The Potential Protective Effects of Avocado peels Against Doxorubicin toxicity in Experimental Rats

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Abstract:

The current study evaluated the potential protective effects of bioactive compounds in avocado peels against doxorubicin toxicity in rats. Twenty four male rats divided into two main groups, The first group (6 rats) fed basal diet and served as negative control. The second group (18 rats) received doxorubicin (15 mg/kg i.p.) on the 28th day to induce toxicity. The second group was divided into 3 subgroups as following: Group (1) fed basal diet only (and served as a positive control), Group (2) fed on basal diet + 2.5% of dried avocado peels, Group (3) fed on basal diet + 5% of dried avocado peels. At the end of the experiment, the nutritional and biological parameters including body weight gain (BWG) and feed intake (FI) were estimated. blood samples were taken, heart tissue was collected and weighted. Serum was separated to biochemical analysis. Tissue lipid peroxidation and activity of antioxidant enzymes in heart were also performed. Heart functions and lipid profile were determined in serum. The obtained results revealed that doxorubicin caused a significant elevation ($p<0.05$) in malondialdehyde (MDA), creatine kinase-myocardial bound (CK-MB), creatine phosphokinase (CPK), Troponin (CTNI)

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and lactate dehydrogenase (LDH), whereas reduced the biological parameters and antioxidants such as superoxide dismutase (SOD), catalase (CAT) and glutathione Peroxidase (GPx) levels. On the other hand administration of avocado peels improved heart functions and levels of cardiac antioxidant enzymes. Furthermore, histopathological examination of heart tissue confirmed these findings. In conclusion, Avocado peels can be used as a potent preventive agent against doxorubicin toxicity in rats.
Key words: heart functions _ Serum Lipids – phenolic compounds – Lipid peroxidation _ antioxidants

INTRODUCTION

Cardiovascular diseases (CVD) are the globally leading cause of morbidity and mortality; many people die each year due to CVD than for any other reason. In 2019, about 523 million prevalent cases of total CVD and nearly 18.6 million people died of CVD, this constitutes more than 30% of all deaths worldwide. These deaths predominantly occur in low- and middle-income regions. Globally, the total number of deaths due to Ischemic heart disease (IHD) was 9.14 million and 197 million prevalent cases of IHD. while, the total number of deaths due to stroke was 6.55 million and 101 million prevalent cases of stroke in 2019 (Roth *et al.*, 2020).

Doxorubicin-(Dox) (trade name Adriamycin) is an anthracycline derivative, clinically used for treatment of a variety of cancerous growth, such as breast cancer, lung cancer, and acute leukemias (Pugazhendhi *et al.*, 2018). Cardiotoxicity is the severe adverse effect associated with its use. Dox-induced cardiac toxicity is a multifactorial process that includes oxidative stress, thereby stimulating lipid peroxidation (Vallejo *et al.*,

2017), iron metabolism, inflammation, endoplasmic reticulum (ER) stress, mitochondrial permeability transition, loss of mitochondrial integrity, and function which is essential for Ca homeostasis and signaling, as well as activation of the reninangiotensin system (Yu *et al.,* 2018).

Avocado (*Persea americana Mill*.) is the most commonly sold fruits in the world Avocado comprises one to two times more protein than any other fruits. It has a higher content of iron, phosphorous, manganese and potassium, while it is low in sodium . It is an excellent source of monounsaturated fat and is a good source of linoleic acid (Bergh., 1992). Avocado is loaded with nutrients such as vitamins E, C, thiamin, riboflavin, nicotinic acid and folate as well as β–carotene (Rainey *et al.*, 1994).It contains several structural polysaccharides, including cellulose and lignin (insoluble fiber), hemicelluloses and pectin (Sanchez-Castillo *et al.,* 1995). The high content of potassium and lutein in the avocado may improve the blood pressure (BP) values by controlling oxidative stress and inflammation. Also diets rich in monounsaturated fatty acids (MUFA) may improve systolic and diastolic BP levels when compared to diets with low content of MUFA(Schwingshack *et al.,* 2011).

Recently, fruit by-product has become one of the main sources of municipal solid by-products, which have been an increasingly tough environmental issue. One of the solutions to this problem was directed to use fruit by-products as a source of valuable compounds; the bioactive constituents and using them in the food, pharmaceutical, as well as cosmetics industry. Thus, their utilization might be of considerable economic benefits and has become increasingly attractive (Deng *et al.,* 2012). The byproducts of fruits and vegetables used to make up of peels and seeds of different shapes and sizes that normally have no

further usage and commonly wasted or discarded (Varzakas *et al.,* 2016).

