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Berberine efficacy against doxorubicin-induced cardiotoxicity: A systematic review

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ABSTRACT

Cardiotoxicity is one of the main complications of chemotherapy that increases morbidity and mortality in cancerous patients. The present systematic review aimed to investigate the protective effects of berberine (Ber) on doxorubicin (Dox)-induced cardiotoxicity. The study protocol was developed following the PRISMA statement. An extensive search was performed in multiple databases, including Embase, PubMed, Cochrane library, Web of Science, and Scopus. After defining the inclusion/exclusion criteria of the study, 12 records were included. The desired data of the retrieved articles were extracted from the studies and imported into an Excel form and ultimately, the effects, probable outcomes and mechanisms were surveyed. By activating sirtuin 1 (SIRT1), Ber caused reduced oxidative damage and loss of mitochondria integrity in cardiomyocytes. It also regulated autophagy and apoptosis via down-regulating AMP-activated protein kinase (AMPK), nucleotide-binding oligomerization domain, leucine rich repeat, and pyrin domain containing protein (NLRP) activation. Moreover, Ber increased superoxide dismutase (SOD), catalase (CAT), and plasma glutathione peroxidase (GSH-Px) activities, reduced the levels of malondialdehyde (MDA), up-regulated SIRT3, and subsequently reduced oxidative stress in cardiomyocytes and loss of mitochondria integrity, leading to developed apoptosis and regulating the histopathological and electrocardiogram changes in the myocardium. It also ameliorated the DOX-induced calcium ions (Ca^{2+}) and iron overload. Ber reduced oxidant and inflammatory activity, and regulated apoptosis of cardiomyocytes, thus protecting the cells against DOX-induced cardiotoxicity.

Implication for health policy/practice/research/medical education:
The protective effects of Ber in preventing or reducing complications caused by doxorubicin consumption were shown in this study. The cardioprotective effects of Ber were mainly due to the antioxidant and anti-inflammatory activities, and it also could improve heart function. Therefore, this herbal substance might be used under the supervision of physicians to reduce cardiotoxicity in cancer treatment centers to minimize the side effects of chemotherapy.

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Introduction

Cardiotoxicity is one of the serious side effects of antineoplastic treatments that leads to high morbidity and mortality around the world (1). Anticancer drugs such as doxorubicin (Dox), fluoropyrimidines, taxanes, and alkylating drugs may lead to adverse cardiovascular effects, which cause cardiac dysfunction in cancer patients (2). These common cardiovascular side effects are generally referred to as cardiotoxicity. Cardiotoxicity regardless of the oncological prognosis strongly has an adverse impact on the patient's quality of life and overall survival (3).

In this regard, by reducing the disorders associated with chemotherapy-induced cardiotoxicity, it is possible to minimize cardiomyopathy, hypertension, and pulmonary hypertension, as well as myocardial, vascular, and arrhythmia disorders associated with the use of these drugs (4,5). So, some drugs may be used in the treatment of diseases but they may have dangerous side effects (6). Although there are limited data on the mechanism of chemotherapy-induced cardiotoxicity, there are different therapeutical approaches to reduce anticancer drug-associated cardiovascular toxicity. These treatments

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include iron-chelating drugs, late inward sodium current selective inhibitors, renin-angiotensin-aldosterone system inhibitors, β-blockers, sodium-glucose cotransporter-2 inhibitors, metabolic agents, phosphodiesterase-5 inhibitors, and statins (2).

Dox is an anthracycline class medication derived from the *Streptomyces peucetius* bacterium that uses as antibiotic and anti-tumor agent (7). In the meantime, medicinal plants and their derivatives have been considered due to their fewer side effects, cheapness, readily availability and their antitoxic effects on healthy cells (8-10). One of the phytochemicals whose positive effects have been proven in various diseases is berberine (Ber). Ber is an isoquinoline alkaloid compound with strong pharmacological activities extracted from the *Coptis chinensis*, *Berberis vulgaris* L, barberry, and Oregon grape (11,12). Studies have shown that this plant metabolite, due to its antioxidant, anti-inflammatory, and apoptotic properties, in addition to its anti-cancer effects, also insert cardioprotective properties (11,13). Considering that the possible effects and mechanisms of Ber in reducing the chemotherapy-induced cardiotoxic effects are still unclear and debated, the present study investigated the protective effects of Ber to reduce the side effects of DOX-induced cardiotoxicity.

