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Pomegranate Molasses Ameliorates Some Pathophysiological Parameters of Cisplatin-Induced Oxidative Stress in Rats

Kochar I. Mahmood*, Shler A. Mahmood, and Zana J. Kareem*****

** School of Basic Education, University of Charmo*
***College of Medicine –university of Sulaimani*
****College of science –university of Sulaimani*

ABSTRACT

Pomegranate molasses (PM) is one of a main compound of the eastern diets, which is used for popular medicine treatment of various diseases. Most of these effects were attributed to its high phenolic antioxidant effects, but without much scientific investigations. For this reason, we have studied the effects of pomegranate molasses (PM) on cisplatin (CP)-induced oxidative stress in male albino rats. Thirty adult male rats, of about 300-320g body weight, were allocated into three groups; Control (n = 5) receiving standard rat chow and tap water *ad libitum*. For the model group, CP-induced oxidative stress, animals were injected (intraperitoneal) with CP (2 mg/kg BW/week). Whereas the third group, in addition to the CP, animals received PM (traditionally homemade) (0.5ml/kg BW/day) for eight weeks. Results showed that the concentrations of liver function enzymes (ALP, ALT, AST) and serum total bilirubin were significantly (*P<0.05*) improved by PM treatment after their significant elevation by CP- injection. On the other hand, the level of serum urea and uric acid decreased significantly (*P<0.05*) in PM treated rats in comparison to CP-injected group. Unexpectedly the serum creatinine concentration was not recovered by PM. Furthermore, pomegranate molasses statistically recovered the lipid profiles especially serum TAG, VLDL, HDL and LDL but not total cholesterol. In addition, concentration of serum MDA (a well-known marker of the degree of lipid peroxidation) was significantly(*P<0.05*) improved in PM supplemented group. In conclusion, this study supported the idea that the supplementation of pomegranates molasses, through its antioxidant activity, significantly ameliorates the oxidative stress in rats, providing a variety of health benefits.

Keywords: Pomegranate molasses, Cisplatin, Oxidative stress, antioxidant

I. INTRODUCTION

Pomegranate (*punica granatum* L.) is a deciduous tree distributed everywhere in the world. It has been used in various regions and folk or traditional medical systems as food supplement or medicine because of its enormous compounds with lots of activities and without the toxicity (Lansky and Newman 2007, Colombo, Sangiovanni et al. 2013). Nowadays, it is widely approved that the beneficial health effects of fruits and vegetables in the prevention of disease are due to the bioactive component they contain. The existence of a significant amount of bioactive compounds such as phenolic acids, flavonoids, and

tannins in pomegranate fruit assures them great nutritional value (Aviram, Dornfeld et al. 2000).
It is a rich source of polyphenols as anthocyanins, ellagitannins and other phenolic compounds that are confirmed to have antioxidant and antitumoral activities (Pérez-Vicente, Serrano et al. 2004)

Pomegranate juice has a significant ability to decrease oxidative stress by 40–80% and to increase the antioxidant activity (Aviram, Rosenblat et al. 1998, Aviram, Rosenblat et al. 2004).

Pomegranate molasse (PM) is a large compound of the eastern diets, yet limited research has performed on this product. It is a highly nutritive product due to it is more concentrated and high mineral content. Traditional methods are still used to produce PM. It is simply concentrated by boiling, without the addition of further sugar or other additives(Kaya and Sözer 2005). Typical processing requires cleaning, crushing, extraction, filtration, clarification and evaporation in the open container or under vacuum(Kaya and Sözer 2005, İncedayi, Tamer et al. 2010). Recent study indicated that high temperature does not alter the antioxidant activity of PM against ROS. On the other hand it seems that the high temperature helps polyphenols to be released from pomegranate fruit cell as there is no extraction with a solvent in the preparation of pomegranate molasses(Chalfoun-Mounayar, Nemr et al. 2012).
Cisplatin or cis-Diaminedichloroplatinum is (CP) an antineoplastic agent with vast therapeutic potential, especially against solid tumours, such as bladder, testicular, ovarian, brain etc. The major side effects of this anticancer drug are its nephrotoxicity and mielotoxicity(Luo, Tsuji et al. 2008).
Mode of action of CP is still not completely understood, but it is thought to depend on hydrolysis reactions that believed to be the active species inhibiting replication, transcription and other nuclear functions in addition, considerable evidence indicates that CP can kill cells through the induction of apoptosis (Takahara, Frederick et al. 1996, Gonzalez, Fuertes et al. 2001, Turchi 2006). The present study was performed to investigate the effects of oral administration of pomegranate molasses on some pathophysiological parameters in cisplatin-induced oxidative stress in male albino rats.