Avocado peels contain high levels of bioactive phytochemicals such as condensed tannins, phenolic acids, and flavonoids, including flavonols, procyanidins, hydroxycinnamic acids and hydroxybenzoic acids that can perform many biological functions, such as anti-inflammatory properties and antioxidant (Figueroa *et al.,* 2018). Therefore, the current study aimed to investigate the potential protective effects of avocado peels against doxorubicin toxicity in rats.

MATERIAL AND METHODS

Plant material, drug, chemical and biochemical kits:

-Avocados were obtained from Carrefour local market, in Tanta, Egypt.

-Corn oil and starch were purchased from Carrefour local market. Casein, cellulose, vitamins, minerals, dextrin, L-cysteine and choline chloride were obtained from El-Gomhoriya Company for Trading Drugs, Chemicals and Medicals Instruments, Cairo, Egypt.

-Doxorubicin was purchased from Sigma Chemical Company, Cairo, Egypt .

- Twenty four *Sprague Dawley* male albino rats, weight 150± 10g, were purchased from the Laboratory Animal Colony, Helwan, Cairo, Egypt.

-Kits were purchased from Egyptian American Company for Laboratory Service and Supplied by Alkan Company, Cairo, Egypt.

Methods:

Preparation of the raw materials

Avocado fruits were washed individually with tap water; the various parts of the fruit were detached by a manual process to

peel, pulp and seeds (Mohamed and Amr, 2013). The peels were cut into slices and dipped in 0.5% (W/V) citric acid solution for 10 min (Alkarkhi *et al.,* 2011), drained avocado peels were divided into two parts. The first part was steamed for 5 min, the second part was blanched for 3 min. Then the peels were dried in (contherm thermotec 2000) oven at 50°C and 60°C for 12 and 9 hour respectively, to reduce enzymic browning. The dried peel slices were ground in a Retsch Mill Laboratory to pass through 40 mesh screen to obtain avocado peel powder. Then powder stored in plastic packs in cold storage (5 c^o) for further analyses.

Chemical composition of avocado peel

Moisture, protein, fat, crude fibers, ash of avocado peels were determined according to the methods of the A.O.A.C., (2010). Total carbohydrates were calculated as following: Carbohydrates % = 100 - (moisture % + protein % + fat % + ash %).

Fractionation and identification of phenolic compounds

Phenolic compounds were fractionated and identified by HPLC according to the method of Goupy *et al.,* (1999). Five g of sample were mixed with methanol and centrifuged at 10.000 rpm for 10 min under cooling temp. The supernatant was filtered through a 0.2 µm Millipore membrane filter, then 1-3 ml was collected in a vial for injection into Agilent 1260 infinity HPLC series (Agilent, USA) equipped with Quaternary pump, akinetex®5µm EVO c18 100 x 4.6 mm (Phenomenex, USA),operated at 30°C. The separation was achieved using a ternary linear elution gradient with (A) HPLC grade water 0.2 % H_3PO_4 (v/v), (B) methanol and (C) acetonitrile as a mobil phase at flow rate 1 ml/min. Phenolic acids standard from Sigma Co. were dissolved in a mobile phase and injected into HPLC. Injected volume was 20µl. Detection: VWD detector

set at 284 nm. Retention time and peak area were used to calculation of phenolic compounds concentration by the data analysis of Agilent software program.

Experimental design

The animals were acclimatized for one week, fed basal diet according to Reeves *et al.,* (1993) and water supply *ad libitum*. Then rats were divided into two main groups: The first group (6 rats) fed on basal diet and served as negative control. The second group (18 rats) received Dox (15 mg/kg i.p.) according to Tao *et al.*, (2019) on the 28th day to induce toxicity. The second group were divided into 3 subgroups as follows: Group (1) fed on basal diet only (and served as positive control). Group (2) basal diet + 2.5% of dried avocado peels. Group (3) basal diet + 5% of dried avocado peels. The body weight gain (BWG%) and feed intake were determined according to Chapman *et al.*, (1959) . At the end of experiment 28 days, the animals were deprived of food and water overnight before being sacrificed. Blood samples were collected in dry centrifuge tubs from hepatic portal veins. Serum samples were separated by centrifugation at 3000 rpm for 10 minutes and kept in plastic vial at -20°C till analysis. Heart tissues were removed, washed with isotonic saline, dried by filter paper and weighted. Two samples of heart were taken. The first sample was kept in formalin saline 10% for histopathological examination. The second sample of heart was kept at -20°C for preparation of tissue homogenate for determination of antioxidant parameters.

