 signalling. On top of that, orientin shields cardiac cells from hypoxia-reoxygenation damage [64]. The prevention of oxidative stress is central to orientin's protective actions.

Hawthorn Leaf Flavonoids

Hawthorn leaf flavonoids are the extract of the hawthorn dry leaves of *Rosaceae*. It possesses antioxidant, anti-inflammatory, and hypolipidemic activities [65]. Hawthorn leaf flavonoids were found to enhance the activity of antioxidant enzymes and inhibit the oxidative modification of LDL-C, while also improving oxidative stress-induced damage to the rat myocardium through the PKC-alpha signaling pathway. Further, the extract was shown to activate PPAR-α signaling to reduce blood triglycerides and regulate the vascular pathological response [66]. It was also found that hawthorn leaf flavonoids could protect vascular endothelial cells from free oxygen radicals by reducing lipid peroxidation and enhancing the activity of antioxidant enzymes and radical scavenging [67]. Therefore, hawthorn leaf flavonoids may be used for the prevention of myocardial injury induced by oxidative stress.

Anemarrhenoside

Anemarrhenoside is a steroidal saponin monomer extracted from the dried rhizome of *Anemarrhena asphodeloides*, while also being its most abundant component [68–70]. Saponins E-I, E-II, B-II, B-III, and A-III of *Anemarrhena asphodeloides* can promote the production of SOD. Anemarrhenosides E-I and E-II can also inhibit the expression of prooxidative stress proteins and the abnormal aggregation of platelets [71]. It is reported that 35 different metabolites related to oxidative stress can be found in the H_2O_2-induced oxidative stress injury model of PC12 cells, and Anemarrhenoside B-II may play a protective role against

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oxidative stress by decreasing the formation of free radicals via regulation of oxidative stress-related metabolites [72]. In addition, Anemarrhenoside A-III has been reported to regulate the formation of ROS in cells and increase SOD and catalase (CAT) in a concentration-dependent manner, thus regulating intracellular oxidative homeostasis [73].

Hesperidin

Hesperidin is a flavonoid widely found in lemon or citrus fruits and has strong antioxidant activity [74]. Hesperidin has been reported to have a wide range of pharmacological effects, such as regulation of lipid metabolism abnormalities, protection of cardiovascular endothelial cells, antioxidant activity, and regulation of autophagy [75, 76]. Research shows that hesperidin can inhibit oxidative stress by regulating Nrf2/ARE/HO-1 and TGF-beta1/Smad3 signal transduction [77]. The Nrf2/ARE-HO-1 axis mediated by ERS-PERK signaling is a new target for the treatment of myocardial ischemia-reperfusion injury [78]. Moreover, hesperidin can inhibit autophagy by activating the PI3K/Akt/mTOR signaling pathway, contributing to its myocardial protective effect on ischemia-reperfusion injury. Hesperidin's mechanism of action is related to the inhibition of oxidative stress [79].

Hypertension

Hypertension is a clinical syndrome characterized by high blood, which may be accompanied by functional damage of the heart, brain, and kidney [80, 81]. It has been proven that ROS play an important role in the pathophysiological process of hypertension. Increased oxidative stress is an important mediator of endothelial damage in hypertension, which is related to the increased synthesis of oxidants, such as hydrogen peroxide (H_2O_2) and nitric oxide (NO), and decreased antioxidant bioavailability [82, 83]. During hypertension, plasma myeloperoxidase levels and oxidative stress are significantly increased. Treatment with antioxidants inhibiting NADPH oxidase and ROS can effectively prevent the abnormal increase in blood pressure [84, 85].

ROS, as regulatory signaling molecules, can regulate the endothelial function of blood vessels as well as the relaxation and growth of vascular smooth muscle cells. In addition, ROS can stimulate cells to produce growth factor-like cell responses [86, 87]. MAPK signal transduction is a major mechanism that mediates vascular damage in hypertension. ROS-induced oxidative stress can inhibit the activity of tyrosine phosphatase and enhance the activity of MAPKs. Overexpression of MAPKs causes the abnormal activation of NF-κB and HIF-1α, induces vascular damage caused by lipid peroxidation, and thus aggravates the vascular remodeling, which occurs during hypertension [88–90]. Recent studies have found that polyphenols in medicinal plants can slow down the progress of lipid peroxidation-induced vascular damage by regulating oxidative stress. These observations provide new options for the treatment of hypertension.

