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REVIEW ARTICLE

Today's Breast Cancer Survivors Are Tomorrow's Cardiac Sufferers: A Narrative Review Implementing Resveratrol Against Doxorubicin-Induced Cardiotoxicity

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ABSTRACT

Background: Breast cancer (BC) is the most frequently diagnosed malignancy and a leading cause of mortality among females worldwide. Despite the prodigious advances of chemotherapeutic agents advocated for BC, however, a substantial coincident complication, particularly cardiotoxicity, is inevitably encountered and appears as devastating as cancer itself. It remains a conundrum that has not yet been solved. On this ground, "today's breast cancer survivors might be tomorrow's cardiac sufferers".

In this narrative review, we are spotting light on doxorubicin (DOX)-induced cardiotoxicity and cropping up a snapshot on the polyphenolic resveratrol supplement as a promising prophylactic approach. DOX is highly effective in managing BC by virtue of its cytotoxic, oxidant, pro-inflammatory, and pro-apoptotic effects. However, its clinical applicability has been curbed by its associated dose-dependent cardiotoxicity. This complication is a pressing argument and a highly challenging issue to be tackled.

Nowadays, natural polyphenolic compounds conquer the field of cardio-oncology for the sake of their profound health benefits. Resveratrol, one of the most prevailing polyphenols, is merited to be discussed since it was renowned for its antioxidant, anti-inflammatory, and anti-apoptotic properties. These attributes have conferred it a promising cardioprotective effect that overlooked to date in various in vitro, in vivo, and clinical trial studies.

Conclusion: Early detection and monitoring of DOX-induced cardiotoxicity is of great worth and incorporating resveratrol supplement as a cardioprotective DOX adjuvant must gain much concern as a novel insight and a hopeful avenue to mitigate bad sequel of cardiotoxicity in DOX-treated BC patients and even survivors.

Key words: Breast cancer, Doxorubicin, Cardiotoxicity, Resveratrol, Mitochondrial biogenesis

INTRODUCTION

Breast cancer (BC) is the most common malignancy among women and the second frequently occurring cancer worldwide. It is one of the leading causes of cancer mortality. There is a big challenge in the management of the female BC due to the heterogeneity of this tumor. The current treatment involves either systemic treatment options (chemotherapy, hormonal agents, immunotherapy, targeted therapy) and/or local options (surgery and radiation) **[1]**.

It is well known that a combined chemotherapy of doxorubicin (Adriamycin) and Cyclophosphamide (AC) has long been considered one of the most effective and potent cytotoxic regimens for the treatment of BC ever invented so far. This regimen is often used either as a part of neoadjuvant (pre-surgical) or adjuvant (post-surgical) chemotherapy protocols, particularly for high-risk or aggressive forms of BC, including the triple-

negative BC (TNBC) **[2]**.

Doxorubicin (DOX) (trade name; Adriamycin®, Rubex®) is a metabolite of the chemically mutated strain of the aerobic bacterium ―Streptomyces peucetius var. Caesius‖. While cyclophosphamide (trade name; Endoxan®, Cytoxan®) belongs to a class of cytotoxic drugs called alkylating agents **[3]**.

Despite the fact that DOX is a well-known highly effective cytotoxic drug for treating BC, nevertheless, it is a double-edged sword where it affects the normal neighboring non-cancerous cells and thereby insults healthy tissues with inevitable vast side effects. One of the major side effects of DOX is its dose-dependent, and long-term cumulative cardiotoxicity during the treatment course and even many years after its cessation in the BC survivors **[4]**.

Notably, little pharmaceutical adjuvant drugs including mercaptopropionyl glycine (MPG), superoxide dismutase, blockers of calcium channel, beta-adrenergic, and angiotensin receptors, and Phosphodiesterase 5 Inhibitors (PDE5 inhibitors) have been discussed in the previous literature for their potential role in alleviating DOX-induced cardiotoxicity. Unfortunately, the aforementioned-synthetic drugs have several deleterious side effects, expensive and non-specific **[4]**.

In that regard, this review was settled down to spot a light on resveratrol which is a natural non-flavonoid polyphenol phytochemical found abundantly in several plants that is being well tolerated, cost effective, and of high therapeutic efficacy with almost null side effects **[5]**.

Cragg and Pezzuto [6] have shown that concomitant administration of natural products with cytotoxic chemotherapeutic agents can play a synergistic role in alleviating this chemotherapy-coupled adverse effects and enhancing their therapeutic efficacy.

Therefore, in this review we attempt to inform the cardio-oncology field about the adjuvant role of concurrent administration of resveratrol in conjunction with the AC protocol as a proposed novel approach to protect the myocardium at the early asymptomatic stage in BC female patients. We hope this work directing the future research realm toward the knowledge gap of lacking large-scale clinical trials of resveratrol supplementation in BC patients treated with DOX.

1. Cardio-oncology “a new emerging multi-disciplinary field”

Considering the growing scientific focus on chemotherapy-induced cardiotoxicity, the development of a field dedicated to the effect of chemotherapeutic agents on cardiovascular is crucial for the early detection, monitoring, and mitigation of cardiovascular comorbidities resulting from the remarkable efficacy of the potent chemotherapeutic agent specially "DOX" in BC patients **[7]**. DOX is causally associated with diverse cardiovascular toxicities, which has evolved as a significant hallmark of morbidity/ mortality among cancer patients. The insult of the heart may occur during or after DOX treatment that manifested as heart failure, coronary heart disease, pericarditis, arrhythmias, valvular affection, and fibrosis of the myocardium **[4]**.

Therefore, evolution of the cardio-oncology field constitutes a major paradigm shifts within the research realm. It has the potential to further improve awareness of DOX-induced cardiotoxicity, as well as the pursuit of finding prophylactic regimens that mitigate this toxicity.

2. Breast Cancer “the most prevalent female malignancy”

2.1. Incidence of BC

Female BC has the highest incidence rates globally. It corresponds to 23.8% of all women cancers and accounts for 1 in every 4 cancer cases followed by lung cancer **[8]**. The American Cancer Society 2023 (ACS, 2023) has reported that there is a roughly 3 million cases of female BC in the world in 2023 **[9]**. In 2024, around 310,720 new cases of invasive BC and 56,500 cases of ductal carcinoma in situ (DCIS) are expected to be diagnosed in women in the United States, with 42,250 women dying from BC **[10]**. It is estimated that by 2040 there will be ~35% rise of female BC incidence, which reveals a nearly 2.3 million

new cases diagnosed annually **[11]**.

2.2. Therapeutic strategies of BC

There are myriads of treatment modalities and wide range of treatment options for female BC, but the essential aspect of BC management involves the utilization of systemic regimen therapies that include chemotherapy, hormonal agents, targeted therapy, and immunotherapy **[1]**. Chemotherapy is a well-known systemic cytotoxic treatment for BC that can be administered as either neoadjuvant or adjuvant therapy, depending on the specific characteristics of the tumor. Neoadjuvant chemotherapy is employed for locally advanced, inflammatory, and large BC to reduce their size before breast-conserving surgery (BCS). It is also used for smaller tumors with molecular subtypes that have poor prognosis. In contrast, adjuvant chemotherapy aims to target any remaining BC cells after surgery, as well as micro metastatic cells that may have spread beyond the breast and regional lymph nodes but have not yet identified as detectable distant metastases **[2]**. A variety of chemotherapeutic drugs are commonly used in the treatment of female BC, depending on the molecular subtypes. These include cyclophosphamide, 5-fluorouracil/capecitabine, taxanes (such as paclitaxel and docetaxel), anthracyclines (such as doxorubicin and epirubicin), and carboplatin **[12]**.

3. Doxorubicin is a frontline therapy of BC

DOX was approved as a therapeutic drug in US in 1974, and since then, it has been regarded as a first-line treatment for BC, due to its broad-spectrum cytotoxic effect on rapidly dividing cells. DOX belongs to the anthracycline antibiotic family that considered a mainstay cytotoxic chemotherapy for medical treatment of early or invasive BC including triple negative BC (TNBC) in which cells lack estrogen or progesterone receptors (ER or PR respectively), and also do not make any or too much of the HER2 protein. TNBC is regarded as the most aggressive type of invasive BC, with a worse prognosis, fewer treatment options, and cancer cells that proliferate and spread more quickly **[13]**, **[14]**.

