International Journal of Botany Studies
www.botanyjournals.com
ISSN: 2455-541X
Received: 25-03-2022, Accepted: 11-04-2022, Published: 26-04-2022
Volume 7, Issue 4, 2022, Page No. 140-149

A detailed review on mechanisms of cardioprotection in the plants

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Abstract
Cardio-protection refers to any systems and treatments that help to protect the heart by avoiding or decreasing cardiac damage. If discovered at a stage of development, it can manifest as a traditional heart attack, sudden death, or a silent infarct. Cardiovascular disease includes hypertension, coronary artery disease, congestive heart failure, Stroke. When the supply of blood to a section of the heart is cut off, cardiac cells die. This is known as a myocardial infarction. The most prevalent cause is a blockage in a coronary artery. Herbal drugs have been demonstrated to have beneficial therapeutic benefits in the treatment of heart problems, and they should be researched further to see if they may be used to treat cardiac problems.

Keywords: cardioprotective, myocardial infarction, cardiovascular disease, cardiotoxicity

Introduction
Medicinal plants are possible sources of medication because they are high in secondary metabolites and therapeutic essential oils. [1] Medicinal plants are cost-effective, economical, safe, utilized to cure a variety of diseases. [2] As a result of these advances, traditional medicine practitioners have increased their use of medicinal plants in their daily practice. [3] Plants create a diverse range of non-nutrient phytochemicals for defence, other biological purposes. [4] Ischemia is a condition that occurs in a body as a result of free radicals. Vitamin C, E, beta-carotene, polyphenolics, antioxidant components found in fruits, vegetables have been related to a lower risk of a number of chronic diseases. Antioxidants protect the body from free radicals by scavenging them. [5] A total of 2000 plants have been collected in the traditional system of medicine for treating people suffering from cardiovascular diseases like hyperlipidaemia, ischemic heart diseases [6].

Mechanisms of cardioprotection in plants
Reduction in Glutathione (GSH) level
The plant offers cardioprotective activity by the mechanism of a reduction in Glutathione (GSH) level using cardiomyocytes from new-born rats. Andrographolide pre-treatment protected cardiomyocytes from reoxygenation ad hypoxia and also rise in GSH levels and antioxidant enzyme activity. Glutathione is a substance made from amino acids, cysteine, glycine, and glutamic acid, produced by the liver, involved in tissue building and cardiac disease. Andrographolide's cardioprotective effects are time-dependently correlated with GSH upregulation. Buthionine Sulfoxime, a particular gamma glutamate-cysteine ligase (GCL) inhibitor that depletes cellular GSH levels, fully abrogated the cardioprotective action, while andrographolide raised GCL catalytic subunit (GCLC) and modifier subunit m RNA, protein level (GCLM). [7] Andrographis paniculata, Acanthaceae, contains andrographolide, 14-deoxyandrographolide, neoandrographolide, 14-deoxy-11, 12-didehydroandrographide. [8]

Fig 1: Andrographis Paniculata

Restoration of hemodynamic, biochemical, histopathological parameters:

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The plant offers cardioprotective activity on the grounds of hemodynamic, biochemical, and histopathological parameters in isoprenaline-induced myocardial infarction with vitamin E, which gave cardioprotective antioxidant activity. Isoprenaline is a synthetic catecholamine that causes myocardial toxicity, damages the heart by producing extremely cytotoxic free radicals as a consequence of catecholamine auto-oxidation. The dose of isoprenaline for the induction of myocardial infarction is 25 mg/kg subcutaneously. [9] In the isoprenaline group, there was a fall observed in hemodynamic parameters such as MAP, SAP, DAP, and HR. While in biochemical parameters, isoprenaline shows a fall in LDH and SGOT. And in histopathological parameters, the presence of focal myonecrosis with myophagocytosis and lymphocytic infiltration in the isoprenaline group, there was an increase in LDH in hearty homogenates, a decrease in SGOT and a decrease in LDH in serum in vitamin E control group. [10]

