The protective effects of traditional Chinese medicine ingredients against doxorubicin-induced cardiotoxicity

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Author contributions
Wang Z was involved in the designing of the study, manuscript writing and proofreading of the manuscript; Wang Z and Wu Q were all involved in the designing and manuscript writing.

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Abbreviations
DOX, doxorubicin; ROS, reactive oxygen species; ILs, interleukins; GSH, glutathione; mtDNA, mitochondrial DNA.

Citation

Abstract
Doxorubicin (DOX), also known as Adriamycin, is an anthracycline chemotherapy drug that exerts anticancer effects. However, the clinical application of DOX is severely limited by its cardiotoxicity. Recent researches show that the mechanism of DOX-induced cardiotoxicity is very complex and includes oxidative stress, inflammation, mitochondrial dysfunction, autophagy, cell apoptosis and death. These factors jointly promote the occurrence and development of DOX-induced cardiotoxicity. In addition, a large number of studies have shown that some active ingredients of traditional Chinese medicine antagonized DOX-induced cardiotoxicity. The combination of doxorubicin and relevant traditional Chinese medicine can maximize the therapeutic effect of tumor patients, reduce mortality rates, and improve the quality of life of tumor patients. In conclusion, this review provides new insights to further explore ingredients of traditional Chinese medicine in the treatment of DOX-induced cardiotoxicity.

Keywords: traditional Chinese medicine; doxorubicin; cardiotoxicity
Tumor is a major disease that seriously threatens human health, with a high incidence rate and mortality, and places a great economic burden on the country and individuals. Doxorubicin (DOX), also known as adriamycin, is an anthracycline chemotherapy drug that exerts anticancer effects by targeting the synthesis of tumor cell RNA and DNA and inducing tumor death [1, 2]. DOX has a broad-spectrum antitumor effect and is widely used to treat hematological tumors, such as acute leukemia and malignant lymphoma, and solid tumors, such as breast cancer, liver cancer, bladder cancer, esophageal cancer, gastric cancer, prostate cancer, thyroid cancer, and osteosarcoma [3, 4]. DOX is a commonly used chemotherapy drug in clinical practice due to its low price and clear efficacy, but the clinical application is severely limited by its cardiotoxicity [5, 6].

Research has shown that DOX-related cardiac injury is dose-dependent and can be divided into acute and chronic cardiotoxicity based on the clinical manifestations [7, 8]. Among them, acute cardiotoxicity is mainly characterized by massive necrosis and apoptosis of cardiomyocytes, accompanied by rapid elevation of B-type natriuretic peptide and myocardial enzymes, leading to acute cardiac insufficiency and congestive heart failure [5, 9]. Chronic cardiotoxicity is characterized by compensatory proliferation of residual cardiomyocytes and interstitial cells, with cardiac hypertrophy, interstitial and perivascular fibrosis as the main manifestations, leading to dilated cardiomyopathy [5, 9]. In addition, numerous studies have shown that the process of doxorubicin-induced cardiotoxicity is accompanied by changes in cardiac electrophysiology, including various types of arrhythmias and nonspecific electrocardiogram changes, such as ST-T depression, reduced QRS complex amplitude, and prolonged QT interval [6, 10]. Clinical data show that doxorubicin-related cardiac injury is related to its accumulated dose. When the accumulated dose in the body is 400 mg/m², the incidence of heart failure is only 3%; when the accumulated dose is 700 mg/m², the incidence of heart failure increases to 18% [11].

Sufficient evidence suggests that the mechanism of DOX-induced cardiotoxicity is very complex and is also a result of multiple factors working together [7, 12]. Currently, the clear mechanisms include oxidative stress, inflammation, mitochondrial dysfunction, autophagy, apoptosis and ferroptosis (Figure 1). These factors jointly promote the occurrence and development of DOX-induced cardiotoxicity [7, 13]. The latest research shows that some active ingredients and formulas of traditional Chinese medicine can antagonize DOX-induced cardiotoxicity [14, 15]. Therefore, searching for active ingredients with cardioprotective effects from commonly used traditional Chinese medicine to antagonize DOX-induced cardiotoxicity has become a hot topic in current research. In addition, the combination of doxorubicin and relevant traditional Chinese medicine can maximize the therapeutic effect of tumor patients, reduce mortality rates, and improve the quality of life of tumor patients. In this study, we provide a review of the research progress on the mechanism of the antagonistic effect of effective ingredients of traditional Chinese medicine on doxorubicin-induced cardiotoxicity.

### Antioxidative stress effect

Oxidative stress is a state of imbalance between free radical and antioxidant effects [16–18]. Under normal circumstances, there is an...
antioxidant system in cardiomyocytes, such as SOD, glutathione (GSH)-Px, catalase, and peroxidase, which clear free radicals through their respective reactions and protect cardiomyocytes from damage [19–21]. However, DOX can reduce the antioxidant enzyme activity of cardiomyocytes, which cannot effectively protect cardiomyocytes from free radical damage [22, 23]. Research has shown that once DOX enters cardiomyocytes, it is converted into semiquinone free radicals through the action of cytochrome P450 reductase [24]. After a series of electron transfers, superoxide anions and superoxide radicals are formed, disrupting the structure and function of cell membranes and leading to myocardial damage [24, 25]. In addition, DOX can also reduce the expression of the antioxidant stress gene Nrf2 and its downstream target genes and induce oxidative stress damage in cardiomyocytes [26, 27]. Therefore, reducing myocardial oxidative damage has also been proven to be an important strategy for treating DOX-induced cardiotoxicity.

