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None Herbal Agents as Preventive and Therapeutic Measures for Doxorubicin Induced Hepatotoxicity: A Comprehensive Review

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ABSTRACT

Cancer is one of the most common human diseases and a leading cause of human mortality in rencent years. Doxorubicin (DOX) is an important anti-cancer agent belonging to anthracyclines drug category. This chemotherapeutic agent acts against cancer cells through different mechanisms; however, its use is related with numerous acute and chronic dose-related side effects and toxicities including hepatotoxicity. The aim of this study was to conduct a comprehensive review of in vitro, in vivo and any human studies regarding the protective effects of synthetic compounds against DOX-induced liver injury. The search was conducted in embase, PubMed and Scopus databases using the following keywords: "doxorubicin", "Adriamycin", "hepatotoxicity", "liver injury", "liver damage" and "hepatoprotective" to find experimental and preclinical studies regarding the effects of various compounds on DOX-induced hepatotoxicity. Twenty-one eligible studies to the end of May 2022 finally were reviewed (19 in vivo and 2 both in vivo and in vitro studies). Our results demonstrated that all of these drugs, except acetylsalicylic acid, had considerable hepatoprotective effects against DOX (deferoxamine had a mild effect). In addition, except glutathione, none of the studied drugs and compounds attenuated the antitumor efficacy of DOX treatment. Moreover, no human study was available in this fieild. Altogether, our results demonstrated that most of compounds with anti-apoptosis, anti-inflammatory and antioxidant properties are efficacious against DOX-induced hepatotoxicity and may have potential for being considered for inclusion in the chemotherapeutic regimes of cancer patients, after fully been assessed in well-desgined large clinical trials.

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Introduction

Cancer is one of the most common human diseases with the incidence rate of over 440 per 100,000 men and women and a total number of 19.3 million people are diagnosed annually. This devastating disease is the second leading cause of human mortality after cardiovascular disease, accounting for up to 10 million deaths in 2020, worldwide (1). The most prevalent drugs used for the systemic therapy of cancer patients are chemotherapeutic agents, which generally target the uncontrolled growth and proliferation of cancer cells (2). Doxorubicin (DOX) is a chemotherapeutic agent belonging to anthracyclines, which first is extracted from Streptomyces peucetius (3).DOX can act against cancer cells through multiple mechanisms, mainly including (I) intercalation into the DNA double helix and interference with topoisomerase II-mediated DNA repair and (II) generation of free radicals which can damage cell membrane, DNA molecules and proteins. The later mechanism is mediated through oxidization of DOX to an unstable metabolite, semiquinone, which is then converted back to DOX in a process that generate reactive oxygen species (ROS) (3). These mechanisms have made DOX to be a popular agent for systemic treatment of cancer. Currently, DOX is routinely used for the treatment of a wide range of human malignancies, such as acute leukemias and lymphomas, carcinomas, sarcomas, breast, bladder, ovarian, gastric, bone and also some pediatric cancers (4). However, high doses and prolonged use of this drug for the treatment of cancer is associated with several side effects and post-treatment debacles e.g., hepatotoxicity, cardiotoxicity, adverse effects on adipose tissue and recurred and resistant tumors formation (5).

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Lots of available studies on doxorubicin adverse effects are focused on its cardiotoxicity. However, the administration of DOX is also frequently associated with toxic injury to the liver, and may intensify the rate of transient increase in serum liver enzyme and acute liver injury with jaundice that can be severe and even life-threatening (6). The production of ROS is the major consequence of its redox cycling profile and is considered as a double-edged sword, which functions not only on cancer cells but also on several normal cells throughout the body. Various enzymes, including xanthine oxidases, NADPH oxidases, nitric oxide synthases, and peroxidases, which are located in several subcellular compartments, e.g., mitochondria, endoplasmic reticulum and cytoplasm, account as major sources of ROS. These alterations may result in various histopathological change as well as induction of apoptosis (7). The probable mechanisms of hepatotoxicity are summarized in Figure 1. Furthermore, pharmacokinetics studies of DOX in patients with abnormal liver biochemistry tests have revealed that patients with reduced DOX clearance not only had an increased bilirubin level, but also revealed elevated levels of liver enzymes, such as aspartate aminotransaminase (AST) and alanine aminotransaminase (ALT) (8). Approaches to doxorubicin dosing in patients with impaired liver function are variable now. The United States Prescribing Information for doxorubicin and pegylated liposomal doxorubicin recommend a 50 percent dose reduction for bilirubin 1.2 to 3 mg/dL, and a 75 percent dose reduction for bilirubin 3.1 to 5 mg/dL. Others suggest omission of the drug for bilirubin >5 mg/dL (9). In this regard, an increasing body of evidence demonstrate that different synthetic drugs and naturally-occurring flavonoids may be effective against DOX hepatotoxicity (10). The ameliorative effects of such drugs include the reduction in the inflammatory cytokines, diminishing apoptosis through the down-regulation of pro-apoptotic proteins and up-regulation of antiapoptotic proteins, resulting in liver enzymes serum level reduction and decreasing hepatic collagen fibers deposition scores, to mention a few (10). However, in spite of the extensive studies on the protective effects of these drugs against DOX, the full potentials and benefits and the detailed mechanisms remain to be elucidated. The objective of this study was to conduct a review of published preclinical and clinical studies regarding the protective effects of various drugs and compounds against DOX-induced liver injuries and to define the cellular and molecular mechanisms underlying this hepatoprotection.

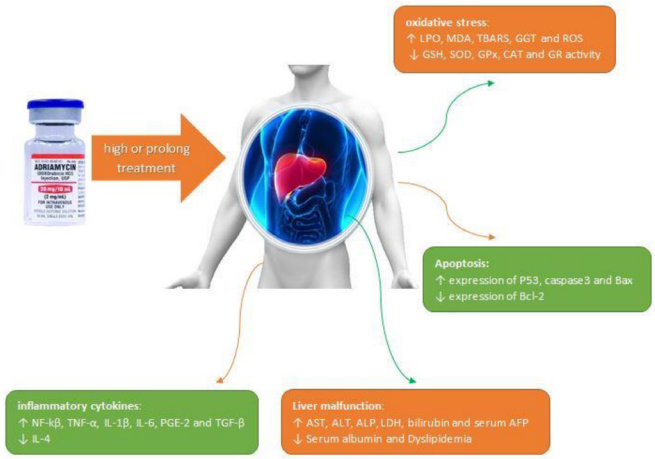

Figure 1. Probable mechanisms of doxorubicin induced hepatotoxicity.

Methods

In May 2022, we explored scientific databases including Embase, PubMed and Scopus with the following keywords: "doxorubicin", "adriamycin", "hepatotoxicity", "liver injury", liver damage and "hepatoprotective". We considered no restriction on the availability of the full text, if enough data could be accessed from the abstract and publication date of the article. We chose the related articles based on their title and abstract. Our inclusion criteria were papers written in English that assessed the protective effect of various compound against DOX-induced hepatotoxicity. All in vitro, in vivo and clinical studies which were accordant with our criteria were included. Duplicated or unrelated articles or articles published in languages other than English, and also studies on herbal compounds were excluded. Data collection was carried out between May 5 and May 28, 2022. The search process and initial selection of eligible studies were done by the first author. Finally, in the result section, we gathered and compared the effectiveness in ameliorating DOX-induced hepatotoxicity, based on liver function test (serum level of AST, ALT and bilirubin).

