Can Dietary Nutrients Prevent Cancer Chemotherapy-Induced Cardiotoxicity? An Evidence Mapping of Human Studies and Animal Models

Xin-Yu Zhang, Ke-Lu Yang, Yang Li, Yang Zhao, Ke-Wei Jiang*, Quan Wang* and Xiao-Nan Liu*

1 Ambulatory Surgery Center, Xijing Hospital, Air Force Military Medical University, Xi’an, China, 2 Nursing Department, Chengdu BOE Hospital, Chengdu, China, 3 Academic Center for Nursing and Midwifery, Department of Public Health and Primary Care, University of Leuven (KU Leuven), Leuven, Belgium, 4 Department of Gastroenterological Surgery, Laboratory of Surgical Oncology, Peking University People’s Hospital, Beijing, China, 5 Department of Cardiology, Xijing Hospital, Air Force Military Medical University, Xi’an, China

Introduction: Chemotherapy has significantly improved cancer survival rates at the cost of irreversible and frequent cardiovascular toxicity. As the main dose-dependent adverse effect, cardiotoxic effects not only limit the usage of chemotherapeutic agents, but also cause the high risk of severe poor prognoses for cancer survivors. Therefore, it is of great significance to seek more effective cardioprotective strategies. Some nutrients have been reported to diminish cardiac oxidative damage associated with chemotherapy. However, the currently available evidence is unclear, which requires a rigorous summary. As such, we conducted a systematic review of all available evidence and demonstrated whether nutrients derived from food could prevent cardiotoxicity caused by chemotherapy.

Methods: We searched Medline (via PubMed), Embase and the Cochrane Library from inception to Nov 9, 2021 to identify studies reporting dietary nutrients against cancer chemotherapy-related cardiotoxicity. We performed descriptive summaries on the included studies, and used forest plots to demonstrate the effects of various dietary nutrients.

Results: Fifty-seven eligible studies were identified, involving 53 animal studies carried on rats or mice and four human studies in cancer patients. Seven types of dietary nutrients were recognized including polyphenols (mainly extracted from grapes, grape seeds, and tea), allicin (mainly extracted from garlic), lycopene (mainly extracted from tomatoes), polyunsaturated fatty acids, amino acids (mainly referring to glutamine), coenzyme Q10, and trace elements (mainly referring to zinc and selenium). Dietary nutrients ameliorated left ventricular dysfunctions and myocardial oxidative stress at varying degrees, which were caused by chemotherapy. The overall risk of bias of included studies was at moderate to high risk.

Conclusion: The results indicated that dietary nutrients might be a potential strategy to protect cardiovascular system exposed to the chemotherapeutic agents, but more human studies are urged in this field.

Systematic Review Registration: https://inplasy.com/inplasy-2022-3-0015/.

Keywords: chemotherapy, cardiotoxicity, heart diseases, oral nutrition, diet therapy, systematic review
INTRODUCTION

Advances in chemotherapy and comprehensive supportive care have contributed to the steadily declined cancer mortality rates over the past decades (1–3). As a result, the survivors have been an increasingly large population (e.g., more than 16.9 million in the USA in 2019) with longer life expectancy (4, 5). However, the great success of chemotherapy has been accompanied by severe cardiovascular toxicity, which is caused by the direct damage to the myocardium through production of oxygen free radicals (5–7). Cardiac toxicity could manifest as subclinical cardiomyopathies at the early stage, such as asymptomatic changes along with left ventricular dysfunction and abnormal cardiac markers. Around 12% (123/1022) pediatric patients with acute myeloid leukemia were reported to suffer cardiotoxicity during and after the chemotherapy regimen over a five-year follow-up (8). In addition, cardiotoxicity would progress to congestive heart failure (CHF) and even cardiac death (5, 9) and these complications have been the leading cause of long-term morbidity and mortality (10–13). The incidence of CHF reported in patients treated with doxorubicin (DOX) was 2.2% (88/4018) (14) and the two-year mortality rate associated with anthracyclines-induced cardiovascular diseases (CVD) was up to 60% (15). Therefore, appropriate early prevention and management for cancer survivors should be implemented to prevent and avoid chemotherapy-induced cardiotoxic progression (16, 17).

Early detection and treatment of chemotherapy-induced cardiac damage have been gradually studied. The common used monitoring methods are echocardiography and cardiac biomarkers. Several drugs were previously investigated as cardioprotective agents for preventing cardiotoxicity (6, 7, 18, 19), but only dexrazoxane was approved by Food and Drug Administration (FDA) to protect the chemotherapy-exposed heart (7, 20). However, dexrazoxane has not been routinely applied in the clinic at present along with debate about its long-term safety. This is largely due to the concerns over its impact on anticancer treatments (21, 22). In addition, the cost and accessibility have also been quite essential impediments for cancer survivors who have already borne considerable treatment overheads in the long-term survivals (5). So, it is of great significance to explore alternative effective, safe, economical, and consistent cardiac protection strategies for long-term cancer survivors.

Dietary nutrients (defined as various nutrients derived from food) are increasingly playing an important role in medicine. Due to the restriction of conventional medicine treatments for cancer, complementary and alternative medicine (CAM) has been playing a broader and more active role in cancer patients (23). Currently, several studies indicated that some fruit and vegetables have been considered as natural antioxidants that could reduce oxidative stress and inhibit chemotherapy-related cardiotoxicity (24–26). Furthermore, dietary factors such as polyunsaturated fatty acids (PUFA) and coenzyme Q10 (CoQ10) have also been reported to be able to protect the chemotherapy-exposed heart on animal models (27, 28). Although there are some narrative reviews (27, 29–32), it seems that the evidence on whether dietary nutrients could alleviate cardiotoxicity induced by chemotherapy has not been systematically summarized.

As such, we hypothesized that dietary nutrients could serve as a novel cardioprotective strategy to prevent cancer chemotherapy-induced cardiotoxicity and conducted a systematic review of the current evidence.

METHODS

This systematic review was conducted based on the guidelines of Systematic Review Protocol for Animal Intervention Studies (33) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (34), and was registered at https://inplasy.com as INPLASY202230015.

Inclusion and Exclusion Criteria

The inclusion criteria were as follows: (1) subjects: cancer patients or healthy/tumor-bearing animal models, treated with chemotherapeutic agents, with no restrictions on cancer types, animal species and chemotherapeutic agents; (2) intervention: oral intake of dietary nutrients; If the source of the nutrient was reported in the article, we only included cases which the nutrient source was food rather than non-food like drugs. If it was not reported, then we included articles that the nutrient can be obtained from food; (3) comparison: placebo or no intervention (without dietary nutrients mentioned above); (4) outcomes: imaging or biological measures of cardiotoxicity, including echocardiography, serum cardiac markers, oxidative stress markers, and histopathological examinations. Echocardiography is the most common and noninvasive method which measures left ventricular systolic functions like left ventricular ejection fraction (LVEF) and left ventricular fractional shortening (LVFS). It is also the most widely used screening method for monitoring cardiotoxicity both during and years after anticancer treatment (16). Cardiac markers, such as cardiac troponin (cTn), N-terminal pro-brain natriuretic peptide (NT-proBNP), creatine kinase (CK), creatine kinase-MB (CK-MB) and lactate dehydrogenase (LDH), can indicate abnormal left ventricular structure and increased cardiac stress (17). Measurements of antioxidant defense can reflect the cardiac oxidative stress status in cancer patients, including malondialdehyde (MDA), superoxide dismutase (SOD) and glutathione (GSH). The details of detection indicators are represented in Supplementary Table 1. Conference abstracts, case reports, reviews, trial protocols, duplicate publications, in vitro experiments, and non-controlled studies were excluded.

Search Strategy and Study Selection

A comprehensive search was performed through three separate electronic databases, including Medline (via PubMed), Embase, and the Cochrane Library, from the inception to Nov 9, 2021. In addition, a manual search was also conducted by screening the reference lists from relevant reviews. The search strategies used are provided in Supplementary Table 2.

Two reviewers (X-YZ and K-LY) screened the titles and abstracts of records retrieved from the databases and independently screened the full text for eligible studies. Any
disagreements between the two reviewers were resolved through discussion by achieving a consensus.