Salviae Miltiorrhizae Radix et Rhizoma is a traditional Chinese medicine that dilutes blood vessels and improves myocardial ischemia, and its main active ingredients are salvianolic acid and tanshinone [28]. Jiang et al. reported that salvianolic acid can reduce MDA content, increase oxygen radical absorbance capacities, and alleviate DOX-induced myocardial oxidative damage [29]. Tanshinone has also been proven to alleviate myocardial oxidative damage in DOX-treated hearts by activating the Nrf2 pathway [30, 31]. Resveratrol, mainly extracted from Polygoni Cuspidati Rhizoma et Radix, is a nonflavonoid polyphenol that can alleviate DOX-induced oxidative stress and ERS by activating the Nrf2 and SIRT1 pathways [32]. Lycii Fructus delays aging and enhances immunity, and its active ingredient, Lycium barbarum polysaccharide, can reduce MDA content and upregulate SOD and GSH-Px activity after DOX treatment [33]. Lin et al. reported that Astragaloside IV, extracted from Astragali Radix, can increase the levels of myocardial NOX2 and NOX4 and improve myocardial injury in DOX-treated mice and neonatal rat cardiomyocytes [34]. Matrine is the main active ingredient of Sophorae Flavescentis Radix and has recently been reported to alleviate DOX-induced cardiac damage and oxidative stress by activating the AMPK/UCP2 pathway [35]. Schisandrin B is extracted from the traditional Chinese medicinal Schisandrae Chinesis Fructus and has strong antioxidant effects in liver and kidney diseases [36]. Studies have shown that schisandrin B can enhance glutathione redox cycling and reduce myocardial oxidative stress after DOX treatment [37, 38]. Berberine, also known as Huanglianzu, is a quaternary ammonium isoquinoline alkaloid isolated from the traditional Chinese medicine Coptidis Rhizoma [39, 40]. Wu et al. reported that berberine alleviates DOX-induced cardiac injury and oxidative stress by activating SIRT1 and inhibiting the p66Shc pathway [41]. Ginkgo biloba L is a diterpene lactone and is an important active component in Ginkgo Folium. Ginkgo biloba has been reported to reduce the production of reactive oxygen species (ROS) and alleviate oxidative damage in DOX-treated hearts and cardiomyocytes [42]. These studies indicated that traditional Chinese medicine ingredients have the ability to scavenge free radicals and resist oxidative stress, which can exert a protective effect on DOX-induced cardiotoxicity (Table 1).

<table>
<thead>
<tr>
<th>Active ingredient</th>
<th>Structure type</th>
<th>Main sources</th>
<th>Experimental model</th>
<th>Drug dosage</th>
<th>Protective mechanism</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salvinolic acid</td>
<td>Phenolic acids</td>
<td>Salviae Miltiorrhizae Radix et Rhizoma</td>
<td>Mice</td>
<td>40 mg/kg, for 3 days</td>
<td>Reduce MDA content and increase oxygen radicals absorbance capacities</td>
<td>[29]</td>
</tr>
<tr>
<td>Tanshinone I</td>
<td>Diterpenoids</td>
<td>Salviae Miltiorrhizae Radix et Rhizoma</td>
<td>Mice, H9c2 cells</td>
<td>5 and 10 mg/kg, i.e. for 4 weeks; 10 µM for 24 h</td>
<td>Activating Nrf2-mediated antioxidant pathway</td>
<td>[30]</td>
</tr>
<tr>
<td>Tanshinone IIA</td>
<td>Diterpenoids</td>
<td>Salviae Miltiorrhizae Radix et Rhizoma</td>
<td>Mice, H9c2 cells</td>
<td>15 and 30 mg/kg, i.e. for 7 days; 1, 3, 5 and 10 µM for 4 h</td>
<td>Activating Nrf2-mediated antioxidant pathway</td>
<td>[31]</td>
</tr>
<tr>
<td>Resveratrol</td>
<td>Nonflavonoid polyphenols</td>
<td>Polygoni Cuspidati Rhizoma et Radix</td>
<td>Mice, H9c2 cells</td>
<td>10 mg/kg, i.e. for 7 days; 10 µM for 24 h</td>
<td>Activating Nrf2 and SIRT1 pathway</td>
<td>[32]</td>
</tr>
<tr>
<td>Lycium barbarum polysaccharides</td>
<td>Polysaccharides</td>
<td>Lycii Fructus</td>
<td>Rats, H9c2 cells</td>
<td>200 mg/kg, p.o. for 10 days; 100 µg/ml for 48 h</td>
<td>Reduce MDA content and upregulate SOD and GSH-Px activity</td>
<td>[33]</td>
</tr>
<tr>
<td>Astragaloside IV</td>
<td>Saponins</td>
<td>Astragali Radix</td>
<td>Mice, NRCMs</td>
<td>40 mg/kg, i.e. for 4 weeks; 20 µM for 24 h</td>
<td>Enhancing the AMPK/UCP2 pathway</td>
<td>[34]</td>
</tr>
<tr>
<td>Matrine</td>
<td>Quinolizidine alkaloids</td>
<td>Sophorae Flavescentis Radix</td>
<td>Mice, H9c2 cells</td>
<td>200 mg/kg, i.e. for 4 weeks; 200 µmol/L for 24 h</td>
<td>Activating the AMPK/UCP2 pathway</td>
<td>[35]</td>
</tr>
<tr>
<td>Schisandrin B</td>
<td>Dibenzoctadine ligan</td>
<td>Schisandrae Chinesis Fructus</td>
<td>Mice</td>
<td>100, 50, and 25 mg/kg, i.e. for 3 days</td>
<td>Enhancing glutathione redox cycling and reducing myocardial oxidative stress</td>
<td>[37]</td>
</tr>
<tr>
<td>Berberine</td>
<td>Isoquinoline alkaloids</td>
<td>Coptidis Rhizoma</td>
<td>Rats, H9c2 cells</td>
<td>10 and 20 mg/kg, p.o. for 10 days; 0.1, 1 and 10 µM for 24 h</td>
<td>Activating SIRT1 and inhibiting the p66Shc pathway</td>
<td>[41]</td>
</tr>
<tr>
<td>Ginkgolide B</td>
<td>Diterpene lactones</td>
<td>Ginkgo Folium</td>
<td>Mice, H9c2 cells</td>
<td>100 mg/kg, i.e. for 9 days; 1, 5 and 50 µM for 24 h</td>
<td>Reducing ROS production</td>
<td>[42]</td>
</tr>
</tbody>
</table>

DOX, doxorubicin; NRCMs, neonatal rat cardiomyocytes; ROS, reactive oxygen species; GSH, glutathione.

