

Online Research @ Cardiff

This is an Open Access document downloaded from ORCA, Cardiff University's institutional repository: <http://orca.cf.ac.uk/125428/>

This is the author's version of a work that was submitted to / accepted for publication.

Citation for final published version:

Sedighi, M., Sewell, Robert D. E., Nazari, A., Abbaszadeh, S., Cheraghi, M., Amini, A., Heydari, Z. and Rafieian-Kopaei, M. 2019. A review of the most important medicinal plants effective on cardiac ischemia-reperfusion injury. *Current Pharmaceutical Design* 25 (3) , pp. 352-358.
10.2174/1381612825666190329144016 file

Publishers page: <https://doi.org/10.2174/1381612825666190329144016>
<<https://doi.org/10.2174/1381612825666190329144016>>

Please note:

Changes made as a result of publishing processes such as copy-editing, formatting and page numbers may not be reflected in this version. For the definitive version of this publication, please refer to the published source. You are advised to consult the publisher's version if you wish to cite this paper.

This version is being made available in accordance with publisher policies. See <http://orca.cf.ac.uk/policies.html> for usage policies. Copyright and moral rights for publications made available in ORCA are retained by the copyright holders.



A review of the most important medicinal plants effective on cardiac ischemia-reperfusion injury

Mehrnoosh Sedighi¹, Robert D. E. Sewell², Afshin Nazari³, Saber Abbaszadeh⁴,
Mostafa Cheraghi¹, Abdolhakim Amini⁴, Zahra Heydari⁵, Mahmoud Rafieian-Kopaei⁶

¹Razi Herbal Medicines Research Center, Lorestan University of Medical Sciences, Khorramabad, Iran

²Cardiff School of Pharmacy and Pharmaceutical Sciences, Cardiff University, Cardiff, CF10 3NB. Wales, U.K

³Razi Herbal Medicines Research Center, Department of Physiology, Lorestan University of Medical Science, Khorramabad, Iran

⁴Student Research Committee, Lorestan University of Medical Sciences, Khorramabad, Iran

⁵ Department of microbiology, Faculty of Basic Sciences, Lorestan University of Medical Sciences, Khorramabad, Iran.

⁶Medical Plants Research Center, Basic Health Sciences Institute, Shahrekord University of Medical Sciences, Shahrekord, Iran

*Corresponding author: rafieian@yahoo.com

Abstract

Introduction: Ischemia, referring to reduction and restriction of perfusion to myocardial tissue which involves coronary arteries through the formation of misplaced clots and thrombosis, is one of the most important cardiovascular diseases. Plant-based compounds help to improve or prevent disease through affecting the factors involved in the disease. This review was conducted to report the medicinal plants and factors effective on cardiac ischemia-reperfusion (I/R) injury to supplement the knowledge about this disease and its prevention and treatment using certain medicinal plants and their active compounds. For this purpose, medicinal plants and their potential antioxidant activities, effects on lipid levels and plaque formation, atherosclerosis and development of cardiovascular diseases and ischemia were reviewed.

Methods: To conduct this review, relevant articles published between 1983 and 2018 were retrieved from the Google Scholar, PubMed, Scientific Information Database, Web of Science, and Scopus using search terms antioxidant, ischemia, reperfusion, heart, infarct, inflammation, cholesterol, and the medicinal plants. Then, the eligible articles were reviewed.

Results: The active compounds of plants including phenolic compounds, flavonoids, and antioxidant compounds can be effective on certain pathogenic factors particularly for decreasing cholesterol and blood pressure, preventing increases in free radicals and ultimately reducing blood clots and vascular resistance to reduce and prevent ischemic disease and its harmful effects.

Conclusion: Medicinal plants presented in this article appear to be able to prevent cardiac damage and disease progression via affecting the factors that are effective on ischemia.

Key words: Cardiac ischemia, Antioxidant, Blood, Cholesterol, Infarction

INTRODUCTION

Cardiovascular diseases (CVDs) may have various causes such as hypertension, hypoxia, elevated total cholesterol, cholesterol, and low-density lipoprotein (LDL), decreased serum high-density lipoprotein (HDL) level, diabetes mellitus, increasing age, oxidative stress, and inflammation [1-5]. As one of the vital organs of the body, the heart can be exposed to ischemia that causes tissue injury and dysfunction [6]. Myocardial infarction (MI) is the most common cause of heart failure that occurs mainly due to a sudden reduction in coronary circulation following thrombotic obstruction in one of the coronary arteries already constricted due to atherosclerosis. The incidence of MI is associated with the ST segment elevation in the electrocardiogram compared to the isoelectric line. MI is associated with certain changes such as cardiomyocytes hypertrophy, myocardial arrhythmia, systolic and diastolic left ventricular dysfunction, decreased contractility of the left ventricle, increased fibrosis and apoptosis, and reduced capillary density [7].

Physicians seek to find the safest possible pattern in cardiac ischemia-reperfusion (I/R) so that contractile function can be restored in the shortest possible time and at the same time irreversible damage to muscle cells can be prevented. Unfortunately, reperfusion in the ischemic heart itself causes tissue injury referred to as I/R injury. Reperfusion can lead to dangerous and sometimes fatal ventricular arrhythmias, such as tachycardia, ventricular fibrillation, and decreased contractility. Immediately after reperfusion, necrosis and cell death begin and if perfusion persists, further apoptosis and necrosis are continued. This may also result in other complications such as renal impairment [8-11]. Free radicals can lead to cell death (via apoptotic pathways) and therefore left ventricular dysfunction through damaging lysosomes, enzyme membrane, and DNA as well as increasing intracellular calcium [12, 13].

