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CHEMISTRY AND PHARMACOLOGY OF PLANT CARDIOPROTECTIVES: A REVIEW

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Cardioprotection, Myocardial, Antioxidant, Extract

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ABSTRACT

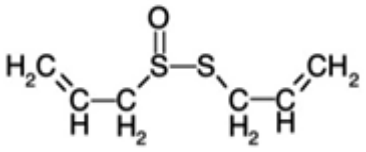
Cardiovascular disease remains a leading cause of death in most industrialized countries. Therefore, finding ways to reduce the mortality of cardiovascular disease remains an important public health goal. This review deals with medicinal plants possessing cardioprotective and cardiotonic activity. This review work explains chemical and pharmacological status of various cardioprotective plants including phytoconstituents responsible for cardioprotection, extract employed, dosage, pharmacological screening model and mechanism involved in cardioprotection. This review work definitely potentiates the work on cardioprotective plants.

INTRODUCTION: There is a large and increasing global burden of cardiovascular disease. Approximately 14 million individuals died of cardiovascular disease in 1990, and this is projected to rise to about 25 million by 2020 [1]. The global burden of disease due to cardiovascular diseases (CVDs) is escalating, principally due to a sharp rise in the developing countries which are experiencing rapid health transition [2]. The continuous increase in incidences of cardiovascular disease is a manifestation of chronic poor diet and lifestyle choices, which lead to diabetes and obesity [3].

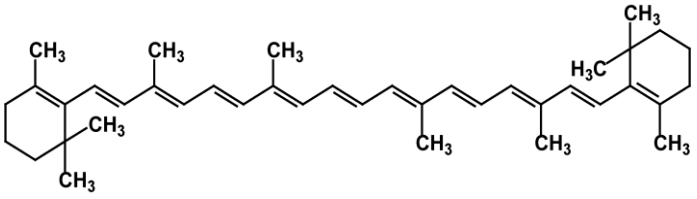
More than 2000 plants have been listed in the Traditional (Herbal/Alternative) systems of medicine and some of these are providing comprehensive relief to the people suffering from cardio-vascular diseases, specially "hyperlipidemia" and "ischemic heart disease". WHO reports indicate that around eighty percent of the global population still relies on botanical drugs and several herbal medicines have advanced to clinical use in modern times [4]. The use of Western medicinal drugs for the treatment of hypertension, congestive heart failure and post myocardial infarction are widely accepted.

Although, some traditional Chinese Medicines have been used in mainland, Hong Kong, Taiwan of China in clinics and other Chinese communities worldwide for centuries [5]. For cardiovascular diseases, herbal treatments have been used in patients with congestive heart failure, systolic hypertension, angina pectoris, atherosclerosis, cerebral insufficiency, venous insufficiency and arrhythmia [6]. A brief description of some cardioprotective plants has been shown in **table 1**.

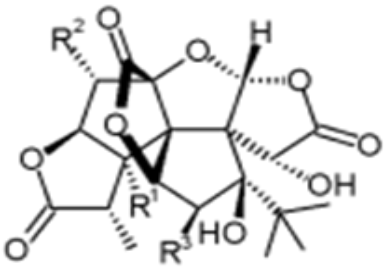
Chemistry of Natural Cardioprotectives: Various phytoconstituents from plants were responsible for cardioprotective activity including carotenoids (*Eugenia uniflora)*; triterpenes (*Ganoderma lucidum)*; flavonoids (*Anacardium occidentale, Nelumbo nucifera*); cardiac glycosides (*Digitalis purpurea, Antiaris toxicaria)*; alkaloids (*Desmodium gangeticum, Erythroxylon coca Tinospora cordifolia)*; saponins (*Asparagus racemosus, Vaccaria pyramidata)*; terpenoids (*Ginkgo biloba*); fatty acids (*Elaeis guineensis*) etc [7-81]. Various reported phytoconstituents from plant sources has been shown in **figure 1**.



