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A Review on the Most Important Medicinal Plants Effective in Cardiac Ischemia-Reperfusion Injury

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Abstract: Ischemia, referring to reduction and restriction of perfusion to myocardial tissue which involves coronary artery 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 by affecting the factors involved in the disease. This review was conducted to report the medicinal plants and factors effective in 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 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 in decreasing cholesterol and blood pressure, preventing an increase in free radicals and ultimately reducing blood clots and vascular resistance to reduce and prevent ischemic disease and its harmful effects.

Conclusion: Medicinal plants discussed in this article seem to be able to prevent cardiac damage and the disease progression via affecting the factors that are involved in ischemia.

Keywords: Cardiac ischemia, antioxidant, blood, cholesterol, infarction.

1. INTRODUCTION

Cardiovascular diseases (CVDs) may have various certain 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 is the most common cause of heart failure that occurs mainly due to a sudden reduction in coronary circulation following thrombolytic 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 nonenzymatic 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 allopase, strepase, urokase, and streptokase, thrombolytic therapy is used to treat I/R injuries [15-17]. But their side effects such as generalized leticine, effects on misplaced platelet nails, and allergic reactions have limited their use. Considering the increasing prevalence of CVDs and decreasing the age at 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 fewer. This has led to an increase in the tendency to use herbal medicines over the last decade. Researches have also demonstrated the positive effects of herbal medicines on cardiac ischemia. Besides, it has been reported that 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 and its prevention and treatment using certain medicinal plants and their active compounds. For this purpose, medicinal plants and their potential antioxidant effects, effects 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 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 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 through 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, myocardium causes shift of aerobic metabolism toward anaerobic mechanism and reduction in heartbeats and the amount of myocyte shortening during systolic contraction through decreasing oxygen consumption, and therefore energy reserves decrease. In addition, the work of the heart requires maintenance of energy from the 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 forming fatty acids, which eventually kills the 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, and coronary artery endothelial injury. Due to this injury, the coronary artery response to vasodilators declines; the endothelial injury also causes activation of the platelets; and the leukocytes adhere to the endothelium and release cytotoxic and chemotoxic agents such as leukotrienes, proteases, cytokines, and oxygen free radicals in the myocardium perfused area through the neutrophils migration to this area, and therefore tissue injury is exacerbated [27].

