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Oxidative stress and histopathological evaluation of ethyl acetate propolis extract in doxorubicin induced cardiotoxicity

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ABSTRACT

Cardiovascular diseases have high incidence and are leading to cause high morbidity and mortality worldwide. Doxorubicin (DOX), a potent broad-spectrum chemotherapeutic anthracycline agent, it is largely limited due to its serious side effects on non-target organs. Propolis also Known as bee glue is complex phytocompound, resinous, sticky, balsamic, gum gathering by worker bees from the leaf buds of trees. Its have different pharmacological action including antioxidant. Through maceration method for 7 days in ethanol then 7 days in absolute ethyl acetate, flavonoidal propolis extract was obtained. fifteen albino Rats were divided in to three equal groups: Control rats that received BPS for 10 days, DOX-treated rats that received a single I.P injection of DOX (25 mg/kg BW) on day 7 from beginning of experiment. Rats received propolis extract orally for 10 consecutive days and single dose of doxorubicin (25 mg/kg BW IP) on day 7 from beginning of experiment. The hearts were excised for oxidative stress markers analysis as well as for microscopic examination. The administration of DOX in single dose showed high lipid peroxidation (MDA). The activities of catalase , glutathione-S-transverase (GST) and superoxide dismutase (SOD) were decrease significantly than in the negative group. Treatment with propolis extract shown ameliorated the DOX-induced cardiac tissue damage by decline the MDA and Significant improvements in the enzymatic status Catalase, GST, and SOD. Histopathological findings of heart also support the biochemical outcomes and revealed the anti-toxic effects of propolis extract in contrast to DOX on the cardiac tissue. The experiment parts endorsed conclusion that propolis extract may exhibit remarkable protective effect in DOX-induced cardiac toxicity through improve a number of cardiac biomarkers linked with cardiac toxicity, and may be represent a potential agents for attenuation and prevention of the serious complications accompanied with DOX in clinical practice.

Keywords: *ethyl acetate propolis, oxidative stress, doxorubicin, cardiotoxicity*

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INTRODUCTION

Cardiotoxicity is a frequent undesirable phenomenon observed during oncological treatment that limits the therapeutic dose of antitumor drugs and thus may decrease the effectiveness of cancer eradication and almost all antitumor drugs exhibit toxic properties towards cardiac muscle [1]. It is a fatal side-effect of the anthracyclines and other medications, which often limits their clinical use for disease therapy [2]. Although there is no universally accepted definition of cardiotoxicity, it has been defined as a decline of more than 10% in the left ventricular ejection fraction (LVEF) to a final value of 55% in asymptomatic subjects or a decline of at least 5% in LVEF to a final value of 55% in symptomatic patients [3]. So the prevention of antitumor-induced cardiotoxicity may be helpful to improve future medications therapy [4].

Propolis also known as bee glue is plant origin bee product has been used in the traditional medicine by humans for centuries for treatment of the different conditions disorders through alleviate many ailments including chronic, nutrition-related, and metabolic syndrome-related diseases [5]. Every year, several scientific studies are published in various international journals, and numerous research teams have concentrated their efforts on the chemical constituents and biological activities of propolis [6]. Phytochemical analysis is critical for identifying bioactive molecules that may lead to medication development and discovery [7].

Under the light of these facts, The primary goal of this study will depend on the use of natural substance as the active moiety for the intention of protection the heart from the harmful effects of doxorubicin *invivo*. For this purpose, ethyl acetate propolis extract will be prepare to evaluate cardioprotective role in rats model.

MATERIAL AND METHODS

Propolis preparation and extraction

crude propolis sample wascollected between October-December of 2021 directly from bee keepers located in the Al-Diwaniya province, and cleaned manually from any undesirable materials. The extraction process was done according to the method reported by [8] with slight modifications. The propolis was prepared in small pieces and then grinded to the powder by an electrical grinder, 50 grams of the powdered was mixed with 500 ml of 80% ethanol solution 1:10 w/v in an amber glass container. The mixture was remained for 7 days at room temperature and manually stirred 10 minutes once a day then filtered by Whatman filter paper No. 1. to remove insoluble constituents, The final filtrate was evaporated off using a rotary evaporator under reduced pressure at 60 °C. to remove the residual ethanol content within the filtrate. The final step led to represent the balsam of propolis and is referred to as ethanolic extract of propolis (EEPs). In order to obtain a larger amount of flavonoids compounds in extract a part of the ethanolic dry extracts (EEPs) were subsequently suspended in 500 mL of ethyl acetate and kept at room temperature for 7 days and manually stirred once a day. The suspension was then filtered through a Whatman No. 1 paper, the solvent was subsequently evaporated to dryness to obtain the ethyl acetate propolis extract (EAPE).

