International Journal of Modern Science and Technology, 2018;3(11):220-229.
ISSN: 2456-0235.
www.ijmst.co

Review Article

Current Pharmacological Status of Cardioprotective Plants against Doxorubicin-Induced Cardiotoxicity: A Scoping Review

T. Gouri Sai Kiran*, K. Raj Kiran, M. Vinodkumar

Department of Pharmacology, Vignan Institute of Pharmaceutical Technology, Visakhapatnam, India-530049.

*Corresponding author's e-mail: tgsaikiran@gmail.com

Abstract

Cardiovascular disease is the leading cause of morbidity and mortality in the world. Cardiotoxic effects can lead to heart failure, the inability of the heart to pump enough blood throughout the body which is due to cardiomyopathy. The present review is focusd on the plants that have been evaluated for cardioprotective activity against doxorubicin-induced cardiotoxicity. This review is based on pertinent papers that were retrieved by a selective search using relevant keywords in PubMed and Science Direct. The literature mainly focusing on natural products and herb extracts with therapeutic efficacies against experimental models both in vitro and in vivo was identified. Three phase screening was applied to select the most relevant studies that suit the objective of the review. Current evidence revealed that multiple molecules and signaling pathways, such as oxidative stress, iron metabolism, and inflammation, are associated with Doxorubicin (DOX) induced cardiotoxicity. Based on this knowledge, various strategies were proposed, and thousands of compounds were screened. A number of herbal extracts and natural products demonstrated potency in limiting DOX cardiotoxicity toward cultured cells and experimental animal models. This review, therefore, provided a useful resource to enable a thorough assessment of the profile of plants that have cardioprotective activity against doxorubicin-induced cardiotoxicity.

Keywords: Cardioprotective; Plants; Doxorubicin; Cardiotoxicity; Antioxidants.

Introduction

Cardiovascular diseases are the foremost cause of morbidity and mortality globally; more people die annually from cardiovascular diseases than from any other cause. An estimated 17.7 million people died from cardiovascular diseases in 2015, representing 31% of all global deaths. Over three-quarters of cardiovascular disease, deaths take place in low- and middle-income countries. There are 32.4 million myocardial infarctions and strokes cases worldwide every year [1]. The progress in the management of myocardial infarction is a result of several major trends, including improvements in risk stratification, more widespread use of an invasive strategy, and implementation of care delivery systems prioritizing immediate revascularization year [2]. Myocardial infarction (i.e., heart attack) is defined pathologically as the irreversible death (necrosis) of myocardial cells secondary to prolonged lack of oxygen supply (ischemia) [3]. Oxygen demand can be reduced by decreasing cardiac exertion or, according to recent studies, by shifting myocardial metabolism to substrates that involve less oxygen per unit of adenosine triphosphate (ATP) produced. Among the pharmacological agents used in the treatment of infarction are nitro vasodilators, β-adrenergic receptor antagonists, calcium channel antagonists, and antiplatelet through percutaneous coronary intervention (or fibrinolysis), advances in antiplatelet agents and anticoagulants, and greater use of secondary prevention strategies such as statins [4].

Doxorubicin is an anticancer drug which belongs to anthracycline antibiotics and is being used widely for the treatment of various hematological and solid tumor malignancies including breast cancer, leukemia, and sarcomas [5, 6]. However, its clinical uses are limited by a dose-dependent side effect of cardiotoxicity, which may lead to irreversible cardiomyopathy and eventually heart failure [7, 8]. The incidence of doxorubicin-related cardiotoxicity increases

Received: 20.10.2018; Received after Revision: 30.10.2018; Accepted: 31.10.2018; Published: 14.11.2018

sharply above a cumulative dose of 550 mg/m2 body surface area. So, the maximum recommended a cumulative dose of Doxorubicin was tentatively set at 500 or 450 mg/square meters [9]. Doxorubicin-induced cardiotoxicity is mediated through different mechanisms including free radical production, calcium overloading, mitochondrial dysfunction, and peroxynitrite formation have been proposed [10-11]. Doxorubicin is enzymatically reduced to its semi Quinone radical [12]. This Doxorubicin semi Quinone radical directly transfers its electron to molecular oxygen, generating superoxide radical and hydrogen peroxide [13]. As reactive oxygen species (ROS) play important roles in Doxorubicin-induced toxicity. Many compounds with antioxidant properties have been examined as potential therapeutic and/or protective agents [14]. Various phytoconstituents from plants were responsible for the cardioprotective activity as mentioned in table 1.

Table 1. Phytoconstituents from plants were responsible for the cardioprotective activity

Phytoconstituents	Plant name	Family
Allicin, sulfur compounds	Allium sativum	Liliaceae
Flavonoids, carotenoids	Anacardiumoccidentale	Anacardiaceae
Cardiac glycosides	Antiaristoxicaria	Moraceae
Saponins-Shatavarins I–IV	Asparagus racemosus	Asparagaceae
Triterpenes	Ganodermalucidum	Ganodermataceae
Triterpenoid	Leptadeniapyrotechnica	Asclepiadaceae
Cardiac glycosides	Digitalis purpurea	Scrophulariaceae
Alkaloidal constituents, including berberine; bitter principles, including columbin, chasmanthin, palmarin and tinosporon, tinosporic acid and tinosporol	Tinosporacordifolia	Menispermaceae
Caffeic acid	Raphanussativus	Cruciferae
Protein	Euryale ferox	Nymphaeaceae

Literature search strategy

Search terms like “cardioprotective” “doxorubicin” “cardiotoxicity” “adriamycin” “plants” were combined with suitable Boolean markers AND, OR and searched in databases PubMed and Science Direct. Studies which employed primary research, which suits the aim of the study, English language papers, the time period between 2004 to 2018 were included in the study. Abstracts, letters to the editor, short communications are excluded from the study. The articles thus obtained were screened by a three-stage process. In the first stage, the titles were evaluated for suitability of inclusion in the study. In the second stage, abstracts of suitable articles were evaluated for inclusion. In the third stage, the full paper of suitable articles was evaluated for inclusion.

