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Protective effects of curcumin against doxorubicin-induced toxicity and resistance: A review

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ABSTRACT

Doxorubicin (DOX)-induced toxicity and resistance are major obstacles in chemotherapeutic approaches. Despite effective in the treatment of numerous malignancies, some clinicians have voiced concern that DOX has the potential to cause debilitating consequences in organ tissues, especially the heart. The mechanisms of toxicity and resistance are respectively related to induction of reactive oxygen species (ROS) and up-regulation of ATP-binding cassette (ABC) transporter. Curcumin (CUR) with several biological and pharmacological properties is expected to restore DOX-mediated impairments to tissues. This review is intended to address the current knowledge on DOX adverse effects and CUR protective actions in the heart, kidneys, liver, brain, and reproductive organs. Coadministration of CUR and DOX is capable of ameliorating DOX toxicity pertained to antioxidant, apoptosis, autophagy, and mitochondrial permeability.

1. Introduction

The anthracycline antibiotic adriamycin (Doxorubicin; DOX) is an effective anti-cancer agent commonly applied to treat hematological and solid malignancies, namely leukemia, lymphomas, soft-tissue sarcomas, breast carcinoma, osteosarcoma, Kaposi's sarcoma, Hodgkin's and non-Hodgkin's lymphomas (Bonadonna et al., 1969; Bonadonna et al., 1970; Morabito et al., 2004; Novitzky et al., 2004). This molecule, {(7S, 9S)-7-[(2R, 4S, 5S, 6S)-4-amino-5-hydroxy-6-methyloxan-2-yl]oxy-6, 9, 11-trihydroxy-9-(2-hydroxyacetyl)-4-methoxy-8, 10-dihydro-7H-tetracene-5, 12-dione}, is derived from the fungus *Streptomyces peucetius* constituted an amino sugar and four rings of anthraquinone (Singal et al., 2000). Although effective in blocking the progression of various tumors, the administration of DOX may cause the development of toxicity or resistance related to its specific chemical structure (Bonadonna et al., 1969; Bonadonna et al., 1970; Dayton et al., 2011; Di Marco et al., 1969). Indeed, the clinical use of DOX as a chemotherapeutic agent is usually associated with manageable adverse effects including nausea, vomiting, alopecia, myelosuppression, stomatitis, and gastrointestinal disturbances (Carvalho et al., 2009; Singal and Iliskovic, 1998). Moreover, there have some reports concerning the presentation of cardiac toxicity and cardiomyopathy in patients treated with DOX (Bonadonna et al., 1970; Steinherz et al., 1991). It has been shown that acute cardiotoxicity affects approximately 11% of the patient under treatment (Swain et al., 2003; Takemura and Fujiwara, 2007). The heart is not only the only target organ of DOX since a body of literature has addressed its toxicity in the kidney, liver, brain, reproductive organs, and so forth (Injac et al., 2008; Mohan et al., 2010; Yilmaz et al., 2006). Multidrug resistance (MDR) arises from the repeated treatment with DOX or increased doses that culminate in high cumulative doses (Szakács et al., 2006). On the other hand, it is demonstrated that some risk factors can afford to decrease the toxicity threshold, such as combination with chemotherapy regimens (paclitaxel or trastuzumab), mediastinal radiation therapy, age, gender, and a previous history of heart or liver disease and hypertension (Singal and Iliskovic, 1998; Takemura and Fujiwara, 2007). Of note, not all subjects who undergo DOX therapy, even its high doses, present symptoms of cardiomyopathy, indicating the intrinsic genetic background disparity between patients (Pereira et al., 2011). In this regard, some evidence has pointed out that polymorphic variants in genes encoding proteins involved in inflammatory response and immune trafficking can affect the effectiveness and toxicity of anti-cancer drugs (Tecza et al., 2015; Todorova et al., 2017). Therefore, the idea of polymorphic variations in DOX-induced toxicity deserves more attention to not only attenuate its debilitating damage but also to influence target cells' insensitivity to DOX (Lehenbauer Ludke et al., 2009; Robert et al., 2005; Tecza et al.,