Resveratrol

Resveratrol is a natural polyphenol present in peanuts, wine, mulberries, and other plants. It is an antioxidant compound that may be used to prevent and treat CVD [91–93]. Resveratrol can scavenge free oxygen radicals in the body [94], and studies have reported that it can prevent and treat hypertension by inhibiting oxidative stress [95, 96].

Resveratrol inhibits the formation of oxygen free radicals and reduces oxidative stress and blood pressure by enhancing the ability of redox proteins to alter the redox environment of cells [97]. Moreover, resveratrol can increase the expression of endothelial nitric oxide synthase (eNOS) by activating SIRT1 [98] and can effectively inhibit the uncoupling of eNOS and the generation of superoxide radicals through the inhibition of oxidative stress and ROS formation, thus maintaining normal vascular function and reducing blood pressure. The interaction between resveratrol and SIRT1 can also inhibit the expression of the angiotensin-II receptor, hindering vasoconstriction caused by angiotensin-II, resulting in blood vessel relaxation and a lower blood pressure [99].

Tea Polyphenols

Tea is a traditional drink in China and one of the most popular drinks in the world. Tea polyphenols, the most important bioactive components of tea, also have beneficial effects for the prevention and treatment of hypertension [20]. Tea polyphenols can enhance endogenous SOD activity, inhibit lipid peroxidation, increase ATP levels, and inhibit the formation of free radicals [100].

Tea polyphenols have no regulatory effect on normal blood pressure but can significantly reduce the abnormal increases in blood pressure. The underlying mechanism is related to the increase in antioxidant enzyme activity and the decrease in oxidative stress [101]. It has been reported that intravenous injection of tea polyphenols can reduce blood pressure in rats with acute hypertension while also effectively inhibiting ROS formation, downregulating homocysteine-metabolizing enzymes and related metabolites in the rat aorta, and effectively reducing hypertension [102].

Saponins of Panax notoginseng

Saponins of *Panax notoginseng* (SPN) have significant antioxidant effects on hypertension [103]. SPN can inhibit the formation of free oxygen radicals and regulated erythrocyte rheology in patients with hypertension. SPN can also significantly reduce MDA, increase the expression of SOD, increase the deformability, and reduce the aggregation of red blood cells [104]. *Panax notoginseng*, a medicinal plant, also contains ginsenoside Rb3, which can increase the endothelium-dependent relaxation of spontaneously hypertensive rats *in vitro*. The regulatory pathways behind this mechanism are related to antioxidant signaling [105]. SPN can also reduce the content of LPO in the brain and blood, allowing for enhanced resistance

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against aging and oxidative stress. Further, it increases the levels of GSH and CAT in serum, enhancing antioxidant defenses and lowering blood pressure [106]. Thus, SPN represents a novel option for the treatment of hypertension.

Berberine

Berberine is a natural extract from *Rhizoma coptidis*. It is reported that berberine has therapeutic effects on a variety of CVDs. Further, berberine has antioxidant, anti-inflammatory, antiatherosclerosis, and antihypertensive effects [107–109].

The antihypertensive activity of berberine is due to inhibiting the activity of cholinesterase, thus activating the M-receptor on vascular endothelial cells and promoting the release of the vasodilator NO from endothelial cells, which results in peripheral vascular smooth muscle relaxation. This mechanism may also contribute to the antioxidant effect of berberine [110, 111]. In addition, it has been reported that berberine can regulate AMPK signaling and inhibit the overexpression of p-mTOR. Further, berberine can reduce the levels of CRP, TNF-α, and IL-6 in plasma. This extract is also able to reduce myocardial autophagy and apoptosis through the AMPK/mTOR pathway, thus alleviating myocardial injury. In conclusion, berberine may be used to regulate blood pressure and prevent myocardial injury.