3.1. Pharmacokinetics of DOX

DOX is usually known as “The Red Devil” because it is available in the form of a distinctive clear bright red color liquid. It is a water-soluble drug that is administered intravenously in a 21-day interval regimen. Typically, DOX is administered at a dose of 60 mg/m² for four cycles **[15]** with a slow infusion over 60 minutes recommended to minimize the risk of the two different types of infusion reactions either non-immune-mediated such as cytokine-release syndrome that characterized by fever, tachypnea, tachycardia, headache hypotension, rash, and/or hypoxia or immune-mediated like anaphylactic reactions which manifested as breathing difficulties, dizziness, hypotension, cyanosis, and loss of consciousness that usually occur during or within minutes to hours after rapid drug infusion **[16]**.

DOX is metabolized in the liver, yielding three metabolites. The primary active metabolite is Doxorubicinol (DOX-OL) that contributes to the antineoplastic activity of DOX. The second metabolite is DOX aglycone (DOX-AG) and the third one is the 7-Deoxydoxorubicinol aglycone that has a minimal antitumor activity but implicated in DOX toxicity via intercalating into the mitochondrial membrane lead to superoxide radical formation. Finally, 4–5% of DOX and its metabolites are eliminated by the urine, while the bulk are eliminated through the bile in their unaltered form **[17]**.

3.2. Pharmacodynamics and antineoplastic effects of DOX

Emerging evidence suggests that DOX has pleiotropic anticancer properties, including its capability to intercalate inside DNA base pairs resulting in breakage of DNA strands and inhibition of transcription and replication of both DNA and RNA. This prevents the host's cancer cells from proliferating **[17]**.

By creating Topo II-DNA complexes, DOX could inhibit the activity of the Topo II enzyme in its catalytic step. This enzyme is responsible for chromosome condensation, decatenation of intertwined DNA strands, and relaxation of tension in the DNA strand; as a result, its inhibition stops the DNA double helix from re-ligating and re-sealing, which stops the replication of rapidly dividing cancer cells **[18]**.

Another antitumor mechanism of DOX includes free radical-mediated oxidative damage to mitochondrial DNA of cancer cells since DOX binds specifically to cardiolipin which is a phospholipid on the inner mitochondrial membrane serves for maintaining the structure and function of the electron transport chain (ETC). The binding of DOX to cardiolipin inhibits complex I and II of the ETC, leading to energy depletion within cancer cells beside increased reactive oxygen species (ROS) generation **[19]**.

Moreover, DOX acts as an iron chelator, binding to iron in the tissues to form a DOX- iron complex. This complex plays a significant role in generating ROS, particularly through the Fenton reaction in which the intracellular hydrogen peroxide (H_2O_2) and superoxide anion (O_2^-) is converted into hydroxyl radicals (OH•) and hydroxyl anions (OH^-) in the presence of ferrous ions **[20]**.

Therefore, the DOX-iron complex engaged in the Fenton reaction results in the formation of highly reactive hydroxyl radicals that can induce oxidative damage to lipids, proteins and DNA, which plays a role in both the antitumor effectiveness of DOX and its cardiotoxicity **[21]**.

4. Today's breast cancer survivors are tomorrow's cardiac sufferers

Notably, DOX-based chemotherapy shows a remarkable increase in the survival rates of treated cancer patients, which is unfortunately overshadowed by its negative impact on cardiac structure and function in those patients and even survivors **[4]**. The risk of cardiac toxicity from this chemotherapy drug exceeds the likelihood of tumor recurrence, with a tenfold higher incidence of cardiovascular disease (CVD) and a fifteen fold increased rate of heart failure compared to the general population. There are several reasons that make the heart a particularly susceptible organ to DOX-induced toxicity. First, the heart has low levels of antioxidant defenses against DOX generated ROS when compared with other tissues. Second, DOX concentration within mitochondria is about 100 times greater than its concentration in the plasma, and unfortunately heart cells contain a higher density of mitochondria per unit volume compared to most other organs. This makes the heart a site of DOX -redox reactivity **[22]**.

4.1. Clinical picture of DOX-induced cardiotoxicity

Acute DOX-induced cardiotoxicity presents as reversible myopericarditis, left ventricular dysfunction, cardiomyopathy, or arrhythmias. Arrhythmias related to doxorubicin occur in up to 26% of patients receiving the treatment and may include sinus tachycardia, premature atrial and ventricular contractions, and supraventricular tachycardia. Importantly, the cumulative dose of anthracyclines is the primary risk factor for the development of cardiotoxicity. It was found that the DOX subclinical cardiotoxicity developed at a cumulative dose of less than 300 mg/m2 **[23]**.

Whilst chronic DOX-cardiotoxicity is irreversible and potentially lethal in ~50% of DOX-treated patients. It is a dose-dependent and can lead to congestive heart failure (CHF) in >4% of the patients receiving cumulative doses of 500-550 mg/m2, in >18% of the patients receiving cumulative doses of 551-600 mg/m2 and in ~36% of the patients receiving higher cumulative doses than 601 mg/m2 **[24]**.

Accumulating evidence indicates that subclinical alterations in left ventricular structure and function can occur even at lower doses of doxorubicin (< 200–300 mg/m²). As a result, it is believed that no dose of doxorubicin is entirely safe **[25]**.

4.2. Molecular mechanisms of DOX-induced cardiotoxicity

Several molecular mechanisms have been postulated for DOX-induced cardiotoxicity **(Fig 1)**. The most documented mechanism is primarily linked to oxidative stress in cardiac tissue as DOX-evoked generation of ROS and lipid peroxidation could damage the cardiomyocytes. By the capability of DOX to inhibit the DNA topoisomerase 2-β (Top 2β) enzyme, it could damage not only the DNA of cancer cells but also the DNA of the myocardium. It also could reduce the antioxidant enzyme gene transcription and impede the mitochondrial biogenesis by activating cell death pathways **[17]**.

Additionally, DOX reduces the activity of the DNA methyltransferase 1 (DNMT1) enzyme, leading to a decrease in DNA methylation. This indirectly causes dysregulation of mitochondrial genes such as peroxisome proliferator-activated receptor coactivator (PGC-1α), nuclear respiratory factor 1 (NRF-1), and mitochondrial transcription factor A (TFAM) in the heart, resulting in significant mitochondrial dysfunction. This mitochondrial dysfunction is considered one of the key mechanisms of DOX-cardiotoxicity **[26]**.

Interestingly, the cationic nature of DOX facilitates its attachment to the mitochondrial membrane of cardiac cells forming an irreversible complex that causes disruption of the mitochondrial ETC where DOX acts as a one-electron acceptor, accepting one electron from NADH at the expense of NADH dehydrogenase (complex I) leading to inhibition of complex I activity. By inhibiting this complex, DOX impairs the flow of electrons to the next ETC complexes and hence the mitochondrial ATP production is compromised, with decreased energy production within the high-energy demands' cardiac cells that contribute to their injury with eventual cardiomyopathy **[27]**.

Furthermore, DOX binds to the endothelial nitric oxide synthase (eNOS) enzyme, leading to the formation of DOX-semiquinone, which subsequently converts oxygen into the superoxide (O2--) radical. Additionally, DOX enhances the transcription and protein expression of inducible nitric oxide synthase (iNOS), promoting the formation of nitrotyrosine (NT) and elevating mitochondrial superoxide levels in cardiac tissue **[28]**.

Moreover, DOX results in calcium dysregulation, as it raises intracellular calcium levels and triggers cardiomyocyte death by activating cellular caspases. Unfortunately, a toxic metabolite of DOX has the ability to inhibit the sodium-calcium exchanger channel on the sarcoplasmic membrane of the cardiac cells that play a unique role in regulating cardiac contractility.