In response to MI, oxidative stress accompanied by the 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 renin-angiotensin system [30], activation of neutrophils and inflammation [31], accumulation of the platelets and products released from them such as thromboxane A2, and activation of the complement system [27]. Besides, misplaced clots and thromboembolism are developed through hemostatic disorders. The thrombosis developed in the circulation due to hemostatic system defects causes 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 12000000 people worldwide die due to CVDs. The prevalence of non-communicable diseases is rising in developing countries including Iran, and the burden due to 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 works have indicated that arterial endothelium plays a significant role in modulating ventricular dysfunctions and regenerating blood vessel 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 in 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 angiotastic factors. Among angiogenic factors, vascular endo-
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<table>
<thead>
<tr>
<th>Results</th>
<th>Plant Part Used</th>
<th>Dose</th>
<th>Family</th>
<th>Plant Name</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>sativa</em> contains different vitamins including vitamin C with the antioxidant property that decrease blood cholesterol and arterial blockade [43, 44].</td>
<td>Seed</td>
<td>Treating male Wistar rats with 125 mg/kg</td>
<td>Poaceae</td>
<td><em>Avena sativa</em> L</td>
<td>1</td>
</tr>
<tr>
<td>Beta-glucan derived from <em>H. vulgare</em> decreases cholesterol and LDL, increases LDH, and prevents arterial blockage and ischemia [45].</td>
<td>Seed</td>
<td>Treating male Wistar rats with 62.5 mg/kg</td>
<td>Poaceae</td>
<td><em>Hordeum vulgare</em></td>
<td>2</td>
</tr>
<tr>
<td>Proanthocyanidins present in <em>V. vinifera</em> seed maintain hydroxyl radicals, cause a decrease in intracellular calcium, enhance the resistance of ischemia/reperfusion injuries, and decrease infarct size and arrhythmias [46].</td>
<td>Seed</td>
<td>Treating male Wistar rats with 1, 10, and 100 mg/kg</td>
<td>Vitaceae</td>
<td><em>Vitis vinifera</em></td>
<td>3</td>
</tr>
<tr>
<td>Preventing the formation of free radicals and reducing necrosis, the heart inflammation, and infarct [47].</td>
<td>Whole</td>
<td>Treating male Wistar rats with 0.5%, 0.25%, and 125%</td>
<td>Mel-Honey</td>
<td><em>Mel, Honey</em></td>
<td>4</td>
</tr>
<tr>
<td>Decreasing platelet accumulation and preventing oxidation of low-density lipoproteins due to their antioxidant effects and preventing infarct [48, 49].</td>
<td>Leave</td>
<td>1 per day in human subjects</td>
<td>Theaceae</td>
<td><em>Camellia sinensis</em></td>
<td>5</td>
</tr>
<tr>
<td>Scavenging reactive oxygen species, decreasing inflammation, and preventing ischemia [50].</td>
<td>Fruits</td>
<td>Treating male Wistar rats with 500 mg/ml</td>
<td>Rosaceae</td>
<td><em>Rosa canin</em></td>
<td>6</td>
</tr>
<tr>
<td>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].</td>
<td>Root</td>
<td>Treating male Wistar rats with 0.03 and 0.06 mg/ml</td>
<td>leguminosa</td>
<td><em>Prosopis farcta</em></td>
<td>7</td>
</tr>
<tr>
<td>Scavenging free radicals and preventing arterial blockage, and reducing ischemia through decreasing malondialdehyde levels [52, 53].</td>
<td>Seed</td>
<td>Treating male Wistar rats with 400 mg/ml</td>
<td>Punicaceae</td>
<td><em>Punica granatum</em></td>
<td>8</td>
</tr>
<tr>
<td>Positive inotropic and chronotropic effects on the heart or a mechanism different from the intracellular mechanism [54].</td>
<td>Flowering shoots</td>
<td>Treating male Wistar rats with 1, 2, and 50 mg/ml</td>
<td>Labiatae</td>
<td><em>Teucrium polium</em></td>
<td>9</td>
</tr>
<tr>
<td>Increasing antioxidant property and decreasing lipid peroxidation [49].</td>
<td>Aerial parts</td>
<td>Treating male Wistar rats with 150 and 300</td>
<td>Portulaceae</td>
<td><em>Portulaca oleracea</em> L</td>
<td>10</td>
</tr>
<tr>
<td>Dilating coronary arteries outside the nitric oxide mechanism [55].</td>
<td>Leave</td>
<td>Treating male Wistar rats with 5, 22, 15, 5, 7, and 30</td>
<td>Umbellifera</td>
<td><em>Falcaria vulgaris</em></td>
<td>11</td>
</tr>
<tr>
<td>Hypolipidemic, lipid peroxidation-reducing, and antioxidant enzyme activity-increasing [56].</td>
<td>Leave</td>
<td>Treating male Wistar rats with 50, 75, and 100</td>
<td>Oleaceae</td>
<td><em>Olea europaea</em></td>
<td>12</td>
</tr>
<tr>
<td>Antiarrhythmic, tachycardia-treating, calcium-blocking, cholesterol-reducing, and antioxidant [57, 58]</td>
<td>Flowers</td>
<td>Dose-dependent in human subjects</td>
<td>Iridaceae</td>
<td><em>Crocus sativus</em></td>
<td>13</td>
</tr>
<tr>
<td>Fibrinolytic and clot-lysis effects and prevention of heart diseases and ischemia [59].</td>
<td>Leave</td>
<td>0.1, 0.01, and 0.001 ml adjacent to the clot</td>
<td>Labiatae</td>
<td><em>Zataria miltiorrhiza</em></td>
<td>14</td>
</tr>
<tr>
<td>Fibrinolytic and clot-lysis effects and prevention of heart diseases and ischemia [59]</td>
<td>Fruits</td>
<td>0.1, 0.01, and 0.001 ml adjacent to the clot</td>
<td>Umbellifera</td>
<td><em>Heracleum persicum</em></td>
<td>15</td>
</tr>
<tr>
<td>Fibrinolytic and clot-lysis effects and prevention of heart diseases and ischemia [59].</td>
<td>Bark</td>
<td>0.1, 0.01, and 0.001 ml adjacent to the clot</td>
<td>Zingiberaceae</td>
<td><em>Curcuma domestica</em></td>
<td>16</td>
</tr>
<tr>
<td>Protecting the heart against antioxidant property, hypolipidemic and hypotensive effects, and decreasing infarct size [60, 61].</td>
<td>Leaf</td>
<td>Treating male Wistar rats with 1 and 3 mg/ml</td>
<td>Asteraceae</td>
<td><em>Chichorium intybus</em></td>
<td>17</td>
</tr>
</tbody>
</table>

(Table 1) Contd....
Antioxidant property, antiarrhythmic effect, and decreasing infarct size [53].

Preventing production of free radicals, increasing glutathione peroxidase and superoxide dismutase through decreasing creatine kinase, lactate dehydrogenase, and malondialdehyde and decreasing infarct size [62].

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].

Potent antioxidant property, decreasing peroxidation of lipids such as malondialdehyde and decreasing cardiac troponin I, blood pressure, and infarct size [65].

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].

Decreasing lipid peroxidation and superoxide and hydroxyl radicals and increasing antioxidative enzymes [67].

Antioxidant effects and scavenging radicals [68].

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].

Decreasing the levels of cholesterol, triglycerides, and increasing antioxidative enzymes[70]

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 have 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 capcehin and quercetin, and ethanol exert support 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 enzymes activities 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 diseases through different mechanisms, and patients with these diseases are recommended to use these plants.

CONCLUSION
This article reveals that there is a negative correlation between the use of medicinal plants, full of polyphenols having antioxidants, and the occurrence of heart diseases especially I/R, so that medicinal plants and their compounds can decrease the cardiac ischemia injuries through several pathways in heart and other organs like kidney. The mechanisms involved include dilating coronary arteries, enhancement of antioxidant enzymes such as SOD and GPX, oxygen supply to the heart and subsequently increase in 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 sum, medicinal plants are beneficial in ischemic heart disease through various mechanisms, and patients with these diseases are recommended to use them.

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CONFLICT OF INTEREST
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