Allicin

Allicin is a sulfur-containing compound extracted from the bulb of *Allium* (*Liliaceae*). Allicin is modified by alliinase and has strong hydrophobicity. It can quickly reach the intracellular space through the cell membrane [112, 113]. Allicin can exert an antioxidant effect by scavenging free radicals, reducing reactive oxygen species, inducing glutathione production, and regulating NOS. It has also been described as a potential drug for the prevention and treatment of hypertension [114, 115].

Studies have reported that allicin can strongly inhibit the formation of ROS, reduce H_2O_2-induced apoptosis, and increase SOD and NO levels, as well as the expression of eNOS. It is suggested that allicin protects vascular endothelial function through its antioxidant activity, thus reducing vascular endothelial damage caused by oxidative stress [116]. Studies have revealed that allicin can reduce the vascular response to angiotensin-II, downregulate the expression of AT1R/KEAP1, increase the expression of Nrf2, upregulate antioxidant enzymes, reduce oxidative stress, and relieve the high tension of blood vessels [114]. Therefore, allicin may be another promising agent for treating hypertension.

Curcumin

Curcumin is a polyphenol compound extracted from the rhizome of a turmeric plant. Curcumin has anti-inflammatory, antioxidant, antifibrosis, and antitumor pharmacological activities [117–119]. Experimental studies have demonstrated curcumin's strong antioxidant effect. Curcumin inhibits oxidative stress by reducing the formation of peroxides in blood vessels, reduces vascular resistance, restores vascular reactivity, and inhibits the occurrence and development of hypertension [120]. Curcumin can also inhibit H/R-induced apoptosis and autophagy in H9c2 cardiomyocytes by upregulating Bcl-2 and inhibiting the expression of Bax, BECN1, BNIP3, and SIRT1 [22]. Curcumin regulates autophagy by inhibiting PI3K-AKT-mTOR signal transduction, promoting the dissociation of BECN1 and Bcl-2, preventing FOXO1 acetylation, and reducing oxidative stress, thus protecting vascular endothelial cell function and controlling blood pressure [121].

Heart Failure

Heart failure is considered the end-stage of various heart diseases, and cardiomyocyte apoptosis caused by oxidative stress has been described as the most important factor in heart failure [122]. Since the discovery of SOD in 1969, animal experiments and clinical trials have strongly supported the close relationship between oxidative stress and heart failure. Antioxidant drugs can prevent some of the pathological processes leading to heart failure, including cardiac hypertrophy, cardiomyocyte apoptosis, and ischemia-reperfusion injury [123]. Research by Liu et al. revealed that during the stage of compensatory cardiac hypertrophy, SOD and GSH-PX levels increased, LPO decreased, animal blood flow was stable, and the enhanced activity of the endogenous antioxidant system could effectively resist damage induced by exogenous ROS and reperfusion [124, 125]. It has been reported that in animal models of compensatory cardiac hypertrophy, the production of ROS by NADPH oxidases will gradually increase to a peak, which is at the level of heart failure decompensation [126].

Research has also reported that the increase in oxidative stress is related to the increase in autophagy during heart failure following pressure overload. In H9c2 cardiomyocytes, high concentrations of H_2O_2 increased autophagy. Therefore, the autophagy and oxidative stress may contribute to heart failure after chronic pressure overload [122]. Active components of CHM can regulate oxidative stress and autophagy and, thus, may be helpful in the treatment of heart failure [127, 128].

Astragaloside IV

Astragaloside IV (As-IV) is a natural saponin purified from *Astragalus membranaceus*. As an exogenous antioxidant, As-IV can significantly protect myocardial cells and mitochondria during the process of heart failure [129–131]. This protective effect is mainly achieved by an increase in the reserve respiratory capacity of cardiomyocytes and mitochondrial ATP after oxidative stress injury, as well as through the increased activity of T-SOD, GSH-Px, and CAT in cardiomyocytes [132, 133]. As-IV can also improve the metabolic rate of cardiomyocytes, reduce the release of MDA and NOS, and inhibit the generation of free

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oxygen radicals, alleviating damage to the membrane of cardiomyocytes and thus improving their viability [134].