Materials and Methods

Data sources and search strategy

This meta-analysis was conducted according to PRISMA guidelines (http://prisma-statement.org/prismastatement/Checklist.aspx). To this end, a systematic review was carried out on January 21, 2023 in PubMed, Cochrane library, Web of Science (ISI), Embase, and Scopus databases. The key and MeSH search terms were used for the search: ((“berberine” OR “umbellatine”) AND (“chemotherapy” OR “doxorubicin” OR “adriablastin”) AND (“cardiotoxicity” OR “cardiac toxicity”)).

Study selection

The articles retrieved from the databases were imported into the EndNote X8 (8 November 2016, Thomson Reuters) software and duplicates were set aside. All articles were separately screened for titles/abstracts detected in the databases by two researchers. Based on our inclusion criteria, the studies on the impact of Ber on cardiotoxicity were examined. Unavailability of full text, articles published in non-English languages, and studies on fruits and plant extracts containing Ber (rather than specifically investigating Ber’s impact on cardiotoxicity) were considered as exclusion criteria. After the systematic literature review was finished and articles were screened for exclusion and inclusion criteria, the full texts of all eligible articles were examined by two groups of investigators. If any disagreement rose between the investigators, it would be resolved through discussion.

The steps of screening and possible exclusion of results as per the PRISMA 2020 flowchart are illustrated in Figure 1.

Data extraction

Following examination of the publications, the data below were drawn and recorded in Excel: leading investigator’s name, year of publication, experimental approach, drug and dosage, time of exposure, follow-up, and outcomes. If the data were not relevant to the aim of the study, they were set aside from further analysis.

Results

Search results, study characteristics of selected studies

The PRISMA flowchart (Figure 1) indicates the search strategy used to conduct this review. In the initial electronic search, 124 titles/abstracts were retrieved. From the total articles imported in EndNote, 8 articles were removed due to duplicate titles. One study was removed because of not retrieving the full text (14), the other one was removed because of studied palmatine (protoberberine) (15), and 3 other records were omitted because of not consistent with the study aims (16-18). Finally, 11 articles were selected for the final assessment (19-30).

The included studies were all *in vivo* and *in vitro* studies. All the studies confirmed the positive effects of Ber on reducing cardiotoxicity. Ber regulates autophagy and apoptosis by increasing sirtuin 1 (SIRT1) and SIRT3 expression, upregulating mitochondrial biogenesis markers, and reducing mitochondrial dysfunction. In addition, it reduces calcium ions (Ca^{2+}) and Iron overload, oxidation malondialdehyde (MDA), nitric oxide (NO), and inflammation and increases catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GSH-Px) activities. In addition, it prevents the accumulation of DOX in heart cells and reduces its toxicity, regulates the heart rhythm, and improves cardiac dysfunction. All the mentioned mechanisms are tabulated in Table 1.

Discussion

This systematic review study aimed to investigate the association between Ber administration on chemotherapy-induced cardiotoxicity. Anti-neoplastic treatments cause adverse effects in cancer patients, which is one of the main problems of these patients and can lead to the selection of different types or even discontinuation of antineoplastic drugs. The main goal of treatments or complementary medicine is the improvement of proliferation and survival of cardiomyocytes. These strategies are used to protect or restore heart tissue and improve its function. This study showed that Ber could reduce DNA damage and mitochondrial dysfunction and structure by different mechanisms such as effect on inflammatory pathways, antioxidant activity, reducing the toxic effects of anticancer drugs and ferroptosis in cardiomyocytes, fibroblasts, and also the regulation of blood biochemical factors. These mechanisms prevent complications such as heart failure, bradycardia, fibrosis, myocardial infarction, and ultimately cardiac dysfunction. Other review studies also show that the mechanism of cardiotoxicity caused