II. MATERIALS AND METHODS

Animals & Housing

Thirty adult male rats of about 300-320g body weight were acclimated for one week prior the experiment that was achieved in the animal house belonged to Biology Department / Faculty of Science and Science Education / University of Sulaimani. Animals

were housed in plastic cages bedded with wooden chips. During the experimental period, five animals were kept in each cage & Climate controlled conditions were maintained and temperature was set as (23±2). Regular 12-hours diurnal cycles were kept using an automated light-switching devise (Markova, Adamekova et al. 2004). The animals were *ad libitum* access to water and diet.

Experimental Design

The animals were randomly divided into three groups of five animals each placed into cages as follows:

Group 1: Control: Rats of this group (n = 5) were given standard rat chow and tap water *ad libitum*.

Group 2: Cisplatin(CP)- induced oxidative stress (Model): Intraperitoneal (i.p.) injection of CP (2 mg/kg BW/week) (Amate, Ishida et al. 1996, Gonzalez, Romay et al. 2005). CP obtained from Vitane pharmaceutical inc., USA.

Group 3: CP-induced oxidative stress(Model) + administration of Pomegranate Molasses(PM): Rats were treated with cisplatin (2 mg/kg BW/week.) intaperitoneally then administration of PM (traditionally homemade) 0.5ml/kg BW/day (for eight weeks) orally by gavage tube.

The production of molasses consisted of peeling the fruits, dispersing the grains and pressing them manually to have a juice. The juice is boiled for more than six hours in order to obtain a concentrated substance called "molasses."

At the end of the experiments, all rats were fasted overnight and then anesthetized with chloroform. Blood samples were taken by cardiac puncture into sample tubes and then the sera were separated by centrifugation at 3000 rpm for 15 min. then measuring the folowing parameters:

Biochemical Parameters measurement:

Some pathophysiological markers were determined related to liver functions (serum ALP, ALT (GPT), AST (GOT) and serum total bilirubin), serum glucose, some renal function parameters (serum urea, creatinine, uric acid, total protein, albumin and globulin) and lipid profile(Total cholesterol(TC), Triacylglycerol(TAG), VLDL (Triacylglycerol/5), HDL and LDL). Using standard kits for each tests all parameters were determined in the serum using Automatic biochemistry analyzer (KENZA 240 TX, BIOLABO; France). LDL cholesterol was determined by applying the Friedewald formula as follow: LDL-cholesterol (mg/dl) = Total cholesterol- (HDL+Triglyceride/5) (Sözmen, Kazaz et al. 1998). The level of serum Malondialdehyde (MDA) was determined spectrophotometrically with a TBA solution. In

brief to 150µl serum sample added the followings: 1ml trichloroacetic acid (TCA) 17.5 %, 1ml of 0.66 % thiobarbituric acid (TBA), mixed well by vortex, incubate it in boiling water for 15 minutes and then allowed to cool. Then add 1ml of 70 % TCA, & let the mixture to stand at room temperature for 20 minutes, centrifuged at 2000 rpm for 15 minutes and take out the supernatant for scanning spectrophotometrically (Weinstein, Chagnac et al. 2000). The concentration of MDA calculated as follow:

MDA (µmol/L) = Absorbance at 532 nm x D/ L x E_o
Where
L: light bath (1cm)
E_o: Extinction coefficient 1.56 x 10^5 $M^{-1}.Cm^{-1}$
D: Dilution factor = 1 ml Vol. used in ref./ 0.15 =6.7

Statistical Analysis

Analysis of data was performed by using SPSS (Version 18.0). Results are expressed as mean ± standard error (mean ± SE). Statistical differences were determined by Duncan's test for multiple comparisons after analysis of variance (ANOVA).