Results

874 articles were found by searching abovementioned databases. 643, 151, 23, 3 and 33 articles were omitted because of nonrelevant, duplication, review articles, papers in other languages and focusing on herbal compounds, respectively. Finally, 21 relevant and eligible studies were chosen for review (Figure 2). The included studies are summarized in Table 1. Twenty compounds are assessed as hepatoprotective against DOX and related studies are reviewed in the following sections.

Table 1. Summarized list of studies on non-herbal compounds against doxorubicin induced hepaptoxicity.

Study (year) (reference)	Drug	Type of study	Study design	Results/mechanisms
Sikandar et al. 2020 (13)	TMZ	*In vivo*	40 balb/c mice 5 groups: CTRL: NS i.p. DOX: 10 mg/kg i.p. on the 3rd day TMZ: 10 mg/kg/day p.o. for 5 days TMZ+DOX5: 10 mg/kg/day TMZ p.o. for 5 days+10 mg/kg DOX i.p. on the 3rd day. TMZ+DOX10: 10 mg/kg/day TMZ p.o. for 10 days+10 mg/kg DOX i.p. on the 3rd and 8th days.	Sig ↓ LDH levels in TMZ+DOX10 group due to longer treatment with TMZ. Sig ↓ ALT levels in TMZ+DOX10 group. Sig ↓ AST in both short and longer treatment with TMZ. Sig protection of DOX-induced hepatic damages in 10 days treatment with TMZ.
Salouege et al. 2014 (12)	TMZ	*In vivo*	24 Wistar rats 3 groups: CTRL: NS. DOX: 3.7 mg/kg/day i.p. DOX+TMZ: DOX+10 mg/kg/day TMZ 3 days	Sig ↓ AST level in DOX+TMZ. Sig ↑ ALT level in DOX and DOX+TMZ groups compared to CTRL group. Quantifying lidocaine metabolites revealed DOX-induced deflection of metabolic pathway of lidocaine biotransformation. This effect is highlighted by TMZ treatment.
Mansouri et al. 2017 (14)	PRV	*In vivo*	24 SD rats. 4 groups: CTRL: NS p.o. PRV: 20 mg/kg/day p.o. DOX: 15 mg/kg single i.p. on day 6 PRV+DOX: 15 days	Sig ↓ in PRV+DOX group. Sig reverse of DOX-induced ↑ ALT, AST, ALP, TG, chol, LDL, total BL and also ↓ HDL and serum ALB. Sig ↓ histopathological changes caused by DOX. Sig ↓ microscopic score in PRV+DOX. Sig ↓ MDA level in PRV+DOX group. Sig ↑ SOD, CAT and GPx levels in PRV+DOX.
Alkhatib et al. 2021 (15)	PRV in LNE	*In vivo*	160 Swiss albino mice 8 groups: NS: 200µl to healthy mice. EAC: injected with tumor cells. BL-NE: 0.2 ml. DOX/LNE: 2mg/kg DOX solubilized in 200 µl NE. DOX-Sol: 2mg/Kg DOX in 200 µL NS. DOX+PRV/LNE: 2 mg/Kg DOX with 4 mg/Kg PRV solubilized in 200 µL NE. DOX+PRV-Sol: 2mg/kg DOX with 4mg/kg PRV in 200 µL NS. PRV/LNE: 4mg/kg PRV solubilized in 200 L NE.	Sig ↓ BW in DOX-Sol and DOX+PRV-Sol groups compared to CTRL group. Although, sig ↑ BW in other treated groups. Sig ↑ liver enzymes (ALT, AST, ALP) and total BL in all DOX-treated groups compared to CTRL and EAC groups. Sig ↓ liver enzyme activities and total BL in DOX+PRV/LNE and PRV/LNE groups compared to DOX-sol group. Sig ↑ AST and total BL in EAC and BL-NE groups compared to CTRL group. Normal histological structure in CTRL, EAC, DOX/LNE and DOX+PRV/LNE groups. Sig hepatic alterations in DOX-sol group. Moderate histopathological changes in DOX-PRV-Sol group. The lowest MST in DOX-Sol group. Sig ↑ MST in DOX+PRV/LNE compared to DOX+PRV-Sol group. Absolute survival rate in DOX/LNE as well as CTRL group.

Table 1. Continued

Akindele et al. 2017 (16)	CRV, DLT and PRD	*In vivo*	70 Wistar rats 10 groups: CTRL: 10ml/kg NS. DOX: NS+40 mg/kg DOX Positive CTRL: 200 mg/kg gallic acid+40 mg/kg DOX CRV75+DOX: 0.075mg/kg, subclinical dose. CRV150+DOX: 0.15mg/kg, clinical dose CRV300+DOX: 0.3mg/kg, supraclinical dose. DLT+DOX: 3.43mg/kg DLT+DOX DLT+CRV150+DOX: PRD+DOX: 0.57mg/kg PRD+DOX PRD+CRV150+DOX: 16 days DOX injection on day 14	Sig ↓ DOX-induced ALT, AST and ALP elevations in CRV (all doses) +DOX groups. Sig ↓ ALT and AST in DLT+CRV+DOX. Sig ↓ DOX-induced elevation of ALT in PRD+CRV+DOX group. Sig ↓ MDA level in groups 5, 7,8,9 and 10 in comparison with groups 2, 4 and 6. Sig ↑ DOX-induced reduction of SOD and CAT levels in DLT+CRV150+DOX group. Sig ↑ DOX-induced reduction of CAT and GSH levels in PRD+CRV150+DOX group. Normal structure of liver in all groups but DOX (steatosis in liver cells).
Abd El-Aziz et al. 2001 (18)	CPT and ENP	*In vivo*	48 Rats 6 groups: CTRL: 0.5ml/day water i.g. CPT: 10 mg/kg/day i.g. ENP: 2mg/kg/day i.g. DOX: 15 mg/kg single i.p. on day 7 DOX+CPT DOX+ENP 7days	Sig ↓ serum markers (ALT, AST and LDH) with CPT and ENP pre-treatment groups. Sig protection against DOX-induced oxidative stress by ↓ LPO and ↑ SOD and CAT activities with both ENP and CPT pre-treatments. No sig changes in GSH level.
Yamgurca et al. 2007 (20)	EDT	*In vivo*	30 SD rats 3 groups: CTRL: NS p.o. daily DOX: 20mg/kg, i.p. on the 3rd day EDT: 10mg/kg/day EDT p.o. +DOX 12 days	Sig ↓ DOX-induced liver histopathological changes. Sig ↓ MDA and PCC levels. Sig ↑ activities of SOD and CAT enzymes.