In addition, cardiac muscle cells have two enzymatic and non-enzymatic mechanisms to balance oxidative stress. Superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPX) are the most important antioxidant enzymes. In response to MI, oxidative stress is associated with decreased antioxidant enzymes [14]. With alteplase, streptase, urokinase, and streptokinase, thrombolytic therapy is used to treat I/R injuries [15-17]. But their side effects such as generalized lethargy, effects on misplaced platelets, and allergic reactions have limited their use. Considering the increasing prevalence of CVDs and the decreasing age of the incidence of these diseases, it is essential to seek out drugs and medicinal plants that can be used routinely in the diet, help control and prevent clotting, and also reduce the risk factors for heart diseases and ischemia. Although synthetic drugs have desirable effects, they lead to long-term side effects that, in some cases, are transmitted to the next generation, while the side effects of herbal medicines are generally lower. This has led to an increase in the tendency to use herbal medicines over the last decade. Researchers have also demonstrated the positive effects of herbal medicines on cardiac ischemia. Moreover, it has been reported that the use of flavonoids and antioxidant compounds is associated with decreased risk of coronary heart disease,

atherosclerosis and MI [18, 19].

This review was conducted to report the medicinal plants and factors effective in I/R injury, to supplement the knowledge about this disease, its prevention and treatment using certain medicinal plants and their active compounds. For this purpose, medicinal plants and their potential antioxidant effects, activity on lipid levels and plaque formation, atherosclerosis and development of cardiovascular diseases and ischemia were reviewed.

2. MATERIALS AND METHODS

To conduct this review, relevant articles published between 1983 and 2018 were retrieved from the Information Sciences Institute (ISI), PubMed, Scientific Information Database (SID), and Scopus using the search terms antioxidant, ischemia, reperfusion, heart, infarct, inflammation, cholesterol and medicinal plants. Then, the eligible articles were reviewed.

3. RESULTS

3.1. Ischemia Pathology

MI and heart arrhythmia are two fatal complications of coronary artery disease [20]. MI refers to the death of myocardial cells due to long-term ischemia. Ischemia refers to the reduction and restriction of perfusion to myocardial tissue [21]. Indeed, ischemia is characterized by a lack of oxygen and inadequate removal of the metabolites due to reduced perfusion. It usually leads to several biochemical, metabolic, functional and morphological changes. Formation of tissue metabolites, particularly organic phosphates, decreases contraction intensity by reducing the sensitivity of myofilaments to calcium that can lead to death. Such conditions, referred to as ischemic storage, may lead to MI and unstable thoracic angina [22].

In response to ischemia, the myocardium causes a shift of aerobic metabolism towards anaerobic mechanisms, a reduction in heartbeats in addition to the amount of myocyte shortening during systolic contraction through decreased oxygen consumption and therefore the energy reserves decrease. In addition, the work of the heart requires the maintenance of energy from oxidative phosphorylation pathways in the mitochondria that is much greater than the total content of its ATP, which is the reason for cardiac ischemia-reperfusion injury. Clearly, immediately after blockage of the coronary artery or cell death, the heart loses its function within a few hours [23].

Ionic disturbances and activation of intracellular enzymes can also cause certain damaging changes such as the effects of proteases on cellular skeletal proteins and those of lipases on the membrane phospholipid components. Lipids also provide a good substrate to form oxygen free radicals through the formation of fatty acids, which eventually kills cells by destroying the cell membrane [24].

Over the past two decades, reperfusion in ischemic myocardium has been considered as one of the most important treatments [25]. However, it can cause tissue injury [26]. These injuries (namely I/R injuries) are widely varied and lead to life-threatening and sometimes fatal ventricular arrhythmias such as tachycardia, ventricular fibrillation, myocyte apoptosis and necrosis, as well as coronary artery endothelial injury. Due to this injury, the coronary artery response to vasodilators declines. The endothelial injury also causes activation of platelets and leukocytes adhere to the endothelium releasing cytotoxic and chemotoxic agents such as leukotrienes, proteases, cytokines and oxygen free radicals in the myocardium perfused area through neutrophil migration to the area exacerbating tissue injury [27].

In response to MI, oxidative stress accompanied by cell damage causes an increase in cardiac enzymes and decrease in antioxidant enzymes such as SOD, CAT, and GPX [14].

Pathophysiological mechanisms include release of oxygen free radicals [28], accumulation of calcium [29], activation of the renin angiotensin system [30], activation of neutrophils and inflammation [31], accumulation of platelets and products released from them such as thromboxane A₂, and activation of the complement system [27]. Furthermore, misplaced clots and thromboembolism are developed through hemostatic disorders. The thrombosis developed in the circulation due to hemostatic system defects cause arterial blockage, atherothrombotic diseases, MI, stroke, and ultimately death [15].

3.2. Epidemiology

CVDs are the most common causes of mortality worldwide. According to the WHO report, annually 12,000,000 people worldwide die due to CVDs. The prevalence of non-communicable diseases is rising in developing countries including Iran, and the burden from CVDs and associated outcomes is significant such that CVDs represent the leading cause of death. Although the available data are not reliable, approximately 300 people die in Iran each day, according to the Ministry of Health and Medical Education. The mortality rate due to CVDs in Iran is the fifth leading one worldwide, and therefore Iran has one of the highest mortality rates due to CVDs in the world. MI is the most common cause of heart failure [32].

Despite the increased public awareness of the need for prevention of heart disease and the government planning for this issue, the number of people who refer to healthcare centers for CVDs is increasing every day. Clearly, managers and officials should adopt appropriate viewpoints regarding the conditions of patients with cardiac ischemia in the community to do more efficient and accurate planning. A snapshot shows that patients with cardiac ischemia require special services that may not only be costly, but will also result in irreversible complications if their reception is delayed. It is therefore necessary for health managers and officials to have correct information about the frequency of this disease and required services as well as its epidemiological patterns [33].

3.3. Etiology

Hypertension and heart valve diseases are the underlying and exacerbating cause of heart failure and MI in 65.1% of the cases. MI refers to myocardial cell death due to the loss of circulation and the onset of severe and prolonged ischemia. In most cases, arteriosclerosis leads to MI. MI also leads to certain changes including cardiomyocytes hypertrophy, myocardial arrhythmia, systolic and diastolic left ventricular dysfunction, decreased contractility of the left ventricle, increased fibrosis and apoptosis and reduced capillary density [7]. Clinical and experimental work has indicated that the arterial endothelium plays a significant role in modulating ventricular dysfunctions and regenerating blood vessels in heart failure. In this regard, angiogenesis seems vital for blood re-supply to a region of the heart that is affected by hypoxia after MI [34].