**Data Extraction**

Two reviewers (X-YZ and K-LY) independently used a data extraction sheet to extract data from the included studies. The following information was extracted: first author, year of publication, characteristics of subjects, study design, intervention characteristics, and outcome measures. The primary outcomes included LVEF and cTn, and the secondary outcomes were LVFS, CK, CK-MB, LDH, MDA, SOD, and GSH.

**Risk of Bias Assessment**

Two reviewers (X-YZ and YL) independently assessed the risk of bias for the included studies. For animal studies, we used the risk of bias tool of Systematic Review Center for Laboratory Animal Experimentation (SYRCLE). This tool is designed based on the Cochrane Risk of Bias (RoB) tool for animal experiments. It consists of 10 items, including selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases (35). Each item is rated as “Y” (low risk of bias), “N” (high risk of bias), and “U” (unclear risk of bias). For randomized controlled trials (RCT), we used the Cochrane risk of bias tool (36). It covers 6 domains of bias, namely sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other biases. The items are also assessed as “Y” (low risk of bias), “N” (high risk of bias), and “U” (unclear risk of bias). For non-randomized clinical trials and observational studies, we used the Newcastle-Ottawa Scale (NOS) which contains 8 items in three dimensions of selection, comparability, and outcome (37). It scores from 0 to 9 and higher scores show the lower risk of bias. Any disagreements were resolved by consulting a third reviewer (QW).

**Data Analysis**

The primary and secondary outcomes of the review were treated as continuous variables represented by mean ± standard deviation. Number of cases and percentages were used to indicate the number of included studies. Effectiveness of dietary nutrients against cardiotoxicity was presented by the comparison between chemotherapy with dietary nutrients groups and chemotherapy groups. Statistical analyses of all outcomes were performed in forest plots using RevMan Software (Version 5.3). When there were more than two arms in the included studies, we presented all the results separately. Due to high heterogeneity from the variations in the baseline of included studies, we used a random-effects model and didn’t provide a pooled result as well.

The work flowchart describing the process of the study is shown in Figure 1.

**RESULTS**

**Literature Search and Study Selection**

A total of 4025 potentially relevant records were initially identified. However, 341 of those were excluded due to duplication, 3,590 studies were excluded by reading titles and abstracts based on the inclusion and exclusion criteria, and 94 potential studies were eligible for full-text screening. We finally included 57 studies, including 53 animal studies and four human studies. The PRISMA flowchart of the literature search and study selection process is shown in Figure 2. The reasons for excluding reviews are listed in Supplementary Table 3.

**Animal Studies**

**Study Characteristics**

The 53 animal studies included were conducted in 14 countries, with most in Egypt (n = 15), India (n = 8), Saudi Arabia (n = 6), Turkey (n = 6), and China (n = 5). The publication years ranged from 1996 to 2021, with 42 before 2010. DOX (n = 48) comprised a significant majority of the included studies, and the other chemotherapeutic agents were cisplatin (n = 3), mitoxantrone (n = 1), and fluorouracil (n = 1). The covered dietary nutrients contained polyphenols (n = 29) (38–66), allicin (n = 3) (67–69), lycopene (n = 2) (70, 71), PUFA (n = 5) (72–76), amino acids (n = 4) (77–80), CoQ10 (n = 5) (81–85), trace elements (n = 3) (86–88), and others (n = 2) (89, 90). 79.24% of the included studies were investigated in Asia and Africa and most studies commonly used allicin from garlic (67–69) and polyphenols from local fruit such as grape (38–43), date palm (55, 56), cranberry (58), cardamom (59), pomegranate (60) and hawthorn (61) as the nutritional interventions. However, American and European studies tended to use amino acid like glycine and glutamine which were rich in animal food or special supplements (77–80). The characteristics of the included animal studies are summarized in Table 1 and Figure 3.

**Risk of Bias Assessment**

The overall risk of bias of included animal studies was at moderate to high risk and most of the items of SYRCLE depicted unclear risk (Figure 4 and Supplementary Table 4). All animal studies failed to report the sequence generation methods (item 1), allocation concealment (item 3), and random outcome assessment (item 6). Other items also revealed poor outcomes. Four studies (73, 77–79) reported baseline characteristics (item 2), one (84) mentioned the methods of performance blinding (item 5), and another (77) documented the blinded outcome assessment (item 7). In comparison, all the animal studies were free from selective outcome reporting (item 9), and 52 studies did not involve any other sources of bias (item 10).

**Effectiveness of Dietary Nutrients**

The protective effects of dietary nutrients above on myocardium against cardiac toxicity can be observed by the comparison between chemotherapy with nutrients groups and chemotherapy groups in Supplementary Figures 1–7.

**Polyphenols**

In animal studies of our review, polyphenols were defined as a broad class of compounds with multiple phenolic hydroxyls (PhOH) and were reported in 29 studies (38–66). These covered proanthocyanidin (n = 6, all derived from grape seed extract) (38–43), anthocyanin (n = 1, derived from purple corn) (44), resveratrol (n = 2) (45, 46), curcumin (n = 5) (47–51), catechins
Cancer chemotherapy-induced cardiotoxicity

(n = 3, derived from green tea and black tea) (52–54), and mixed phenolic compounds extracted from local products [n = 12, derived from date (55, 56), orange (57), cranberry (58), cardamom (59), pomegranate (60), hawthorn (61), naringenin (62), p-coumaric acid (63), honey (64), yogurt (65) and yellow wine (66)]. Three studies demonstrated that supplementation of polyphenols could improve DOX-induced cardiac dysfunctions evaluated by echocardiography (45, 57, 66). LVEF significantly reduced in DOX groups, but was similar in DOX+Nutrients groups and control groups. Cardiac morphological and systolic changes led by DOX were attenuated by polyphenolic nutrients through scavenging free radicals and blocking lipid peroxidation. Biochemical analyses were estimated by serum cardiac markers and antioxidant parameters in 28 studies (38–43, 45–66). LDH, MDA and SOD were reported most. The concentrations of myocardial enzymes in animals received chemotherapy and nutrients were significantly lower compared with those treated with chemotherapeutic agents alone. Oral administration of polyphenols improved the cardiac oxidative changes led by chemotherapy and enhanced the antioxidant enzymatic activities. Histopathological analyses of cardiac tissue captured under the microscope were reported in 16 studies (38, 40, 41, 45, 46, 48–50, 53, 56, 59–62, 65, 66). The incidences of myocardial atrophy, cytoplasmic vacuoles, nuclear pyknosis, and cytoplasmic eosinophilia were significantly higher in heart exposed to DOX, while the polyphenolic substance protected or even restored cardiac disrupted histological structure induced by DOX (Supplementary Figure 1).

**Allicin and Lycopene**

Three studies showed that allicin (all derived from garlic extract) effectively decreased the expression of myocardial tumor necrosis factor-alpha (TNF-α) and mitigated cardiac oxidative damage (67–69) (Supplementary Figure 2). Abdel-Daim et al.
referred that allicin could be a promising cytoprotective agent against DOX-related cardiotoxicity. Two studies revealed that lycopene (all derived from tomatoes) reduced the levels of cardiac oxidative markers and made the histopathological changes maintain nearly normal after the injection of DOX (70, 71) (Supplementary Figure 3).

Polyunsaturated Fatty Acids
PUFA were reported in five studies, derived from black chia seed (72), flaxseed (73), fish oil (74, 76), and sesame oil (75). All these studies proved that PUFA attenuated the myocardial necrosis and overall myocardium enlargement and alleviated histopathological alteration in rats/mice treated with DOX (Supplementary Figure 4). PUFA were considered as a potential chemoprotectant nutraceutical in combination with chemotherapy to limit the cardiotoxic side effects (72).

Amino Acids, Coenzyme Q10, and Trace Elements
Four studies reported that amino acids [derived from glycine (77) and glutamine (78–80)] could diminish chemotherapy-induced cardiac oxidative damage (Supplementary Figure 5). As a vital role in maintaining the cellular redox state, dietary glutamine remained normal cardiac GSH levels in animal models treated with chemotherapeutic drugs and prevented cardiac lipid peroxidation (78–80). Coenzyme Q10 (n = 5) (81–85) was proven to be prophylactic in prevention of cardiovascular toxicity through participating with redox function directly in the mitochondrial respiratory chain (Supplementary Figure 6), and trace elements [n = 3, derived from zinc (Zn) (86, 87) and selenium (Se) (88)] were also exhibited to protect myocardium by preventing mitochondrial dysfunctions and acting in concert with SOD and catalase (Supplementary Figure 7).