Plants and their cardio-protective activity against doxorubicin induced cardiotoxicity

Dried stigmas of *Saffron* methanolic extract restored inflammatory marker (lactate dehydrogenase), cardiac markers (C-reactive protein, troponin-T, and creatine kinase-muscle/brain [MB]), and lipid peroxidase activity to normal levels in Doxorubicin Toxicity in Isolated Rabbit Hearts [15]. Ethanolic extract of *Boswellia ovalifoliolata* bark and leaf restored the doxorubicin-induced cardiotoxicity by attenuating oxidative stress and lipid peroxidation in the heart to the normal [16]. The administration of Water extract of *pomegranate* aril, rind, and seeds in male Wistar albino rats possesses significant cardioprotective potential against doxorubicin-induced cardiotoxicity as it significantly increased in serum CK-MB, LDH, and cardiac marker enzymes, and prevented the depletion of antioxidant parameters[17].

The treatment of Wistar Albino rats with *green tea extract* showed significant cardioprotective activity by bringing all the parameters such as cardiac markers (creatine kinase MB, lactate dehydrogenase, and aspartate aminotransferase), some antioxidant enzymes, interleukin (IL)-1 β, monocyte chemoattractant protein-1, myeloperoxidase, collagen-1, galectin-3, and serum corticosterone to near normal level in doxorubicin-induced cardiotoxicity in rats[18]. The dry roots of *Astragalus membranaceus* elicited a significant cardioprotective activity by lowering the levels

of serum marker enzymes (aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, and creatine phosphokinase) and lipid peroxidation and elevated the levels of glutathione. The cardioprotective effects of *Astragalus* polysaccharide in doxorubicin-induced oxidative damage may be due to an augmentation of the endogenous antioxidants and inhibition of lipid peroxidation of the membrane [19]. Cardioprotective effects of hydroalcoholic extract of raw garlic (*Allium sativa*) in doxorubicin-induced cardiotoxicity in rats is by significantly decreasing creatine kinase and lactate dehydrogenase and by increasing the heart rate. Garlic pretreatment increased the activity of Na+–K+ ATPase and decreased the activity of Ca+2 ATPase in the heart and aorta simultaneously along with decreasing the levels of cholesterol and triglycerides and increasing phospholipids in the heart and aorta [20].

The aqueous extract of *Allium cepa* bulb significantly recovered the altered parameters (troponin-I, creatine kinase-MB, glutamate-pyruvate transaminase, heart rate, R-R interval, and oxidative stress markers) in doxorubicin-induced cardiotoxicity in Wistar albino rats [21]. Pretreatment with the aqueous leaf extract of Mangiferin (*Mangifera indica L*) prevented the elevation of serum marker enzymes, namely, lactate dehydrogenase, aspartate transaminase, alanine transaminase, and ALP (Alkaline phosphatase) in doxorubicin-induced cardiotoxicity in rats. The extract also attenuated lipid peroxidation in the heart and improved the imbalance in glutathione reductase, glutathione peroxides, superoxide dismutase, glutathione, and lipid profile caused by doxorubicin [22]. The ethanol and aqueous extracts of *Terminalia arjuna* bark significantly restored the level of total cholesterol, triglyceride, low-density lipoprotein, high-density lipoprotein and myocardial and serum of lactate dehydrogenase, creatine kinase, and aspartate aminotransferases which were altered by doxorubicin induction[23]. *Ginkgo biloba* phytosomes and *proanthocyanidin* extract significant restored doxorubicin depleted activities and levels of endogenous antioxidants (superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase, and glutathione) heart homogenate. A significant decrease in doxorubicin-induced serum marker enzyme (aspartate aminotransferase, lactate dehydrogenase, and creatine phosphokinase) elevations and a significant attenuation of the doxorubicin elevated myocardial lipid peroxidation marker MPO demonstrates significant cardiac protection of G. biloba phytosomes and proanthocyanidin extract[24].

Ficus racemosa stem bark acetone extract improved cardiac function by increasing the heart rate, mean arterial pressure, contractility, and relaxation along with decreasing left ventricular end diastolic pressure and also significantly restored the reduced form of glutathione and endogenous antioxidant enzymes superoxide dismutase, catalase, and glutathione peroxidase from the heart, which were depleted after doxorubicin administration. It protects the heart from doxorubicin-induced cardiac injury by reducing oxidative stress and modulating hemodynamic and ventricular functions of the heart [25]. The ethanolic extract of Cranberry (*Vaccinium macrocarpon)* pretreatment reversed the lipid profile level, liver marker enzymes (SGPT and SGOT), cardiac marker enzymes (creatine kinase-MB and lactate dehydrogenase), and antioxidants (superoxide dismutase, catalase, glutathione peroxidase, and lipid peroxidase) to near normal than doxorubicin-induced rats [26].

