Mitochondria-Targeting Small Molecules Effectively Prevent Cardiotoxicity Induced by Doxorubicin

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Abstract: Doxorubicin (Dox) is a chemotherapeutic agent widely used for the treatment of numerous cancers. However, the clinical use of Dox is limited by its unwanted cardiotoxicity. Mitochondrial dysfunction has been associated with Dox-induced cardiotoxicity. To mitigate Dox-related cardiotoxicity, considerable successful examples of a variety of small molecules that target mitochondria to modulate Dox-induced cardiotoxicity have appeared in recent years. Here, we review the related literatures and discuss the evidence showing that mitochondria-targeting small molecules are promising cardioprotective agents against Dox-induced cardiac events.

Keywords: doxorubicin; cardiotoxicity; mitochondria; small molecules

1. Introduction

Cancer is a serious public health problem and the second leading cause of death in the world [1]. Cancer chemotherapy has made significant progress in the treatment of both solid and hematologic malignancies [2]. Anthracycline chemotherapy plays an important role in the modern era of cancer treatment [3]. Doxorubicin (Dox) is an anthracycline antibiotic drug that has been widely used to treat various types of tumors, such as leukemia and solid tumors [4]. Unfortunately, its clinical use has been greatly limited by dose-dependent and cumulative cardiotoxicity [5,6]. Sometimes, even at low doses of Dox exposure (200–250 mg/m²), cardiotoxic events still may occur in 10% of patients [7]. Recent studies demonstrated that the onset of the cardiotoxicity may be delayed more than 10 years after cessation of Dox chemotherapy [8].

Currently, the precise mechanisms underlying Dox-induced cardiotoxicity have not been fully understood but are likely to be multiple. In particular, overgeneration of reactive oxygen species (ROS) and inhibition of topoisomerase-II have been implicated as key mechanisms of Dox-induced cardiotoxicity [9,10]. Additionally, accumulated studies have suggested that Dox-induced mitochondrial dysfunction is a major cause of Dox-induced cardiotoxicity [11,12]. Mitochondria are among the key intracellular sites for the production of active free radical intermediates [9,13]. Dox has a high affinity for cardiolipin, which is involved in the reactions and processes of mitochondrial biogenesis. Dox binds to cardiolipin then enters the mitochondria and inhibits the respiratory chain [14]. Other proposed mitochondrial cardiotoxicity mechanisms include impaired expression of sundry important cardiac proteins [15]; mitochondrial membrane potential rapid depolarization; induction of mitochondrial DNA damage [16], destruction of mitochondrial bioenergetics [17];
metabolism of Dox into cardiotoxic and more hydrophilic substances; disruption of cellular and mitochondrial \(Ca^{2+}\) homeostasis [18]; and interference with different kinds of pro-survival kinases [19]. Therefore, it seems clear that mitochondrial maintenance plays an important role in preventing Dox-induced cardiotoxicity. In recent years, the use of small molecules targeting mitochondria to prevent Dox-induced cardiotoxicity has been extensively investigated and has made considerable progress. Although several reviews on small molecules to attenuate Dox-induced cardiotoxicity have been published in recent years, they mainly focus on the reduction of Dox-induced cardiotoxicity by phenolic compounds [20,21], plant-derived small molecules [22], and some natural products [23]. One issue was still unclear: the common mechanism underlying this action exerted by most of the small molecules. In this review, for the first time, we summarize the findings about the possible mode of actions of 42 small molecules that target mitochondria to reduce Dox-induced cardiotoxicity.

2. Small Molecules that Attenuate Dox-Induced Cardiotoxicity

In this section, we systematically describe the myocardial protection for small molecules against Dox-induced cardiotoxicity. They are divided into three categories: natural products, semisynthetic small molecules, and synthetic compounds. A brief description of their effects on anti-tumor activity when co-treated with Dox and their roles in pathways or targets are listed in Table 1.