Homogenization of heart tissue

A portion of each heart sample was added to ice-cold 0.1 M Trise_HCl buffer (pH 7.5) containing 1 mM of the phenylmethylsulfonyl fluoride protease inhibitor, respectively. Samples were then homogenized using a mechanical homogenizer (Ul-

tra Turrax T25 Basic; IKA, Wilmington, NC) at 16.000 rpm for 2 min at 4°C. The resultant homogenates were then used to measure MDA and GSH levels and SOD and CAT activities.

Assessment of oxidant/antioxidant activity in heart tissue

The thiobarbituric acid substrate assay was used to measure MDA (nmol/g wet tissue) with a spectrophotometer Elisa (micro plate reader Ryto2100 C) at (520 and 535 nm)(Uchiyama and Mihara, 1978). Ellman method was used to measure reduced GSH (nmol/g wet tissue) with a spectrophotometer (Ellman., 1959). The XO assay was used to estimate SOD activity (U/mg protein) by measuring the amount of reduced nitroblue tetrazolium, with one unit of SOD defined as the amount of protein that inhibits the rate of nitroblue tetrazolium reduction by 50% (Sun *et al.*, 1988). Aei method was used to measure CAT activity by spectrophotometric (at 240 nm) determination of the rate constant k (dimension: s-1) of H2O2 (initial concentration 10 mM) at 240 nm, and the measured activity was reported as the constant rate (k) per gram (U/g) of protein (Casado *et al.*, 2001).

Biochemical analysis of serum

Serum samples were used for the determination of lactate dehydrogenase (LDH), creatine phosphokinase (CPK) and creatine kinase-myocardial bound (CK-MB), measured using automated biochemistry analyzer (SPIN120-Spinreact-benchtop 8 wave lengths: 340 and 670 nm). The levels of serum total lipids, total cholesterol and triglycerides were determined according to (knight *et al.*, 1972; Allain *et al.*, 1974 and Fossati and Prencipe, 1982) respectively . High, low and very low density lipoprotein- cholesterol in serum was determined according to Lopes-Virella *et al., (*1977) and Henriksen *et al.*, (1981).

Histopathological study

Heart samples were executed, instantly after removing from the body, put in a fixative (10% formalin neutral buffered solution) and enclosed in a 5 m thick sectioned paraffin. Subsequently, the pieces were treated with Mayers' hematoxylin and eosin. For microscopic examination, The stained samples were studied under a10× magnification light microscope. The slides have been captured and recorded (Bancroft *et al.,* 1996).

Statistical analysis

Results were expressed as mean ± standard deviation (SD). Differences between means indifferent groups were tested for significance using a one-way analysis of variance (ANOVA) followed by Duncan's test and P value of 0.05 or less was considered significant. Comparative of means were performed according to least significant differences test (LSD) according to Snedecor, (1969) using SPSS version20.

Results and Discussion

In Table (1) avocado peels were analyzed for the chemical composition (Protein, moisture, fat, carbohydrates, crude fiber and ash) per 100g on the dry weight basis. peels recorded the highest percent of moisture, carbohydrate and crude fiber 7.13, 33.62 and 17.24 respectively. These data agree with Rotta *et al.,* (2015) who found that avocado peels contain 12.21 g of total lipids, 21.62 g of crude protein and 19.21 g of ash per 100mg of avocado peels.

Table 1: Chemical composition of avocado peels (g/100g) on the dry weight basis

Compositions	Avocado Peels(g/100g)
Moisture	7.13 ± 0.01
Protein	8.97 ± 0.02
Carbohydrate	33.62 ± 0.03
Fat	19.61 ± 0.021
Crude Fiber	17.24 ± 0.025
Ash	13.43 ± 0.015

Values are means ± standard deviation of three determinations (n=3)

From Table (2) avocado peels were analyzed for the phenolic compounds content. Avocado Peels recorded a high content of total phenolic compounds (680.08 mg/100 g).The highest percent of compounds are P-Hydroxy benzoic, benzoic, Vanillic and O-coumaric acid contents (280.17,78.53,70.43 and 37.22 respectively). Our data are in agreement with Wang *et al.*, (2010) who found that total phenolic content of avocado peels is 1260 mg/100g on fresh weight basis as the peels lost 78% of weight on average as moisture after freeze drying. Calderón-Oliver *et al.*, (2016) found that avocado peels contain 10.96 mg of chlorogenic acid, 13.2 mg of epicatechin gallate and 28.4 mg of p-coumaroyl-D-glucose /100 g of avocado peel. Figueroa e*t al.*, (2018) showed that avocado peels contain 137.025 mg of hydroxybenzoic acid, 121.0298 mg of benzoic acid and 123.00 of vanillic acid. Rosero *et al.*, (2019) found that total polyphenolic content of avocado peels is 527.8 mg/100 g.

