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The Use of *Panax Ginseng* to Reduce the Cardiotoxicity of Doxorubicin and Study its Effect on Modulating Oxidative Stress, Inflammatory, and Apoptosis Pathways

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Abstract

BACKGROUND: Doxorubicin (DOX) is a broad-spectrum anti-cancer drug that is used to treat a variety of cancers, including blood cancers such as leukemia and solid tissue cancers. However, its use some time limited because of its cardiotoxicity.

OBJECTIVE: The objective of the study was to determine the cardioprotective effect of ginseng in the case of cardiotoxicity caused by doxorubicin therapy.

Methods: Thirty experimental animals (male Sprague Wistar rats) were used in this research and they were separated into three groups: Rats in Group I (n# = 10) were given distilled water plus normal saline, rats in Group II (n# = 10) were given distilled water plus doxorubicin, and rats in Group III (n# = 10) were given *Panax ginseng* plus doxorubicin. Serum concentration, malondialdehyde (MDA), glutathione reductase (GSH), lipid peroxidase (LPO), TNF (ng/L), cardiac troponin (ng/L), brain natriuretic peptide BNP(g/L), and caspase-3 (pmol/L) levels were measured in all groups.

RESULTS: Doxorubicin caused substantial cardiotoxicity as a result of a significant increase in the elevation of cTnI to 40.09 ± 6.67 (ng/L). In addition, MDA, LPO, TNF-α, and caspase-3 levels were increased in doxorubicin group compared to the control group $p < 0.05$. *Panax ginseng* reduced cardiac troponin (cTnI) However, its effect on reduction of BNP levels insignificantly compared to the doxorubicin group $p = 0.06$. *Panax ginseng* reduced LPO and MDA and raised the antioxidant potential biomarker GSH significantly compared to the doxorubicin group $p < 0.05$. *Panax ginseng* significantly reduced inflammatory (TNF-α) and apoptotic (caspase-3) biomarkers when compared to the doxorubicin group.

CONCLUSIONS: According to the findings of this study, *Panax ginseng* suppresses reactive oxygen species and inflammatory and apoptotic pathways in experimental rats, thereby preventing doxorubicin-induced cardiovascular events.

Introduction

Doxorubicin (DOX) is a broad-spectrum anti-cancer drug that is used to treat a variety of cancers, including blood cancers such as leukemia and solid tissue cancers. After the liver metabolizes doxorubicin and converts it into an active metabolite, doxorubicin accumulates intracellularly after entering cells through passive diffusion, bringing its concentration in cells to 10–500 times that of the fluid and extracellular components [1].

Despite its effectiveness, the use of doxorubicin is beginning to decline due to some side effects such as cardiotoxicity. Doxorubicin cardiotoxicity can either be acute and result in end-stage heart failure, or chronic and lead to congestive heart failure [2].

The mechanisms of this cardiotoxicity are caused by several factors, including an increase in free radicals, DNA destruction, inactivation, a decrease in the cell's ability to revive DNA processes and an acceleration of apoptosis, which eventually results in cell death. An increase in the immune response of cells alters calcium levels and metabolism in the body [3]. Despite the above effects, oxidative stress and depletion of endogenous antioxidant enzymes are the most influential. The heart is particularly vulnerable to oxidative damage due to its low antioxidant activity, high mitochondrial density and rapid rate of oxygen consumption. The most common cause of cardiotoxicity is free radicals and their increase due to doxorubicin, and some free radicals consist of semiquinone, which can spontaneously oxidize to the parent compound in the presence of O2 or undergo further oxidation and increase the formation of other radicals [4]. In addition, doxorubicin enhances the production of nitric oxide (NO) by increasing the expression of inducible NO synthase. As a result of NOS incorporation, peroxynitrite is produced, which attacks the cellular biomolecules that cause cell death [5], [6]. In addition, doxorubicin inhibits iron-regulating proteins increasing intracellular

free iron, which generates free radicals and causes oxidative stress. Thus, dexrazoxane iron chelate binds to free iron and prevents free radical formation during doxorubicin-induced cardiotoxicity [5], [7], [8]. Due to their powerful antioxidant effects, *Panax ginseng* and other herbal agents (such as alpha-lipoic acid, Vitamin C, cloves, and cinnamon that have an antioxidant effect) may have a role in the protective mechanism and decrease the toxicity of doxorubicin [9], [10], [11].

