ZANCO Journal of Pure and Applied Sciences
The official scientific journal of Salahaddin University-Erbil
https://zancojournals.su.edu.krd/index.php/JPAS

ISSN (print):2218-0230**, ISSN (online):** 2412-3986**, DOI:** http://dx.doi.org/10.21271/zjpas

RESEARCH PAPER

Hypotensive Action of Pomegranate Seed Extract and Zinc Chloride in Hypertensive Rats

Zana Rafiq Majeed[1], Firas Khalid Qasim[2], Hedy Ahmed Hassan[3]

[1,2,3]Department of Biology, College of Science, Salahaddin University-Erbil, Erbil, Kurdistan Region, Iraq.

A B S T R A C T:

This study investigated the effects of pomegranate seed extract and supplementary zinc chloride (ZnCl2) on Dexamethasone (DEX) and NaCl induced hypertension in rats. For this purpose, female albino rats were divided into five groups: control and four DEX and NaCl induced hypertensive rats. The animals were given pomegranate seed extract, ZnCl2, or a combination of both for two weeks. Our results show a significant decrease in systolic blood pressure (SBP) in each of the treated groups, except the combination group. DEX and NaCl combination significantly decreased the total body weight in rats. The body weight was not changed with pomegranate seed extract or ZnCl2 administration. Besides WBC, RBC, HGB, HCT, and PLTs levels were not altered. There were no significant differences in the levels of serum K+, Ca2+, and Cl- ions among the treated groups. Nevertheless, the Na+ level in the serum increased significantly in rats of the combination group. Taken together, we conclude that pomegranate seed extract and ZnCl2 consumption can be beneficial for lowering blood pressure in hypertensive patients when consumed separately.

KEY WORDS:. Pomegranate,Zinc chloride,Toxicity, Hypertension,Blood parameters .
DOI: http://dx.doi.org/10.21271/ZJPAS.31.5.6
ZJPAS (2019) , 31(5);44-52 .

INTRODUCTION :

The most common cause of human mortality is cardiovascular diseases, and one of the main risk factors for heart diseases is hypertension (Sahebkar et al., 2017). There are many pharmaceutical drugs, dietary supplements, and herbal folk medicine that are used to manage increased blood pressure. In this study, we have sought to investigate the effectiveness of a herbal medicine and a dietary supplement on lowering blood pressure in experimental animals; and those are pomegranate seed extract and zinc chloride (ZnCl2).

*** Corresponding Author:**
Zana Rafiq Majeed, PhD
E-mail: zana.majeed@su.edu.krd
Article History:
Received: 29/10/2018
Accepted: 17/06/2019
Published: 17/10 /2019

fruit has a nutritional, industrial, pharmaceutical values (Teixeira da Silva et al., 2013). It is composed of peel, aril, seed, and juice. Pomegranate juice is reported to have antioxidant effects on humans. The antioxidant activities are highly linked to the phenolic content of the pomegranate fruit, including anthocyanins, ellagic acid and its derivatives, and hydrolyzable tannins (Kalaycıoğlu and Erim, 2017, Jing et al., 2012, Hmid et al., 2016, Fawole and Opara, 2013). One of the major components of pomegranate seed is tocopherol, such as γ-tocopherol. Additional components of the seeds are tocotrienols, phytophenols, triterpene, and phospholipids. Therefore, pomegranate seed considered a rich source of biolipids (Verardo et al., 2014). Pomegranate extracts have been reported to have antiparasitic (Fahmy et al., Al-Megrin, 2017), antibacterial (Silva et al., 2016, Labsi et al., 2016), anti-inflammatory(Achraf et al., 2018, Ambarwati

et al.), and anticancer activities (An et al., 2015). It enhances male fertility (El Ghazzawy et al., 2011) and learning and memory of rats(Adiga et al., 2010), and it has anti-diabetic properties as well (Mestry et al., 2017).

Malondialdehyde (MDA), and protein carbonyls (CARB) are reduced in plasma after consumption of the pomegranate juice for 15 days, indicating less lipid peroxidation and less protein oxidation conditions. The antioxidant glutathione (GSH) levels were increased after pomegranate consumption (Matthaiou et al., 2014). Increased oxidative stress alters the balance between reactive oxygen species and nitric oxide (NO), which lowers NO bioavailability, that are the preliminary steps in atherosclerosis and cardiovascular diseases (Sahebkar et al., 2016).