Experimental rats

A total of 15 healthy adult male wistar rats with initial body weights of 200-210 gm. were obtained from the animal house of the Veterinary Medicine College / Al-Qadisiyah University. The ages of rats used in this study ranged between 10 - 12 weeks, The animals were housed under standard laboratory conditions with a 12 h light dark cycle at a 24±3˚C, 40–60% relative air humidity and food and water provided *ad libitum.*

Cardiotoxicity induction

Cardiotoxicity was induced in male rats on day 7 from beginning of experiment by using single dose of doxorubicin at 25 mg/kg BW Intraperitonially [9]**.**

Animal grouping and treatment.

Male rats were randomly divided into three equal groups; each one comprised of five male rats. Cardiotoxicity was induced as mention in the previous paragraph. The rats received respective treatments daily for 10 days. The dosed amounts were administered orally in a 2 ml oral gavage.

Negative control group:(NC) rats' treatment by vehicle (PBS) which are used for preparation of selected drug (n= 5 rats)

Doxorubicin group: (DOX) Receive single dose of doxorubicin (25 mg/kg BW IP) on day 7 from beginning of experiment (n= 5 rats)

Propolis extract treated group: (PEE) Receive propolis extract orally for 10 consecutive days and single dose of doxorubicin (25 mg/kg BW IP) on day 7 from beginning of experiment (n= 5 rats)

Rat scarification and samples collection.

At the end of the study, the rats were fasted for overnight but were allowed free access to water. The whole heart was isolated immediately after sacrificing the animal and washed with normal saline, rinsed, and weighted then a part of the heart was fixed in 10% paraformaldehyde. The other part of the heart was used for the analysis of oxidative stress biomarkers.

Heart homogenates.

The heart specimen was minced and squeezed to homogenized 1/10: w/v in a glass homogenizer by using phosphate-buffered saline at 4°C the homogenized was filtered by 4 layers of gauze residual tissue and non-homogenized blood vessels. The homogenate was centrifuged at 12000× g for 20 minutes at 4°C., The supernatant was separated and stored at -20 °C to be used for estimation of the oxidative stress markers **(10).**

Determination oxidative stress markers.

Assessment MDA concentration.

Heart tissue MDA concentration (nmol/mg protein) was measured colorimetrically using TCA and TBA kit. MDA react with thiobarbituric acid forming a pink color compound could be absorbed strongly at 532 nm **(11)**

Assessment catalase activity

Heart tissue catalase (K/mg) activity was measured colorimetrically through measurement of the degradation rate H2O2, and expressed as units of H2O2 consumed /min/mg protein **(12)**

Assessment of GST level.

Heart tissue Glutathione S-transferase (GST) activity was measured. The absorbance of the reduced chromogen is measured at 340 nm and this directly proportional to the GSH concentration **(13)**

Assessment of SOD level.

Heart tissue Superoxide diamutase (SOD) activity was measured colorimetrically through **(14)**

Histopathological analysis

After 24 hours of fixation of heart tissues in 10% formalin solution, tissue samples were dehydrated subsequently in graded alcohol include 50% ethanol for 48 hours, in 70% ethanol for 48 hours, in 90% ethanol for 24 hours, and in 100% ethanol for 24 hours. -thereafter, heart tissues were kept in xylene till the tissues become transparent. Later, tissues were embedded in paraffin wax to prepare the block by using embedding rings, and tissue blocks were kept at −18°C for 24 hours. -then, histological sections of 4 µm thicknesses were taken by using a rotary microtome. -the sectioned tissues were kept in water bath for fixing in lysine coated slides. -thereafter, slides fixed with tissues were dried in a hot plate, and following that, staining was performed using Hematoxylin and Eosin (H & E) for microscopic observations. All the pathological findings were verified by a pathologist [9].

Statistical analysis

Statistical evaluations were performed using One-way ANOVA test was used to find the differences between groups followed by least significant difference (LSD) multiple comparisons post hoc. Values of $P < 0.05$ were considered significant. All values are expressed as mean ±standard error. All statistical analysis were performed using SPSS program version 31 [15].