III. RESULTS

In current study, the rats with cisplatin-induced oxidative stress (model group) were associated with a significant (*P<0.05*) elevation in the levels of serum ALP (313.600 ± 15.015 IU/L), ALT (106.200 ± 4.893 IU/L), AST (212.200 ± 11.006 IU/L) and total bilirubin (0.4.4 ± 0.028 mg/dl), as well as serum glucose (206.200 ± 12.932 mg/dl), when compared with their levels in control group (205.200 ± 16.157 IU/L, 71.600 ± 5.784 IU/L, 131.800 ± 8.941 IU/L, 0.228 ± 0.019 mg/dl and 92.800 ± 5.877 mg/dl) respectively (Table 1).

When the injected rats treated by Pomegranate Molasses (PM), the serum level of each one of ALP, ALT, AST and total bilirubin (207.200 ± 21.497 IU/L, 67.200 ± 7.109 IU/L, 128.600 ± 13.239 IU/L and 0.174 ± 0.036 mg/dl respectively) were significantly(*P<0.05*) decreased in comparison with those of model group. In contrast, the administration of PM was failed to treat the elevated level of serum glucose (190.000 ± 20.890 mg/dl).

The level of serum urea (121.800 ± 6.733 mg/dl) creatinine (1.554 ± 0.194 mg/dl) and uric acid (3.980 ± 0277 mg/dl) were significantly (P<0.05) elevated in model group when compared with their control groups (27.380 ± 1.514 mg/dl, 0.730 ± 0.030 mg/dl, 1.820 ± 0.150 mg/dl respectively),While the induction of CP reveled no significant (*P<0.05*) alteration in the level of serum total protein(6.280 ± 0.208 g/dl), albumin(3.520 ±

0.073 g/dl) and globulin(2.620 ± 0.132 g/dl) in comparison with their level in control group(6.460 ± 0.068 g/dl, 3.560 ± 0.068 g/dl, 3.080 ± 0.132 g/dl respectively) (Table 2).
The administration of PM was returned the elevated levels of serum urea (85.700 ± 3.760 mg/dl) and uric acid (1.672 ± 0.149 mg/dl) significantly (*P<0.05*) to the control level, while the levels of serum creatinine (1.450 ± 0.240 mg/dl), total protein (5.960 ± 0.451 g/dl) and albumin (3.540 ± 0.093 g/dl) were not changed. In addition the treatment with PM showed no significant(*P<0.05*) alteration in the level of serum globulin (2.480 ± 0.198 g/dl) when compared with model but not control group (Table 2).
The levels of serum triacylglycerol (61.000 ± 2.702 mg/dl), VLDL (12.200 ± 0.540 mg/dl), and LDL (45.000 ± 3.885 mg/dl) were significantly (*P<0.05*) elevated in model group in comparison with control group (28.600 ± 0.980 mg/dl, 5.720 ± 0.196 mg/dl, 35.280 ± 5.924 mg/dl respectively). In contrast, serum level of HDL (21.200 ± 0.860 mg/dl) was significantly (*P<0.05*) decreased (Table 3). Administration of PM significantly (*P<0.05*) treated the elevated level of serum TAG (33.200 ± 3.121 mg/dl), VLDL (6.640 ± 0.624 mg/dl) and (32.160 ± 6.544 mg/dl). Also the level of serum HDL (34.800 ± 3.734 mg/dl) significantly decreased in comparison to model group, while the level of serum total cholesterol (TC) no altered significantly(*P<0.05*) neither in model group (78.400 ± 3.763 mg/dl) nor in treatment group(73.600 ± 5.418 mg/dl).
The level of serum MDA (2.920 ± 0.139 µmol/L) elevated significantly (*P<0.05*) in CP-injected group when compared with control group (1.826 ± 0.059 µmol/L). PM significantly drop the level of serum MDA (1.918 ± 0.102 µmol/L) when compared with model group (Table 3).