ALLICIN



β- CAROTENE



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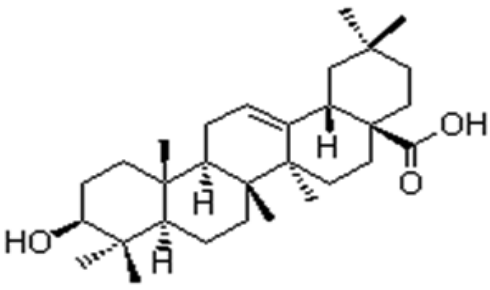
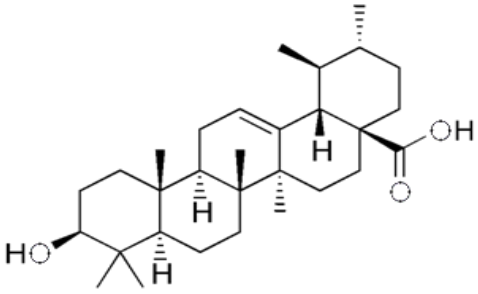
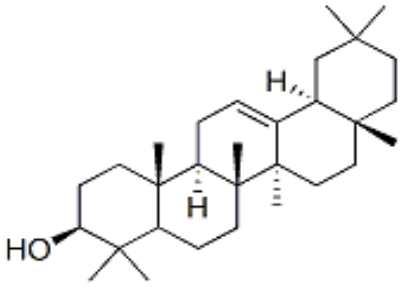


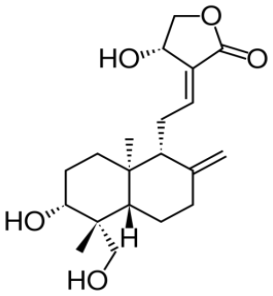
OLEANOLIC ACID



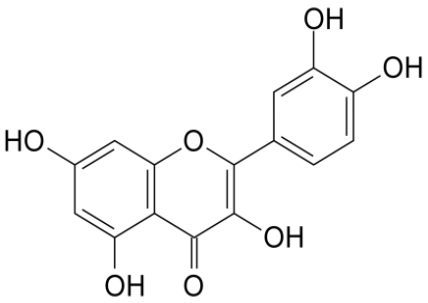
URSOLIC ACID



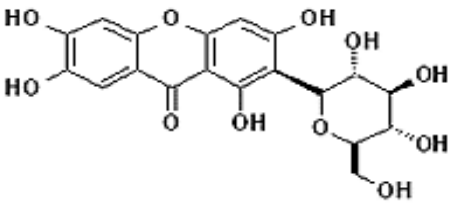
β- AMYRIN



ANDROGRAPHOLIDE



QUERCETIN



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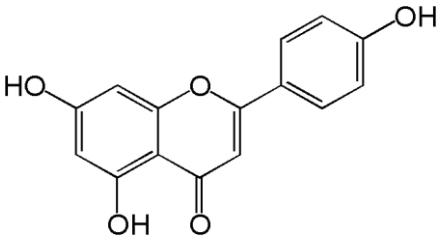

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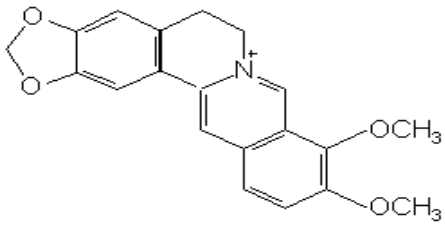
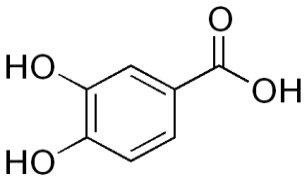
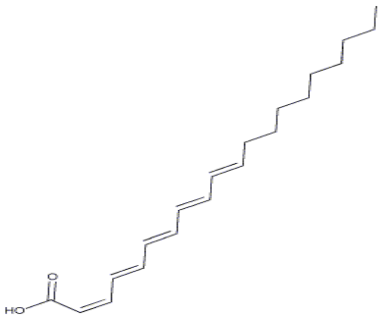