Panax is a medicinal plant found all over the world that belongs to the Panax family. *Panax* ginseng is known for its unique components, as it contains more than 40 active substances and ingredients such as ginsenosides, polyacetylenes, polysaccharides, and peptidoglycans [10], [12]. This ginseng plant has recently received much attention for its use in the diagnosis and treatment of many diseases including kidney failure prevention, hepatoprotections, reduction of neurotoxicity and may also reduce cardiotoxicity due to oxidative stress [13], [14], for that reason several studies have been asked about its potency to treat this disorder but till now few studies success by powerful biomarkers and histological methods.

For that reason, the purpose of this study was to demonstrate *Panax ginseng's* cardioprotective effect in doxorubicin-induced free radical and oxidative stress cardiotoxicity.

Materials and Methods

Animals

In this research, thirty experimental Sprague Wistar male rats were used, obtained from the Iraqi center for cancer and medical genetic research, Almustansria University Iraq, and their ages and body weights ranged from 2 to 3 months and 200–400 g, respectively [15]. The rats were housed in cages in groups of three, with a comfortable room temperature and a non-natural 12/12 light cycle. They were left alone for 1 week to acclimatize to their new surroundings and given unlimited access to meal pellets and water. Experimental animals are treated ethically as per the guide (which received special approval from Iraqi Medical Research Center- ethical Ref.no. IMRC\11789\7\2018) and given laboratory grade animal care.

Medication and ELISA kits

In this study, Doxorubicin HCl 50 mg vial/Pfizer and standardized *Panax ginseng* obtained from the college pharmacy at the University of Baghdad were used, as well as ELISA Kits (BNP, cTn-1, caspase-3, GSH-Px, LDH, LPO, MDA, TNF-α) from the Kono biotech company in China.

Histopathological studies

After removing the hearts from the animals, to obtain the desired cuts, we used formaldehyde (10%) to fix and harden the cardiac tissue before sectioning, cross-sectioning, and cutting the ventricles. The samples were then placed in plastic tissue cassettes and gradually dehydrated before the infiltration process, embedding, and using hard paraffin to solidify the tissue and microtome to cut the slides. The sections were then viewed under a microscope (Micros, Austria) [16].

Study design

The animals were divided into three groups after an acclimation period, in accordance with the Al-kuraishy *et al*., experiment [3]. Group I (*n# = 10*): Rats were given distilled water (2.5 ml/kg) orally for ten days before the administration of a single intraperitoneal dose of normal saline (2.5 ml/kg) on the eighth day. Group II (*n# = 10*): On the eighth day, rats were given a single intraperitoneal administration of doxorubicin (20 mg/kg) after ten days of being given distilled water (2.5 ml/kg) orally. Group III (*n# = 10*): Rats were given *Panax ginseng* (100 mg/kg/day) (which is usually used as stander dose in many researchers) for 10 days before receiving a single intraperitoneal injection of doxorubicin 20 mg/kg on the eighth day [17].

Sample collection

On the 11th day, the rats were anaesthetized with chloroform and decapitated with sharp scissors. The blood samples were collected and centrifuged at room temperature for five minutes at 5000 rpm. The formed serum was kept at –20°C for later analysis. Some research proposed management of Hb concentration, Mean corpuscular volume (MCV), MCV, Mean Corpuscular Hemoglobin (MCH), Mean Corpuscular Hemoglobin Concentration (MCHC), Packed cell volume(PCV), and other blood markers to assess medication toxicity [15]. Other research suggests using histological change after medication toxicity [12], [18].

Assessment of biochemical variables and cardiac biomarkers

Serum malondialdehyde (MDA), glutathione-disulfide reductase (GSH), lipid peroxide (LPO), TNF (ng/L), cardiac troponin cTnI (ng/L), BNP (μg/L), and caspase-3 (pmol/L) were measured.

