

# Reversal of Doxorubicin-induced Cardiotoxicity by Using Phytotherapy: A Review

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## Key Words

adriamycin, cardiotoxicity, chemotherapy, phytochemicals.

## Abstract

Doxorubicin as a chemotherapeutic drug is widely used for the treatment of patients with cancer. However, clinical use of this drug is hampered by its cardiotoxicity, which is manifested as electrocardiographic abnormalities, arrhythmias, irreversible degenerative cardiomyopathy and congestive heart failure. The precise mechanisms underlying the cardiotoxicity of doxorubicin are not clear, but impairment of calcium homeostasis, generation of iron complexes, production of oxygen radicals, mitochondrial dysfunction and cell membrane damage have been suggested as potential etiologic factors. Compounds that can neutralize the toxic effect of doxorubicin on cardiac cells without reducing the drug's antitumor activity are needed. In recent years, numerous studies have shown that herbal medicines and bioactive phytochemicals can serve as effective add-on therapies to reduce the cardiotoxic effects of doxorubicin. This review describes different phytochemicals and herbal products that have been shown to counterbalance doxorubicin-induced cardiotoxicity.

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## 1. Introduction

Doxorubicin is used for the treatment of patients with different types of cancer, but the cardiotoxicity of this drug is a major limitation for its clinical application [1]. Doxorubicin-induced cardiotoxicity is manifested as electrocardiographic changes, irreversible degenerative cardiomyopathy, arrhythmias and congestive heart failure [2, 3]. Different factors are involved in doxorubicin-induced cardiotoxicity. One of the important mechanisms is the generation of free radicals which cause lipid peroxidation, reduction of sulfhydryl groups and depletion of antioxidant enzymes. In addition, doxorubicin causes apoptosis and DNA damage in cardiac cells [4]. Owing to the role of free radicals in doxorubicin-induced cardiotoxicity, antioxidant compounds can be of potential therapeutic value.

Animals and isolated cardiomyocytes are widely used as models for the investigation of doxorubicin-induced toxic effects. The H9c2 cell line is applied for the investigation of the protective effects of compounds against doxorubicin-induced toxicity [5-7]. In vitro studies have shown that doxorubicin induces hypertrophy in adult H9c2 cells [8, 9]. Beta blockers have been shown to improve left ventricular function by exerting an antioxidant activity [10, 11]. Dexrazoxane has also been reported to decrease the cardiotoxicity of doxorubicin, but this compound can reduce the chemotherapeutic activity of doxorubicin [12]. Drugs that are commonly used to reduce doxorubicin-induced cardiotoxicity can have adverse effects; therefore, replacing these drugs with antioxidant compounds that have fewer

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side effects and are less expensive, such as herbal medicines, would be better [13, 14]. In this review, we describe medicinal herbs and some active phytochemicals that have been reported to exert protective effects against doxorubicin-induced cardiotoxicity *in vitro* and *in vivo*.

## 2. Reduction of Doxorubicin-induced Toxicity by Using Medicinal Herbs *in vitro*

H9c2 is an appropriate cell line for the investigation of doxorubicin-induced cardiotoxicity. This cell line is able to differentiate skeletal or cardiac muscle phenotypes [15] (Table 1). *R. turkestanicum* Janisch is found in Asia and northeastern of Iran. In traditional medicine, the roots of this plant are applied for the treatment of patients with diabetes, hypertension and cancer [16]. Recent studies have shown that the rheum species contain antioxidant compounds. The antioxidant compounds, such as rhapontigenin and rhaponticin, that have been isolated from *R. undulatum* scavenge free radicals, hydrogen peroxide and 1,1-diphenyl-2-picrylhydrazyl [17]. Membrane lipids and DNA are important targets for reactive oxygen species (ROS). The above-mentioned compounds reduce damage to lipids and DNA via their antioxidant properties. Doxorubicin reduces the viability of cells via generation of (ROS) and peroxidation of lipids. Hosseini et al. showed that *R. turkestanicum* decreased doxorubicin toxicity in H9c2 cells by attenuation of ROS production, lipid peroxidation and apoptosis. This protective effect may be related to the presence of antioxidant compounds [18].

*N. sativa*, *G. glabra* and *Z. officinale* are applied in different industries. *N. sativa* is used as a preservative in food [19]. *N. sativa* has been found to decrease the cardiotoxic effect of lead via reduction of oxidative stress, the levels of pro-inflammatory cytokines and cardiac damage [20]. This plant has also been found to reduce cyclosporine-A-induced cardiotoxicity [21]. *Z. officinale* has different pharmacological uses such as the treatment of patients with cardiovascular disease. The beneficial effects of this plant on the cardiovascular system are related to its active compounds, such as gingerols [22]. *G. glabra* possesses nephroprotective [23], hypoglycemic [24] and hypocholesterolemic [25] properties. The combination of the foregoing three herbs (NGZ) was used against doxorubicin toxicity in H9c2 cells. Results showed that the combination of herbs increased cell viability and decreased lipid peroxidation. NGZ has been found to have a much higher protective effect than each plant alone because it reduces oxidative stress and inhibits apoptosis [26].