The details of outcomes are summarized in Supplementary Table 5.

Human Studies
Study Characteristics
Four human studies were conducted in Egypt [in 2021 (91) and 2020 (92)], Italy [in 1994 (93)] and the USA [in 1978 (94)]. Three studies (91–93) recruited pediatric patients diagnosed with acute lymphoblastic leukemia (ALL) aged 1 to 16 years and one (94) recruited adults with bronchogenic carcinoma. Two studies (91, 92) were RCTs using DOX as the chemotherapy agent, and the other two studies (93, 94) were non-randomized controlled trials using anthracyclines. The covered dietary nutrients contained PUFA [n = 2, derived from omega 3 fatty acids (91) and black
TABLE 1 | The characteristics of the included animal studies.

| Dietary nutrients | Studies Country | Randomization | Animals | Intervention | Chemotherapeutic agents | Food intake | Main ingredients | Duration | Sample size | Grouping | Control groups | Treated groups | Outcomes |
|-------------------|-----------------|---------------|---------|-------------|--------------------------|-------------|------------------|----------|-------------|----------|----------------|---------------|----------|
| Polyphenols       | Adiyaman et al. (38) Turkey | Not reported | Rats, sprague dawley | Healthy | DOX | Grape seed extract | Proanthocyanidin | 35 days | 28 | 4 | (1) CON | (4) DOX + grape seed extract | b, c, d |
| Ammar et al. (39) Egypt | Not reported | Rats, sprague dawley | Healthy | DOX | Proanthocyanidin | Proanthocyanidin | 10 days | 24 | 4 | (1) CON | (4) DOX + proanthocyanidin | b, c, e |
| Boghdady (40) Egypt | Yes | Rats, wistar albino | Healthy | DOX | Grape seed extract | Proanthocyanidin | 15 days | 32 | 4 | (1) CON | (5) DOX + grape seed extract 50 | c, d |
| Yalcin et al. (41) Turkey | Yes | Mice, albino | Healthy | DOX | Grape seed extract | Proanthocyanidin | 21 days | 36 | 6 | (1) CON | (5) DOX + grape seed extract 150 | c, d |
| Yousef et al. (42) Egypt | Not reported | Rats, sprague dawley | Healthy | Cisplatin | Grape seed extract | Proanthocyanidin | 15 days | 32 | 4 | (1) CON | (4) cisplatin + grape seed extract | b, c, f |
| Zhang et al. (43) China | Yes | Mice, balb/c | Sarcoma | DOX | Proanthocyanidin | Proanthocyanidin | 10 days | 56 | 4 | (1) CON | (4) DOX + proanthocyanidin | b, c |
| Petroni et al. (44) Italy | Not reported | Mice, c57bl/6 | Healthy | DOX | Cyanidin 3-glucoside Anthocyanin | 74 days | 24 | 2 | (1) DOX + yellow diet | (2) DOX + red diet | f |
| Shoukry et al. (45) Egypt | Yes | Rats, wister | Healthy | DOX | Resveratrol | Resveratrol | 42 days | 32 | 4 | (1) CON | (2) DOX + resveratrol | a, b, d, f |
| Arafa et al. (46) Egypt | Not reported | Rats, wistar albino | Healthy | DOX | Resveratrol | Resveratrol | 28 days | 40 | 4 | (1) CON | (4) DOX + resveratrol | b, c, d, f |
| Ibrahim Fouad and Ahmed. (47) Egypt | Yes | Rats, wistar albino | Healthy | DOX | Curcumin | Curcumin | / | 24 | 4 | (1) CON | (4) DOX + curcumin | b, c |
| Bahadir et al. (48) Turkey | Yes | Rats, wistar albino | Healthy | Cisplatin | Curcumin | Curcumin | 14 days | 49 | 7 | (1) CON | (5) cisplatin + beta-carotene | b, c, d |
| Benzer et al. (49) Turkey | Yes | Rats, wistar albino | Healthy | DOX | Curcumin | Curcumin | 7 days | 35 | 5 | (1) CON | (4) DOX + curcumin 100 | b, c, d |

(Continued)
| Dietary nutrients | Studies | Country | Randomization | Animals | Intervention | Food intake | Main ingredients | Duration | Sample size | Grouping | Control groups | Treated groups | Outcomes |
|-------------------|---------|---------|---------------|---------|--------------|-------------|----------------|----------|-------------|----------|----------------|---------------|----------|
| Dietary nutrients | Swamy et al. (50) | India | Yes | Rats, albino | Healthy | DOX | Curcumin | Curcumin | 14 days | 24 | 4 | (1) CON | (2) DOX | (3) curcumin | (4) DOX + curcumin | b, c, d, f |
|                   | Venkatesan (51)  | India | Not reported | Rats, wistar | Healthy | DOX | Curcumin | Curcumin | 7 days | 24 | 4 | (1) CON | (2) curcumin | (3) DOX | (4) DOX + curcumin | b, c, e |
|                   | Ibrahim et al. (52) | Saudi Arabia | Yes | Mice, balb/c | Healthy | Cisplatin | Green tea extract, vitamin E | Catechins, vitamin E | 30 days | 48 | 6 | (1) CON | (2) green tea extract | (3) vitamin E | (4) cisplatin | b, c, f |
|                   | Saeed et al. (53) | Egypt  | Yes | Rats, wistar | Healthy | DOX | Epigallocatechin-3-gallate | Catechins | 12 days | 40 | 5 | (1) CON | (2) DOX | (3) DOX + epigallocatechin-3-gallate 10 | b, c, d, e |
|                   | Amanullah et al. (54) | India | Not reported | Rats, wistar albino | Healthy | DOX | Black tea extract, resveratrol | Catechins, polyphenols | 30 days | 30 | 6 | (1) CON | (2) DOX | (3) black tea extract + resveratrol | (4) DOX + black tea extract + resveratrol | b, c, f |
|                   | Mubarak et al. (55) | Egypt | Not reported | Rats, albino | Healthy | DOX | Date palm fruit extract | Anthocyanins, quercetin, procyanidins | 30 days | 40 | 4 | (1) CON | (2) date | (3) DOX | (4) DOX + date | b, c |
|                   | Sabbah et al. (56) | Saudi Arabia | Yes | Rats, wistar albino | Healthy | DOX | Ajwa date aqueous extract | Polyphenols, flavonoids, Mn | 28 days | 60 | 6 | (1) CON | (2) date 0.75 | (3) date 1.5 | (4) DOX | b, c, d |
|                   | Ribeiro et al. (57) | Brazil | Not reported | Rats, wistar | Healthy | DOX | Pera orange juice, Moro orange juice | Hesperidin, anthocyanins | 28 days | 120 | 6 | (1) CON | (2) Pera juice | (3) Moro juice | (4) DOX | (5) DOX + Pera juice | a, c, f |
|                   | Elberry et al. (58) | Saudi Arabia | Yes | Rats, wister | Healthy | DOX | Cranberry extract | Flavonoids, flavonoids | 10 days | 30 | 4 | (1) CON | (2) cranberry extract | (4) DOX | (4) DOX + cranberry extract | b, c, e |
|                   | Abu Gazia and Egypt El-Magd (59) | Yes | Rats, albino | Healthy | DOX | Cardamom extract | Flavonoids | 21 days | 30 | 3 | (1) CON | (2) DOX | (3) DOX + cardamom extract | b, c, d |
|                   | Hassannpour Fard et al. (60) | India | Not reported | Rats, wistar albino | Healthy | DOX | Whole fruit extract of Gallic acid, pomegranate | | 18 days | 24 | 3 | (1) CON | (2) DOX | (3) DOX + pomegranate | b, c, d, e, f |
|                   |                     |       |       |       |       |       |       |       |       |       |                     |       |       |                     |       |