As-IV has also been reported to inhibit ROS and NADPH production by upregulating PGC-1α and TFAM, as well as to promote mitochondrial autophagy and mitochondrial biogenesis, contributing to the protection of damaged mitochondria through its antioxidant activity [135]. As-IV can also reduce the activities of CPK and LDH, reduce the loss of mitochondrial membrane potential, and ultimately slow down cardiomyocyte apoptosis [136–138].

Tetramethylpyrazine

Tetramethylpyrazine (TMP) is the main active alkaloid ingredient of *Ligusticum* [139, 140]. TMP can reverse the PI3K/Akt signal pathway inactivation caused by hypoxia and reduce oxidative stress-induced cardiomyocyte apoptosis by downregulating miR-499a and upregulating SIRT1 signaling [141]. Oxidative stress induced by oxygen deficiency after heart failure causes great damage to cardiomyocytes, and TMP can directly enhance myocardial protection by reducing oxidative damage. Further, it can also inhibit cardiomyocyte apoptosis by regulating the expression of apoptosis-related proteins such as Bcl-2, Bax, and caspase-3 and the NF-κB pathway [142].

Recent studies show that TMP could relieve vascular tension and counteract oxidative stress by scavenging ROS, downregulating ERK1/MAPK signaling, and inhibiting NF-κB. TMP can also protect vascular endothelial cells from H_2O_2-induced injury by increasing the content of phosphatidylcholine, reducing the release of arachidonic acid, and inhibiting the phosphorylation of cytosolic phospholipase A [143, 144]. TMP, as an NADPH oxidase inhibitor and ROS scavenger, may be a potential antioxidant drug for the treatment of heart failure [145].

Gastrodin

Gastrodin is a glucoside extracted from the rhizome of *Gastrodia elata* Blume [146]. It was found that gastrodin could inhibit the formation of and scavenge oxygen radicals as well as inhibiting LPO in the myocardium during the decompensated stage of heart failure [147, 148]. Further, gastrodin was found to inhibit oxidative stress by activating ERK1/2 signaling and reducing GSK-3β overexpression [149].

Gastrodin can also mitigate myocardial injury caused by myocardial ischemia-reperfusion and improve the morphology of damaged myocardial tissue. These effects were related to the enhancement of SOD-mediated inhibition of oxidative stress [150]. In addition, during myocardial ischemia-reperfusion, free oxygen radical production occurs along with the outflow of potassium ions, resulting in the overexpression of inflammatory cytokines and subsequent injury of myocardial cells. Reduced numbers of inflammatory and red blood cells in the interstitial space were observed in myocardial ischemia-reperfusion injury after gastrodin pretreatment. Further, the degree of myocardial cell damage was also lower, which may be related to the antioxidant mechanism of gastrodin [151].

Safflower

Safflower is an extract of *Crocus sativus* L. and is commonly used in the treatment of CVD. Clinical studies have shown that safflower has antioxidant and antiarrhythmic effects, as well as protective effects on damaged myocardium [152–154]. Thus, safflower is an antioxidant with potential for the prevention and treatment of heart failure. It has been reported that safflower can significantly inhibit the overexpression of proapoptotic genes *Bad* and *Bax* by inducing autophagy. Further, safflower treatment reversed apoptosis induced by angiotensin-II (Ang-II) in H9c2 cells [155]. Safflower also inhibited H_2O_2-induced oxidative stress injury by upregulating Nrf2/HO-1/NADPH/NQO1 signaling and Akt phosphorylation [156]. Therefore, safflower may have potential for the treatment and prevention of heart failure through its antioxidant and antiapoptotic activities.