Angiogenesis refers to the generation of vasculatures from the preexisting ones that are most important to the maintenance of the integrity of the vessels for both the process of repairing damaged tissues (wound healing) and the formation of lateral vessels in response to myocardial ischemia [35]. In its broadest sense, angiogenesis cannot be considered a single process, but rather a complicated process that is controlled by the balance between angiogenic and angiostatic factors. Among the angiogenic factors, vascular endothelial growth factor (VEGF) is known as the most potent endothelial cell-specific mitogen that causes growth, proliferation, viability, and migration of the endothelial cells and an increase in vascular permeability through receptor tyrosine kinases. The presence of VEGF after MI is vital for cardiac angiogenesis and cardiac rescue [36]. Increased availability of nitric oxide (NO) improves many of the impaired cardiac processes including angiogenesis. NO, directly and indirectly, increases gene expression and the half-life of VEGF and reduces the amount of angiostatin ultimately stimulating the process of angiogenesis [37, 38].

Reviews have reported that NO contributes significantly to protecting myocardial arteries and the myocardium itself through antioxidant and anti-apoptotic properties, prevention of Ca²⁺ overload, vasodilation, and angiogenesis [36]. In this regard, inhaled NO has been reported to cause a decrease in the myocardial tissue size and improve left ventricular function after I/R through decreasing the neutrophils [37]. In addition, exacerbating causes such as patient lack of adherence to drug regimes, age, sex, alcohol consumption, pulmonary embolism, infection, stress, and hyperthyroidism should all be taken into account.

3.4. Diagnosis

Ischemic heart diseases are diagnosed by typical pain, changes in the ECG, echocardiography, and medical history. Diagnosis of the disease is also made by determining the levels of total cholesterol, high-density lipoprotein, low-density lipoprotein, and triglyceride, blood pressure, and body mass index, history of smoking and MI, the severity of angina, and the diagnosis of coronary artery stenosis by coronary angiography [39].

3.5. Treatment

Recent studies have demonstrated that percutaneous coronary intervention and thrombolytic therapy have been used in treating I/R injuries in clinical trials. Thrombolytic agents such as alteplase, streptase, urokinase, and streptokinase are also used to treat these patients [15, 17]. These compounds have various side effects [18, 40, 41].

Treatment with medicinal plants and their compounds has the potential to prevent acute coronary syndromes, cardiac and cerebral ischemia, or ischemia in other tissues through inhibition of coagulant, inflammatory, plaque-developing activities, and cardiac enzymes as well as by increasing antioxidant enzymes. Regarding this disease, it can be said that many medicinal plants have considerable antioxidant potential and can therefore play significant roles in fighting free radicals [42].

The positive effect of a vegetarian diet is confirmed by the slowing down of growth, stopping and reversibility of coronary lesions as well as beneficial clinical effects in reducing angina, total cholesterol, LDL, and BMI in patients. The main aim of conducting this review is to study and introduce these nutritional and herbal compounds with potent antioxidant and hypolipidemic effects, and their preventive effects on the formation of free radicals and plaques as well as the development of atherosclerosis, CVDs and ischemia.

Table 1 summarizes the studies on the protective effects of medicinal plants on I/R. The botanical names, family names, used parts, studied concentrations, and action mechanisms of the plants have also been tabulated.

Table 1. Effective medicinal plants and compounds on cardiac ischemia-reperfusion

Results	Plant Part Used	Dose	Family	Plant Name	No
<i>sativa</i> contains different vitamins including vitamin C with the antioxidant property that decrease blood cholesterol and arterial blockage [43, 44].	Seed	Treating male Wistar rats with 125 mg/kg	Poaceae	<i>Avena sativa</i> L.	1
Beta-glucan derived from <i>H. vulgare</i> decreases cholesterol and LDL, increases LDH, and prevents arterial blockage and ischemia [45].	Seed	Treating male Wistar rats with 62.5 mg/kg	Poaceae	<i>Hordeum vulgare</i>	2
Proanthocyanidins present in <i>V. vinifera</i> seed maintain hydroxyl radicals, cause a decrease in intracellular calcium, enhance the resistance of ischemia/reperfusion injuries, and decrease infarct size and arrhythmias [46].	Seed	Treating male Wistar rats with 1, 10, and 100 mg/kg	Vitaceae	<i>Vitis vinifera</i>	3
Preventing the formation of free radicals and reducing necrosis, the heart inflammation, and infarct [47].	Whole	Treating male Wistar rats with 0.5%, 0.25%, and 125%	Mel. Honey	<i>Mel, Honey</i>	4
Decreasing platelet accumulation and preventing oxidation of low-density lipoproteins due to their antioxidant effects and preventing infarct [48, 49].	Leave	1 per day in human subjects	Theaceae	<i>Camellia sinensis</i>	5
Scavenging reactive oxygen species, decreasing inflammation, and preventing ischemia [50].	Fruits	Treating male Wistar rats with 500 mg/ml	Rosaceae	<i>Rosa canin</i>	6
Significantly reducing cardiac function and exacerbating Ischemia-reperfusion injuries through activating proteases and changing contractile proteins, oxidizing pyruvate in the mitochondria, producing lactate, and decreasing pH [51].	Root	Treating male Wistar rats with 0.03 and 0.06 mg/ml	leguminosa	<i>Prosopis farcta</i>	7
Scavenging free radicals and preventing arterial blockage, and reducing ischemia through decreasing malondialdehyde levels [52, 53].	Seed	Treating male Wistar rats with 400 mg/ml	Punicaceae	<i>Punica granatum</i>	8
Positive inotropic and chronotropic effects on the heart or a mechanism different from the intracellular mechanism [54].	Flowering shoots	Treating male Wistar rats with 1, 2, and 50 mg/ml	Labiatae	<i>Teucrium polium</i>	9
Increasing antioxidant property and decreasing lipid peroxidation [49].	Aerial parts	Treating male Wistar rats with 150 and 300.	Portulacaceae	<i>Portulaca oleracea</i> L.	10
Dilating coronary arteries outside the nitric oxide mechanism [55].	Leave	Treating male Wistar rats with 5, 22, 15, 5, 7, and 30	Umbelliferae	<i>Falcaria vulgaris</i>	11