Withania somnifera leaf extract preserves the integrity of myocardial cell membrane by maintaining the activities of cardiac Troponin I levels and serum lipid profiles, as well as the activities of marker enzymes of doxorubicin-induced cardiac toxicity. Cardioprotective activity may be due to antilipoperoxidative and antioxidant effects [27]. *Melissa officinalis* exhibited significant cardioprotective activity by reversing the doxorubicin-induced cardiotoxicity in rats by increasing mean arterial pressure, heart rate, contractility, and relaxation along with decreased left ventricular end diastolic pressure, increased antioxidant enzymes, superoxide dismutase, catalase, and glutathione peroxidase and myocyte-injury-specific marker enzymes, creatine phosphokinase-MB, and lactate dehydrogenase in heart along with restoration of reduced glutathione and decreasing thiobarbituric acid reactive substances beside histopathological salvage of myocardium. The cardioprotective potential of M. officinalis is attributed to its potent antioxidant and free radical scavenging activity [28].

Pretreatment with ethanolic extract of *Panax notoginseng* saponins prevented the increase in serum and tissue lipid peroxidation, serum cardiac marker enzymes such as lactate dehydrogenase aspartate transaminase and alanine transaminase and the decrease in both enzymatic and non-enzymatic antioxidants in doxorubicin-treated mice [29]. *Kolaviron* and *Garcinia kola* seed extract significantly decreased the elevated levels of cardiac marker enzymes such as creatine kinase-MB, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase and ALP in serum, doxorubicin-induced cardiotoxicity in Wistar rats [30]. Administration of plant extract of Taiwanese and Japanese yam (*Dioscorea spp*.) reduced the oxidative stress by decreased lipid peroxidation and reduced glutathione and also normalized the levels of cardiac marker enzymes such as creatine kinase, lactate dehydrogenase; SGOT, SGPT, and cardiac specify protein Troponin I in cardiotoxicity induced by doxorubicin. Taiwanese and Japanese yam (Dioscorea spp.) treated animals showed a lesser degree of cellular infiltration in histopathological studies [31]. *Lycium barbarum* elicited a significant cardioprotective effect by augmentation of the endogenous antioxidants and inhibition of lipid peroxidation of the membranes. Significant cardiotoxicity, increase serum marker enzymes (lactate dehydrogenase, glutamate oxaloacetate transaminase, and creatine kinase) by doxorubicin were reversed by pretreatment with aqueous extract of Lycium barbarum [32].

Lyophilized hydroalcoholic extract of *Moringa oleifera* leaf exhibited significant cardioprotective effect by reducing effects on doxorubicin-induced cardiotoxicity. Chronic M. oleifera treatment resulted in significantly favorable modulation of the biochemical enzymes and prevented the deleterious histopathological and ultrastructural perturbations caused by doxorubicin [33]. Cardioprotective effect of *strawberry* fruits in doxorubicin-induced cardiotoxicity in rats is due to a decrease in the level of lipid peroxides and cardiac biomarker enzymes in the serum and heart [34]. *Beetroot juice* in increasing concentrations enhanced doxorubicin-induced cancer cell death, while lower concentrations of BRJ in combination with DOX proved to be the most effective combination for both cardioprotection and chemoprevention. These findings are clinically significant for potential use of BRJ in cardioprotection against DOX in patients with cancer. So BRJ can be a dietary nutritional supplement to reduce DOX-induced cardiotoxicity in cancer patients [35]. Significant cardioprotective effects were observed on protein, urea, creatinine, serum lipid profile, and antioxidants when treated with a hydroethanolic extract of *Grape Seed* and Skin against doxorubicin-induced chemotoxicity in rat heart [36]. The methanol extract of *Acacia hydaspica*, ameliorated the biochemical (creatine kinase-myoglobin, SGOT, lactate dehydrogenase, serum glutamate pyruvate transaminase [SGPT], and total protein) and antioxidant parameters (catalase, superoxide dismutase, reduced glutathione, glutathione peroxidase, glutathione reductase, and MPO) levels significantly in doxorubicin-induced oxidative stress thereby offering significant cardioprotection [37].

Diosgenin, a steroidal saponin of *Dioscorea opposita*, has been reported to have antioxidant activity. DOX treatment led to a significant decrease in the ratio of heart weight to body weight, and increases in the blood pressure and the serum levels of lactate dehydrogenase (LDH), creatine phosphokinase (CPK) and creatine kinase-myocardial bound (CK-MB), markers of cardiotoxicity. In the heart tissue of the DOX-treated mice, DOX reduced activities of antioxidant enzymes, including superoxide dismutase (SOD) and glutathione peroxidase (GPx), were recovered by diosgenin. Diosgenin also decreased the serum levels of cardiotoxicity markers, cardiac levels of thiobarbituric acid relative substances (TBARS) and reactive oxygen species (ROS), caspase-3 activation, and mitochondrial dysfunction, as well as the expression of nuclear factor kappa B (NF-κB), an inflammatory factor [38]. Davallialactone (DAVA) extracted from mushroom *Inonotus xeranticus* significantly increased the viability of doxorubicin-injured H9c2 cells and inhibited ADR-induced ROS production, apoptosis, and the expression of Cu/Zn SOD and Mn-SOD. DAVA also inhibited the expression of the extracellular signal-regulated kinase (ERK) and c-Jun N-terminal kinase (JNK), which was activated by ADR. In the in vivo animal model, treatment involving DAVA significantly reduced cardiomyocyte lesions [39].