Azadirachtin, nimbolinin, Nimbin, nimbidin, nimbidol, sodium nimbinate, gedunin, sala-nin, and quercetin are all found in Azadirachta Indica, Meliaceae, the leaves include Nimbanene, nimbin, 6-desacetylnimbinene, nimbanidol, nimbolide, ascorbic acid, n-hexacosanol amino acid. [11, 12]

Fig 2: *Azadirachta Indica*

Rise of Endogenous antioxidants and decrease in MDA

The plant has cardioprotective properties due to an increase in endogenous antioxidants and a depletion in MDA. By significantly restoring endogenous antioxidant CK-MB isoenzyme activities and lowering malondialdehyde levels, Bacopa Monnieri gives optimum cardiac protection. The cardioprotective effect of Bacopa Monnieri at dosages of 25, 75, and 150 mg/kg was examined in the Isoproterenol model of myocardial necrosis. Bacosides are the antioxidant, immunomodulatory, and adaptogenic characteristics of bacosides. [13, 14] The Scrophulariaceae plant Bacopa Monnieri includes bacosides, which are dammarane triterpenoid saponins. [15, 16]

Fig 3: Bacopa Monnieri

Prevention of altered biochemical variation such as marker enzymes, lipid profile, antioxidant parameters

Preventing biochemical variation such as marker enzymes, lipid profile, antioxidant properties from becoming altered. The plants have a cardioprotective effect by preventing biochemical changes, which could be credited to an increase in endogenous antioxidants and cell membrane lipid peroxidation inhibition. BA pre-treatment of DOX-induced rats reduced altered biochemical variations in marker enzymes (SGPT, SGOT, CPK, ALP, LDH), lipid profile (LDL, VLDL, TGs, HDL, Total cholesterol), antioxidant parameters (SOD, GSH, CAT, GPx, MDA, GR).

Serum urea and uric acid, which rose after DOX delivery, returned to near-normal levels after BA treatment. The current data suggest that BA's cardioprotective effects on DOX-induced oxidative damage may be underestimated. [17] 1-Amino-2,6-dimethylpiperidine, 2-Octenoic acid, 4,5,7-trihydroxy, à-Methyl-D-mannopyranoside, 2,3-dihydro-3,5-dihydroxy-6-methyl Naphthalene, and 1,2,3,4-tetrahydro-1,1,6-1,1,6-trimethyl are all found in Buchanania Axillaries, Anacardiaceae.

Fig 4: Buchanania Axillaries

Decrease in the elevated marker enzyme level in serum

The plants have a cardioprotective impact by reducing the concentration of elevated marker enzymes. Calotropis Procera latex alcoholic extract has anti-myocardial infarction action. Isoproterenol produced myocardial infarction by acting on the sarcolemma membrane, stimulating adenylate cyclase, activating Na+ and Ca2+ channels, exaggerating Ca2+ inflow energy consumption, resulting in cellular death, and also by causing enzyme leakage from the heart, leading to necrosis. [18] Lowering Ca2+ inflow and minimizing enzyme leakage are the mechanisms that protect the heart, resulting in less myocardial damage. [19] Voruscharin, uzarigenin, calotroposide, calactin, calotoxin, ascleposide, calotropagenin, coroglaucigenin, proceroside, proceragenin are all found in Calotropis Procera, Asclepiadaceae. [20]

Fig 5: Calotropis Procera

Decrease in serum enzymes (SGOT, SGPT, LDH)

The herbal drug protects the heart by lowering serum enzymes. Cardiopathy and CVDs are treated with Cassia Fistula. Doxorubicin is administrated at a dose of 10mg/kg of body weight. It induces heart damage, resulting in elevated levels of cardiac markers such as AST, ALT, LDH, and CKMB significant degeneration of myofibrils with localized necrosis & vacuolated cytoplasm as well as histological parameter assessment methanolic extract pre-treatment reduces increased serum enzymes, histological abnormalities, and ECG to normal myocardial function. [21] Anthraquinones flavonoid, flavon-3-ol derivative can be found in cassia fistula. [22] Sesquiterpenes, coumarins, lignans, neolignans, and alkaloids are found in Nardostachys Jatamansi, Valerianaceae. [23] In isoproterenol-induced cardiotoxicity, N. jatamansi showed cardioprotective effects, with cardiac markers decreasing in plasma and increasing in the heart. It was discovered that pretreating mice with ethanolic extract restored all enzyme levels and lipid profiles to normal. [24]