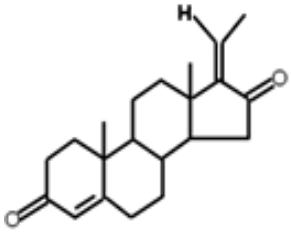
BERBERINE



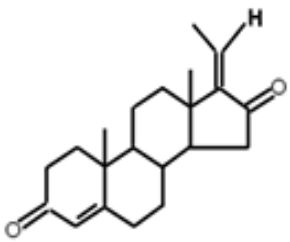
PROTOCATECHUIC ACID



OMEGA -3- FATTY ACID



GUGGULSTERONE-Z



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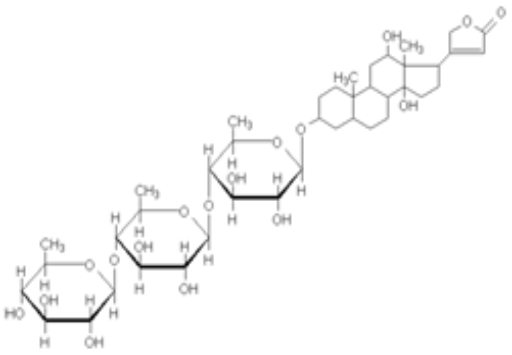
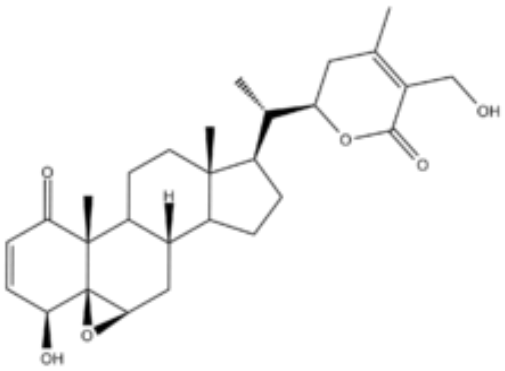
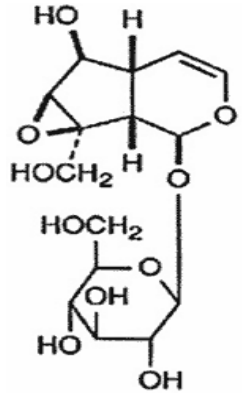


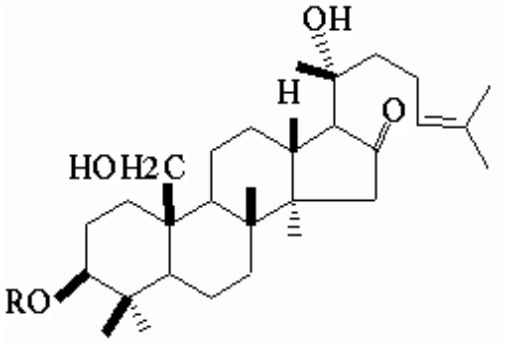
DIGOXIN



WITHAFERIN A



IRRIDOID GLYCOSIDES



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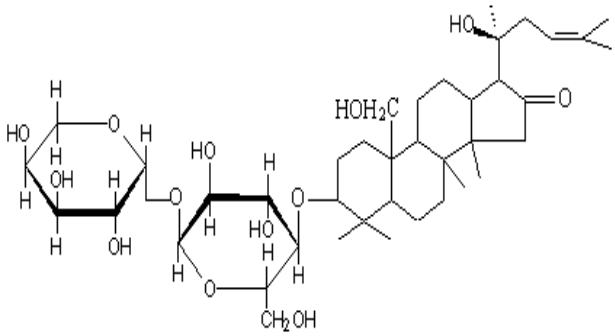
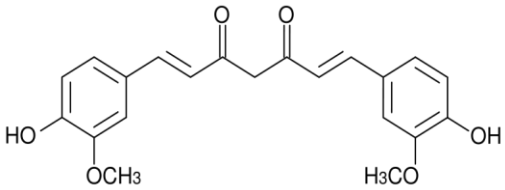
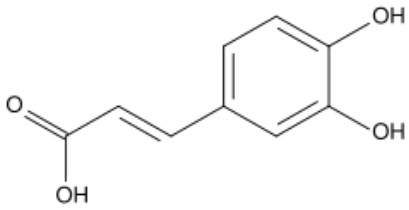