Table 2: Total phenolic compounds of avocado peels (mg/100 g) on the dry weight basis

Phenolic Compounds	Avocado Peels (mg/100 g)
Gallic acid	7.04
catechol	6.39
P-Hydroxy benzoic acid	280.17
Catechin	26.59
Chlorogenic	11.06
Vanillic acid	70.43
Caffeic acid	17.19
Syringic acid	6.81
P-coumaric acid	21.28
Benzoic acid	78.53
Ferulic acid	5.77
Rutin	25.42
Ellagic	_
O-coumaric acid	37.22
Resvertol	9.67
Cinnamic acid	7.61
Quercitin	37.17
rosemarinic	15.79
Myricetin	5.24
Kampherol	10.7
Total	680.08

Results in Table (3) show that there were a significant decreases ($p<0.05$) in feed intake (FI) , BWG and heart weight in a DOX group (+ve) when compared to normal control group (-ve). These results agree with (Herman *et al.,* 2000; Rašković *et al.,* 2011; Zordoky *et al.,* 2011; Zhao *et al.,* 2012 and Liu *et al.,* 2017) Who observed that Dox caused a marked reduction in feed intake and mean body weight. On the other hand treated groups with (Avocado Peels 2.5%& 5%), feed intake, BWG

and heart weight were significantly increased compared to DOX group (+ve). Reduced body weight gain may be attributed to the direct toxic effects of this chemotherapy (DOX) on the intestinal mucosa and the subsequent action on the gastrointestinal tract. This influence the appetite, eating behavior, consumption and assimilation of food as well as a deterioration in metabolism of glucose and fatty acids which leads to malnutrition. DOX usually causes symptoms such as diarrhea , nausea, vomiting , anorexia, sores in the mouth, myofibrillar loss, excessive bleeding and affect renal tubules, which resulted in decreased water reabsorption and excessive sodium excretion resulting in dehydration, polyuria and decreased body weight (Herman *et al.,* 2000; Carvalho *et al.,* 2009; Sánchez-Lara *et al.,* 2013 and Biondo *et al.,* 2016). also Chatterjee *et al.,* (2010) found that DOX caused a total or partial loss of myofibrils and degeneration in myocyte vacuolar With lack of myofilaments. The improvement in treated groups is due to that avocado peels contain high levels of bioactive phytochemicals such as condensed tannins, phenolic acids, and flavonoids, including flavonols, procyanidins, hydroxycinnamic acids and hydroxybenzoic acids that can perform many biological functions, such as anti-inflammatory properties and antioxidant which have a positive effects on health, reduce the risk of cancer and fight the toxicity caused by DOX without compromising its anti-tumor function (Figueroa *et al.,* 2018). Avocado peel is a great source of phytochemicals, particularly polyphenolic compounds including derivatives of hydroxycinnamic acid, proanthocyanidins and flavonoids (Kate *et al.,* 2009 and Rosero *et al.,* 2019) as well as having anticancer, antioxidant and antibacterial activities (Wang *et al.,* 2010; Araújo *et al.,* 2018; Vinha *et al.,* 2013; Antasionasti *et al.,* 2017 and Tremocoldi *et*

al., 2018) suggested that avocado peels can be a good alternative to the synthetic antioxidants.

Table 3: Effect of avocado peels on changes in feed intake (FI), body weight gain (BWG) and heart weight in rats with doxorubicin toxicity

Parameters Groups	FI(g/day)	BWG %	Heart weight (g)
(- Ve) Control	20.57 ± 0.12[a]	19.00 ± 0.23[a]	0.43 ± 0.10[a]
(+Ve)control group (dox)	14.00 ± 0.15[d]	10.45 ± 0.55[d]	0.37 ± 0.05[d]
Avocado Peels 2.5% + dox	15.50 ± 0.21[c]	12.00 ± 0.53[c]	0.38 ± 0.02[c]
Avocado Peels 5% + dox	15.87 ± 0.24[b]	12.50 ± 0.66[b]	0.39 ± 0.09[b]

Each value represents the mean ±SD. Means in the same column with different superscript letters were significant at $p \leq 0.05$