Oxidative degeneration of lipids

The plant Commiphora Mukul exhibited cardioprotective properties, resulting in lower levels of SOD, CAT, GSH, and the myocyte damage marker enzyme CKMB increased lipid peroxidation is also a factor Reduced SOD could be caused by an increase in superoxide anion generation or a decrease in superoxide anion elimination, both of these could cause myocardial damage. Guggulsterone isomers reduce oxidative lipid degradation in rat liver microsomes human low-density lipoprotein produced by metal ions. [25] Pretreatment with C. Mukul reversed isoproterenol-induced oxidative alterations in rat myocardium and decrease in SOD, CAT, and GSHPX, all of which are directly linked to free radical scavenging, resulting in the protection of these enzymes from reactive oxygen species. Commiphora Mukul, Burseraceae, contains myrcene.[26]

Fig 6: Commiphora Mukul

Decrease in antioxidant enzymes and increased rate of ADP-stimulated oxygen uptake and respiratory coupling ratio

The plant Crataegus Oxycantha has a cardioprotective effect because it reduces antioxidant enzymes, ISP-induced decreases in antioxidant enzymes in the heart are inhibited by the rate of ADP stimulated O2 absorption & respiratory coupling ratio. [27] Flavonoids and oligomeric proanthocyanidins are the principal cardioprotective agents. To prove if they could protect against myocardial infarction was produced in animal model researchers looked at the activity of a marker enzyme, antioxidant levels, lipid peroxidation, mitochondrial response coupling ratio, and histological alterations in serum. [28] Hyperoside, vitexin-2-rhamnoside, is found in Crataegus Oxycantha, Rosaceae.

Fig 7: *Crataegus Oxycantha*

Modulation in activities of myocardial creatinine CK-MB isoenzyme

The plant Crocus Sativus provides cardioprotective benefits by modulating the activities of myocardial creatinine CK-MB isoenzymes. In comparison to isoproterenol-induced mice, saffron components alter the activity of many enzymes involved in free radical scavenging, reduce lipid peroxidation, and improve antioxidant status. Crocin reduces the toxicity of diazinon by correcting the aorta's altered contractile and relaxing responses through lipid peroxidation. [29] Level of serum LDH, CKMB are all lower after pre-treatment. Crocetin and crocins, safranal and picrocrocin, beta-carotene, lycopene, and zeaxanthin are all found in Crocus Sativus (Iridaceae). [30]

Fig 8: Crocus Sativus

Decreased the leakage of CK-MB

The herb Tribulus Terrestris has cardioprotective potential. The cardiac injury was caused by isoproterenol, & this resulted in a decrease in activities of endogenous antioxidant defence enzymes viz. SOD, CAT, GSHPx, tissue antioxidant, a decrease in GSH, and increase in lipid peroxidation product MDA. Reduced mean arterial pressure (MAP), HR, LV dp/dt, and greater left ventricular end-diastolic pressure were all signs of cardiac dysfunction. The restoration of endogenous antioxidant status or free radical scavenging activity in myocardium with corrected altered hemodynamic parameters could be the mechanism of cardioprotection of T. Terrestris. [31] Tribulus Terrestris, Zygophyllaceae, and tannins are found in Tribulus Terrestris, Zygophyllaceae. [32]

Fig 9: *Tribulus Terrestris*

A decline in the activation of cardiac markers (ALT, AST, LDH)

The leaves of Trichopus zeylanicus were examined for their cardioprotective properties. Plasma, heart aspartate aminotransferase, LDH, and CK levels were assessed to find out cardioprotection. Isoproterenol-treated groups had fewer cardiac markers in plasma, more lipid peroxidation, and lower reduced glutathione concentrations in the heart and plasma. T. Zeylanicus was given before Isoproterenol to avoid Isoproterenol-induced changes and to restore cardiac indicators. [33] Luteolin (3', 4', 5, 7-tetrahydroxyflavone) is found in Trichopus Zeylanicus, Trichopaceae, Acacetin is an O-methylated flavone found in Robiniapseudo-acacia, Apigenin (4′, 5, 7-trihydroxyflavone) is extracted from a wide range of plants. Silymarin is a flavonoid complex made up of silybin, silydianin, and silicristin, as well as kaempferol, salvigenin, and quercetin. [34]