Table 1. Small molecules that target mitochondria effectively prevent the cardiotoxicity induced by Dox.

| Name of Molecules | Model          | Key Mechanisms of the Action Against Dox | Anti-Cancer Effect | Refs.   |
|------------------|----------------|------------------------------------------|-------------------|---------|
| AA               | NRC, rats      | ↓Disruption of \(\Delta \Psi_m\)         |                   | [24]    |
|                  |                | ↓Mitochondrial apoptotic pathway         |                   |         |
| Baicalein        | Chick cardiomyocytes | ↓Disruption of \(\Delta \Psi_m\) |                   | ↔ [25–28] |
|                  |                | ↓ROS                                     |                   |         |
|                  |                | ↓JNK activation                           |                   |         |
| Berberine        | NRC, MCF-7 cells, rats | ↓Disruption of \(\Delta \Psi_m\) | ↑                  | [29–34] |
|                  |                | ↓Mitochondrial apoptotic pathway         |                   |         |
|                  |                | ↓Mitochondrial \(Ca^{2+}\)              |                   |         |
| Curcumin         | Rats, Mice     | ↑Mitochondrial \(K_{ATP}\) channel      |                   | - [35–40] |
|                  | H9c2           | ↓Mitochondrial phosphate carrier         |                   |         |
|                  |                | ↓Mitochondrial superoxide radicals       |                   |         |
| CRY              | Rats           | ↑Mitochondrial biogenesis                |                   | - [41]  |
|                  |                | ↑Activities of mitochondrial respiratory chain complex |             |         |
| Chrysin          | Rats           | ↓Mitochondrial apoptotic pathway         |                   | - [42]  |
|                  |                | ↓MAPK and NF-\(\kappa\)B activation     |                   |         |
|                  |                | ↑VEGF/AKT pathway                        |                   |         |
| CVB-D            | Mice           | ↑Mitochondrial biogenesis                |                   | - [43]  |
| CBD              | Mice, rats     | ↑Mitochondrial function                  |                   | - [13,44] |
|                  |                | ↑Mitochondrial biogenesis                |                   |         |
|                  |                | ↓Pro-inflammatory response                |                   |         |
| Name of Molecules | Model | Key Mechanisms of the Action Against Dox | Anti-Cancer Effect | Refs. |
|------------------|-------|-----------------------------------------|-------------------|-------|
| Esculetin         | H9c2  | ↑Mitochondrial function                 |                   | [45]  |
|                  |       | ↑Bmi-1 expression                      |                   |       |
|                  |       | ↓ROS                                   |                   |       |
| HKL              | Mice  | ↑Cardiac mitochondrial respiration     |                   | [46,47]|
|                  |       | ↑Sirt3                                 | ↔                 |       |
|                  |       | ↑PPARγ                                 |                   |       |
| HT               | Rats  | ↑Mitochondrial dysfunction             |                   | [48]  |
|                  |       | ↑Mitochondrial electron transport chain|                   |       |
| Isorhamnetin     | H9c2, rats, MCF-7, HepG2 and Hep2 | ↓Mitochondria-dependent apoptotic Pathway | ↑| [49] |
|                  |       | ↓MAPK pathway                          |                   |       |
|                  |       | ↓ROS                                   |                   |       |
| Kaempferol       | H9c2, rats | ↑Disruption of ∆Ψm                     | ↑| [50,51]|
|                  |       | ↓Mitochondrial apoptotic pathway       |                   |       |
| LUTG             | H9c2  | ↓Disruption of ∆Ψm                     | ↓| [52,53]|
| Myricitrin       | H9c2, rats | ↓Mitochondrial apoptotic pathway       |                   | [54]  |
|                  |       | ↓ROS                                   |                   |       |
| Naringin         | H9c2, rats | ↓Disruption of ∆Ψm                     |                   | [55,56]|
|                  |       | ↓P38 MAPK                              |                   |       |
|                  |       | ↓ROS                                   |                   |       |
| OMT              | H9c2, rats | ↓Mitochondrial apoptotic pathway       |                   | [57,58]|
|                  |       | ↓ROS                                   |                   |       |
| OP-D             | H9c2, mice | ↓Disruption of ∆Ψm                     |                   | [59]  |
|                  |       | ↓Autophagy and ROS                     |                   |       |
| PD               | H9c2  | ↓Disruption of ∆Ψm                     |                   | [60]  |
|                  |       | ↓ROS                                   |                   |       |
|                  |       | ↓NF-κB activation                      |                   |       |
| Quercetin        | H9c2, mice | ↓Disruption of ∆Ψm                     |                   | [61–64]|
|                  |       | ↓ROS                                   |                   |       |
|                  |       | ↑Bmi-1 expression                      |                   |       |
| RV               | NRC   | ↑Sirt1 pathway                         |                   | [65–67]|
|                  |       | ↓ROS                                   |                   |       |
| RA               | H9c2  | ↓Disruption of ∆Ψm                     |                   | [68,69]|
|                  |       | ↓ROS                                   |                   |       |
| Ses              | H9c2, rats | ↑Disruption of ∆Ψm                     |                   | [70]  |
|                  |       | ↑Sirt1 and Mn-SOD pathway              |                   |       |
|                  |       | ↑Nrf2                                  |                   |       |
| Sulforaphane     | H9c2, NRC, rats | ↓Disruption of ∆Ψm                     | ↑| [71,72]|
|                  |       | ↓Mitochondrial apoptotic pathway       |                   |       |
| Name of Molecules | Model | Key Mechanisms of the Action Against Dox | Anti-Cancer Effect | Refs. |
|------------------|-------|----------------------------------------|-------------------|-------|
| SAI              | Rats  | ↓Membrane sclerosis                     | ↔                 | [73,74]|
| Tetrandrine      | Rats  | ↑Mitochondrial function                 | ↑                 | [75]  |
| THSG             | Mice, NRC | ↓Disruption of ∆Ψm                   | ↑                 | [76,77]|
| Visnagin         | Zebrafish, Mice, NRC, HL1, MCF7, DU145, LNCaP, MDA-MB-231 | ↓Mitochondrial malate dehydrogenase 2 activity | ↔ | [78,79]|
| ALA              | Rats  | ↓Mitochondrial apoptotic pathway        | ↑Nrf2             | -     | [80,81]|
| ATRA             | H9c2  | ↑Mitochondrial function                 | ↑                 | [82,83]|
| BAY60-2770       | H9c2, rats | ↓Disruption of ∆Ψm                  | -                 | [84,85]|
| Ghrelin          | NRC, H9c2, mice | ↑mitochondrial bioenergetics     | -                 | [86–88]|
| Melatonin        | NIH3T3 cells | ↑Mitochondrial biogenesis              | ↑                 | [89,90]|
| D006             | H9c2, zebrafish | ↓mitochondrial biogenesis              | ↑                 | [91]  |
| Mdivi-1          | Rats, NRC, HL60 | ↓Mitochondrial fission                | ↔                 | [92,93]|
| STS              | Mice, Rats | ↓Mitochondrial lipid peroxidation and swelling | - | [94,95]|
| Bafilomycin A1, rapamycin | H9c2, mice | ↑Autophagy                              | ↔                 | [96]  |
| Diazoxide        | Rats, mice | ↑Mitochondrial K<sub>ATP</sub> channel | -                 | [97–99]|
| Dxz              | NRC, Mice, Rats, Rats | ↓Mitochondrial iron accumulation | ↔ | [11,100,101]|
| Met              | Mice, rats, HL-1 | ↑Mitochondrial function                | ↑                 | [102–104]|
| Nicorandil       | Rats, HL-1 | ↓Mitochondrial apoptotic pathway       | ↔                 | [105–107]|
| Sildenafil        | Mice, mouse cardiomyocytes | ↑Mitochondrial K<sub>ATP</sub> channel | ↓Disruption of ∆Ψm | ↑ | [108–110]|