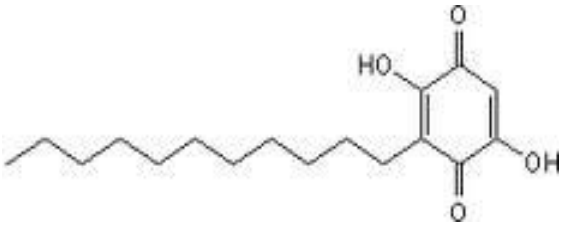
BACOSIDE B



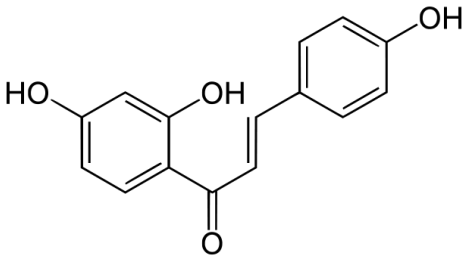
CURCUMIN



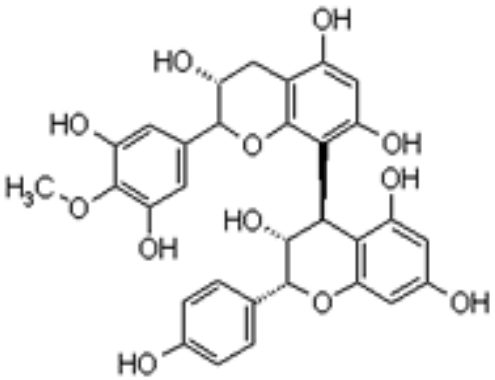
CAFFEIC ACID



EMBELLIN ACID



ISOLIQUIRITIGENIN



PROCYANIDINS

FIG. 1: VARIOUS CARDIOPROTECTIVE PHYTOCONSTITUENTS FROM PLANTS

TABLE 1: A BRIEF DESCRIPTION OF COMMON CARDIOPROTECTIVE PLANTS [7-38]

Plant name	Family	Chemical Constituents
Allium sativum	Liliaceae	Allicin, sulphur compounds
Anacardium occidentale	Anacardiaceae	Flavonoids, carotenoids
Antiaris toxicaria	Moraceae	Cardiac glycosides
Asparagus racemosus	Asparagaceae	Saponins-Shatavarins I–IV
Cinnamomum tamala	Lauraceae	Cinnamaldehyde
Delphinium denudatum	Ranunculaceae	Campesterol, stigmasterol, sitosterol, cholesterol, deltaavenasterol and alkaloids
Digitalis purpurea	Scrophulariaceae	Cardiac glycosides
Eugenia uniflora	Orchidaceae	Carotenoids, flavonoids
Ganoderma lucidum	Ganodermataceae	Triterpenes
Ginkgo biloba	Ginkgoaceae	Ginko flavone glycosides, terpenoids (ginkgolides and bilobalide)
Hemidesmus indicus	Asclepiadaceae	Coumarino-lignoids, hemidesmine
Leptadenia pyrotechnica	Asclepiadaceae	Triterpenoid
Nelumbo nucifera	Nelumbonaceae	Quercetin, luteolin, alkaloids
Onosma bracteatum	Boraginaceae	Tannins, Glycosides, resins, alkaloids
Elaeis guineensis	Arecaceae	Fatty acids, omega-3- fatty acid
Quercus resinosa	Fagaceae	Tannins
Rosa damascene	Rosaceae	Lycopene, rubixanthin, zeaxanthin, quercetin, kaempferol and cyanidin
Tinospora cordifolia	Menispermaceae	Alkaloidal constituents, including berberine; bitter principles, including columbin, chasmanthin, palmarin and tinosporon, tinosporic acid and tinosporol
Erythroxylon coca	Erythroxylaceae	Alkaloids including cocaine, tropacocaine, Cinnamoylcocaine
Hordeum vulgare	Gramineae	Vitamin C, β-glucan-enriched fraction
Citrus aurantium	Rutaceae	Volatile oil, alkaloid
Glycine max	Papilionaceae	Protein, lecithin, saponins
Aesculus hippocastanum	Hippocastanaceae	Hydroxycoumarin
Hippophae rhamnoides	Elaeagnaceae	Polyphenols
Raphanus sativus	Cruciferae	Caffeic acid
Vaccaria pyramidata	Caryophyllaceae	Saponins
Euryale ferox	Nymphaeaceae	Protein
Stachytarpheta jamaicensis	Verbenaceae	Friedelin, stigmasterol, ursolic acid, hispidulin, scutellarein, choline, phenolic acids
Desmodium gangeticum	Fabaceae	Alkaloids