Results

Serum levels in the doxorubicin research groups compared to the control groups

Doxorubicin produced significant cardiotoxicity through significant elevation of cTnI of up to 40.09 ± 6.67 (ng/L) compared to 6.98±2.63 (ng/L) in the control group p = 0.001. BNP serum levels were also significantly increased during DIC by p = 0.001. Doxorubicin significantly reduced endogenous antioxidant capacity as revealed by a reduction of GSH serum levels from 20.11 ± 7.07 pmol/L in the control group to 12.91 ± 6.55 pmol/L in the doxorubicin group, p = 0.02. Doxorubicin-induced oxidative stress during DIC was observed through a significant elevation of LPO and MDA compared to the control group, p = 0.002. Moreover, doxorubicin caused significant inflammatory changes and apoptosis induction through significant elevations of TNF and caspase-3 levels compared to the control group, at p = 0.02 and p = 0.004, respectively.

Cardiac biomarker after using Panax ginseng

Panax ginseng reduced myocardial injury, as revealed by a significant reduction of cTnI compared to the doxorubicin group p = 0.002. However, when compared to the doxorubicin group, *Panax ginseng* reduced BNP levels insignificantly at p = 0.06. Furthermore, *Panax ginseng* reduced oxidative stress during DIC by lowering oxidative biomarkers (LPO, MDA) and significantly increase antioxidant potential biomarkers (GSH) linked to the doxorubicin group p < 0.05. *Panax ginseng* attenuated DIC through significant reduction of inflammatory and apoptotic biomarkers compared to the doxorubicin group p < 0.05, as shown in Table 1.

Table 1: Cardiac and inflammatory biomarker levels during doxorubicin-induced cardiotoxicity compared to the Panax ginseng group

Cardiac biomarkers	Doxorubicin (n=10)	*Panax ginseng* (n=10)	Differences	95% CI	p
LPO (nmol/L)	22.18 ± 4.46	18.6 ± 2.21	−3.5	−6.80–0.19	0.03
MDA (nmol/L)	1.93 ± 0.74	1.10 ± 0.19	−0.83	−1.33–0.322	0.003*
TNF (ng/L)	30.31 ± 8.67	22.0 ± 7.07	−8.3	−15.73–0.86	0.03
Caspase-3 (pmol/L)	20.65 ± 6.84	13.8 ± 7.14	−6.85	−13.41–0.28	0.04
cTnI (ng/L)	40.09 ± 6.67	30.2 ± 5.67	−9.89	−15.70–4.07	0.002*
BNP (µg/L)	14.29+4.56	9.8 ± 3.33	−3.49	−7.24–0.26	0.06
GSH (pmol/L)	13.91 ± 6.55	20.2 ± 6.38	6.29	0.21–12.36	0.04

Results are expressed as mean ± SD; *p < 0.01, ¶p < 0.05, LPO: Lipid peroxidase, MDA: Malondialdehyde, TNF: Tumor necrosis factor-alpha, cTnI: Cardiac troponin, BNP: Brain natriuretic peptide, GSH: Glutathione peroxidase.

Histopathological study result

Sections from the control group show normal activity with no changes and normal myocardial tissue (Figures 1 and 2).

The doxorubicin section group shows several changes including dilation in blood vessels and congestion with extravasation of RBC decrease in the number of nuclei, and reduce the numbers of myofibers were observed (as in Figure 3).