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can induce activation of the innate immune system, leading to excessive release of proinflammatory factors, including interleukins (ILs), interferon, tumor necrosis factor, and chemokines [44]. In addition, DOX can also cause myocardial damage and cardiac dysfunction by regulating the function of immune cells, including neutrophils, macrophages, and natural killer cells [43]. The NF-κB signaling pathway plays an important role in inducing the release of proinflammatory factors, and doxorubicin treatment can significantly activate the NF-κB signaling pathway, leading to cardiac inflammation [45, 46]. The NLRP3 inflammasome, as an important component of innate immunity, plays an important role in the immune response [47–49]. Research has shown that DOX promotes the maturation of the proinflammatory factors IL-1β and IL-18 and induces pyroptosis by regulating the NLRP3 inflammasome [50, 51]. Thus, inhibiting immune cell infiltration and reducing the release of proinflammatory cytokines have also been proven to be important strategies for treating doxorubicin-induced cardiotoxicity.

As a nonflavonoid polyphenol compound, resveratrol has been proven to alleviate DOX-induced cardiac and systemic inflammation by inhibiting the NLRP3 inflammasome signaling pathway [52]. Hyperoside is a flavonoid glycoside extracted from various traditional Chinese medicines, including *Hyperici Perforati Herba*, *Ramulus et Folium Rhododendri Microanthi*, and *Cuscutae Semen* [53, 54]. Wei et al. reported that hyperoside protects the heart from DOX-induced cardiac inflammation and oxidative damage by preventing the activation of the NADPH oxidase/NLRP3 inflammasome [53]. Calycosin is the main active ingredient of *Radix Astragali* and can mitigate cardiac inflammation and oxidative damage in DOX-treated hearts and cardiomyocytes by regulating the Sirt1-NLRP3 signaling pathway [55]. Palmatine, also known as berberiscine, hindarine and huangtengsu, is an isoquinoline alkaloid extracted from the *Uncariae Ramulus Cum Uncis* and *Sanguisorbae Radix* [56, 57]. Cheng et al. reported that palmatine restores the expression of IL-1β, IL-6, interferon-γ and tumor necrosis factor-α in the serum and heart by activating SIRT1 and reducing the NF-κB signaling pathway in a mouse model of DOX-induced cardiotoxicity [58]. *Scutellariae Radix* is a traditional Chinese medicine and has been proven to enhance immune function, improve microcirculation, and delay aging [59, 60]. Baicalin is the main active ingredient of *Scutellariae Radix* and can reduce cardiac inflammation and myocardial damage in DOX-treated hearts by inhibiting the activation of the TLR4/NF-κB signaling pathway [61]. These studies suggested that traditional Chinese medicine ingredients can reduce cardiac inflammation and improve DOX-induced cardiotoxicity (Table 2).

### Table 2 The anti-inflammatory effects of traditional Chinese medicine ingredients in the treatment of DOX-induced cardiotoxicity

<table>
<thead>
<tr>
<th>Active ingredient</th>
<th>Structure type</th>
<th>Main sources</th>
<th>Experimental model</th>
<th>Drug dosage</th>
<th>Protective mechanism</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resveratrol</td>
<td>Nonflavonoid polyphenols</td>
<td>Polygoni Caulipadi Rhizoma et Radix</td>
<td>Mice</td>
<td>Diets with resveratrol for 4 weeks</td>
<td>Inhibiting NLRP3-inflammasome signaling pathway</td>
<td>[52]</td>
</tr>
<tr>
<td>Hyperoside</td>
<td>Flavonoids</td>
<td>Hyperici Perforati Herba, Ramulus et Folium Rhododendri Microanthi, and Cuscutae Semen</td>
<td>Mice, NRCMs</td>
<td>15 and 30 mg/kg, p.o., for 15 days; 100 and 200 μM for 48 h</td>
<td>Preventing the activation of NADPH oxidase and NLRP3 inflammasome</td>
<td>[53]</td>
</tr>
<tr>
<td>Calycosin</td>
<td>Flavonoids</td>
<td>Astragali Radix</td>
<td>Mice, H9c2 cells</td>
<td>50 and 100 mg/kg, i.p., for 7 days; 50, 100, and 200 μM for 24 h</td>
<td>Regulating the Sirt1-NLRP3 signaling pathway</td>
<td>[55]</td>
</tr>
<tr>
<td>Palmatine</td>
<td>Isoquinoline alkaloids</td>
<td>Uncariae Ramulus Cum Uncis and Sanguisorbae Radix</td>
<td>Mice, NRCMs</td>
<td>25 and 50 mg/kg, i.p., for 8 days; 5, 50, and 100 μM for 12 h</td>
<td>Activating SIRT1 and reducing the NF-κB signaling pathway</td>
<td>[58]</td>
</tr>
<tr>
<td>Baicalin</td>
<td>Flavonoids</td>
<td>Scutellariae Radix</td>
<td>Rats, H9c2 cells</td>
<td>100 mg/kg, i.p., for 4 weeks; 50 μM for 24 h</td>
<td>Inhibiting the activation of TLR4/NF-κB signaling pathway</td>
<td>[61]</td>
</tr>
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</table>

DOX, doxorubicin; NRCMs, neonatal rat cardiomyocytes.

Mitochondria, as places for aerobic respiration and energy supply for cell metabolism, are crucial for maintaining the function of normal cell and the balance of energy metabolism [62, 63]. Mitochondrial homeostasis is mainly regulated by mitochondrial quality control processes, such as mitochondrial biogenesis, mitochondrial fusion and fission, and mitochondrial autophagy [64–66]. DOX has a high affinity for cardiolipin that located on the inner membrane of mitochondria, forming irreversible complexes by binding with cardiolipin and then accumulating in mitochondria and disrupting mitochondrial homeostasis [67, 68]. Research has shown that DOX can open the mitochondrial permeability transition pore, lead to changes in mitochondrial membrane potential (ΔΨm), and then promote mitochondrial osmotic swelling and rupture [69, 70]. In addition, DOX can directly or indirectly interact with mitochondrial DNA (mtDNA) and lead to mitochondrial respiratory chain dysfunction, which in turn generates additional ROS and causes mtDNA mutations [71].

