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Review article

The role of melatonin on doxorubicin-induced cardiotoxicity: A systematic review

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ABSTRACT

Purpose: Doxorubicin, as an effective chemotherapeutic drug, is commonly used for combating various solid and hematological tumors. However, doxorubicin-induced cardiotoxicity is considered as a serious adverse effect, and it limits the clinical use of this chemotherapeutic drug. The use of melatonin can lead to a decrease in the cardiotoxic effect induced by doxorubicin. The aim of this review was to evaluate the potential role of melatonin in the prevention of doxorubicin-induced cardiotoxicity.

Methods: This review was conducted by a full systematic search strategy based on PRISMA guidelines for the identification of relevant literature in the electronic databases of PubMed, Web of Science, Embase, and Scopus up to January 2019 using search terms in the titles and abstracts. 286 articles were screened in accordance with our inclusion and exclusion criteria. Finally, 28 articles were selected in this systematic review.

Results: The findings demonstrated that doxorubicin-treated groups had increased mortality, decreased body weight and heart weight, and increased ascites compared to the control groups; the co-administration of melatonin revealed an opposite pattern compared to the doxorubicin-treated groups. Also, this chemotherapeutic agent can lead to biochemical and histopathological changes; as for most of the cases, these alterations were reversed near to normal levels (control groups) by melatonin co-administration. Melatonin exerts these protection effects through mechanisms of anti-oxidant, anti-apoptosis, anti-inflammatory, and mitochondrial function.

Conclusion: The results of this systematic review indicated that co-administration of melatonin ameliorates the doxorubicin-induced cardiotoxicity.

1. Introduction

After cardiovascular diseases, cancer is considered as the second cause of death in the world [1]. According to a recent report on global cancer incidence and mortality, it was estimated 18.1 million new cancer cases and 9.6 million deaths from cancer in the world in 2018 [2]. Also, a rapidly growing cancer incidence and mortality has been reported worldwide [2]. There are several modalities for cancer treatment including surgery, radiation therapy, chemotherapy, *etc.* [3]. Chemotherapy, as a systemic therapeutic modality, is effectively used for the treatment of various cancers; however, its clinical utility is restricted due to a wide range of adverse effects on normal cells and tissues [4,5].

Doxorubicin (Adriamycin), as an effective chemotherapeutic drug, is commonly applied since the late 1960s against solid tumors such as breast, lung, testicular, thyroid, ovarian cancers, and hematological tumors of Hodgkin Lymphoma, and non-Hodgkin lymphomas [6,7]. The immediate side effects of this chemotherapeutic drug such as arrhythmia, myelosuppression, nausea, and vomiting are reversible or clinically manageable [7]. Nevertheless, cardiotoxicity induced by doxorubicin is considered as a serious adverse effect, and it limits the clinical use of this chemotherapeutic drug; this side effect can lead to reduced quality of life and sometimes fatalities. In this regard, various methods are proposed to decrease cardiotoxic effect induced by doxorubicin [8,9].

When it is found that the formation of reactive oxygen species (ROS)

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can have an important effect in the doxorubicin-induced cardiotoxic mechanism by reducing indigenous anti-oxidant systems in the body, the use of exogenous anti-oxidants was introduced [10,11]. Melatonin, as an indole-derived hormone, is principally generated and secreted by the pineal gland, and it has applied to protect against the oxidative damage [12]. This hormone exerts an antioxidative effect through two direct and indirect mechanisms. The direct pathway of melatonin is exerted mostly by formation of radical adduct, hydrogen transfer, and single electron transfer. In another pathway (indirect), the anti-oxidative effects of this hormone can be exerted by stimulation of anti-oxidant enzymes, protection of anti-oxidant enzymes against oxidative damage, modulation of genomic expressions, *etc.* Furthermore, it has been reported that oxidative stress has key role in triggering inflammation and apoptosis, and melatonin with its anti-inflammatory and anti-apoptotic properties can relieve these effects [4,5].

In this study, a systematic search was performed on the role of melatonin on doxorubicin-induced cardiotoxicity. In addition, it was tried to answer the following issues: 1) the mechanisms underlying doxorubicin-induced cardiotoxicity, 2) the role of melatonin in the prevention of doxorubicin-induced cardiotoxicity, and 3) the mechanisms related to the preventive role of melatonin.

2. Methods

2.1. Search strategy

In the current study, a systematic search was done based on the guideline of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [13]. Literature search was carried out to assess all relevant studies in both medical subject heading (MeSH) or advance on electronic databases including PubMed, Web of Science, Embase, and Scopus up to January 2019 using the keywords “Melatonin” AND “Doxorubicin” OR “Adriamycin” AND “Heart” OR “myocardium” OR “Myocardial” OR “Cardiomyopathy” OR “Myocyte cardiac muscle cell” OR “Cardiopathic” OR “Cardiopathy” OR “cardiotoxicity” OR “cardiomyocyte” in title, abstract or keywords.

2.2. Study selection

The inclusion criteria considered in this systematic review were full-text articles with (a) English language, (b) the aforementioned key search, (c) adequate information, and (d) without restriction in publications with *in-vivo* or *in-vitro*. The exclusion criteria were (a) hemodynamic studies, (b) poster, (c) not related paper, (d) case report, (e) review paper, (f) editorials, and (g) letter to the editor.

2.3. Data extraction

Each eligible article was reviewed by two researchers and the following data were extracted: (a) author name and the year of publication; (b) models; (c) doxorubicin dosage and route of administration type; (d) outcomes of doxorubicin on cardiac tissue; (e) melatonin dosage and route of administration; and (f) melatonin co-administration outcomes.

3. Results

3.1. Literature search

The process of study selection is illustrated in the Fig. 1.

286 articles were obtained by searching on the above-mentioned databases up to January 2019. After the screening articles, 243 of them were excluded by investigating their titles and abstracts and 43 studies were qualified for assessment of their full-text. Thereafter, the studies inconsistent with inclusion criteria or the studies with missing information were omitted. Finally, 28 remaining articles were included in this systematic review. A summary of the extracted data related to the eligible studies is listed in the Table 1.

3.2. The protective role of melatonin against doxorubicin-induced cardiotoxicity

3.2.1. Survival study

The findings showed that mortality in the groups treated by doxorubicin was significantly higher than the control group [14,15,23,29,31,36]. Furthermore, it has been reported that the survival rate after doxorubicin treatment in rats had a dose-dependent manner [29]. Kim et al. [29] represented that the survival rates for control, 5 mg/kg, 15 mg/kg, and 25 mg/kg doxorubicin groups were 100%, 100%, 85%, and 14%, respectively.