Table 1. Continued

Saad et al. 2001 (22)	DFX	*In vivo*	42 Wistar albino rats. 7 groups: CTRL: NS DOX: 25mg/kg i.v. DFX: 25, 125, 250, 375 and 500mg/kg i.p. 30min prior to DOX injection.	Sig ↓ ALT and AST levels in all pre-treatments with DFX in a dose-dependent manner. Sig ↓ liver per-oxidative changes (↓ GSH and ↑ MDA levels) In DFX pre-treatment groups in a dose dependent manner. Moderate amelioration of DOX-induced hepatocyte changes in DFX groups up to 250mg/kg doses. Sig aggrevation of hepatocyte structures in higher doses of DFX.
Bulucu et al. 2009 (23)	NAC, DFX and Se	*In vivo*	56 SD rats 5 groups: CTRL: NS i.v. DOX: 5mg/kg i.v. NAC: 20 mg/kg NAC i.v.+DOX DFX: 20 mg/kg DFX i.v.+DOX DFX+NAC: DFX+NAC+DOX Se:15 mg/kg Se i.p.+DOX	Sig ↓ LPO and MDA levels in NAC, Se and DFX groups. Sig ↓ CAT activity in DFX and DFX+NAC groups. Sig ↑ SOD activity in all treated groups. Sig ↑ GPx activity in NAC and DFX groups. Sig ↑ liver tissue Cu levels in NAC, DFX and DFX+NAC groups. Sig ↑ liver tissue Zn levels in DFX+NAC. Sig ↓ Zn levels in Se group. Sig ↑ liver tissue Fe levels in DFX+NAC and Se groups. Sig ↑ serum ALT levels in NAC and DFX groups compared to DOX group. Sig ↑ serum AST levels in DFX compared to DOX group. Sig ↑ serum ALP levels in NAC, DFX and Se groups compared to DOX group. Sig ↑ serum total pr and ALB levels in NAC, DFX and Se groups compared to DOX group. Sig ↓ DOX-induced overt proteinuria in DFX group.
Cengiz et al. 2020 (24)	Se	*in vivo*	64 Wistar albino rats 8 groups: CTRL: 1ml/kg NS DOX: 5mg/kg/week i.p. Se1,2,3: 0.5, 1, 2 mg/kg/day i.p. for 28 days DOX+ Se1,2,3 33 days	Normal liver structure in 0.5mg Se, 1mg Se and DOX+0.5 or 1mg Se groups. necrosis and liver damage in DOX, 2mg Se and DOX+2mg Se groups. Sig ↓ level of TNF-α and IL1-β in the liver in DOX+0.5 mg Se group. Sig ↓ DOX-induced inflammation and cell damage with co-administration of 0.5 and 1 mg Se; no beneficial effect with 2 mg Se. Sig ↓ DOX-induced hepatocytes proliferation (PCNA) in DOX+0.5mg Se group. Moderate ↑ PCNA in DOX+1 or 2mg Se group.

Table 1. Continued

Petrovic et al. 2018 (28)	FNP/DOX-nanoC	*In vivo*	36 Wistar rats 6 groups: 1. CTRL: 0.9% NaCl 2. FNP: 0.125 mg/kg 3. DOX4: 4mg/kg 4. FNP+DOX4 5. DOX2: 2mg/kg 6. FNP+DOX2 - 24h treatment	Sig ↓ CAT, SOD and GR activity and ↓ GST levels in FNP+DOX2 group. Non-sig changes in these enzymes' activities in FNP+DOX4 group. Non-sig ↑ DOX-induced reduction of GPx activity in FNP treatments. Sig ↑ CAT and ↓ SOD in FNP compared to CTRL group. Sig ↓ SOD mRNA levels in FNP+DOX treatment with either dose. Sig ↓ CAT mRNA levels in FNP+DOX2, while no sig difference in FNP+DOX4. Sig ↑ Bax and ↓ Bcl-2 in all treatments. Hence, apoptosis takes place in all treated groups. Sig ↑ expression of Bcl-2 only in FNP+DOX4 group. Sig protective effect of FNP treatments against DOX-induced severe liver histological damages.
Jacevic et al. 2015 (27)	FNP-nanoP	*In vivo*	40 Wistar rats 5 groups: CTRL: NS FNP100: 100mg/kg i.p. FNP. DOX10: 10mg/kg iv DOX. DOX10+FNP50 DOX10+FNP100 FNP injection 30 min before DOX. 14 days	Sig ↑ survival rate, body and liver weight at both doses of FNP treatments. Sig ↓TBARS, LPO and anti-oxidative enzymes activity (SOD, CAT, GR and GPx) in the liver rat tissue at both doses of FNP treatments. Sig ↓ DOX-induced hepatic damages in pre-treatment with FNP100. No sig liver histological preservation with FNP50.
Aljobaily et al. 2020 (31)	Cr	*In vivo*	60 SD rats. 3 groups: CTRL: STD food; 4 weeks. 2% Cr: food supplemented with 2% Cr; 4 weeks. 4%/2% Cr: food supplemented with 4% Cr for 1 week followed by 2% Cr for other 3 weeks. 6 subgroups: CTRL/DOX; 2% Cr/DOX; 4%/2% Cr/DOX; CTRL/NS; 2% Cr/NS; 4%/2% Cr/NS. 15mg/kg DOX i.p. 0.9% NS i.p. as placebo.	Sig ↓ liver-to-body weight ratio in 4%/2% Cr/NS and 2% Cr/DOX groups in comparison with CTRL/DOX group. ↓ AST-to-ALT ratio in 4%/2% Cr/DOX. No sig histological alterations in CTRL/DOX group compared to CTRL/NS. Sig ↓ fibrosis in 2% Cr/DOX and 4%/2% Cr/DOX. ↓ FN-1 expression in 4%/2% Cr/DOX. ↓ CD45 expression in 2% Cr/DOX and 4%/2% Cr/DOX. No sig ↓ NF-kB expressions in 2% Cr/DOX and 4%/2% Cr/DOX. ↓ levels of IL-1β in 2% Cr/DOX and 4%/2% Cr/DOX. ↑ expressions of NF-kB and IL-1β in 4%/2% Cr/DOX compared to 2% Cr/DOX group suggesting potencial inflammatory stress with higher dosage of Cr. ↓ oxidative stress biomarkers (8-OHdG, NRF-2) in 4%/2% Cr/DOX. Sig ↓ DOX-induced cellular senescence (β-galactosidase and MCP-1 expression) in Cr groups. No sig ↑ global methylation and furthermore chromosomal stability in DOX combined with Cr groups.