Bilberry extract significantly inhibited doxorubicin-provoked reduced glutathione depletion and accumulation of oxidized glutathione, malondialdehyde and protein carbonyls in cardiac tissues. This was accompanied by significant amelioration of reduced cardiac catalase, superoxide dismutase, and glutathione peroxidase activities; and increased cardiac myeloperoxidase activity in response to DOX challenge. Pretreatment with bilberry significantly guarded against a DOX-induced increase in serum activities of lactate dehydrogenase, creatine phosphokinase, and creatine kinase-MB, as well as the level of troponin I [40]. *Cannabidiol* (CBD) exerts protective effects against doxorubicin-induced cardiotoxicity and cardiac dysfunction by (i) attenuating oxidative and nitrative stress, (ii) improving mitochondrial function, (iii) enhancing mitochondrial biogenesis, (iv)decreasing cell death and expression of MMPs and (v) decreasing myocardial inflammation [41].

Honokiol is an active component extracted from the bark of *Magnolia Officinalis*, treatment protects the heart from Doxorubicin-cardiotoxicity via facilitating mitochondrial respiration and exerting anti-oxidant and anti-inflammation, effects, not only by repressing mitochondrial protein de-acetylation but also activating PPARγ signaling [42]. The aqueous *Schisandra Chinensis* fruit extract maintains near normal levels of cardiac biomarker enzymes (cardiac troponin-T, creatinine kinase, and lactate dehydrogenase) and antioxidant enzymes (glutathione, MPO, catalase, and superoxide dismutase). ADR cardiotoxicity is associated with the antioxidant deficit and SC treatment changes the antioxidant status of the heart to improve cardiac function [43]. *Cryptotanshinone* protects the energy production by increasing the complexes activities in ETC and the ATP generation. CRY also increases the MMP and inhibits the superoxide anion free radicals. The expressions of mitochondrial biogenesis-relative genes can be up-regulated by CRY. Remarkable augmentations of NO, iNOS, and increased activity of GSH-PX are detected after the treatment of CRY. However, these structural and functional protections are partly recovery [44].

Baicalein, a natural antioxidant component of *Scutellaria baicalensis*, produced maximum cardioprotection as evidenced by significant restoration of endogenous antioxidants (superoxide dismutase, catalase, glutathione peroxidase, and reduced glutathione), myocyte-specific injury markers (myocardial lactate dehydrogenase and creatine kinase-MB isoenzyme), and decrease in lipid peroxidation marker Myeloperoxidase (MPO) Against Doxorubicin-Induced Cardiotoxicity [45]. Ethanolic extract of root of *Rheum turkestanikum* strongly protected the heart against doxorubicin-induced cardiotoxicity and elicits cardioprotective effects which could be related to antioxidant activities. Animals treated with root extract of Rheum turkestanikum showed a significant decrease in triglycerides, aspartate aminotransferase, ALP, antioxidant enzymes, namely, superoxide dismutase, lipid hydroperoxide, an increase in high-density lipoprotein cholesterol [46]. *Theobroma cacao* stem bark aqueous extract (TCAE) protects doxorubicin intoxication caused by a significant increase in concentrations of H2O2 generated, MDA and PC, XO, MPx and NOX activities with a concomitant decrease in CAT, SOD, GPx and GST activities, and in concentrations of GSH, AsA and α-Toc in the brain and cardiac tissues. Pre-, co- and post-treatment with TCAE significantly reversed the oxidative damage to the organs induced byDOX-intoxication. The result affirmed that T. cacao stem bark aqueous extract protected against DOX-induced oxidative damage in the brain and cardiac tissues of experimental rats [47].

Administration of root extract of *Oroxylum indicum* reduced the oxidative stress by decreased lipid peroxidation and reduced glutathione and also normalized the levels of cardiac marker enzymes such as creatine kinase, lactate dehydrogenase; SGOT, SGPT, and cardiac specify protein Troponin I in cardiotoxicity induced by doxorubicin. Oroxylum indicum treated animals showed a lesser degree of cellular infiltration in histopathological studies [48]. Pretreatment with *Simvastatin* SIM and *Lagenaria siceraria* (H.L.S.S.E) significantly reduced the elevated cardiac toxicity biomarker enzyme level and raised the level of antioxidants viz CAT, GSH, SOD and decrease LPO in the extract treated groups as compared to the disease control group. In the histopathological studies, H.L.S.S.E and SIM showed protection against cardiotoxicity induced by doxorubicin [49]. *Ganoderma atrum* polysaccharide was found to possess

cardioprotective effects against doxorubicin-induced cardiotoxicity in vivo, as evidenced by improving mitochondrial structure and function through the inhibition of mitochondrial apoptosis signal transduction pathway by maintaining the redox status, Bcl-2 family and mPTP opening [50].

Pretreatment of *Averrhoa bilimbi* (BM) extract controlled doxorubicin-induced toxicities in terms of reduced serum CK-MB, LDH, cardiac tissue-TBARS and elevation of other enzymatic and non-enzymatic antioxidants and protected the body-weightloss and DNA-fragmentation in heart tissue. Further, cardioprotection was established by histopathological examination. BM-extract treatment modulated the antioxidants both in heart and liver tissues of EAC-mice. For mechanistic approach, BM-extract showed in vitro antioxidant activity (measured by DPPH and FRAP assay) and inhibited intracellular generation of ROS and nitrite in RAW264.7 cells [51]. The ethanolic extract of *Lagenaria siceraria* pretreatment reversed the lipid profile level, liver marker enzymes (SGPT and SGOT), cardiac marker enzymes (creatine kinase-MB and lactate dehydrogenase), and antioxidants (superoxide dismutase, catalase, glutathione peroxidase, and lipid peroxidase) to near normal than doxorubicin-induced rats [52].