Hypolipidemic, lipid peroxidation-reducing, and antioxidant enzyme activity-increasing [56].	Leave	Treating male Wistar rats with 50, 75, and 100	Oleaceae	<i>Olea europaea</i>	12
Antiarrhythmic, tachycardia-treating, calcium-blocking, cholesterol-reducing, and antioxidant [57, 58]	Flowers	Dose-dependent in human subjects	Iridaceae	<i>Crocus sativua</i>	13
Fibrinolytic and clot-lysis effects and prevention of heart diseases and ischemia [59].	Leave	0.1, 0.01, and 0.001 ml adjacent to the clot	Labiataeae	<i>Zataria moltiflora</i>	14
Fibrinolytic and clot-lysis effects and prevention of heart diseases and ischemia [59]	Fruits	0.1, 0.01, and 0.001 ml adjacent to the clot	Umbelifera	<i>Heracleum persicu</i>	15
Fibrinolytic and clot-lysis effects and prevention of heart diseases and ischemia [59].	Bark	0.1, 0.01, and 0.001 ml adjacent to the clot	Zingiberaceae	<i>Curcuma domestica</i>	16
Protecting the heart against antioxidant property, hypolipidemic and hypotensive effects, and decreasing infarct size [60, 61].	Leave	Treating male Wistar rats with 1 and 3 mg/ml	Asteraceae	<i>Chichorium intybus</i>	17

(Table 1) Contd....

Results	Plant Part Used	Dose	Family	Plant Name	No
Antioxidant property, antiarrhythmic effect, and decreasing infarct size [53].	Leave	Treating male Wistar rats with 10, 50, and 100 µg/ml	Lamiaceae	<i>Marrubium crassidens</i>	18
Preventing production of free radicals, increasing glutathione peroxidase and superoxide dismutase through decreasing creatine kinase, lactate dehydrogenase, and malondialdehyde and decreasing infarct size [62].	Leave	Treating male Wistar rats with 0.1 g	Ranunculaceae	Shen-Fu	19
Decreasing the indices of lipid peroxidation such as malondialdehyde, superoxide and hydroxyl radicals, and tissue-protecting enzymes with antioxidant property such as glutathione peroxidase and superoxide dismutase; anti-platelet accumulation property and prevention of heart diseases and ischemia [63, 64].	Leave	1% + pulverized food in male Wistar rats	Alliaceae	<i>Allium ursinum</i>	20
Potent antioxidant property, decreasing peroxidation of lipids such as malondialdehyde and decreasing cardiac troponin I, blood pressure, and infarct size [65].	Leave	50, 100, and 200 mg/kg	Lamiaceae	<i>Melissa officinalis</i>	21
Decreasing the levels of cholesterol, low-density lipoprotein, and factor 7 as well as increasing the levels of high-density lipoprotein cholesterol, and apolipoprotein A [66].	Aerial parts and seeds	1.5 g <i>G. tournefortii</i> + 98.5 g base food for two weeks in white adult male rabbits	Asteraceae	<i>Gundelia tournefortii</i>	22

Decreasing lipid peroxidation and superoxide and hydroxyl radicals and increasing antioxidative enzymes [67].	Bulbs	Feeding for three months according to human subjects' clinical needs	Liliaceae	<i>Allium sativum</i>	23
Antioxidant effects and scavenging radicals [68].	Flowers	Normal diet + 150 mg/kg extract for 30 days in adult rabbits	Hypericaceae	<i>Hypericum perforatum</i>	24
Fibrinolytic and clot-lysis effects and prevention of heart diseases and ischemia [59]. decreased serum lactate dehydrogenase · Troponin I and malondialdehyde and increased the serum superoxide dismutase[69].	Bark	50,100,200 mg/kg adjacent to the clot, ischemia	Lauraceae	Cinamomum Spp	26
Decreasing the levels of cholesterol, triglycerides, and increasing antioxidative enzymes[70]	Oil	The groups of rats selected for the study were treated orally with lovastatin (10 mg/kg) and EOAD (15–60 mg/kg) daily for the two weeks.	Asteraceae	<i>Artemisia dracunculus</i>	27

4. DISCUSSION

In this article, the positive effects of a number of medicinal plants in preventing heart disease especially I/R were reviewed. As already mentioned, medicinal plants and their compounds can cause a decrease in injuries due to cardiac ischemia through several pathways in heart and other organs like the kidney [71, 72]. The mechanisms involved include increasing oxygen supply to the heart subsequently increasing cardiac contractility, lowering blood pressure, decreasing cholesterol, triglyceride, and LDL as well as increasing HDL, cholesterol, and apolipoprotein A, reducing lipid peroxidation, MDA, calcium, and prostaglandins, dilating coronary arteries, increasing the expression of anti-apoptotic genes, reducing necrosis and inflammation, myocardial infarct size, arrhythmias, platelet accumulation, fibrinolytic effects, clot lysis, cardiac enzymes creatine kinase, lactate dehydrogenase, malondialdehyde, and cardiac troponin I, and increasing antioxidant enzymes such as SOD and GPX. The most important mechanism is the antioxidant activity.

Cardiac ischemia causes a shift of aerobic metabolism towards anaerobic mechanisms and reduction in heartbeats and the amount of myocyte shortening during contraction.

Evidence also indicates an association of the components of the coagulation system (fibrinogen and factor 7) and fibrinolytic factors including tissue plasminogen activator and plasminogen activator inhibitor with heart diseases [73]. *Zataria multiflora*, *Heracleum persicum* and *Curcuma domestica* prevent ischemia through fibrinolytic and clot lysis effects [59].