Table 1. Continued

Shen et al. 2019 (33)	GSH	*In vitro* and *in vivo*	*In vivo*: HL7702.	↓ DOX-induced ALT and AST elevations in GSH treatments. No effect of GSH on the concentration of DOX in mouse liver. Sig ↓ antitumor efficacy of DOX treatment in combination with GSH. No sig effect of GSH on the concentration of DOX in tumors. Sig ↓ DOX prohibition on cell migration and furthermore wound healing with GSH administration. ↑ the percentage of live cells in co-administration of GSH with DOX. Sig ↓ GSH uptake in tumor cells with DOX administration. No obvious effect of GSH on DOX uptake in tumor cell lines.
Daga et al. 2020 (34)	DOX-GSH-NS	*In vitro*, ex vivo *in vivo*	*In vitro*: Human HepG2 cells *In vivo*: Wistar rats Ex vivo: Organotypic cultures of Wistar rat PCLS	Similar EC50 *in vitro* in both DOX and DOX-GSH-NS treatments. No ↑ toxicity *in vitro* in DOX-GSH-NS as compared to DOX treatment. Sig ↑ intake of DOX-GSH-NS in HepG2 cells compared to DOX alone at 37°c. Sig ↓ intake of DOX-GSH-NS at 4°c in HepG2 cells compared to itself at 37°c indicates the role of active transport. No involvement of P-gp transporter in the efflux mechanism of nanosponges in both *in vitro* and ex vivo studies Sig ↓ PCLS viability in both DOX and DOX-GSH-NS treatments. No sig difference in the uptake of DOX in PCLS between DOX and DOX-GSH-NS at 37°c. Sig ↓ DOX uptake in DOX-GSH-NS at 4°c compared to DOX-GSH-NS at 37°c and DOX at 4°c in ex vivo study confirms the idea of active transport mechanism in NS uptake. ↑ agglomeration of DOX in PCLS after DOX-GSH-NS treatment in comparison with DOX alone. Similar DOX levels between DOX-GSH-NS and free DOX groups.

Table 1. Continued

Anandakumar et al. 2007 (36)	LA	*In vivo*	24 Wistar rats 4 groups: CTRL: NS DOX: 15mg/kg DOX single injection i.p. LA: 75mg/kg LA single injection i.p. DOX+LA: single injection of LA 24h before DOX. 4 days	Sig ↓ of DOX-induced elevation of serum enzymes (ALT, AST and BL) and Sig ↑ of DOX-induced reduction of liver enzymes (ALP, LDH, AST and ALT) in DOX+LA group. Sig ↓of lipid per-oxidations (basal, ascorbate and ferrous-sulfate-induced) in DOX+LA group. Sig ↑ of antioxidants (GSH, CAT, SOD, GPx, GR, GST and G6PD) in DOX+LA group.
Wu et al. 2017 (38)	MgIG	*In vivo*	50 Kunming mice. 5 groups: CTRL: 0.01mg/g/day NS i.p. DOX: 30mg/kg single i.p. on day 8. MgIG10: 10mg/kg/day i.p. for a week. MgIG20: 20 mg/kg/day i.p. for a week. MgIG40: 40mg/kg/day i.p. for a week. 10 days.	Sig dose dependent ↓ liver injuries with MgIG pre-treatments. Sig dose dependent ↓ ALT and AST levels with MgIG pre-treatments. Sig inhibition of DOX-induced oxidative stress by ↑ SOD and GSH markers and ↓ MDA levels in MgIG groups in a dose dependent manner. Sig ↑ anti-apoptotic features of hepatocytes by ↓ DOX-induced upsurge of BAX/Bcl-2, caspase-3 and NF-kB expressions in MgIG groups in a dose dependent manner.
Deepa et al. 2003 (40)	LMWH	*In vivo*	24 Wistar albino rats 4 groups: CTRL: NS DOX: 7.5mg/kg i.v. on first day LMWH: 300µg/day certoparin sodium for 7 days. DOX+LMWH: DOX followed by LMWH 1 week later 14 days.	Sig ↓ DOX-induced elevations of LDH, AST, ALT and ALP activities. Sig protection of liver structure against DOX-induced injuries. Sig inhibition of LPO and restoration of antioxidant enzymes (SOD, CAT and GPx) and non-enzymatic antioxidants (GSH, Ascorbate and α-tocopherol).
Hinkley et al. 2020 (41)	EXR	*In vivo*	28 SD rats. 4 groups. 1. sedentary CTRL 2. sedentary DOX 3. EXR CTRL 4. EXR DOX exercise training: 5 days of treadmill running followed by 10 days of running for 60 min/day. 24h after training, i.p. injection of either NS or DOX (20mg/kg) in both EXR and sedentary groups.	Sig ↓ respiratory CTRL ratio in isolated mitochondria from sedentary DOX group. Sig prohibition of DOX-induced ↑ state 4 respiration by exercise training. Amelioration of DOX-induced ↓ mitochondrial oxidative capacity (citrate synthase protein content) and furthermore mitochondrial efficiency in EXR DOX group. Non-sig preservation of NRF-1 protein expression in EXR DOX group. Sig ↑ mitochondrial mitophagy in DOX group. Sig prevention of DOX-induced ↓ HSP70 and therefore mitochondrial dysfunction in EXR DOX group. Possible effect of Exercise training in ↑ acetylation pr and mitochondrial function as well, by withholding DOX-induced ↑ mitochondrial deacetylase Sirt3.

Table 1. Continued

Alishahi et al. 2013 (42)	AIR	*In vivo*	48 Wistar rats 6 groups: 1. CTRL+placebo (C+P). 2. CTRL+DOX 10 mg/kg (C+DOX10). 3. CTRL+DOX 20 mg/kg (C+DOX20). 4. AIR+placebo (AIR+P). 5. AIR+DOX 10 mg/kg (AIR+DOX10). 6. AIR+DOX 20 mg/kg (AIR+DOX20). AIR pre-treatment for 6 weeks.	Sig ↓ IGF-1 and ↑ IGFBP-3 in AIR+DOX10 compared with C+DOX10. Sig ↓ IGF-1 and non-sig ↑ IGFBP-3 in AIR+-DOX20 compared C+DOX20. Sig amelioration of toxic effects of DOX in liver by prevention of up-regulation IGF-1 and down-regulation of IGFBP-3 in liver tissue.
Gökçe et al. 2020 (44)	ASA	*In vivo*	140 Swiss albino mice 4 groups: CTRL, DOX, ASA, DOX+ASA) and seven subgroups (examined after 6,12,24 and 48 h and 7,14 and 21 days) 10 mg/kg DOX i.p. single dose 200 mg/kg ASA i.p. daily	Sig portal triad area dilation in DOX and ASA+-DOX groups than ASA and CTRL groups. Sig ↑ DOX-induced hepatotoxicity and inflammation in both DOX and DOX+ASA groups. No difference in glycogen density or fibrosis.