↑, increase or open; ↓, decrease or inhibit; ↔, no difference; -, no description; ∆Ψm, mitochondrial membrane potential; NRC, Neonatal rat cardiomyocytes.
2.1. Natural Products

2.1.1. Plant-Derived Small Molecules

Arjunolic acid: Arjunolic acid (AA, 2,3,23-trihydroxyolean-12-en-28-oic acid) is a naturally occurring triterpenoid saponin with various biological functions, including antioxidant [111], hepatoprotective [112], and antifungal properties [113]. The effect of AA on Dox-induced cardiac abnormalities in a rat model and an oxidative stress model was investigated, and the results showed that AA treatment attenuated Dox-induced apoptosis in heart tissue, and could block Dox-induced disrupted MMP (mitogen-activated protein kinase), mitochondria-mediated caspase-dependent apoptosis, and enhanced cell injury in cardiomyocytes [24].

Baicalein: Baicalein (5,6,7-trihydroxy-2-phenyl-4H-1-benzopyran-4-one) is a natural flavonoid derived from Scutellariae radix. Due to its antioxidant potential, in vitro models demonstrated that it could protect cardiomyocytes against ischemia–reperfusion, lysophosphatidylcholine and oxidative stress-induced cell injury [25,26,28]. Another study by Chang et al. indicated that baicalein could attenuate Dox-induced cardiotoxicity not only by attenuation of mitochondrial oxidant injury, but also by suppression of c-Jun NH2-terminal kinase (JNK) activation. Interestingly, treatment of baicalein did not compromise its anticancer efficacy [27].