Furthermore, DOX can induce cardiomyopathy through interfering with genes encoding sarcoplasmic reticulum Ca2+-binding proteins that store Ca2+ inside the cardiomyocytes like calsequestrin 1 (CASQ1), calsequestrin 2 (CASQ2) genes **[29]**.

In addition, DOX interferes with Sarco/endoplasmic reticulum Ca2+ATPase 2a (SERCA2a) and SERCA regulators including phospholamban, sarcolipin which impairs the heart's systolic and diastolic functioning **[30]**. DOX also increases the circulating heat shock protein 70 (HSP70) and its expression in the myocardium and additionally promotes its extracellular release in the heart, which is an important trigger in cardiac hypertrophy, fibrosis, and are associated with the development of cardiac dysfunction **[31]**.

4.3. Monitoring of cardiac function during and after DOX-based protocol

Baseline and regular cardiac monitoring of BC patients under DOX-based protocol is a mandatory practice. Guidelines recommend frequent echocardiographic monitoring of left ventricular ejection fraction (LVEF) before, during, and after DOX therapy in order to identify early signs of cardiotoxicity **[32]**. A normal LVEF is generally considered to be 55-70% and values lower than this indicates impaired cardiac function. Subclinical DOX-cardiotoxicity was predicted when LVEF decreases more than 10% from the baseline or

the LVEF declines under 55% without symptoms of heart failure **[23]**. Patients with pre-existing decreased LVEF are particularly vulnerable to further reduction in cardiac function when exposed to DOX. Therefore, these patients require close monitoring and may need to be given alternative therapies or adjuvant cardioprotective medications **[32]**.

Also, regular cardiac monitoring using ECG, and plasma cardiac biomarkers are essential to predict early signs of cardiotoxicity. Recently, the use of multi-gated acquisition (MUGA) scan offers a more reproducible and accurate measurements of LVEF, that predict even small changes in cardiac function during treatment with DOX chemotherapy **[33]**.

4.4. Management trials against DOX-induced cardiotoxicity

Diuretics, angiotensin-converting enzyme (ACE) inhibitors, beta-adrenergic blockers, and calcium channel blockers are possible treatments that could maintain diastolic cardiac function in patients receiving DOX, however these drugs do not totally protect or improve this disaster comorbidity **[4]**. Interestingly, Carvedilol has a supreme action in preserving both the diastolic and systolic heart function in the DOX-treated individuals beside its potent antioxidant properties.

Dexrazoxane, an iron chelator has been approved by the Food and Drug Administration (FDA) for the clinical prevention of DOX-induced cardiomyopathy. However, Dexrazoxane is cautiously recommended to be co-administered with DOX, as it has a carcinogenic potential **[34]**.

5. Resveratrol as a promising polyphenolic compound

5.1. History and food sources of resveratrol

In early 1990s, it was noticed that French population have lower incidence of CVDs that accompanied with moderate consumption of red wine despite their high-fat diet, this feature is termed "French Paradox" that mainly attributed to the presence of resveratrol in red wine. Since then, resveratrol has been launched and studied for its pleiotropic activities on human health **[35]**.

Resveratrol (3,5,4-trihydroxy-stilbene) is one of the famous Stilbenes. It is a naturally occurring phytoalexin, a substance that plants produce in reaction to mechanical damage or UV radiation. It was first isolated in 1940 from the white hellebore root extract **[36]**. Resveratrol is a non-flavonoid polyphenol that basically has two phenol rings bonded together by a double styrene bond (C—C double bond) and three hydroxyl groups on the phenolic rings which forms the 3,5,4′-Trihydroxystilbene. Resveratrol has been found in about 70 plants include grapes, peanut, hazel nuts, spruce, lily eucalyptus, blueberries, plums, cherries, blueberry, pistachios, and red wine. The highest concentration of resveratrol is present in the roots of Polygonum cuspidatum, a plant known as "kojo-kon" that is utilized in traditional Chinese and Japanese medicine as an anti-inflammatory and anti-platelet agent **[37]**.

5.2. Pharmacokinetics of resveratrol

Resveratrol is primarily administered orally. Following ingestion, it undergoes immediate digestion and is quickly absorbed in the jejunum that serves as the primary site for its absorption while a smaller portion is absorbed in the ileum. Seventy-five percent of resveratrol is absorbed into circulation through the transepithelial diffusion **[38]**.

Resveratrol pharmacokinetic has shown circadian variation, with higher bioavailability after morning oral administration, it attains its peak plasma levels within the first 30-60 minutes. In the blood stream, resveratrol is transported bounded to plasma proteins and lipoproteins particularly, LDL then enters the liver cells via LDL receptors **[39]**. The liver is the primary site of resveratrol metabolism, in which the hepatic cytochrome P450 enzymes (CYPs) are involved in this process. About twenty metabolites of resveratrol have been found in blood plasma, urine, and tissues of humans. The major metabolites identified in the plasma and urine are resveratrol glucuronides and sulphates that vary in concentration with resveratrol dose. Resveratrol-3-O-sulfate has

been reported as the most abundant circulating resveratrol metabolite in humans in contrast to the resveratrol-3-O-glucuronide which is abundant in rodents **[38]**.

The body uses the glucuronic acid conjugate of resveratrol as a reservoir from which tissue deconjugating enzymes like β-glucuronidase and sulphatase can release active resveratrol locally and increase its effectiveness **[38]**. Resveratrol is eliminated from the body primarily through urine and feces. Interestingly, its dosage form and the matrix in which it is delivered have been shown to influence its excretion time **[38]**.

5.3. Pharmacodynamics and biological activities of resveratrol

5.3.1. Antioxidant activity of resveratrol

The common biological activities of almost all polyphenol compounds like resveratrol are attributed to combat oxidative stress, where they are capable of scavenging free radicals to form more stable molecules. This unique antioxidant activity of polyphenolic compounds is primarily ascribed to their unique structure where they possess many phenolic hydroxyl groups.

Being has 3 hydroxyl groups in its structure, resveratrol was reported to have strong antioxidant activity with powerful free radical scavenging property that scavenges OH and O2- radicals, therefore directly protect the cells against oxidative stress. In addition, resveratrol was proved to reduce lipid peroxidation and prevent DNA damage caused by hydroxide radical **[40]**.

Through the modulation of multiple cellular antioxidant pathways, resveratrol can also function as an indirect inducer of the cellular antioxidant system, balancing cellular redox equilibrium by either enhancing endogenously generated defense molecules or reducing excessive ROS generation **[37]**. Furthermore, resveratrol increased the levels of antioxidant enzymes; catalase (CAT), superoxide dismutase (SOD), glutathione reductase (GR), Nicotinamide adenine dinucleotide phosphate (NADPH) quinone oxidoreductase, and glutathione S transferase enzymes in mice **[41]**.

5.3.2. Anti-inflammatory effect of resveratrol

Resveratrol is found to have anti-inflammatory effect confirmed by invitro and in vivo studies. Invitro, resveratrol controls the inflammatory response by down-regulating NF-κB and preventing mitochondrial dysfunction **[42]**. Similarly, by controlling the anti-inflammatory miRNA, resveratrol in vivo has been shown to suppress carcinogenesis, reduce neutrophil infiltration, and limit TNF-α production and NF-κB activation **[43]**.

On top of that, resveratrol has the capability to block signaling pathways that trigger inflammation via direct inhibition of COX-1 and COX-2 activity or indirectly through inhibition of transcription factors regulating COX activity **[44]**. In addition, many mechanisms of action can illustrate the anti- inflammatory role of resveratrol including its ability to reduce the secretion and expression of inflammatory factors and mediators such as tumor necrosis factor-α, interleukin-1, interleukin-6 serum levels, macrophage inflammatory protein-2, and caspase-3/9 **[42]**. Moreover, the anti-inflammatory activity of resveratrol is also attributed to its ability to block the activation of microglia which releases various pro-inflammatory factors and generates ROS **[45]**.

