REVIEW ARTICLE

RECORDS OF PHARMACEUTICAL AND BIOMEDICAL SCIENCES

Mitigating Doxorubicin-Induced Cardiotoxicity: Insights into the Therapeutic Potential of Raspberry Ketone

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Abstract

Doxorubicin (DOX), an anthracycline antibiotic, remains a cornerstone in the management of a wide spectrum of malignancies due to its high antitumor efficacy. Its use, however, is severely limited by dose-dependent and cumulative cardiotoxicity, which can result in irreversible heart failure. The pathophysiology of DOX-induced cardiotoxicity is complex and multifactorial, involving oxidative stress, mitochondrial dysfunction, iron-mediated injury, apoptosis, inflammation, and fibrotic remodeling. Emerging evidence indicates that impairment of the nuclear factor erythroid 2-related factor 2 (Nrf2) antioxidant pathway plays a pivotal role in exacerbating cardiac susceptibility to DOX-induced injury. The identification of pharmacological strategies that can restore Nrf2 function has therefore become a priority. Raspberry ketone (RK), a naturally occurring phenolic compound found predominantly in red raspberries, exhibits potent antioxidant, anti-inflammatory, metabolic regulatory, hepatoprotective, neuroprotective, and dermatological benefits. Several studies suggest that RK may modulate Nrf2 signaling, thereby enhancing the antioxidant defense system and attenuating oxidative damage. This review comperehensively discusses the DOX-induced cardiotoxicity and the cardioprotective potential of RK through its Nrf2-modulating properties.

Keywords: Doxorubicin; cardiotoxicity; raspberry ketone; Nrf2 pathway; oxidative stress; cardioprotection.

1. Background

Doxorubicin (DOX) is a potent anthracycline antibiotic originally isolated from Streptomyces peucetius in the late 1960s **(Di Marco et al., 1969)**. Since its introduction, DOX has become a cornerstone chemotherapeutic agent, used to treat a wide array of malignancies including breast, ovarian, lung, gastric, and bladder cancers, as well as hematological malignancies such as acute leukemias, lymphomas, and multiple myeloma **(Weiss, 1992; Tacar et al., 2013)**. Its broad efficacy stems from multiple mechanisms of action, allowing it to target diverse tumor types and cell cycle phases.

DOX exerts cytotoxic effects primarily by intercalating between DNA base pairs, disrupting the function of topoisomerase II, and generating reactive oxygen species (ROS) **(Hurley, 2002;**

Friedman and Caflisch, 2009). These actions culminate in the inhibition of DNA replication and transcription, induction of DNA strand breaks, and activation of apoptotic pathways in rapidly dividing cells **(Aliprantis et al., 2000; Chen et al., 2012)**. While these mechanisms effectively kill cancer cells, they also contribute to off-target toxicity in non-proliferating tissues, most notably the myocardium.

Cardiotoxicity represents one of the most severe adverse effects of DOX therapy, significantly limiting its clinical utility **(Octavia et al., 2012)**. Manifestations range from acute arrhythmias and myocarditis to chronic progressive cardiomyopathy and congestive heart failure **(Songbo et al., 2019; Rawat et al., 2021)**. Chronic cardiotoxicity is particularly problematic, as it is largely irreversible and may develop months or even years after completion of chemotherapy. The risk is strongly correlated with cumulative dose, with a sharp increase in incidence observed beyond 400–550 mg/m² **(Weiss, 1992)**.

Current preventive strategies include limiting cumulative doses, prolonging infusion times, and co-administering cardioprotective agents such as dexrazoxane **(Ventura-Clapier et al., 2011)**. However, these measures are not always effective and may interfere with antitumor efficacy or cause additional side effects. This has spurred interest in novel cardioprotective approaches, particularly those based on natural compounds with multi-target antioxidant and anti-inflammatory actions (**Liu and Huang, 2016; Iranshahy et al., 2018)**. Among these, raspberry ketone (RK) has emerged as a promising candidate due to its potential to activate nuclear factor erythroid 2-related factor 2 (Nrf2) and reinforce endogenous antioxidant defences **(Chen and Maltagliati, 2018)**.