Paenol is a natural phenol extracted from *Paoniae Radix Alba* and *Moutan Cortex* and widely used for the treatment of inflammation and pain-related diseases in China [72]. Recent studies have shown that paenol protects against doxorubicin-induced cardiotoxicity by promoting mitochondrial fusion through activating the PKC-ε -STAT3-Mfn2 pathway [73]. Quercetin is a natural polyphenol extracted from various medicinal plants, including fructus *Sophorae Flavescentis Radix*, *Phragmites Rhzoma* and *Zingiberis Rhizoma Recens* [74]. Chen et al. reported that quercetin restores DOX-related cardiomyocyte mitochondrial dysfunction and oxidative stress by upregulating 14-3-3ε levels [75]. Luteolin is a natural flavone extracted from *Platycondonis Radix*, *Lonicerae Japonicae Flos* and *Perillae Fructus* that is widely used to treat respiratory diseases, cardiovascular diseases, and malignant tumors [76, 77]. Research has shown that luteolin significantly reduces excessive mitochondrial fission and maintains mitochondrial homeostasis in cultured cardiomyocytes after DOX treatment [78]. In addition, luteolin can inhibit the proliferation and metastasis of cancer cells and enhance the antitumor effect of...
DOX [78]. Ginsenoside Rg3, an important active ingredient of *Ginseng Radix et Rhizoma*, can relieve mitochondrial swelling and crista reduction and restore mitochondrial oxidative respiratory function in DOX-treated hearts and cardiomyocytes [79]. In addition, ginsenoside Rg3 also maintains mitochondrial arrays, increased mitochondrial ΔΨm and decreased mtDNA [79]. Resveratrol has been reported to maintain mitochondrial activity, reduce mitochondrial ROS production, and reduce DOX-induced myocardial oxidative damage [80]. In addition, the protective mechanism of resveratrol is related to the activation of the SIRT1 signaling pathway [80]. Berberine has been proven to promote mitochondrial biogenesis and prevent mitophagy in DOX-treated cardiomyocytes [81]. These data indicate that traditional Chinese medicine ingredients can alleviate DOX-induced myocardial damage by maintaining mitochondrial homeostasis and restoring mitochondrial function (Table 3).

### Regulating autophagy

Autophagy is a metabolic process that eliminates misfolded proteins and damaged or aged cellular organelles by regulating Atg gene expression and lysosomal protein hydrolysis to maintain cellular homeostasis [82, 83]. Under physiological conditions, autophagy is an essential way for cardiomyocytes to perform normal functions and survive by eliminating misfolded proteins and damaged organelles. Under pathological conditions, autophagy can be activated to protect cardiomyocytes from stress stimuli, but excessive autophagy can damage the structural function of cardiomyocytes and contribute to cardiomyocyte death [84, 85]. Research has shown that DOX can induce autophagy in cardiomyocytes through various pathways, such as ERS and oxidative stress, and upregulation of autophagy is one of the pathogenic mechanisms of DOX-induced cardiotoxicity [84, 86]. DOX can increase the expression of the autophagy markers LC3-II, Atg5, Atg6, Atg8, and Atg12 by activating AMPK and inhibiting p38 MAPK, inhibiting the expression of mTOR, and promoting autophagy [87]. In addition, DOX can enhance autophagy by regulating P38K/Act/mTOR/ULK1 signaling, and P38K inhibition can alleviate DOX-induced heart damage [71].

Glycyrhizae is a natural saponin that is isolated from *Glycyrrhiza Radix et Rhizoma* and *Radix Glycyrrhizae Preparata* and is reported to have anti-inflammatory, antibacterial, antiviral and antiarrhythmia, heart, liver, and kidney protection effects [88]. Lyu et al. reported that glycyrhrizin can restore the impairment of autophagic flux in DOX-treated hearts and cardiomyocytes, which is related to the downregulation of the Akt/mTOR pathway [89]. Resveratrol is a nonflavonoid polyphenol and can accelerate autophagy and reduce cardiomyocyte apoptosis in DOX-treated hearts and cardiomyocytes by inhibiting the E2F1/AMPKg2 and E2F1/mTORC1 pathways [90]. Tanshinone IIA is an important active ingredient of *Salviae Miltiorrhizae Radix et Rhizoma* that promotes autophagosome formation and autolysosome degradation and improves DOX-induced cardiac dysfunction, which is related to the activation of the Beclin1/LAMF1 pathway [91]. Scutellarin is the main active ingredient of the traditional Chinese medicine Erigeronits Herba and *Scutellarietae Radix*, which is widely used to treat stroke sequelae, coronary heart disease, and angina pectoris in China [92]. Sun et al. reported that scutellarin prevented excessive autophagy and cardiomyocyte apoptosis in DOX-treated hearts by inhibiting AMPK signaling and activating mTOR signaling [93].

### Table 3 The effect of traditional Chinese medicine ingredients on mitochondrial function in the treatment of DOX-induced cardiotoxicity

<table>
<thead>
<tr>
<th>Active ingredient</th>
<th>Structure type</th>
<th>Main sources</th>
<th>Experimental model</th>
<th>Drug dosage</th>
<th>Protective mechanism</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ginsenoside Rg3</strong></td>
<td>Saponins</td>
<td><em>Ginseng Radix et Rhizoma</em></td>
<td>Rats, NRCMs, 4T1b, MDA-MB-231, and H9c2 cells</td>
<td>10 mg/kg, for 2 weeks; 10 μM for 48 h</td>
<td>Relieve mitochondrial swelling and crista reduction, and restoring mitochondrial oxidative respiratory function</td>
<td>[79]</td>
</tr>
<tr>
<td><strong>Resveratrol</strong></td>
<td>Nonflavonoid polyphenols</td>
<td><em>Polygoni Capsidii Rhizoma et Radix</em></td>
<td>NRCMs</td>
<td>10 μM for 72 h</td>
<td>Maintaining mitochondrial activity, reducing mitochondrial ROS production</td>
<td>[80]</td>
</tr>
<tr>
<td><strong>Berberine</strong></td>
<td>Isoquinoline alkaloids</td>
<td><em>Coptidis Rhizoma</em></td>
<td>H9c2 cells</td>
<td>1 and 10 μM for 72 h</td>
<td>Promoting mitochondrial biogenesis and preventing mitophagy in DOX-treated cardiomyocytes</td>
<td>[81]</td>
</tr>
</tbody>
</table>

DOX, doxorubicin; NRCMs, neonatal rat cardiomyocytes; ROS, reactive oxygen species.