Berberine: Berberine (Ber) is an isoquinoline alkaloid with various biological effects, including anti-tumor and cardiovascular protection [114]. Ber inhibits Dox-induced cardiomyocyte apoptosis by reducing mitochondrial dysfunction and increasing bcl-2 expression [30,34]. Ber significantly reduces mitochondrial Ca\(^{2+}\) overload, increases myocardial energy metabolism, and inhibits Dox-induced acute changes in myocardial calcium homeostasis [29]. In addition, Ber can also inhibit the metabolism of Dox into doxorubicinol (a secondary alcohol metabolite) and exert its cardioprotective effect [31]. Doxorubicinol is stable in the heart and accumulates there to produce a long-lasting poison [33]. Studies have shown that combined Ber with Dox treatment can significantly inhibit cancer cell proliferation [32].

Curcumin: Curcumin, a yellow pigment, is a major component of turmeric. It is reported that turmeric may control Dox-mediated cardiotoxicity and decrease oncogenesis [115]. Several studies have shown that curcumin could protect against Dox-induced cardiotoxicity. The key mechanisms postulated for the cardioprotective activity of curcumin include induction of apoptosis, JNK activation, abrogation of inflammation, and excessive opening of mitochondrial permeability transition pores [35–40]. Therefore, pre-treatment with curcumin could be considered in cancer chemotherapeutic applications.

Cryptotanshinone: Cryptotanshinone (CRY) is one of the major constituents of Salvia miltiorrhiza, which has been widely used to treat various diseases such as myocardial infarction, angina pectoris, and ischemic stroke [116]. In adult male Wistar rats, the administering of CRY could prevent doxorubicin-induced cardiotoxicity by increasing mitochondrial biogenesis and enhancing the activities of the mitochondrial respiratory chain complex [41].

Chrysin: Chrysin, a flavone, is present in honey, mushrooms, and bee propolis [117]. Traditionally, chrysin is used to enhance testosterone concentration. Healthy human volunteers consumed daily doses of up to 2–3 g without side effects [118]. A recent study in rats demonstrated that chrysin could effectively protect against Dox-induced cardiomyopathy. The mechanism appeared to involve suppressing oxidative stress, the mitochondrial apoptotic pathway, MAPK (mitogen-activated protein kinase), and NF-κB (nuclear factor kappa-B) pathways [42].

Cyclovirobuxine D (CVB-D) is a triterpene alkaloid extracted from a traditional Chinese herb, cloves. A study in rats demonstrated that CVB-D has a certain therapeutic effect on heart failure induced by myocardial infarction [119]. CVB-D could ameliorate Dox-induced cardiomyopathy in mice by inhibiting Dox-induced mitochondrial cytochrome c release and mitochondrial biosynthesis damage [43].
Cannabidiol: Cannabidiol (CBD) is a non-psychotropic cannabinoid that has strong antioxidant and anti-inflammatory effects [120]. Studies in experimental models showed it could protect against Dox-induced heart damage [121]. In rat model experiments, CBD may reduce the infarct size of the ischemia–reperfusion model by reducing the inflammatory response [44]. CBD prevented Dox-induced cardiomyopathy/heart failure in mice by reducing oxidative stress and mitochondrial dysfunction and promoting mitochondrial biogenesis [13].

Esculetin: Esculetin is a natural phenolic in Cortex fraxini. It is known to have multiple functions including anticancer and neuroprotective activity [122,123]. Recently, an in vitro study found that esculetin could prevent against Dox-induced cardiotoxicity; the mechanism of the effect is involved in the enhanced Bmi-1 expression, suppression of ROS accumulation and mitochondrial damage, and subsequently reducing Dox-induced cell apoptosis [45].

Honokiol: Honokiol (HKL), a polyphenol derived from the magnolia tree, protected against Dox-induced cardiac hypertrophy in mice through enhancing mitochondrial function by activating Sirt3 without compromising the anti-tumor activity of Dox [46]. A line of evidence showed that HKL attenuated Dox-induced cardiotoxicity by increasing mitochondrial protein acetylation as well as activating PPARγ in a mouse heart [47].

Hydroxytyrosol: Hydroxytyrosol (HT) is a polyphenol composition of leaf oil with a wide variety of beneficial effects on human health, especially its protection against cardiovascular diseases, cancer, and metabolic disorders [124,125]. The protective effects of HT against Dox-induced cardiotoxicity have been investigated in rats. The results demonstrated that HT could effectively ameliorate Dox-induced heart damage by improving the mitochondrial electron transport chain and oxidative damage [48].