It has been shown that Pomegranate peel extract, *Punica granatum* L., Lythraceae, has pro-apoptotic activities and subdue cancer cell proliferation in adult male Sprague-Dawley rats, possibly through suppression of Wnt/β-Catenin signaling pathway (Ahmed et al., 2017). It is reported that pomegranate juice extract reduces epithelial to mesenchymal transition (EMT) in renal cell carcinoma (RCC) cell lines, through inhibition of the NF-kB and JNK pathways (An et al., 2015). Pomegranate also found to protect against oxidative stress in endothelial cells from Preeclampsia pregnant women.

Zinc supplements have protective antioxidant and anti-inflammatory properties. It has been revealed that it decreases hypoxia in obstructive sleep apnea rats. It protects against hypoxia induced cardiac dysfunction (Chen and Chen, 2016). $ZnCl_2$ demonstrates a protective role against cadmium chloride toxicity, which causes severe pathological changes in liver and kidneys in rats. Moreover, Zn balances out cadmium-induced oxidative stress, apoptosis and necrosis (Mahran et al, 2011). $ZnCl_2$ prevents oxidant-induced mitochondrial permeability transition pore (mPTP) opening through stimulation of PI3K/Akt signalling pathway, which is responsible for the inactivation of glycogen synthase kinase-3β (GSK-3β) by phosphorylation at Ser9 site (Chanoit et al., 2008, Lee et al., 2009). Zinc can suppress apoptosis through suppression of caspase-3 and its antioxidant activities in cardiomyocytes. Zinc can activate ERK in SHSY5Y site and prevent apoptosis in neuronal cells (Chanoit et al., 2008). Although Zinc has anti-apoptotic activities, there are reports that it can participate in the induction of necrosis in pulmonary endothelial cells in response to oxidative stress. The necrosis process is likely via *t*-butyl hydroperoxide (tBH) and protein kinase (PK) C pathways (Tang et al., 2001, Kambe et al., 2015). Zinc also affects the expression and production of cytokines. It increases the expression of IL-2 and IFN-ϒ in Human Renal Proximal Tubule Epithelial (TH1). Zinc also downregulates the expression of TNF-α, IL-1β, and IL-8 in the monocyte-macrophage cell line (Bao et al., 2003). The main aim of the current study is to obtain insight into the effectiveness of pomegranate seed extract as well as $ZnCl_2$ on lowering glucocorticoid dexamethasone (DEX) induced hypertension in rats. Moreover, we have investigated the possible toxicity of these two treatments on blood cell counts, animal weight, serum electrolyte levels, and blood glucose level.

2. MATERIALS AND METHODS

2.1 Animal housing

Female albino rats weighed 230- 244 grams, were divided into five groups. The animals were bred and housed at the Animal House of the Department of Biology, College of Science, Salahaddin University-Erbil. The rats kept under a controlled temperature of about 22±2°C, with 12 hours of alternating cycles of light and dark. Before the treatments, the animals were fed a standard diet rat chow containing 0.5% NaCl, 22% protein, and 4-6% dietary fat and tap water *ad libitum*. The standard rat pellet contained wheat 66.6%, soya 25.6%, sunflower oil 4.4%, limestone 1.5%, salt 0.63%, methionine 0.158%, choline chloride 0.062% and trace elements 0.05% (Krinke, 2000).

2.2. Experimental design

The negative control group received a regular diet and tap water (n=6). The second group (n=7) received a combination of Dexamethasone (DEX)-containing water (0.5mg/L), and 4% NaCl containing diet. The (DEX+NaCl) combination is used to induce hypertension in experimental animals. The third group of animals (n=6) was given pomegranate seed (PG) extract *Punica granatum* (Damiana, Turkey) in addition to DEX+NaCl combination. The pomegranate seed powder was dissolved in water (2000mg/L). The fourth group (n=6) was given Zinc chloride ($ZnCl_2$) in addition to DEX+NaCl combination. The $ZnCl_2$ was prepared in a concentration of 420mg/L (50mg/Kg body weight) in water. The fifth group (n=6) was given a combination of PG, $ZnCl_2$, Dexamethasone, and NaCl (PG+ $ZnCl_2$+DEX+NaCl) in concentrations similar to the other groups. The treatment lasted for two weeks.

2.3 Analytical methods

2.3.1 Weight of the animals

The animals were weighed at three time points during the treatment period of two weeks; prior to the treatment, at the end of the first week and at the end of the second week of treatment.

2.3.2 Systolic blood pressure measurement

Systolic blood pressure was measured by using tail-cuff plethymography in un-anaesthetizes rats, pre-warmed for 10 minutes at 37°C, in a thermostatically controlled heating cabinet. The tail pressure pulsations were detected with a pneumatic pulse transducer (ADInstruments PowerLab 2/25). Each blood pressure reading was obtained by averaging 2-4 individual reading values.