5.3.3. Anti-glycation activity of resveratrol

Glycation is a non-enzymatic reaction between the human body proteins and reducing sugars, yielding advanced glycation end products (AGEs) that negatively impact the tissues in a number of ways, such as lipid peroxidation, endothelial dysfunction, and protein structural changes. There is mounting evidence that resveratrol revealed antiglycation activity through combating the damaging effect of the AGEs. Therefore, it is recommended to use resveratrol in preventing or treating cancers associated with increased glycation such as BC **[46]**.

5.3.4. Antineoplastic activity of resveratrol

The major mechanism of resveratrol for attenuating neoplasm is linked to its anti-oxidative, anti-inflammatory, and antiglycation activities. Resveratrol, unlike chemotherapeutic agents, has the proficiency to enhance cancer cell death with no side effects on the other nearby normal healthy cells **[38]**. In addition, through resveratrol inhibiting effect of the expression of NAF-1, an outer mitochondrial membrane protein with anti-apoptotic and anti-autophagy properties, and NF-kB protein, a transcription factor that makes cancer cells resistant to chemotherapy, it could be able to sensitize numerous cancer cells to a variety of chemotherapeutic drugs. Therefore, via downregulation of those two proteins, resveratrol could activate apoptosis and autophagy and hamper the proliferation of cancer cells **[47]**.

5.3.5. Mitochondrial biogenesis capability of resveratrol

It is well known that the pathophysiology of various diseases, including type 2 diabetes, neurodegenerative, CVDs and most cancers, is linked to mitochondrial dysfunction. Recent research has suggested that mitochondrial biogenesis may be a useful target for therapeutic intervention in different diseases; this is due to the mitochondrial critical role in cellular metabolism, control over energy- producing pathways, and well-known antioxidant characteristics **[48]**.

Resveratrol was documented to enhance mitochondrial biogenesis via promoting various signaling pathways and cellular mechanisms (**Fig 2**) **[48]**. The master regulator of mitochondrial biogenesis, peroxisome proliferator-activated receptor coactivator-1α (PGC-1α), can be induced by resveratrol. PGC-1α activates two downstream transcription factors: nuclear respiratory factors 1 and 2 (Nrf-1 and Nrf-2) which in turn activate the mitochondrial transcription factor A (TFAM). Resveratrol activation of PGC-1α/Nrf1-2/TFAM pathway increases mtDNA, protein synthesis, and generates new mitochondria, all of which enhances mitochondrial biogenesis **[49]**.

Resveratrol also plays a function in promoting mitochondrial biogenesis via activating AMPK (adenosine monophosphate-activated protein kinase), which is implicated in the activation of PGC-1α. Also, resveratrol activates silent information regulator-1 (SIRT1) which in turn initiates transcription of nuclear and mitochondrial genes encoding proteins **[50]**. It was reported that resveratrol has the ability to reduce mitochondrial fragmentation, preserve the potential of the mitochondrial membrane, and prevent the attenuation of oxidative phosphorylation process, thus acting as a protective mechanism against the negative impact of ROS. Moreover, resveratrol activates mitochondrial complex 1 by binding to the subunits of nicotinamide adenine dinucleotide (NADH) dehydrogenase **[51]**.

6. Resveratrol: A novel approach in mitigating DOX-induced cardiotoxicity

The pursuit of effective prophylactic modalities for chemotherapy-induced cardiotoxicity remains a complex challenge, necessitating innovative approaches to enhance clinical outcomes. Therefore, increasing scientific attention was directed toward “resveratrol” being a phytochemical polyphenolic compound that attracts a great scientific attention in both invitro **(Table 1)** and in vivo studies **(Table 2)**. A unique role of resveratrol in protecting the heart is via its capability of lowering intracellular calcium levels, preventing apoptosis through induction of enzymes that scavenge ROS and help in reducing the effects of ischemia reperfusion injury **[52]**. In addition, resveratrol could modulate mitochondrial membrane permeability transition pore (mPTP) and induce adenosine monophosphate-activated protein kinase (AMPK) activity in cardiomyocytes. Also, resveratrol is characterized by its ability to improve left ventricle systolic and diastolic function, decrease cardiac hypertrophy, contractile dysfunction and remodeling **[36]**.

Resveratrol supplement could indirectly prevent the CVD via its anti-platelet aggregation properties via suppressing COX-1-derived thromboxane A2 (TXA2) and enhancing production of nitric oxide (NO) via boosting endothelial nitric oxide synthase (eNOS) expression in platelets, this also gives resveratrol its anti-thrombotic and vasodilatory

properties as well **[53]**.

By virtue of its antioxidant, anti-inflammatory, and anti-thrombotic properties, resveratrol supplement is reported to lower the prevalence of CVD. **Magyar, Halmosi [54]** have found that treatment with resveratrol improves flow-mediated dilation (FMD), promotes endothelial function, decreases low density lipoprotein (LDL) cholesterol levels and prevent lipid deposition in clinical trial conducted on patients with stable coronary artery disease. In another clinical trial, resveratrol decreases the expression of vascular cell adhesion molecules (VCAM), intercellular adhesion molecules (ICAM), and inflammatory cytokines interleukin IL-8; all of them contribute to prevention of coronary artery disease and atherosclerosis **[55]**.

7. Conclusion

DOX is a common female BC fighting drug. However, its detrimental cardiotoxicity limited its broad therapeutic applicability by raising the risks of CVD morbidity and mortality. Oxidative stress, compromised mitochondrial function, disrupt Ca^{2+} homeostasis, and increased apoptosis in cardiomyocytes are all components of DOX-induced cardiotoxicity. In the field of cardio-oncology, targeting these changes with concurrent supplementation of the natural polyphenolic phytochemical "resveratrol" has a tremendous potential to lower the mortality rate among DOX-treated BC patients and even survivors.

Author contributions

Conceptualization: N.H. and B.M.R.; Data curation: B.M.R.; Supervision: H.M.E.; Visualization: O.Y.E.; Writing-original draft: B.M.R.; Writing-review & editing: B.M.R., N.H. and H.M.E All authors have read and agreed to the published version of the review.

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Table 1 Invitro studies evaluated the effects of resveratrol supplementation against DOX-induced cardiotoxicity

Cell Type	Doxorubicin dosage	Resveratrol dosage	Outcomes of Resveratrol cotreatment	Proposed mechanism of Resveratrol	Reference
Ratcardiomyoblast H9c2cells	2 μM for 24h	20 μM for 24h	RESV attenuated the cardiotoxic effects of DOX	p-AMPK activation ↑LC3(particularlyLC3-II) ↑BCL-2 ↓BAX expression ↓Apoptosis ↑Autophagy	**[56]**
Rat cardiomyoblast	5 μM for	25 μM for 24h	RESV protected H9c2 cells	↓MDA Expression	**[57]**
H9c2 cells	24h	(Started 24 h prior DOX treatment)	against DOX-induced apoptosis	↑SOD Expression ↑Sirt1 activation	
Starved Rat cardiomyoblast H9c2 cells	1 μM for 24 h	20 μM for 24 h	RESV attenuated DOX-induced cytotoxicity	↓Apoptosis ↑Autophagy	**[58]**
Rat embryonic cardiomyoblast-derived cells(H9c2 cell line)	1μmol/L for 24 h	50 μmol/L of RESV for 48 h Prior to DOX treatment	RESV might be used as a cardioprotective adjuvant in DOX treating cancer therapy	↑Vascular endothelial growth factor B (VEGF-B) ↑Akt ↓GSK3β	**[59]**
H9c2 cardiomyoblast	7.045 μM for 24 h	25 μM for 3 h or 24 h Prior to exposure to DOX	RESV has an antioxidant capacity and cardioprotective effect against DOX-induced cardiotoxicity	↓ROS production after 3 h, 24h incubation ↑Cell survival	**[34]**
Rat cardiomyoblast H9c2 cells	1 μM for 24 h	20 μM for 24 h alone then in co-treatment with DOX	RESV prevented DOX-associated inflammation	↑ SIRT1 expression upregulation of sestrin 2 (SESN2) ↑Activation of AMPKα ↓Nuclear expression of NF-κB p65 ↓Oxidative stress ↓ Apoptosis	**[60]**
H9c2 cell lines	1 μM for 16 h	20 μM with or without DOX	RESV ameliorates DOX-induced cardiotoxicity by activating SIRT1/MFN2 to improve mitochondria function.	↑Levels of Mitofusin2 (MFN2) &Sirtuin1 (SIRT1) ↓Mitochondrial membrane potential damage ↓Caspase 3 expression ↑MnSOD levels ↓ROS levels	**[61]**
H9C2 cardiomyoblast	1 μM for 24 h	20 μM for 6 h before Dox treatment	RESV protected H9C2 cells from RSL3-induced ferroptotic cell death. RESV rescued the DOX- induced cell viability reduction	↓ MAPK signaling pathway ↓Ferroptosis ↓Iron accumulation in the myocardium ↑Level of GSH ↓ROS generation and lipid peroxidation ↓ LDH release	**[62]**
Neonatalrat cardiomyocytes (NRCMs)	2 μM for 24 h				