Pharmacology of cardioprotective plants: Phytoconstituents reported in cardioprotective plants significantly prevented the altered biochemical variation such as marker enzymes serum glutamate-pyruvate transaminase (SGPT) or alanine transaminase (ALT), serum glutamate oxaloacetate transaminase (SGOT) or aspartate transaminase (AST), creatine phosphokinase (CPK), alkaline phosphatise (ALP), lactate dehydrogenase (LDH), lipid profile including low density lipoprotein (LDL), VLDL (very low density lipoprotein), triglycerides (TGs), high density lipoprotein (HDL), total cholesterol and antioxidant parameters including Superoxide dismutase (SOD), glutathione (GSH), catalase (CAT), Glutathione peroxidase (GPx), MDA (malonaldialdehyde) and glutathione reductase (GR) come to near normal status. Cardioprotective activity was evaluated using various pharmacological screening models like isoprenaline induced myocardial necrosis in rats, doxorubicin (DOX) induced cardiotoxicity in albino rats, cyclophosphamide induced oxidative myocardial injury in a rat model, ischemia-reperfusion-induced myocardial infarction in albino rats, cigarette Smoke-exposed Rats, adriamycin-induced cardiomyopathy in rats etc [36-78]. Pharmacological status of some cardioprotective plants has been mentioned in **table 2** given below.

TABLE 2: PHARMACOLOGY OF CARDIOPROTECTIVE PLANTS [39-81]