Data in Table (4) represent the concentrations of plasma creatine kinase-myocardial bound (CK-MB), creatine phosphokinase (CPK), troponin (CTNI) and lactate dehydrogenase (LDH) of the different experimental groups. A significant increases in the heart function, biochemical parameters in DOX treated group (+ve) compared to the normal group (-ve). But there is a significant decrease in the groups treated with avocado peels compared with those untreated. Venkatesan *et al.,* (1998) used curcumin against DOX and found a rising in heart function parameters. Also Kelishomi *et al.*, (2008) used mor-

phine as a potential protective agent against DOX-induced cardiotoxicity in rats, morphine and found that DOX caused an elevation in heart parameters. These findings can be attributed to infiltration of cardiac enzymes due to ventricular remodelling, continuous myocyte degradation and oxidative damage in myocardial tissue related to dox toxicity with eventual releasing its contents into the blood circulation (Keizer *et al.,* 1990; DeAtley *et al.,* 1999; Potluri *et al.,* 2004 and El-Sayed *et al.,* 2011).The improvement in heart biochemical parameters in avocado peel groups due to that avocado peels contains antioxidants such as polyphenols, tocopherols, carotenoids, vitamins E,C (Murcia *et al.,* 2001) that protect cells from the harmful impact of free radical. Since they're removing the hydrogen from the hydroxyl group into peroxyl radical, restrain lipid peroxidation by isolating the free radicals such as singlet oxygen (Schuler *et al.,* 1990; Kamal-Eldin *et al.,* 1996 and Fukuzawa *et al.,* 1998). Also they have an anti-inflammatory effects that prevent atherosclerosis and the thickening of the arteries linked to heart disease (Saldeen and Saldeen, 2005 and Dreher *et al.,* 2013).

Table 4: Effect of avocado peels on changes in the heart function, biochemical indices in rats with doxorubicin toxicity

Parameters Groups	CKMB(U/L)	CPK(U/L)	CTNI (Pg/ml)	LDH(U/L)
(-ve) Control	1392.50 ± 96.15d	443.00 ± 11.62d	0.09 ± 0.00d	443.50 ± 5.81d

(+ve) control group(dox)	3736.00 ± 78.71[a]	996.00 ± 10.73[a]	0.66 ± 0.02[a]	1777.00 ± 68.87[a]
Avocado Peels 2.5% + dox	2497.00 ± 14.31[b]	914.50 ± 10.28[b]	0.56 ± 0.03[b]	1595.50 ± 10.28[b]
Avocado peels 5% + dox	2390.50 ± 8.49[c]	792.50 ± 7.60[c]	0.44 ± 0.01[c]	1409.00 ± 27.72[c]

Each value represents the mean ±SD. Means in the same column with different superscript letters were significant at $p \leq 0.05$

From Table (5) data show that the serum levels of total lipids, total cholesterol (TC), triglycerides (TG), low and very low density lipoprotein-cholesterol (LDL-VLDL) were significantly elevated in DOX group (+ve) compared to (-ve) group, while the level of high density lipoprotein-cholesterol (HDL) was decreased in (+ve) group when compared with normal control. These results agree with the findings of (Afsar *et al.*, 2019 and Ragavendran *et al.*, 2012). Groups protected with avocado (peels 5%,2.5%) respectively gave a significant improve in the mean values compared with DOX group (+ve).These changes in lipid profile attributed to heart sickness in people who treated with DOX therapy. Hyperlipidemia tends to be the primary factor that contributes to DOX -induced heart failure

(Iliskovic *et al.*, 1997) or may be due to that DOX interferes with lipids metabolism and biosynthesis (Chennuru and Saleem, 2013).Our findings show that prior administration of avocado peels to rats resulted in marked reduction in total lipids, TC, TG, LDL,VLDL and increased HDL. Avocado contains dietary phytosterols (plant equivalent of cholesterol) which are anticholesterolemic agents as they inhibit the absorption of intestinal cholesterol as well as reduce the synthesis of hepatic cholesterol (Weihrauch and Gardner, 1978; Ikeda& Sugano, 1983; Moghadasian and Frohlich, 1999 and Duester, 2001). Avocado peel contains insoluble fiber (mainly cellulose) which may be more chemoprotective than soluble fiber (Sanchez-Castillo *et al.*, 1995 and Bidoli *et al.*, 2013). It also bind to toxins, micronutrients and bile acids converts them to inactive form, lowering the fecal toxicity(Cheah and Bernstein, 1990). It implicates in the emulsification and digestion of the dietary fats because of its amphipathic nature (Hofmann and Rods, 1984). It also changes the bacterial profile in gut and lowering serum cholesterol (Sloan *et al.*, 1993). It provides potential protection against CVD as well as metabolic syndrome by decreasing the concentration of serum lipid and glucose and reducing blood pressure, inflammation and oxidative stress (Lu *et al.*, 1998).Usually high fiber diet is high in the monounsaturated fatty acids which is associated with a reduction in atherosclerosis (Ferro-Luzzi and Branca, 1995).