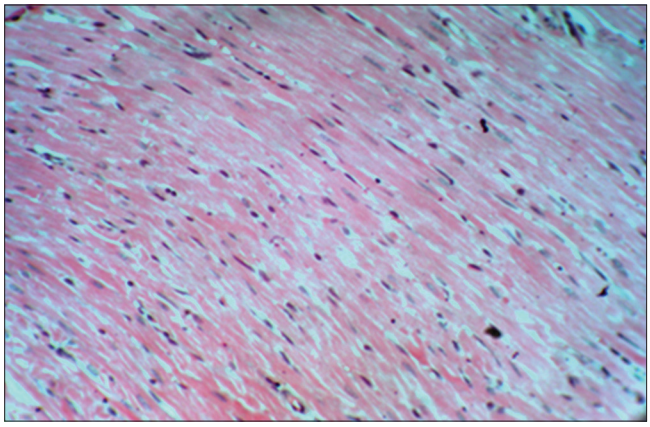

Figure 1: Sections showed normal rat myocardial tissue, magnification ×40, (H&E)

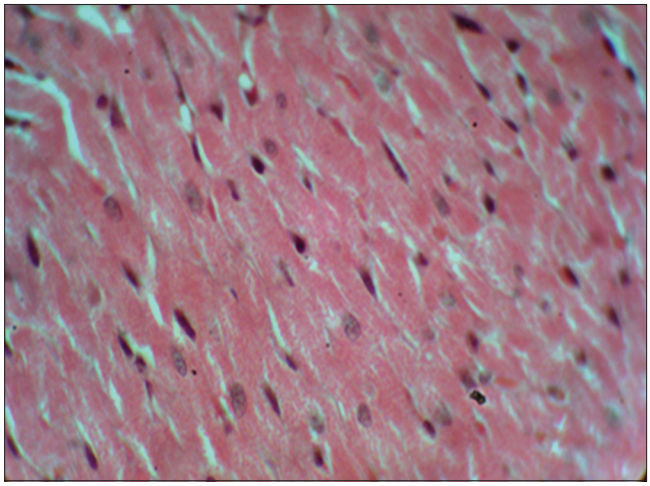

Figure 2: Sections showed normal rat myocardial tissue, magnification ×100, (H&E)

The section of Group III that received *Panax* ginseng and doxorubicin shows an obvious reduction in edema, a decrease in blood vessel abnormality and cardiac fiber disorganization as shown in Figure 4.

A histopathologist's view provides us with a grade of changes following *Panax* ginseng use

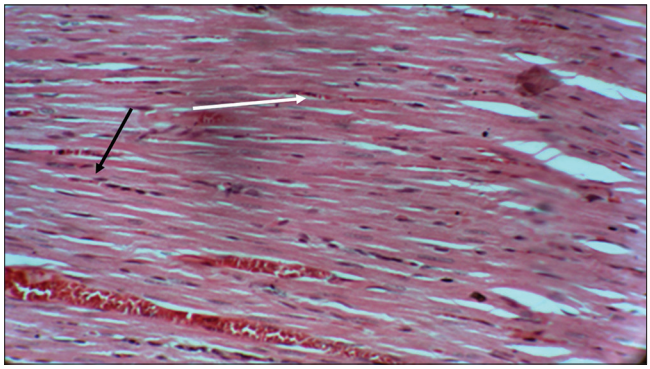

Figure 3: Section of doxorubicin affected myocardial tissue, magnification ×40 showed congested and dilated blood vessel (black arrow) with oedema (white arrow), (H&E)

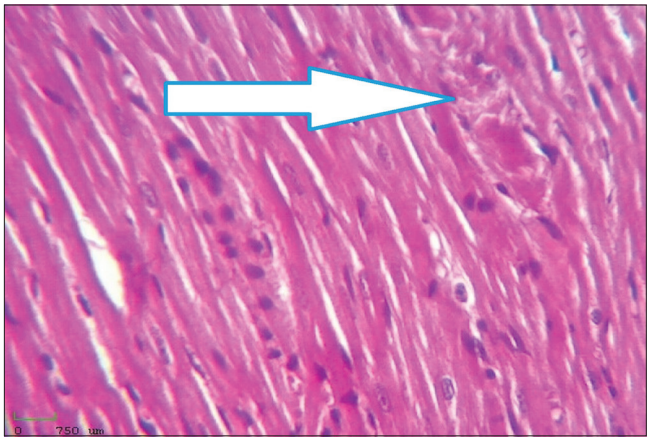

Figure 4: Magnification ×400 also showed improved Doxorubicin induced myocardial damage section shows area of coagulative necrosis, vascular congestion, and chronic inflammation cell (blue arrows), (H&E)

(Table 2), ranging from Grade 0 normal with no histological changes to Grade 3 massive cellular and tissue changes.