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polysaccharide has also been reported to inhibit AMPK signaling, activate mTOR signaling and restore autophagic flux [94]. Ginsenoside Rg1 can relieve DOX-induced excessive autophagy and cardiac dysfunction by inhibiting the JNK1 and p70S6K signaling pathways [95]. As a natural flavone, Luteolin has been reported to reverse mitochondrial autophagy and improve mitochondrial function in DOX-treated adult murine cardiomyocytes by regulating the Drp1/mTOR/TFEB/LAMP1 signaling pathway [96]. Berberine is a quaternary ammonium alkaloid and promotes mitophagy and reduces mitochondrial ROS production in DOX-treated cardiomyocytes by activating the Bcl-XL pathway [97]. These studies suggested that traditional Chinese medicine ingredients can regulate autophagy and mitochondrial autophagy to improve DOX-induced cardiotoxicity (Table 4).

**Inhibiting apoptosis**

Apoptosis is a type of programmed cell death and is precisely and strictly regulated by genes. Apoptosis can be mediated through death receptors, mitochondria, and ERS, playing an important role in maintaining homeostasis in the internal environment and normal cell survival [98, 99]. Caspases are the most critical enzymes in regulating apoptosis, and insufficient or excessive apoptosis can lead to diseases [98]. The Bcl-2 family is an important component in regulating cell apoptosis, which can be divided into antiapoptotic proteins and proapoptotic proteins according to function [98, 100]. The antiapoptotic genes include Bcl-2, Bcl-XL and Bcl-w, and the mechanism is that they directly or indirectly inhibit the release of Cytc from mitochondria and then deactivate caspase-9 [98]. The proapoptotic genes include Bax, Bak, Bad and Bid, and their overexpression can induce cell apoptosis. Bax can form heterodimers with Bcl-2 by inhibiting its activity, promoting apoptosis [98, 100]. DOX-induced cardiotoxicity is associated with p53 nuclear translocation and p53-dependent apoptosis101. DOX activates ERK and phosphorylates p53 at Ser15, and the phosphorylation of p53 can lead to myocardial cell apoptosis by downregulating the antiapoptotic gene Bcl-2, upregulating the proapoptotic gene Bax, and activating caspase-3 and caspase-9 [101].

Salvianolic acid and tanshinone are the main active ingredients of the traditional Chinese medicine *Salviae Miltiorrhizae Radix et Rhizoma*, which is widely used in cardiovascular and cerebrovascular diseases [102]. Research has shown that salvianolic acid B alleviates ERS-mediated cardiomyocyte apoptosis and myocardial injury in DOX-treated hearts by inhibiting the PI3K/Akt signaling pathway [103]. Xu et al. also reported that tanshinone IIA can downregulate p-P38, cleaved caspase-3 and cleaved caspase-8 expression and upregulate DAXX, p-MEK and p-ERK expression in DOX-treated hearts and cardiomyocytes104. In addition, DAXX knockdown abolished the tanshinone IIA-mediated antiapoptotic effect, indicating that the myocardial protective effect of tanshinone IIA is related to the activation of the DAXX/MEK/ERK signaling pathway [104]. Atractaladose IV is a natural saponin extracted from the traditional Chinese medicine *Astragalus Radix* that has also been reported to alleviate DOX-induced cardiomyocyte apoptosis and myocardial injury in DOX-treated hearts by inhibiting the PI3K/Akt signaling pathway [105]. Resveratrol is a nonflavonoid polyphenol compound extracted from the traditional Chinese medicine *Polygonyi Cuspidati Rhizoma et Radix*. Previous studies have shown that resveratrol can increase SIRT1 expression and reduce DOX-induced acetylation of p53 and cardiomyocyte apoptosis [106]. In addition, resveratrol treatment also alleviated the activation of p53 DNA binding and Bax expression cardioprotective and neuroprotective effects [53]. Chen et al. reported

<table>
<thead>
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<th>Protective mechanism</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycyrrhizin</td>
<td>Triterpenoid saponins</td>
<td>Glycyrrhiza Radix et Rhizoma and Radix Glycyrrhiza Preparata</td>
<td>Rats, NRCMs</td>
<td>75, 150 and 300 mg/kg, i.p., for 2 weeks; 50 μM for 24 h</td>
<td>Downregulation of Akt/mTOR pathway</td>
<td>[89]</td>
</tr>
<tr>
<td>Resveratrol</td>
<td>Nonflavonoid polyphenols</td>
<td>Polygoni Cuspidati Rhizoma et Radix</td>
<td>Rats, H9c2 cells</td>
<td>25 and 50 mg/kg, i.p., for 2 weeks; 0.2, 0.4 and 0.8 mM for 24 h</td>
<td>Inhibiting E2F1/AMPKko2 and E2F1/mTORC1 pathway</td>
<td>[90]</td>
</tr>
<tr>
<td>Tanshinone IIA</td>
<td>Diterpenoids</td>
<td>Salviae Miltiorrhizae Radix et Rhizoma</td>
<td>Mice, H9c2 cells</td>
<td>10 mg/kg, p.o., for 4 weeks; 0.5, 1, 5 and 20 μM for 24 h</td>
<td>Activating Bcl11/LAMP1 pathway</td>
<td>[91]</td>
</tr>
<tr>
<td>Scutellariin</td>
<td>Flavonoids</td>
<td>Erigeronits Herba and Scutellariae Radix</td>
<td>Rats</td>
<td>10 mg/kg, i.p., for 6 weeks</td>
<td>Inhibiting AMPK and mTOR signaling</td>
<td>[93]</td>
</tr>
<tr>
<td>Astragalus polysaccharide</td>
<td>Polysaccharides</td>
<td>Astragal Radix</td>
<td>Mice, NRCMs</td>
<td>1.5 mg/kg, p.o., for 4 weeks; 0.5, 5, 10 and 50 μM for 24 h</td>
<td>Inhibiting JNK1 and P70S6K signaling</td>
<td>[95]</td>
</tr>
<tr>
<td>Ginkosodine Rg1</td>
<td>Saponins</td>
<td>Ginseng Radix et Rhizoma</td>
<td>Mice</td>
<td>50 mg/kg, i.p., for 3 weeks</td>
<td>Inhibiting the Drp1/mTOR/TFEB/LAM1 signaling pathway</td>
<td>[96]</td>
</tr>
<tr>
<td>Luteolin</td>
<td>Flavonoids</td>
<td>Platycodonis Radix, Lonicerieae Japonicae Flos and Perillae Fructus</td>
<td>AMCMS</td>
<td>1, 10 and 50 μM for 24 h; 0.25, 0.5, 1, 2, 4 and 8 μM for 24 h</td>
<td>Activating Bcl-xL pathway</td>
<td>[97]</td>
</tr>
</tbody>
</table>