2.3.3 Blood collection and biochemical analysis

At the end of each experiment, the rats were anaesthetized with ketamine hydrochloride (100mg/mg). Blood samples were taken by cardiac puncture into tubes with or without enthylenediaminetetraacetic acid (EDTA) as an anticoagulant. The tubes with EDTA were used for haematological analysis. White Blood Cells (WBC), Red Blood Cells (RBC), haemoglobin (HGB), hematocrit (HCT), and platelets (PLT) counts were determined by using automated haematology analyzer (NIHON KOHDEN), Celtac α, MEK -6400 J/K). Blood glucose level was also measured by using glucometer (ACCU-Check Active, Roche, D-68298, Germany).

The blood samples without EDTA were centrifuged for 15min for sera collection. The sera were stored at -80 °C (Sony, Ultra low, Japan). Blood Gas Analyzer GASTAT-600 (TECHNO MEDICA, Japan) was used for the measurement of serum electrolyte concentrations (Na^+, K^+, Ca^{2+}, and Cl^-).

2.4 Statistical analysis

The statistical analysis was performed using Sigma Plot Statistical Package (Version 12.0) software. Pairwise multiple comparison tests were done using posthoc Bonferroni t-test. Data are shown as mean±SEM. The results were considered statistically significant at $P< 0.05$.

3. RESULTS

3.1 Dexamethasone and NaCl combination reduces weight

All the groups treated with DEX+ NaCl combination showed a significant decrease in the weight of rats after the first week of treatment compared to the untreated control group. This change was further detectable after the second week of the treatment Table (1). The maximum reduction is seen in $ZnCl_2$+DEX+NaCl group.

Table (1): Change in animal weights during the period of the experiment (2 weeks) in Pomegranate and $ZnCL_2$ treated hypertensive rats. Pairwise multiple comparison tests were done using post-hoc Bonferroni t-test. Data are shown as mean±SEM. Treatment groups compared to the control group.

Treatments	Before starting the experiment (gm)	Week 1 of the Experiment (gm)	Week 2 of the Experiment (gm)
Control	233 ± 6.13	249 ± 8.51	252 ± 8.84
DEX-NaCl	239 ± 4.33	214 ± 4.25 (P=0.021)	204 ± 3.79 (P<0.001)
PG + DEX-NaCl	244 ± 7.7	213 ± 7.64 (P=0.016)	208 ± 7.14 (P<0.001)
$ZnCl_2$+ DEX-NaCl	230 ± 7.12	207 ± 6.2 (P=0.004)	199 ± 5.08 (P<0.001)
PG + $ZnCl_2$ + DEX-NaCl	232 ± 7.55	211 ± 8.07 (P=0.009)	203 ± 9.24 (P<0.001)

3.2 Each of pomegranate seed extract and zinc chloride reduces blood pressure

Pomegranate seed extract in PG+DEX+NaCl group reduced systolic blood pressure (mmHg) compared to blood pressure in DEX+NaCl group. Similar results were observed in ZnCl2 treated groups ($ZnCl_2$+DEX+NaCl) compared to DEX+NaCl group. However, the combination of pomegranate and $ZnCl_2$ showed no significant changes compared to the DEX+NaCl group (Figure 1).

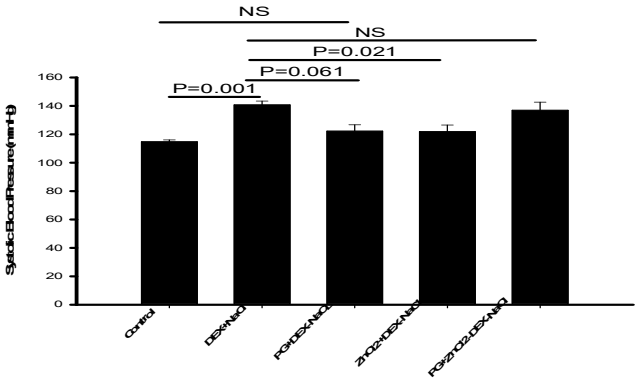
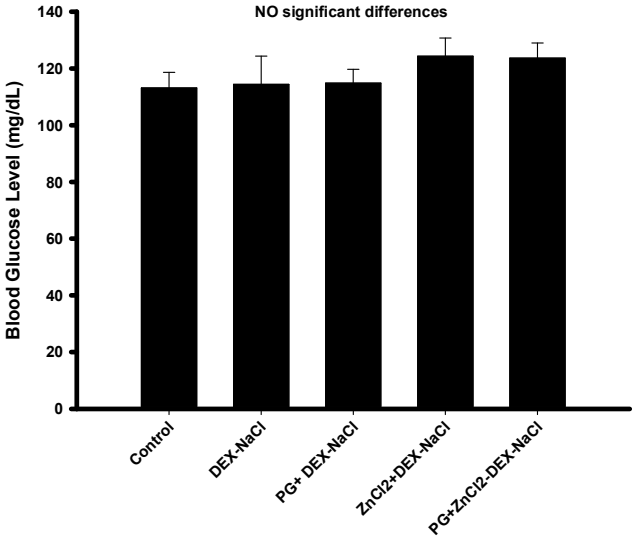