Fig 10: Trichopus zeylanicus

Myocardial adaptation by augmentation of endogenous antioxidants

The plant Curcuma Longa maintains endogenous antioxidant enzyme activity and heart function are used as cardioprotective by myocardial adaptations and augmentation of endogenous antioxidants. Degeneration of myofibers, interstitial edema, subcutaneous congestion, neutrophil and lymphocyte infiltration via altered membrane permeability, increased noradrenaline turnover, cytotoxic free radical production and significant inotropic and chronotropic activities resulting in oxygen requirement. A rise in GSHPx and CAT activities was seen after chronic dosing of C. longa. This Adaptogenic property may have a role to play in its cardioprotective effect by strengthening the heart's defence mechanisms. Vitamin E also has cardioprotective properties as [35] Curcuma longa (Zingiberaceae) contains diarylheptanoids, diarylpentanoids, phenylpropene, and other phenolic chemicals. [36]

Fig 11: Curcuma longa

Improvement in the Hemodynamic factor

Cardioprotection is provided by the plant, which improves hemodynamic parameters. The hydroalcoholic extract reduced the number and length of ventricular tachycardia. The total no. of ischemic ventricular ectopic beats, as well as the length and incidence of ventricular fibrillation during reperfusion time. The antiarrhythmic efficacy of C. dactylon was inversely proportional to the extract concentration. Heart contractility, LVDP, and RPP recovered from an ischemic-reperfused isolated heart have a direct antiarrhythmic impact against I/R-caused arrhythmia. [37] Apigenin, luteolin, orientin, and vitexin carotenoids: beta-carotene, neoxanthin, phytosterols, glycosides, saponins, and volatiles are found in Cynadon dactylon, Poaceae. Glycerin, 9, 12-octadecadienoyl chloride, hexadecanoic acid, and ethyl ester were found in C. dactylon leaves. [38] Apigenin, luteolin, kaempferol, isorhamnetin, tilianin, agastachoside, acacetin-7-O-(6-O-Malonyl-beta-D-glucopyranoside), syringaresinol are found in Dracocephalum moldavica, Labiatae. [39]

Protection of cardiac tissue by scavenging free radicals

The heart protective properities of Ficus hispida leaf extract was investigated for protecting cardiac tissue. Cyclophosphamide is a cytotoxic alkylating chemical that is transformed into Aldo phosphamide, which is then metabolized into phosphoramide mustard and acrolein metabolite, resulting in the generation of extremely reactive oxygen species. Pretreatment with F. hisipida inhibited lipid peroxidation significantly, increased endogenous antioxidants, and reduced CP-induced cardiotoxicity. [40] Ficus hispida, a Moraceae plant, contains all three: lupeol acetate, amyrine acetate, and sitosterol. Ficus Hispida, a Moraceae plant, contains Triacontanol. [41]

Fig 12: Ficus hispida

Activation of JAK2/STAT 3 signal transduction pathway

The heart protective properities of Glycyrrhiza Glabra was studied by activation of signal transduction pathway. The activation of JAK2/STAT3, which is involved in promoting upregulation of Metallothionein MT expression, protected ischemia and reperfusion of myocardium (MI/R). Isoliquertin pretreatment decreased severity of the

reperfusion-induced arrhythmia and the extent of myocardial infarction. Increased metallothionein synthesis lowered LDH and CPK activities while increasing JAK2/STAT3 phosphorylation. [42] Glycyrrhiza Glabra, Papilionaceae, for example, contains liquirtin, rhamnoliquritin, liquiritigenin, prenyllicoflavoneA, glucoliquiritin apioside. [43]

Fig 13: Glycyrrhiza Glabra

Reduction in percent left ventricle (PLVN) and lipid peroxide level

The plant Hydrcotyle Asiatica was studied for cardioprotective activity by a depletion in PLVN and lipid peroxide levels. The cardioprotective activity was measured using infarct size, lipid peroxide level in the blood and heart tissue. Alcoholic extract of H. Asiatica shows a dose-dependent depletion in PLVN and lipid peroxide levels. [44] Asiaticoside, tannic acid and vallarin are found in Hydrocotyle asiatica, Umbelliferae and hydrocotylin.