Ferulic Acid

Ferulic acid (FA) is a phenolic acid found in *Angelica sinensis*, chuanxiong, and other medicinal plants. FA has strong antioxidant capacity and not only inhibits free radical production but also downregulates free radical activity [157]. It has been found that FA can reduce the myocardial infarction area and LDH, CK, and cardiac troponin levels in a dose-dependent manner. FA protects myocardial tissue by activating PI3K/Akt/mTOR signaling and restoring autophagic flux, as well as through its antioxidant activity [158]. It can also increase the expression of Beclin-1/LC3-II and ATG5, while protecting cardiomyocytes from caspase-dependent and caspase-independent apoptosis by activating HSP70 and Bcl-2 [159]. At the same time, FA can counteract excessive ROS production and induce autophagy, thus inhibiting cell apoptosis [160]. Therefore, the antiapoptotic effect of FA may be mediated by its antioxidant and autophagy-inducing activities.

Arrhythmia

Arrhythmia is caused by abnormal sinoatrial node activity. Studies have shown that the mechanism of arrhythmia is closely related to oxidative stress [161]. Slow activation of the sinus node caused by oxidative stress or abnormal conduction can lead to arrhythmia [162]. Studies have shown that ROS, MDA, and other oxidative stress markers in the serum of patients with tachyarrhythmia were significantly increased, while the expression of SOD, TAC, GSH, and other antioxidant markers was decreased. In addition, oxidative stress can promote the occurrence of atrial fibrillation, a vicious circle that will eventually lead to the aggravation of arrhythmia symptoms [163]. These observations suggest that oxidative stress plays an important role in the pathogenesis of arrhythmia. At present, traditional antioxidants cannot achieve the desired therapeutic effect. However, active components derived from

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medicinal plants can regulate the heart rate by inhibiting oxidative stress, suggestive of their potential as an antiarrhythmic drug in the future.

Paeonol

Paeonol is an extract of the rhizome of *Paeonia suffruticosa*, which has antibacterial, anti-inflammatory, and antioxidant effects [164, 165]. Paeonol can prevent the occurrence of arrhythmia, shorten the duration of atrial fibrillation or the conduction block, and protect against ischemia-reperfusion myocardial injury. It has been reported that ischemia-reperfusion causes an increase in free radicals, a decrease in SOD activity, and an increase in MDA content, in parallel to accelerated myocardial injury and increased instability of cardiac bioelectrical conduction, leading to arrhythmia. However, paeonol can enhance SOD scavenging of endogenous radicals and reduce LPO levels, potentially exerting antiarrhythmic effects and improving myocardial injury. Paeonol can also block calcium channels of cardiomyocytes, inhibit the transient outward potassium current, selectively block the fast sodium channel, reduce the range of phase 0 depolarization, and shorten the time course of action potential in ventricular muscle [166]. These outcomes may be related to paeonol's ability to inhibit oxidative stress.

Matrine

Matrine is a natural extract from *Sophora flavescens*. It possesses antioxidant, antiviral, and antiarrhythmic activities [167–169]. Matrine can directly inhibit the flow of sodium ions outside the myocardial cell membrane and maintain the normal heart rhythm [170]. It can also reduce cardiomyocyte stress and improve ectopic heartbeats by affecting the potassium and sodium ion transfer system at the cardiomyocyte membrane [171]. Research has shown that matrine can prolong the refractory period of the atrium and ventricle by inhibiting oxidative stress, can reduce the excitability of the atrium and the ventricular muscle, and can pace the conduction system. Further, matrine stabilizes the heart rhythm by inhibiting oxidative stress and increasing endogenous antioxidant activity, thus protecting the structure and function of mitochondria in cardiomyocytes [172, 173].