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2015). The degree of DOX administration is also found to be a correlate of DOX toxicity, particularly irreversible cardiotoxicity, in such a way that high-dose infusion or higher cumulative doses increases the risk of cardiac complications (Outomuro et al., 2007). More to the point, increased DOX exposure results in the devastating generation of reactive oxygen species (ROS). Accordingly, development of a simultaneous treatment with DOX and chemopreventive agents rich in antioxidant content does not diminish its performance as an anti-tumor drug, but rather augment the efficacy of cancer chemotherapy (Aydin et al., 2011; Lee et al., 2008). Of all phytochemical with anticancer and chemosensitizing abilities, curcumin (CUR) is a natural antioxidant agent considered safe, tolerable, and nontoxic even up to 12 g/day according to human clinical trials (Gupta et al., 2012; Lv et al., 2016; Vogel and Pelletier, 1815). There have been numerous studies on CUR concerning its antioxidant, anti-inflammatory, anti-tumor activities (Ganjali et al., 2014; Lv et al., 2016; Mirzaei et al., 2016; Mohajeri et al., 2017; Momtazi and Sahebkar, 2016; Momtazi et al., 2016; Outomuro et al., 2007; Panahi et al., 2016a, 2016b, 2014; Sahebkar et al., 2016). This bioactive molecule is isolated from the rhizomes of *Curcuma longa* (turmeric) traditionally used for culinary, coloring and medical purposes (Mohajeri et al., 2017). A plenty of research studies has highlighted the role of CUR in inhibition of ROS generation with protective effects against oxidative stress in various cell lines and organ tissues of animals (Cohly et al., 1998; Venkatesan, 1998). Besides, turmeric extract, CUR, and its derivatives are shown beneficial to alleviate DOX-induced toxicity (Dayton et al., 2011; Notarbartolo et al., 2005; Somasundaram et al., 2002) (Table 1. Despite extant evidence in support of CUR efficacy and safety, it has not yet been substantiated as a chemotherapeutic agent owing to its poor bioavailability (Dayton et al., 2011). In view of tumor cell resistance to the cytotoxic activities of DOX as well as low aqueous solubility and weaken stability of CUR, new technology emerges with the assistance of nanoscience and polymer engineering to promote not only the efficacy of chemotherapy, but also to the sensitivity of target cancer cells. With focus on anticancer and antioxidant properties of CUR, this review is an attempt to develop an overall understanding on DOX-induced toxicity in human organs, role of CUR in these medical conditions, its mechanism of actions, and advances in drug delivery systems for DOX-induce MDR.