Plant/Family name	Dose administered mg/kg	Extract	*In vitro/in vivo* model	Mechanism involved and observation
Andrographis paniculata, Acanthaceae	Dose-dependent	Crude	Neonatal rat cardiomyocyte (NRC)	Pretreatment with andrographolide protected the cardiomyocytes against hypoxia/ reoxygenation injury and up-regulated the cellular-reduced glutathione (GSH) level and antioxidant enzyme activities. Andrographolide activated both the GCLC – (catalytic subunit of glutamate cysteine ligase) and the modifier subunit of glutamate cysteine ligase (GCLM) promoters in the transfected rat H9C2 cardiomyocyte cell line
Azadirachta indica, Meliaceae	250, 500, 1000	Leaf extract	Isoprenalin induced myocardial necrosis in rats	*A. indica* extract and vitamin E significantly restores most of the haemodynamic, biochemical and histopathalogical parameters in infected rats
Bacopa monnieri, Scrophulariaceae	50, 100, 150, 200	Hydroalcoholc	Isoproterenol induced myocardial necrosis in rats	Antioxidant components (Bacosides Aand B) caused significant rise in endogenous antioxidants (SOD, CAT, GSH) and decrease in MDA
Buchanania axillaries, Anacardiaceae	250, 500	Ethanolic	Doxorubicin (DOX) induced cardiotoxicity in albino rats	Ethanolic extract of *B. axillaries* significantly prevented the altered biochemical variation such as marker enzymes (SGPT, SGOT,CPK, alkaline phosphatase , LDH), lipid profile (LDL, VLDL, TGs, HDL, Total cholesterol) and antioxidant parameters SOD), GSH, CAT, GPx, MDA, and GR come to near normal status
Calotropis procera, Asclepiadaceae	300	Alcoholic	Isoproterenol induced myocardial infarction in albino rats	Pretreatment with an ethanolic latex extract of *C. procera* significantly reduced the elevated marker enzyme levels in serum and heart homogenates in rats with isoproterenol-induced myocardial infarction. Histopathological observation revealed a marked protection by the extract in myocardial necrotic damage
Cassia fistula, Caesalpiniaceae	400	Methanolic	Doxorubicin (DOX) induced cardiotoxicity in wistar rats	Significant decrease in serum enzymes (SGOT, SGPT, LDH and creatine kinase MB isoenzyme)
Cocos nucifera, Palmae	100 g/ body weight	Water	Isoproterenol induced myocardial infarction in albino rats	Decrease in serum enzymes(CPK, LDH, SGOT, SGPT) and very little myocardial damage in isoproterenol treated rats fed tender coconut water
Cichorium intybus, Compositae	500	Aqueous	Ageing myocardium of albino rats	*Cichorium* extract was found to ameliorate the age induced injury and offered protection to the heart from oxidative damage and also found to decrease serum enzymes
Colebrookea oppositifolia, Lamiaceae	250, 500	Methanolic	Doxorubicin (DOX) induced cardiotoxicity in albino rats	The study of lipid peroxidation and anti-oxidant enzymes reveled that the malondialdehyde level was decreased, GSH, SOD and CAT levels were significantly rised in *C. oppositifolia* extract treated group
Commiphora mukul, Burseraceae	50	Gum resin	Isoproterenol induced myocardial necrosis in rats *(in vivo)*; effect of Guggulsterone on Lipid Peroxidation and Oxygen Free Radical Generation (*in vitro)*	Guggulsterone isomers inhibited oxidative degradation of lipids in human low-density lipoprotein *in vivo* and rat liver microsomes induced by metal ions *in vitro*
Crataegus oxycantha, Rosaceae	0.5 mL/100 g	Tincture	Isoproterenol induced myocardial infarction in albino rats	Tincture prevented the isoproterenol-induced decrease in antioxidant enzymes in the heart and increased the rate of ADP-stimulated oxygen uptake and respiratory coupling ratio. *C. oxycantha* tincture protected against pathological changes induced by isoproterenol in rat heart