Ginkgolide B is a terpenoid obtained from *Ginkgo biloba* leaves. This terpenoid compound has antioxidant effects and reduces oxidative stress in different tissues [27]. This compound has been found to decrease doxorubicin toxicity in H9c2 cells via attenuation of ROS and intracellular calcium levels and elevation of Akt phosphorylation [28]. *C. spinosa* is applied as an anti-inflammatory [29], antibacterial [30], antioxidative [31], anti-diabetic [32], anti-hepatotoxic [33] and anti-proliferative [34] agent. Studies have shown that *C. spinosa* contains antioxidant compounds, such as flavonoids, quercetin and kaemp-

ferol glycosides [35]. *C. spinosa* has been found to decrease doxorubicin-induced cardiotoxicity in H9c2 cells via improvement of the antioxidant capacity and reduction of apoptosis [36].

*Lactuca serriola* (*L. serriola*, Compositae) has different names, such as Kahu, jagged lettuce, prickly lettuce, and Khas [37]. It is found in Atlantic areas, the Himalayas, Siberia, Iran, Pakistan and India [37]. In traditional medicine, different properties have been reported for *L. serriola*, such as antitussive, sedative, expectorant, vasorelaxant, purgative, antiseptic, diuretic and antispasmodic properties [37]. Phytochemical studies have shown that *L. serriola* contains lactucin, lactucone, lactic acids, lactucopicrin, oxalic acid and sesquiterpenes [37].

Pharmacological effects of this plant include anti-inflammatory, analgesic and antioxidant activities, which are related to the high content of phenolic ingredients. This plant also reduces oxidative stress via scavenging of free radicals [37]. *L. serriola* has been reported to decrease lipid peroxidation and ROS production, as well as the levels of bax/bcl2 and caspase3 in H9c2 cells [38].

*Hibiscus Sabdariffa* (*H. sabdariffa*) grows in the south of Iran. Studies have shown that this plant has therapeutic effects against atherosclerosis [39], cardiovascular disease [39], hypertension and liver diseases [40, 41]. Different compounds, such as gossypitrin, anthocyanins, flavonol glycoside, myricetin, sabbaretin, quercetin, hibiscetin, luteolin, luteolin glycoside, chlorogenic acid, flavonoids (gossypetin, hibiscetin and their respective glycosides) and protocatechuic acid, are found in this plant [40]. H9c2 cells were pretreated with *H. sabdariffa* extract and then incubated with doxorubicin. The extract reduced doxorubicin toxicity in H9c2 cells via decreasing the oxidative stress and apoptosis [42].

Paeoniflorin is an active ingredient that is isolated from *Paeonia lactiflora* and *Salvinia molesta*. Doxorubicin elevated apoptosis in cardiac cells via expression of caspase 3, ROS generation and upregulation of NADPH Oxidase (NOX2 and NOX4) expression. Pretreatment of H9c2 cells with paeoniflorin reduced toxicity via reduction of ROS and attenuation of NOX2, NOX4 and NOX activities [43].

Ginkgo biloba extract 761 is obtained from *Ginkgo biloba* extract and has different properties, such as anti-angiogenic and anti-platelet properties [44]. It also reduces cardiotoxicity after ischemia-reperfusion via antioxidant mechanisms [45]. In addition, it decreases doxorubicin toxicity in the heart via downregulation of p53, modulation of the bax/bcl2 ratio, improvement of the mitochondrial function, and free radical reduction [46].

*Citrus maxima* (*C. maxima*) belongs to the citrus family and is found in areas, such as Thailand, China, Japan and India. The juices of *C. maxima* contain antioxidant compounds that scavenge free radicals [47]. This herb reduces doxorubicin cardiotoxicity via decreasing oxidative stress, elevating the GSH level and enhancing the activities of antioxidant enzymes. This protection is related to the antioxidant properties of this herb [48].

Baicalein is a natural flavonoid compound found in *Scutellaria baicalensis* Georgi root. It has antioxidant properties and mitigates oxidative damage [49]. Baicalein has protective effects against ischemia/reperfusion injury and

contractile dysfunction by scavenging mitochondrial ROS [49]. Chang and co-workers reported that baicalein lowered cardiotoxicity by decreasing mitochondrial oxidant injury and Jun N-terminal kinase (JNK) activation [50]. Co-treatment of chick cardiomyocytes with baicalein (25  $\mu$ M) and doxorubicin for 24 h showed that baicalein reduced doxorubicin toxicity by decreasing ROS generation and phosphorylation of JNK. As a result, cell death was attenuated in the presence of baicalein [50].