Isorhamnetin: Isorhamnetin is a naturally occurring flavonoid and can reduce Dox-induced oxidative stress and inhibit the activation of mitochondrial apoptotic pathway and MAPK pathway. It is worth noting that isorhamnetin attenuated cardiac damage without compromising the anticancer efficacy in vivo. Isorhamnetin also improves the anticancer activity of Dox in MCF-7, HepG2, and Hep2 cells [49].

Kaempferol: Kaempferol is a polyphenolic compound widely found in food from plants. It has anti-inflammatory [126], antioxidative [127], and anticancer effects [128]. Studies have shown that Kaempferol may participate in the ERK (extracellular signal-regulated kinase)-dependent MAPK pathway to reduce Dox-induced cardiac toxicity by inhibiting p53-mediated mitochondrial-dependent intrinsic apoptotic signaling [51]. A recent study showed that Kaempferol combined with Dox or cisplatin has a strong synergistic therapeutic effect on HCT-15 and MDA-MB-231 cells [50].

Luteolin-7-O-Glucoside: Luteolin-7-O-Glucoside (LUTG) is a flavonoid isolated from the whole plant of Aspergillus flavus and has a protective effect against Dox-induced cardiotoxicity [129]. A study by Yao et al. demonstrated that LUTG reversed mitochondrial depolarization and decreased apoptosis in H9C2 cells [52]. It was reported that luteolin has a biphasic effect on the survival rate of the human breast cancer cell line MCF-7. That is, luteolin displayed a cell proliferative effect at low concentrations (10 µM), but a cytotoxic effect at high concentrations (above 30 µM) [53].

Myricitrin: Myricitrin, a natural flavonoglycoside, has displayed multiple beneficial biological activities including anti-allergic effects and anxiolytic action [130,131]. In vitro and in vivo studies have demonstrated that myricitrin could significantly attenuate Dox-induced cardiotoxicity. The underlying mechanism is involved in the antioxidant activity and its inhibition of mitochondria-dependent apoptotic signaling [54].

Naringin: Naringin (4′,5,7-trihydroxyflavanone-7-rhamnoglucoside) is present in grapefruit juice and has metal chelating and antioxidant properties [132]. Naringin was effective at reducing the oxidative stress induced by Dox in the liver of mice [133]. In vivo and in vitro studies have demonstrated that Naringin provided mitochondrial protection by inhibiting MAPK expression and ROS generation, without compromising its antineoplastic activity [55,56].

Oxymatrine: Oxymatrine (OMT) is an active ingredient of the traditional Chinese herb Sophora flavescens. OMT has a protective effect on aldosterone-mediated injuries by inhibiting apoptosis-inducing factor signaling pathways and calpain [134]. In vivo and in vitro studies have
shown that OMT reduced oxidative stress, leading to decreased cardiac apoptosis and subsequent changes to myocardial architecture [57]. OMT has a pro-apoptotic effect in human breast cancer MCF-7 cells [58]; further study is needed to determine whether the combination of OMT and Dox interferes with its anti-tumor activity.

Ophiopogonin D: Ophiopogonin D (OP-D), an active component of Ophiopogon japonicas, has been reported to confer protecting endothelial cells from oxidative stress-induced cell injury [135]. Recently, in vitro and mice model studies demonstrated that OP-D exerted a cardioprotective effect against Dox-induced autophagic cell death by relieving ROS-induced mitochondrial impairment [59].

Plantainoside D: Plantainoside D (PD) is an active component isolated from the plant Picrorhiza scrophulariiflora with potential anti-hypertensive function [134]. A recent study by Kim et al. demonstrated that PD could also protect Dox-induced apoptosis in H9c2 cardiomyoblast cells. The mechanism of the protective effect can be explained by the inhibition of ROS production and NF-κB activation [60].

Quercetin: Quercetin is a polyphenolic flavonoid present in many fruits, vegetables, and grains with a wide variety of health benefits, including its pharmacological ability to lower blood pressure [136] and protect the brain, heart, and liver against various factors related to oxidative stress [61–63]. An in vitro and in vivo study showed that quercetin could effectively inhibit Dox-induced cardiotoxicity and mitochondrial dysfunction by upregulation of Bmi-1 expression [64].

Resveratrol: Resveratrol (RV) is present in a variety of food skins including grapes, mulberries, and blueberries. The experimental model in H9c2 cells demonstrated that it could prevent Dox-induced cardiotoxicity via inhibition of cell injury, mitochondrial stabilization, specifically the activation of the Sirt1 pathway [65,67]. Furthermore, RV enhanced cardiac function and prevented oxidant stress responses in rats [66].