DOX, doxorubicin; NRCMs, neonatal rat cardiomyocytes; AMCMS, adult murine cardiomyocytes.

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and reduced the release of cytochrome c in DOX-treated hearts [106]. Hyperoside is a flavonoid glycoside and has been proven to exert that hyperoside alleviates DOX-mediated cardiomyocyte apoptosis and oxidative stress by inhibiting the PI3K/Akt signaling pathway [107]. Osthole is the main active ingredient of the traditional Chinese medicine *Cnidii Fructus* and can alleviate DOX-induced cardiomyocyte apoptosis and oxidative stress by inhibiting the eIF2α signaling pathway [108]. Isorhamnetin is a plant flavonoid extracted from various traditional Chinese medicines, *Hygrophiae Fructus* and *Ginkgo Folium*, which are widely used for the treatment of various cardiovascular and cerebrovascular diseases [109]. Sun et al. reported that isorhamnetin alleviates cardiomyocyte apoptosis and oxidative stress in DOX-treated hearts and cardiomyocytes by inhibiting the MAPK signaling pathway [110]. The above research indicates that the effective ingredients of traditional Chinese medicine exert therapeutic effects by inhibiting cardiomyocyte apoptosis in DOX-induced cardiotoxicity (Table 5).

### Inhibiting ferroptosis

Ferroptosis was first proposed by Dixon et al. in 2012 and is an iron-dependent form of programmed cell death that is significantly different from necrosis, apoptosis, autophagy, and pyroptosis [111]. Research suggests that ferroptosis is caused by excessive accumulation of lipid peroxides due to disordered intracellular metabolic pathways and is closely related to intracellular iron metabolism and lipid homeostasis [112–114]. Lipid metabolism is the core process of ferroptosis, and the Fenton reaction in iron metabolism can promote lipid peroxidation, leading to cell death. Numerous studies have shown that GPX4 is an important regulator of lipid metabolism and can use GSH as a substrate to reduce lipid peroxidation, while SLC7A11 is a key subunit of the cystine/glutamate reverse transporter, which can be used to synthesize GSH by transporting cystine [115–117]. In addition, the ferroptosis inducer erastin inhibits the SLC7A11-GSH-GPX4 axis, and lipid hydroperoxides accumulate continuously and trigger ferroptosis [111]. Research has shown that ferroptosis plays an important role in DOX-induced cardiotoxicity, and inhibiting ferroptosis can improve myocardial damage caused by DOX [118, 119]. The DOX-Fe⁺ complex can reduce myocardial GPX4 activity and increase lipid peroxidation levels, ultimately leading to cardiomyocyte ferroptosis and cardiotoxicity [118, 119].

Salidroside is a natural phenolic compound extracted from the traditional Chinese medicine *Rhodiola Crenulatae Radix* and *Rhizoma* and has been proven to have various pharmacological effects such as anti-fatigue, anti-aging, immune regulation, and free radical scavenging [120]. Chen et al. reported that salidroside reduces ferroptosis and lipid peroxidation, improving mitochondrial function in DOX-treated hearts and cardiomyocytes by activating the AMPK signaling pathway [121]. Cinnamaldehyde is a bioactive component isolated from the traditional Chinese medicines *Cinnamomum Cortex* and *Cinnamomum Japonicum* and possesses potent antioxidative, anti-inflammatory, and anti-apoptotic potential [122]. Mao et al. reported that cinnamaldehyde reduces DOX-induced cardiomyocyte ferroptosis and oxidative stress by activating the Nrf2 signaling pathway [123]. Aloe-emodin is a natural anthraquinone derivative extracted from the traditional Chinese medicine *Rhei Radix et Rhizoma* and *Aloe* and can relieve ferroptosis and oxidative damage in DOX-treated cardiomyocytes by upregulating the Nrf2 signaling pathway [124]. Resveratrol is a nonflavonoid polyphenol and can prevent ferroptosis and mitochondrial ROS in DOX-treated hearts and cardiomyocytes by activating the p62-Nrf2 signaling pathway [125]. Fisetin is a natural flavonoid extracted from the *Rhus sylvestris*, which is also abundant in vegetables and fruits such as apples, strawberries, onions, and cucumbers [126]. Li et al. reported that fisetin inhibited DOX-induced cardiomyocyte ferroptosis and oxidative damage by activating the SIRT1/Nrf2 signaling pathway [127]. Astragaloside IV is a natural saponin extracted from the traditional Chinese medicine *Astragali Radix*. It has also been reported to alleviate cardiomyocyte ferroptosis and apoptosis in DOX-treated hearts and neonatal mouse cardiomyocytes by inhibiting the GPX4 signaling pathway [128].