Aspalathus linearis contains different polyphenolic compounds such as aspalathin (ASP) that has pharmacological properties, including antioxidant, anti-inflammatory and anti-apoptotic properties [51-53]. Co-treatment of H9c2 cells with doxorubicin and aspalathin (0.2  $\mu$ M) for 5 days attenuated apoptosis via reduction of the bax/bcl2 ratio. Also, ASP enhanced autophagy via decreasing nucleoporin p62 through induction of adenosine monophosphate-activated protein kinase (AMPK) [52].

**Table 1** Cardioprotective effect of herbal medicine against doxorubicin in in vitro studies

Herbal medicine	Model of study	Protocol	Results	Ref.
R. turkestanicum	In vitro/H9c2	Pretreatment with extract for 2 h; then, incubated by using 5- $\mu$ M DOX for 24 h	▼lipidperoxidation ▼ROS ▼Apoptosis	18
Nigella sativa with Glycyrrhiza glabra and Zingiber officinale	In vitro/H9c2	Pretreated with extracts for 2 h; then, incubated by using 5- $\mu$ M DOX for 24 h	▼lipidperoxidation ▼ROS ▼Apoptosis	26
Ginkgolide B	In vitro/H9c2	Cell were pretreated with GB for 30 min; then, incubated with DOX for 48 h	▼Intracellular calcium ▼ROS ▼Apoptosis ▼Activation of AKT	28
C. spinose	In vitro/H9c2	Pretreatment with extract for 2 h; then, incubated by using 5- $\mu$ M DOX for 24 h	▼lipidperoxidation ▼ROS ▼Apoptosis	36
L. serriola	In vitro/H9c2	Pretreatment with extract for 2 h; then, incubated by using 5- $\mu$ M DOX for 24 h	▼lipidperoxidation ▼ROS ▼Apoptosis ▼Bax/bcl2 and cas3	38
H. sabdariffa	In vitro/H9c2	Pretreatment with extract for 2 h; then, incubated by using 5- $\mu$ M DOX for 24 h	▼lipidperoxidation ▼ROS ▼Apoptosis	42
Paeoniflorin	In vitro/H9c2	Pretreatment with for 2 h; then, incubated by using 5- $\mu$ M DOX for 24 h	▼ROS ▼Cas3 ▼NOX2, NOX4	43
Ginkgo biloba extract 761	Primary cultured neonatal rat cardiomyocytes	Treated with doxorubicin (1 $\mu$ M) and EGb761(25 $\mu$ g/mL)	▼p53 mRNA expression ▼Apoptosis Improvement of mitochondrial membrane potential	46
C. maxima	In vitro/H9c2	Pretreated with extract (10, 100, and 1000 g/mL) for 30 min; then, DOX was added (0.1 $\mu$ M)	▲GST ▲GSH Reduction of ROS	48

Reactive oxygen species (ROS), Glutathione (GSH), Glutathione s-transferase (GST)

### 3. Reduction of Doxorubicin Toxicity by Using Medicinal Herbs in vivo

Doxorubicin-induced heart damage in rats is manifested as decreased left ventricular systolic and diastolic pressures, ejection fraction, fractional shortening, and contractility index as demonstrated by echocardiography, electrocardiography, and hemodynamic parameters relative to control animals (Table 2).

Ellagic acid is a polyphenolic compound found in nuts and berries; it has different properties in biological systems. The pharmacological properties of this compound include antioxidant, antiapoptotic, chemopreventive, cardioprotective, anti-inflammatory, anti-cataractogenic, gastroprotective, ulcer healing, antifibrotic, antidiabetic, hypolipidemic, anti-atherosclerotic, and estrogenic/anti-estrogenic properties [54-57]. Doxorubicin reduced the level of antioxidant enzymes, such as superoxide dismutase (SOD), catalase, and glutathione, and elevated the level of malondialdehyde (MDA) in rats. Ellagic acid treatment at doses of 100 mg/kg and 200 mg/kg for 6 weeks reduced the cardiotoxic effects of doxorubicin in animals [58]. *Ganoderma lucidum* (*G. lucidum*) grows in the South of India and has different properties, such as anti-inflammatory, antitumor, nephroprotective and anti-nociceptive properties [59-61]. Doxorubicin was reported to enhance serum creatine kinase (CK) activity and lipid peroxidation in cardiac tissue, but *G. lucidum* extract at doses of 500 and 1000 mg/kg elevated the levels of glutathione (GSH) and the activities of SOD, glutathione peroxidase (GPx) and catalase (CAT). The CK activity, ROS generation, and lipid peroxidation were all decreased following *G. lucidum* administration [62].