IV. DISCUSSION

Pomegranate molasses (PM) has the strongest antioxidant properties *in vitro* compared to pomegranate juice at a very low concentration, in which, polyphenols in molasses are four times greater than those found in the juice (Chalfoun-Mounayar, Nemr et al. 2012).
In current study, the level of liver functions parameters especially ALP, ALT, AST and serum total bilirubin were significantly elevated in cisplatin-injected animals in comparison to their levels in the control group. The enzymatic activity of alanine (ALT) and aspartate (AST) aminotransterases and alkaline phosphatase (ALP) were studied to evaluate liver malfunctions (Zeashan, Amresh et al. 2009). Hepatic enzymes originally present in higher concentration in the cytoplasm when there is hepatopathy; these enzymes leak into the blood stream in conformity with the extent of liver damage. As a result of the injury of hepatic cells by cisplatin, the leakage of cytosol resulted in increasing levels of the liver

specific enzymes in the rat serum (Zeashan, Amresh et al. 2009, Uthandi and Ramasamy 2011, Al-Malki and Sayed 2014).

In the present study, the capability of PM in ameliorating the CP-induced hepatotoxicity was observed in that; the rats of treated group significantly exhibited lower levels of the hepatic enzymes in the serum when compared with the animals of model group. These results may be due to antioxidant and antifibrotic properties of pomegranate and also from potential therapeutic value in protecting the liver from fibrosis and oxidative injury via suppression of oxidative stress (Al-Moraie, Arafat et al. 2013). In addition to antioxidant effects and scavenging the ROS, pomegranate enhance or maintains the activity of the hepatic enzymes such as catalase, superoxide dismutase (SOD), and peroxidase (Chidambara Murthy, Jayaprakasha et al. 2002, Chalfoun-Mounayar, Nemr et al. 2012).

The phenolic core can act as a buffer and capture electrons from ROS. (Pérez-Vicente, Serrano et al. 2004, Chalfoun-Mounayar, Nemr et al. 2012). De Nigris *et al.*, (2005) reported that the antioxidant level in pomegranate juice was higher than that of the blueberry, cranberry, orange and green tea.

In this study, CP-injection significantly elevated the levels of serum urea, creatinine, and uric acid. CP causes lipid peroxidation and denatures the proteins, which lead to enzymatic inactivation. As a result, renal activities of superoxide dismutase, glutathione peroxidase, and catalase are decreased (Mohan, Khan et al. 2006, Yao, Panichpisal et al. 2007). Some evedence indicated that the renal contents of peroxynitrite and nitric oxide is increase in CP treated rats (Yao, Panichpisal et al. 2007). Admminstration of pomegranate significantly ameliorated the elevated levels of urea and uric acid which may be due to the activation of anioxidant enzyames especially superoxide dismutase (SOD) and catalase (CAT), in addition to its potent antioxidant effect (Moneim, Dkhil et al. 2011). PM failed to restore the elevated serum creatinine. CP-induced oxidative stress in addition to induction of appoptosis. Recent studies indicated that CP significantly increases the concentration of serum creatinine ($P < 0.05$) by about 170% (an indicator of reduced glomerular filtration rate, hence renal failure), which may require further chronic treatment (Ali, Al-Moundhri et al. 2008).

In current study, the level of serum MDA which is a well known marker of degree of lipid peroxidation (Niranjan Gopal and SPrakash 2012), significantly elevated in model group. Hepatotoxicity not only causes lipid peroxidation but also inhibit tissue glutathione peroxidase (GSH-px), glutathione s- transferase (GST), CAT, and SOD activities (Moneim, Dkhil et al. 2011). However, we showed that PM significantly reduced MDA formation. In other words, the mechanism of the inhibitory effects, by which pomegranate molasses protects against lipid peroxidation, may involve radical scavenging capability and

antioxidant enzymes activation, and this depletion may result from oxidative modification of these proteins. Our results are in agreement with other previous studies (Türk, Sönmez et al. 2008, Chalfoun-Mounayar, Nemr et al. 2012, Al-Moraie, Arafat et al. 2013).Our study showed no statistical alteration in the level of serum TC in the model group. This result in agreement with anohter previuos study (Ellis, Fitzharris et al. 1992). However, a significant elevation in levels of serum TAG, VLDL, and LDL in CP- injected rats were observed. In addition, the concentration of serum HDL reduced significantly. The lipid peroxidation has been associated with the pathogenesis of many degenerative diseases, such as atherosclerosis (Nair, Bartsch et al. 2007). In turn, the oxidative stress impaired or altered antioxidant status have been suggested as pivotal keys in the onset of certain chronic diseases(Rao and Kiran 2011).