2. Mechanisms of Doxorubicin-Induced Cardiotoxicity

2.1. Multifactorial pathogenesis

The cardiotoxicity of DOX is a result of complex interactions between ROS generation, mitochondrial injury, iron dysregulation, and cell death signaling pathways. These processes form a vicious cycle in which oxidative stress perpetuates mitochondrial dysfunction, further increasing ROS production and leading to irreversible myocardial injury **(Doroshow, 1986; Songbo et al., 2019)**.

2.2. ROS generation and redox cycling

DOX undergoes redox cycling via one-electron reduction catalyzed by mitochondrial complex I, NADPH-cytochrome P450 reductase, and other flavoproteins **(Gutteridge, 1984)**. This produces a semiquinone radical that rapidly reacts with molecular oxygen, generating superoxide anions **(Bates and Winterbourn, 1982) (Figure 1)**. Superoxide dismutase converts these to hydrogen peroxide, which in the presence of ferrous iron undergoes the Fenton reaction to yield highly reactive hydroxyl radicals **(Vásquez-Vivar et al., 1997)**. These ROS species damage proteins, lipids, and nucleic acids **(Rahman, 2007)**.

2.3. Mitochondrial damage and bioenergetic collapse

Mitochondria are both a primary site of DOX ROS production and a major target of oxidative damage (Lemieux and Hoppel, 2009). DOX binds to cardiolipin in the inner mitochondrial membrane, disrupting electron transport chain (ETC) complexes, impairing ATP synthesis, and increasing electron leakage **(Zhao and Zhang, 2017)**. Oxidative damage to mitochondrial DNA, which lacks robust repair mechanisms, further compromises ETC function and energy production **(Szeto, 2014)**. Severe mitochondrial dysfunction promotes opening of the permeability transition pore, cytochrome c release, and caspase activation **(Vedam et al., 2010)**.

2.4. Iron-mediated oxidative injury

DOX's anthraquinone structure facilitates iron binding, forming DOX-iron complexes that exacerbate ROS generation **(Kappus et al., 1980; Tacar et al., 2013)**. Mitochondrial iron accumulation enhances lipid peroxidation and membrane destabilization, worsening cardiomyocyte injury **(Hashemzaei et al., 2020)**.

2.5. Apoptotic and necrotic pathways

DOX activates both intrinsic (mitochondrial) and extrinsic (death receptor-mediated) apoptotic pathways **(Priya et al., 2017)**. The intrinsic pathway is characterized by B-cell lymphoma 2 protein (Bcl-2) downregulation, Bcl-2-associated X protein (Bax) upregulation and mitochondrial membrane permeabilization, and cytochrome c release, leading to caspase-9 activation **(Zhao et**

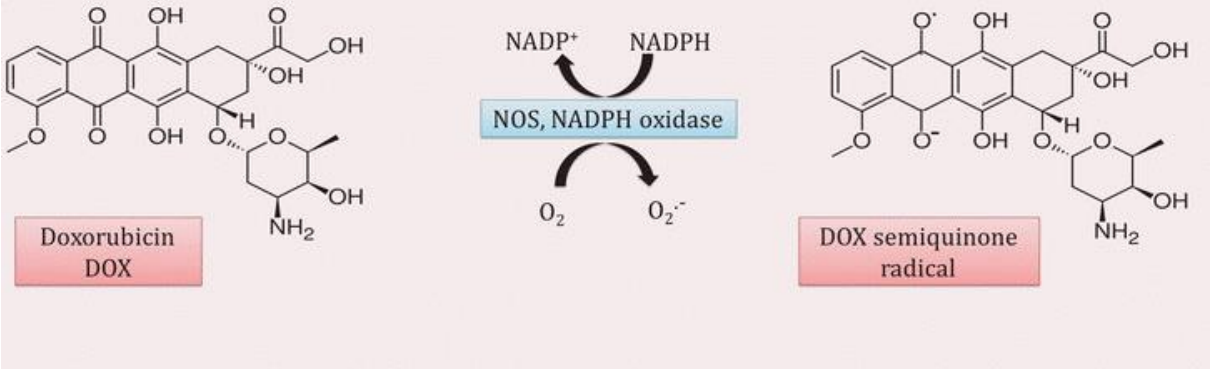


Figure 1. Doxorubicin (DOX) can be reduced to the semiquinone radical by nitric oxide synthases (NOSs) and NADPH oxidase **(Damiani et al., 2016).**