*Citrus hystrix* (*C. hystrix*) contains high levels of flavonoids, such as naringenin and hesperidin which have antioxidant properties [61]. The ethanolic extract of *C. hystrix* peels reduced doxorubicin toxicity in cardiac tissue, which was related to the presence of antioxidant compounds in the extract [63].

Pomegranate (*Punica granatum* L.) is applied for different purposes. The peel of *P. granatum* has beneficial properties, such as antibacterial [64], immunomodulatory [65] and antioxidant [66] properties. Pomegranate extract decreased cardiac histopathological changes. The extract elevated the levels of antioxidant enzymes such as SOD and GSH and reduced the levels of lactate dehydrogenase (LDH), creatinine kinase-MB (CK-MB), and MDA [67].

Grape seed extract (GSE) contains high levels of antioxidant compounds which cause different pharmacological effects [68]. It improves liver function [69], arrhythmias, and lipid profiles [70, 71]. In vivo and in vitro studies have reported that this extract scavenges free radicals and reduces lipid peroxidation [72]. Isolated pro-anthocyanidins from grape seed scavenge free radicals, such as superoxide anions and hydroxyl radicals, in a way similar to  $\beta$ -carotene and vitamins C and E [73]. The GSE improved ventricular function and reduced histopathological modifications and antioxidant contents in the heart, but it did not decrease the antitumor effect of doxorubicin. GSE treatment has been shown to attenuate markedly doxorubicin-induced toxicity and structural changes of myocardium and to improve ventricular function. Additionally, GSE did not intervene with the antitumor effect of doxorubicin [74].

*Solanum Torvum* (*S. torvum*) is known as Turkey berry. It has pharmacological activities, such as antiviral [75], immunomodulatory [76], antioxidant [77], cardioprotective and anti-platelet [78] activities. These observed activities are related to the presence of antioxidant compounds, such as flavonoids which are able to scavenge free radicals [79]. *S. torvum* decreases doxorubicin toxicity via reductions of electrocardiogram (ECG) changes and CK-MB and LDH levels, as well as elevations of the levels of antioxidant enzymes, such as SOD and CAT [80].

In traditional medicine, *Parkia biglobosa* (*P. biglobosa* (Jacq.)) is applied for the treatment of arterial hypertension, amoebiasis, abscesses, burns, coughs, zoster, and bronchitis [81]. Its antioxidant effects have been previously reported [82]. Phytochemical studies have shown that this herb contains total flavonoids, tannins, saponins and cardiac glycosides. The extract decreases lipid peroxidation and the levels of CKMB and LDH, but increases the levels of cardiac glutathione, GSH, and SOD in rats treated with doxorubicin [81].

*Solanum nigrum* (*S. nigrum*) belongs to the Solanaceae family. In folk medicine, it is applied to treat patients suffering from inflammation, pain, enteric diseases and fever [83, 84]. The pharmacological effects include antioxidant, cardioprotective, anti-seizure, anti-cancer and anti-inflammatory effects [84-87]. The extract attenuates the levels of LDH, CKMB, aspartate aminotransferase (AST) and alanine aminotransferase (ALT). In addition, following doxorubicin toxicity, *S. nigrum* extract decreases histopathological changes and lipid peroxidation and increases the activities of antioxidant enzymes [88].

Green tea is consumed in Asia without causing side effects [89]. It contains a high level of epigallocatechin-3-gallate (EGCG), which has beneficial effects for the treatment of patients with different diseases [90]. Green tea also increases the levels of glutathione peroxidase, SOD, CAT, and glutathione s-transferase (GST) in rats experiencing doxorubicin-induced cardiotoxicity [91].

*Withania somnifera* (*W. somnifera*) belongs to the Solanaceae family and is used in folk medicine [92]. Withanolides are active compounds in the roots and the leaves of this plant [92, 93]. This plant has several pharmacological effects, including antitumor, immunomodulatory and hepatoprotective effects [3,9]. The extract has cardioprotective effects against toxic agents, such as strophanthin-K [95]. The administration of this extract has been shown to decrease myelosuppression and urotoxicity [96] in mice challenged with anti-neoplastic drugs. The animals that were pretreated with the extract showed lower degeneration in heart muscle fibers. The extract has also been shown to prevent elevation of oxidative stress following doxorubicin treatment and to increase the contents of antioxidants such as SOD and CAT. The extract also attenuates apoptosis via enhancement of Bcl2 expression [97].