2. Toxicology

2.1. Adriamycin-induced adverse reaction

2.1.1. Heart

High cumulative doses of DOX are associated with adverse effects on the heart, including congestive heart failure, dilated cardiomyopathy, and early death (Dunn, 1994; Ewer and Ewer, 2010; Jain, 2000; Takemura and Fujiwara, 2007; Tokarska-Schlattner et al., 2006; Unverferth et al., 1982). Different signaling mechanisms are implicated in the pathogenesis of cardiotoxicity and heart failure caused by DOX, such as oxidative stress, nitrogen species, mitochondrial dysfunction/damage, and activation of mitogen-activated protein kinases (MAPK) (Jin et al., 2003; Kalyanaraman et al., 2002; Kotamraju et al., 2000; Small et al., 2007; Takemura and Fujiwara, 2007; Vibet et al., 2008). Recent evidence has shown that an increase in MAPK, p38, and c-Jun N-terminal kinase (JNK) plays a pivotal role in DOX-induced cell death and cardiotoxicity (Kim and Freeman, 2003; Timolati et al., 2006).As for oxidative stress, DOX-mediated production of reactive oxygen species (ROS) may be partially involved in severe cardiac complications (Kalyanaraman et al., 2002; Kim et al., 2006a; Zhou et al., 2001a). Nevertheless, there is a controversy regarding the inhibitory effects of antioxidants (Antunes and Takahashi, 1998; Teicher et al., 1994; van Acker et al., 2001; Vile and Winterbourn, 1988; Wahab et al., 1999). Several studies on the use of antioxidant supplements cannot demonstrate a relevant protective influence against chronic toxicity (Breed et al., 1980; Legha et al., 1982; Myers et al., 1983; Van Vleet et al., 1980). Accordingly, the chronic form is more likely to arise from some non-ROS mechanisms (Ferreira et al., 2007b; Minotti et al., 1995; Olson et al., 1988), namely reduced mitochondrial calcium release channel (Dodd et al., 1993; Zhou et al., 2001b) and/or fatty acid metabolism in the myocardium (Hong et al., 2002). On the contrary, cardiotoxicity as a result of acute DOX exposure in animals was rescued by antioxidant supplementation (Lü et al., 1996; Yilmaz et al., 2006). Indeed, DOX-dependent cardiomyopathy occurs chiefly due to the oxidation-reduction cycle, the rupture of the cell membrane, the progressive loss of myofibrils, and mitochondrial vacuolization (Yoon et al., 2003), that denote lipid peroxidation (Bagchi et al., 1995). DOX stimulates ROS generation through two pathways (De Beer et al., 2001). Firstly, the enzymatic pathway leads to the synthesis of a semiquinone radical following a reduction of DOX by the enzyme nicotinamide adenine dinucleotide phosphate (NADPH)-cytochrome P450 reductase (Ferreira et al., 2008); put it differently, the quinone at the central ring (Fig. 1) has an inclination to reduction with a redox potential hovering around −320 mV, which is akin to reduced nicotinamide adenine dinucleotide (NADH) (Wallace, 2003). As a result, DOX is able to divert electrons from Complex I along with a number of other cellular dehydrogenases, including NADH transdehydrogenase, xanthine oxidase, and cytochrome P450 that culminates in the formation of semiquinone radical (Wallace, 2003). Thereafter, this radical produces superoxide radical in the presence of O_2 ($O_2^{-}\cdot$) along with the regeneration of the parent DOX molecule. Besides this, the semiquinone radical could enter into a reaction with hydrogen peroxide (H_2O_2) and produce hydroxyl radical ($\cdot OH$), which, further, initiates aggressive lesions (Solem and Wallace, 1993; Szewczyk and Wojtczak, 2002). In the second place, the production of free radicals increases after a DOX molecule puts in contact with iron, known as the nonenzymatic pathway; put it differently, H_2O_2 can be synthesized from the reaction between DOX-Fe^{++} radical and O_2. Besides this, iron can function as a catalyst for the synthesis of $HO\cdot$ based on Fenton reaction with DOX semiquinone (Pereira et al., 2011). The significant levels of free iron in cells may imply that DOX probably causes an initial dysregulation of iron homeostasis. Aconitase appears prone to changes in oxidative stress. Therefore, iron is diverted from aconitase iron-sulfur clusters, having led to an increase in free iron upon possible damage in mitochondria. Interestingly, this enzyme plays another role in its iron-free form; in other words, it can serve as an iron-regulating protein whereby iron uptake increases instead of iron sequestration, subsequently augmenting the free iron available to enter into reaction with DOX (Doroshow, 1983; Jung and Reszka, 2001; Minotti et al., 2004; Nohl et al., 1998; Šimůnek et al., 2009; Wallace, 2003). Despite some evidence indicating the partial role of oxidative stress in cardiotoxicity mechanism, it is worthy of notice given the vulnerability of the cardiac tissue to impairment caused by free radicals. That is, the heart shows the strong oxidative metabolism and the weakened antioxidant defense in comparison with other organs, including the liver and kidneys. In addition to cardiomyocytes possessing low levels of catalase (CAT) and superoxide dismutase (SOD), DOX exposure still reduces endogenous antioxidants, such as glutathione (GSH) (BayIr and Kagan, 2008; Ott et al., 2007), which, in turn, comes up with an elevation of oxidative stress preceding cardiomyopathy and heart failure (Feissner et al., 2009; McBride et al., 2006). Interestingly, DOX has a high affinity for cardiolipin, which is a phospholipid placed in the myocytic mitochondrial membrane. This not only ends up as an accumulation of DOX in the interior of cardiac cells, but also increases toxicity since the DOX-cardiolipin complex serves as the substrate for the beginning of lipid peroxidation (Goormaghtigh and Ruysschaert, 1984; Jung and Reszka, 2001). More to the point, free radicals as well as hypoxia induce cyclooxygenase-2 (COX-2), an isoform of COX that catalyzes the transformation of arachidonic acid to prostaglandins (Hemler and Lands, 1976; Adderley and Fitzgerald, 1999; Fitzpatrick et al., 2011). It was shown that inhibition of COX-2 contributed to the progression of heart failure upon DOX exposure, proposing that COX-2 is more likely a key component in the final pathway of DOX-induced