Acute Myocardial Infarction

Acute myocardial infarction (AMI) is a disease with high mortality and is caused by persistent ischemia and hypoxia of the coronary artery. Early reperfusion following myocardial infarction is the most essential form of treatment. However, when blood supply is restored, excessive free oxygen radicals will damage tissues leading to ischemia-reperfusion injury. Studies have shown that myocardial ischemia-reperfusion injury is closely related to oxidative stress and myocardial autophagy. Autophagy can protect cardiomyocytes from ischemia and accelerate cell death during reperfusion [174, 175]. Moreover, trimetazidine treatment can reduce the oxidative stress and autophagic flux induced by acute myocardial infarction, thus reducing infarction size. Studies have indicated that cardiomyocytes, oxidative stress, and autophagy are involved in the pathological process of AMI and ischemia-reperfusion injury. In AMI, the increase in ROS/autophagy and the decrease in SOD can enhance oxidative stress and aggravate myocardial injury. The induction of autophagy may be related to the activation of the ROS-ATM-LKB1-AMPK signal axis [176]. This axis could represent a new therapeutic target in the treatment of AMI through CHM active components.

Astragalus Polysaccharides

Astragalus polysaccharides (APS) are water-soluble polysaccharides with biological activity, extracted from *Astragalus*. APS are increasingly considered potential exogenous antioxidants. It is reported that APS have antioxidant, antiviral, and anti-inflammatory pharmacological effects [177, 178]. APS can remove superoxide anions and hydrogen free radicals, improve the activity of SOD, GPX, and CAT, and reduce the levels of LPO. APS can also reduce cell apoptosis, the production of DHE, cytosolic nitrotyrosine products, and nuclear oxidative stress (8-OH-AD), while reducing ROS generation [179]. APS can also reduce the troponin and creatine phosphokinase, as well as the mRNA expression of Bcl-2, Bax, caspase-3, p53, Apaf-1, and AIF, leading to an improved antioxidant capacity and enhanced protection against cardiac injury caused by myocardial cell apoptosis [180].

Quercetin

Quercetin is one of the most well-known flavonoids. It can form complexes with superoxide anions (O_2^-) to reduce the production of oxygen radicals and couples with Fe_2^+ to prevent the formation of Fenton radicals. Quercetin also reduces the consumption of NADPH by inhibiting aldose reductase, improving the body's antioxidant capacity [181]. Quercetin can also scavenge free radicals produced in macrophages, inhibit the oxidation of LDL, protect tocopherol, and regenerate oxidized α-tocopherol [182].

According to a previous report, quercetin can maintain proper ST segment elevation in myocardial infarction model rats, reduce the level of LPO products in the rat serum and heart, and protect the damaged myocardium [183]. Quercetin could reverse the increase in NO, MDA, MPO, and caspase-3 activity, while decreasing GSH and SOD activity in the ischemia-reperfusion group. It has also been suggested that quercetin can alleviate tissue injury induced by AMI through its antioxidant and antiapoptotic effects [184]. Moreover, quercetin protects vascular endothelial cells and reduces blood pressure through antioxidant activity [185]. Thus, quercetin is a potential drug for the treatment of AMI and hypertension in the future.

Tanshinone II-A

Tanshinone II-A is a lipid-soluble phenanthraquinone extracted from the rhizome of *Salvia miltiorrhiza*. It possesses antioxidant properties,

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regulates autophagy, and has certain advantages in the protection of myocardial cells [186, 187]. Tanshinone II-A can alleviate oxidative stress injury of H9c2 cells induced by DOX, enhance autophagy in H9c2 cells, and mitigate myocardial injury [188]. Tanshinone II-A exerts its antioxidant effects through NRF-2, reducing DOX cardiotoxicity. These antioxidant properties of tanshinone II-A play an important role in protecting myocardial cells after AMI [189]. Autophagy is a protective mechanism allowing cells within plaques to fight against and resist oxidative stress. An excessive reduction or increase in autophagic activity will affect the extent of oxidative stress-induced damage and atherosclerotic plaque development. Tanshinone II-A can also affect autophagic activity by regulating autophagy genes ATG and LC3, contributing to its antioxidant effects [190].