Table 5: Effect of avocado peels on changes in total lipids, total cholesterol, triglycerides, high, low and very low density lipoprotein-cholesterol in rats with doxorubicin toxicity

Parameters Groups	T.C (mg/dl)	T.G (mg/dl)	HDL (mg/dl)	LDL (mg/dl)	VLDL (mg/

					dl)
(-ve) control	88.26 ± 3.70^{d}	63.45 ± 2.71^{d}	54.41 ± 0.56^{a}	22.95 ± 5.42^{d}	12.69 ± 0.54^{d}
(+ve) control group (dox)	223.46 ± 6.29^{a}	179.85 ± 1.38^{a}	42.00 ± 0.57^{d}	128.93 ± 7.20^{a}	32.83 ± 2.53^{a}
Avocado Peels 2.5% + dox	157.08 ± 3.03^{b}	139.00 ± 4.29^{b}	43.51 ± 0.40^{c}	84.38 ± 0.51^{b}	27.80 ± 0.85^{b}
Avocado Peels 5% +dox	139.88 ± 2.21^{c}	99.25 ± 0.67^{c}	43.90 ± 0.11^{b}	72.48 ± 1.60^{c}	19.85 ± 0.13^{c}

Each value represents the mean ±SD. Means in the same column with different superscript letters were significant at $p \leq 0.05$

From Table (6) as a result of administering DOX, there was a marked reduction in the levels of some antioxidants in the heart tissue, such as catalase (CAT), superoxide dismutase (SOD) and glutathione Peroxidase (GPX) in DOX treated group (+ve) as compared to the negative control group. Also, administration of DOX stimulated lipid peroxidation as estimated by a significant elevation in lipid peroxidation by-product malondialdehyde (MDA) (Akindele *et al.*, 2018). Avocado peels reduced the levels of MDA and stimulated antioxidant activity in heart tissue compared to (+ve) group. These findings attributed to that DOX induces the production of free radicals e.g reactive oxygen species (ROS) (Mukhopadhyay *et al.,* 2009),oxidative

stress and apoptosis in cardiomyocytes which ultimately leads to cardiotoxicity (Childs *et al.*, 2002 and Tsang *et al.*, 2003), (ROS) that induced by doxorubicin mainly superoxide and peroxynitrite (Mihm *et al.*, 2002 and Luanpitpong *et al.*, 2012) cause a hypertrophy in left ventricular and finally lead to heart failure (Scott *et al.*, 2011).Some evidence have reported that factors which scavenge ROS such as antioxidants including (glutathione, flavonoids and phenolics) (Michiels *et al.*, 1994), protect cardiac cells from dox-induced oxidative stress and apoptosis (Kalyanaraman *et al.*, 2002; Konorev *et al.*, 2002; Kim *et al.*, 2007; Tatlidede *et al.*, 2009 and Wang *et al.*, 2013). Avocado peels contains various bioactive phytochemicals for instance flavonoids, proanthocyanidins, phenolic acids and hydrocinnamic acids (Kosińska *et al.*, 2012) which have an antioxidant activity, this is because they scavenge oxidative free radicals and regulate oxidative stress (Murakami *et al.*, 2015). avocado raises the cardiac glutathione, because of its content of glutathione (Jones *et al.*, 1992).

Table 6: Effect of avocado peels on changes in Malondialdehyde and some antioxidants levels in the heart homogenate in rats with doxorubicin toxicity

Parameters GROUPS	SOD (U/mg)	MDA (nmol/mg)	CAT (ng/mg)	GPX (ng/mg)
(-ve) control	0.38 ± 0.00^{a}	0.09 ± 0.01^{d}	0.39 ± 0.01^{a}	0.41 ± 0.01^{a}
(+ve) control group (dox)	0.11 ± 0.00^{d}	0.39 ± 0.01^{a}	0.09 ± 0.00^{d}	0.11 ± 0.00^{d}
Avocado Peels 2.5% + dox	0.17 ± 0.00^{c}	0.24 ± 0.00^{b}	0.18 ± 0.01^{c}	0.19 ± 0.00^{c}

Avocado Peels 5% + dox	0.28 ± 0.01^{b}	0.13 ± 0.00^{c}	0.29 ± 0.01^{b}	0.30 ± 0.01^{b}