(Continued)
| Dietary nutrients | Studies | Country | Randomization | Animals | Intervention | Chemotherapeutic agents | Tumor-bearing | Species | Food intake | Main ingredients | Duration | Sample size | Grouping | Control groups | Treated groups | Outcomes |
|-------------------|---------|---------|---------------|---------|--------------|-------------------------|---------------|---------|-------------|-----------------|----------|-------------|----------|-----------------|--------------|----------|
|                   | Shatoor and Said Ahmed, (61) | Saudi Arabia | Yes | Rats, wistar albino | DOX | Hawthorn extract | Healthy DOX | 28 days | 36 | 6 | (1) CON | (2) hawthorn | (3) DOX | (4) DOX+hawthorn(st) | (5) DOX+hawthorn(post) | (6) hawthorn+DOX(pre) | b, c, d, f |
|                   | Subburaman et al. (62) | India | Not reported | Rats, albino | DOX | Naringenin | Healthy DOX | 70 days | 18 | 3 | (1) CON | (2) DOX | (3) DOX+naringenin | b, c, d, f |
|                   | Abdel-Wahab et al. (63) | Egypt | Not reported | Rats, swiss albino | DOX | P-coumaric acid (pca) | Healthy DOX | 5 days | 24 | 4 | (1) CON | (2) P-coumaric acid | (3) DOX | (4) DOX+p-coumaric acid | b, c |
|                   | Alhumaydi (64) | Saudi Arabia | Yes | Mice, balb/c | DOX | Honey | Healthy DOX | 10 days | 40 | 4 | (1) CON | (2) honey | (3) DOX | (4) DOX+honey | b |
|                   | Abu-Elsaad et al. (65) | Egypt | Not reported | Rats, sprague dawley | DOX | Tested food: yogurt, green tea extract, carrot | Healthy DOX | 154 days | 60 | 5 | (1) CON | (2) DOX | (3) DOX+tested food | (4) DOX+tested food+carvedilol | b, c, d, e |
|                   | Lin et al. (66) | China | Yes | Rats, sprague dawley | DOX | Yellow wine polyphenolic compounds | Healthy DOX | 28 days | 50 | 5 | (1) CON | (2) yellow wine | (3) DOX | (4) DOX+yellow wine | a, c, d, e, f |
|                   | Allicin Abdel-Daim et al. (67) | Egypt | Yes | Mice, swiss albino | DOX | Allicin | Healthy DOX | 14 days | 40 | 5 | (1) CON | (2) allicin 20 | (3) DOX | (4) DOX+allicin 10 | (5) DOX+allicin 20 | b, c |
|                   | Demirkaya et al. (68) | Turkey | Yes | Rats, wistar albino | DOX | Aged garlic extract, grape seed extract, hazelnut | Healthy DOX | 42 days | 135 | 9 | (1) CON | (2) DOX 15 | (3) DOX 7.5 | (4) DOX 15+aged garlic extract | (5) DOX 7.5+aged garlic extract | (6) DOX 15+grape seed extract | (7) DOX 7.5+grape seed extract | (8) DOX 15+hazelnut | (9) DOX 7.5+hazelnut | b, c, d |
|                   | Mukherjee et al. (69) | India | Not reported | Rats, wistar albino | DOX | Garlic homogenate | Healthy DOX | 30 days | 40 | 5 | (1) CON | (2) DOX | (3) DOX+PRO | (4) DOX+garlic 250 | (5) DOX+garlic 500 | c, f |
|                   | Lycopene Ferreira et al. (70) | Brazil | Not reported | Rats, wistar | DOX | Tomato-oleoresin supplement | Healthy DOX | 49 days | 34 | 4 | (1) CON | (2) lycopene | (3) DOX | (4) DOX+lycopene | d |
|                   | Yilmaz et al. (71) | Turkey | Not reported | Rats, sprague dawley | DOX | Lycopene | Healthy DOX | 10 days | 24 | 4 | (1) CON | (2) DOX | (3) DOX+lycopene(pre) | (4) DOX+lycopene(post) | c, d |
|                   | PUFA Ahmed et al. (72) | India | Yes | Rats, wistar | DOX | Chia seed oil | Healthy DOX | 7 days | 24 | 4 | (1) CON | (2) DOX | (3) DOX+chia seed oil 2.5 | (4) DOX+chia seed oil 5 | b, c, d, e | (Continued) |
| Dietary nutrients | Studies | Country | Randomization | Animals | Chemotherapeutic agents | Food intake | Main ingredients | Duration | Sample size | Grouping | Control groups | Treated groups | Outcomes |
|-------------------|---------|---------|---------------|---------|-------------------------|------------|------------------|----------|-------------|----------|----------------|----------------|----------|
|                   | Asselin et al. (73) | Canada | Yes | Mice, c57bl/6 | Healthy | DOX+TRZ | Flaxseed, α-linolenic acid, secoisolariciresinol diglucoside | 42 days | 84 | 5 | (1) CON | (2) DOX+TRZ | (3) DOX+TRZ+flaxseed | a, d, e |
|                   | Saleh et al. (74) | Egypt | Not reported | Rats, wistar albino | Healthy | DOX | N-3 PUFA | n-3 PUFA | 28 days | 35-40 | 5 | (1) CON | (2) DOX | (3) DOX+n-3 PUFA 25 | b, c, d, e, f |
|                   | Saleem et al. (75) | India | Not reported | Rats, wistar albino | Healthy | DOX | Sesame oil | Linoleic acid, α-linolenic acid, sesamin | 30 days | 30 | 5 | (1) CON | (2) DOX | (3) DOX+sesame oil 1 | b, c, d |
|                   | Teng et al. (76) | China | Yes | Rats, sprague dawley | Healthy | DOX | N-3 PUFA | Timnodonic acid, docosahexaenoic acid | 112 days | 32 | 3 | (1) CON | (2) DOX | (3) DOX+n-3 PUFA | a, d |
| Amino acids       | Maneikyte et al. (77) | Austria | Yes | Rats, wag/h | Colorectal cancer liver metastasis | FOLFOX | Glycine | Glycine | 21 days | 44 | 6 | (1) casein+sham | (2) glycine+sham | (3) casein+CON | a, b, d |
|                   | Todorova et al. USA (78) | Yes | Rats, fisher344 | Mammary carcinoma | DOX | Glutamine | Glutamine | / | 50 | 3 | (1) CON | (2) DOX | (3) DOX+glutamine | a, b |
|                   | Todorova et al. USA (79) | Yes | Rats, fisher344 | Mammary carcinoma | DOX | Glutamine | Glutamine | 7 days | 20 | 2 | (1) CON | (2) DOX | (3) DOX+CON | a, c |
|                   | Cao et al. (80) | China | Yes | Rats, fisher 344 | Healthy | DOX | Glutamine | Glutamine | 28 days | 42 | 6 | (1) H2O+saline | (2) H2O+DOX | (3) glutamine+saline | c |
| CoQ10             | Rahmanifard et al. (81) | Iran | Yes | Rats, sprague dawley | Healthy | DOX | CoQ10 | CoQ10 | 21 days | 42 | 6 | (1) CON | (2) Isotopril | (3) CoQ10 | (4) DOX+CoQ10 | d, e, f |
|                   | Shabaan et al. Egypt (82) | Yes | Rats, wistar | Healthy | DOX | CoQ10 | CoQ10 | 7 days | 28 | 4 | (1) CON | (2) CoQ10 | (3) DOX+CoQ10 | c, d |
|                   | Botelho et al. Brazil (83) | Yes | Rats, wistar albino | Healthy | DOX | CoQ10 | CoQ10 | 14 days | 20 | 4 | (1) CON | (2) CoQ10 | (3) DOX+CoQ10 | b, c, d, e |
|                   | Chen et al. (84) | China | Yes | Rats, sprague dawley | Healthy | DOX | CoQ10 | CoQ10 | 21 days | 24 | 4 | (1) CON | (2) DOX | (3) DOX+CoQ10 | d, f |
|                   | Mustafa et al. Saudi Arabia (85) | Not reported | Rats, wistar albino | Healthy | DOX | CoQ10 | CoQ10 | 15 days | 72 | 6 | (1) CON | (2) DOX | (3) DOX+CoQ10 | b, c, e, f |