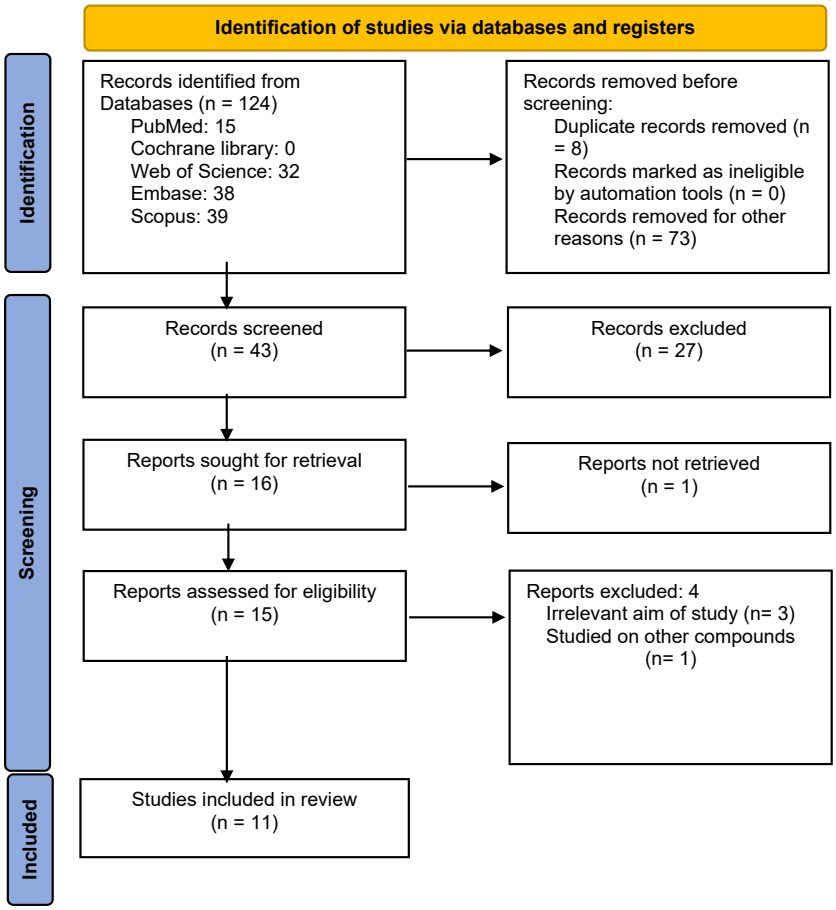

Figure 1. Flowchart for including studies in the meta-analysis.

by other drugs is still unclear. However, various reasons such as oxidative stress, apoptosis, and inflammation can aggravate this condition (31-34).

Oxidative stress and inflammation are considered risk factors for serious diseases such as heart diseases and cancers (35-38). Various studies reviewed in this study showed that Ber attenuated DOX-induced nephrotoxicity by reducing total reactive oxygen species (ROS), lipid peroxides, NF-κB p65, interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and caspase-3 (39). It also inactivates extracellular signal-regulated kinase 1/2 (ERK1/2) and suppresses sirtuin 2 (SIRT2)/ murine double-minute 2 (MDM2)-triggered renal fibrosis (40). Also, with its anti-oxidant and immune modulator properties, inhibiting oxidative stress, inflammatory response, and hepatocyte necrosis, Ber has shown hepatoprotective capacity against DOX (41,42). Plant alkaloids such as Ber insert potent antioxidant and anti-inflammation activity and thus can prevent cardiotoxicity of heart cells and further damage due to DOX (13,43,44).

Ferroptosis is iron-dependent cell death, but another cause of cytotoxicity is ferroptosis, which is caused by excessive accumulation of iron and also ROS in the cell. This accumulation also causes lipid peroxidation and ultimately causes apoptosis and necrosis (18). Studies have shown that ferroptosis is one of the causes of ischemia/ cardiomyopathy caused by reperfusion and DOX induce-cardiotoxicity (18,45). Ber prevented ferroptosis by decreasing lipid peroxidation and ROS generation in RSL3 and erastin-treated cardiac cells (18).

In general, the mechanisms for eliminating cardiotoxicity can be described in Figure 2.

In spite of various molecular and cellular mechanisms recommended to alleviate the cardiotoxic effect of anti-neoplasm drugs, cardiomyocyte death has been raised as the main reason for long-term irreversible cardiac dysfunction (2). Cardiomyocyte necrosis cannot be effectively regenerated because of the extremely poor capability of the adult mammalian heart for the production of new cardiomyocytes. However, the cytotoxic effect of anticancer drugs can be produced by widely varied biological mechanisms, and the design of strategies to increase cardiomyocyte viability is advisable to reduce anticancer drug-induced cardiomyocyte necrosis and subsequently prevent permanent damage (2). However, several factors can affect the results of studies. Conventional risk factors, such as age, arrhythmias, hypertension, and coronary heart disease, have contributed to detecting genetic variants associated with increased predisposition to cardiotoxicity in targeted therapy and chemotherapy (2,46).