Each value represents the mean ±SD. Means in the same column with different superscript letters were significant at $p \leq 0.05$

Histopathological examination

Stained cardiac sections in Microscopic pictures of H&E showing normal arrangement of cardiomyocytes with normal blood vessels and interstitial tissue in control –ve group (A&B). Cardiac sections from control +ve group (C&D) showing disrupted arrangement of cardiomyocytes with congested blood vessels (red arrows), wide interstitial space due to interstitial edema (black arrows), focal hyalinization of cardiomyocytes (yellow arrows). Cardiac sections from group 3 (peel 5%) appears normal (I&J) as in control –ve group. Cardiac sections from group 6 (peel2.5%)(K&L) show interstitial edema (black arrows) and congested blood vessels (red arrows).These data agree with Elsadek., (2012) who reported that heart muscles in the doxorubicin group showed apparent oedema that was dispersed the hyalinized myocardial bundles. Abdelrahman *et al.*, (2019) found that inflammation, atrophy, and collagen deposition, characteristic for fibrosis in the heart tissue.

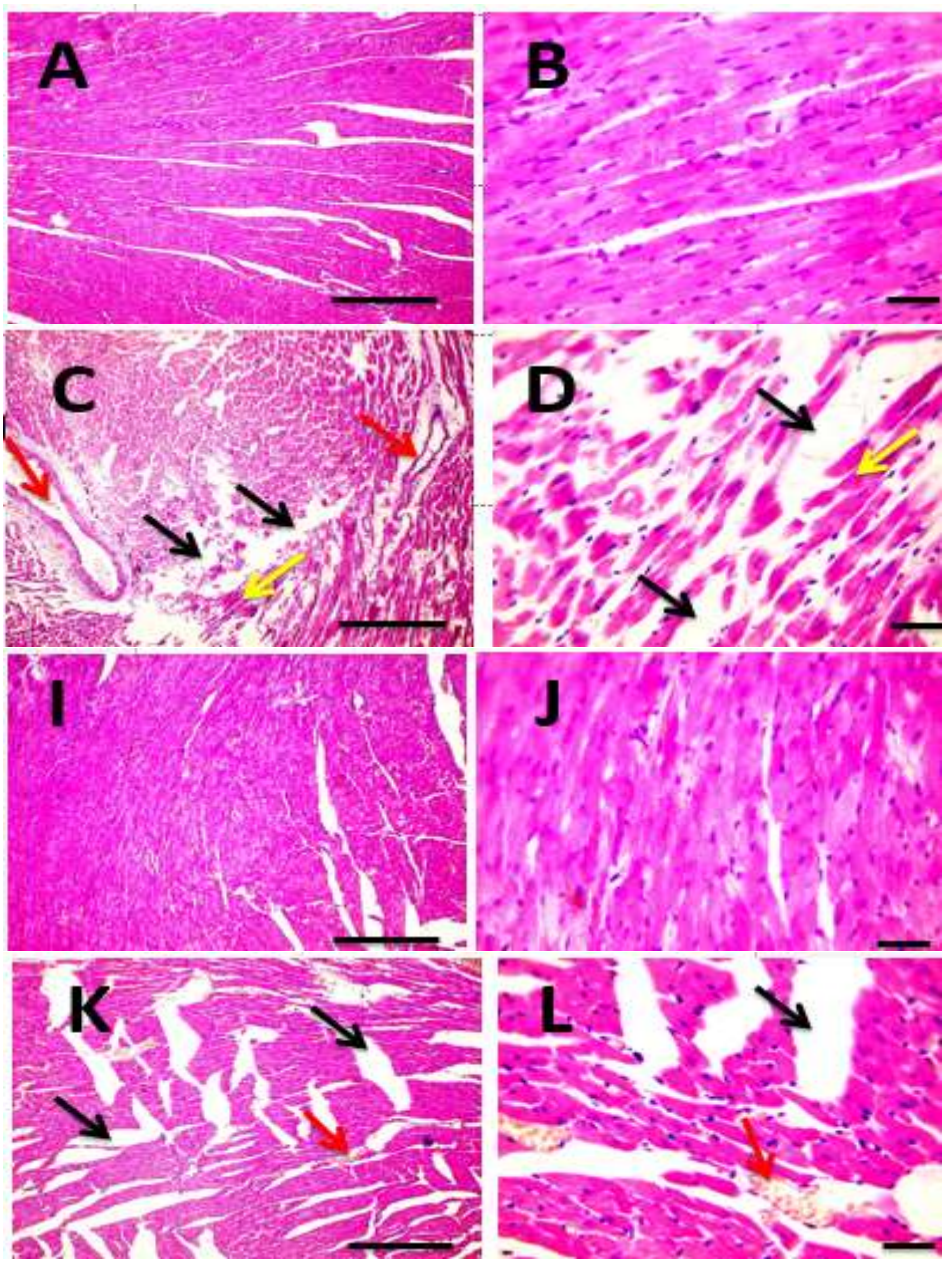

Fig (1): (A&B) Heart of rats from group 1 (- ve) control group showing normal arrangement of cardiomyocytes with normal