al., 2020). The extrinsic pathway involves Fas and tumor necrosis factor receptor 1 (TNFR1) activation, triggering caspase-8–mediated apoptosis **(Zhao and Zhang, 2017)**. In cases of severe energy depletion, necrosis predominates, releasing damage-associated molecular patterns (DAMPs) that amplify inflammation **(Kobayashi et al., 2016)**.

2.6. Inflammation and fibrotic remodeling

ROS-mediated nuclear factor kappa B (NF-κB) activation stimulates the expression of pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6) **(Reuter et al., 2010)**. Chronic inflammation promotes fibroblast proliferation and collagen deposition, culminating in myocardial fibrosis, wall stiffening, and impaired contractility **(Persson et al., 2014; Szabo et al., 2018)**.

3. Nrf2 Signaling Pathway in Cardioprotection

3.1. Structure and activation mechanisms

Nrf2 is a transcription factor that regulates the expression of antioxidant and detoxification genes by binding to antioxidant response elements (ARE) in target gene promoters **(Itoh et al., 1999)**. Under basal conditions, Nrf2 is bound to kelch-like ECH-associated protein 1 (Keap1), which facilitates its ubiquitination and proteasomal degradation. Oxidative stress or electrophilic agents modify Keap1 cysteine residues, preventing Nrf2 degradation and allowing its nuclear translocation **(Figure 2) (Kobayashi et al., 2016)**.

3.2. Antioxidant and cytoprotective targets

Nrf2 activation induces genes encoding antioxidant enzymes such as heme oxygenase-1 (HO-1), NAD(P)H:quinone oxidoreductase 1 (NQO1), superoxide dismutase (SOD), glutathione peroxidase (GPx), and glutamate cysteine ligase (GCL), as well as phase II detoxification enzymes. These enzymes collectively restore redox homeostasis, detoxify reactive metabolites, and repair oxidative damage **(Chen and Maltagliati, 2018)**.

3.3. Nrf2 suppression in DOX cardiotoxicity

DOX disrupts Nrf2 signaling by impairing upstream kinase activation Phosphoinositide 3-kinase/A protein kinase B/Mitogen-Activated Protein Kinase (PI3K/Akt, MAPKs) and enhancing Keap1-mediated degradation. This reduces antioxidant enzyme expression, leaving cardiomyocytes more vulnerable to oxidative injury **(Li et al., 2014; Zhao et al., 2023)**.

3.4. Nrf2 as a therapeutic target

Pharmacologic and nutraceutical activators of Nrf2, including sulforaphane, curcumin, and resveratrol, have been shown to attenuate DOX-induced oxidative stress, preserve mitochondrial function, and improve cardiac outcomes in preclinical models **(Guo et al., 2018; Iranshahy et al., 2018)**.