#### Table 5 The antiapoptotic effects of traditional Chinese medicine ingredients in the treatment of DOX-induced cardiotoxicity

<table>
<thead>
<tr>
<th>Active ingredient</th>
<th>Structure type</th>
<th>Main sources</th>
<th>Experimental model</th>
<th>Drug dosage</th>
<th>Protective mechanism</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salvianolic acid B</td>
<td>Phenolic acids</td>
<td><em>Salviae Miltiorrhizae Radix et Rhizoma</em></td>
<td>Mice</td>
<td>2 mg/kg, i.v., for 1 weeks</td>
<td>Inhibiting the PI3K/Akt signaling pathway</td>
<td>[103]</td>
</tr>
<tr>
<td>Tamshinone IIA</td>
<td>Tamshinone</td>
<td><em>Salviae Miltiorrhizae Radix et Rhizoma</em></td>
<td>Mice, H9c2 cells</td>
<td>2.5, 5 and 10 mg/kg, i.p., for 4 weeks; 10, 20 and 40 μM for 24 h</td>
<td>Activating DAXX/MEK/ERK signaling pathway</td>
<td>[104]</td>
</tr>
<tr>
<td>Astragaloside IV</td>
<td>Saponins</td>
<td><em>Astragali Radix</em></td>
<td>NRCMs</td>
<td>3.75, 7.5, 15, 30, 60 μg/mL for 24 h</td>
<td>Inhibiting the PI3K/Akt signaling pathway</td>
<td>[105]</td>
</tr>
<tr>
<td>Resveratrol</td>
<td>Nonflavonoid polyphenols</td>
<td><em>Polygoni Cuspidati Rhiiza et Radix</em></td>
<td>Mice</td>
<td>Chow at 0.01% resveratrol for 7 weeks</td>
<td>Increasing SIRT1-mediated p33 deacetylation</td>
<td>[106]</td>
</tr>
<tr>
<td>Hyperoside</td>
<td>Flavonoids</td>
<td><em>Hyperici Perforati Herba, Ramulus et Folium Rhododenri Micranthi, and Cuscutae Semen</em></td>
<td>HL-1 cells</td>
<td>100 μM for 24 h</td>
<td>Inhibiting the ASK1/p38 signaling pathway</td>
<td>[107]</td>
</tr>
<tr>
<td>Osthole</td>
<td>Coumarins</td>
<td><em>Cnidii Fructus</em></td>
<td>NRCMs</td>
<td>10, 20, 40 μM for 28 h</td>
<td>Inhibiting the eIF2α signaling pathway</td>
<td>[108]</td>
</tr>
<tr>
<td>Isorhamnetin</td>
<td>Flavonoids</td>
<td><em>Hipppophae Fructus and Ginkgo Folium</em></td>
<td>Rats, H9c2 cells</td>
<td>5 mg/kg, i.p., for 6 weeks; 6.25 and 12.5 μg/mL for 36 h</td>
<td>Enhance glutathione redox cycling and reduce myocardial oxidative stress</td>
<td>[110]</td>
</tr>
</tbody>
</table>

DOX, doxorubicin; NRCMs, neonatal rat cardiomyocytes.

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above research indicates that the effective ingredients of traditional Chinese medicine exert therapeutic effects by inhibiting ferroptosis in DOX-induced cardiotoxicity (Table 6).

**Other mechanisms**

Research has shown that the active ingredients of traditional Chinese medicine can also protect against DOX-induced cardiotoxicity through other mechanisms [129, 130]. Calcium homeostasis plays an important role in maintaining the normal function of cardiomyocytes, and calcium overload is closely related to the occurrence of various cardiovascular diseases [131]. Research has shown that DOX can increase the permeability of cardiomyocyte membranes and inhibit Na+/K+-ATPase activity, leading to an increase in calcium ion influx [132]. In addition, DOX can stimulate the release of stored calcium from mitochondria and the sarcoplasmic reticulum, and the sustained increase in intracellular calcium ion concentration can cause myocardial contraction and diastolic dysfunction [132, 133]. Salvianolic acid B has been reported to reduce DOX-induced ERS and calcium overload in rats and adult rat ventricular myocytes by inhibiting the activity of TRPC3 and TRPC6129. Berberine is the main active ingredient of *Coptidis rhizoma* and can reduce mitochondrial calcium overload and improve mitochondrial function in DOX-treated cardiomyocytes [130].

Ferroptosis, a new form of programmed cell death, is characterized by a dependence on caspase-1, 4, 5, and 11 and the release of a large number of proinflammatory factors [134, 135]. Numerous studies have shown that DOX can trigger cardiomyocyte pyroptosis, and inhibiting excessive pyroptosis can improve DOX-induced cardiac damage [136, 137]. Curcumin is a natural phenolic compound extracted from *Curcuma Longae Rhizoma*, and has anti-tumor, anti-inflammatory, and antioxidant effects. Curcumin mitigates cardiomyocyte autophagy, apoptosis, and pyroptosis in DOX-treated hearts and cardiomyocytes by activating the Akt/mTOR pathway [138]. Amentoflavone is a natural flavonoid extracted from the traditional Chinese medicine *Selaginellae Herba* and has been reported to reduce DOX-induced cardiomyocyte pyroptosis and the inflammatory response by inhibiting the STING/NLRP3 signaling pathway [139].

The above research indicates that the effective ingredients of traditional Chinese medicine protect against DOX-induced cardiotoxicity through other mechanisms (Table 7).

**Summary**

With the widespread application of DOX, severe cardiotoxicity limits its continuous application and therapeutic effectiveness. Therefore, the early detection and prevention of DOX-induced cardiotoxicity are increasingly valued, and the development of drugs that can reduce or antagonize DOX-induced cardiotoxicity is of great significance. Corresponding to the etiology of DOX cardiotoxicity, traditional Chinese medicine ingredients have shown significant advantages in reducing adverse reactions to DOX. Its mechanisms involve antioxidant stress, inhibiting inflammatory reactions and calcium overload, restoring mitochondrial function, and antagonizing cardiomyocytes autophagy, apoptosis, and pyroptosis (Figure 2). However, the above studies are mostly based on cell or animal models and lack systematic clinical research, especially evidence from randomized controlled trials. In addition, due to the complex multi-target and multi-drug rational characteristics of traditional Chinese medicine, it is difficult to elucidate its pharmacological substances and mechanisms. With the continuous innovation of systems biology methods such as transcriptomics, metabolomics, network pharmacology, and biotechnology, the mechanism of traditional Chinese medicine ingredients can be more scientifically elucidated. Therefore, we believe that traditional Chinese medicine ingredients will be safely and reasonably applied in the clinical treatment of DOX cardiotoxicity in the future.

