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Natural strategies of preventing anthracycline-induced cardiotoxicity – a review

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Abstract. Cardiotoxicity is one of the worst long-term effects of cancer therapy and doxorubicin is one of the main compounds responsible for cardiovascular complications. There are several biologically active compounds that can alleviate or prevent cardiotoxicity through multiple directions. Therefore, one of the aims of this paper is to emphasize the mechanisms by which several naturally occuring substances can improve the cardiac activity after drug-induced cardiotoxicity. The second part of this paper aims to update the molecular mechanism by which physical exercise and nutrition improve the life of a person with cardiovascular disease. The data collected showed that an active life and following a diet rich in polyphenols, coenzyme Q10, magnesium, may enhance the cardiovascular activity after exposure cu cardiotoxic drugs.

Keywords: cardiotoxicity, antioxidants, prevention, polyphenols

Introduction

Over the last decades, the number of cancer survivors has increased significantly due to progress in the methods of early detection and in antitumor treatment. For example, in the USA in 1975 the number of cancer survivors was 3.6 million, whereas in 2016 it was 15.5 million, and it is further estimated that in 2040 the number will be around 26.1 million (Shapiro, 2018). In Great Britain, the number of adult survivors has doubled in 40 years, and that of

children survivors has tripled (Cancer Research UK, 2014). Worldwide, the ten-year survival rate is approximately 50% for 20 of the most common cancers and over 80% for breast, uterus, lymphoma and melanoma cancers, and it is estimated that the rate will increase by 3% per year (Coleman *et al.*, 2011). In children, the survival rate exceeds 80% (Nathan *et al*., 2022).

Paradoxically, the survival of cancer patients is endangered by cardiotoxicity induced by antitumor treatment and especially by anthracyclines (doxorubicin, epirubicin, daunorubicin, idarubicin), which can be fatal. Doxorubicin (DOX) is highly efficient in treating solid and metastatic tumors (Sritharan and Sivalingam, 2021), malign lymphomas and leukemia (Benzer *et al.*, 2018). Cardiovascular complications of anthracyclines are due to high, cumulative doses, although problems may also occur at low doses and require discontinuation of treatment. Cardiotoxicity consists of the progressive decrease of the left ventricle ejection fraction (LVEF), which leads to the development of heart failure, high blood pressure, valvular disease, thromboembolism, arrhythmias (supraventricular and ventricular), myocarditis and pericarditis (Salvatici and Sandri, 2015; Nonaka *et al*., 2021).

Recently, several pharmacological compounds (modified anthracyclines, antioxidants, renin-angiotensin antagonists, cardioselective beta-blockers, statins etc.) have been tested for prophylaxis or treatment of cardiotoxicity, but their efficacy has not been proven by clinical trials (McGowan *et al.*, 2017). As such, natural compounds with cardioprotective properties have been studied and their result, both *in vitro* and *in vivo* animal studies, have shown that they could be used as an adjuvant treatment in cardiotoxicity.

The aims of this paper are 1) to emphasize the mechanisms of several naturally substances that can improve the cardiac activity after drug-induced cardiotoxicity and 2) to update the molecular mechanism by which physical exercise improves the life of a person with cardiovascular disease.

1. Natural alternatives for cardioprotection

Polyphenols are biologically active compounds found in plants, where they form defense systems, protecting them from pathogen invasions. There are thousands of polyphenols, which differ in the number of phenolic nuclei and hydroxyl groups, but also in the type of organic acids and carbohydrates attached. Polyphenols serve an important function in preventing cardiotoxicity mainly due to their antioxidant properties. One of the main mechanisms involved in the occurrence of cardiotoxicity is oxidative stress**,** therefore in order to mitigate its harmful effects polyphenolic treatments could be very effective (Wallace, 2003; Rana *et al*., 2022).

Resveratrol is a polyphenol found in the skin of grapes, berries and red wine. It has antioxidant, anti-inflammatory, anti-tumor properties and it is known as a modulator of lipid metabolism and inhibitor of LDL oxidation (Meng *et al.*, 2021). Resveratrol attenuates the effects of doxorubicin by reducing oxidative stress and lipid peroxidation, preventing apoptosis, and inhibiting cardiomyocyte autophagy without reducing the effectiveness of antitumor therapy (Hu *et al*., 2016; Tatlidede *et al*., 2009; Sin *et al*., 2015; Dutta *et al*., 2014).

Curcumin is the active compound extracted from the rhizomes of *Curcuma longa*, a plant popularly known as turmeric. It has many pharmacological and biological properties, such as antioxidant, anti-inflammatory, antitumor, antimicrobial and antifungal (Stanić, 2017). The cardioprotective effects of curcumin on doxorubicin treatment relies in improving cardiac biomarkers, reducing oxidative stress and inhibiting apoptosis (Imbaby et al., 2014).