Gypenoside

Gypenoside (GPS) is a commonly used drug for the prevention and treatment of CVDs [191]. Its benefits include antioxidant and antiatherosclerosis properties, as well as protection of the damaged myocardium. GPS can enhance the antioxidant capacity of aging rats by increasing SOD activity and can promote c-sis gene expression in endothelial cells, as well as the synthesis and release of NO, while also improving blood circulation of the coronary artery. GPS has also been reported to restore the normal redox state of ox-LDL in HUVECs through antioxidant regulation via PI3K/Akt. Further, GPS upregulated the ratio of Bcl-2 to Bax and inhibited the expression of caspase-3, leading to apoptosis [192]. GPS has protective effects on myocardial ischemia and systolic function in rats and exerts its cardiotonic and central inhibitory effects by inhibiting the activities of Na^+/K^+-ATPase in the heart [193]. GPS contributes to the resistance of oxygen radical damage to the heart, protects the integrity of the myocardial cell membrane, and supports normal diastolic function of the heart during acute myocardial ischemia [194].

Soybean Isoflavones

Soybean isoflavone (SI) is a bioactive secondary metabolite formed during soybean growth. Studies have shown that SI can protect the cardiovascular system through its antioxidant effects [195–197]. SI enhanced the activity of SOD, decreased the level of thiobarbituric acid reactant in plasma, and enhanced the antioxidant capacity of plasma, as well as the activity of GSH-PX in erythrocytes [198]. Moreover, SI inhibited the production of peroxides and the activity of NADPH oxidase in ischemia injury [199]. Studies have reported that different concentrations of SI can inhibit the apoptosis of vascular endothelial cells in a concentration-dependent manner, thus reducing vascular endothelial damage [200].

Hydroxy Safflower Yellow

Hydroxy safflower yellow (HSYA) is a natural active component of *Carthamus tinctorius* L. of *Compositae*, which has significant anticoagulant and antioxidant activity. HSYA reduces the level of LDH and caspase-3 in the heart of ischemia-reperfusion injury models, indicative of lower apoptosis rates [201]. HSYA can also inhibit the apoptosis of myocardial cells after AMI by increasing the level of Bcl-2/Bax [202], improve the dysfunction of mitochondrial energy metabolism by activating the PI3K/Akt signaling pathway, and play a protective role for the myocardium [203]. HSYA is a water-soluble antioxidant active component, capable of clearing oxygen radicals and inhibiting LPO generation, thus protecting the myocardial cell membrane. It has also been found that HSYA has a chalcone structure and various phenolic hydroxyl groups. HSYA's antioxidant effect may be related to the action of these phenolic hydroxyl groups [204]. HSYA can also increase the expression of NADPH and NQO1, increase the phosphorylation of Akt, and inhibit H_2O_2-induced oxidative stress injury by activating Nrf2/HO-1 [156]. Overall, there is a growing body of evidence for the antioxidant properties of HSYA.

III. SOME HERBAL PLANT USED AS CARDIOPROTECTIVE

Nerium oleander

An evergreen shrub native to Anatolia, northern America, and the Easter Mediterranean, Nerium oleander (NO) is a member of the Apocynaceae family. No concentration has been demonstrated in experiments to act as a cardioprotective agent by increasing antioxidant components that fight oxidative stress.All four seasons—leaves, blossoms, roots, and bark—are utilized in medicinal formulations. The phytochemicals found in this plant include tannic acid, oleanolic acid, uzarigenin, neriodorein, oleandrose, karabin, neriodin, nerium D, nerium F, oleanolic acid, digitoxigenin, gitoxigenin, neriantin, odoroside, adyresin, ursolic acid, oleandrin, scopolin, scopoletin, oleandrigenin, 16-acetyl gitoxigenin, deacetyloleandrin, and dambonitol.[205] After inducing myocardial oxidative stress in mice with isoproterenol,[206] looked into the cardioprotective potential of NO flowers and discovered that it had good action.