SD: Sprague-Dawley; CTRL: control; NS: normal saline; p.o.: orally; DOX: doxorubicin; i.p.: intraperitoneal; sig: significant; ALB: albumin; AST: aspartate aminotransferase; ALT: alanine aminotransferase; MDA: malondialdehyde; GSH: glutathione; SOD: superoxide dismutase; Bax: Bcl-2 associated X protein; Bcl-2: B-cell lymphoma 2; pr: protein; PI3k: phosphoinositide 3-kinase; Akt: protein kinase B; TNBC: triple negative breast cancer; GPx: glutathione peroxidase; CMC: carboxymethyl cellulose; QOD: every other day; GGT: Gamma-glutamyl transferase; AFP: alpha-fetopotein; BL: bilirubin; LPO: lipid peroxidation; GST: glutathione-S-transferase; NF-kB: nuclear factor-kappa B cells; COX-2: cyclooxygenase-2; VitE: vitamin E; Na-CMC: sodium carboxymethyl cellulose; TMZ: trimetazidine; DLA: Dalton's Lymphoma Ascites; PRV: pravastatin; ALP: alkaline phosphatase; TG: triglyceride; chol: cholesterol; LDL: low-density lipoprotein; HDL: high-density lipoprotein; LNE: lipid nanoemulsion; EAC: Ehrlich Ascites Carcinoma; BL-NE: blank-nanoemulsion; NE: nanoemulsion; MST: mean survival time; CRV: carvedilol; DLT: diltiazem; PRD: prednisolone; CPT: captopril; ENP: enalapril; i.g.: intragastric; Bcl-xL: B-cell lymphoma-extra large; PARP: poly-ADP-ribose polymerase; P53: tumor protin P53; XOD: xanthine oxidase; CGA:chlorgenic acid; P-AKt: protein kinase B; AMPK: AMP-activated protein kinase; TNF-α: tumor necrosis factor-α; IL-1β: interleukin-1β; CAF: cyclophosphamide 600 mg/m2+doxorubicin 60 mg/m2+5-FU 600 mg/m2; TSB: total seum bilirubin; FL: fatty liver; PT: prothrombin time; NRF-2: nuclear factor erythroid2-related factor 2; HO-1: heme oxygenase 1; AML-12 cells: alpha mouse liver 12 cells; ROS: reduced reactive oxygen species; TUNEL: terminal deoxynucleotidyl transferase dUTP nick end labeling; FOXO1: forkhead box rotein O1; keap1: kelch like ECH associated protein 1; IL-6: interleukin-6; DFX: deferoxamine; NAC: N-acetyl cysteine; Se: selenium; i.v.: intravenous; PCNA: proliferating cell nuclear antigen; GR: glutathione reductase; TBARS: thiobarbituric acid reactive substances; LT: losartan; NO: nitric oxide; iNOS: inducible nitric oxide synthase; eNOS: endothelial nitric oxide synthase; Cr: creatine; STD: standard; 8-OHdG: 8-hydroxydeoxyguanosine; MCP-1: chemoattractant protein-1; PGE-2: prostaglandin-E2; TGF-β: transforming growth factor beta; DOX-GSH-NS: responsive cyclodestrin-based nanosonges loaded with doxorubicin; PCLS: precision-cut liver slices; EC50: half maximal effective concentration; P-gp: p-glycoprotein; LA: DL-alpha lipoic acid; G6PD: glucose-6-phosphate dehydrogenase; POD: peroxidase; MgIG: Magnesium isoglycyrrhizinate; LMWH: low molecular weight heparin; NM: nutrient mixture; RCD: regular chow diet; CAR: carvecrol; QR: quinone reductase; CT: clinical-trial; AC-T regimen: doxorubicin, cyclophosphamide and paclitaxel regimen; EXR: short term exercise; NrF-1: nuclear respiratory factor 1; HSP70: heat shock protein 70; Sirt1: sirtuin 1; AIR: regular aerobic training; IGF-1: insulin-like growth factor-1; IGFBP-3: insulin-like growth factor binding protein-3; ASA: acetylsalicylic acid

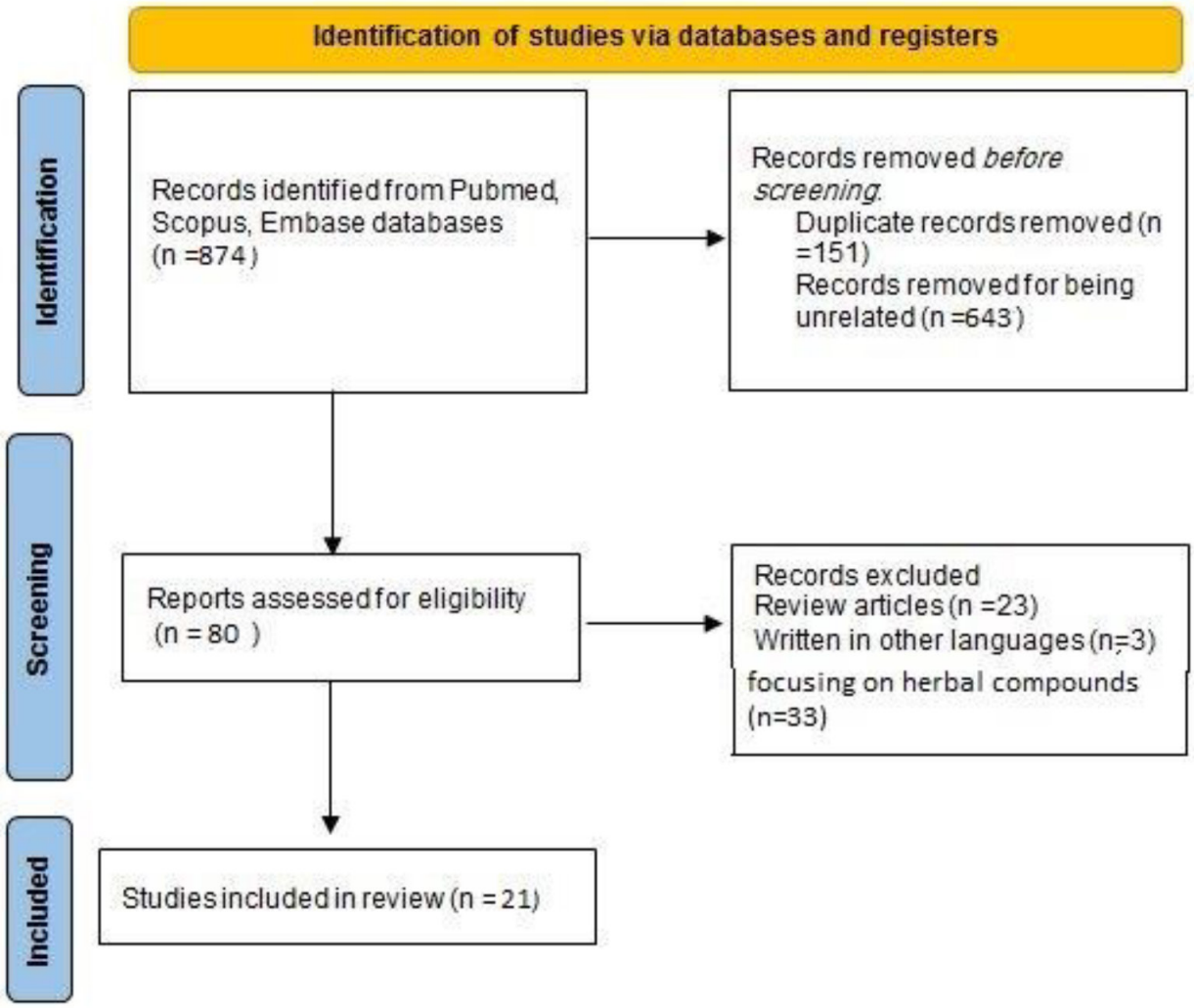

Figure 2. Diagram of the study selection process

Trimetazidine

Trimetazidine is a well-known drug which is traditionally considered for cardio-protection. This drug is now called "metabolic agent" because of its high ability to reserve intracellular ATP production and antioxidant characteristics (11). Given to these potentials, some researchers have evaluated the hepatoprotective effects of this drug against anticancer drugs. In this regard, in a study, Salouege et al., evaluated the hepatoprotective effect of trimetazidine in Wistar rats, administrated concomitantly with DOX for 3 days. Their study revealed that DOX (3.7 mg/kg/day) caused liver (and heart) injury. On the other hand, concomitant administration of trimetazidine (10 mg/kg/day) attenuated the DOX-induced hepatotoxicity and cardiotoxicity (12).