Following ischemia, inflammatory factors are activated, macrophages produce certain cytokines such as

interleukin 1(IL 1) and tumor necrosis factor (TNF) that cause enhancement of leukocyte binding, platelet accumulation and monocyte chemotactic proteins enhance leukocyte function in atheromatous plaques. The free radicals produced from macrophages cause muscle cell proliferation by oxidizing LDL. The main complications of this condition are MI and stroke [74]. Most plants introduced in the present review and some other ones such as *Chichorium intybus* and *Rosa canin* have been reported to contribute towards protecting the heart or kidney against ischemia through antioxidant, hypolipidemic, hypotensive, anti-inflammatory, and infarct size reducing effects [60, 61, 75, 76].

Hypolipidemia is another risk factor for atherosclerosis and progression of diabetes complications especially CVDs and ischemia [77, 78]. Investigations have demonstrated an inverse correlation between the use of medicinal plants or polyphenol-rich foods and CVDs. This is related to the ability of polyphenols to prevent LDL cholesterol oxidation. For example, *Olea europaea*, *Cinamomum Spp* and *Artemisia dracunculus* cause a decrease in cholesterol levels and lipid peroxidation as well as an increase in antioxidant enzymes [56, 69, 70].

In addition, beta-glucan, isolated from *Hordeum vulgare*, decreases cholesterol and LDL, increases LDH, and prevents arteriosclerosis and ischemia [45].

In patients with heart disease, arrhythmia is one of the most predisposing factors for heart failure and cardiac ischemia. The causes of cardiac arrhythmia involve one or more sets of disorders such as disruption of rhythm production by the SA node, the blockage at different points in the pathway of impulse transfer in the heart, the production of abnormal impulses, and a change of pacemaker location in the cardiac conduction rhythm generating system [13].

Certain medicinal plants such as *Crocus sativa* can reduce arrhythmia and ischemic complications via blocking calcium channels, exerting anti-arrhythmic, hypolipidemic, and antioxidant effects and inhibiting tachycardia. In response to MI, oxidative stress, accompanied by cell damage, leads to an increase in cardiac enzymes and a decrease in antioxidant enzymes such as SOD, GPO, and CAT [78, 79]. Lipid peroxidation on unsaturated fatty acids leads to the production of MDA, which can be due to the weakness of the antioxidant system [80, 81].

In MI, total LDH levels begin to increase within 2-48 hours and return to normal levels 2-3 days after the incidence of MI. Troponin is one of the contractile proteins of muscle including heart muscle. Serum troponin levels are used for MI diagnosis [82]. Cardiac troponins consist of troponins T, C, and I. In MI patients, cardiac troponins T and I begin to elevate up to three hours after the incidence of MI. Troponins T and I remain high for 10-12 and 7-10 days, respectively [83, 84]. For example, *Melissa officinalis* and *Allium ursinum* possess potent antioxidant effects and decrease peroxidation of lipids such as MDA, cardiac enzyme CTnI, blood pressure, and infarct size [63, 65].

Evidence on heart and renal diseases indicate that flavonoids and phenolic compounds in plants have

several biological effects including antioxidant, free radical-scavenging, anti-inflammatory, and anticancer activities [85-90]. Many polyphenols including catechin, quercetin and ethanol exert supportive effects against vascular diseases that can be attributed to increased fibrinolytic activity and the expression of the proteins involved in the fibrinolytic system [91]. These polyphenols cause a decrease in lipid peroxidation and enhancement of antioxidant enzyme activity through their antioxidant effects [92]. In addition to affecting cardiac ischemia positively, these antioxidant effects of the plants lead to optimal effects on many other diseases from which the patient may be suffering. Altogether, medicinal plants can be effective in ischemic heart disease through different mechanisms and patients with such diseases may be recommended to use these plants.

CONCLUSION

This article reveals that there is a negative correlation between the use of medicinal plants, full of antioxidant polyphenols and the occurrence of heart disease especially I/R, so that medicinal plants and their compounds can decrease cardiac ischemia injury via several pathways in the heart and other organs like the kidney. The mechanisms involved include dilating coronary arteries, enhancement of antioxidant enzymes such as SOD and GPX and increased oxygen supply to the heart. Subsequently there is increased cardiac contractility, reduction of blood pressure, cholesterol, triglyceride, cholesterol, LDL, lipid peroxidation, MDA, prostaglandins, necrosis, inflammation, myocardial infarct size, arrhythmias, platelet accumulation, fibrinolytic effects, clot lysis, cardiac enzymes as well as increase in HDL, and apolipoprotein A and expression of anti-apoptotic genes. In summary, medicinal plants are beneficial in ischemic heart disease through various mechanisms, and patients with these diseases are recommended to use them.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

REFERENCES

- [1] Thom TJ. International mortality from heart disease: rates and trends. *Int J Epidemiol* 1989; 18(3)(Suppl. 1): S20-8.
- [2] Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO III, Criqui M, et al. AHA/CDC scientific statement. *Circulation* 2003; 107: 499-511.