The use of melatonin significantly attenuated doxorubicin-induced mortality [14,15,23,29,31,36]; for instance, doxorubicin-induced mortality decreased from 86% to 20% ($P < 0.05$) by melatonin treatment [29]. Moreover, it was observed no difference between the control and melatonin groups [29].

3.2.2. Body weight, heart weight, and ascites changes

According to the obtained results, it was revealed that the body weight, heart weight and ratio of heart to the body weight of rats/mice were decreased in the doxorubicin group than the control group [14,15,18,20,23,29,41]. In addition, a significant accumulation of ascites was reported in the rats treated with doxorubicin compared to the control rats; the survival rate in the group with high ascites value was significantly higher than the other rats [14,15].

When both melatonin and doxorubicin was administered to the rats/mice, it was found an increase in the body weight, heart weight and ratio of heart to body weight compared to the doxorubicin-treated group [14,15,18,41]. Administration of melatonin also resulted in a significant decrease of doxorubicin-induced ascites value [14,15].

3.2.3. Biochemical changes

The biochemical changes of heart tissue can be observed in the doxorubicin-treated group, as listed in the Table 1. For example, the malondialdehyde (MDA), 4-hydroxyalkenes (4-HDA), serum creatine phosphokinase (CPK), serum creatine kinase, serum troponin I, leptin, triglycerides, cholesterol, lactate dehydrogenase (LDH), serum aspartate aminotransferase (AST), myocardial and plasma thiobarbituric acid reactive substances (TBARS), creatine kinase isoenzyme (CK-MB), glutamic-oxaloacetic acid transaminase (GOT), glutamic-pyruvic acid transaminase (GPT) in plasma, plasma concentrations of transferrin, ferritin, iron and protein carbonyl levels were increased significantly in the doxorubicin-treated group than the control group [14–16,18–20,22,23,25–33,37,40]. In addition, blood and tissue glutathione (GSH), superoxide dismutase (SOD), and Glutathione-S-Transferase (GST) levels were decreased significantly compared to the control groups [16,19,25,28,30–32].

The findings showed that melatonin administration preserved doxorubicin-induced biochemical changes (for most of the cases) [14–16,18,19,22,23,25–31,33,37,40].

3.2.4. Histological changes

The obtained results from histological evaluation of the doxorubicin-treated groups revealed the following histological changes: cellular edema, loss of myofibril, swelling of mitochondria, vacuolization of cytoplasm, dilation of sarcotubular system, decrease of β-adrenoceptor (BAR) density in cell membrane, increase of membrane permeability of cultured neonatal myocytes, decrease of myocytes, decrease of myocyte size, increase of mitochondrial fission (round-shaped mitochondria), decrease of mitochondrial major/minor aspect ratio, fibers with dark acidophilic cytoplasm and pyknotic nuclei, disarrangement of sarcomeres, disruption of microfilaments and Z-line, increase of number and size of mitochondria, presence of oval-shaped cells with thin long

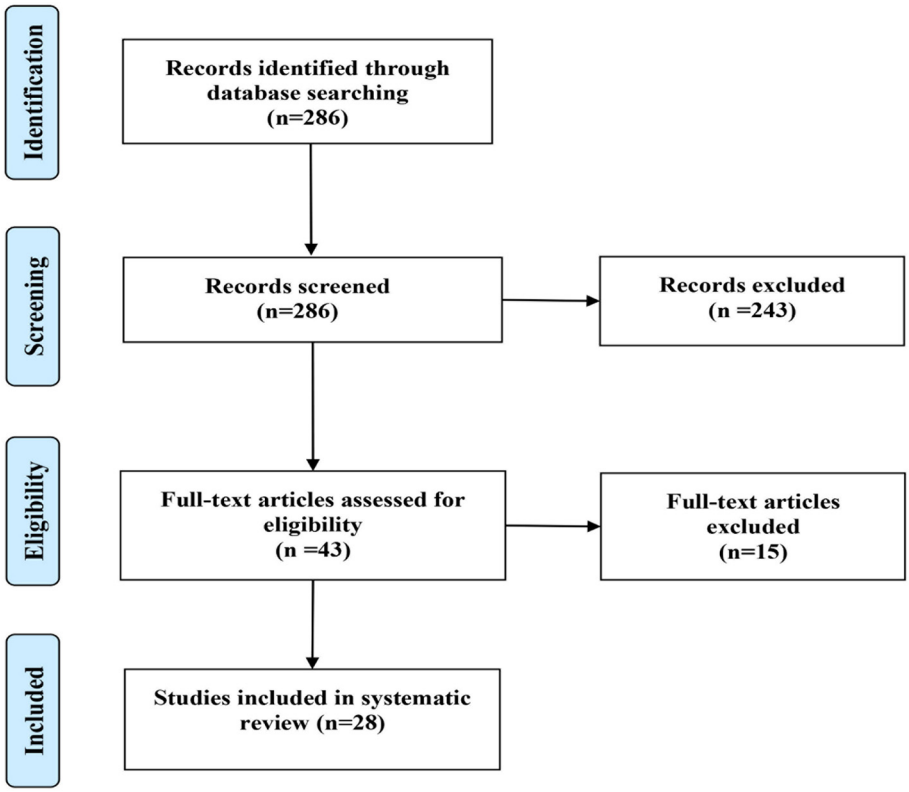

Fig. 1. Flow diagram used in the present study for selection process.

processes, *etc.* (The rest of the histological changes is listed in the Table 1) [14–16,18,19,22,23,25–31,33,37,40].

The results of most studies showed that co-administration of doxorubicin and melatonin resulted in the prevention of doxorubicin-induced histological changes [14–16,18,19,22,23,25–31,33,37,40].

4. Discussion

In the present study, we aimed to review a serious adverse effect (cardiotoxicity) induced by doxorubicin as well as co-administration effects of melatonin on this disorder. Some of the important cardiac complications induced by doxorubicin as well as the effects of melatonin on these adverse effects are shown in the Fig. 2.

