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Review article

Polyphenols, autophagy and doxorubicin-induced cardiotoxicity

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ABSTRACT

Doxorubicin is a highly effective, first line chemotherapeutic agent used in the management of hematological and solid tumors. The effective use of doxorubicin in cancer therapy has been severely limited owing to its well-documented cardiotoxic side effect. Oxidative stress, lipid peroxidation, apoptosis as well as dysregulation of autophagy, has been implicated as a major contributor associated with doxorubicin-induced cardiotoxicity. Increased oxidative stress and lipid peroxidation are known to enhance the production of reactive oxygen species, while autophagy has been reported to protect the cell from stress stimuli or, alternatively, contribute to cell death. Nonetheless, to date, no single chemical synthesized drug is available to prevent the harmful action of doxorubicin without reducing its anti-cancer efficacy. Therefore, the search for an effective and safe antagonist of doxorubicin-induced cardiotoxicity remains a challenge. In recent years, there has been much interest in the role plant-derived polyphenols play in the regulation of oxidative stress and autophagy. Therefore, the present review renders a concise overview of the mechanism associated with doxorubicin-induced cardiotoxicity as well as giving insight into the role plant-derived phytochemical play as a possible adjunctive therapy against the development of doxorubicin-induced cardiotoxicity.

Contents

Abbreviations: Akt, protein kinase B; AMPK, adenosine monophosphate-activated protein kinase; ASP, aspalathin; ATP, adenosine triphosphate; Atgs, autophagy-related genes; Bax, B-cell lymphoma-2-like protein 4; Bcl-2, B-cell lymphoma 2; BNIP3, Bcl-2 interacting protein 3; CAT, catalase; CVD, cardiovascular disease; Cyt c, cytochrome c; Dox, doxorubicin; Dexra, dexrazoxane; DNA, deoxyribonucleic acid; FDA, Food and Drug Administration; Fe^{2+}, ferrous iron; Fox01, forkhead box protein 01; GSH, glutathione; GPx, glutathione peroxidase; H_2O_2, hydrogen peroxide; HF, heart failure; JNK, c-Jun N-terminal kinase; LC3, light chain 3; MAPK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; NAD, nicotinamide adenine dinucleotide; NCD, non-communicable disease; Nrf2, nuclear factor erythroid 2-related factor; $O_2^{\bullet -}$, superoxide radicals; OH•, hydroxyl radical; OXPHOS, oxidative phosphorylation process; PE, phosphatidylethanolamine; PI3K3, phosphatidylinositol 3-phosphate kinase; ROS, reactive oxygen species; SOD, superoxide dismutase; ULK1, serine-threonine kinase othrology of Unc-51-like; WHF, World Heart Federation; WHO, World Health Organization.

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1. Introduction

Non-communicable diseases (NCDs) are a major contributor to the global burden of disease and can be defined as a chronic condition that is non-transmissible and non-infectious [50]. Globally, NCDs are responsible for almost 70% of all deaths and this number is said to increase by a further 17% over the next 10 years [121]. This increase in morbidity and mortality of NCDs does not only result in a reduced quality of life and loss of human life expectancy, but imposes a heavy financial cost on a country's health system and national budget. Globally, cardiovascular disease (CVD) is the leading cause of premature mortality, accounting for 17.5 million deaths, followed by cancers (8.2 million) [120]. The combination of CVDs and cancers accounts for 68% of all global NCD mortality rate. Improvement of cancer therapeutics has led to a better prognosis and increased survival rate for cancer patients. However, this increase in cancer survival has resulted in an associated risk for cardiovascular complications, contributing to the mortality rate of CVDs and creating a fascinating overlap in the prevalence of cancer and CVDs [1].