Rosmarinic acid: Rosmarinic acid (RA) is a water-soluble natural phenolic compound that is isolated from the rosemary plant and has a high content in the Labiatae and the Boraginaceae families. RA could ameliorate cardio-nephrotoxicity induced by Dox in rats through their anti-inflammatory, antioxidant, and anti-apoptotic activities [68]. It was also found to exhibit inhibitory effects on Dox-induced apoptosis in H9c2 cardiomyocytes by inhibiting the activations of ROS, JNK and extracellular signal-regulated kinases [69].

Sesamin: Sesamin (Ses) is one of the main active ingredients in sesame seeds and has multiple pharmacological functions, including hepatoprotection, cholesterol-lowering, and cardiovascular protective properties [137–139]. The pre-clinical evidence demonstrated that Ses could also protect cardiac tissue and H9c2 cells against Dox-induced cardiac injury. The major underlying mechanism of this effect is contributed to Sirt1 activation [70].

Sulforaphane: Sulforaphane, a natural compound present in cruciferous vegetables, is a potent Nrf2 inducer. The study in mice demonstrated that sulforaphane treatment significantly enhanced the activity of the mitochondrial respiratory complex and exhibited protective effects against Dox-induced cardiotoxicity [71]. Additionally, a recent study in rats and neonatal rat cardiomyocytes demonstrated that sulforaphane could not only protect the heart against Dox-induced toxicity via protection of mitochondrial function and integrity, but also synergistically exhibited an anti-tumor effect with Dox [72].

Salvianolic acid A: Salvia miltiorrhiza is widely used in the treatment of cardiovascular diseases in China. Salvianolic acid A (SAI) is the main bioactive component of Salvia miltiorrhiza. In addition, the antioxidant effect of SAI suggests that it protects the heart through blocking oxidative stress [74]. Several studies have indicated that SAI can inhibit Dox-induced myocardial mitochondrial lipid peroxidation, while it has no antagonizing effect on the anti-tumor activity of Dox [73].

Tetrandrine: Tetrandrine is an alkaloid derivative isolated from the roots of the Stephania tetrandra plant. The experimental study in a rat model found that tetrandrine has protective potential in Dox-induced cardiotoxicity. The underlying mechanisms of the effect were involved in the protective effects against Dox-induced impairment of mitochondrial oxidative phosphorylation and oxidative phosphorylation [75].
2,3,5,4′-tetrahydroxystilbene-2-O-β-D-glucoside (THSG), one of the active ingredients of the traditional anti-aging drug Polygonum multiflorum, has strong antioxidant [140] and anti-inflammatory effects [141]. Experimental studies have demonstrated that THSG protects Dox-induced cardiotoxicity by reducing ROS production and intracellular Ca^{2+}, inhibiting apoptotic pathways, reducing mitochondrial membrane potential rapid depolarization and dysfunction [77]. Previous reports have demonstrated that THSG inhibits DNA synthesis and lung metastasis in tumor cells [76].

Visnagin: Visnagin naturally occurs in a kind of flowering plant, Ammi visnaga, which has been used as a herbal medicine to treat kidney stones [142]. Visnagin could protect Dox-induced cardiac dysfunction in zebrafish and mice without reducing the chemotherapeutic efficacy of Dox in vitro. The further mechanism study demonstrated that the inhibition of mitochondrial malate dehydrogenase (MDH2) is responsible for the cardioprotection of visnagin [78]. Interestingly, an editorial suggested that further exploration is warranted to develop protective agents against Dox cardiotoxicity in the clinic [79].

2.1.2. Others

α-Linolenic acid: α-Linolenic acid (ALA) is an essential dietary fatty acid that cannot be synthesized by the body itself [143]. ALA could inhibit oxidative stress and reduce the damage of acute myocardial ischemia–reperfusion injury in the heart [144]. An in vivo study showed that ALA could protect the heart against Dox-induced cardiotoxicity by regulating mitochondrial apoptosis pathways and inhibiting oxidative stress [81]. Compared with free Dox, Dox conjugate ALA showed a good anti-tumor effect and low toxicity in terms of longevity, inhibition of tumor growth, and body weight changes [80].