Treatment with *date palm* fruit extract restored the aforementioned parameters. Doxorubicin produced a significant increase in creatine kinase-MB and lactate dehydrogenase activities. It also decreased the activities of cardiac glutathione peroxidase and superoxide dismutase but increase levels of cardiac malondialdehyde and also of urinary 8-hydroxy-2-deoxyguanosine. Cardiotoxicity of Dox also appeared in the elevation of serum total cholesterol, triglycerides, and low-density lipoprotein cholesterol levels, while the level of high-density lipoprotein cholesterol decreased. Histopathological studies revealed alteration of cardiac tissue structure by Dox [53].

The hydroethanolic extract of *Urtica parviflora* leaf treatment significantly protected the myocardium by decreasing the elevated level of MDA; elevating the diminished levels of GSH, SOD, CAT, and HDL, with a concomitant decrease in the elevated levels of HDL, LDL, and TG. EEUP also significantly reduced the increased activities of AST, ALT, ALP, CPK, and LDH [54]. The extract of *sea cucumber* and *valsartan* significantly decreased the cardiac marker enzyme creatinine phosphokinase and lactate dehydrogenase and increased the levels of creatinine phosphokinase and lactate dehydrogenase of superoxide dismutase and catalase exhibiting cardioprotective activity against doxorubicin-induced cardiac damage [55]. Treatment with *Hypericum hircinum* significantly decreased the levels of LPO and marker enzymes, increased the levels of GSH and, reversed the changes in ECG and prevented the decrease in the heart weight in the DOX-treated group. The results suggest that H. hircinum has the potential to prevent the cardiotoxic effects induced by DOX [56].

The ethanolic extract of aerial parts of *Thespesia populnea* significantly suppressed the elevation of MPO levels, suppressed ST-segment elevation and severe myocardial necrosis and fibrosis with a sharp reduction in left ventricular contractility and a marked increase in left ventricular end-diastolic pressure induced by doxorubicin [57].

The of aqueous leaf extract of *Guazuma ulmifolia* significantly decreased the cardiac marker enzyme (creatinine phosphokinase and lactate dehydrogenase) and increased the antioxidant enzymes (superoxide dismutase and catalase) signifying it is cardioprotective effect against the acute cardiac damage induced by doxorubicin in rats [58]. The ethanol extract of *Buchanania axillaris*, ameliorated the biochemical (creatine kinase-myoglobin, SGOT, lactate dehydrogenase, serum glutamate pyruvate transaminase [SGPT], and total protein) and antioxidant parameters (catalase, superoxide dismutase, reduced glutathione, glutathione peroxidase, glutathione reductase, and MPO) levels significantly in doxorubicin-induced oxidative stress thereby offering significant cardioprotection [59].

Pretreatment with the ethanolic extract of the whole plant of *Boerhaavia diffusa* and Vit-E significantly protected myocardium from the toxic effects of Dox by reducing the elevated level of biomarker enzymes like LDH, CK-MB, biochemical parameters such as AST and ALT, the absence of cTnI and restoring of disorganized myocardial tissue to normal [60]. The ethanolic leaf extract of *Ipomoea batatas* (EEIB) significantly decreased the levels of cardiac markers like creatinine kinase (CK-MB),

CK, lactate dehydrogenase and lipid peroxides. In heart superoxide dismutase, catalase, tissue protein, and glutathione levels were significantly increased in the extract and ascorbic acid pretreated rats when compared to doxorubicin [61]. Gingerols and shogaols present in *Zingiber officinale* showed decrease in all the cardiac enzyme activities, i.e., cardiac Troponin I, creatine kinase-MB isoenzyme, lactate dehydrogenase, alanine transaminase, and aspartate transaminase against doxorubicin-induced cardiac toxicity along with significant rises in the activity of glutathione peroxide, catalase, and superoxide dismutase apart from improvement in membrane cell integrity [62].

Treatment with *Solanum torvum* significantly reversed the changes in ECG; decreased the levels of CK-MB and LDH; and increased the antioxidant defense enzyme levels of SOD and CAT. S. torvum treated animals showed a lesser degree of cellular infiltration in histopathological studies. The results suggest that S. torvum has the potential of preventing the cardiotoxicity induced by Doxorubicin [63].The methanolic extract of *Piper longum* Pretreatment ameliorated the effect of ADR on lipid peroxide formation and restored activities of marker enzymes. Activities of myocardial antioxidant enzymes like catalase, superoxide dismutase, glutathione peroxidase, glutathione reductase along with reduced glutathione were significantly lowered due to cardiotoxicity in rats administered with ADR. PLM pretreatment augmented these endogenous antioxidants. Histopathological studies of the heart revealed degenerative changes and cellular infiltrations in rats administered with ADR and pretreatment with PLM reduced the intensity of such lesions [64].

Conclusions

The present review reveals the importance of medicinal plants in preventing and reversing cardiovascular diseases and makes an attempt to compile some of the cardioprotective plants. Medicinal plants and their supplements can help in lowering the risk of cardiovascular diseases. Secondary metabolites such as carotenoids, cardiac glycosides, alkaloids, flavonoids, polyphenolic compounds, saponins, terpenoids [triterpenes], fatty acids which are present in medicinal plants were considered as the responsible agents for potent cardio-protective activity.

Conflicts of interest

The authors declare no conflict of interest.

References

[1] Laurence LB, Chabner BA, Knollmann BC, Chabner BA, Knollmann BC. Treatment of myocardial ischemia and hypertension. The Goodman and Gilman's Manual of Pharmacology and Therapeutics. 12th ed. New York: McGraw-Hill Medical; 2014:745-65.

[2] Cardiovascular Diseases (CVDs). World Health Organization. Geneva: World Health Organization; 2017. Available from: http://www.who.int/mediacentre/factsheets/fs317/en.

