



EDITORIAL COMMENT

Decreasing doxorubicin-induced cardiotoxicity with *Nigella sativa* seed extract: Traditional medicine targeting a severe clinical problem

Diminuição da cardiotoxicidade da doxorubicina com extratos de sementes de *Nigella sativa*: medicina tradicional direcionada a um problema clínico severo

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Anthracyclines are a family of approved anticancer agents that are clinically effective for treating both solid tumors and leukemias. One member, doxorubicin (DOX), is one of the most frequently prescribed chemotherapeutic drugs worldwide, due to its broad spectrum of therapeutic efficacy. DOX is effective against various types of cancer, among them leukemias, lymphomas, and several solid tumors, including gynecological, urogenital, endocrine, breast and brain tumors, stomach cancer, and Ewing and Kaposi's sarcoma. As with other anticancer agents, the clinical use of DOX is associated with several off-target effects. Notably, the most limiting adverse DOX side-effect is the incidence of cardiovascular toxicity, resulting in hypotension, tachycardia, arrhythmias, and ultimately the development of congestive heart failure, the most serious and dose-limiting consequence, if not detected in time.¹

Acute DOX toxicity is rarely severe. It may involve transient electrophysiological alterations, which can occur immediately after each treatment or appear a week after the last course,² disappearing with cessation of the treatment. Some reports indicate that pericarditis or myocarditis may play a part in some severe or even fatal events, resulting from cardiomyocyte damage and release of proinflammatory molecules³ or from the activation of NF-κB.⁴

Cardiomyopathy and eventual congestive heart failure are the most severe events associated with DOX therapy. The incidence of DOX cardiomyopathy in treated patients depends on the cumulative treatment dose used, rising to 36% when the dose exceeds 600 mg/m². Heart failure affects 26% of patients receiving DOX in a cumulative dose exceeding 550 mg/m².¹ Early-onset and progressive DOX cardiotoxicity may occur within a year or not become apparent until years after the last treatment course. It can manifest as chronic dilated cardiomyopathy in adult patients or as restrictive cardiomyopathy in pediatric patients, who have

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decreased left ventricular ejection fraction, and occasionally results in fatal events.⁵ Importantly, early detection of subclinical cardiovascular events caused by DOX within the first year post-treatment can result in total or partial recovery of cardiac function.⁶

Many mechanisms underlie DOX cardiotoxicity, prominent among which is increased generation of reactive oxygen species. In the early 1980s, Davies and Doroshow proposed that DOX undergoes redox cycling in cardiac mitochondria, being activated to a highly reactive semi-quinone, which reacts with oxygen to produce the superoxide anion.⁵ The extensive network of mitochondria in the cardiomyocyte and lower efficacy of the antioxidant network in the heart compared to other tissues may explain the selective cardiotoxicity.⁷ Mitochondrial alterations, including reduced capacity to produce adenosine triphosphate (ATP), combined with altered metabolic and transcriptomic profiles, are also involved in DOX cardiomyopathy.⁵

Hundreds of publications have proposed different molecules capable of decreasing DOX cardiotoxicity. Potential interventions to reduce this cardiotoxicity have mostly revolved around the pro-oxidant nature that underlie the side effects. So far, dexrazoxane is the only FDA-approved protective therapy against DOX toxicity. Its mechanism of protection is not entirely clear. Although it was initially thought to be mediated by iron chelation, thus indirectly decreasing oxidative stress through Fenton-type reactions, potent iron chelators such as desferrioxamine B do not confer the same degree of cardioprotection.⁸ Inhibition of cardiac nuclear topoisomerase II beta and inhibition of DOX-induced DNA breaks are also possible mechanisms for cardioprotection by dexrazoxane.⁹

Several natural molecules have been tested for prevention of DOX cardiotoxicity, including melatonin, genistein, vitamin E, caffeic acid phenethyl ester and epigallocatechin-3-gallate, to mention a few.¹⁰

The paper by Adiyaman et al. published in this issue of the *Journal*¹¹ reports the protection afforded against DOX cardiotoxicity by *Nigella sativa* (NS), a flowering plant in the Ranunculaceae family, in the form of its black seeds. The plant has a widespread distribution, including southwest Asia, the Mediterranean, India and the Middle East.

The authors used an in vivo rat model of DOX cardiotoxicity, with a single 10 mg/kg intraperitoneal dose. The animals in the NS group were given standard rodent feed together with a daily 100 mg/kg dose of NS extract diluted in water and administered through gavage for 35 days. A single 10 mg/kg intraperitoneal dose of DOX was administered on day 28. The protocol used by the authors resulted in DOX-induced cardiotoxicity, as observed by a significant increase in troponin and NT-proBNP levels. Animals in the NS+DOX group showed lower markers of cardiac toxicity markers, including histological markers. A potential mechanism for the protection observed involves antioxidant protection, since animals in the NS+DOX group showed higher total serum antioxidant capacity and lower oxidative stress markers than animals treated only with DOX.

Although this study is very promising, there are two points requiring caution. The extracts used contain thymoquinone, which in large amounts can cause liver toxicity. High dosages

of NS also have proinflammatory effects, which means that uncontrolled use of the extract to counteract DOX cardiotoxicity may be hazardous. Secondly, the effects of NS on the anticancer effects of DOX were not determined. Ideally, protective agents should have no effect or even increase the anticancer activity of the primary treatment.

Despite these potential caveats, the paper by Adiyaman et al. adds another natural extract to the list of coadjuvants that potentially reduce DOX cardiotoxicity. Follow-up studies aimed to address the above points and to identify the active components responsible for cardioprotection should increase the interest in this extract in the context of anthracycline cardiotoxicity.

Conflicts of interest

The author has no conflicts of interest to declare.

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