*Curcuma longa* (*Curcuma longa*) is a known plant in traditional and modern medicine because of its numerous pharmacological effects, such as its antioxidant, anticancer-

cer, immunomodulatory, hepatoprotective and anti-inflammatory effects [98-110]. Moreover, curcumin metabolites, such as tetrahydrocurcumin, are active and inhibit oxidation of the membranes of erythrocytes. Ethanolic or water extract of *C. longa* at a dose of 200 mg/kg administered orally reduced mortality in rats that had been administered doxorubicin. It decreased the CK-MB, LDH, MDA, serum nitric oxide and cardiac calcium levels while increasing the levels of GSH and cardiac ascorbic acid. The protective effect of this herb is linked to the presence of polyphenolic compounds [111].

Crocin is a carotenoid found in *Crocus sativus* and has pharmacological effects, such as anti-hyperlipidemic, anti-inflammatory, antidepressant, antitumor, antioxidant and anti-atherosclerotic effects [112, 113]. Crocin also plays a role in the treatment of patients with conditions such as depression [114], anxiety [115], memory dysfunction [116] and Alzheimer's disease [117]. Crocin reduces cardiac histopathological changes, ventricular pressure, ejection fraction, and systolic and diastolic pressures following doxorubicin administration without affecting the antitumor activity of doxorubicin [118].

Ginkgo biloba is a known plant owing to its antibiotic and anti-fungal properties [119]. People in China use the leaves of this herb as a medicine. *G. biloba* possesses antioxidant activity, scavenges free radicals, and reduces cyclosporine-induced hepatotoxicity. *G. biloba* reduces doxorubicin toxicity in cardiac cells via reducing ascites and lipid peroxidation, improves the levels of antioxidant enzymes, and reduces changes in the ECG [120].

Phyllanthus niruri (*P. niruri*) has different pharmacological effects, including hepatoprotective, wound healing [121], antitumor [122], antioxidant, and anti-amnesic [123] effects. The antioxidant activity of this plant is related to the presence of hypophyllanthin, phyllanthin, niruriflavone, gallic acid and ellagic acid [124]. The protective effects of this herb against the cardiotoxicity of doxorubicin have been reported to be exerted via a reduction in lipid peroxidation and increases in the levels of antioxidant enzymes such as glutathione, SOD and CAT [125]. The observed effects may be related to the antioxidant properties of the plant.

Saffron (*C. sativus*) is known for its medicinal properties [126] such as its anticonvulsant [127-129], antioxidant [129-131], antitumor [132] and antidepressant [114, 133-136] properties. This plant also alleviates memory problems [137]. Doxorubicin induces ROS production and lipid peroxidation; it also decreases ventricular pressure, the heart rate, coronary flow, the levels of antioxidant enzymes, and changes in the myocardial structure. Treatment of animals with saffron reduced doxorubicin toxicity, decreased toxic indices, and improved cardiac function [138]. During ischemia-reperfusion, doxorubicin leads to toxicity while administration of saffron in the beginning of reperfusion prevents the p38MAPK and AKT/mTOR/4EBP1 pathways. Nevertheless, the antioxidant and the antiapoptotic effects of saffron decrease doxorubicin toxicity in cardiac tissue under ischemia-reperfusion [139].

*Glycyrrhiza uralensis* (*G. uralensis*, *Radix Glycyrrhizae*) is used in tobacco, dietary supplements, foods, beverage

s and candies [140]. It has also pharmacological effects, such as antiulcer, anti-inflammatory and anti-carcinogenic effects [141-142]. Glycyrrhizin is the active compound of *G. uralensis* which is used as an antidote for the alkaloid urethane, carbon tetrachloride, benzene, and saponin poisoning [143]. Studies have also reported other effects, such as anti-genotoxic and hepatoprotective effects for glycyrrhizin [144]. A recent study showed that *G. uralensis* decreased the levels of LDH and CK-MB and improved the activities of antioxidant enzymes, as well as the heart's morphology, without changing the antitumor activity of doxorubicin [145].

*Crataegus aronia* syn. *Azarolus* (L) (*C. aronia*) grows in the mountains of the Mediterranean region and is consumed in traditional medicine as a remedy for diabetes, cancer, hyperlipidemia and cardiovascular diseases [146]. Treatment with *C. aronia* leads to amelioration of cardiac oxidative stress, improvement of antioxidant activity, normalization of B-type natriuretic peptide (BNP) levels and reduction of lipid peroxidation. These effects are probably related to the antioxidant activity of *C. aronia* [147].

