Biomedicine & Pharmacotherapy 68 (2014) 1149–1159

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Review

The flavonoid quercetin: Possible solution for anthracycline-induced cardiotoxicity and multidrug resistance

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ARTICLE INFO

Article history:
Received 9 September 2014
Accepted 16 October 2014

Keywords:
Flavonoid
Quercetin
Antioxidant
Anthracycline
Cardiotoxicity
Multidrug resistance

ABSTRACT

Anthracycline chemotherapy is often used in the treatment of various malignancies. Its application, however, encounters several limitations due to development of serious side effects, mainly cardiotoxicity and may be ineffective due to multidrug resistance (MDR). Many different compounds have been evaluated as poorly effective in the protection against anthracycline side effects and in the prevention from MDR. Thus, continuous investigational efforts are necessary to find valuable protectants and the flavonoid quercetin (Q) seems to be a promising candidate. It is present in relatively high amounts in a human diet and the lack of its toxicity, including genotoxicity has been confirmed. The structure of Q favours its high antioxidant activity, the potential to inhibit the activity of oxidative enzymes and to interact with membrane transporter proteins responsible for development of MDR, e.g. P-glycoprotein. Furthermore, Q can influence cellular signalling and gene expression, and thus, alter response to exogenous genotoxicants and oxidative stress in normal cells. It accounts for its chemopreventive and anticancer properties. Overall, these properties might indicate the possibility of application of Q as cardioprotectant during anthracycline chemotherapy. Moreover, numerous biological properties displayed by Q might possibly result in the reversal of MDR in tumour cells and improve the efficacy of chemotherapy. However, these beneficial effects towards anthracycline-induced complications of chemotherapy have to be further explored and confirmed both in animal and clinical studies. Concurrently, investigations aimed at improvement of the bioavailability of Q and further elucidation of its metabolism after application in combination with anthracyclines are needed.

1. Introduction

Anthracycline anticancer drugs belong to the most frequently used agents in chemotherapy of various tumours. Despite substantial toxicity, especially to the heart, anthracyclines constitute crucial drugs for the treatment of many cancers in adults. Moreover, the treatment of childhood cancers requires the use of anthracyclines in prevailing number of cases.

These drugs are used both in a single-agent treatment and in regimens where they are incorporated with other anticancer agents, e.g. taxanes. The use of anthracyclines in clinical practice is, however, limited by their high toxicity displayed to all cells that are not targets for their anticancer activity. The achievement of specific cumulative dose is associated with development of serious side effects, mainly cardiotoxicity [1]. The heart muscle is particularly susceptible to action of xenobiotic compounds, which induce oxidative stress and cause other cellular perturbations. The level of the activity of antioxidant enzymes and low-molecular weight antioxidants is lower in myocardium in comparison to other organs [2]. Cardiotoxicity is related to the occurrence of various cardiac events, including heart failure. These cardiac events may appear at the time of administration of an anthracycline or at any other time after treatment. In cancer survivors, symptoms of cardiotoxicity might arise up to many years

Abbreviations: AIF, Apoptosis-inducing factor; BCRP, Breast cancer resistance protein; CDK2, Cyclin-dependent kinase 2; CHF, Congestive heart failure; DMBA, Dimethyl benz(*a*)anthracene; DNR, Daunorubicin; DOX, Doxorubicin; EPI, Epirubicin; EpRE, Electrophile-responsive element; GSH, Glutathione reduced; GSSG, Glutathione oxidized; HDL, High-density lipoprotein; HIF-1α, Hypoxia-inducible factor-1 α; HOMO, Highest unoccupied molecular orbital; IDA, Idarubicin; IUPAC, International Union of Pure and Applied Chemistry; LDH, Lactate dehydrogenase; LDL, Low-density lipoprotein; LOX, Lipooxygenase; LUMO, Lowest unoccupied molecular orbital; LVEF, Left ventricular ejection fraction; MDR, Multidrug resistance; MRP, Multidrug resistance-associated protein; NF-κB, Nuclear factor κB; Nrf2, Nuclear factor erythroid 2-related factor 2; P-gp, P-glycoprotein; Q, Quercetin; RCTs, Randomised controlled trials; ROS, Reactive oxygen species; SAR, Structure–activity relationship; SEDDS, Self-emulsifying drug delivery system; TNF-α, Tumour necrosis factor-α; XO, Xanthine oxidase.

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http://dx.doi.org/10.1016/j.biopha.2014.10.013
0753-3322/

after chemotherapy which is particularly important to childhood cancer patients [3].

New drug generations and derivatives have been developed in order to lower the toxicity of first-generation anthracyclines (daunorubicin, DNR and doxorubicin, DOX). Second generation of anthracyclines include epirubicin (EPI), aclarubicin, idarubicin (IDA) and pirarubicin. Furthermore, many newer anthracycline derivatives have been also developed [4]. Compounds, which possess strong anticancer properties with concurrent lower cardiotoxicity, are among those being investigated in vitro and in vivo, e.g. hyrubicin [5]. One of the compounds based on the structure of anthracyclines is an anthraquinone drug mitoxantrone [6], which has only three planar rings and do not possess a sugar part in its molecule. Also, new formulations (liposomal drugs, hydrogel and nanoparticle carriers for drug delivery) and conjugates have been developed to improve the targeting of drugs to cancer cells and reduce toxicity towards normal cells [7,8]. Unfortunately, none of the new drugs and improvements in formulations applied clinically did not completely abrogate cardiotoxicity and other side effects and efficacy of recent advancements still needs to be evaluated [7].