[3] Silverstein DC, Kate H. Myocardial Infarction. Small Animal Critical Care Medicine. 2nd ed. St Louis, MO: Saunders; 2014:174-6.

[4] Grant WR, Jeffrey ER, Christopher PC. Acute myocardial infarction. Lancet 2017; 389:197-210.

[5] Fisher PW, Salloum F, Das A, Hyder H, Kukreja RC. Phosphodiesterase-5inhibition with sildenafil attenuates cardiomyocyte apoptosis and left ventricular dysfunction in a chronic model of doxorubicin cardiotoxicity. Am Heart Assoc 2005;111:1601-10.

[6] Rahimi Balaei M, Momeny M, Babaeikelishomi R, Ejtemaei Mehr S, Tavangar SM, Dehpour AR. The modulatory effect of lithium on doxorubicin-induced cardiotoxicity in the rat. Eur J Pharmacol 2010;641:193-98.

[7] Shan K, Lincoff AM, Young JB. Anthracycline-induced cardiotoxicity. Ann Intern Med 1996;125:47-58.

[8] Huda A, Damanhouri ZA, Ahmed M, Slevin M, Ali SS, Osman AM. Aged garlic extract protects against doxorubicin-induced cardiotoxicity in rats. Food Chem Toxicol 2010; 48:951-56.

[9] Roohollah BK, Ejtemaeemehr S, Tavangar SM, Rahimian R, Mobarakeh JI, Dehpour AR. Morphine is protective against doxorubicin-induced cardiotoxicity in the rat. Toxicol 2008;243:96-104.

[10] Olson RD, Mushlin PS. Doxorubicin cardiotoxicity: analysis of prevailing hypotheses. FASEB J 1990;4(13):3076-86.

[11] De Beer EL, Bottone AE, Voest EE. Doxorubicin and mechanical performance of cardiac trabeculae after acute and chronic treatment: a review. Eur J Pharmacol 2001; 415:1-11.

[12] Shuai Y, Guo JB, Peng SQ, Zhang LS, Guo J, Han G, Dong YS. Metallothionein protects against doxorubicin-induced cardiomyopathy through inhibition of superoxide generation and related nitrosative impairment. Toxicol Lett 2007;170 (1):66-74.

[13] Minotti G, Parlani M, Salvatorelli E, Menna P, Cipollone A, Animati F, Maggi CA, Manzini S. Impairment of myocardial contractility by anticancer anthracyclines: the role of secondary alcohol metabolites and evidence of reduced toxicity by a novel disaccharide analogue. Br J Pharmacol 2001;134(6):1271-78.

[14] Gille L, Nohl H. Analyses of the molecular mechanism of adriamycin-induced cardiotoxicity. Free Radic Biol Med 1997;23(5):775-782.

[15] Chahine N, Makhlouf H, Duca L, Martiny L, Chahine R. Cardioprotective Effect of Saffron Extracts against Acute Doxorubicin Toxicity in Isolated Rabbit Hearts Submitted to Ischemia-Reperfusion Injury. Zeitschrift für Naturforschung C 2014;69(11-12):459-70.

[16] Uma Mahesh B, Shrivastava S, Kuncha M, Sahu B, Swamy C, Pragada RR, Naidu VG, Sistla R. Ethanolic extract of Boswellia ovalifoliolata bark and leaf attenuates doxorubicin-induced cardiotoxicity in mice. Environ Toxicol Pharmacol 2013;36(3):840-9.

[17] Hassanpour Fard M, Ghule A, Bodhankar S, Dikshit M. Cardioprotective effect of whole fruit extract of pomegranate on doxorubicin-induced toxicity in the rat. Pharm Biol 2011;49(4):377-382.

[18] Gyas K, Syed E, Mohd N, Mohammad M S. Cardioprotective Effect Of Green Tea Extract On Doxorubicin-Induced Cardiotoxicity in Rats. Acta Pol Pharm 2014;71(5):861-8.

[19] Cao Y, Ruan Y, Shen T, Huang X, Li M, Yu W, Zhu Y, Man Y, Wang S, Li J. Astragalus Polysaccharide Suppresses Doxorubicin-Induced Cardiotoxicity by Regulating the PI3k/Akt and p38MAPK Pathways. Oxid Med Cell Longev 2014;2014:674219.

[20] Alkreathy H, Damanhouri Z, Ahmed N, Slevin M, Ali S, Osman A. Aged garlic extract protects against doxorubicin-induced cardiotoxicity in rats. Food Chem Toxicol. 2010; 48(3):951-6.

[21] Alpsoy S, Aktas C, Uygur R, Topcu B, Kanter M, Erboga M, Karakaya O, Gedikbasi A. Antioxidant and anti-apoptotic effects of onion (Allium cepa) extract on doxorubicin-induced cardiotoxicity in rats. J Appl Toxicol 2013;33(3):202-8.

[22] Arozal W, Suyatna F, Juniantito V, Rosdiana D, Amurugam S, Aulia R, Monayo ER, Siswandi R. The Effects of Mangiferin (*Mangifera indica* L) in Doxorubicin-induced Cardiotoxicity in Rats. Drug Res (Stuttg) 2015;65(11):574-80.

[23] Bishop S, Liu S. Cardioprotective action of the aqueous extract of Terminalia arjuna bark against toxicity induced by doxorubicin. Phytomedicine 2017;36:210-216.

[24] [24] Boghdady N. Antioxidant and antiapoptotic effects of proanthocyanidin and ginkgo biloba extract against doxorubicin-induced cardiac injury in rats. Cell Biochem Func 2012; 31(4):344-51.