The cardiovascular system is one of the most important systems of the body, and malfunction in this system strongly relates to patients' morbidities, demanding huge cost consuming, and is considered as one of the major reasons of mortality [42]. Most of the current literature data indicate that melatonin in combination with chemotherapeutic agents reduces the anti-cancer effects of these agents in the cancerous cells. Melatonin also provides benefits in reduction of toxicity in the normal cells [4,5]. To better understand this issue, it is reported that formation of ROS can exert both positive and negative effects on normal and cancerous tissues. ROS have a positive role in signal transduction and gene transcription while they may act as a trigger for carcinogenesis *via* persistent DNA injuries [43]. It is also reported that reduced sensitivity and resistance of cancer cells to chemotherapeutic agents are common, which may result from genomic instability of the malignant cells. The researchers concluded that melatonin by its pleiotropic property exerts effects on sensitization of the cancer cells to the anti-cancer agents *via* modulating the expression and phosphorylation status of drug targets, the reduced clearance of drugs by affecting their metabolism and transport within the body, decreased survival of malignant cells *via* altering DNA repair and telomerase activity, and enhanced responses to cell death-associated mechanisms such as apoptosis and autophagy [4,5].

The mechanistic effects of doxorubicin on the cardiac cellular pathway as well as the protective effects of melatonin and its reported mechanisms on doxorubicin-induced cardiotoxicity are discussed below.

4.1. Anti-oxidant actions

It is well-known that free radicals are commonly produced in the normal cells, and the cells have several defense mechanisms against them [44]. In oxidative stress conditions, there is an imbalance between the free radical amounts and anti-oxidant defense systems, causing an elevation of free radicals [45,46]. The cardiotoxicity induced by doxorubicin mainly exerts its effects through inhibiting the oxidative stress defense systems and producing several more kinds of free radicals. The free radicals attack cell macromolecules, resulting in their malfunction [47,48]. Oxidative stress also relates strongly to many disorders including cancers, neurotoxicity, aging, diabetes, *etc.* [49–51]. Furthermore, doxorubicin increases free radicals especially through impairment of mitochondrial malfunction, as the main source of free radicals. It is clearly demonstrated that free radicals are normally produced in the cells, especially through electrons leakage from the mitochondrial electron transport chain (ETC), and this process increases during mitochondria injury [48]. O_2^- is one of the ROS molecules, which is turned to H_2O_2 by SOD enzyme [52]. Furthermore, non-radical ROS including H_2O_2 is produced during malfunction of mitochondrial NADPH oxidases and transferred by aquaporins to the cytoplasm [53,54]. H_2O_2 has several destinations: 1) CAT enzyme produces H_2O and O_2 from H_2O_2 [55], 2) H_2O_2 through Fenton and Haber-Weiss Net reactions produces OH [56], and 3) H_2O_2 *via* the activity of glutathione peroxidase (GPx) enzyme and consuming GSH produces $2H_2O$ [57]. Normally, there is a low amount of nitric oxide (NO) in the cardiac cells, and doxorubicin increases its level. In this context, NO is known to exert important roles in cellular signaling during pathological processes

Table 1
The characteristics of included studies.

Author & year	Models	Doxorubicin dosage & route of administration type	Outcomes of doxorubicin on cardiac tissue	Melatonin dosage & protocol of usage & route of administration	Melatonin co-administration outcomes
Morishima et al., 1998 [14]	*In vivo*/rat	Six doses of 2.5 mg/kg & *ip*	↑Mortality, ↑Ascites volume, ↓Heart weight, ↓Ratio of heart to body weight, ↑Myocardial & plasma TBARS levels, ↑Myocardial lesions (cytoplasmic vacuolization, myofibril loss & disarrangement, mitochondrial degeneration)	4 mg/kg/day for 21 days & *ip*	↓Mortality, ↓Ascites volume, ↑Heart weight, ↑Ratio of heart to body weight, ↓Myocardial & plasma TBARS levels, ↓Myocardial lesions
Morishima et al., 1999 [15]	*In vivo*/rat	Six doses of 2.5 mg/kg & *ip*	↑Mortality, ↑Ascites volume, ↓Heart weight, ↓Ratio of heart to body weight, ↑Myocardial & Plasma TBARS levels, ↑Myocardial zinc levels & ↓Plasma zinc levels	4 mg/kg/day for 21 days & *ip*	↓Mortality, ↓Ascites volume, ↑Heart weight, ↑Ratio of heart to body weight, ↓Myocardial & plasma TBARS levels, ↓Myocardial & ↑Plasma zinc levels