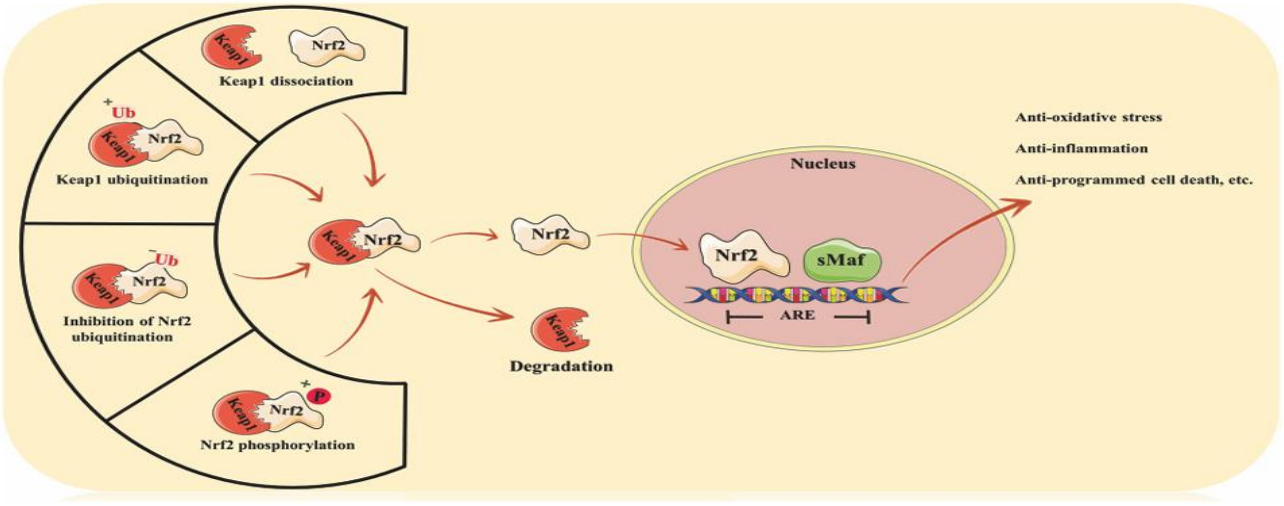


Figure 2. The activation of Nrf2 **(Zhao et al., 2023)**.

4. Raspberry Ketone: Chemistry, Sources, and Pharmacology

4.1. Chemical structure and natural occurrence

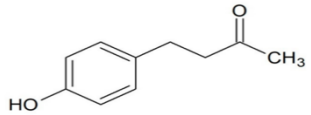
Raspberry ketone (RK), chemically known as 4-(4-hydroxyphenyl)-2-butanone, is a naturally occurring phenolic compound responsible for the characteristic aroma of red raspberries (*Rubus idaeus*) **(Beekwilder et al., 2007; Lim and Choi, 2021)**. It is also found in trace amounts in other fruits such as cranberries, blackberries, and kiwifruit, as well as in some vegetables and plants like rhubarb **(Lin et al., 2011)**.

Due to its low natural abundance, RK is frequently synthesized chemically or produced via biotransformation for commercial use **(Beekwilder et al., 2007)**.

4.2. Pharmacological properties

RK has been reported to exhibit a wide spectrum of pharmacological effects, including antioxidant, anti-inflammatory, anti-obesity, skin-protective, hepatoprotective, and neuroprotective activities **(Lim and Choi, 2021; Rao et al., 2021)**. Its antioxidant action is primarily attributed to its phenolic hydroxyl group, which can scavenge ROS and inhibit lipid peroxidation **(Khan et al., 2019)**.

Table 1: The physicochemical properties of RK (Rao et al., 2021)

Chemical Structure	
Chemical Formula	$C_{10}H_{12}O_2$
Molecular Weight	164.204 g·mol−1
Solubility	propanol, 2-propanol, 1-butanol, 2-butanol, acetic acid, methyl acetate, ethyl acetate, acetone, and binary mixtures of ethanol + acetone
Melting Point	81–85 °C
Boiling Point	292.2 ± 15.0 ◦C at 760 mmHg
Lambda Max	280 nm

In metabolic studies, RK has been shown to modulate adipokines, enhance lipolysis, and improve insulin sensitivity **(Harada et al., 2008; Arent et al., 2018)**. Additionally, RK demonstrates protective effects in various organ systems, including attenuation of cyclophosphamide-induced pulmonary toxicity **(Mohamed et al., 2020)** and protection against isoproterenol-induced myocardial injury **(Khan et al., 2019)**.

5. Nrf2 Modulation by Raspberry Ketone

5.1. Evidence for Nrf2 activation

Several studies indicate that RK can modulate the Nrf2 pathway, enhancing the transcription of antioxidant genes such as HO-1, NQO1, and GCL. By disrupting Keap1–Nrf2 interactions, RK promotes Nrf2 nuclear translocation, thereby augmenting cellular defenses against oxidative stress. This effect has been observed in models of oxidative tissue injury, including chemically induced organ toxicities **(Mohamed et al., 2020)**.