- [3] Landmesser U, Spiekermann S, Dikalov S, et al. Vascular oxidative stress and endothelial dysfunction in patients with chronic heart failure: role of xanthine-oxidase and extracellular superoxide dismutase. *Circulation* 2002; 106(24): 3073-8.
- [4] Kotur-Stevuljevic J, Memon L, Stefanovic A, et al. Correlation of oxidative stress parameters and inflammatory markers in coronary artery disease patients. *Clin Biochem* 2007; 40(3-4): 181-7.
- [5] Asadi-Samani M, Bahmani M. Trends on the treatment of atherosclerosis; new improvements. *Angiol Persica Acta* 2016; 1(1): e01.
- [6] Chan PH. Reactive oxygen radicals in signaling and damage in the ischemic brain. *J Cereb Blood Flow Metab* 2001; 21(1): 2-14.
- [7] de Waard MC, van Haperen R, Soullié T, Tempel D, de Crom R, Duncker DJ. Beneficial effects of exercise training after myocardial infarction require full eNOS expression. *J Mol Cell Cardiol* 2010; 48(6): 1041-9.
- [8] Tzivoni D, Keren A, Granot H, Gottlieb S, Benhorin J, Stern S. Ventricular fibrillation caused by myocardial reperfusion in Prinzmetal's angina. *Am Heart J* 1983; 105(2): 323-5.
- [9] Tavafi M. Suggestions for attenuation of renal ischemia reperfusion injury based on mechanisms involved in epithelial cells damages. *J Nephropharmacol* 2015; 4(1): 1-3.
- [10] Ahmadvand H, Babaeenezhad E, Hadipour-Moradi F, CheraghiVenool A. Effect of gallic acid on liver oxidative stress markers in renal ischemia-reperfusion injury in rats. *Ann Res Antioxid* 2017; 2(1): e03.
- [11] Hasanvand A. Ischemia and post-injury regeneration in proximal convoluted tubule cells. *Acta Persica Pathophysiol* 2017; 2: e01.
- [12] Piper HM, Meuter K, Schäfer C. Cellular mechanisms of ischemiareperfusion injury. *Ann Thorac Surg* 2003; 75(2): S644-8.
- [13] Manning AS, Hearse DJ. Reperfusion-induced arrhythmias: mechanisms and prevention. *J Mol Cell Cardiol* 1984; 16(6): 497518.
- [14] Tiet Z. *Fundamentals of clinical chemistry Philadelphia*. W.B. Saunders, Philadelphia 2001:352-66.
- [15] Capstick T, Henry MT. Efficacy of thrombolytic agents in the treatment of pulmonary embolism. *Eur Respir J* 2005; 26(5): 86474.
- [16] Levine MN, Raskob G, Landefeld S, Kearon C. Hemorrhagic complications of anticoagulant treatment. *Chest* 2001; 119(1)(Suppl.): 108S-21S.
- [17] Wardlaw JMBE, Zoppo G, Yamaguchi T. Thrombolysis for acute ischemic stroke. *Stroke* 2004; 35: 2914-5.
- [18] Kee NLA, Mnonopi N, Davids H, Naudé RJ, Frost CL. Antithrombotic/anticoagulant and anticancer activities of selected medicinal plants from South Africa. *Afr J Biotechnol* 2008; 7(3): 217-223.

- [19] Heidari M, Norooz Zadeh R, Abbasi M. The use of herbal drugs in cardiovascular diseases: A review article. *Iranian Journal of Cardiovascular Nursing* 2013; 2: 70-7.
- [20] Walden R, Tomlinson B. *Cardiovascular Disease* 2011; Chapt 16. In: Benzie IFF, Wachtel-Galor S, eds. *Herbal Medicine: Biomolecular and Clinical Aspects*. 2nd ed. Boca Raton (FL): CRC Press/Taylor & Francis.
- [21] Hearse DJ. Myocardial ischaemia: can we agree on a definition for the 21st century? *Cardiovasc Res* 1994; 28(12): 1737-44.
- [22] Jong JW, et al. The role of adenosine in preconditioning *Pharmacol Ther* 2000; 87: 14-9.
- [23] Ganz PGW. Hypertensive and atherosclerotic cardiovascular disease: Coronary blood flow and myocardial ischemia. *Heart Disease* W.B. Saunders, USA 2001:600-5
- [24] Sommerschild HT, Kirkebøen KA. Preconditioning - endogenous defence mechanisms of the heart. *Acta Anaesthesiol Scand* 2002; 46(2): 123-37.
- [25] Liem DA, Honda HM, Zhang J, Woo D, Ping P. Past and present course of cardioprotection against ischemia-reperfusion injury. *J Appl Physiol* 2007; 103(6): 2129-36.
- [26] Braunwald E, Kloner RA. Myocardial reperfusion: A double-edged sword? *J Clin Invest* 1985; 76(5): 1713-9.
- [27] Moens AL, Claeys MJ, Timmermans JP, Vrints CJ. Myocardial ischemia/reperfusion-injury, a clinical view on a complex pathophysiological process. *Int J Cardiol* 2005; 100(2): 179-90.
- [28] Raedschelders K, Ansley DM, Chen DD. The cellular and molecular origin of reactive oxygen species generation during myocardial ischemia and reperfusion. *Pharmacol Ther* 2012; 133(2): 230-55.
- [29] Gross GJKJ, Kersten JR, Warltier DC. Mechanisms of postischemic contractile dysfunction. *Ann Thorac Surg* 1999; 68(5): 1898-904.
- [30] Neves LA, Almeida AP, Khosla MC, Campagnole-Santos MJ, Santos RA. Effect of angiotensin-(1-7) on reperfusion arrhythmias in isolated rat hearts. *Braz J Med Biol Res* 1997; 30(6): 801-9.
- [31] Kloner RA, Giacomelli F, Alker KJ, Hale SL, Matthews R, Bellows S. Influx of neutrophils into the walls of large epicardial coronary arteries in response to ischemia/reperfusion. *Circulation* 1991; 84(4): 1758-72.
- [32] Brown DA, Jew KN, Sparagna GC, Musch TI, Moore RL. Exercise training preserves coronary flow and reduces infarct size after ischemia-reperfusion in rat heart. *J Appl Physiol* 2003; 95(6): 2510-8.
- [33] Talebizadeh N, Haghdoost A, Mirzazadeh A. Epidemiology Model of Ischemic Heart Disease in Iran. *Payesh Quarterly* 1998; 8: 16370.
- [34] Chen L-L, Yin H, Huang J. Inhibition of TGF- β 1 signaling by eNOS gene transfer improves ventricular remodeling after myocardial infarction through angiogenesis and reduction of apoptosis. *Cardiovasc Pathol* 2007; 16(4): 221-30.
- [35] Murohara T, Asahara T. Nitric oxide and angiogenesis in cardiovascular disease. *Antioxid Redox*

Signal 2002; 4(5): 825-31.