In a recent study, Sikandar et al., evaluated the hepatoprotective (and also cardioprotective) effects of trimetazidine (10 mg/kg orally for five and ten consecutive days) against DOX (10 mg/kg, intraperitoneal injection on the 3rd day). Their study demonstrated that administration of trimetazidine for ten days significantly attenuated the upsurge of the ALT, AST, LDH and CKMB serum level. However, five-day administration only caused a nonsignificant reduction in ALT and CKMB level. Hepatic and cardiac histological changes were restored in both (five day and ten-day) groups (13). Further studies for defining its mechanism of action are necessary.

Pravastatin

Pravastatin is a statin medication used for preventing cardiovascular disease by lowering "bad" cholesterol and fats (such as LDL, triglycerides) and raising "good" cholesterol (HDL) in the blood. In a study by Mansouri

et al., the potential of pravastatin against DOX-induced hepatic oxidative stress and dysfunctions was investigated in SD rats. Their results demonstrated that DOX (15 mg/kg single i.p. on day 6) resulted in significant increase in the levels of ALT, AST, ALP, TG, cholesterol, LDL and total bilirubin levels, whereas pravastatin (20 mg/kg/day p.o.) reduced the liver injury and protected liver functions and other biochemical parameters ($p < 0.01$). In addition, malondialdehyde levels reduced in the doxorubicin group, which was attenuated by pravastatin treatment (14). These results demonstrated that pravastatin has a significant hepatoprotective effects against DOX in SD rats.

In other study, Alkhatib et al., aimed to evaluate the tolerability of a nanoemulsion formulation containing DOX and pravastatin (DOX+PS/LNE) in Swiss albino mice bearing Ehrlich Ascites Carcinoma (2 mg/Kg DOX with 4 mg/Kg pravastatin solubilized in 200 µL NE). They measured the efficacy and tolerability of this formulation by monitoring body weight changes, biochemical and histopathological profiles of hepatic (as well as cardiac) tissues. They observed that DOX+PS/LNE caused a significant decrease in body weight e and more than 200% increase in the mean survival time compared to EAC-challenged mice. In addition, no significant changes in biochemical parameters were detected compared to the corresponding controls (15). Therefore, according to their study, nanoemulsion formulation of doxorubicin with pravastatin could be a promising novel cancer therapy with good tolerability and low hepatotoxicity rate.

Carvedilol, diltiazem and prednisolone

Akindele et al., investigated the protective effects of carvedilol (0.075 mg/kg) alone or in combination with prednisolone (0.15 mg/kg) and diltiazem (3.43 mg/kg) on the hepatotoxicity of DOX (40 mg/kg) as well as 5-fluorouracil (5-FU) in Wistar rats. The drugs were administrated p.o. for 16/14 days and DOX was administered i.p. to the rats on day 14/10-14. On day 17/15, blood samples were taken and liver of the rats were investigated for antioxidant and histological assessments. According to this study, the administration of carvedilol alone and in combination with prednisolone resulted in decreasing DOX-induced elevation of ALT. In addition, carvedilol alone and coadministered with diltiazem significantly diminished the levels of creatinine and highly increased the level of hepatic superoxide dismutase and catalase, and decreased malondialdehyde compared with DOX administration alone. Histological observations showed significant correlations with the biochemical and antioxidant analyses results, but carvedilol with either diltiazem or prednisolone did not improve the hepato-protection, compared to carvedilol alone (16).

Angiotensin-converting enzyme (ACE) inhibitors

Captopril and enalapril are angiotensin-converting enzyme (ACE) inhibitors, which are usually used as cardioprotective drugs against DOX (14). In addition, These ACE inhibitors have been shown to act as scavengers of free radicals (17). Therefore, Abd El-Aziz et al., decided to investigate the hepatoprotective (and also cardioprotective) effects of these ACE inhibitors against adriamycin. They used captopril and enalapril in daily doses of 10 mg/kg and 2 mg/kg respectively intragastrically, followed by a single dose of adriamycin (15 mg/kg) 7 days later. According to their results, the administration of adriamycin alone, resulted in significant elevation in thiobarbituric acid reactive substances (TBARS), an indicator of lipid peroxidation and inhibited superoxide dismutase activity in liver and heart tissues, as well as a significant increase in the cardiac or hepatic glutathione (GSH) content or catalase (CAT) activity, but hepatic CAT activity was elevated. Pretreatment with captopril and enalapril also significantly reduced the TBARS concentration in both heart and liver and resulted in the amelioration of cardiac and hepatic SOD activity inhibition (18). These results suggest that captopril and enalapril have antioxidative potentials which may protect the heart and liver against adriamycin-induced acute oxidative toxicity.

Erdosteine, N-acetylcysteine, deferoxamine and selenium

Erdosteine is a thiol derivate drug which contains two sulfur atoms, one presenting in an aliphatic side-chain and the other in heterocyclic ring. The reducing potential of these SH groups has a role in scavenging free radicals (19). In this regard, Yamgurca et al., evaluated the protective effects of this antioxidant compound on DOX-induced hepatotoxicity. They treated SD mice with DOX alone (20 mg/kg, i.p. on the 3rd day) or in combination with erdosteine (10 mg/kg/day EDT p.o. + DOX 12 days). The results demonstrated that treatment with DOX caused histopathological changes, e.g., sinusoidal dilatation, cell necrosis, hepatocyte degeneration, and hemorrhage. However simultaneous treatment of the mice with erdosteine resulted in significant reduction in hepatic damage (20).

Deferoxamine (DFX) is an iron chelator, which eliminates the harmful effects of iron overload. Studies have demonstrated that DFX can decrease DOX toxicity in both normal and iron-loaded heart cells (21). In our review, we found that Saad et al., evaluated the protective effects of DFX (25, 125, 250, 375 and 500 mg/kg i.p., 30 min prior to DOX injection) against DOX (25 mg/kg i.v.)-induced hepatic (as well as cardiac) toxicity in Wistar albino rats. The peroxidative damages were evaluated 48 h after DOX

administration. This study demonstrated that DFX at a dose equivalent to 10-fold of DOX resulted in significant hepatoprotection, but higher doses did not show any further improvement in DOX-induced hepatotoxicity, but exhibited higher cardioprotective action. These results suggest that DFX provides a dose-dependent protection against cardiotoxicity, but its ameliorative effects on hepatotoxicity was mild, as detected by biochemical and histological assessments (22).