[25] Ahmed F, Urooj A. Cardioprotective activity of standardized extract of Ficus racemosastem bark against doxorubicin-induced toxicity. Pharm Biol 2011;50(4):468-473.

[26] Elberry AA, Abdel-Naim AB, Abdel-Sattar EA, Nagy AA, Mosli HA , Mohamadin AM, Ashour OM. Cranberry (Vaccinium macrocarpon) protects against doxorubicin-induced cardiotoxicity in rats. Food Chem Toxicol 2010;48(5):1178-84.

[27] Amin A, Hamza A, Daoud S. The protective effect of a purified extract of Withania somnifera against doxorubicin-induced cardiac toxicity in rats. Cell Biol Toxicol 2008;24(1):63-73.

[28] Hamza AA, Ahmed MM, Elwey HM, AminA. Melissa officinalis Protects againstDoxorubicin-Induced Cardiotoxicity in Rats and Potentiates Its Anticancer Activity on MCF-7 Cells. PLoS ONE 2016;11(11):e0167049.

[29] Liu L, Shi R, Shi Q, Cheng Y, Huo Y. Protective Effect of Saponins from Panax notoginseng against Doxorubicin-Induced Cardiotoxicity in Mice. Planta Medica 2008;74(3):203-9.

[30] Oyagbemi AA, Omobowale TO, Olopade JO, Farombi EO. Kolaviron and Garcinia kola attenuate doxorubicin-induced cardiotoxicity in Wistar rats. J Complement Integr Med. 2017;15(1). pii: /j/jcim.2018.15.issue-1/jcim-2016-0168/jcim-2016-0168.xml.

[31] Chen CT, Wang ZH, Hsu CC, Lin HH, Chen JH. Taiwanese and Japanese yam *(Dioscorea* spp.) extracts attenuate doxorubicin-induced cardiotoxicity in mice. J Food Drug Anal 2017;25(4):872-880.

[32] Xin YF, You ZQ, Gao HY, Zhou GL, Chen YX, Yu J, Xuan YX. Protective Effect of Lycium barbarum Polysaccharides Against Doxorubicin-induced Testicular Toxicity in Rats. Phytother Res 2011;26(5):716-21.

[33] Fikriansyah F, Widiastuti M, Wulandari N, Tirtanirmala P, Murwanti R. Cardioprotective Effect of Kelor (*Moringa oleifera*) Leaf Ethanolic Extract against Doxorubicin-Induced Cardiotoxicity in Rats. Indonesian Journal of Cancer Chemoprevention 2015;6(2):53.

[34] Giampieri F, Alvarez-Suarez J, Gasparini M, Forbes- Hernandez T, Afrin S, Bompadre S Rubini C , Zizzi A , Astolfi P , Santos-Buelga C , Gonzalez-Paramas AM , Quiles JL , Mezzetti B , Battino M . Strawberry consumption alleviates doxorubicin-induced toxicity by suppressing oxidative stress. Food Chem Toxicol. 2016;94:128-137.

[35] Das S, Filippone S, Williams D, Das A, Kukreja R. Beetroot juice protects against doxorubicin toxicity in cardiomyocytes while enhancing apoptosis in breast cancer cells. Mol Cell Biochem 2016;421:89-101.

[36] Mokni M, Hamlaoui-Guesmi S, Amri M, Marzouki L, Limam F, Aouani E. Grape Seed and Skin Extract Protects Against Acute Chemotherapy Toxicity induced by Doxorubicin in Rat Heart. Cardiovasc Toxicol. 2012;12(2):158-165.

[37] Afsar T, Razak S, Batoo K, Khan M. Acacia hydaspica R. Parker prevents doxorubicin-induced cardiac injury by attenuation of oxidative stress and structural Cardiomyocyte alterations in rats. BMC Complement Altern Med 2017;17(1).

[38] Chen C, Wang Z, Hsu C, Lin H, Chen J. In Vivo Protective Effects of Diosgenin against Doxorubicin-Induced Cardiotoxicity. Nutrients 2015;7(6):4938-4954.

[39] Arunachalam S, Kim S, Lee S, Lee Y, Kim M, Yun B, Yi HK , Hwang PH . Davallialactone protects against adriamycin-induced cardiotoxicity in vitro and in vivo. Journal of Natural Medicines 2011;66(1):149-157.

[40] Ashour O, Elberry A, Alahdal A, Al Mohamadi A, Nagy A, Abdel-Naim AB, Abdel-Sattar EA, Mohamadin AM.. Protective effect of bilberry (Vaccinium myrtillus) against doxorubicin-induced oxidative cardiotoxicity in rats. Med Sci Monit 2011;17(4):BR110-BR115.

[41] [41] Hao E, Mukhopadhyay P, Cao Z, Erdelyi K, Holovac E, Liaudet L, Lee WS, Hasko G, Mechoulam R, Pacher P. Cannabidiol Protects against Doxorubicin-Induced Cardiomyopathy by Modulating Mitochondrial Function and Biogenesis. Mol Med 2015;21(1):38-45.

[42] Huang L, Zhang K, Guo Y, Huang F, Yang K, Chen L, Kai Hg, Fengxue Zg, Qinqiang Lg, Qinglin Yg. Honokiol protects against doxorubicin cardiotoxicity via improving mitochondrial function in mouse hearts. Scientific Reports 2017;7(1).11989.

[43] You JS, Pan TL, Hou YC. Schisandra Chinensis protects against adriamycin-induced cardiotoxicity in rats. Chang Gung Med J 2006; 29(1):63-70.