5.2. Mechanistic insights

RK's electrophilic properties may enable it to modify cysteine residues on Keap1, similar to other natural Nrf2 activators like sulforaphane **(Chen and Maltagliati, 2018)**. Additionally, RK may activate upstream kinases such as PI3K/Akt and Extracellular signal-regulated kinase 1/2 (ERK1/2), which phosphorylate Nrf2 and enhance its stability **(Han et al., 2021)**. Through these mechanisms, RK could counteract the suppression of Nrf2 observed during DOX exposure **(Li et al., 2014)**.

5.3. Antioxidant and anti-inflammatory effects relevant to cardioprotection

By boosting Nrf2 activity, RK enhances glutathione synthesis, ROS scavenging, and detoxification of electrophilic intermediates, thereby limiting DOX-induced oxidative damage. Concurrently, Nrf2 activation suppresses NF-κB–mediated transcription of pro-inflammatory cytokines, reducing inflammation and potentially attenuating fibrotic remodeling **(Kobayashi et al., 2016)**.

6. Potential Role of Raspberry Ketone in Mitigating Doxorubicin Cardiotoxicity

6.1. Preclinical evidence from related models

Although direct studies of RK in DOX-induced cardiotoxicity are limited, evidence from other models of oxidative cardiac injury supports its potential role. In isoproterenol-induced cardiotoxicity, RK improved cardiac function, reduced lipid peroxidation, and enhanced antioxidant enzyme activities **(Khan et al., 2019)**. In cyclophosphamide-induced pulmonary toxicity, RK reduced oxidative stress and inflammatory mediator levels via Nrf2 activation **(Mohamed et al., 2020)**. These findings suggest a plausible cardioprotective effect in the DOX setting.

6.2. Hypothesized cardioprotective mechanisms

RK could confer cardioprotection in DOX-treated patients via multiple mechanisms:

- Enhancement of antioxidant defenses through Nrf2-mediated induction of HO-1, NQO1, SOD, GPx, and GCL.
- Suppression of oxidative damage by scavenging free radicals and reducing lipid peroxidation.
- Inhibition of inflammatory cascades by blocking NF-κB activation and cytokine production.
- Preservation of mitochondrial function through stabilization of cardiolipin and maintenance of ETC efficiency.

6.3. Synergy with existing cardioprotective strategies

RK could be used alongside dexrazoxane or beta-blockers to provide additive or synergistic benefits, especially in patients at high risk of DOX cardiotoxicity. Unlike synthetic drugs, RK's natural origin and potential nutraceutical status might offer a favorable safety profile, though this requires rigorous validation **(Lee, 2016)**.

7. Translational Challenges and Future Directions

7.1. Dose optimization and bioavailability

One challenge in translating RK to clinical use is its limited oral bioavailability due to rapid metabolism and elimination **(Ulbricht et al., 2013)**. Strategies such as nanoparticle delivery, liposomal encapsulation, or structural analog development may enhance its pharmacokinetics.

7.2. Safety considerations

Although generally recognized as safe at low doses in foods, the safety of high-dose RK supplementation remains under investigation **(Lee, 2016)**. Potential off-target effects, endocrine interactions, and long-term safety profiles must be established before clinical application.

7.3. Need for direct experimental evidence in DOX models

While indirect evidence supports RK's cardioprotective potential, direct studies in DOX-induced cardiotoxicity models—both in vitro and in vivo—are essential. These should assess cardiac function, histopathology, oxidative stress markers, and Nrf2 target gene expression.

8. Conclusion

DOX remains a cornerstone of cancer therapy, but its clinical utility is hampered by cardiotoxicity, driven largely by oxidative stress, mitochondrial dysfunction, and impaired antioxidant responses. Nrf2 plays a pivotal role in defending the myocardium against oxidative injury, yet its activity is suppressed during DOX treatment. RK, a natural phenolic compound with demonstrated antioxidant and anti-inflammatory effects, shows promise as a modulator of Nrf2 signaling. Optimizing RK's bioavailability, establishing safety, and conducting preclinical and clinical trials will be essential to determine its role in cardio-oncology. If proven effective, RK could represent a safe, accessible, and multi-targeted approach to mitigating DOX-induced cardiac injury.

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