Abdel Wahab et al., 2000 [16]	*In vivo*/mice	Four doses of 4 mg/kg & *ip*	↑MDA, ↓GSH, ↓Total protein content, ↑Average life span, ↓Body weight.	5 mg/kg/day for 30 days & *po*	↓MDA, ↑GSH, ↑SOD, ↑Total protein content, ↑Average life span, ↑Body weight.
Granzotto et al., 2001 [17]	*In vitro*/HBL-100, MCF-7, LoVo, & P388 lines & *in vivo*/mice	10 nM (HBL-100), 1 μM (MCF-7), 0.3 μM (LoVo), 0.5 nM (P388), and 14 mg/kg (mice) & *iv*	↓Cell growth	10–2000 pg/mL	Inhibition of cell growth, ↑Life span
Han et al., 2001 [18]	*In vivo*/rat	Single doses of 5, 15, 25 mg/kg & *ip*	↑Lethality rate, ↓Body weight, ↑MDA, ↑LDH, Loss of myofibril, Swelling of mitochondria, Vacuolization of cytoplasm	10 mg/kg/day for 6 days & *sc*	↓Lethality rate, Amelioration of body weight, ↓MDA, ↓LDH, Regular myofibrillar arrangement, Preservation of mitochondria
Karim et al., 2001 [19]	*In vivo*/rat	Single dose of 10 mg/kg & *iv*	↑Serum AST, ↓Blood & tissue GSH, ↑TBARS	4 mg/kg/day for 5 days & *po*	↓Serum AST, ↑Blood and tissue GSH, ↓TBARS
Xu et al., 2001 [20]	*In vivo*/rat	Four doses of 3 mg/kg & *iv*	↓Body's hair & weight, loss & disorganization of myofibrils, vacuolization of cytoplasm & dilation of sarcotubular system, ↑TBARS, ↑CD	6 mg/kg/day for 15 days & *ip*	Regular myofibrillar, maintaining sarcotubular reticulum structure, ↓TBARS, ↓CD
Xu et al., 2001 [21]	*In vivo*/rat	Four doses of 2.5 mg/kg & *iv*	↓BAR density in cell membrane, ↑Membrane permeability of cultured neonatal myocytes, ↓Myocyte size, disappearing of myofibrils, ↑LDH	6 mg/kg/day for 15 days & *ip*	↑BAR density in cell membrane, preventing changes of density & shape of cultured myocyte, ↓LDH
Dziegiel et al., 2002 [22]	*In vivo*/rat	Single dose of 10 mg/kg or 3 mg/kg, weekly for 3 weeks, & *iv*	↑MDA & 4-HDA, ↑Cardiac muscle cell lesions	10 mg/kg, before and after every doxorubicin injection & *sc*	↓MDA & 4-HDA, ↓Cardiac muscle cell lesions
Liu et al., 2002 [23]	*In vivo*/mouse	Single dose of 25 mg/kg & *ip*	↓Body weight & ascites, diarrhea, ↓Survival rate, ↑Cardiac damage (mitochondrial degeneration & swelling, intracytoplasmic vacuolization, & focal myofilament disarray), ↑Cytosolic mono- or oligonucleosomes, ↑Serum CPK	10 mg/L & 24 h before doxorubicin injection & administration in drinking water	↑Survival rate, ↓Cardiac damage, ↓Apoptosis of cardiac myocytes, inhabitation of DNA fragmentation, ↓Serum CPK, ↓Necrosis in mouse hearts
Xu and Ashraf, 2002 [24]	*In vitro*/myocyte	20 μmol/L	↑LDH, ↓Mitochondrial membrane potential	1 mmol/L for 1 h prior to incubation with doxorubicin	↓LDH, ↑Mitochondrial membrane potential
Dziegiel et al., 2003 [25]	*In vivo*/rat	Four doses of 2.5 mg/kg & *ip*	↑MDA & 4-HDA, ↓GSH, ↑GPx, & SOD & CAT	20 mg/kg & 15 min before doxorubicin injection & *sc*	↓MDA & 4-HDA, ↑GSH & CAT
Sahna et al., 2003 [26]	*In vivo*/rat	Single dose of 20 mg/kg & *ip*	↑MDA, ↑Morphological damage (inflammatory cell infiltration & myocardial fibrosis)	4 mg/kg & 1 h before or 24 h after doxorubicin injection for 2 days & *ip*	↓MDA, ↓Morphological damage
Balli et al., 2004 [27]	*In vivo*/rat	Four doses of 3 mg/kg & *ip*	↑MDA, destruction of myofibrils, disorganization of sarcomeres, mitochondrial degeneration & formation of giant mitochondria & lipid accumulation, accumulation of filamentous structures in sarcoplasm, structural changes in capillaries, ↑Collagen fibers forming bundles	6 mg/kg/day & 3 h before each doxorubicin injection & *ip*	↓MDA, preservation of all structural changes
Ahmed et al., 2005 [28]	*In vivo*/rat	Single dose of 15 mg/kg & *ip*	↑Serum TPI & leptin, TGs & cholesterol & LDL, ↓Serum T3 & T4 & IL-1a, ↑MDA & NO, ↓SOD & GPx & CAT levels	5 mg/kg/day & for 10 consecutive days starting 3 days before doxorubicin injection & *ip*	↓Serum TPI & leptin, TGs & cholesterol & LDL, ↑Serum T 3 & T 4 & IL-1a, ↓MDA & NO, ↑SOD & GPx & CAT levels
Kim et al., 2005 [29]	*In vivo*/rat	Single doses of 5, 15, 25 mg/kg & *ip*	↑Mortality, ↓Body weight, mitochondrial swelling, vacuolization of cytoplasm, thinning of Z lines, loss of myofibrils, ↓Cell length & area of myocytes, comet-like morphology, ↑DNA migration distance ↑MDA & LDH, ↑Serum creatine kinase	10 mg/kg/day & 1 h before doxorubicin injection and every 12 h thereafter for 6 days & *sc*	↓Mortality, regular myofibrillar arrangements, preserved mitochondria, normal length of Z line, restoration of cell length, ↓DNA damage, prevented DNA migration distance, ↓MDA & LDH, ↓serum creatine kinase
	In vivo/rat	Single dose of 45 mg/kg & *iv*			