[44] Zhang Y, Chen L, Li F, Wang H, Yao Y, Shu J, Ying M. Cryptotanshinone protects against adriamycin-induced mitochondrial dysfunction in cardiomyocytes. Pharm Biol 2015;54(2):237-242.

[45] Chang W, Li J, Huang H, Liu H, Han M, Ramachandran S, Li C, Sharp W, Hamann K, Yuan C, Vanden Hoek T, Shao Z. Baicalein protects against doxorubicin-induced cardiotoxicity by attenuation of mitochondrial oxidant injury and JNK activation. J Cell Biochem 2011; 112(10):2873-2881.

[46] Hosseini A, Rajabian A. Protective effect of Rheum turkestanikum root against

doxorubicin-induced toxicity in H9c2 cells. Rev Bras Farmacogn 2016;26(3):347-351.

[47] Kosoko A, Olurinde O, Akinloye O. Doxorubicin-induced neuro- and cardiotoxicities in experimental rats: Protection against oxidative damage by Theobroma cacao Stem bark. Biochem Biophys Rep 2017;10:303-17.

[48] Menon S, Lawrence L, Sivaram VP, Padikkala J. *Oroxylum indicum* root bark extract prevents doxorubicin-induced cardiac damage by restoring redox balance. J Ayurveda Integr Med 2018. pii: S0975-9476(17)30055-4.

[49] Singh MK, Faisal Mohd, Ahmad Ayaz, Sonkar Ankur, Yadav Jyoti. Protective effect of Lagenaria siceraria against doxorubicin-induced cardiotoxicity in Wistar rats. Int J Drug Dev Res 2012;4(2):298-305.

[50] Li W, Zhang X, Wu R, Song Y, Xie M. Ganoderma atrum polysaccharide improves doxorubicin-induced cardiotoxicity in mice by regulation of apoptotic pathway in mitochondria. Carbohydr Polym 2018;202:581-590.

[51] Francis A, Nayak Y. Modulation of Doxorubicin-Induced Cardiotoxicity by *Averrhoa bilimbi* extract. J Young Pharm 2017;9(1):69-77.

[52] Dikshit M, Hassanpour Fard M, Bodhankar S. Cardioprotective Activity of Fruit of Lagenaria siceraria (Molina) Standley on Doxorubicin-Induced Cardiotoxicity in Rats. Int J Pharmacol 2008;4(6):466-471.

[53] Mubarak S, Hamid S, Farrag A, Samir N, Hussein J. Cardioprotective Effect of Date Palm Against Doxorubicin-Induced Cardiotoxicity. Asian J Pharm Clin Res 2018;11(7):141.

[54] Barman NR, Prasanna K, Prakash K, Himadri SP, Arvind K, Sanjib B, Pallab *K*. Haldar. Cardioprotective effect of *Urtica parviflora* leaf extract against doxorubicin-induced cardiotoxicity in rats. Chin J Nat Med 2014;11(1):38-42.

[55] Ibrahim D, Radwan R, Abdel Fattah S. Antioxidant and antiapoptotic effects of sea cucumber and valsartan against doxorubicin-induced cardiotoxicity in rats: The role of low dose gamma irradiation. J Photochem Photobiol B 2017;170:70-8.

[56] Shah S, Mohan M, Kasture S, Ballero M, Maxia A, Sanna C. Protective effect of hypericum hircinumon doxorubicin-induced cardiotoxicity in rats. Natural Product Research 2013;27(16):1502-7.

[57] Rajbanshi SLA, Paranjape AN, Appanna V. Counteraction of adriamycin-induced alterations in cardiac enzymes by *Thespesia populnea* leaf extract. Journal of Appl Pharm Sci 2017;7:150-157.

[58] [58] dos Santos J, Alfredo T, Antunes K, da Cunha J, Costa E, Lima E, Silva D B, Carollo C A, Schmitz WO, Boleti A, Santos E , Souza KP . *Guazuma ulmifolia* Lam. Decreases Oxidative Stress in Blood Cells and Prevents Doxorubicin-Induced Cardiotoxicity. Oxidative Medicine and Cellular Longevity. 2018;2018:1-16.

[59] Kanagavalli U, Santhosh Kumar B, Arumugam G, Mohammed Sadiq A, Nagalingam M, Gopikrishnan M. Cardioprotective Potential of Buchanania axillaris on Doxorubicin-Induced Cardiotoxicity in Albino Rats. International Journal of Pharmaceutical and Biological Archives. 2014;5(2):76-80.

[60] Nimbal S, Koti B. Effect of Ethanolic Extract Fractions of *Boerhaavia diffusa* in Doxorubicin-induced Myocardial Toxicity in Albino Rats. J Young Pharm 2017;9(4):545-9.

[61] Rai S, Somashekar B, Shivalinge Gowda K.p. Cardioprotective Effects of Ethanolic Leaf Extract of Ipomoea Batatas on Doxorubicin-Induced Cardiotoxicity in Rats. Asian J Pharm Clin Res 2015; 8(2):444-50.

[62] Ajith T, Aswathy M, Hema U. Protective effect of Zingiber officinale Roscoe against anticancer drug doxorubicin-induced acute nephrotoxicity. Food Chem Toxicol 2016;46(9):3178-81

[63] Sarika K, Mahalaxmi M, Sanjay K. Protective Effect of *Solanum Torvum* on Doxorubicin-Induced Cardiac toxicity in Rats. Pharmacol online 2009;2:1192-204.

[64] Wakade A, Juvekar A, Kulkarni M, Shah A. Ameliorative effect of Piper longum fruits against experimental myocardial oxidative stress-induced injury in rats. Planta Med 2007;73(09):442.

****