[36] Wu G, Rana JS, Wykrzykowska J, et al. Exercise-induced expression of VEGF and salvation of myocardium in the early stage of myocardial infarction. *Am J Physiol Heart Circ Physiol* 2009; 296(2): H389-95.

[37] Naseem KM. The role of nitric oxide in cardiovascular diseases. *Mol Aspects Med* 2005; 26(1-2): 33-65.

[38] Dulak J, Józkwicz A, Guevara I, Dembińska-Kieć A. Gene transfer of vascular endothelial growth factor and endothelial nitric oxide synthase--implications for gene therapy in cardiovascular diseases. *Pol J Pharmacol* 1999; 51(3): 233-41.

[39] Braunwald E. The History. In: *Heart disease: a textbook of cardiovascular medicine* ed: Braunwald E. publ Saunders. 1997; pp12.

[40] de Medeiros JMR, Macedo M, Contancia JP, Nguyen C, Cunningham G, Miles DH. Antithrombin activity of medicinal plants of the Azores. *J Ethnopharmacol* 2000; 72(1-2): 157-65.

[41] Rastegari F. The healthy diet for cardiovascular disease. *Acta Persica Pathophysiol* 2016; 1: e02.

[42] Rashidi B, Mohammadi M, Mirzaei F, Badalzadeh R, Reisi P. Amlodipine treatment decreases plasma and carotid artery tissue levels of endothelin-1 in atherosclerotic rabbits. *Pathophysiology* 2011; 18(2): 137-42.

[43] Gürbüz I, Akyüz C, Yeşilada E, Şener B. Anti-ulcerogenic effect of *Momordica charantia* L. fruits on various ulcer models in rats. *J Ethnopharmacol* 2000; 71(1-2): 77-82.

[44] Khan IA, Abourashed EA. *Leung's encyclopedia of common natural ingredients: used in food, drugs and cosmetics* 2002; 23-97.

[45] El-Arab AE, Foheid S, El-Said M. Effect of yeast and botanical beta-glucan on serum lipid profile and cecum probiotic bacteria using rats fed cholesterol diet. *Pol J Food Nutr Sci* 2009; 59: 169-74.

[46] Najafi M, Vaez H, Zahednezhad F, Samadzadeh M, Babaei H. Study the effects of hydroalcoholic extract of grape seed (*Vitis vinifera*) on infarct size and cardiac arrhythmias in ischemic reperfused isolated rat heart. *Pharm Sci* 2011; 16: 187-94.

[47] Lusby PE, Coombes A, Wilkinson JM. Honey: A potent agent for wound healing? *J Wound Ostomy Continence Nurs* 2002; 29(6): 295-300.

[48] Nègre-Salvayre A, Salvayre R. Quercetin prevents the cytotoxicity of oxidized LDL on lymphoid cell lines. *Free Radic Biol Med* 1992; 12(2): 101-6.

[49] Hozayen W, Bastawy M, Elshafeey H. Effects of aqueous purslane (*Portulaca oleracea*) extract and fish oil on gentamicin nephrotoxicity in albino rats. *Nat Sci* 2011; 9: 47-62.

[50] Daels-Rakotoarison DA, Gressier B, Trotin F, et al. Effects of *Rosa canina* fruit extract on neutrophil respiratory burst. *Phytother Res* 2002; 16(2): 157-61.

[51] Fuster V RR, Walsh R, Pool-Wilson Ph. *Hurst the heart*. China: McGraw-Hill companies 2008; 12

[52] de Nigris F, Balestrieri ML, Williams-Ignarro S, et al. The influence of pomegranate fruit extract

in comparison to regular pomegranate juice and seed oil on nitric oxide and arterial function in obese Zucker rats. *Nitric Oxide* 2007; 17(1): 50-4.

[53] Rameshrad M, Vaez H, Toutounchi NS, Fathiazad F, Garjani A. Effect of methanolic extract of *marrubium crassidens boiss* on ischemia/reperfusion induced arrhythmias and infarct size in isolated rat heart. *Pharm Sci* 2014; 20: 80.

[54] Niazmand S, Ahmadpour E, Mousavian M, Saberi Z. The inotropic and chronotropic effects of aqueous ethanolic extract from *teucrium polium*. on guinea pig isolated heart. *Majallah-i Danishgah-i Ulum-i Pizishki-i Babul* 2008; 10: 7-13.

[55] Santos RL, Abreu GR, Bissoli NS, Moysés MR. Endothelial mediators of 17 beta-estradiol-induced coronary vasodilation in the isolated rat heart. *Braz J Med Biol Res* 2004; 37(4): 569-75. [56] Andreadou I, Iliodromitis EK, Mikros E, et al. The olive constituent oleuropein exhibits anti-ischemic, antioxidative, and hypolipidemic effects in anesthetized rabbits. *J Nutr* 2006; 136(8): 2213-9.

[57] Liu N, Yang Y, Mo S, Liao J, Jin J. Calcium antagonistic effects of Chinese crude drugs: preliminary investigation and evaluation by ⁴⁵Ca. *Appl Radiat Isot* 2005; 63(2): 151-5.

[58] Xi L, Qian Z, Xu G, et al. Beneficial impact of crocetin, a carotenoid from saffron, on insulin sensitivity in fructose-fed rats. *J Nutr Biochem* 2007; 18(1): 64-72.

[59] Naderi Gh, Jafari Dinani N, Jafarian Dehkordi A, Asgari S. Shami Analysis of the compounds in the four-seasoned essential oil and study the fibrinolytic activity of these compounds in the in vitro environment. *Physiology and Pharmacology* 1988; 4: 423-9.

[60] Sadeghi N, Dianat M, Badavi M, Malekzadeh A. Cardioprotective effect of aqueous extract of *Chichorium intybus* on ischemiareperfusion injury in isolated rat heart. *Avicenna J Phytomed* 2015; 5(6): 568-75.

[61] Khaksari M, Sajadi M, Bahremand F, Vefa M. Effect of kidney bean and chicory diets on control of blood sugar in diabetic rats. *Kowsar Medical Journal* 2001; 6: 1-8.