(*continued on next page*)

Table 1 (*continued*)

Author & year	Models	Doxorubicin dosage & route of administration type	Outcomes of doxorubicin on cardiac tissue	Melatonin dosage & protocol of usage & route of administration	Melatonin co-administration outcomes
Oz et al., 2006 [30]			↑MDA, ↓GSH, ↑Serum creatine kinase, ↑Serum AST, cellular edema, mitochondrial deformation, decreased glycogen stores, disordered myofibrillary structures	10 mg/kg & once a day for 7 days before or after doxorubicin injection & *sc*	↓MDA, ↑GSH, ↓Serum CPK-MB, ↓Serum AST, preservation of cellular structures
Othman et al., 2008 [31]	*In vivo*/rat	Single dose of 10 mg/kg & *ip*	↑Mortality rate, ↑CK-MB & LDH & GOT & GPT in plasma, ↑Plasma levels of transferrin & ferritin & iron, ↑TBARS & PC levels, ↑CAT & GPx, ↓GST & GSH	15 mg/kg/day & 5 days before and 5 days after doxorubicin injection & *ip*	↓Mortality rate, ↓CK-MB & LDH & GOT & GPT in plasma, ↓Plasma levels of transferrin & ferritin & iron, ↓TBARS & PC levels, ↓CAT & GPx, ↑GST & GSH
Aydemir et al., 2010 [32]	*In vivo*/rat	Single dose of 15 mg/kg & *ip*	↑Tissue TBARS, ↓SOD, ↑Tissue CAT	5 mg/kg/day & for two consecutive days before doxorubicin injection plus on first day and then a daily injection six consecutive days	↓Tissue TBARS, ↑SOD
Ozturk et al., 2011 [33]	*In vivo*/rat	Single dose of 20 mg/kg & *ip*	↑MDA, ↓SOD & GPx, ↑Serum CK-MB, presence of cell infiltration, single fiber necrosis, interstitial edema, disorganization of muscle fibers & vacuolization	20 mg/kg/day & twice daily, 36 h before and continued for 72 h after doxorubicin injection & *po*	↓MDA, ↑SOD and GPx, ↓Serum CK-MB, no necrotic areas or cell infiltration, histologic protection of cardiac tissue
Sag et al., 2011 [34]	*In vitro*/myocyte	10 μmol/L	↑Intracellular ROS, ↓Intracellular Ca transient amplitude, ↑Diastolic intracellular Ca level, ↑Diastolic SR Ca loss, ↓SR Ca content, ↑CaMKII phosphorylation	100 μmol/L	↓Diastolic intracellular Ca level, ↓Diastolic SR Ca loss, ↑SR Ca content
Arif et al., 2013 [35]	*In vitro*/myocyte & fibroblast	0.6–10 μM	↓Cell viability, ↓Number of intact sarcomeres, ↓Cyclin D1 level, ↓Expression of procollagen by fibroblasts	1 pM, 1 nM, 1 μM & 12 h prior to treatment	↓Viability of fibroblasts
Zhang et al., 2013 [36]	*In vivo*/rat	Seven doses of 2.5 mg/kg & *ip*	↓Survival rate, ↑LPO, ↓SOD & GPx, changing in shapes, sizes & weights of hearts (congested & swollen, with increased volumes & visible petechiae on pericardium), myocardial injuries	10 mg/kg/day & once a day for a total of 15 times before doxorubicin injection & *ip*	↑Survival rate, ↓LPO, ↑SOD & GPx, normal shapes of hearts with mild congestion & without visible petechiae on pericardium, alleviation of myocardial injuries
Bilginoglu et al., 2014 [37]	*In vivo*/rat	Cumulative dose of 18 mg/kg (doxorubicin injection on 5th, 6th and 7th days) & *ip*	↑CK & CK-MB & cTnT & LDH & AST, ↓SOD & GPx, ↑ MDA, ↑TGs & LDL & VLDL, ↓HDL	10 mg/kg/day for 7 days & *ip*	↓CK & CK-MB, LDH & AST & cTnT, ↑SOD & GPx, ↓ MDA, ↓TGs & LDL & VLDL, ↑HDL
Asensio-López et al., 2016 [38]	*In vitro*/HL-1 cardiomyocyte	5 μM	↑ROS, ↑Resting Ca^{2+} level, ↓Ca^{2+} peak amplitude, ↑ DCF accumulation, ↓Mitochondrial membrane potential	100 mM & 1 h after doxorubicin treatment	↓ROS, ↓Resting Ca^{2+} level, ↑Ca^{2+} peak amplitude, ↓ DCF accumulation
Yassien & Elsaid, 2017 [39]	*In vivo*/rat	Four doses of 3 mg/kg & *ip*	Fibers with dark acidophilic cytoplasm & pyknotic nuclei, ↑Apoptosis, dilatation of vessels with mononuclear cellular infiltrations & deposited collagen fibers, disarrangement of sarcomeres, disruption of microfilaments & Z-line, ↑Number & size of mitochondria, dilated SER & T tubules, presence of oval shaped cells with thin long processes	6 mg/kg/day & 1 day before doxorubicin injection for 15 days and 3-h before each doxorubicin injection & *ip*	Suppression of cardiomyopathy induced by doxorubicin
Liu et al., 2018 [40]	*In vitro*/H9c2 cells & *in vivo*/mouse	1 μM (for *in vitro*) & two doses of 20 mg/kg (for *in vivo*) & *ip*	↓Cell viability, ↑ROS, ↓Cellular ATP, ↑MDA, ↑Apoptotic index (Bax, cleaved caspase 3, Bcl2), inhibition of p-AMPK & PGC1α, ↓NRF1 & UCP2 & TFAM	100 μM (for *in vitro*) & 20 mg/kg/day & every day for a total of 8 times and 1 day before initial doxorubicin injection (for *in vivo*) & *ip*	↑Cell viability, ↓ROS, ↑Cellular ATP, ↓MDA, ↓Apoptotic index (Bax, cleaved caspase 3, Bcl2), ↑p-AMPK & PGC1α & NRF1, UCP2 & TFAM
Govender et al., 2018 [41]	*In vitro*/H9c2 cells & *in vivo*/rat	3 μM (for *in vitro*) & three doses of 4 mg/kg (for *in vivo*) & *ip*	↓Cell viability, ↓Body & heart weight, ↑Cleaved caspase-3 & cleaved-PARP, ↑Pink1 & PARKIN, ↓Mfn2, ↑Drp1 & hFis1, ↓PGC-1α protein & SIRT1, ↑ Mitochondrial fission (round-shaped mitochondria), ↓ Mitochondrial major/minor aspect ratio, ↑Degree of mitochondrial branching, ↓ATP	10 μM (for *in vitro*) & 6 mg/kg/day & every day for a total of 14 times and after tumor inoculation (for *in vivo*) & *po*	↓Cell death, ↑Stroke volume, ↑Heart weight, ↓Tumor volume, ↓Cleaved caspase-3 & cleaved-PARP, ↓ Pink1, ↑Mfn1 & Mfn2, ↓↑Drp1 & hFis1, ↑PGC-1α protein & SIRT1, ↓Mitochondrial fission, ↑ Mitochondrial major/minor aspect ratio, ↓Degree of mitochondrial branching, ↑ATP

↑, increase; ↓, decease; &, and; *ip*, intraperitoneal; *iv*, intravenous; *sc*, subcutaneous; *po*, *per os*; MDA, malondialdehyde; NO, nitric oxide; GPx, glutathione peroxidase; TBARS, thiobarbituric acid reactive substances; GSH, glutathione; SOD, superoxide dismutase; CAT, catalase; GST, glutathione S-transferase; LPO, lipid peroxidation; LDH, lactate dehydrogenase; GOT, glutamic oxaloacetate transaminase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; PARP, poly (ADP-ribose) polymerase; 4-HDA, 4-hydroxyalkenal; LDL, low density lipoprotein; HDL, high density lipoprotein; VLDL, very low density lipoprotein; IL, interleukin; CK-MB, creatine kinase-myocardial bound; GPT, glutamate pyruvate transaminase; CK, creatine kinase; ATP, adenosine triphosphate; TPI, troponin I, TGs, triglycerides; PC, protein carbonyl; Mfn; mitofusin, Drp; dynamin-related protein, hFis1; human mitochondrial fission protein, AMPK; AMP-activated protein kinase; BAR, β-adrenoceptor; DCF, 2′,7′-dichlorofluorescein; SER, smooth endoplasmic reticulum.