The results of our study demonstrated that, PM significantly recovered the altered concentration of serum TAG, VLDL, HDL and LDL in model group. Some evidence indicated that PM significantly recoverd the abnormality in lipid profiles (Aviram, Dornfeld et al. 2000, Rosenblat and Aviram 2006, Tezcan, Gültekin-Özgüven et al. 2009). The potent antioxidative capacity of PM against lipid peroxidation may be the central link for its anti-atherogenic effects on lipoproteins and macrophages(Aviram, Dornfeld et al. 2000). pomegranate polyphenols can inhibit oxidized LDL (ox-LDL), increase the activity of serum HDL associated paraoxonase 1 (PON1), which can in turn hydrolyze lipid peroxides in ox-LDL and convert them to a less atherogenic LDL, thus causing a further reduction in ox-LDL content (Rosenblat and Aviram 2006).

Aviram, Dornfeld *et al*. (2000) reported that pomegranate juice consumption by atherosclerotic mice significantly reduced cholesterol accumulation and foam cell formation in heart tissues. Furthermore PM can affect the triacylglycerol (TAG) biosynthesis that could be attributed to its direct effects on diacylglycerol acyltransferase 1 (DGAT1) activity (Rosenblat and Aviram 2011).

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Table (1): Effects of Pomegranate Molasses on serum ALP, ALT, AST serum glucose and total bilirubin in Cisplatin-induced oxidative stress (Mean ± SE).

Parameters / Groups	Serum ALP (IU/L)	Serum ALT (GPT) (IU/L)	Serum AST (GOT) (IU/L)	Serum Glucose (mg/dl)	Serum total Bilirubin (mg/dl)
Control	205.200 ± 16.157 [a]	71.600 ± 5.784 [a]	131.800 ± 8.941 [a]	92.800 ± 5.877 [a]	0.228 ± 0.019 [a]
Model (Cisplatin)	313.600 ± 15.015 [b]	106.200 ± 4.893 [b]	212.200 ± 11.006 [b]	206.200 ± 12.932 [b]	0.4.4 ± 0.028 [b]
Treatment	207.200 ± 21.497 [a]	67.200 ± 7.109 [a]	128.600 ± 13.239 [a]	190.000 ± 20.890 [b]	0.174 ± 0.036 [a]

The same letters mean no significant differences while the different letters mean significant differences (P<0.05

Table (2): Effects of Pomegranate Molasses on serum total cholesterol, HDL, Triacylglycerol, VLDL, LDL and MDA in Cisplatin-induced oxidative stress (Mean ± SE).

parameters / Groups	Serum TC (mg/dl)	Serum HDL (mg/dl)	Serum TAG (mg/dl)	Serum VLDL (mg/dl)	Serum LDL (mg/dl)	Serum MDA (µmol/L)
Control	74.000 ± 4.722 [a]	33.000 ± 1.871 [a]	28.600 ± 0.980 [a]	5.720 ± 0.196 [a]	35.280 ± 5.924 [a]	1.826 ± 0.059 [a]
Model (Cisplatin)	78.400 ± 3.763 [a]	21.200 ± 0.860 [b]	61.000 ± 2.702 [b]	12.200 ± 0.540 [b]	45.000 ± 3.885 [b]	2.920 ± 0.139 [b]
Treatment	73.600 ± 5.418 [a]	34.800 ± 3.734 [a]	33.200 ± 3.121 [a]	6.640 ± 0.624 [a]	32.160 ± 6.544 [a]	1.918 ± 0.102 [a]

The same letters mean no significant differences while the different letters mean significant differences (P<0.05).

Table (3): Effects of Pomegranate Molasses on serum Urea, Creatinine, Uric acid, Total protein, Albumin and globulin in Cisplatin-induced oxidative stress (Mean ± SE).