Fig 14: Hydrcotyle Asiatica

The rise in lipid peroxidation in myocardial tissue:

The plant offers a cardioprotective effect in an isoproterenol-induced model of myocardial infarction by a rise in lipid peroxidation. Several hemodynamic measures were detected after delivery, including MAP, HR, and negative LV dp/dt. Chronic processing of the extract reduced lipid peroxidation in cardiac tissue via modulating a biochemical enzyme. Antioxidant and antiperoxidative myocardial preservation effects have also been demonstrated for M. oleifera. [45] [46]

Fig 15: Moringa Oleifera

Effect on markers enzymes and serum uric acid level

The plant protects the heart by affecting marker enzymes and serum uric acid levels. The activity of marker enzymes was significantly affected by Muntingia leaf extract. Isoproterenol raises serum levels of CK, LDH and transaminase while lowering enzyme levels in tissue. Pretreatment with calabura had a substantial effect on

marker enzymes, and isoproterenol administration with the treatment extract elevated blood uric acid. [47] Example: Muntinga Calabura of family Elacarpaceae contains (2S)-50 -hydroxy-7,30,40 - trimethoxyflavan, (2S)-7,8,30,40,50 -pentamethoxyflavan, (2S)-20 -hydroxy-7,8,30,40,50 -pentamethoxyflavan, (2S)-50 -hydroxy-7,8,30,40 -tetramethoxyflavan, (2S)-8- hydroxy-7,30,40,50 -tetramethoxyflavan, (2S)-8,20 -dihydroxy-7,30,40,50 -tetramethoxyflava. [48]

Fig 16: *Muntinga Calabura*

Lowering activities of heart lysosomal enzymes

The plant Terminalia chebula has therapeutic efficacy in protecting the heart from isoproterenol-induced lysosomal membrane destruction. Isoproterenol caused heart injury, which was validated by a triphenyl tetrazolium chloride assay, as well as changes in lysosomal enzyme activity. Pretreatment with T. chebula preserved or stabilized lysosomal enzyme activity, preventing myocardial injury. [49] Chebulic acid, chebulagic acid, corilagin, and gallic acid are all found in Terminalia Chebula, a Combretaceae plant. [50]

Fig 17: *Terminalia Chebula*

Conclusion

The current review indicates that plant phytoconstituents offer the therapeutic and preventive potential for the management cardiovascular illnesses, despite the fact that the molecular processes are still unknown. Phytoconstituents appear to protect the heart by blocking critical enzymes, decreasing certain factors, and scavenging oxygen-free radicals. This review found that phytochemical have a wide range of cardioprotective actions. The nutraceutical and pharmaceutical sectors can take the lead in developing new drugs and nutraceutical supplements based on medicinal plants. Due to limited access to research articles and our search strategy, we were unable to include all studies describing the cardioprotective effects of medicinal plants.

Abbreviations

ALP: Alkaline Phosphatase
ALT: Alanine Transaminase
ANP: Atrial Natriuretic Peptide
AST: Aspartate aminotransferase
CAT: Catalase
CK-MB: Creatinine kinase myocardial band
DOX: Doxorubicin
E2: Estrogen
EC: Endothelial cells
GCL: Glutamate Cysteine Ligase
GCLM: Glutamate Cysteine Ligase Modifier subunit
GCLC: Glutamate Cysteine Ligase Catalytic subunit
GPx: Glutathione peroxidase
GR: Glutathione Reductase
GSH: Glutathione
HR: Heart rate

ISP: Isoproterenol
MDA: Malondialdehyde
LDH: Lactated dehydrogenase
SGPT: Serum Glutamic pyruvic transaminase
SGOT: Serum Glutamic oxaloacetic transaminase

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