Anthracyclines are a group of highly effective chemotherapeutic agents that are used in the treatment of a wide variety of adult and pediatric cancers [79]. The family of anthracyclines was identified in the early 1950s with the discovery of daunorubicin from the soil bacterium *Streptomyces peucetius* [17,117]. However, daunorubicin was only found to be effective against the treatment of specific leukemias and lymphomas [108]. In the 1960′s, doxorubicin (Dox), a derivative of daunorubicin, was identified and found to be a more effective chemotherapeutic agent [117]. Since the introduction of these chemotherapeutic agents, the 5-year cancer survival rate has increased from ~40% in the mid-1970s to ~80% in 2010 and this was observed in both male and female cancer survivors (Fig. 1) [8,57]. However, concomitant to the improved cancer survival rate an increase in the incidence of heart failure (HF) was observed [17,79,108,117]. This was confirmed by various observational studies, which showed that anthracyclines such as Dox are known to cause long-term cardiovascular side effects decreasing the quality of life of cancer survivors [79,91].

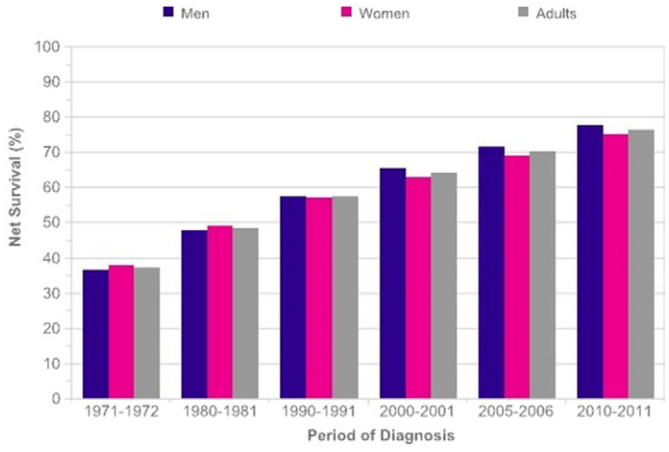

Fig. 1. The 5-year cancer survival rates: the survival rate has increased from <50% in 1971 to approximately 80% in 2010.
Taken from Cancer Research UK [8].

2. Doxorubicin efficacy and cardiotoxicity

Doxorubicin (Dox), sold under the trade name of Adriamycin, has been used in the treatment of a wide variety of hematological malignancies, carcinomas and solid sarcomas [18]. Dox has become one of the most effective chemotherapeutic agents. However, its efficacy has been hindered by its dose-dependent (acute) and cumulative (chronic) cardiotoxic side effects [117]. Dox-induced cardiotoxicity usually occurs within 2–3 days after receiving a high dose of Dox, also referred to as acute onset [39,107]. This type of cardiotoxicity is characterized by a prolonged Q-wave and T-wave interval (QT interval) and is frequently identified in adults older than 65 and children younger than 5 years [107]. Acute cardiotoxicity can be reversed and clinically managed [12]. However, this is not the case with chronic Dox-induced cardiotoxicity that is known to develop 10–15 years after the cessation of Dox chemotherapy [54]. Chronic Dox-induced cardiotoxicity is characterized by left ventricular dysfunction, a distinctive HF pathology that cannot be clinically managed or reversed [86]. The manifestation of this lethal form of cardiotoxicity is directly related to the cumulative dose of Dox. In a study done by Swain et al. [106], it was shown that patients who received a cumulative dose of 400 mg/m^2 of Dox were associated with a 5% increased risk of HF. This risk increased by 26% and 48% with the use of 550 mg/m^2 and 700 mg/m^2 of Dox, respectively (Table 1) [106]. Furthermore, in the retrospective analyses, which included clinical data from >4000 patients on Dox treatment, 2.2% of these patients developed congestive HF [117]. Additionally, in a study done by Billingham et al. [6], the authors showed that as little as 240 mg/m^2 of Dox was able to induce histopathological changes in heart tissue obtained from patient biopsies that were on Dox treatment. However, of great concern is the development of Dox-induced cardiotoxicity in pediatric cancer survivor's years after cessation of Dox treatment [58]. This is of particular interest as these young cancer survivors would be in the prime of their life during the onset of the disease and instead of being part of the work force, they will be a financial burden on the country's health system and the national budget. Despite these pitfalls, the use of traditional cytotoxic drugs continues to be the mainstay treatment for several types of cancer.

Table 1
The effect of a cumulative dose of doxorubicin on cardiac function.
Taken from Swain et al. [106].

Doxorubicin dosage (mg/m^2)	Heart failure incidence (%)
400	3–5
450	5–8
500	6–26
700	48