(Continued)
| Dietary nutrients | Studies | Country | Randomization | Animals | Intervention | Duration | Sample size | Comparison | Outcomes |
|-------------------|---------|---------|---------------|---------|--------------|----------|-------------|------------|----------|
| Trace elements    | Maryoosh et al. (86) | Iraq | Yes | Rats, wistar albino | Healthy | mitoxantrone | Zinc sulfate | Zinc | 20 days | 48 | 6 | (1) CON (2) Zinc 15 (3) Zinc 30 (4) mitoxantrone b, c |
|                   | Wu et al. (87) | China | Yes | Rats, sprague dawley | Healthy | DOX | ZnCM | Zinc, curcumin | 28 days | 42 | 6 | (1) CON (2) DOX (3) DOX+curcumin 100 (4) DOX+ZnCM 25 (5) DOX+ZnCM 50 (6) DOX+ZnCM 100 a, b, e |
|                   | Coudray et al. (88) | France | Not reported | Rats, wistar | Healthy | DOX | Selenium | Selenium | 49 days | 60 | 5 | (1) CON (2) saline (3) DOX (4) selenium c, f |
| Others            | Radeva-Ilieva et al. (89) | Bulgaria | Yes | Rats, wistar | Healthy | DOX | Methylxanthine from bancha | Methylxanthine | 17 days | 36 | 6 | (1) CON (2) DOX (3) methylxanthine 5 (4) methylxanthine 1 b |
|                   | Wahab et al. (90) | Egypt | Yes | Mice, swiss albino | Ehrlich ascites carcinoma | DOX | Vitamin E | Vitamin E | 30 days | 140 | 4 | (1) DOX (2) DOX+vitamin E c |

CON, control; CoQ10, coenzyme Q10; DOX, doxorubicin; FOLFOX, 5-fluorouracil+leucovorin+oxalipatin; PUFA, polyunsaturated fatty acids; TRZ, trastuzumab; ZnCM, zinc+curcumin.
a, echocardiography; b, serum cardiac markers; c, oxidative stress markers; d, histopathological examinations; e, electrocardiogram; f, survival, body weight, heart weight.
The characteristics of the included animal studies. Distribution of countries of included animal studies are shown in the left. The percentages represent the proportion of included studies in each continent, and the numbers are the number of studies in each country. Among them, African and Asian countries account for the largest share with most studies in Egypt (n = 15), India (n = 8), Saudi Arabia (n = 6), Turkey (n = 6), and China (n = 5). Types of dietary nutrients are listed in the right, containing polyphenols, allicin, lycopene, polyunsaturated fatty acids, amino acids, coenzyme Q10, and trace elements.

The risk of bias assessment of the included animal studies. The overall risk of bias of included human studies was at moderate to high risk. All items of Cochrane risk of bias tool were rated as low risk in one RCT (91), and three items (blinding of participants and personnel, blinding of outcome assessment, and selective outcome reporting) were rated as unclear risk in another RCT (92). The NOS’s scores of the non-randomized trials were 5 (93) and 6 (94) respectively, due to the lack of blind evaluation, follow-up and loss to follow up, and the inadequate reports of confounders adjustment. The details of the assessment are presented in Supplementary Tables 6, 7.

Effectiveness of Dietary Nutrients
Four studies all showed the cardioprotective effects of the dietary nutrient used in the trials. El Amrousy et al. (91) randomly...
TABLE 2 | The characteristics of the included human studies.

| Studies Country | Study design | Participants | Intervention | Comparison | Outcomes |
|-----------------|--------------|--------------|--------------|------------|----------|
| [80] Egypt       | RCT          | Male, 25, female, 15 | DOX          | CoQ10      | CON, control; CoQ10, coenzyme Q10; DOX, doxorubicin; PUFA, polyunsaturated fatty acids; RCT, randomized controlled trial. |
| [81] Italy      | Non-randomized, observational trial | Male, 11, 56.87 years | DOX          | CoQ10      | CON, control; CoQ10, coenzyme Q10; DOX, doxorubicin; PUFA, polyunsaturated fatty acids; RCT, randomized controlled trial. |
| [82] USA        | NON-RANDOMIZED CONTROLLED TRIAL | Male, 25, 12-16 years | DOX          | CoQ10      | CON, control; CoQ10, coenzyme Q10; DOX, doxorubicin; PUFA, polyunsaturated fatty acids; RCT, randomized controlled trial. |
| [83] Egypt      | RCT          | Male, 36, Female, 24 | DOX          | placebo    | CON, control; CoQ10, coenzyme Q10; DOX, doxorubicin; PUFA, polyunsaturated fatty acids; RCT, randomized controlled trial. |
| [84] Egypt      | RCT          | Male, 25, female, 15 | DOX          | CoQ10      | CON, control; CoQ10, coenzyme Q10; DOX, doxorubicin; PUFA, polyunsaturated fatty acids; RCT, randomized controlled trial. |

DISCUSSION

Our systematic review included 57 studies published in 14 countries from 1978 to 2021 consisting of 53 animal studies and four human studies, and summarized the cardioprotective effects of dietary nutrients derived from food on target subjects treated with chemotherapy. The descriptive synthetic evidence demonstrated that seven types of dietary nutrients (polyphenols, allicin, lycopene, PUFA, amino acids, CoQ10, and trace elements) might alleviate cardiovascular toxicity induced by chemotherapeutic agents.

As post-mitotic cells, cardiomyocytes are more sensitive to free radical damage due to their high oxidative metabolism and low antioxidant defense level (24). As a result, clinical and subclinical cardiac injuries related with chemotherapy have been a notorious issue. The incidence rates of CHF caused by anthracyclines and cyclophosphamides range 0.14–48% and 7–28%, respectively (6, 95). The childhood cancer survivors are 15 and 10 times more likely to suffer CHF and coronary artery disease, respectively than their siblings (96, 97). As early as in 1967, Tan et al. (98) first described the anthracycline-induced cardiotoxicity and reported that the development of
tachycardia, arrhythmia and CHF in daunomycin patients could be associated with daunomycin. Simultaneously, it was found that cardiovascular toxicity was dose-dependent with a 5% incidence of cardiomyopathy at a cumulative dose of 400 mg/m² of anthracyclines, 26% at a cumulative dose of 550 mg/m² and up to 48% at 700 mg/m² (99). That is the reason why the recommended cumulative dose is limited to 450–500 mg/m² (100). Currently, cardiotoxic effects led by anthracyclines, especially DOX, have been most thoroughly studied (7, 19). And this is consistent with our review, in which 90.6% of the included animal studies generated cardiac dysfunctions by the injection of DOX in rats/mice. The most widely proposed mechanism is the anthracyclines’ inhibition of topoisomerase 2β, which leads to promote cell apoptosis and generate oxidative damage in cardiomyocytes (13). At present, cardiotoxicity is a broader term without a formal definition (7, 101). The American Society of Echocardiography defines it as a ≥10% drop of LVEF from baseline or the absolute value <53% (101). 2016 European Society of Cardiology Position Paper considers the lower limit of normal LVEF as 50% (102). A clinical trial conducted on pediatric patients with acute myeloid leukemia also defined cardiotoxicity as LVEF <50% on the basis of the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3) definitions (8). However, significantly abnormal cardiac parameters were considered as cardiotoxicity in most of the studies included in our review. Similarly, improved measurements or even back to normal was recognized as the signs of positive cardioprotective effects of nutritional intervention.

The relevant guideline recommended that oncologists considered prevention against chemotherapy-induced cardiotoxicity through long-term management during the early stage of anticancer treatment with support from cardiologists (6). Compared with dexrazoxane, dietary nutrition is more accessible at ordinary times and easier to comply with in long-term survivals. In other words, it can meet the two main advantages of daily and long-term usage. Consequently, it is an additional prevention measure that cancer survivors cannot miss. While the nutritional support has been depicted to improve the adverse effects of chemotherapy (103–105), the current evidence against cardiotoxicity was limited due to the lack of enough clinical studies (29, 30). In addition, the guidelines did not report in detail the aspect of nutrition against cardiomyopathy associated with cancer therapy (6, 20, 96). Several published reviews introduced the application of nutritional intervention in the prevention of cardiac toxicity and covered CoQ10, grape seed extract and ω-3 PUFA (27, 28, 106). But none of them systematically summarized the effectiveness of overall dietary nutrients in this respect. Koss-Mikołajczyk et al. (29) showed that natural products (including fruit, vegetables, herbs, mushrooms, and phytochemicals) could counteract cardiac injury caused by DOX. Despite the comprehensive list of products included in this study, these were all edible plant extracts and foodborne phytochemicals. Nutrients derived from animal food as cardioprotective agents have not been explored. Therefore, our review summarized the current available evidence and filled in the corresponding gaps.