Quercetin, which is found in all plant organisms except fungi and algae, is one of the most potent natural antioxidants (Hosseini, 2021). Its protective actions consist of chelating metal ions, removing free radicals, modulating lipid peroxidation and improving antioxidant systems, thus protecting DNA integrity (Muthukumaran *et al*., 2008; Matouk *et al*., 2013). Co-administered with doxorubicin, quercetin enhances the chemosensitivity of breast tumor cells to doxorubicin and in the liver potentiates the effects of doxorubicin in tumor cells, while protecting normal hepatocytes (Li *et al*., 2013; Wang *et al*., 2012). Quercetin attenuates cardiotoxicity by restoring the activity of antioxidant enzymes and lowering the concentration of proinflammatory cytokines, especially when co-administered with losartan (Matouk *et al*., 2013).

Epigallocatechin, the main polyphenol in green tea (*Camellia sinensis*), is known for its antioxidant and antitumor properties. Epigallocatechin improves both doxorubicin-induced and cisplatin-induced cardiotoxicity. After treatment with doxorubicin, it inhibits apoptosis and the formation of reactive oxygen species, both *in vitro* and *in vivo*. It prevents cardiotoxicity by inhibiting the formation of free radicals, apoptosis in normal cardiomyocytes and their overload with calcium (Shabalala *et al*., 2017). In the case of cisplatin treatment, epigallocatechin alleviates cardiotoxicity by improving histological parameters and the activities of antioxidant enzymes (Ibrahim *et al*., 2019).

Cardioprotective effects have also been noticed for other polyphenols, but they have a limited spread. For example, soybean genistein, parsley apigenin, celery and chamomile, rooibos aspalathin, hesperetin, naringenin and bergamot from citrus, oleuropein from olive leaves, extract of *Achillea fragrantissima* (Shabalala *et al*., 2017; Caressi *et al*., 2016; Hijazi *et al*., 2019).

To prevent or reduce anthracycline-induced cardiotoxicity, a number of plant extracts are being studied for their well-known cardioprotective effects. For example, extracts of *Citrus paradise*, *Passiflora incarnata*, *Angelica sinensis*,

Salvia miltiorrhiza, *Prunella vulgaris*, *Camellia sinensis*, *Phyllanthus urinaria*, *Acacia hydaspica* and *Centella asiatica* prevent cardiotoxicity through antioxidant properties. Extracts of *Astragalus polysaccharide*, *Azadirachta indica*, *Ganoderma atrum* and *Allium sativum* inhibit cardiomyocyte apoptosis and reduce DNA damage. Extracts of *Urtica parviflora*, *Flacourtia indica* and *Curcuma longa* decrease plasma triglycerides and LDL levels in doxorubicin-treated rats. Extracts of *Ginkgo biloba*, *Berberis vulgaris*, *Rhodiola rosea*, *Ixora coccinea*, *Vaccinium myrtillus* and *Panax notoginseng saponins* improve the contractile function of the left ventricle. Unfortunately, the plant extracts listed above will not soon be subject of clinical trials because 1) there is no information on the bioavailability of the active compounds in humans, and 2) most studies have been performed in tumor-free animals, so it is unknown whether these extracts affect antitumor activity of doxorubicin (Abushouk *et al*., 2017; Yu *et al*., 2018; Li *et al*., 2018; Xing *et al*., 2019; Afsar *et al*., 2019).

Coenzyme Q10, also known as ubiquinol, is synthesized in the human body in the smooth endoplasmic reticulum. It is involved in redox reactions in the mitochondrial respiratory chain, regulating the permeability of cell membranes, regulates endothelial function by regenerating vitamin E and preventing lipid peroxidation. Naturally, it is found in meat, fish, cereals, broccoli, spinach, and its synthetic form is available as capsules and solutions with different concentrations. Coenzyme Q10 is used to treat paracetamol poisoning, inflammatory diseases and heart failure. Recently, it has been shown to prevent doxorubicin-induced cardiotoxicity by reducing left atrium remodeling, improving myocardial oxygenation, reducing necrosis, fibrosis, and lipid infiltration into the heart muscle (Botelho *et al*., 2019).

Magnesium is involved in many intra- and extracellular processes. It has anti-inflammatory and antioxidant properties, inhibits apoptosis and reduces calcium overload in cardiomyocytes, and attenuates necrosis and apoptosis caused by CO poisoning. Food sources of magnesium are almonds, sesame seeds, bananas, cashews, and tofu. In doxorubicin-treated rats, magnesium reduces mortality, restores myocardial contractility, and improves antioxidant activity (Khalilzadeh *et al*., 2018).