All-trans retinoic acid: All-trans retinoic acid (ATRA) is one of the major bioactive products of vitamin A metabolism. ATRA is a differentiation agent of cancer stem cells [145]. The combination of ATRA, low molecular weight heparin, and Dox exerts a stronger anti-tumor effect and significantly reduces side effects [146]. A study found that ATRA could protect against Dox-induced cardiotoxicity in H9c2 cells and primary cardiomyocytes by activating the ERK2 signaling pathway and restoring mitochondrial function [82]. A recent study in rats demonstrated that ATRA could also ameliorate Dox-induced cardiotoxicity. The mechanism of the protective effect can be explained by antioxidative and anti-inflammatory properties [83].

BAY60-2770: BAY 60-2770, a soluble guanylyl cyclase (SGC) activator, has been shown to ameliorate the impairment of urethral relaxation in obese mice [147]. An in vivo and in vitro study demonstrated that BAY 60-2270 has a chemosensitization effect on cancer and the potential to decrease Dox anti-tumor resistance [84]. BAY 60-2270 reduces Dox-induced mitochondrial membrane potential loss by upregulating mitochondrial ferritin expression [85].

Ghrelin: Ghrelin is a multifaceted gut hormone mostly produced by the stomach. In addition to its function in mediating energy homeostasis, ghrelin also has a powerful cardioprotective effect [148], and was shown to regulate the secretion of insulin [149]. Ghrelin and Des-acyl ghrelin have protective effects against chemotherapy-induced cardiotoxicity [88]. The principal finding of the studies was that ghrelin maintains mitochondrial shapes, reduces autophagic vacuoles [87], and can prevent mitochondrial bioenergetic dysfunction and reduce mitochondrial pathways of apoptosis [86].

Melatonin: Melatonin, a natural endocrine hormone, is non-toxic and is both a sedative and a cardioprotective agent [150]. Melatonin prevents the mitochondrial damage induced by Dox in mouse fibroblasts, while melatonin co-treatment with Dox increased the PPAR-gamma and AMPK levels. Melatonin could protect cardiomyocytes against Dox’s cytotoxicity by increasing cell proliferation and inhibiting apoptosis [90]. In addition, we have demonstrated that melatonin inhibits mitochondrial ROS production and preserves mitochondrial membrane potential during Dox-induced cardiotoxicity [89].

2.2. Semisynthetic Small Molecules

D006: D006 is a new danshensu (DSS) derivative, derived from coupling the structures of DSS, TMP (tetramethylpyrurizine), and ACS (4-(3-thioxo-3H-1, 2-dithiol-4-yl)-benzoic acid). Recently,
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an in vivo and in vitro study showed that Do06 has cardioprotective effects against Dox-induced cardiotoxicity. The mechanism may be mediated by the promotion of HO-1 protein expression and the preservation of mitochondrial biogenesis. Do06 also enhanced Dox-induced breast cancer cell apoptosis through p53 activation [91].

Mitochondrial division inhibitor: Mitochondrial division inhibitor (Mdivi-1) is a derivative of quinazolinone. It was identified as the most efficacious inhibitor during chemical screening of mitochondrial division inhibitors; it selectively inhibits the Dynamin-related protein 1 (Drp1 is required for mitochondrial division) [151]. Mdivi-1 inhibited mitochondrial fission and played an important role in ameliorating heart failure [93]. A study by Gharanei et al. demonstrated that Mdivi-1 reversed Dox-induced depolarization of cardiac myocytes and reduced myocardial infarct size without affecting its anticancer properties [92].

Sodium tanshinone IIA sulphonate (STS): STS, a water-soluble derivative of tanshinone IIA, has anti-inflammatory [152] and protective effects on myocardial ischemia [153]. In vitro and in vivo experimental data demonstrated that STS acts as a protective agent against Dox-induced cardiotoxicity [154]. STS has been shown to reduce cardiotoxicity by attenuating Dox-induced mitochondrial lipid peroxidation and swelling [94,95].

2.3. Synthetic Compounds

Bafilomycin A1, rapamycin: Bafilomycin A1 and rapamycin are traditional autophagy inducers. Recent studies have shown that macroautophagy is involved in Dox-induced cardiotoxicity [155]. The study indicated that Bafilomycin A1 and rapamycin attenuate the cardiotoxic effects of Dox in H9c2 cells as well as in a breast tumor-bearing mouse model. The result indicated that Bafilomycin A1 or rapamycin could effectively reduce the total production of mitochondrial ROS, increase mitochondrial function, and resist Dox-induced toxicity [96].