Aged garlic (*Allium sativum* or garlic) is used in the food and drug industries in different forms, such as tablets, dried raw plant parts, and fresh, boiled and cooked products [148]. The pharmacological effects of garlic include hepatoprotective, anti-mutagenic, immunomodulatory, antioxidant and anti-carcinogenic effects [149-151]. Administration of aged garlic extract following doxorubicin treatment reduces the LDH and creatinine phosphokinase (CPK) activities and the MDA content and elevates the total antioxidant content in cardiac tissue. Aged garlic extract also reduces edema, congestion and vascular dilation, as well as histopathological changes induced by doxorubicin [152].

Gallic acid is a polyphenol found in most fruits and vegetables [153]. Gallic acid is obtained from hydrolysis of galloyl compounds. It scavenges free radicals and has antioxidant properties [154]. Recent studies have reported antiviral, anti-inflammatory, antibacterial and anticancer effects for this polyphenol [155-157]. Cardioprotective effects of gallic acid have been shown against isoproterenol and linden, following induction of diabetes [97]. Gallic acid decreases ROS generation and the MDA level, but increases the levels of CAT, SOD, GSH and alleviates histopathological changes and ECG modifications [158].

*Zingiber officinale* (*Z. officinale*) belongs to the Zingiberaceae family and is commonly known as ginger. Numerous pharmacological effects, such as anti-microbial, anti-proliferative, anti-inflammatory, antioxidant, neuro-protective and hepatoprotective effects, have been reported for ginger. The cardioprotective effect of *Z. officinale* is related to the presence of active compounds, such as gingerols [6], shogaols, methyl isogingerol [6] and paradol [159]. The ethanolic extract of ginger reduces the cardiotoxicity of doxorubicin via reductions of oxidative stress, lipid peroxidation, and ECG changes, increases in the levels of antioxidant enzymes, and decreases in histopathological alterations [160].

*Centella asiatica* (*C. asiatica* L.) is a herbal medicine that has been suggested for the treatment of patients with a memory deficit [161], hypertension, atherosclerosis and

cancer [162, 163]. The active compounds of this plant include triterpenes, asiatic acid and asiaticoside [164]. Its extract has been reported to reduce ROS production, lipid peroxidation, and the levels of LDH, CPK, ALT and AST while elevating the levels of antioxidant enzymes, such as SOD, CAT, GPx and GST [165].

*Terminalia arjuna* (T. arjuna) is used in traditional medicine to treat patients with different types of cardiac problems. Studies have reported that the aqueous extract of this herb increases cardiac contraction [166] and exerts anti-anginal effects via a reduction in the number of anginal episodes [167]. Also, the alcoholic extract of the plant reduces the blood pressure and the heart rate in animals

[168]. Moreover, T. arjuna has protective effects against doxorubicin-induced cardiotoxicity via decreasing the CKMB level, reducing morphological changes and lipid peroxidation, and increasing the levels of antioxidant enzymes [169].

The fruits of *Lycium barbarum* (L. barbarum) are known to possess antisenility, anti- inflammation and antipyretic effects. Antioxidant activity, scavenging of superoxide anions and prevention of superoxide production are other properties of L. barbarum [170, 171]. This herb decreases doxorubicin toxicity in the heart via a reduction of oxidative stress and a normalization of antioxidant enzymes [172].

**Table 2** Cardioprotective effect of herbal medicine against doxorubicin in in vivo studies

Herbal medicine	Model of study	Protocol	Results	Ref.
Ellagic acid	rat	DOX injected at a dose of 3.75 mg/kg at weeks 2, 3, 4, and 5. Extract was administered (100 and 200 mg/kg, orally) for 6 weeks.	▲SOD ▲CAT ▲GSH ▼MDA ▼CK-MB ▼LDH Reduction morphological changes	(58)
G. lucidum	rat	Extract was administered (500 and 1,000 mg/kg orally) 1 h before the doxorubicin (6 mg/kg) injection.	▲GSH ▲CAT, ▲SOD and GPx ▼MDA ▼CK	(62)
C. hystrix	rat	Animals received extract (500 and 1000 mg/kg, p.o.) for 11 days, Dox (4.67 mg/kg, i.p.) was administered on the 1st and the 6th days.	Improved histopathological changes in the heart and liver. Did not reduce AST and ALT	(63)
P. granatum	rat	Extract was administered (5 mL/kg) for 18 days and Dox was injected (10 mg/kg).	▲GSH ▼QT ▼LDH ▼CK-MB Histopathological changes showed low protection against Dox	(67)
Grape seed	rat	DOX (2 mg/kg/48 h, for 12 days) and GSE (100 mg/kg/24 h, for 16 days)	Improved ventricular function, structural changes and ECG	(74)
S. torvum	rat	DOX (67.75 mg/kg, i.v., 2 days), S. torvum extract (100 and 300 mg/kg, p.o.)	Decreased the changes in the ECG; ▼CK-MB ▼LDH ▲SOD ▲CAT Histopathological studies showed cellular infiltration.	(80)
P. biglobosa	rat	Animals received extract (25 - 100 mg/kg/day) for 14 days and DOX (15 mg/kg) on the 13th day.	▼CK-MB ▼LDH ▲SOD ▲CAT	(81)
S. nigrum	rat	Received S. nigrum 1 g/kg/day p.o. daily and DOX at a dose of 20 mg/kg i.p.	▼CK-MB ▼LDH ▲SOD ▲CAT	(88)