Table 2: Comparative grade of myocardial tissue abnormality

Grade	0	1	2	3
Group I negative control	10	0	0	0
Group II doxorubicin group	0	0	0	10
Group III doxorubicin+*panax* ginseng	1	6	2	1

Discussion

Our findings show that *Panax* ginseng causes numerous changes in the levels of several substances associated with heart failure and cardiotoxicity. First, *Panax ginseng* reduces cardiac troponin and brain natriuretic peptide during doxorubicin-induced cardiotoxicity and has a protective effect. This modulation of cardiac troponin reinforces the research of Jang *et al*. [12], [19].

Moreover, the research suggests that *Panax ginseng* has a significant effect on GSH elevation compared to the doxorubicin group. According to one study, *Panax ginseng* extract treatment dramatically increases hepatic glutathione peroxidase activity, which is consistent with the findings of Im Chung *et al*. [10], [20].

Oxidative stress is linked to the progression of various disorders due to the mismatch between the production of free radicals and the ability of endogenous antioxidants [21]. During DIC, oxidative stress was augmented as illustrated through the elevation of MDA and LPO. In this study, *Panax ginseng* reduced oxidative stress biomarkers by reducing these biomarkers as illustrated by Sun *et al*. [22], [23]. Furthermore, *Panax ginseng* prevents lipid peroxidation, increases antioxidant substance activity and suppresses free radicals in diabetic rats induced by streptozotocin [15]. In our study, *Panax ginseng* attenuated DIC by inhibiting the apoptotic pathway mediated by caspase-3. The effect of *Panax ginseng* on caspase-3 levels is due to the inhibition of pro-apoptotic protein, which induces the expression of the pro-apoptotic level of caspase-3. Therefore, *Panax ginseng* attenuates apoptosis by modulating the intrinsic pathway [19], [23]. Moreover, a study found that an increase in caspase-3 is related to *Panax ginseng*'s anticancer effect since ginsenoside inhibits cell growth through a caspase-3-mediated apoptosis mechanism [19].

Furthermore, TNF-α is affected, as shown by the current research which found that rats that were pre-treated with *Panax ginseng* had a significant decrease in serum TNF levels when compared to doxorubicin treated rats. The findings are consistent with previous research that reported that *Panax ginseng* leads to a decrease in TNF-α serum by inhibiting TNF-α expression in the myocardium and cultured cardiomyocytes [11], [23]. The suppression mechanism of *Panax ginseng* on TNF-α is proposed in a study by Chen *et al*. and claims that pre-treatment with *Panax ginseng* inhibits myocardial nicotinamide adenine dinucleotide phosphate-oxidase (NOX2) expression and superoxide production. *Panax ginseng* also inhibits lipopolysaccharide-induced ERK1/2phosphorylation during acute inflammatory changes [10], [24].

Furthermore, TNF-α levels are also changed as the experimental rats pre-treated with *Panax ginseng* illustrated a significant reduction in serum TNF-α when compared to the doxorubicin group. This result supports and strengthens the study previously conducted on *Panax ginseng* by Chen *et al*., where the potential to reduce TNF-α in the serum, heart and tissues where *Panax ginseng* acts as an anti-inflammatory can reduce and treat the symptoms of inflammation [23], [25], [26]. Histopathological changes associated with doxorubicin administration in tissue such as edema, congestion, extravasation and myofibers disorientation are significantly reduced in the doxorubicin/*Panax ginseng* group.

Conclusion

Panax ginseng reduces doxorubicin-induced cardiotoxicity in experimental rats by inhibiting oxidative stress, inflammatory and apoptotic pathways. Future research on *Panax ginseng* and its effect on caspase-3 may be required to determine, whether it increases the anti-cancer effect.

Acknowledgment

Ethical approvals: Approval to research on experimental animals was obtained by the Iraqi Medical Research center, Baghdad, Iraq.

Approval number: 11789\7\2018

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