blood vessels and interstitial tissue. (C&D) Heart of rats from group 2 (+ ve) control group showing disrupted arrangement of cardiomyocytes with congested blood vessels (red arrows), wide interstitial space due to interstitial edema (black arrows), focal hyalinization of cardiomyocytes (yellow arrows). (I&J) Heart of rats from group 3 (peel5%) appears normal as in control (–ve) group. (K&L) Heart of rats from group 4 (peel 2.5%) showing interstitial edema (black arrows) and congested blood vessels (red arrows).

Conclusion

Feeding on avocado peels protected heart tissues from toxicity induced damage, improved heart functions and antioxidant activity. This confirmed the protective effects of avocado peels against doxorubicin toxicity in experimental rats due to its content of many bioactive phytochemical compounds including (phenloics and flavonids) and their anti-oxidant and anti-inflammatory activities. Therefore, patients who are prone to heart toxicity can use avocado peels to prevent injury.

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الملخص العربى

التأثيرات الوقائية المحتملة لقشور الأفوكادو ضد التسمم المحدث بالدوكسوروبيسين في فئران التجارب

أجريت الدراسة الحالية لتقييم التأثيرات الوقائية المحتملة للمركبات النشطة حيويا الموجودة في قشور الأفوكادو ضد التسمم الذي يحدثه الدوكسوروبيسين في الفئران. تم تقسيم (٢٤ فأر) إلى مجموعتين رئيسيتين: المجموعة الأولى (٦ فئران) تم تغذيتها على غذاء قياسي كمجموعة ضابطة سالبة. تلقت المجموعة الثانية (١٨ فأر) دوكسوروبيسين (١٥ مجم / كجم من وزن الجسم) في اليوم الثامن والعشرين لإحداث التسمم. تم تقسيم المجموعة الثانية إلى ثلاث مجموعات فرعية على النحو التالى: المجموعة (١): تم تغذيتها على غذاء قياسي فقط (كمجموعة ضابطة موجبة)، المجموعة (٢): تم تغذيتها على غذاء قياسي + ٢.٥٪ مطحون قشور الأفوكادو المجففة، المجموعة (٣): تم تغذيتها على غذاء قياسي + ٥٪ مطحون قشور الأفوكادو المجففة. تم تقدير العوامل الغذائية والبيولوجية بما في ذلك المأخوذ

الغذائي، والنسبة المئوية للزيادة في وزن الجسم، والوزن النسبي للقلب . وفي نهاية التجربة والتى استغرقت فترة ٢٨ يوم، تم أخذ أنسجة القلب لتقدير العوامل المؤكسدة ومضادات الأكسدة واجراء الفحص الهستوباثولوجي. كما تم تقدير وظائف القلب ودهون الدم. وكشفت النتائج أن استخدام الدكسوروبيسين تسبب في ارتفاع معنوي ($p<0.05$) في مستويات العوامل المؤكسدة (المالوندهيد) وكذلك مؤشرات وظائف القلب (كرياتنين كيناز،كرياتنين فسفوكيناز، التروبونين،لاكتات ديهيدروجينيز) بينما أدي الي انخفاض قيم العوامل البيولوجية والغذائية ومستويات مضادات الأكسدة (الكتاليز، سوبر اكسيد ديسموتيز، جلوتاثيون بيروكسيديز). ومن ناحية أخرى ، فإن تناول قشور الأفوكادو أحدث تحسن ملحوظ في وظائف القلب ومستويات إنزيمات القلب المضادة للأكسدة. كما أكد الفحص الهستوباثولوجي لأنسجة القلب هذه النتائج. لذا يمكن استخدام قشورالأفوكادو كعوامل وقائية فعالة ضد السمية التي يسببها الدوكسوروبيسين في الفئران.

الكلمات المفتاحية: وظائف القلب – دهون الدم – المركبات الفينولية – بيروكسيد الدهون – مضادات الأكسدة