Herbal medicine	Model of study	Protocol	Results	Ref.
Green tea	rat	Extract (100, 200 and 400 mg/kg, p.o.) s administered for 30 days. DOX (20 mg/kg) was administered on the 29th day.	▲GPX ▲GST ▲GR ▲SOD ▲CAT	(91)
W. somnifera	rat	Extract (300 mg/kg) was administered for 14 days and DOX (10 mg/kg) as a single dose.	▲SOD ▲CAT ▲Bcl2 Decreasing histo-pathological changes	(97)
C. longa	rat	Extract (200 mg/kg) was administered for 7 days and DOX (15 mg/kg) as a single dose.	▼CK-MB ▼LDH ▼MDA ▼Cardiac calcium ▲SOD	(111)
Crocic	rat	DOX (2 mg/kg/12 days), and animals received DOX (20 and 40 mg/kg/24 h for 20 days).	Reduced DOX-induced heart damage, structural changes in the myocardium and ventricular function.	(118)
Ginkgo biloba	mice	Received extract (100 mg/kg) for 4 weeks and DOX (4 mg/kg, cumulative dose 16mg/kg)	Reduced mortality, ascites, and myocardial lipid peroxidation; normalization of antioxidant enzymes; reversal of ECG changes	(120)
P. niruri	rat	Aqueous extract was administered (200 mg/kg) for 2 weeks and DOX was injected (2.5 mg/kg i.p.) to make 15 mg/kg.	▲SOD, CAT and GSH ▼MDA	(125)
Saffron	rabbit	The isolated heart rabbit were perfused with 30- $\mu$ M DOX and 10 $\mu$ g/mL of saffron.	▼ROS ▼MDA Improvement of myocardial function	(139)
G. uralensis	mice	The extract was administered (100 mg/kg) for 8 days and DOX (20mg/kg) once.	▼CK-MB ▼LDH ▲GSH	(145)
C. aronia	rat	DOX was injected (2.5 mg/kg) every 2 days for 14 days. Animals received 200 mg/kg of aqueous extract for 14 days.	▼Myofibrils, infiltration of mononuclear cells, fibrosis and vacuolation ▼Oxidative stress ▼Lipidperoxidation ▼BNP	(147)
A. sativum	rat	Garlic extract (250 mg/kg) for 27 days and a single dose of DOX (25 mg/kg)	▼MDA ▼CPK ▼LDH	(152)
Z. officinale	rat	DOX was injected 2.5 mg/kg (cumulative dose, 15mg/kg) and animals were received extract (200mg/kg) for 6 weeks	▼MDA Improvement of ECG	(160)
C. asiatica	rat	Extract was given orally (200 mg/kg) for 3 weeks. DOX was injected 2.5 mg/kg (cumulative dose, 15mg/kg)	▲SOD, CAT, GPx, GST ▼LDH and CPK	(165)
T. arjuna	rat	Dox 20 mg/kg, single dose, extract was given (0.42 mg/kg, 0.85 mg/kg, 1.7 mg/kg, 3.4 mg/kg and 6.8 mg/kg) for 6 days/week for 4 weeks.	▼CK-MB ▼MDA Improvement of morphological changes	(169)
L. barbarum	rat	DOX (5 mg/kg) three times, i.e. at 7, 14 and 21 days. The extract was given 25mg/kg for 3 weeks	Normalization of antioxidative enzymes and serum AST and CK, improvement of arrhythmias	(172)

Catalase (CAT), malondialdehyde (MDA), super oxide dismutase (SOD), glutathion (GSH), aspartate aminotransferase (AST), alanine aminotransferase (ALT), glutathione peroxidase (GPX), glutathione reductase (GR), glutathione s-transferase (GST), B-type natriuretic peptide (BNP), lactate dehydrogenase (LDH), creatinine phosphokinase (CPK), creatinine kinase-MB (CK-MB), creatinine kinase (CK), electrocardiogram (ECG), doxorubicin (DOX).