RESULTS

Oxidative stress biomarkers

As illustrated in the Table 1 the our results displayed remarkable oxidative stress associated with the doxorubicin administration rats and remarkable alteration during treatment and shown through significant ($p<0.05$) elevation MDA levels 0.782±0.06 nmol/mg protein, accompanied with a significant ($p<0.05$) reduction for each of catalase activity 0.621±0.062 K/mg protein, and GST activity 9.06±0.52 nmol/mg protein and SOD 12.34±0.62 u/mg protein in the heart tissue as compared with the negative control rats 0.438±0.08 nmol/mg protein, 1.210±0.041 K/mg protein, 14.22±0.18 nmol/mg protein,18.46±0.98 u/mg protein respectively. However, the propolis extract treated group rats showed a significant ($p<0.05$) reduction in the MAD levels and significant ($p<0.05$) elevation in each of catalase, GST and SOD activity as compared with DOX group rats.

Table 1 Effect of PEE on oxidative parameters in DOX-treated rats

Groups	symbol	MDA (nmol/mg protein)	Catalase (K/mg protein)	GST (u/mg protein)	SOD (u/mg protein)
Negative control(G1)	NC	$0.438±0.08^{C}$	$1.210±0.041^{A}$	$14.22±0.18^{A}$	$18.46±0.98^{A}$
Doxorubicin (G2)	DOX	$0.782±0.06^{A}$	$0.621±0.062^{C}$	$9.06±0.52^{C}$	$12.34±0.62^{C}$
propolis ethyl acetate extract (G4)	PEAE	$0.618±0.016^{B}$	$0.917±0.066^{B}$	$13.02±0.23^{B}$	$14.13±0.56^{B}$
LSD (P<0.05)		**0.061**	**0.036**	**0.48**	**1.21**

Data presented as mean ± SEM. The different superscript letters denoted to significant differences $p<0.05$, n=5, PEE: Propolis ethanolic extract, FPL:Propolis flavonoids liposome

Histopathological changes

The histology of the heart tissue from the Group (1) rats showed normal morphological appearance figure (1) whereas in dox group, disorganization of muscle fibers and necrosis of several cardiac muscle cells, accumulation of muscle cells, presence of extravasated RBCs disruption and vacuolization of the cytoplasm, enlarged swollen mitochondria, and few inflammatory cells were observed figure (2). The Photomicrograph of heart tissue from group 3 showed normal architectures with slight interfibrillar congestion, mild edema, and hydropic degeneration of single cell figure (3)

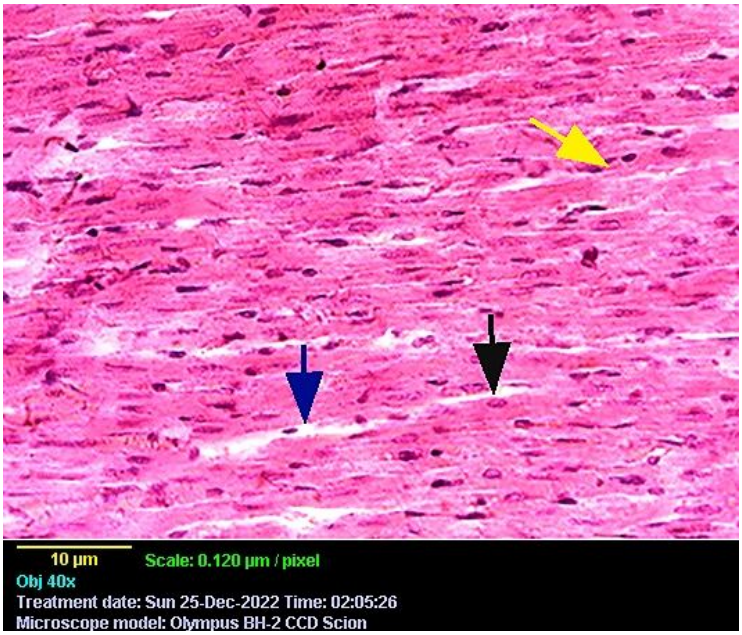

Figure 1 Negative control. Photomicrograph of heart showing normal Purkinje fibers between muscle cells (Blue arrow), single central nucleus for each cell (black arrow), and branching cardiac muscle cells (yellow arrow). H&E stain, 400X.