Abbreviations: DOX: Doxorubicin, **RESV**: Resveratrol, **p-AMPK**: Adenosine monophosphate-activated protein kinase, **LC3**: Microtubule-associated Protein 1 Light Chain 3, **BCL-2**: B-cell leukemia/lymphoma 2 protein, **BAX**: Bcl-2-associated X protein, **MDA**: Malondialdehyde, **SOD**: Superoxide dismutase, **SIRT1/ Sirt1**: Sirtuin 1, **VEGF-B**: Vascular endothelial growth factor B**, Akt**: serine/threonine protein kinase or protein kinase B, **GSK3**β: Glycogen synthase kinase 3, **ROS**: Reactive oxygen species**, SESN2**: Sestrin -2, **NF-κB**: Nuclear factor-kappa B, **MFN2**: Mitofusin2, **MnSOD**: Manganese superoxide dismutase, **NRCMs**: Neonatal rat cardiomyocytes, **MAPK**: Mitogen-activated protein kinase, **GSH**: glutathione, **LDH**: Low-density lipoproteins,
↓: Decrease, ↑: Increase

Table 2 In vivo studies evaluated the effects of resveratrol supplementation against DOX-induced cardiotoxicity

Strain	Doxorubicin dosage	Resveratrol dosage	Outcomes of Resveratrol cotreatment	Proposed mechanism of Resveratrol	Reference
Adult female F344 rats	2.5 mg/kg i.p. 6 times over 2 weeks	2.5 mg/kg/day by oral gavage concomitantly with DOX then after DOX by 1 week	RESV alleviated end-diastolic pressure/volume relationship. ↓Fibroblast activation and fibrosis	SIRT1 activation ↓pSMAD3/SMAD3 level ↓TGF-β levels ↓p53 levels ↑Mn-SOD	**[63]**
Male C57BL/6 mice	5 mg/kg/day i.p. 4 times for 4 weeks (Cumulative dose of 20 mg/kg)	10 mg/kg i.p. prior to each DOX injection	RESV reversed DOX induced apoptosis counteracting DOX cardiotoxicity.	↓Expression of E2F1, AMPKα2 and mTORC1 ↑Expression of LC3-II/LC3-I	**[58]**
Male Kunming mice	single intraperitoneal injection of 20 mg/kg of DOX solution	20 mg/kg free RESV solution 3 days prior to DOX injection	Res-SLN improves the cardiac function and mitigate the collapse of the heart caused by DOX.	↑Body weight ↑Survival rate ↑ HR ↑ EF ↑ FS of the heart Rearrangement of myocardial fibers.	**[64]**
Adult male albino Wistar rats	2 mg/kg i.p. twice per week for 5 weeks (Cumulative dose of 20 mg/kg)	20 mg/kg orally for 6 weeks	RESV attenuates cardiac inflammation and prevents oxidative stress in DOX-intoxicated rats. RESV results in reduction in degenerated myocardium cells with inflammatory cellular infiltration	↓Serum troponin-I levels ↓CK-MB and LDH activities ↓TNF-α, IL-6, iNOS ↓TLR-4 immune reactivity ↓MDA,↑GSH,↑SOD	**[65]**
Male C57Bl/6N mice	4 mg/kg i.p. once a week for 3 weeks	320 mg/kg/day for 1 week before, during, and 1 week after the DOX administration	RESV reduced late-onset overt hypertension-induced cardiomyopathy. RESV protects against subclinical DOX-induced cardiac fibrosis.	↓Cardiac NLRP3 inflammasome activation in the heart ↓IL-1β, IL-1α, and IL-18 ↓Galectin-3-positive cells ↓Levels of macrophage infiltration markers ↓Levels of TNF-α, IL-5, IL-6, and CXCL 10	**[66]**
Male Sirt1-CKO mice	5 mg/kg i.p. once a week for 4 weeks (Cumulative dose of 20 mg/kg).	10 mg/kg/day i.p. every day for 5 weeks	RESV recovered DOX-reduced expression of SIRT1 in hearts so prevent cardiac dysfunction. RESV reversed DOX-decreased SESN2 expression through SIRT1 activation. RESV improves DOX-induced cardiac injury and dysfunction via upregulation of SESN2.	↑SIRT1 activation ↑SESN2 gene expression ↑Activation of SESN2/AMPK pathway ↓Nuclear expression of NF-κB p65	**[60]**
Sprague–Dawley male rats	15 mg/kg i.p.	5 mg/kg/day i.p. every	RESV may prevent	↓MTRNL	**[67]**

		day for 14 days	cardiac tissue damage by showing antiapoptotic and antioxidant effects against DOX-induced cardiotoxicity.	immunoreactivity ↓TRPM2 immunoreactivity ↑BCL-2 ↓MDA Levels ↑SOD Levels ↑GSH Levels ↑CAT Levels	
Male C57BL/6 J mice	6 intraperitoneal injections of DOX over two weeks for a cumulative dose of 24 mg/kg	20 mg/kg/day i.p. started two weeks before DOX injection.	RESV alleviated the abnormal morphological alterations of the myocardium. RESV attenuated DOX-induced decrease in body weight, heart weight, and the ratio of heart weight to tibia length. RESV improves DOX-induced cardiac dysfunction through alleviating ferroptosis	↓Iron accumulation ↑Level of GSH ↓Protein levels of PTGS2, ACSL4, and NCOA4 ↑Protein level of GPX4 ↓Ferroptosis	**[62]**

Abbreviations: i.p.: Interperitoneally, **TGF-β**: Transforming growth factor-β, **RSL3:** RAS-selective lethal 3, **E2F1**: E2 promoter binding factor 1, **mTORC1**: mammalian target of rapamycin complex 1, **Res-SLN**: Resveratrol solid lipid nanoparticle, **HR**: Heart rate, **EF**: Ejection fraction, **FS**: Fractional shortening, **CK-MB**: Creatine kinase-MB, **IL-6**: Interleukin 6, **iNOS**: inducible nitric oxide synthase, **TLR-4:** Toll-like receptor 4, **NLRP3:** NOD-like receptor protein 3, **IL-1β**: Interleukin-1 beta, **IL-1α**: Interleukin-1 alpha, **IL-18**: Interleukin-18, **TNF-α:** Tumor necrosis factor alpha, **IL- 5**: Interleukin-5, **CXCL 10**: C-X-C motif chemokine ligand 10, **METRNL**: Meterorin-like protein, **TRPM2:** Transient receptor potential melastatin 2, **CAT**: Catalase, **PTGS2:** Prostaglandin-Endoperoxide Synthase 2, **ACSL4:** Acyl-CoA Synthetase Long Chain Family Member 4, **NCOA4:** Nuclear receptor coactivator 4, **GPX4**: Glutathione peroxidase 4 **.**