Table 1. Characteristics of included studies of the effect of Berberine on Doxorubicin-induced cardiotoxicity

First author	Year of publication	Study type	Drug and dosage	Time of exposure	Chemotherapy drug	Outcomes
Zhao (19)	2011	*In vivo* study on BALB/c mice	60 mg/kg for a 14-day period	1 h before injection with DOX	Dox	Ber reduced mortality, increased body weight, reduced LDH activity, QRS duration, and myocardial injury
Lv (20)	2012	*In vitro* and *in vivo* studies on neonatal rat, cardiomyocytes, and rats	*In vivo*: 30, 60 or 120 mg/kg and *in vitro*: 0.25, 1.0, 4.0, 16 µM	*In vivo*: Once a day for another 3 consecutive days and *in vitro*: 12 h or 24 h	DOX	Ber attenuated apoptosis and mitochondrial dysfunction and increased expression which reduces cardiomyopathy
Hao (21)	2015	*In vitro* and *in vivo* studies on male Sprague-Dawley rats 2 weeks Ber administration	*In vivo*: 50, 100 and 200 mg/kg and *in vitro*: 10 µM	Ber at for 60 min	DOX	Inhibited the accumulation of doxorubicinol in the heart, and decreased the activity of myocardial enzymes, such as CK, AST, LDH, and creatine kinase isoenzyme.
Zhi (16)	2015	*In vitro* and *in vivo* studies on adult male albino rats	60 mg/kg injected Ber	Every other day for 2 weeks	DOX	Ber ameliorated loss of normal cross striations, swelling of mitochondria, irregular indented nuclei, focal lysis of myofibrils, and distortion of intercalated. Also, an increase was seen in nuclear factor kappa-light-chain-enhancer of activated B cells, TLR2, and activated caspase-3 immunoreaction
Elwan (22)	2016	*In vivo* study on male albino rats	60 mg/kg injected Ber	Every other day for 2 weeks	DOX	Reduced structural changes in the cardiac muscle induced by DOX
Coelho (23)	2017	*In vitro* study on H9c2 cardiomyoblasts	1 and 10 µM	72 hours	DOX	Ber modulated autophagy in H9c2 cardiomyoblasts, upregulated mitochondrial biogenesis markers, inhibiting the caspase-dependent mitochondrial apoptosis, by the modulation of SIRT3-mediated pathways, and modulates Sirtuin function
Xiong (24)	2018	*In vitro* and *in vivo* studies on Sprague-Dawley rats	5, 10, and 20 mg/kg, 1 mL/100 g body weight administered orally	Once daily for 10 consecutive days	DOX	Ber attenuated intracellular Ca^{2+} ($[Ca^{2+}]i$) accumulation and ameliorated mitochondrial Ca^{2+} overload. Moreover, it reduced free radical injury in heart tissue by decreasing CK, CK-MB, and MDA levels and increase in SOD and CAT levels
Wu (25)	2019	*In vivo* study: Sprague-Dawley rats and *In vitro*: H9c2 cardiomyoblasts	*In vivo*: 10 and 20 mg/kg orally administered *In vitro*: 0.1, 1, or 10µM	*In vivo*: 10 days *In vitro:* 24 h	DOX	Ber elevated SOD, CAT, and GSH-Px activities decreased the levels of MDA and increased the SIRT1 expression and electrocardiogram and histopathological changes in the myocardium. Moreover, Ber reduced oxidative insult and mitochondrial damage in H9c2 cells
Zhang (26)	2020	*In vitro* and *in vivo* studies on female BALB/c mice	12 mg BER/Kg	4, 8, 12 and 24 h	DOX	Co-loaded liposome of berberine and doxorubicin reduced the myocardial rupture toxicity caused by DOX.
Chen (28)	2022	*In vivo*: Larval and adult zebrafish *In vitro*: human AC16 cells	*In vivo*: Adult zebrafish were treated with 10-30 µM *In vitro*: 0.25–8 µM	*In vivo*: 7 days *In vitro*: 24 h	DOX	Ber reduced cytotoxicity and apoptosis. Moreover, it increased mitophagy by inhibiting the binding Beclin1 with Bcl-xL and reducing ROS accumulation. So, Ber can block apoptosis and activate mitophagy
Rawal (29)	2022	*In vitro* study on H9c2	Ber (10 µM) and Ber-SLNs (1 and 10 µM)	24 h	DOX	Percentage cytotoxicity was reduced especially by Ber-SLNs. Oxidative stress, inflammation markers, and apoptosis were lower with Ber and Ber-SLNs.
Zhang (30)	2022	*In vivo* study on Male Sprague Dawley rats	*In vivo*: 40 mg/kg oral administration and 1 mg/kg intravenous *In vitro*: 1 mg	*In vivo*: 0-10 days *In vitro*: 2-20 min	DOX	Ber attenuated heart damage by the arrangement of blood biochemical and electrocardiogram parameters reverted to the normal level. Moreover, it regulated MDA and SOD levels.