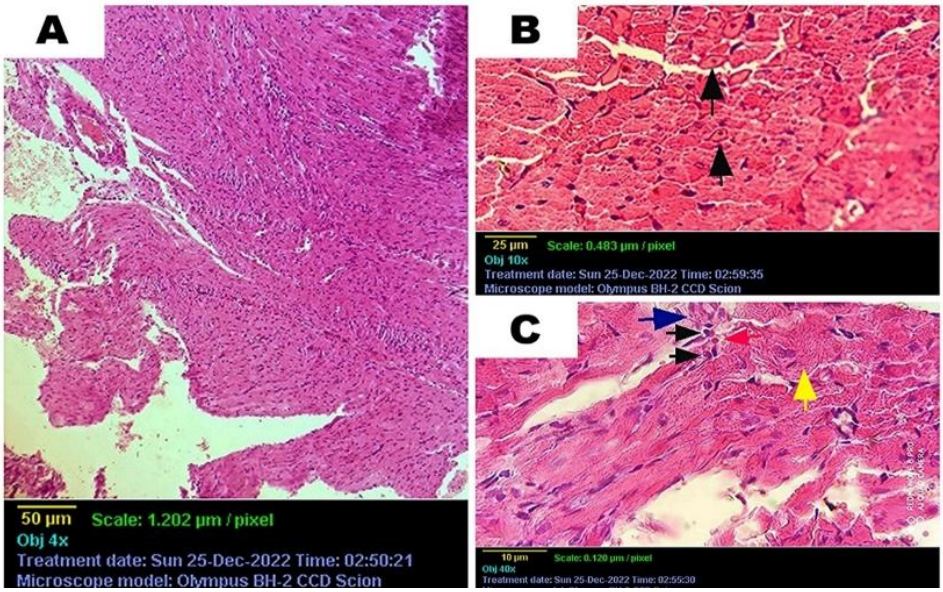

Figure 2 Dox. Group. Photomicrograph of heart showing (A) disorganization of muscle fibers and necrosis of several cardiac muscle cells (Black arrows). H&E stain, 40X. (B) disorganization of cardiac muscle and necrosis of several cardiac muscle cells (black arrows). H&E stain, 100X. (C) disorganization of cardiac muscle (yellow arrow), accumulation of some muscle cells (blue arrow), presence of extravasated RBCs (red arrow), and infiltration of few inflammatory cells (black arrows). H&E stain, 400X

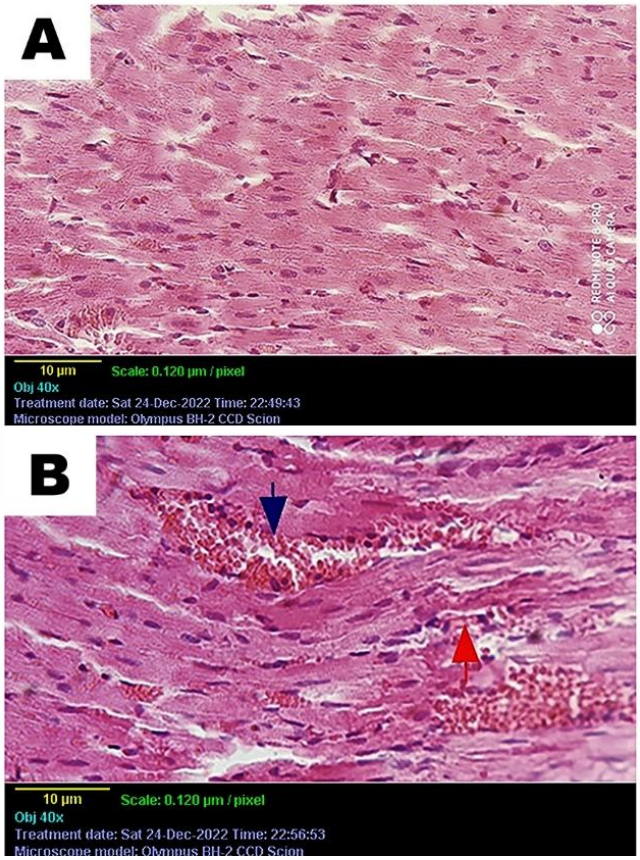

Figure 4 propolis extract group Photomicrograph of heart showing (A)- normal architectures. (B)- Photomicrograph of heart showing interfibrillar congestion (blue arrow), mild edema, and hydropic degeneration of single cell (red arrow). H and E stain, 400X.