#### 4. Conclusion

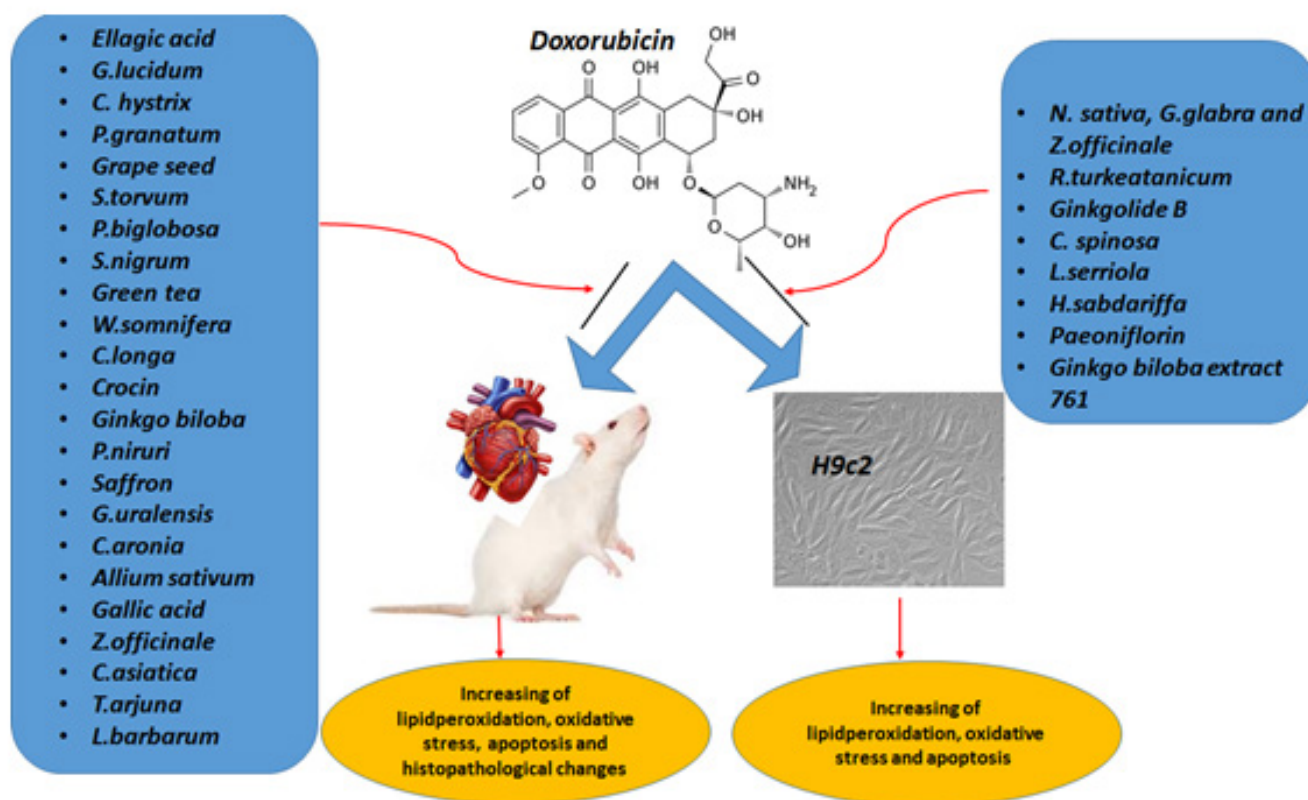
As detailed above, doxorubicin-induced toxicity is an important challenge for successful chemotherapy. For that reason, the introduction of adjuvants capable of decreasing this toxicity without impairing the drug's anti-tumor efficacy is of particular interest. For this purpose, several plant extracts and phytochemicals have been tested and shown to attenuate the cardiotoxicity of doxorubicin (Figure 1). According to mechanistic investigations, antioxidant effects may be the main mechanism behind the cardioprotective action of phytochemicals; mitigation of inflammation and apoptosis are other mechanisms that have been repeatedly reported as well.

While the reported protective activities of phytochemicals and medicinal plants against doxorubicin-induced cardi-

otoxicity certainly hold promise for future developments, most of the available evidence emanates from preclinical studies. This highlights the necessity for confirmatory studies in clinical practice. However, before proof-of-concept clinical trials are carried out, it is imperative to ensure sufficient bioavailability of herbal products, particularly those that are known to have low water solubility and to cause extensive metabolism. Therefore, an elaboration of tailored pharmaceutical delivery systems might be needed to optimize bioavailability and to ensure the clinical efficacy of cardioprotective phytochemicals.

#### Conflict of interest

The authors report no conflicts of interest.



**Figure 1** Different herbal products and phytochemicals with protective activity against doxorubicin-induced cardiotoxicity.



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