Diazoxide: Diazoxide, a molecular formula of C₈H₇ClN₂O₂S, has powerful protective properties against cardiac ischemia [156]. An in vivo study demonstrated that diazoxide protects against Dox-induced cardiotoxicity through open mitochondrial K⁺ ATP channels [97,98]. Recently, the cardioprotective effects of diazoxide against Dox-induced cardiotoxicity were further confirmed by enhancing the expression of mitochondrial connexin 43 [99].

Dexrazoxane (Dxz): Dxz, is the only drug approved by the FDA to prevent Dox-induced cardiotoxicity. Dxz significantly reduces Dox-induced cardiotoxicity in pediatric solid tumor patients [157]. Dxz limits heart damage by chelating free iron, and reduces mitochondrial iron levels [11]. The results from an animal study indicated that Dxz can ameliorate Dox-induced cardiac injury by protecting myocardial mitochondria from genetic and functional impairment [100,101].

Metformin (Met): Met is an effective and safe oral drug for the treatment of type II diabetes. A study indicated that Met supplementation could attenuate the conduction abnormalities and mechanical dysfunction caused by Dox in rats [158]. Met plays an important role in cardiomyocytes by regulating the expression of transcription factor NF-κB, thereby protecting cardiomyocytes against Dox-induced oxidative stress and apoptosis [102]. Recently, Elashmawy et al. showed that Met combined with Dox has a marked anti-tumorigenic effect [103]. A recent study in human breast carcinoma (MCF7/ADR) cells suggested that Met can be used for the treatment of chemotherapy-resistant tumors, and can restore the sensitivity of Dox [104].

Nicorandil: Nicorandil, a mitochondrial K⁺ ATP channel opener and nitric oxide donor, has been administered to successfully counteract the toxic effects of Dox [159]. Nicorandil was effective in ameliorating Dox-induced heart failure in rats [105]. The underlying mechanism is the activation of the mitochondrial ATP-sensitive K⁺ channel, causing mitochondrial depolarization, inhibition of mitochondrial NADPH oxidase, and mitochondrial ultrastructural changes [106,107].

Sildenafil: Sildenafil is a PDE-5 inhibitor that can reduce Dox-induced apoptosis, depletion of pro-survival proteins such as bcl-2, and dissipation of mitochondrial membrane potential (∆Ψm) [108]. In addition, sildenafil increased eNOS/NOS in the heart and opened the mitochondrial K⁺ ATP
channels, thereby improving the cardiac contractile function that was impaired by Dox [109]. Interestingly, the combination of Dox and sildenafil can enhance the anti-tumor activity of Dox [110]. The molecular mechanisms underlying the different responses of the combined treatment to application of cardiomyocytes and tumor cells remain unclear. Undoubtedly, it would be an interesting issue that is worth investigating in the future.

3. Conclusions and Future Directions

In recent years, the mitochondria-related mechanisms of chemotherapeutic drug-induced cardiotoxicity have been extensively studied, and Dox is one of them [160]. Accumulated evidence shows that small molecules in pre-clinical and clinical studies have proven to be effective in preventing this toxicity. However, most of the experiments have not been translated into clinical trials in humans, which are required to provide explicit information about the efficacy of these small molecules.

Aside from the protective efficacy of small molecules against Dox-induced cardiotoxicity, it is significant to ensure that the anticancer effects of Dox are not minimized by a combined use of small molecules. This question has been addressed in a number of studies, and we can conclude from Table 1 that baikalein, visnagin, Mdivi-1, bafilomycin A1, Dxz, and nicorandil did not influence the anti-tumor activity of Dox. Interestingly, berberine, isorhamnetin, kaempferol, sulforaphane, tetrandrine, THSG, ATRA, melatonin, D006, Met, and sildenafil not only attenuated cardiotoxicity, but also potentiated anti-tumor activity in various models.

Here, we summarized the potential small molecules that can be used to limit the cardiotoxic effect of Dox. We have found that the potential utilities of small molecules targeting mitochondria deserve further studies in order to develop them into potential therapeutic agents for protecting thousands of cancer patients against Dox-induced cardiotoxicity while undergoing chemotherapy. Small molecules play a key role in maintaining mitochondrial stability from different aspects. (Figure 1).

Understanding the effects and the underlying mechanisms of the combined utilization will help guide future efforts in developing agent modulators against Dox-associated cardiotoxicity. In the future, mitochondrial directed therapies involving small molecules will open up novel avenues for the management of mitochondrial function, providing protection from Dox-related cardiotoxicity.

![Figure 1](image-url). This image shows that establishing mitochondrial stability by small molecules is a critical step of potential therapeutic mechanisms in Dox-induced cardiotoxicity.
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