Amaranthus viridis

The plant family Ginkgoaceae includes Ginkgo biloba L. This plant is considered a "living fossil" because to its position among the earliest seed specimens. Ginkgolides, flavones glycosides, flavonol, ascorbic acid, diterpen lactones, catechin, sesquiterpenes, and superoxide dismutase based on iron are all present. There is evidence that this plant has a wide range of biological effects, such as those associated with antioxidants, microbes, inflammation, memory, liver protection, depression, blood clotting, ulcers, cytotoxicity, anti-aging, and stress. Many people also seek out this plant for its nutritional and therapeutic properties. In addition to fatty acids, tannins, essential

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oils, carotenoids, quercetin, and myricetin, ginkgo biloba has a plethora of additional phytoconstituents. Through the secretion of prostaglandins and NO, ginkgo biloba extract was found to increase blood flow, reduce hypoxia, improve blood rheology, cause platelet aggregation, and decrease capillary permeability.[207]

Terminalia arjuna

With a typical height of sixty to eighty feet, Terminalia arjuna is a massive evergreen tree. Combretaceae is the family to which this plant belongs. The sub-Himalayan regions of India are its most plentiful habitat. The bark is crimson on the inside and gray-brown on the outside. Phytoconstituents found in arjuna include tannins, triterpenes, and flavonoids.60 Cardioprotective action is found in the Arjuna plant's bark and leaves. The various plant substances that make up phytoconstituents include arjunetin, polyphenols, freidelin, arjunic acid, and triterpenes. By orally delivering extract dosage concentrations to Wistar rats for 28 days, the cardioprotective effect of T arjuna alcoholic extract was examined against isoproterenol-induced myocardial damage. To produce myocardial damage, all rats treated with isoproterenol (85 mg/kg body weight) were given subcutaneous injections for 2 days in a row after the 4-week treatment period ended. The rats in the control group, which consisted of normal, untreated rats, did not receive this injection. The study found that T arjuna protected the myocardium against isoproterenol-induced myocardial ischemic-reperfusion injury.[208] The cardioprotective effects of a water-based extract of T. arjuna bark were examined in a separate investigation that aimed to protect mice models against DOX-induced cardiotoxicity. According to the results, T arjuna aqueous extract has cardioprotective properties and is a safe cardiotonic. This plant's bark extract has cardioprotective properties and could be employed as an adjuvant chemotherapy medication for cancer patients. It is good for a healthy heart.

Picrorhiza kurroa

The Scrophulariaceae family includes the highly prized medicinal plant Picrorhiza kurroa, more often known as "Kutki." The northern western Himalayan region, from Kashmir to Kum, and the Indian districts of Garhwal and Sikkim are the primary habitats for this plant, which prefers to grow at an altitude of 3000 to 4500 miles above mean sea level. P kurroa compositions have shown promise in numerous chemical and pharmacological studies, and the genus Picrorhiza has recently garnered a lot of attention.64 out of 63 Among picrorhiza kurroa's many biological properties are those of an antioxidant, anticholestatic, anti-inflammatory, immunomodulatory, and hepatoprotective agent. The bitter medicine is also rich in iridoid glycosides.64 Berberine, kurrin, picrorhizetin, kutkisterol, apocynin, sesquiterpene, cathartic acid, and kutkin are some of the chemical components identified in this plant.[209] Researchers looked at the cardioprotective effects of an ethanolic extract of P. kurroa in a rat model of isoproterenol-induced myocardial infarction. At a dosage concentration of 80 mg/kg body weight, the cardioprotective effects of P kurroa extract were clearly noticeable.

IV. CONCLUSION

From prehistory up to the modern day, herbal and plant-based medicines have taken a great part in attending to our cardiovascular health. CVDs such as atherosclerosis, HTN or IRI are expected to continually rise at unprecedented rates in the coming years. With the elevating rates of CVD, exploration of herb- and plant-derived medicine with antioxidant, anti-inflammatory and anti-hypertensive properties as well as efficacy of these medicines in humans is crucial to further assess the biocompatibility of naturally derived medicine in humans. Furthermore, it is important to delve deeper into natural derivatives and their potential with nanoparticles for remedies for synergistic effects of modern improvement of technology and naturally derived medicine.

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