LDH, lactate dehydrogenase; CK, creatine kinase; AST, aspartate aminotransferase; TLR2, toll-like receptor 2; SOD, superoxide dismutase; CAt, catalase; MDA, malondialdehyde; SIRT1, sirtuin 1; GSH-Px, plasma glutathione peroxidase; ROS, reactive oxygen species; SLNs, solid lipid nanoparticles.

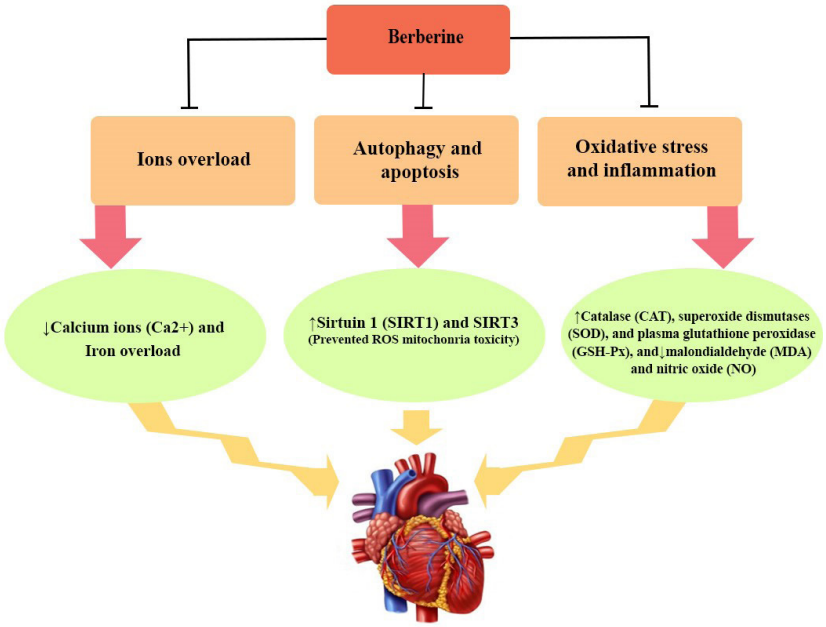

Figure 2. Possible mechanisms of the protective effect of Ber against Doxorubicin-induced cardiotoxicity

Although Ber revealed beneficial effects on various diseases, some limitations such as slow bioavailability, slight absorption, and poor aqueous solubility have prevented its applications (47-49). So, as long as there are obstacles from the time of administration to the increase of its concentration in the plasma or target tissue, its positive effects cannot be used optimally.

Today, various methods are available for the bioavailability of plant active compounds. If the use of nanotechnology and other herbal synergistic compounds can increase the solubility and finally, we can lower the Ber's absorption barrier and thus increase its positive effects due to increased bioavailability (29,30).

Although the general opinion is that drugs and herbal compounds do not have many side effects, the results of studies have shown that Ber, as a useful herbal compound, especially in reducing heart toxicity, can sometimes act like a poison. A study showed that the simultaneous use of Ber with macrolides may cause potential drug toxicity, especially cardiotoxicity. Hence, its use together with drugs such as Azithromycin should be considered by clinicians (16).

There were limitations in the studies conducted such as the lack of clinical trial studies in this regard. Short follow-ups and lack of adjustment of confounding variables are some important limitations, which can overshadow the results of the study.

Conclusion

The findings of this study revealed that Ber has a wide range of cardioprotective activities against Dox-induced cardiotoxicity. These activities generally include antioxidant and anti-inflammatory activity, as well as the regulation of apoptosis activity and the concentration of calcium and iron ions. Since clinical studies in this area are low, more studies are needed to prove its utility in protecting against cardiotoxicity.

Authors' contribution

All authors progressed the concept of this study. AK and MRK wrote the protocol. AK and ER collated the data for the study. The first draft of the manuscript was written by AK and thoroughly revised by MRK.

Conflict of interests

Authors declare there are no conflicts of interest.

Ethical considerations

Authors have carefully monitored ethical issues such as text plagiarism, duplicated publication, misconduct, data fabrication, and falsification.

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