Seven types of dietary nutrients were represented in our review. Among them, polyphenols were in more than half of the included studies possibly due to more than 8,000 species in nature (including flavonoids and non-flavonoids) (107, 108). Polyphenols can eliminate oxygen free radicals by owning multiple PhOH (107) and the oxidation resistance has also made itself as a toxicity-related preventive strategy in some reviews (24, 26, 109). Thus, the extract of fresh fruit (rich in flavonols and flavonoids), grape seeds (rich in proanthocyanidin), and green tea (rich in catechins) were commonly used to ameliorate the chemotherapy-related cardiac damage in the included studies. Besides vegetable food, animal food was also made clear to protect the heart exposed to chemotherapy. PUFA are dietary factors with multiple beneficial effects and could likely protect cardiovascular tissues by adjusting cellular processes and molecular pathways (27, 110). The amino acids can preserve myocardial high-energy phosphate levels and prevent lactate accumulation. Our study refers to glutamine and glycine, which involve GSH synthesis (a vital intracellular antioxidant) (111). CoQ10 is a free-radical scavenger primarily present in metabolically active organs, such as the heart, liver, and kidney (82). Zn has a critical role in maintaining health, primarily through antioxidative stress and anti-inflammation, by catalyzing more than 300 enzymes and binding with over 2,500 proteins. Se prevents oxidative stress and maintains antioxidant enzymes such as the four glutathione peroxidases (GPxs) (112, 113).

There were several limitations in our systematic review. First, 93.0% of the included records (53/57) were animal studies along with a relatively moderate to high risk of bias, so the interpretation of results should be more cautious. Second, our findings may still remain a certain distance approaching the clinical application due to the majority of the included studies being animal research. Third, due to the lack of standardization in definition of cardiotoxicity and the high heterogeneity from the variations of included studies, it was a pity that we couldn’t provide pooled results in our review.

**CONCLUSION**

Early prevention and management of cancer chemotherapy-induced cardiotoxicity have been increasingly focused due to the attention to event-free survival during and after cancer therapy. The existing studies have indicated that cardiotoxicity not only puts the patients under high risk of suffering cardiac deterioration but also develops as a social issue concerning the increase of Health System spending (114). The evidence of dietary nutrients against cardiovascular toxicity was still lacking. Our systematic review demonstrated that dietary nutrients (comprising polyphenols, allicin, lycopene, PUFA, amino acids, CoQ10, Zn, and Se) may be a potential strategy to protect cardiovascular system exposed to the chemotherapeutic agents, but more human studies are needed in future. On this basis, the development of cardioprotective strategies for special population, like children,
the pregnant, and the elderly, is now essential for the reason that their vulnerable physical conditions demand much more cardiac protection.

**DATA AVAILABILITY STATEMENT**

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author/s.

**AUTHOR CONTRIBUTIONS**

K-WJ, QW, and X-NL contributed to the conception and design of the study. X-YZ and K-LY carried out the search strategy independently and wrote the draft manuscript. YL and YZ contributed to the analysis of the included studies. All authors are responsible for the final content of the manuscript and approved the final manuscript.

**REFERENCES**

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2021. *CA Cancer J Clin.* (2021) 71:7–33. doi: 10.3322/caac.21654
2. Richards MA. The National Awareness and Early Diagnosis Initiative in England: presenting the evidence. *Br J Cancer.* (2009) 101:S1–4. doi: 10.1038/sj.bjc.6605382
3. Urruticoechea A, Alemany R, Balart J, Villanueva A, Vinals F, Capella G. Recent advances in cancer therapy: an overview. *Curr Pharm Des.* (2010) 16:3–10. doi: 10.2174/13816121079891487
4. Miller KD, Nogueira L, Marritto AB, Rowland JH, Yabroff KR, Alfano CM, et al. Cancer treatment and survivorship statistics, 2019. *CA Cancer J Clin.* (2019) 69:363–85. doi: 10.3322/caac.21565
5. Conway A, McCarthy AL, Lawrence P, Clark RA. The prevention, detection and management of cancer treatment-induced cardiotoxicity: a meta-review. *BMC Cancer.* (2015) 15:366. doi: 10.1186/s12885-015-1407-6
6. Curigliano G, Lenihan D, Fradley M, Ganatra S, Barac A, Blaes A, et al. Strategies to prevent anthracycline-induced cardiotoxicity in cancer survivors. *Cardio-Oncol.* (2019) 5:18. doi: 10.1016/j.ejco.2019.0054-5
7. Gets KD, Sung L, Ky B, Gerbing RB, Leger KJ, Leahy AB, et al. Occurrence of treatment-related cardiotoxicity and its impact on outcomes among children treated in the AAML0531 clinical trial: a report from the children’s oncology group. *J Clin Oncol.* (2019) 37:12–21. doi: 10.1200/JCO.18.00013
8. Middleman E, Luce J, Frei E. Clinical trials with adriamycin. *Cancer.* (1971) 28:844–50. doi: 10.1002/1097-0142(1971)28:4<844::AID-CCCR280280407-3.0.CO;2-9
9. Tukenova M, Guibout C, Oberlin O, Doyon F, Mousannif A, Haddy N, et al. Role of cancer treatment in long-term overall and cardiovascular mortality after childhood cancer. *J Clin Oncol.* (2010) 28:1308–15. doi: 10.1200/JCO.2008.20.2267
10. Reulen RC, Winter DL, Frobisher C, Lancashire ER, Stiller CA, Jenney ME, et al. British childhood cancer survivor study steering group. Long-term cause-specific mortality among survivors of childhood cancer. *JAMA.* (2010) 304:172. doi: 10.1001/jama.2010.923
11. Mavrogeni SI, Slendarzaki E, Markoussis-Mavrogenis G, Rigopoulos A, Noutsias M, Kolovou G, et al. Cardiac oncoLOGY, the myth of Sisyphus, and cardiovascular disease in breast cancer survivors. *Heart Fail Rev.* (2019) 24:977–87. doi: 10.1007/s10741-019-09805-1

**FUNDING**

This work was financially supported by Disciplinary Booster Program of Xijing Hospital, China (Project Nos. XJZT21CM27, XJZT19X11, and XJZT18Z22).

**ACKNOWLEDGMENTS**

We appreciate the guidance of Dang Wei, Department of Global Public Health, Karolinska Institute, Stockholm, Sweden (dang.wei@ki.se).