Parameters / Groups	Serum urea (mg/dl)	Serum creatinine (mg/dl)	Uric acid (mg/dl)	Total protein (g/dl)	Serum albumin (g/dl)	Serum globulin (g/dl)
Control	27.380 ± 1.514 [a]	0.730 ± 0.030 [a]	1.820 ± 0.150 [a]	6.460 ± 0.068 [a]	3.560 ± 0.068 [a]	3.080 ± 0.132 [a]
Model (Cisplatin)	121.800 ± 6.733 [b]	1.554 ± 0.194 [b]	3.980 ± 0.227 [b]	6.280 ± 0.208 [a]	3.520 ± 0.073 [a]	2.620 ± 0.132 [ab]
Treatment	85.700 ± 3.760 [c]	1.450 ± 0.240 [b]	1.672 ± 0.149 [a]	5.960 ± 0.451 [a]	3.540 ± 0.093 [a]	2.480 ± 0.198 [b]

The same letters mean no significant differences while the different letters mean significant differences (P<0.05).

پوختە

ڕووبەهەنار یەکێکە لە پێکهاتە سەرەکیەکانی ژەمە خۆراکە ڕۆژهەلاتییەکان، کە لە پزیشکی میللی دا بۆ چارەسەرکردنی چەندین نەخۆشی بەکار دێت. زۆربەی کاریگەرییەکانی دەگەڕێتەوە بۆ چالاکییە بەهێزەکانی دژەئۆکسانە فینۆلییەکان، بەڵام بەبێ ئەوەی وەکو پێویست تویژینەوەی زانستی لەبارەیەوە هەبێت. هەر بۆیە، ئەم لێکۆڵینەوەیە لەسەر کاریگەرییەکانی ڕووبەهەنار لە جرجی نێرەی سپی هاندراو بە ئۆکسێنەفشار بە سیسپلاتین،ئەنجام درا. سی جرجی نێرە کە کێشی لەشیان لەنیوان 300- 320 گم بوو کران بە سێ گروپەوە، گروپی کۆنترۆ (ژ=5) تەنها ئالیکی تاییەتی جرج و ئاوی بەلوعەیان پێدرا، سەبارەت بە گروپی مۆدێل: جرجەکان سیسپلاتینیان (ناو پریتون) لێدرا (2مل/کگم کێشی لەش/ڕۆژ). لە گروپی سێهەمدا سەرەڕای سیسپلاتین، جرجەکان بۆ ماوەی 8 هەفتە ڕووبەهەناری خۆمالّی ماڵەوەیان پێدرا (0.5 مل/کگم کێشی لەش/ڕۆژ).ئەنجامەکان پیشانیان دا کە چڕی ئەنزیمەکانی فرمانی جگەر(ALP,ALT, AST) وە کۆی بلیرۆبینی سیرەم بەهۆی پێدانی ڕووبەهەنارەوە بە شێوەیەکی بەرچاو (P<0.05)باش ببونەوە. پاش ئەوەی بەهۆی لێدانی سیسپلاتینەکەوە بەرزببونەوە.لە لایەکی ترەوە ئاستی یۆریا و ترشی یۆریکی سیرەم لەو جرجانەی کە ڕووبەهەناریان پێدرا بە شێوەیەکی بەرچاو کەمیکرد بە بەراورد بەو گروپەی کە تەنها سیسپلاتینیان لێدرابوو. بەڵام بە شێوەیەکی چاوەڕوان نەکراو چڕی کریاتینینی سیرەم بە پێدانی ڕووبەهەنار باشتر نەبوو. لەوەش زیاتر، ڕووبەهەنار پرۆفیلەکانی چەوری بەتاییەت (TAG, VLDL, HDL, LDL)جگەلە تێکرای کولسترۆڵ لەڕوی ئاماریەوە چاك کردەوە. سەرەڕای ئەوەش،چڕی مالۆندەڵدیهاید (MDA) (ئاماژەپێدەرێکی ناسراوی ڕێژەی پیرۆکساندنی چەوریە) لەو گروپەی کە ڕووبەهەناریان پێدرا بە شێوەیەکی بەرچاو(P<0.05) باشبویەوە. دەرئە نجام، ئەم تویژینەوەیە ئەو بیرۆکەیە پشتڕاست دەکاتەوە کە پێدانی ڕووبەهەنار، لەڕێی چالاکییە دژەئۆکسێنەکەیەوە، بەشێوەیەکی بەرچاو ئۆکسێنەفشاری لە جرجەکاندا چاککردەوە و جۆرەها سودی تەندروستی بۆ دەستەبەر کردن.