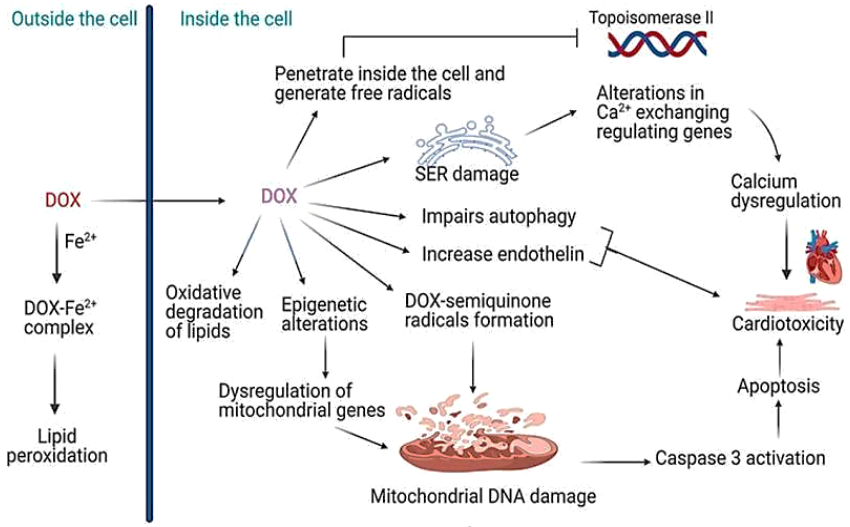


Fig 1. Different mechanisms of Dox-induced cardiotoxicity ($Fe^{2+:}$ Ferrous ions, DOX: Doxorubicin, SER: Smooth endoplasmic reticulum) (Quoted from Rawat et al. (2021))

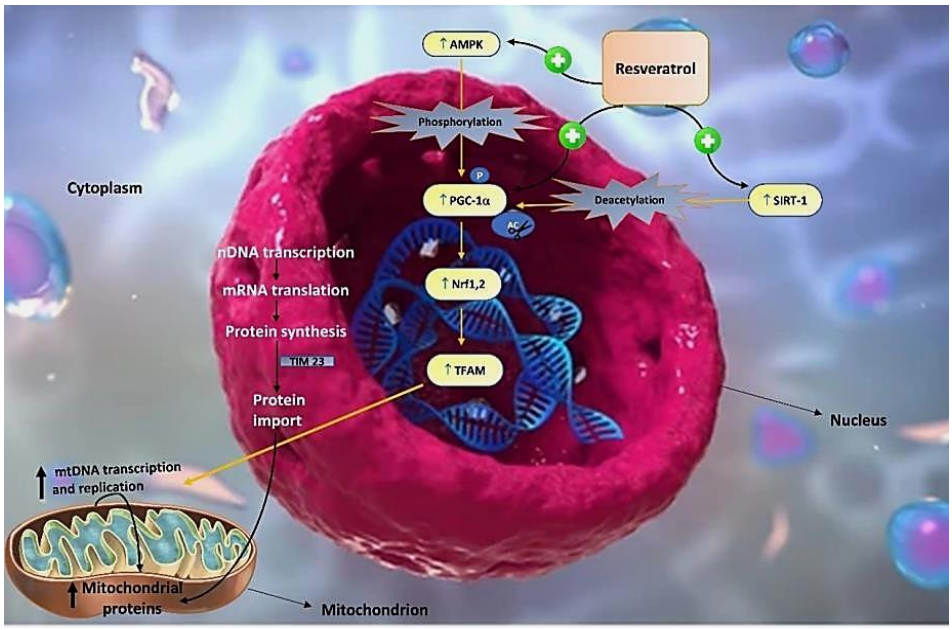
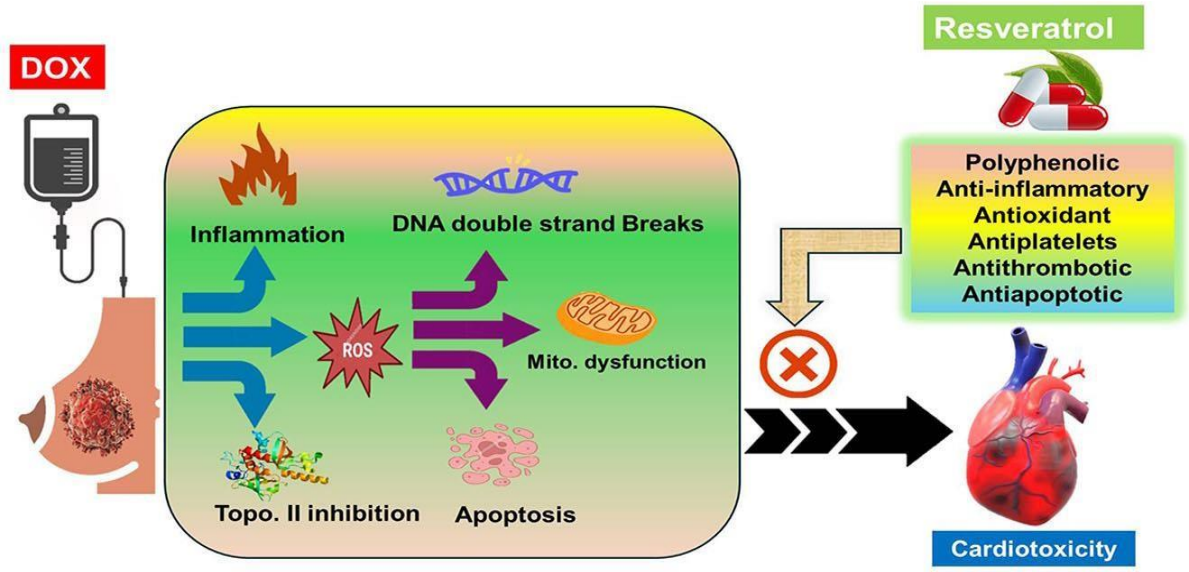


Fig 2. A schematic diagram representing the role of resveratrol in mitochondrial biogenesis through activating different signaling pathways (AMPK: 5' AMP-activated protein kinase, SIRT-1: Sirtuin 1, PGC- 1α: Peroxisome proliferator-activated receptor gamma coactivator 1-alpha, P: Phosphorylation, AC: Acetylation, Nrf: Nuclear respiratory factor, TFAM: mitochondrial transcription factor A, TIM23: Mitochondrial import inner membrane translocase subunit, and mtDNA: mitochondrial DNA)



"Graphical abstract"