**SUPPLEMENTARY MATERIAL**

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.921609/full#supplementary-material
25. Conklin KA. Dietary antioxidants during cancer chemotherapy: impact on chemotherapy effectiveness and development of side effects. *Nutr Cancer.* (2000) 37:1–8. doi: 10.1080/016355809031701

26. Frasad KN. Multiple dietary antioxidants enhance the efficacy of standard and experimental cancer therapies and decrease their toxicity. *Integr Cancer Ther.* (2004) 3:310–22. doi: 10.1177/153473540427906

27. Serini S, Ottes Vasconcelos R, Nascimento Gomes R, Calviello G. Protective effects of o-3 PUFA in anthracycline-induced cardiotoxicity: a critical review. *Int J Mol Sci.* (2017). 28:18369. doi: 10.3390/ijms1812689

28. Roffe L, Schmidt K, Ernst E. Efficacy of coenzyme Q10 for improved therapeutic use against doxorubicin induced cardiotoxicity. *PLOS ONE.* (2017) 12:e0181535. doi: 10.1371/journal.pone.0181535

29. Othman SNN, Lum PT, Gan SH, Mani S, Sekar M. Protective effect of curcumin and β-carotene on cisplatin-induced cardiotoxicity: an experimental rat model. *Anatol J Cardiol.* (2018) 19:213–21. doi: 10.14744/anatolJ.cardiol.2018.53039

30. Koss-Mikołajczyk I, Todorovic V, Sobajic S, Mahajna J, Geric M, Tur JA, et al. Natural products counteracting cardiotoxicity during cancer chemotherapy: the special case of doxorubicin, a comprehensive review. *Int J Mol Sci.* (2021) 22:10037. doi: 10.3390/ijms221010037

31. Othman SNN, Lum PT, Gan SH, Mani S, Sekar M. Protective effect of natural products against chemotherapeutic-induced cardiotoxicity: a review. *Pharmacog J.* (2020) 12:1180–9. doi: 10.5530/pj.2020.12.166

32. Czepea G. Gwozdziński A. The flavonoid quercetin: Possible solution for anthracycline-induced cardiotoxicity and multidrug resistance. *Biomed Pharmacother.* (2014) 68:1149–59. doi: 10.1016/j.biopha.2014.10.013

33. Tan ML, Hamid SBS. Beetroot as a potential functional food for cancer chemoprevention, a narrative review. *J Cancer Prev.* (2021) 26:1–9. doi: 10.15340/jcp.2021.26.1.1

34. de Vries RBM, Hooijmans CR, Langendam MW, van Luijck J, Leenaars M, Ritskes-Hoitinga M, et al. Protocol format for the preparation, registration and publication of systematic reviews of animal intervention studies: protocol format for animal systematic reviews. *Evid-Based Prev Clinin Med.* (2015) 1:1–9. doi: 10.1002/ebhm.2

35. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol.* (2000) 15:829–31. doi: 10.1023/A:1008984704730

36. Hooijmans CR, Rovers MM, de Vries RB, Leenaars M, Ritskes-Hoitinga M, et al. SYRCLE’s risk of bias tool for animal studies. *Int J Mol Sci.* (2012) 13:1180–9. doi: 10.3390/ijms13061180

37. Langendam MW. SYRCLE’s risk of bias tool for animal studies. *Res Methodol.* (2014) 14:43. doi: 10.1186/1471-2288-14-43

38. Ibrahim MA, Bakhath GA, Tammam HG, Mohamed RM, El-Naggar SA. Cardioprotective effect of grape seed extract and vitamin E on Cisplatin-induced cardiotoxicity in mice: toxicological, histological and immunohistochemical studies. *Biomed Pharmacother.* (2011) 65:108731. doi: 10.1016/j.biopha.2011.10.073

39. Boghdady NAE. Antioxidant and antiapoptotic effects of proboscisierony and ginkgo biloba extract against doxorubicin-induced cardiac injury in rats: modulation of doxorubicin cardiotoxicity. *Cell Biochem Funct.* (2013) 31:534–51. doi: 10.1002/cbf.2907

40. Elbbery AA, Abdel-Naim AB, Abdel-Sattar EA, Nagy AA, Mosli HA, Mohamadin AM, et al. Cranberry (Vaccinium macrocarpon) protects against doxorubicin-induced cardiotoxicity in rats. *Food Chem Toxicol.* (2010) 48:1178–84. doi: 10.1016/j.fct.2010.02.008

41. Zhang XY, Li WG, Wu YJ, Gao MT. Amelioration of doxorubicin-induced myocardial oxidative stress and immunosuppression by grape seed proboscisierony in tumour-bearing mice. *J Pharm Pharmacol.* (2005) 57:1043–52. doi: 10.1211/2002357055623

42. Porzini T, Trinei M, Fornari M, Calvenzani V, Marinelli A, Micheli LA, et al. Dietary cyanidin 3-glucoside from purple corn ameliorates doxorubicin-induced cardiotoxicity in mice. *Nutr Metab Cardiovasc Dis.* (2017) 27:462–9. doi: 10.1016/j.numecd.2017.02.002

43. Shoukry HS, Ammar HI, Rashed LA, Zikri MB, Shamaa AA. Abou elfadl SG, et al. Prophylactic supplementation of resveratrol is more effective than its therapeutic use against doxorubicin induced cardiotoxicity. *PLOS ONE.* (2017) 12:e0181535. doi: 10.1371/journal.pone.0181535

44. Paina MH, Mohammad NS, Atteia HH, Abdel-Elaziz HR. Protective effect of resveratrol against doxorubicin-induced cardiac toxicity and fibrosis in male experimental rats. *J Physiol Biochem.* (2014) 70:701–11. doi: 10.1007/s13105-014-0339-y

45. Ibrahim Fouad G, Ahmed KA. Curcumin ameliorates doxorubicin-induced cardiotoxicity and hepatotoxicity via suppressing oxidative stress and modulating inOS, NF-κB, and TNF-α in rats. *Cardiovasc Toxicol.* (2022) 22:156–66. doi: 10.1007/s12112-021-09710-w

46. Bahadir A, Ceyhan A, Oz Gergin O, Yalcin B, Ugener M, Ozyazgan TM, et al. Protective effects of curcumin and β-carotene on cisplatin-induced cardiotoxicity: an experimental rat model. *Anatol J Cardiol.* (2018) 19:213–21. doi: 10.14744/anatolJ.cardiol.2018.53039

47. Prasad KN. Multiple dietary antioxidants enhance the efficacy of standard and experimental cancer therapies and decrease their toxicity. *Integr Cancer Ther.* (2004) 3:310–22. doi: 10.1177/153473540427906
Zhang et al. Prevention for Chemotherapy-Induced Cardiotoxicity

78. Todorova VK, Kaufmann Y, Hennings L, Klimberg VS. Oral glutamine protects against acute doxorubicin-induced cardiotoxicity of tumor-bearing rats. *J Nutr.* (2010) 140:44-8. doi: 10.3945/jn.109.113415

79. Cao Y, Kennedy R, Klimberg VS. Glutamine protects against doxorubicin-induced cardiotoxicity. *J Surg Res.* (1999) 85:178-85. doi: 10.1006/jsre.1999.7667

80. Rahnamand F, Vessal M, Noorafshan A, Karbalay-Doust S, Naseh M. The Protective effects of coenzyme Q10 and Lisinopril against doxorubicin-induced cardiotoxicity in rats: a stereological and electrocardiogram study. *Cardiovasc. Toxicol.* (2021) 21:936–46. doi: 10.1007/s12120-021-09685-8

81. Shabaan DA, Mostafa N, El-Desoky MM, Arafat EA. Coenzyme Q10 protects against doxorubicin-induced cardiomyopathy via antioxidant and anti-apoptotic pathway. *Tissue Barriers.* (2021) 3:2019954. doi: 10.20516/21686370.2021.2019954

82. Botelho AFM, Lempek MR, Branco SEMT, Nogueira MM, de Almeida ME, Costa AG, et al. Coenzyme Q10 cardioprotective effects against doxorubicin-induced cardiotoxicity in Wistar rat. *Cardiovasc. Toxicol.* (2020) 20:222–34. doi: 10.1007/s12120-019-09547-4

83. Chen PY, Hou CW, Shibu MA, Day CH, Piu P, Liu ZR, et al. Protective effect of Co-enzyme Q10 On doxorubicin-induced cardiomyopathy of rat hearts. *Environ. Toxicol.* (2017) 32:679–89. doi: 10.1002/tox.22270

84. Mustafa HN, Hegazy GA, Awdan SAE, Abdel-Basset M. Protective role of CoQ10 or L-carnitine on the integrity of the myocardium in doxorubicin induced toxicity. *Tissue Cell.* (2017) 49:410–26. doi: 10.1016/j.tice.2017.03.007

85. Maryouob TM, N. Al-Shawi N, Salih E. Effects of two different doses of zinc sulfate on serum troponin I 3 enzyme level and cardiac malondialdehyde contents in mitoxantrone-induced cardiotoxicity in rats. *Iraqi. J Pharm. Sci.* (2020) 29:115–22. doi: 10.33151/vol29iss1pp115-122

86. Wu R, Mei X, Wang J, Sun W, Xue T, Lin C, et al. Zn (II) –Curcumin supplementation alleviates gut dysbiosis and zinc dyshomeostasis during doxorubicin-induced cardiotoxicity in rats. *Food. Funct.* (2019) 10:5587–604. doi: 10.1039/C9FO01034C