[62] Zheng S-Y, Sun J, Zhao X, Xu J-G. Protective effect of shen-fu on myocardial ischemia-reperfusion injury in rats. *Am J Chin Med* 2004; 32(2): 209-20.

[63] Štajner D, Popović BM, Canadanović-Brunet J, Štajner M. Antioxidant and scavenger activities of *Allium ursinum*. *Fitoterapia* 2008; 79(4): 303-5.

[64] Hiyasat B, Sabha D, Grötzinger K, et al. Antiplatelet activity of *Allium ursinum* and *Allium sativum*. *Pharmacology* 2009; 83(4): 197-204.

[65] Joukar S, Asadipour H, Sheibani M, Najafipour H, Dabiri S. The effects of *Melissa officinalis* (lemon balm) pretreatment on the resistance of the heart to myocardial injury. *Pharm Biol* 2016; 54(6): 1005-13.

[66] Coruh N, Celep AS, Özgökçe F, İşcan M. Antioxidant capacities of *Gundelia tournefortii* L. extracts and inhibition on glutathione-S-transferase activity. *Food Chem* 2007; 100: 1249-53.

[67] Rietz B, Isensee H, Strobach H, Makdessi S, Jacob R. Cardioprotective actions of wild garlic

- (*allium ursinum*) in ischemia and reperfusion. *Mol Cell Biochem* 1993; 119(1-2): 143-50. [68] Kabiri N, Setorki M. Regression of hypercholesterolemic atherosclerosis in rabbits by hydroalcoholic extracts of *Hypericum perforatum*. *J Med Plants Res* 2012; 6: 2540-9.
- [69] Sedighi M, Nazari A, Faghihi M, et al. Protective effects of cinnamon bark extract against ischemia-reperfusion injury and arrhythmias in rat. *Phytother Res* 2018; 32(10): 1983-91.
- [70] Jalilzadeh-Amin G, Anassori E, Namvar M-T. Renal ischemia/reperfusion injury; from pathophysiology to treatment *J Renal Inj Prev* 2015; 4(2): 20-7.
- [71] Malek M, Nematbakhsh M. Renal ischemia/reperfusion injury; from pathophysiology to treatment. *J Renal Inj Prev* 2015; 4(2): 207.
- [72] Baradaran A. Administration of herbal drugs in geriatric individuals; trends on its help and hazards. *Geriatr Persia* 2017; 1(1): e01.
- [73] Gensini GF, Comeglio M, Colcila A. Hemostatic factors, atherogenesis and atherosclerosis. *Biomed Pharmacother* 1996; 50: 395-405.
- [74] Leopold JA, Loscalzo J. Oxidative risk for atherothrombotic cardiovascular disease. *Free Radic Biol Med* 2009; 47(12): 1673-706.
- [75] Siregar S, Romdam T, Stanzah H, Firmansyah I. The effect of long-acting PDE-5 inhibitor on renal ischemia/reperfusion injury in Wistar rats; a study on serum cystatin C and renal histopathological findings. *J Nephropathol* 2019; 8(1): e07.
- [76] Shahzamani F, Monajemi R, Nematbakhsh M. High-salt intake during pregnancy may influence the outcome of renal ischemia/reperfusion in adult offspring. *J Renal Inj Prev* 2018; 7(2): 69-72.
- [77] de Wardener HE. Salt reduction and cardiovascular risk: the anatomy of a myth. *J Hum Hypertens* 1999; 13(1): 1-4.
- [78] Chen Y, Reaven G. Insulin resistance and atherosclerosis. *Diabetes Rev (Alex)* 1997; 5: 331-42.
- [79] Tiet Z. *Fundamentals of Clinical Chemistry* 5th ed. 2001; 352-66.
- [80] Pérez JM, Arenas FA, Pradenas GA, Sandoval JM, Vásquez CC. *Escherichia coli* YqhD exhibits aldehyde reductase activity and protects from the harmful effect of lipid peroxidation-derived aldehydes. *J Biol Chem* 2008; 283(12): 7346-53.
- [81] Mohammadi MRM, Rasouli M. *Laboratory of Medical Biochemistry 1 and 2* 2015; 1.
- [82] Basso C, Calabrese F, Corrado D, Thiene G. Postmortem diagnosis in sudden cardiac death victims: macroscopic, microscopic and molecular findings. *Cardiovasc Res* 2001; 50(2): 290-300.
- [83] Burtis CA. Ashwood ER *Fundamentals of Clinical Chemistry* 5th ed. 2001.
- [84] Greager MA, Libby P, Zipes DP, Bonow RO, Braunwald E. Peripheral arterial disease. *Braunwald's heart disease: A textbook of cardiovascular medicine* 7th ed. 2005; 1437-61.
- [85] Kumar S, Kumar D. Evaluation of antioxidant potential, phenolic and flavonoid contents of

hibiscus liliaceous flowers. EJAF CHE 2008; 7: 2863-71.

[86] Nasri H. Help or hindrance; administration of herbal drugs for kidney diseases. Toxicol Persa 2016; 1(1): e04.

[87] Baradaran A. The role of biomarkers to detect progression of diseases. J Negat Results Clin Exp Stud 2018; 1(1): e05.

[88] Dehghan Shahreza F. Oxidative stress, free radicals, kidney disease and plant antioxidants. Immunopathol Persa 2017; 3(2): e11.

[89] Nasri H. Trends toward amelioration of renal inflammation and fibrosis in various kidney diseases. J Inj Inflamm 2016; 1(1): e02.

[90] Dehghan Shahreza F. Vascular protection by herbal antioxidants; recent views and new concepts. J Prev Epidemiol 2016; 1(1): e05.

[91] Grenett H, Abou-Agag L, Parks D, Booyse F. Ethanol and polyphenols (CAT, QUER) increase expression of fibrinolytic protein mRNAs in vivo in rat aortic endothelium. Biol Res 2004; 37: 342.

[92] Prasad K, Kalra J. Oxygen free radicals and hypercholesterolemic atherosclerosis: effect of vitamin E. Am Heart J 1993; 125(4): 95