REFERENCES

1. Katsura, C., et al., Breast cancer: presentation, investigation and management. British Journal of Hospital Medicine, 2022. **83**(2): p. 1-7. DOI:https://doi.org/10.12968/hmed.2021.0459
2. Montemurro, F., I. Nuzzolese, and R. Ponzone, Neoadjuvant or adjuvant chemotherapy in early breast cancer? Expert Opin Pharmacother, 2020. **21**(9): p. 1071-82. DOI: https://doi.org/10.1080/14656566.2020.1746273
3. Tadesse, F.A. and A.A. Leminie, Effects of Adriamycin-Cytoxan chemotherapy on hematological and electrolyte parameters among breast cancer patients. Frontiers in Oncology, 2023. **13**: p. 1103013. DOI: https://doi.org/10.3389/fonc.2023.1103013
4. Chatterjee, K., et al., Doxorubicin cardiomyopathy. Cardiology, 2010. **115**(2): p. 155-62. DOI: https://doi.org/10.1159/000265166
5. Liu, C., et al., Cardiotoxicity of doxorubicin-based cancer treatment: what is the protective cognition that phytochemicals provide us? Pharmacological research, 2020. **160**: p. 105062. DOI: https://doi.org/10.1016/j.phrs.2020.105062
6. Cragg, G.M. and J.M. Pezzuto, Natural products as avital source for the discovery of cancer chemotherapeutic and chemopreventive agents. Medical Principles and Practice, 2016. **25**(Suppl. 2): p. 41-59. DOI: https://doi.org/10.1159/000443404
7. Trachtenberg, B.H., The Burgeoning Field of Cardio-Oncology. Methodist DeBakey cardiovascular journal, 2019. **15**(4): p. 241. DOI: https://doi.org/10.14797/mdcj-15-4-241
8. Bray, F., et al., Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians, 2024. **74**(3): p. 229-63. DOI: https://doi.org/10.3322/caac.21834
9. Siegel, R.L., et al., Cancer statistics, 2023. CA: a cancer journal for clinicians, 2023. **73**(1). DOI: https://doi.org/10.3322/caac.21763
10. Giaquinto, A.N. and H. Sung, Breast cancer statistics 2024. 2024. **74**(6): p. 477-95. DOI: https://doi.org/10.3322/caac.21863
11. Arnold, M., et al., Current and future burden of breast cancer: Global statistics for 2020 and 2040. The Breast, 2022. **66**: p. 15-23. DOI: https://doi.org/10.1016/j.breast.2022.08.010
12. Łukasiewicz, S., M. Czeczelewski, and A. Forma, Breast Cancer-Epidemiology, Risk Factors, Classification, Prognostic Markers, and Current Treatment Strategies-An Updated Review. 2021. **13**(17). DOI: https://doi.org/10.3390/cancers13174287
13. Cianfrocca, M. and L.J. Goldstein, Prognostic and predictive factors in early-stage breast cancer. Oncologist, 2004. 9(6): p. 606-16. DOI: https://doi.org/10.1634/theoncologist.9-6-606
14. Yin, L., et al., Triple-negative breast cancer molecular subtyping and treatment progress. Breast Cancer Res, 2020. 22(1): p. 61. DOI: https://doi.org/10.1186/s13058-020-01296-5
15. Citron, M.L., Dose-Dense Chemotherapy: Principles, Clinical Results and Future Perspectives. Breast Care (Basel), 2008. **3**(4): p. 251-55. DOI: https://doi.org/10.1159/000148914
16. Barroso, A., et al., Management of infusion-related reactions in cancer therapy: strategies and challenges. ESMO Open, 2024. 9(3).DOI: https://doi.org/10.1016/j.esmoop.2024.102922
17. Rawat, P.S., et al., Doxorubicin-induced cardiotoxicity: An update on the molecular mechanism and novel therapeutic strategies for effective management. Biomedicine & Pharmacotherapy, 2021. **139**: p.111708. DOI: https://doi.org/10.1016/j.biopha.2021.111708
18. Srinivasan, M., M. Rajabi, and S. A. Mousa, Chapter 3 - Nanobiomaterials in cancer therapy, in Nanobiomaterials in Cancer Therapy, A.M. Grumezescu, Editor. 2016, William Andrew Publishing.p.57-89. DOI: https://doi.org/10.1016/b978-0-323-42863- 7.00003-7
19. Carvalho, C., et al., Doxorubicin: the good, the bad and the ugly effect. Current medicinal chemistry, 2009. **16**(25):p.3267-85. DOI: https://doi.org/10.2174/092986709788803312
20. Abe, C., T. Miyazawa, and T. Miyazawa, Current Use of Fenton Reaction in Drugs and Food. Molecules, 2022. 27(17): p. 5451.DOI: https://doi.org/10.3390/molecules27175451
21. Minotti, G., et al., Anthracyclines: molecular advances and pharmacologic developments in antitumor activity and cardiotoxicity. Pharmacological reviews, 2004. **56**(2): p. 185-29. DOI: https://doi.org/10.1124/pr.56.2.6
22. Berthiaume, J. and K.B. Wallace, Adriamycin-induced oxidative mitochondrial cardiotoxicity. Cell biology and toxicology, 2007. **23**: p. 15-25. DOI: https://doi.org/10.1007/s10565-006-0140-y
23. Chung, W.-B., et al., Early cardiac function monitoring for detection of subclinical doxorubicin cardiotoxicity in young adult patients with breast cancer. Journal of breast cancer, 2013. **16**(2): p. 178-83. DOI: https://doi.org/10.4048/jbc.2013.16.2.178
24. Singal, P.K. and N. Iliskovic, Doxorubicin-induced cardiomyopathy. N Engl J Med, 1998. **339**(13): p. 900-5. DOI: https://doi.org/10.1056/nejm199809243391307
25. Leger, K., et al., Subclinical cardiotoxicity in childhood cancer survivors exposed to very low dose anthracycline therapy. Pediatric blood & cancer, 2015. **62**(1): p. 123-27. DOI: https://doi.org/10.1002/pbc.25206
26. Ferreira, A., et al., Altered mitochondrial epigenetics associated with subchronic doxorubicin cardiotoxicity. Toxicology, 2017. **390**: p. 63-73. DOI: https://doi.org/10.1016/j.tox.2017.08.011
27. Chen, Y., et al., Potential targets for intervention

against doxorubicin-induced cardiotoxicity based on genetic studies: a systematic review of the literature. Journal of Molecular and Cellular Cardiology, 2020. **138**: p. 88-98. DOI:https://doi.org/10.1016/j.yjmcc.2019.11.150

28. Mukhopadhyay, P., et al., Role of superoxide, nitric oxide, and peroxynitrite in doxorubicin-induced cell death in vivo and in vitro. American Journal of Physiology-Heart and Circulatory Physiology, 2009. **296**(5): p. H1466-83. DOI: https://doi.org/10.1152/ajpheart.00795.2008

29. Subra, A.K., et al., Molecular mechanisms of pharmaceutical drug binding into calsequestrin. Int J Mol Sci, 2012. 13(11): p. 14326-43. DOI: https://doi.org/10.3390/ijms131114326

30. dos Santos, D.S. and R.C. dos Santos Goldenberg, Doxorubicin-induced cardiotoxicity: from mechanisms to development of efficient therapy. Cardiotoxicity, 2018: p. 3-24. DOI: https://doi.org/10.5772/intechopen.79588

31. Liu, P., et al., Targeting extracellular heat shock protein 70 ameliorates doxorubicin-induced heart failure through resolution of toll-like receptor 2–mediated myocardial inflammation. Journal of the American Heart Association, 2019. **8**(20): p. e012338. DOI: https://doi.org/10.1161/jaha.119.012338

32. Nousiainen, T., et al., Early decline in left ventricular ejection fraction predicts doxorubicin cardiotoxicity in lymphoma patients. British journal of cancer, 2002. **86**(11): p. 1697-17. DOI: https://doi.org/10.1038/sj.bjc.6600346

33. Huang, W., et al., Clinical Manifestations, Monitoring, and Prognosis: A Review of Cardiotoxicity After Antitumor Strategy. Front Cardiovasc Med, 2022. **9**: p. 912329. DOI:https://doi.org/10.3389/fcvm.2022.912329

34. Monahan, D.S., et al., Resveratrol significantly improves cell survival in comparison to dexrazoxane and carvedilol in a h9c2 model of doxorubicin induced cardiotoxicity. Biomedicine & Pharmacotherapy, 2021. **140**: p. 111702. DOI: https://doi.org/10.1016/j.biopha.2021.111702

35. Sun, A.Y., A. Simonyi, and G.Y. Sun, The "French Paradox" and beyond: neuroprotective effects of polyphenols. Free Radic Biol Med, 2002. **32**(4): p. 314-8. DOI: https://doi.org/10.1016/s0891-5849(01)00803-6

36. Shen, M., et al., Cardioprotective effect of resvaratrol pretreatment on myocardial ischemia–reperfusion induced injury in rats. Vascular pharmacology, 2006. **45**(2): p. 122-26. DOI: https://doi.org/10.1016/j.vph.2006.04.002

37. Salehi, B., et al., Resveratrol: A double-edged sword in health benefits. Biomedicines, 2018. **6**(3): p. 91. DOI: https://doi.org/10.3390/biomedicines6030091

38. Azorin-Ortuno, M., et al., Pharmacokinetic study of trans-resveratrol in adult pigs. Journal of agricultural and food chemistry, 2010. **58**(20): p. 11165-71. DOI: https://doi.org/10.1021/jf102799m

39. Delmas, D. and H.Y. Lin, Role of membrane dynamics processes and exogenous molecules in cellular resveratrol uptake: consequences in bioavailability and activities. Mol Nutr Food Res, 2011. **55**(8): p. 1142-53. DOI: https://doi.org/10.1002/mnfr.201100065