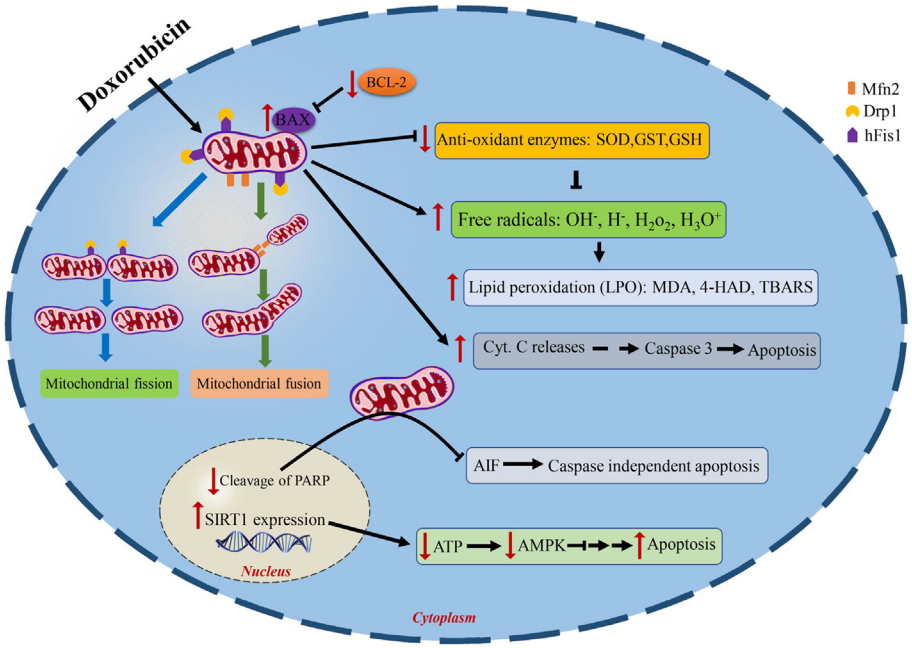

Fig. 2. The molecular mechanisms of cardiac cytotoxicity-induced by doxorubicin. Doxorubicin induces oxidative stress mostly through mitochondrial dysfunction. Also, doxorubicin through inhibition of SOD, GST, and GSH enzymes induces increasing free radicals and elevation in LPO markers. Furthermore, doxorubicin elevates apoptosis through reduction in BCL-2 and elevation of BAX activations as well as it increases cytochrome C releases and caspase 3 levels. In addition, this chemotherapeutic drug involves in caspase independent apoptosis *via* reduction of PARP cleavage. In this content, doxorubicin *via* up-regulation of SIRT1 and reduction in ATP and AMPK levels induces apoptosis. Also, doxorubicin *via* up-regulation of Mfn2, and elevation of Drp1 and hFis1 induces mitochondrial fission. Melatonin, through an opposite pattern induced by doxorubicin, reduces cardiac doxorubicin-induced cytotoxicity.
↑ increased by doxorubicin; ↓ decreased by doxorubicin; SOD, superoxide dismutase; GST, glutathione-S-transferase; GSH, glutathione; MDA, malondialdehyde; 4-HDA, 4-hydroxyalkenes; TBARS, thiobarbituric acid reactive substances; PARP, *poly (ADP-ribose) polymerase*; Mfn2, mitofusin2; Drp1, dynamin-related protein1; hFis1, human mitochondrial fission 1 protein; AIF, Apoptosis Inducing Factor; AMPK, AMP-activated protein kinase.

[58,59]. Interaction of NO with O_2^- produces $ONOO^-$ that is a potential free radical [60]. The $ONOO^-$ can turn to NO_2^-, NO_3^-, OH^-, and CO_3^-. Thus, O_2^- can induce production of reactive nitrogen species (RNS). It is demonstrated that doxorubicin *via* increasing the oxidative stress and decreasing the activity of poly (ADP-ribose) polymerase (PARP) activity induces DNA damage. Doxorubicin increases lipid peroxidation (LPO) markers including MDA, 4-HDA, and TBARs, resulting in the cell membrane devastation and malfunctions [61,62]. In this condition, extracellular ions, especially Ca^{2+}, easily enter the cells and lead to the cell dysfunction and apoptosis [63]. Moreover, peroxyl radical, as the production of LPO, worsens the oxidative stress [64].

Melatonin or some of its metabolites have a strong anti-oxidant role. Melatonin through its small size and amphiphilic property easily passes into the cell and performs its pleiotropic effect at both lipid and water conditions [4,5]. It is also reported the anti-oxidant potential of melatonin is several times more than the well-known antioxidants [65]. Generally, melatonin through both direct and indirect anti-oxidant properties reduces cellular oxidative stress. Melatonin donates an electron to neutralize free radicals in a direct way. Melatonin can perform such action possibly *via* radical adduct formation, single electron transfer, and hydrogen atom transfer [66]. The possible mechanisms for melatonin's indirect way are *via* interaction with calmodulin, which is involved in inhibition of nuclear RAR-related orphan receptor alpha (RORa) receptor, epigenetic mechanisms, and modulating function or expression of Nuclear factor erythroid 2–related factor 2 (Nrf2) [67,68]. Nrf2 acts as a transcription factor for several molecules which are involved in an anti-oxidant activity, such as NAD(P)H Quinone Dehydrogenase 1, heme oxygenase 1 (HO-1), GST, c-glutamylcysteine synthase, and γ-glutamylcysteine synthetase (γ-GCS) [69]. Interaction between each molecule of melatonin with two HO^- produces cyclic 3-hydroxymelatonin (3-OHM) which is oxidized to N1-acetyl-N2-formyl-methoxykynuramne (AFMK). AFMK converts to N2-acetyl-5-methoxykynuramine (AMK) through a deformation process. Moreover, it is worth-noting that 3-OHM, AFMK, and AMK also have anti-oxidant properties [70]. GSH is an important intracellular anti-oxidant agent that plays a primary role against oxidative stress [71]. GPx is another anti-oxidant enzyme which turns H_2O_2 to $2H_2O$, and lipid peroxides to lipid alcohols. By activity of GPx, two molecules of GSH in its thiol's sulfur atom are oxidized into one glutathione disulfide (GSSG) [72]. GSH is recycled through reduction of GSSG by glutathione reductase (GR) enzyme through consuming NADPH as a co-factor which is turned to $NADP^+$ [73]. As mentioned, doxorubicin decreases heart GSH and GR activity, which are both modified by melatonin. Melatonin would do such action through its anti-oxidant activity, its synergistic effects with other anti-oxidants agents, up-regulation of GSH, and elevation of g-glutamylcysteine production [74]. Melatonin *via* its pleiotropic effect inhibits elevation of NO and RNS induced by doxorubicin [4,5]. Melatonin through its anti-oxidant effect and elevation of PARP enzyme activity decreases doxorubicin-induced DNA damage [75].

Previous studies have clearly and strongly mentioned that there is a relation between the elevation of oxidative stress with the initiation of inflammation and apoptosis pathway [76,77].