<table>
<thead>
<tr>
<th>Active ingredient</th>
<th>Structure types</th>
<th>Main sources</th>
<th>Experimental model</th>
<th>Drug dosage</th>
<th>Protective mechanism</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salidroside</td>
<td>Glycosides</td>
<td><em>Radix</em> et <em>Rhiza</em></td>
<td>Mice, H9c2 cells</td>
<td>50 and 100 mg/kg, i.p., for 17 days</td>
<td>Activating the AMPK signaling pathway</td>
<td>[121]</td>
</tr>
<tr>
<td>Cinnamaldehyde</td>
<td>Aldehydes</td>
<td><em>Cinnamomi</em> Cortex and <em>Cinnamomum Japonicum</em></td>
<td>Rats, H9c2 cells</td>
<td>50 mg/kg, i.g., for 6 weeks; 20, 40, 80, 100, 160 and 200 μM for 24 h</td>
<td>Activating the Nrf2 signaling pathway</td>
<td>[123]</td>
</tr>
<tr>
<td>Aloe-emodin</td>
<td>Anthraquinone derivatives</td>
<td><em>Rhei Radix</em> et <em>Rhiza</em> and <em>Aloe</em></td>
<td>H9c2 cells</td>
<td>1 and 2 μM for 28 h</td>
<td>Activating the Nrf2 signaling pathway</td>
<td>[124]</td>
</tr>
<tr>
<td>Resveratrol</td>
<td>Nonflavonoid polyphenols</td>
<td><em>Polygoni Cuspidati Rhiza</em> et <em>Radix</em></td>
<td>H9c2 cells</td>
<td>0.5 and 1 μM for 24 h</td>
<td>Activating the p62-Nrf2 signaling pathway</td>
<td>[125]</td>
</tr>
<tr>
<td>Fisetin</td>
<td>Flavonoids</td>
<td><em>Rhus sylvestris</em></td>
<td>Rats, H9c2 cells</td>
<td>20 and 40 mg/kg, i.g., for 6 weeks; 40 μM for 24 h</td>
<td>Inhibiting the GPX4 signaling pathway</td>
<td>[127]</td>
</tr>
<tr>
<td>Astragaloside IV</td>
<td>Saponins</td>
<td><em>Astragali Radix</em></td>
<td>Mice, NMCMs</td>
<td>1 and 2 mg/kg, i.g., for 5 days; 1 μM for 48 h</td>
<td>Inhibiting the GPX4 signaling pathway</td>
<td>[128]</td>
</tr>
</tbody>
</table>

DOX, doxorubicin; NMCMs, neonatal mouse cardiomyocytes.

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**Table 6 The anti-ferroptosis effects of traditional Chinese medicine ingredients in the treatment of DOX-induced cardiotoxicity**
<table>
<thead>
<tr>
<th>Active ingredient</th>
<th>Structure types</th>
<th>Main sources</th>
<th>Experimental model</th>
<th>Drug dosage</th>
<th>Protective mechanism</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salvianolic acid B</td>
<td>Phenolic acids</td>
<td><em>Salvias</em> <em>Miltiorrhizae</em> Radix et <em>Rhizoma</em></td>
<td>Rats, ARVMs</td>
<td>0.25, 0.5 and 1 mg/kg, i.v., for 21 days; 20 μg/ml for 6 h</td>
<td>Reducing calcium overload by inhibiting the activity of TRPC3 and TRPC6</td>
<td>[129]</td>
</tr>
<tr>
<td>Berberine</td>
<td>Isoquinoline alkaloids</td>
<td><em>Coptidis</em> <em>Rhizoma</em></td>
<td>Rats, ARVMs</td>
<td>100, 200, and 400 mg/kg, i.g., for 16 days; 10 μM for 24 h</td>
<td>Reducing mitochondrial calcium overload and improving mitochondrial function</td>
<td>[130]</td>
</tr>
<tr>
<td>Curcumin</td>
<td>Polyphenolic</td>
<td><em>Curcumae Longae Rhizoma</em></td>
<td>Mice, H9c2 cells</td>
<td>100, 200, and 400 mg/kg, i.g., for 16 days; 10 μM for 24 h</td>
<td>Mitigating cardiomyocyte pyroptosis by activating the Akt/mTOR pathway</td>
<td>[138]</td>
</tr>
<tr>
<td>Amentoflavone</td>
<td>Flavonoids</td>
<td><em>Selaginellae Herba</em></td>
<td>Mice, NRCMs</td>
<td>5, 10, 20, and 50 mg/kg, for 3 weeks; 20 μM for 24 h</td>
<td>Reducing cardiomyocyte pyroptosis and inflammatory response by inhibiting the STING/NLRP3 signaling pathway</td>
<td>[139]</td>
</tr>
</tbody>
</table>

DOX, doxorubicin; NRCMs, neonatal rat cardiomyocytes; ARVMs, adult rat ventricular myocytes.

Figure 2 The protective mechanism of traditional Chinese medicine ingredients in DOX-induced cardiotoxicity. Traditional Chinese medicine ingredients have shown significant advantages in reducing adverse reactions to DOX. Its mechanisms involve antioxidant stress, inhibiting inflammatory reactions and calcium overload, restoring mitochondrial function, and antagonizing cardiomyocytes apoptosis, pyroptosis, and ferroptosis and pyroptosis. 

References


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against doxorubicin-induced toxicity by suppressing oxidative stress and improving mitochondrial function via 14-3-3-γ.


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119. Ta N, Qu C, Wu H, et al. Mitochondrial outer membrane protein FUNDC2 promotes ferroptosis and contributes to