Crocus sativus, Iridaceae	5, 10, 20	Aqueous	Isoproterenol induced cardiotoxicity rats	Crocin modulated the activities of myocardial creatine CK-MB isoenzyme, LDH and cause rise in antioxidant enzymes SOD, CAT and reduced GSH
Cucumis trigonus, Cucurbitaceae	75, 150	Ethanolic	Isoproterenol induced myocardial infarction in albino rats	Orally administered ethanolic extract showed a decrease in serum enzyme levels and the ECG changes brought to the near normal values. The observed results were further confirmed by histopathological findings
Curcuma longa, Zingiberaceae	100	Hydroalcoholic	Isoproterenol induced hemodynamic, biochemical and histopathological alternations in rats	Administration of hydroalcoholic extract causes myocardial adaptation by augmenting endogenous antioxidants and protects rat hearts from decline in cardiac function and oxidative stress associated with isoproterenol induced myocardial injury
Cynodon dactylon, Poaceae	25, 50, 100, 200 µg/ml	Hydroalcoholic	Ischemia/reperfusion-(I/R)induced arrhythmias	*C. dactylon* produce protective effects against I/R-induced arrhythmias in isolated rat hearts probably by increase in the myocardial contractility and as a result by improvement of hemodynamic factors
Daucus carota, Umbeliferae	250, 500	Aqueous	Isoproterenol induced myocardial infarction in albino rats	Aqueous extract showed a decrease in serum aspartate Transaminase(AST), alanine transaminase(ALT), lipid peroxidase, lactate dehydrogenase levels and cardiac total protein lipid peroxidase, and lactate dehydrogenase
Dracocephalum moldavica, Labiatae	25-200 µg/ml	Total extract (Methanol-water)	Ischemia/Reperfusion induced arrhythmias and infarct size in the isolated rat heart	Total extract of *D. moldavica* caused a significant reduction in the number of ventricular tachycardia (VT), total ventricular ectopic beats (VEBs) and VT duration in ischemic and reperfusion periods
Embelica ribes, Myrsinaceae	100	Aqueous	Isoproterenol induced myocardial infarction in albino rats	Pretreatment with an aqueous extract of *E. ribes*, significantly reduced the elevated marker enzyme levels in serum and heart homogenates and also enhances the antioxidant defence system against isoproterenol-induced myocardial infarction
Ficus hispida, Moraceae	400 mg/kg	Methanolic	Cyclophosphamide induced oxidative myocardial injury in a rat model	Methanolic extract of *F. hispida* protected the cardiac tissue by scavenging the free radicals, which was proved by normalisation of biochemical parameters
Glycyrrhiza glabra, Papilionaceae	20	Isoliquiritigenin extract	Metallothiein mediates cardiac protection	Isoliquiritigenin extract protected myocardial ischemia-reperfusion (MI/R) injury through activation of Janus kinase 2 /signal transducers and activators of transcription 3 (JAK 2/STAT 3) signal transduction pathway, which might be involved in mediating the upregulation of metallothionein (MT) expression
Vitis vinifera, Verbenaceae	50, 100, 150	Grape seed proanthocyanidins(GSP)	Isoproterenol induced myocardial infarction in albino rats	Pretreatment with GSP positively altered the levels of all the parameters studied and restored normal mitochondrial function when compared with isoproterenol -induced rats
Hydrocotyle asiatica, Umbelliferae	100-1000	Alcoholic	Ischemia-reperfusion induced myocardial infarction in rats	A reduction in percent left ventricle necrosis (PLVN) as well as in lipid peroxide levels was observed in rats treated with alcoholic extract of *H. asiatica*
Inula racemosa, Compositae	100	Hydroalcoholic	Myocardial ischemic reperfusion injury	Significantly restored the myocardial antioxidant status evidented by increased SOD, CAT, and reduced glutathione and also prevented leakage of cardiospecific enzymes CK-MB and MDA
Lagenaria Siceraria, Cucurbitaceous	10 mL	Fruit juice	Doxorubicin (DOX) induced cardiotoxicity in albino rats	Administration of fruit juice prevented DOX-induced cardiotoxicity and decreased myocardial injury by preservation of endogenous antioxidants and reduction of lipid peroxidation in rat heart
Mangifera indica, Anacardiaceae	100 mg/g	Magniferin	Isoproterenol induced myocardial infarction in albino rats	Magniferin administration prevented isoproterenol induced cardiotoxicity and decreased lipid peroxide formation and retained the myocardial enzymes at the normal level