4.2. Anti-apoptotic actions

Apoptosis is a physiological pathway that regulates cell death and has critical roles in homeostasis and cell survival. Apoptosis is needed to eliminate the harmed or transformed cells; this is required for shaping the organs or controlling the cell numbers [78]. Any irregularity or reduction of this pathway could induce tissue disorders or cancer [79,80]. Doxorubicin-induced cardiomyocyte apoptosis as a pathogenic mechanism in acute cardiotoxicity [46,81] and mitochondrial-dependent intrinsic apoptosis are the major reasons for cardiac dysfunction [82]. Elevation of mitochondrial transition pore opening (mPTP) and mitochondrial membrane permeabilization (MMP) constitutes an essential step of the intrinsic pathway leading to apoptosis [83]. In addition, cardiotoxicity of doxorubicin occurs possibly due to the inducible effect of free radicals-induced on opening of mPTP. It is demonstrated that free radicals are involved in mitochondrial damage and protein oxidation, leading to irreversible formation of large holes in the inner membrane, the so-called permeability transition causing loss of MMP. It has been reported that aglycone metabolites of doxorubicin increase Ca^{2+}-dependent permeability of the inner mitochondrial membrane to small solutes [84], which is accompanied by the release of mitochondrial Ca^{2+}, mitochondrial swelling, and the collapse of the membrane potential. Doxorubicin also causes alterations in calcium homeostasis which may accelerate through the chance of opening of

sarcoplasmic reticulum calcium channels and inhibition of Na^+/Ca^{2+} exchanger, thus inducing Ca^{2+} overload of sarcoplasm and membrane injury [39,85].

Several studies have indicated that melatonin exerts cardiac protection against apoptosis under above-mentioned diverse conditions [86,87]. Melatonin markedly enhances anti-apoptotic Bcl2 protein level and reduces pro-apoptotic proteins like Bax and caspase 3 in doxorubicin-induced apoptosis [40]. PARP is a nuclear enzyme which is involved in some of the cellular processes like programmed cell death and DNA repair. Doxorubicin induces elevation activity of caspases 3 and 7, and thus initiation of PARP cleavage [88–90]; these alterations are modified by melatonin. Another pathway related to the anti-apoptotic effects of melatonin against doxorubicin-induced cardiotoxicity is through AMPK/PGC1 pathway. Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), one of the transcriptional co-activators, is a master regulator of mitochondrial biogenesis and energy metabolism [91]. The diminished activity or expression of PGC1α is a usual sign of cardiac dysfunction [92]. The studies have demonstrated that doxorubicin reduces the activity and expression of PGC1α in cardiomyocytes thus worsening acute cardiotoxicity [93,94]. However, *in-vivo* and *in-vitro* studies showed that melatonin markedly increases PGC1α expression [95]. 5′ AMP-activated protein kinase (AMPK) has the main role in cell growth and survival *via* several mechanisms including protein synthesis, mitochondrial biogenesis, and energy homeostasis in the heart. AMPK activation occurs by phosphorylation of Thr172 site, and this activation maintains myocytes' energy balance [96]. It has been demonstrated AMPK's activity significantly reduces during doxorubicin-induced cardiotoxicity [97]. However, melatonin administration can effectively reverse reduction of AMPK, and down-regulation of PGC1α expression induced by doxorubicin, thereby diminishing cardiomyocyte apoptosis [98]. Furthermore, anti-apoptotic property of melatonin is exerted *via* inhibiting nuclear and mitochondrial DNA damage, prevention of mPTP and direct modulation of different proteins involved in the cell death related processes [99]. These findings are further confirmed by the fact that mitochondrial membrane potential is restored by melatonin as a potent anti-oxidant. The protective effects of melatonin against doxorubicin-induced loss of MMP may occur by inhibition of apoptosis and maintenance of mitochondria anti-oxidant capacity [24].

4.3. Anti-inflammatory actions

The inflammatory process is a biological phenomenon occurring in response to harmful stimuli. The rate of inflammatory response must be in balance, which is for reducing the harm of hazardous stimuli. Inflammation is identified through elevation in leukocyte migration to injured area, enhanced production of pro-inflammatory cytokines, and increased chemotaxis of leukocytes [4,5]. Doxorubicin can induce heart inflammation during chemotherapy. It has been previously mentioned that oxidative stress induced by doxorubicin is involved in LPO and may induce activation of lysosomal enzymes, and thereby promoting inflammation in heart tissue. It is well-known that ROS take roles for activation of NF-kappaB and IκB *via* IκB kinase (IKK). Inhibitory proteins of kB family (IkB) hinder nuclear translocation of NF-kappaB. IKK activation induces phosphorylation of IKB and NF-KB. Inactivation of phosphorylated IKB promotes nuclear translocation of phosphorylated NF-KB and its attachment to genomic promoter of numerous inflammatory mediators. Several studies revealed that the use of doxorubicin induces up-regulation of pro-inflammatory cytokines including TNF-α, cyclooxygenase-2 (COX-2), intercellular adhesion molecule-1 (ICAM-1) and IL-6 [100–102]. Melatonin is reported to reduce oxidative stress and activation of NF-KB as well as upregulation of inflammatory cytokines [103]. ICAM-1 is a surface protein that exerts important role in the infiltration of leucocytes to the damaged areas of heart tissue [104].

In histological studies, it has been demonstrated that doxorubicin-induced infiltration of inflammatory cells is reduced by melatonin.

4.4. Mitochondrial actions

The main site for the production of melatonin in organisms is mitochondria [105]. Serotonin *N*-acetyltransferase (SNAT) is an enzyme synthesizes melatonin, produced by cell genomic and translocated to mitochondria matrix and intermembrane. Moreover, it is assumed that melatonin production mainly occurs in matrix of mitochondria [106].