DISCUSSION

The resulted cardiomyopathy associated with oxidative stress which observed markedly through significant alterations in the in lipid peroxidation markers (MDA), antioxidant enzymes activities (Catalase, GST, SOD) in heart homogenate which are use as clear indicators of tissue injury and oxidative stress in the heart tissue [16]**.** This was further confirmed by the histopathological changes in the heart as illustrated in the photomicrographs in figures 4 to 5. In fact, the heart is considered the main organ for DOX-induced oxidative stress due to the lower levels of antioxidant enzymatic defenses in the cardiac muscle, compared to other organs [17]**.** These results were in accordance with previous findings of direct toxic effects induced by DOX on rats myocardial tissue [18-20]**.** DOX is believed to be induced cardiomyoinjury through endogenous antioxidant deficiencies and increased lipid peroxidation [21]**.** In the cardic tissue, Its converted into its semiquinone form, which is a toxic, short-lived metabolite that can interacts with molecular oxygen initiating a cascade of reaction leading to ROS generation [22]. Studies have reported that the acute cardiotoxicity caused by DOX is observed within 2-3 days of its single-dose administration related with excessive production of free radicals induced lipid peroxidation that ultimately caused injury to the membrane intergrity [9]**.** In the present model, exposure to DOX drug led to reduced antioxidant enzyme (SOD) activity and endogenous antioxidant (GST) content, which suggests that the intracellular antioxidant defense system was damaged. The well-known cardiotoxic effects are primarily attributed to overproduction of free radicals at high DOX doses [17]**.** Many scientific reports demonstrated that Several hazardous effects, including lipid peroxidation, oxidative stress, DNA/RNA damage, inhibition of autophagy, endoplasmic reticulum-mediated apoptosis and disturbance of calcium homeostasis have been associated with DOX-induced cardiotoxicity [22]**.**

The alterations in the antioxidant enzymes and components outcome confirms the cardiotoxicity induced by DOX in rats that is supported by histopathological changes observed in heart tissues of experimental animals. DOX induced these biochemical, histopathological changes that were brought back to close to normal in both rats groups propolis extract. The significant ($P<0.05$) alteration in tissue oxidative defense in DOX treatment group correlates with the previous reports which suggest that DOX-induced oxidative stress can lead to lipid peroxidation that is accompanied by the release of vital cardiac indicators into

serum [23, 24]. In the same time, We also found that DOX administration lead to increase in MDA and decrease in GST levels. These outcomes were in agreement with the previous works [16]. Shaker *et al*. stated that DOX induces oxidative damage to heart tissue that results in lipid peroxidation with the concomitant production of MDA and reduction of GSH content [25].

Propolis and its components, especially flavonoids as quercetin and kampeferol, are known to have powerful anti-apoptotic, anti-oxidative, and anti-inflammatory properties in many tissues, including the heart and capable of scavenging free radicals and thereby protecting the cell membrane against lipid peroxidation [26]. The present study demonstrated that ethyl acetate propolis extract markedly minimized the cardiomyotoxicity induced by high dose DOX administration. Pretreatment with propolis extract ameliorated the DOX-induced cardiac injury via decrease histopathological damage, such as hemorrhage, inflammation and necrosis of the cardiac muscle induced by DOX were also attenuated by propolis. However, the mechanism underlying the effects of propolis is not completely clear, The protective effects of propolis pre-treatment could be due to increase in the antioxidant enzyme activities result in suppression of the oxidative stress damage of DOX in cardiomyocytes [27]. Several naturally occurring antioxidants as propolis, butterfield, spinach, arabic gum and proanthocyanidin have demonstrated protective roles against doxorubicin (Doxo) cardiotoxicity [28]. *In vitro* studies indicated that kaempferol, one component of the propolis extract, may have action by suppressing the DOX-activated p53 signaling and ERK-dependent MAPK pathways [29]. Additionally, one of its major propolis components is caffeic acid phenethyl ester (CAPE) which is able to block ROS production in several systems [30].

Some studies have justified cardioprotective activity for both propolis and its components *in vitro* and *in vivo* model [31]. Caffeic acid phenethyl ester, an active component of propolis purified from honeybee hives has been recorded to exhibits antioxidant and anti-inflammatory properties in various oxidant conditions that cause tissue injury [32, 33]. In other works, CAPE treatment caused a decrease in lipid peroxidation in spinal cord and brain ischaemia–reperfusion injury [34]. The observed improvement in the lipid peroxidation in the heart tissue of rats following propolis dosing indicated to had free radical scavenging capacity which helps to prevent cellular damage and thereby reduce lipid peroxidation. These nutraceutical products might presumably behave capably to re-activation of the antioxidant enzymes via its active components that enhanced the removal of ROS thereby restricting its oxidative injury in the affected Fadillioglu tissue [35]. These results may be because propolis has diverse pharmacological activities amongst them antioxidant [36].

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