Moringa oleifera, Moringaceae	200	Hydroalcohol	Isoproterenol induced myocardial damage in albino rats	*Moringa* treatment significantly prevented the rise in lipid peroxidation in myocardial tissue. Furthermore, *M. oleifera* also prevented the deleterious histopathological and ultrastructural perturbations caused by Isoproterenol
Muntingia calabura, Elaeocarpaceae	100, 200, 300	Leaf extract	Isoproterenol induced myocardial infarction in rats	*Muntingia* leaf extract had a significant effect on the activities of marker enzymes compared to the other groups. Serum uric acid level, which increased on isoproterenol administration, registered near normal values on treatment with the leaf extract under study
Nardostachys jatamansi, Valerianaceae	85	Hydroalcoholic	Isoproterenol induced cardiotoxicity	Orally administered ethanolic extract showed a decrease in serum enzyme levels
Ocimum sanctum, Labiatae	25, 50, 75, 100, 200, 400	Hydroalcoholic	Isoproterenol induced myocardial infarction in albino rats	Hydroalcoholic extract reduced significantly modulates various biochemical parameters like GSH, SOD and LDH levels. It also inhibited the lipid peroxidation
Picrorrhiza kurroa, Scrofulariaceae	50	Ethanolic	Adriamycin-induced cardiomyopathy in rats	*Picrorrhiza* extract showed a decrease in serum enzyme levels and protect against cardiotoxicity
Piper betle, Piperaceae	75, 150, 300	Leaf extract	Isoproterenol induced cardiotoxicity in rats	Significant increase in myocardial antioxidants SOD, CAT, GPx, GSH, reduced the leakage of CK-MB isoenzyme and LDH along with decreased lipid peroxidation in heart
Premna serratifolia, Verbenaceae	100 mg/100g	Ethanolic	Isoproterenol induced myocardial infarction in rats	Presence of Phytoconstituents like iridoid glycosides, alkaloids, flavonoids and phenolic compounds might caused significant cardioprotection
Semecarpus anacardium, Anacardiaceae	150	Hydroalcoholic	Isoproterenol induced myocardial damage in rats	Hydroalcoholic extract caused significant elevation in SOD and CAT activities The creatine phosphokinase -MB activities and LDH were fallen in serum
Sesbania grandiflora, Papilionaceae	1000	Aqueous	Cigarette Smoke–exposed Rats	Aqueous suspension of *S. grandiflora* restored the antioxidant status and retained the levels of micronutrients in rats exposed to cigarette smoke
Sida cordifolia, Malvaceae	100, 500 mg/kg	Hydroalcoholic	Isoproterenol induced myocardial infarction in rats	Hydroalcoholic extract of *S. cordifolia* cause marked decrease in the activities of CK-MB isoenzyme, LDH and cause rise in antioxidant enzymes like SOD, CAT and reduced GSH Moreover, biochemical findings were supported by histopathological observations
Silybum marianum, Compositae	100 , 250, 500	Aqueous	Ischemia-reperfusion-induced myocardial infarction in albino rats	The present study showed that silymarin protected the endogenous antioxidant enzymes, suppressed the neutrophil infiltration during ischemia-reperfusion and limited the infarct size. Pretreatment with silymarin also protected rat hearts from a further drop in mean arterial blood pressure during reperfusion and restored heart rate at the end of the reperfusion period
Syzygium cumini, Myrtaceae	500	Seeds	Isoproterenol induced myocardial infarction in rats	Pretreatment with *S. cumini* extract had a more significant effect on the activities of marker enzymes. Serum uric acid level, also registered near normal values on treatment with *S. cumini* extract under study. Presence of multiple chemical constituents in the methanolic seeds extract might be responsible for its cardioprotection
Terminalia arjuna, Combretaceae	3.4, 6.75, 9.75	Alcoholic	Isoproterenol induced myocardial ischemic reperfusion injury	The present study demonstrates that the *T. arjuna* extract augments endogenous antioxidant compounds of the rat heart and also prevents the myocardium from isoproterenol induced myocardial ischemic reperfusion injury
Terminalia chebula, Combretaceae	250	Ethanolic	Isoproterenol induced cardiac (lysosomal) membrane damage	*T. chebula* extract pretreatment resulted in significantly lower activities of heart lysosomal enzymes compared with rats given isoproterenol alone

Tribulus terrestris, Zygophyllaceae	250	Hydroalcoholic	Isoproterenol induced myocardial infarction in rats	*T. terrestris* hydroalcoholic extract decreased the leakage of CK-MB and LDH enzymes from myocardium. Presence of antioxidant constituents (flavanoids) in the extract might be responsible for its cardioprotection
Trichopus zeylanicus, Trichopodaceae	500	Ethanolic	Isoproterenol induced myocardial infarction in rats	Significant decline was shown in the activities of cardiac markers such as ALT, AST, LDH and CK in the heart of acute isoproterenol-treated rats
Withania somnifera, Solanaceae	300	Ethanolic	Doxorubicin-induced cardiotoxicity in rats	Significant decrease in serum enzymes
Zingiber officinale, Zingiberaceae	200	Ethanolic	Isoproterenol induced oxidative myocardial necrosis in rats	Significant decline was shown in the activities of cardiac markers such as ALT, AST, LDH and CK

CONCLUSION: Secondary metabolites like carotenoids, triterpenes, flavonoids, cardiac glycosides, alkaloids saponins, polyphenols, terpenoids, fatty acids *etc* were responsible for cardioprotective activity at a particular dose which was evaluated using appropriate pharmacological screening approach.

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