On a molecular level, the mitochondrial disorder is an apparent sign of doxorubicin-induced cardiotoxicity. The selective removal of damaged mitochondria is called mitophagy, a process responsible for selective degradation of mitochondria by autophagy, which is a necessary process to keep mitochondrial quality control and cellular homeostasis [107]. PARKIN and Pink1 are two vital proteins involved in mitophagy. Pink1 binds to defected mitochondria and cytosolic PARKIN to initiate mitophagic elimination [108]. It has been reported that in doxorubicin-treated rats, the level of Pink1 protein significantly increases in the heart tissue. Furthermore, PARKIN protein level significantly increased in response to doxorubicin treatment. However, other studies have indicated that melatonin elevates mitophagy and preserves mitochondrial homeostasis [109]. Mitochondrial fusion in mammalian cells is controlled by mitofusin (Mfn) proteins including Mfn1 and Mfn2. Mfn facilitates the binding of two separate mitochondria during early stages of mitochondrial fusion [110]. Mitochondrial fission is controlled *via* dynamin-related protein1 (Drp) and hFis1 (human mitochondrial fission 1 protein); hFis1 is located in the outer mitochondrial membrane, and it forms protein-protein interaction sites, which are protruding toward the cytosol [111]. Drp1 is mainly located in the cytosol, and upon fission Drp1 is recruited to the mitochondria *via* hFis1. When Drp1 interacts with hFis1 at fission sites, a collar around the mitochondrion is formed. The constriction of collar leads to a separation of the outer mitochondrial membrane, yielding two independent organelles [112]. Thus, the results indicated that doxorubicin induces mitochondrial fission and disrupting mitochondrial fusion *via* diminishing Mfn1 and Mfn2 expression as well as increasing mitochondrial fission protein (Drp1 and hFis1) expression. Melatonin reversed the changes in expression of mitochondrial fission and fusion proteins, favoring mitochondrial fusion during doxorubicin-induced cardiotoxicity. In the cardiac cells, mitochondrial fission and fusion are critical processes, where the morphology of mitochondria adapts to meet the high metabolic needs of the heart.

As it has been reported mitochondria is the main source of ROS production, which is detoxified by melatonin. AFMK is produced by melatonin interaction with cytochrome C, and it acts as a carrier of electron in mitochondria electron transport chain [106]. Cytochrome P450 isoform B in mitochondria is responsible for metabolizing melatonin to *N*-acetylserotonin, and it exerts important roles in the anti-tumor effects of melatonin [113]. Melatonin in normal cells has beneficial effects, whereas in cancerous cells it increases apoptosis due to increasing release of cytochrome C into the cytoplasm *via* elevated activation of *N*-acetyl serotonin. As reported in several studies, melatonin has protective effects on mitochondrial injury in organisms. It is demonstrated that melatonin preserves normal mitochondrial morphology [106]. Moreover, the use of melatonin caused a remarkable increase in cellular ATP levels in comparison with the doxorubicin-treated group. Furthermore, melatonin treatment alone is able to maintain cellular ATP at basal levels suggesting that melatonin has a protective effect on mitochondria during stressful conditions such as doxorubicin-induced cardiotoxicity [39]. Melatonin would do such actions possibly through influencing mitochondrial dynamics, including blockade of mitochondrial fission and induction of mitochondrial fusion [106]. Melatonin counteracts markedly inhibitory effect of doxorubicin on Mfn proteins. In addition, melatonin is found to reduce the expression of Drp1 and hFis1 proteins, which are both increased by doxorubicin. It was reported that the level of Pink1 protein in the heart tissue

markedly diminished by melatonin [41]. It was demonstrated electron leakage is the main mechanism for ROS elevation [114]. Melatonin upregulates gene expression and increases activities of uncoupling proteins (UCPs). Melatonin accelerates the electron flow in the ETC and reduces the electron leakage, thereby avoiding ROS formation [115].

It is also likely that melatonin maintained cellular ATP levels by reducing electron leakage from the ETC *via* modulation of uncoupling protein activity and thereby limiting molecular damage to the ETC [41]. The proposed mechanism for this is melatonin inducible effect on UCPs activities in the mitochondrial inner membrane. The activation of UCPs induces transferring of protons from intermembrane space to the matrix and can be used to produce ATP [116,117].

5. Perspective of future research

It is known the use of doxorubicin, as a chemotherapy agent, is an important way to battle cancer, especially in the progressive stage. However, this chemotherapy agent has harmful effects on the normal cells which limit its usage as an option for cancer treatment [118]. The recent research on different *in-vivo* or *in-vitro* models demonstrated that some agents can decrease the non-specific side effects related to chemotherapy on normal cells and even potentiate the effects of chemotherapy agents on cancerous cells or decrease drug resistance [4,5]. This property could be very effective and important during chemotherapy which especially needs more research. Cardiac injury related to chemotherapy may be associated with the treatment strategy, personal features such as individual rate of doxorubicin metabolisms, or even functions of other tissues that are involved in excretion of doxorubicin [119,120].

It is of noting that oxidative stress is involved in the initiation and progress of cancers, and that induction of oxidative stress is considered as one of the main mechanisms of battling cancer cells. Non-specific induction of oxidative stress may combat both cancer cells and normal cells in the target cells or even non-target cells [121]. In this context, it has previously been reported that melatonin can be served as both pro-oxidant agent for combating cancer cells, and as an anti-oxidant to reduce free radical accumulation in normal cells, thus it can be proposed as a wonderful agent to use for patients receiving chemotherapy. The dual melatonin role has also been proposed for targeting doxorubicin-related inflammation and apoptosis. Sometimes the chemotherapy process is the best and most effective way for cancer treatment, but the non-specific side effects and toxic injury to normal cells can be the main problems that limit chemotherapy treatment [4,5]. Doxorubicin-induced cardiotoxicity is common during chemotherapy of other cancerous tissues, which are not related to heart [122]. Thus, it seems necessary to discover some agents effective for protection of normal cells from the perilous effect of doxorubicin.

As already stated, the use of melatonin, as an adjuvant treatment alongside chemotherapy, has a double effect, as it would decrease side effects induced by chemotherapy agents on the normal cells and increase the pathway which leads to death of cancerous cells [123,124]. Previously, it has been demonstrated that melatonin reduces the toxic effect of doxorubicin on the cardiac cells, but it needs to discover the role of co-treatment of melatonin on cardiac cancerous cells, and to identify underlying mechanisms [68]. In the present study, it can be understood that melatonin reduces doxorubicin-induced cardiotoxicity mainly by decreasing the oxidative stress *via* its direct and indirect antioxidant property [70]. The limitation of this study is that the results were interpreted according to the studies performed on animal models. Because sometimes findings are different between the animal and clinic studies, and thus further clinical studies are needed.

6. Conclusion

According to the results of the present study, it was found that co-treatment of melatonin resulted a decrease in the rate of mortality, an increase in the body weight and heart weight, and a decrease in the ascites value compared to doxorubicin-treated groups. Co-administration of doxorubicin and melatonin also ameliorated the doxorubicin-induced biochemical and histopathological changes (for most of the cases) by mechanisms of anti-oxidant, anti-apoptosis, anti-inflammatory, and mitochondrial function.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Declaration of competing interest

Author M.N declares that he has no conflict of interest. Author MR.HSH declares that he has no conflict of interest. Author K.M declares that he has no conflict of interest. Author B.F declares that he has no conflict of interest. Author H.H-A declares that he has no conflict of interest.

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