40. Lin, M.-H., et al., The bioactivities of resveratrol and its naturally occurring derivatives on skin. Journal of food and drug analysis, 2021. **29**(1): p. 15. DOI: https://doi.org/10.38212/2224-6614.1151

41. Rubiolo, J.A., G. Mithieux, and F.V. Vega, Resveratrol protects primary rat hepatocytes against oxidative stress damage: activation of the Nrf2 transcription factor and augmented activities of antioxidant enzymes. Eur J Pharmacol, 2008. **591**(1-3): p. 66-72. DOI: https://doi.org/10.1016/j.ejphar.2008.06.067

42. Zhou, Z.X., et al., Anti-inflammatory activity of resveratrol prevents inflammation by inhibiting NF-κB in animal models of acute pharyngitis. Molecular medicine reports, 2018. **17**(1): p. 1269-74. DOI: https://doi.org/10.3892/mmr.2017.7933

43. Patel, K.R., et al., Clinical pharmacology of resveratrol and its metabolites in colorectal cancer patients. Cancer research, 2010. **70**(19): p. 7392-99. DOI: https://doi.org/10.1158/0008-5472.can-10-2027

44. Kong, F., et al., Resveratrol raises in vitro anticancer effects of paclitaxel in NSCLC cell line A549 through COX-2 expression. Korean J Physiol Pharmacol, 2017. **21**(5): p. 465-74. DOI: https://doi.org/10.4196/kjpp.2017.21.5.465

45. Zhang, F., J. Liu, and J.S. Shi, Anti-inflammatory activities of resveratrol in the brain: role of resveratrol in microglial activation. Eur J Pharmacol, 2010. **636**(1-3): p. 1-7. DOI: https://doi.org/10.1016/j.ejphar.2010.03.043

46. Shen, Y., Z. Xu, and Z. Sheng, Ability of resveratrol to inhibit advanced glycation end product formation and carbohydrate-hydrolyzing enzyme activity, and to conjugate methylglyoxal. Food Chem, 2017. **216**: p. 153-60. DOI: https://doi.org/10.1016/j.foodchem.2016.08.034

47. Cheng, L., B. Yan, and K. Chen, Resveratrol-Induced Downregulation of NAF-1 Enhances the Sensitivity of Pancreatic Cancer Cells to Gemcitabine via the ROS/Nrf2 Signaling Pathways. 2018. **2018**: p. 9482018. DOI: https://doi.org/10.1155/2018/9482018

48. Chodari, L., et al., Targeting mitochondrial biogenesis with polyphenol compounds. Oxidative Medicine and Cellular Longevity, 2021. **2021**(1): p. 4946711. DOI: https://doi.org/10.1155/2021/4946711

49. Csiszar, A., et al., Resveratrol induces mitochondrial biogenesis in endothelial cells. American Journal of Physiology-Heart and Circulatory Physiology, 2009. **297**(1): p. H13-H20. DOI:

https://doi.org/10.1152/ajpheart.00368.2009
50. Higashida, K., et al., Effects of resveratrol and SIRT1 on PGC-1α activity and mitochondrial biogenesis: a reevaluation. PLoS biology, 2013. **11**(7): p. e1001603. DOI: https://doi.org/10.1371/journal.pbio.1001603
51. Desquiret-Dumas, V., et al., Resveratrol induces a mitochondrial complex I-dependent increase in NADH oxidation responsible for sirtuin activation in liver cells. Journal of Biological Chemistry, 2013. **288**(51): p. 36662-75. DOI: https://doi.org/10.1074/jbc.m113.466490
52. Shen, M., et al., Resveratrol attenuates ischemia/reperfusion injury in neonatal cardiomyocytes and its underlying mechanism. PLoS One, 2012. **7**(12): p. e51223. DOI: https://doi.org/10.1371/journal.pone.0051223
53. Villanueva, C. and C. Giulivi, Subcellular and cellular locations of nitric oxide synthase isoforms as determinants of health and disease. Free Radic Biol Med, 2010. **49**(3): p. 307-16. DOI: https://doi.org/10.1016/j.freeradbiomed.2010.04.004
54. Magyar, K., et al., Cardioprotection by resveratrol: A human clinical trial in patients with stable coronary artery disease. Clin Hemorheol Microcirc, 2012. **50**(3): p. 179-87. DOI: https://doi.org/10.3233/ch-2011-1424
55. Agarwal, B., et al., Resveratrol for primary prevention of atherosclerosis: clinical trial evidence for improved gene expression in vascular endothelium. Int J Cardiol, 2013. **166**(1): p. 246-8. DOI: https://doi.org/10.1016/j.ijcard.2012.09.027
56. Gu, J., et al., Resveratrol-induced autophagy promotes survival and attenuates doxorubicin-induced cardiotoxicity. International Immunopharmacology, 2016. **32**: p. 1-7. DOI: https://doi.org/10.1016/j.intimp.2016.01.002
57. Liu, M.-H., et al., Resveratrol inhibits doxorubicin-induced cardiotoxicity via sirtuin 1 activation in H9c2 cardiomyocytes. Experimental and therapeutic medicine, 2016. **12**(2): p. 1113-18. DOI: https://doi.org/10.3892/etm.2016.3437
58. Gu, J., et al., Resveratrol suppresses doxorubicin-induced cardiotoxicity by disrupting E2F1 mediated autophagy inhibition and apoptosis promotion. Biochemical Pharmacology, 2018. **150**: p. 202-13. DOI: https://doi.org/10.1016/j.bcp.2018.02.025
59. Tian, W., et al., Resveratrol attenuates doxorubicin-induced cardiotoxicity in rats by up- regulation of vascular endothelial growth factor B. The Journal of Nutritional Biochemistry, 2020. **79**: p. 108132. DOI: https://doi.org/10.1016/j.jnutbio.2019.01.018
60. Wang, A.J., et al., Cardiac SIRT1 ameliorates doxorubicin-induced cardiotoxicity by targeting sestrin 2. Redox Biol, 2022. **52**: p. 102310. DOI: https://doi.org/10.1016/j.redox.2022.102310
61. Zhang, Q. and Y. Zhang, Resveratrol activation of SIRT1/MFN2 can improve mitochondria function, alleviating doxorubicin-induced myocardial injury. 2023. **2**(4): p. 253-64. DOI: https://doi.org/10.1002/cai2.64
62. Chen, L., et al., Resveratrol protects against doxorubicin-induced cardiotoxicity by attenuating ferroptosis through modulating the MAPK signaling pathway. Toxicology and Applied Pharmacology, 2024. **482**: p. 116794. DOI: https://doi.org/10.1016/j.taap.2023.116794
63. Cappetta, D., et al., SIRT1 activation attenuates diastolic dysfunction by reducing cardiac fibrosis in a model of anthracycline cardiomyopathy. International journal of cardiology, 2016. **205**: p. 99-110. DOI:https://doi.org/10.1016/j.ijcard.2015.12.008
64. Zhang, L., et al., Resveratrol solid lipid nanoparticles to trigger credible inhibition of doxorubicin cardiotoxicity. Int J Nanomedicine, 2019. **14**: p. 6061-71. DOI: https://doi.org/10.2147/ijn.s211130
65. Alanazi, A.M., et al., Liposomal Resveratrol and/or Carvedilol Attenuate Doxorubicin-Induced Cardiotoxicity by Modulating Inflammation, Oxidative Stress and S100A1 in Rats. 2020. **9**(2). DOI: https://doi.org/10.3390/antiox9020159
66. Maayah, Z.H., et al., Resveratrol reduces cardiac NLRP3-inflammasome activation and systemic inflammation to lessen doxorubicin-induced cardiotoxicity in juvenile mice. 2021. **595**(12): p. 1681-95. DOI: https://doi.org/10.1002/1873-3468.14091
67. Kaya, S., T. Yalçın, and T. Kuloğlu, Resveratrol may reduce oxidative stress and apoptosis in doxorubicin-induced cardiotoxicity by regulating meteorin-like and TRPM2 levels. Comparative Clinical Pathology, 2023. **32**(3): p. 393-4. DOI: https://doi.org/10.1007/s00580-023-03449-2

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