In another study, Bulucu et al., investigated the effects of N-acetylcysteine (NAC, 20 mg/kg), DFX and selenium (15 mg/kg i.p.) on DOX (5 mg/kg i.v.)-induced hepatotoxicity in SD rats. Their results demonstrated that DFX decreased lipid peroxidation. In addition, DFX and NAC decreased CAT activity, whereas they increased GSH-px activities and copper levels. Furthermore, the authors declared that beneficial effects of selenium may result from its stimulatory effects on SOD but not to GSH-px. DFX, NAC and selenium had protective effects on DOX-induced hepatocellular damage. However, DFX+NAC did not result in any additional benefit (23).

In another study, Cengiz et al., used selenium at doses of 0.5, 1 and 2 mg/kg/day i.p. for 28 days in combination with DOX (5 mg/kg/week i.p.) in Wistar albino rats. They performed liver histopathology assessments to determine the dose at which selenium would best protect against DOX-induced hepatotoxicity. Also, they measured the levels of TNF-α and IL-1β expressions and proliferating cell nuclear antigen (PCNA) by immunohistochemistry. Their results demonstrated that DOX caused liver damage and increased TNF-α, IL-1β and PCNA levels, whereas selenium prevented these damages (24).

Fullerenol nanoparticles

Fullerenol is a free radical scavenger with great potential against anthracyclines-induced hepatotoxicity. This compound has been demonstrated to have a high antioxidant activity when compared to natural products, such as: vitamins E, C and A (25). In addition, fullerenol suppresses the microsomal enzymes and inhibits P450-dependent activity of monooxygenase and mitochondrial oxidative phosphorylation. This compound particularly accumulates in liver and kidneys and therefore, may be a good candidate for inhibiting the DOX-induced hepatotoxicity (26). Based on these considerations, Jacevic et al., aimed to evaluate the protective effects of Fullerenols nanoparticles (FNP) on DOX-induced hepatotoxicity. They used DOX (10 mg/kg i.v.) alone or in combination with FNP (100 mg/kg i.p.) in Wistar rats and evaluated the general health conditions, body and liver weight, TBARS level and antioxidative enzyme activity, as well as pathohistological parameters 2 and 14 days after the treatments. Their results demonstrated that FNP alone did not make any changes in the examined parameters. However, when it is used as a pretreatment, FNP resulted in significant increase in survival rate, body and liver weight, and a decrease in TBARS levels and, antioxidative activities of the related enzymes (SOD, CAT, GR and GPx) in liver tissues of the rats. Particularly, FNP administration at a dose of 100 mg/kg attenuated the effects of DOX, including general condition, body and liver weight, antioxidant activities of the abovementioned enzymes, and lipid peroxidation levels in the hepatic tissue (27).

In another study, Petrovic et al., surveyed the effects of FNP at a lower dose (0.125 mg/kg, 30 min before DOX injection) on the hepatotoxicity of DOX2 and DOX4 (2 and 4 mg/kg of DOX, respectively) in Wistar rats. The rats were under treatment for 14 days. The results demonstrated that combinational treatment of FNP with DOX2 resulted in significant decrease in the activities of CAT, SOD, GR and GST levels in FNP+DOX2 group, but changes in the activities of these enzymes in FNP+DOX4 group were non-significant. In addition, FNP and either dose of DOX, significantly reduced the mRNA levels of SOD and increased the Bax/Bcl-2 ratio, demonstrating that apoptosis takes place in all treated groups (28).

Creatine

Creatine (Cr) is a naturally-occurring compound, which is involved in providing energy in the brain, heart and skeletal muscles through phosphocreatine system. In addition, creatine acts as an antioxidant agent to reduce oxidative stress (29). Studies have shown that this protein can protect against oxidative stress-induced cardiovascular damage and DOX-induced toxicity in skeletal myofibers and cardiomyocytes (30). However, the role of Cr in DOX-induced hepatotoxicity remains to be elucidated. In a recent study, Aljobaily et al., examined the effects of Cr supplementation on DOX-induced liver damage in SD rats (15mg/kg DOX injected i.p.). In their study, they fed SD rats with a diet supplemented with 2% Cr for four weeks, 4% Cr for one week followed by 2% Cr for three more weeks, or control diet for four weeks. Then, the animals were evaluated five days-post injection. The results demonstrated that the ALT, AST and liver-body weight ratio were increased in DOX group, whereas Cr supplementation tended to inhibit these values. In addition, 2% Cr/DOX and 4%/2% Cr/DOX treatments resulted in significant reduction in fibrosis, and inhibition in the expressions of FN-1, CD45, IL-1β. However, the levels of NF-kB were significantly expressed in 4%/2% Cr/DOX compared to 2% Cr/DOX group, suggesting the potential inflammatory effect with higher dose of Cr (31). Therefore, the dosage of Cr as a supplementation for amelioration of DOX-induced hepatotoxicity should be

taken into consideration in future studies.

Glutathione

Glutathione (GSH) is a common endogenous antioxidant, which acts in protecting cells against oxidative stress (32). In a study by Shen et al., they evaluated the combinational effects of DOX and GSH in vitro (in H9c2, Caco-2, HepG2, MCF-7 and HL7702 cell lines) and in vivo (in tumor-bearing BALB/c mice). For in vivo study, they used 5, 50 and 100 mg/kg/day GSH and 2 mg/kg DOX i.p. Their results demonstrated that the administration of GSH inhibited DOX-induced ALT and AST levels increment in serum. However, GSH decreased the antitumor efficacy of DOX treatment, evaluated by cell migration and wound healing assay (33).

In another study, Daga et al., investigated the hepatotoxicity of GSH-responsive cyclodextrin-based nanosponges loaded with the anticancer drug doxorubicin (Dox-GSH-NS). This study was carried out in vitro (in HepG2 cells) and ex vivo (in organotypic cultures of rat precision-cut liver slices), while their accumulation in rat liver was assessed in vivo. According to the integration of results from these different models, a good safety profile of Dox-GSH-NSs was evidenced, and their hepatotoxicity seems to be comparable with respect to free DOX both in vitro and ex vivo. Furthermore, in vivo studies showed that the hepatic accumulation of the DOX loaded in the NS is comparable with respect to the free drug (34).

LD-alpha lipoic acid

Lipoic acid is a naturally-occurring compound which has a great potential against oxidative metabolism and participate as protein bound lipoamide in alpha keto acid dehydrogenase complexes in mitochondria. Studies have shown that supplementation of this compound leads to production of the more active antioxidant molecule, dihydroplipoic acid (35). In a study by Anandakumar et al., protective efficacy of DL-alpha lipoic acid (75mg/kg LA single injection i.p., 24 h before DOX) on DOX-induced hepatotoxicity (15 mg/kg i.p.) was investigated in Wistar rats. The administration of DOX resulted in an elevation in ALT, AST, ALP, and LDH level. In addition, DOX increased malondialdehyde and antioxidant markers levels. However, pretreatment with lipoic acid significantly restored various cellular activities suggesting the antioxidant potential and ameliorative effects of this naturally-occurring compound (36).