Leucine is an essential branched chain aliphatic aminoacid used to attenuate proteolysis in hyperthyroidism, during treatment with dexamethasone and also in cancer. In experimental myocardial infarction, leucine serves as an alternative energy substrate, reducing arrhythmias and heart failure. Food sources of leucine are egg whites, meat, fish, dairy products, nuts, beans. Dietary supplementation with 5% leucine in doxorubicin-treated rats prevented the onset of cardiotoxicity by preserving the left ventricular ejection fraction and prevented fibrosis (Fidale *et al*., 2018).

2. Physical activity in the anthracycline-treated patients

In adults with cardiovascular disease, physical activity promotes recovery and improves the quality of life (Buckley *et al*., 2013). In cancer patients, physical activity during both treatment and recovery removes fatigue and depression and slightly improves the quality of life (Furmaniak *et al*., 2016; Lahart *et al*., 2018). For these reasons, the World Cancer Research Fund (WCRF) and the International Agency for Research on Cancer (IARC) recommend that cancer patients have at least 30 minutes of physical activity a day, at least five times a week (WCRF/AICR, 2007; Leitzmann *et al*., 2015). Physical activity may prevent or attenuate doxorubicin-induced cardiotoxicity, whether practiced before, during, or after cessation of treatment (Maia *et al*., 2017).

Although most of the information on cardioprotection provided by physical exercise originates from animal studies, it can be used as a starting point in clinical trials because it has been able to decipher, at least in part, the molecular mechanisms by which physical activity attenuates the side effects of doxorubicin. Physical activity decreases the excessive formation of reactive oxygen species induced by doxorubicin, by stimulating the activity of antioxidant enzymes such as glutathione peroxidase 1, catalase and superoxide dismutase. Aerobic exercise also stimulates the formation of heat shock proteins (HSPs) 60 and 72, which provide cardioprotection probably by controlling protein folding, preventing denaturation and aggregation of intracellular proteins, and accelerating the degradation of damaged proteins (Scott *et al*., 2011).

Physical activity inhibits doxorubicin-induced apoptosis by inhibiting Bax and caspase 3 activity and reducing p53 expression and apoptotic cardiomyocytes (Ascensão *et al*., 2005; Werner *et al*., 2008). Physical activity prevents doxorubicin-induced calcium overload of cardiomyocytes. Exercise restores myocardial contractile, systolic and diastolic function by stimulating calcium release from the smooth endoplasmic reticulum and modulating calpain activity (French *et al*., 2008).

Physical activity prevents doxorubicin-induced autophagy by inhibiting enzymes in its signaling pathway (Smuder *et al*., 2013). Also, it attenuates the accumulation of doxorubicin in the myocardium and thereby maintains its functions (Jensen *et al*., 2013).

There are a small number of studies in humans that have evaluated the ability of physical exercise to prevent or attenuate the cardiotoxicity of doxorubicin in women with early-stage breast cancer. The results are modest, as the studies included a small number of patients and the physical exercises were performed for short periods of time. A single exercise session before each dose did not affect the markers of cardiotoxicity (size and ejection

fraction of the left ventricle, troponin t and NT-proBNP), but improves hemodynamics, body weight and mood (Kirkham *et al*., 2018). Two sessions of aerobic and endurance exercise per week for two weeks before doxorubicin administration only improved plasma concentration of troponin and VO_2 (Howden *et al*., 2019).

Recently, several pilot studies have been proposed to evaluate the ability of exercise to prevent or treat anthracycline-induced cardiotoxicity. Lee *et al*. (2019) aimed to evaluate the effects of high-interval training on vascular function in breast cancer survivors undergoing anthracycline chemotherapy. Antunes *et al.* (2019) proposed a clinical study to determine whether a full-time exercise program (aerobic and endurance) accompanying doxorubicin treatment in 90 patients with invasive breast cancer attenuates cardiotoxicity. Foulkes *et al*. (2020) designed a study to determine if a 12-months structured exercise training can prevent cardiac morbidity in breast cancer patients. Diaz-Balboa *et al*. (2021) proposed a randomized trial to evaluate the impact of exercise-based cardiac prevention for the prevention of chemotherapy-induced cardiotoxicity in patients with breast cancer. No results of the proposed studies listed above have yet been published.

Conclusions

The development of cardiotoxicity complications brought by anticancer therapy is no longer a novelty. Although, finding solutions to reduce their harmful effects is still a challenge. The role of polyphenols and other biologically active compounds mentioned in the present paper, could significantly minimize the toxic effect of doxorubicin, by reducing producing of free radicals, improving myocardial oxygenation, reducing fibrosis, reducing calcium overload in cardiomyocytes and many more. As an additional cardioprotective strategy, performing physical exercise could accelerate the degradation of damaged proteins or stimulate the activity of antioxidant enzymes.

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