87. Coudray C, Boucher F, Hida H, Tirard V, de Leiris J, Favier A. Selenium supplementation decreases the pro-oxidant and cardiotoxicity effects of adriamycin in the rat. *Redox Rep.* (2016) 2:323–32. doi: 10.1080/13510002.1996.11747068

88. Radeva-Ilieva MP, Georgiev KD, Hvarchanova NR, Stoeva SS, Slavova K, Zahanova T, Zaneva P, et al. Protective effect of methylxanthine fractions isolated from *Bancha* tea leaves against doxorubicin-induced cardiotoxicity in rats. *BioMed Res Int.* (2020) 2020:1–9. doi: 10.1155/2020/4018412

89. Wahab MHA, Akoul E-SEMS, Abdel-Aziz AA. Modulatory effects of pomegranate seed extract on doxorubicin-induced cardiotoxicity in rat. *Asian Pac. J. Cancer Prev.* (2017) 18:1005–12. doi: 10.22034/APJCP.2017.18.01005

90. El-Amrousy D, El-Afify D, Khedr R, Ibrahim AM. Omega 3 fatty acids can reduce early doxorubicin-induced cardiotoxicity in children with acute lymphoblastic leukemia. *Pediatr Blood Cancer.* (2020) 6:29496. doi: 10.1002/pbc.29496

91. Hagag AA, Badraia IM, El-Shehaby WA, Mabrouk MM. Protective role of black seed oil in doxorubicin-induced cardiac toxicity in children with acute lymphoblastic leukemia. *J Oncol Pharm Pract.* (2020) 26:1397–406. doi: 10.1177/1751450719872934

92. Larussi D, Auricchio U, Aggetto A, Murzana A, Giuliani M, Casale F, et al. Protective effect of coenzyme Q10 on arrhythmogenic cardiotoxicity: control study in children with acute lymphoblastic leukemia and non-Hodgkin lymphoma. *Mol Aspects Med.* (1994) 15:s207–12. doi: 10.1016/0098-2997(94)90030-2

93. Cortes EP, Gupta M, Chou C, Amin VC, Folkes K. Adriamycin cardiotoxicity: early detection by systolic time interval and possible prevention by coenzyme Q10. *Cancer Treat Rep.* (1978) 62:887–91. Available online at: https://pubmed.ncbi.nlm.nih.gov/6678636/

94. Senkus E, et al. Cardiotoxic effects of systemic cancer treatment. *Cancer Treat Rev.* (2011) 37:300–11. doi: 10.1016/j.ctrv.2011.11.001

95. Lipshultz SE, Adams MJ, Colan SD, Constine LS, Herman EH, Hsu DT, et al. Long-term cardiovascular toxicity in children, adolescents, and young adults who receive cancer therapy: pathophysiology, course, monitoring,
management, prevention, and research directions: a scientific statement from the American heart association. Circulation. (2013) 128:1927–95. doi: 10.1161/CIR.0b013e3182aa8099

97. Oeffinger KC, Mertens AC, Sklar CA, Kawashima T, Hudson MM, Meadows AT, et al. Chronic health conditions in adult survivors of childhood cancer. N Engl J Med. (2006) 355:1572–82. doi: 10.1056/NEJMsa060185

98. Tan C, Tasaka H, Yu K-P, Murphy ML, Karnofsky DA. Daunomycin, an antitumor antibiotic, in the treatment of neoplastic disease. Clinical evaluation with special reference to childhood leukemia. Cancer. (1967) 20:333–53. doi: 10.1002/1097-0142(1967)20:3<333::AID-CNCNR2820200302>3.0.CO;2-K

99. Li DL, Hill JA. Cardiomyocyte autophagy and cancer chemotherapy. J Mol Cell Cardiol. (2014) 71:54–61. doi: 10.1016/j.yjmcc.2013.11.007

100. Cavarretta E, Mastroiacovo G, Lupieri A, Frati G, Peruzzi M. The Positive Effects of Exercise in Chemotherapy-Related Cardiomyopathy. In: Xiao J, editor. Exercise for Cardiovascular Disease Prevention and Treatment. Advances in Experimental Medicine and Biology. Singapore: Springer Singapore (2017). p. 103–129 doi: 10.1007/978-981-10-4304-8_8

101. Cardinale D, Colombo A, Bacchiani G, Meroni CA, Veglia F, et al. Early detection of anthracycline cardiotoxicity and improvement with heart failure therapy. Circulation. (2015) 131:1981–8. doi: 10.1161/CIRCULATIONAHA.114.013777

102. Zamorano JL, Lancellotti P, Rodriguez Muñoz D, Aboyans V, Asteggiano R, Galderisi M, et al. 2016 ESC Position Paper on cancer treatments for cardiovascular health. Eur Heart J. (2016) 37:2768–801. doi: 10.1093/eurheartj/ehw211

103. de van der Schueren MAE, Laviano A, Blanchard H, Jourdan M, Arends J, Baracos VE. Systematic review and meta-analysis of the evidence for oral nutritional intervention on nutritional and clinical outcomes during chemo(radio)therapy: current evidence and guidance for design of future trials. Ann Oncol. (2018) 29:1141–53. doi: 10.1093/annonc/mdy114

104. Kim SH, Lee SM, Jeung HC, Lee JI, Park JS, Song M, et al. The effect of nutrition intervention with oral nutritional supplements on pancreatic and bile duct cancer patients undergoing chemotherapy. Nutrients. (2019) 11:1145. doi: 10.3390/nu11051145

105. Qin N, Jiang G, Zhang X, Sun D, Liu M. The effect of nutrition intervention with oral nutritional supplements on ovarian cancer patients undergoing chemotherapy. Front Nutr. (2021) 8:685967. doi: 10.3389/fnut.2021.685967

106. Olaku OO, Ojukwu MO, Zia FZ, White JD. The role of grape seed extract in the treatment of chemo(radio)therapy induced toxicity: a systematic review of preclinical studies. Nutr Cancer. (2015) 67:730–40. doi: 10.1080/01635581.2015.1029639

107. Luca SV, Macovei I, Bujor A, Miron A, Skalicka-Wozniak K, Aprotosoaie AC, et al. Bioactivity of dietary polyphenols: the role of metabolites. Crit Rev Food Sci Nutr. (2020) 60:626–39. doi: 10.1080/10408398.2018.1546669

108. Bravo L. Polyphenols: Chemistry, dietary sources, metabolism, and nutritional significance. Nutr Rev. (1998) 56:317–33. doi: 10.1111/j.1753-4887.1998.tb01670.x

109. Fraga CG, Croft KD, Kennedy DO, Tomás-Barberán FA. The effects of polyphenols and other bioactives on human health. Food Funct. (2019) 10:514–28. doi: 10.1039/C8FO01997E

110. Sanders TAB. Protective effects of dietary PUFA against chronic disease: evidence from epidemiological studies and intervention trials. Proc Nutr Soc. (2014) 73:73–9. doi: 10.1017/S0033583313003789

111. Gaurav K, Goel R, Shukla M, Pandey M. Glutamine: A novel approach to chemotherapy-induced toxicity. Indian J Med Paediatr Oncol. (2012) 33:13–20. doi: 10.4103/0971-5851.96962

112. Choi S, Liu X, Pan Z. Zinc deficiency and cellular oxidative stress: prognostic implications in cardiovascular diseases. Acta Pharmacol Sin. (2018) 39:1120–32. doi: 10.1038/aps.2018.25

113. Mohammadifar N, Humphries KH, Gotay C, Mena-Sánchez G, Salas-Salvadó J, Esmailzadeh A, et al. Trace minerals intake: risks and benefits for cardiovascular health. Crit Rev Food Sci Nutr. (2019) 59:1334–46. doi: 10.1080/10408398.2017.1406332

114. Bassareo PP, Monte I, Romano C, Deidda M, Piras A, Cugusi L, et al. Mercuro G. Cardiotoxicity from anthracycline and cardioprotection in paediatric cancer patients: J Cardiovasc Med. (2016) 17:e55–63. doi: 10.2459/JCM.0000000000000375

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.