Magnesium isoglycyrrhizinate

Magnesium isoglycyrrhizinate (MgIG) is a magnesium salt of 18α glycyrrhizic acid, which has important pharmacological activities, including anti-inflammatory activity. This anti-inflammatory activity is mediated through the phospholipase A2/arachidonic acid and signal transducer and activator of transcription 3 pathways (37). In a survey to unravel the hepatoprotective effects of MgIG in Kunming mice, Wu et al., used MgIG at daily doses 10, 20 and 40 mg/kg for a week and DOX at a single dose of 30 mg/kg i.p. on day 8 and the investigations were performed on day 10. The results demonstrated that pre-treatment with MgIG significantly diminished DOX-induced liver injuries in a dose-dependent manner and decreased the levels of ALT and AST. In addition, this pre-treatment dose-dependently decreased DOX-induced oxidative stress, marked by measuring SOD, GSH and MDA levels. MgIG also had anti-apoptosis effects on hepatocytes, determined by decreasing DOX-induced upsurge of BAX/Bcl-2, caspase-3 and NF-kB expressions, in a dose dependent manner (38).

Low molecular weight heparin

Low molecular weight heparin (LMWH) is a glycosaminoglycan and a type of commercial grade heparin and produced through depolymerization, and are more advantageous than heparin because of their higher stability, greater bioavailability at low doses and lesser risk of bleeding (39). Deepa et al., investigated the role of LMWH on oxidative injury and cellular abnormalities in adriamycin-induced cardiac and hepatic toxicity in Wistar albino rats. They used LMWH in dose of 300 µg/day for 7 days in combination with 7.5 mg/kg i.v. DOX on first day. Their results demonstrated significant decrease in DOX-induced elevations of LDH, AST, ALT and ALP serum level and significant protection of liver structure against DOX-induced injuries. In addition, LMWH led to inhibition of LPO and restoration of antioxidant enzymes (SOD, CAT and GPx) and non-enzymatic antioxidants (GSH, Ascorbate and α-tocopherol) (40).

Exercise and regular aerobic training

Exer1cise training is an efficient factor to diminish mitochondrial dysfunction and protect against liver injury through various mechanisms, including depletion of the oxidative stress. Therefore, Hinkley et al., aimed to survey whether short-term exercise preconditioning has any protective effect against DOX-induced liver mitochondrial damage. For this purpose, they compared the sedentary SD rats with exercise-trained SD rats who underwent treadmill running habituation for 5 days, and then running for 60 min/day (30 m/min; 0% grade) for 10 days. Following the last training bout, both groups were injected with either DOX (20 mg/kg; i.p.) and then their livers were isolated for mitochondrial assessments. Their results demonstrated that treatment with DOX induced mitochondrial dysfunction of the liver in sedentary animals through adverse effects on mitochondrial

oxidative capacity, biogenesis, degradation, and protein acetylation. Exercise preconditioning protected the liver mitochondria against these damages and significantly reduced DOX-induced state 4 respiration, mitochondrial oxidative capacity (citrate synthase protein content) and HSP70 expression (41). These data suggested a possible effect of exercise training in increasing acetylation of mitochondrial proteins and function by withholding DOX-induced stimulation of mitochondrial deacetylase Sirt3.

In another study, Alishahi et al., evaluated the pretreatment effects of regular aerobic training on DOX-induced hepatotoxicity (as well as the insulin-like growth factor (IGF) system) in Wistar rats. The rats were subjected to treadmill running of 25-54 min/day and 15-20 m/min, 5 days/week for 6 weeks. Thereafter, they were treated with placebo, and doses of 10 and 20 mg/kg of DOX. The results demonstrated that administration of 20 mg/kg DOX caused a significant increase in the components of IGF system. However, after six weeks of aerobic training and DOX treatment with 10 mg/kg or 20 mg/kg, a significant decrease in IGF-1/IGFBP-3 was detected, in comparison to the controls. The authors concluded that hepatotoxicity of doxorubicin is dose-dependent and pretreatment with regular aerobic training may improve DOX-induced hepatotoxicity by up-regulation of IGFBP3 (42).

Acetylsalicylic acid

Acetylsalicylic acid (ASA) is a nonsteroidal anti-inflammatory (NSAID) drug, which is widely used for its anti-inflammatory and anticoagulation properties. Given that thromboembolism is a main complication of DOX, addition of this drug may prevent both thromboembolism (43). In this regard, Gokçe et al., investigated the prophylactic effects of ASA against DOX in Swiss albino mice and used DOX at a dose of 10 mg/kg (single dose) as single or in combination with ASA at a daily dose of 200 mg/kg (examined after 6, 12, 24 and 48 h and 7,14 and 21 days). Their results demonstrated that, at 6 h, the portal triad areas of the DOX and DOX+ ASA groups were significantly higher than the controls and the ASA group (44). In addition, histological assessments revealed a time-dependent increase in the rate of degeneration and necrosis of liver tissues in mice in the DOX and DOX+ ASA groups. These data, contrary to the other studies included in this review, demonstrated that ASA increases the degenerative changes of Swiss albino mice increased DOX-mediated hepatotoxicity and inflammation.

Conclusion

The aim of the current study was to appraise the ameliorative effects of various drugs and non-herbal compounds on the hepatotoxicity of DOX, which is one of the main medications in lots of chemotherapiutic regimes implemented for systematic treatment of cancers. However, the various toxicities of this drug like cardiotoxicity and hepatotoxicity, particularly in high culmulative dose, limit its use.

The production of ROS is the major consequence of oxidative reduction of DOX and causes cell death not only on cancer cells but also on normal cells throughout the body. Furthermore, DOX induces upsurge of inflammatory mediators and cytokines and leads to cell damage. For these reasons various drugs and compounds with anti-oxidant, anti-inflammatory and anti-opoptosis properties have been assessed in vitro and in vivo for protective effects on DOX-induced hepatotoxicity and most of these studies showed encouraging findings. Just ASA, which is used for its anti-inflammatory and analgesic properties, manifested disappointing results and aggrevated the degenerative changes of liver cells in mice.

It is important to mentioned that these compounds mostly have demonstrated promising efficacy on liver injury histopathology (necrosis, fibrosis...) and biochemical factors (AST, ALT, ALP, LDH...), and reducing oxidative stress markers (MDA, ROS, CAT, SOD, GSH...), inflammatory cytokines (IL6, IL-1B, TNFα, ...) and apoptotic pathways (caspase3, Bax, Bcl2...) in cellular and animal studies.

Among the collected articles, Shen et al., demonstrated that GSH, a common endogenous anti-oxidant, mitigated the anti-tumor efficacy of DOX in vivo and in vitro.

Moreover, no human studies are available on preventive and therapeutic effects of these compounds and drugs. Hence, it seems that more animal and well-designed large human studies are necessary for better judgement on these compounds efficacy and safety.

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