A meta-analysis of 55 randomised controlled trials (RCTs) revealed that chemotherapy regimens with the use of anthracycline in comparison with non-anthracycline regimens, e.g. mitoxantrone, increase significantly the risk of development of clinical and subclinical cardiotoxicity. Simultaneously, replacing DOX with EPI, or the use of liposomal DOX, or the addition of a cardioprotective agent to therapy caused a significant reduction of the risk of induction of clinical cardiotoxicity in patients [9]. Conversely, other studies did not decisively favour the use of EPI over the use of DOX when the same doses of these drugs were used. Five RCTs studying administration of equal doses of EPI or DOX revealed no significant differences in the incidence of clinical heart failure between patients from these two groups. Two other RCTs compared the use of liposomal DOX with its conventional form. The lower incidence of clinical and subclinical heart failure in adult patients that received liposomal DOX to treat solid tumours was indicated by meta-analysis as significant with a conclusion to favour this form of administration of DOX [10].

Another approach to solve the problem of anthracycline side effects, mainly cardiotoxicity, include addition of compound/s which would ensure protection against toxicity of these drugs. A number of different compounds have been investigated to find cardioprotectants, including vitamins (mainly vitamin A, C and E), *N*-acetylcysteine, melatonin. Although these substances possess potent antioxidant properties in vitro most of them have been shown to act ineffectively in protection against anthracycline cardiotoxicity in animals [11] or in clinical trials, e.g. vitamin E [12] and *N*-acetylcysteine [13]. No protection against other anthracycline-induced side effects, e.g. oral mucositis caused in children by DOX, was also shown for vitamin E administered topically [14]. The list of other compounds potentially protecting from anthracycline-induced cardiomyopathy include enalapril, probucol, amifostine and carvedilol. Among these compounds carvedilol seems to be the most promising [15]. Enalapril, for example, has been shown to protect against the decline in left ventricular ejection fraction (LVEF) induced in patients by administration of high doses of DOX [16]. The lowering of LVEF was also prevented by carvedilol in patients who received DOX doses exceeding 500 mg/m^2 [17]. A decrease in LVEF caused by different anthracyclines was normalised in a substantial number of the studies cases as a result of administration of enalapril and carvedilol [18]. Probucol, a lipid-lowering drug, has antioxidant properties and it has been found to fully protect rat cardiomyocytes against damage induced by treatment with DOX without changing the anticancer properties of the anthracycline [19]. On the other hand, RCTs investigating the protective effectiveness of eight antioxidants (*N*-acetylcysteine, phenethylamines, coenzyme Q10, a combination of vitamins E and C and *N*-acetylcysteine, L-carnitine, carvedilol, and amifostine) have revealed that none of them displayed a cardioprotective effect against heart damage caused by anthracyclines in children and adult cancer patients. Only dexrazoxane showed a significant decrease in the incidence of the heart failure in adults with advanced breast cancer [20].

Despite many years of investigation only one compound, i.e. dexrazoxane, has been approved and introduced into clinical practice as chemotherapy-supplementing drug preventing from the main side effect of anthracyclines – cardiotoxicity [21]. It has been also shown that dexrazoxane protects from other side effect related to the use of anthracyclines – extravasation [22] and might protect ovarian cells from oxidative damage induced by DOX [23]. A possible delay in the development of multidrug resistance (MDR) might be another important effect of dexrazoxane [24]. Dexrazoxane is a potent antioxidant preventing against cardiotoxicity of anthracyclines, because in vivo it is converted into strong iron chelator, which does not allow for formation of complexes of iron with anthracycline molecules and subsequent reactive oxygen species (ROS) production. It has been pointed out, however, that the use of dexrazoxane may be connected to several limitations, mainly the possibility of lowering the anticancer efficacy of chemotherapeutics and the possibility of induction of secondary tumours [25].

Also, other new potential cardioprotectants with established chelating properties have been investigated recently [26]. Flavonoids belong to compounds with promising essential features. One of the modes of antioxidant action of flavonoids is the chelation of transient metal ions and blocking of their catalytic action in the Fenton and Haber–Weiss reactions, which provide protection of cells from generation of oxygen oxidants.

Various polyphenolic compouds, such as resveratrol, semisynthetic flavonoid monohydroxyethylrutoside (monoHER) and natural flavonoid quercetin (Q) are among substances, which possess a potential to protect normal cells against toxicity displayed by doxorubicin. Antioxidant properties of flavonoids are determined by their chemical structure and vary in different classes of these compounds. Flavonoids can react directly with free radicals ($OH^{\bullet}$, $RO^{\bullet}$, $ROO^{\bullet}$ and other). This activity is of paramount importance to cardiomyocytes, which are particularly susceptible to oxidative damage induced by anthracycline drugs [27].

Diverse polyphenolic compounds, among them flavonoids, have been searched for cardioprotective compounds and proposed as potent inhibitors of toxicity of anticancer therapies, including anthracycline and other chemotherapies [28]. Flavonoids constitute a large, diversified group comprising numerous compounds (more than 8000), from which some of them are present in substantial amounts in a diet in fruits and vegetables [29], e.g. mainly Q, kaempferol, catechin, epicatechin and their gallates, myricetin, hesperetin, naringenin, genistein, daidzein and cyanidin [30]. In plants, they occur prevalently as respective glycosides.

2. Structure, sources and properties of quercetin

Quercetin is one of the flavonoids with already well recognized multiple biological protective properties which have gained much concern. It has been suggested as a compound, which could possibly accomplish several problems aroused due to toxicity of anthracyclines. Q chemical name, according to IUPAC, is 2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxychromen-4-one [31], however, other shorter names are often utilized as well: 3,3′,4′,5,7-pentahydroxyflavanone (3,3′,4′,5,7-pentahydroxy-2-phenylchromen-4-one) [32]. It belongs to flavonoids, which possess 5 hydroxyl groups attached to molecule, and three of these groups are bound