Figure (1): Shows the effect of Pomegranate (PG) and/or $ZnCL_2$ administration on systolic blood pressure in Dexamethasone (DEX)-NaCl-induced hypertensive rats. Pairwise multiple comparison tests were done using post-hoc Bonferroni t-test. Data are shown as mean±SEM.

3.3 Blood glucose level is not altered by pomegranate nor zinc chloride

Blood glucose was not changed when the rats administered pomegranate seed extract. This finding was observed when PG+DEX+NaCl group was compared to the control and DEX+NaCl groups. However, there is a slight increase in blood glucose level in the groups that ingested zinc chloride, even though the results were not statistically significant (Figure 2). The average of glucose levels in DEX+NaCl group is 114±9.94, however in each of $ZnCl_2$+DEX+NaCl, and PG+$ZnCl_2$+DEX+NaCl groups the values are 124±6.39 mg/dL and 124±5.33 mg/dL, respectively.



NaCl			0.00211	1.84
PG +$ZnCl_2$+ DEX-NaCl	151.4 ± 2.59 (P=0.025)*	4.58 ± 0.09	2.36 ± 0.00477	109.2 ± 2.35

Figure (2): Pomegranate and/or $ZnCL_2$ administration does not show any significant changes in blood glucose level in Dexamethasone (DEX)-NaCl induced hypertensive rats. Pairwise multiple comparison tests were done using post-hoc Bonferroni t-test. Data are shown as mean±SEM.

3.4 Hematological parameters are not changed by pomegranate nor zinc chloride

We did not observe significant changes in the levels of RBC, HGB, HCT, and PLTs compared to the controls in all treated groups. However, a slight decrease in the levels of WBC was observed in each of PG+DEX+NaCl (3.6 ± 0.68) and $ZnCl_2$+DEX+NaCl (3.3 ± 0.29) groups compared to the control (5.08 ± 0.44) and DEX+NaCl (5.46 ± 1.27) groups (see Table 2).

Table (2): Haematological parameters in Pomegranate and/or $ZnCL_2$ treated hypertensive rats. Pairwise multiple comparison tests were done using post-hoc Bonferroni t-test. Data are shown as mean±SEM.

Treatments	WBC (x $10^3/\mu L$)	RBC (x $10^6/\mu L$)	HGB (g/dL)	HCT (%)	PLT ($X10^3/\mu L$)
Control	5.08 ± 0.44	6.54 ± 0.23	12.82 ± 0.34	41.2 ± 1.18	809 ± 69
DEX-NaCl	5.46 ± 1.27	6.63 ± 0.21	13.6 ± 0.23	41 ± 1.04	632 ± 119
PG + DEX-NaCl	3.6 ± 0.68	6.54 ± 0.35	13 ± 0.57	39.9 ± 1.82	625 ± 84
ZnCl2+ DEX-NaCl	3.3 ± 0.29	7.01 ± 0.21	14.15 ± 0.25	45.13 ± 0.82	602 ± 28
PG + $ZnCl_2$ + DEX-NaCl	4.23 ± 0.69	7.01 ± 0.32	14.32 ± 0.52	43.93 ± 1.74	564 ± 27

WBC: White Blood Cell count; **RBC**: Red Blood Cell count; **HGB**: haemoglobin concentration; **HCT**: Hematocrit; **PLT**: Platelet count.

3.5 Sodium ion concentration level is changed by pomegranate and zinc chloride combination

There were no significant differences in the levels of serum K^+, Ca^{2+}, and Cl^- among the treated groups. Nevertheless, serum Na^+ ion level increased significantly when the rats ingested a combination of pomegranate and $ZnCl_2$ compared with the control (see Table 3).

Table (3): Serum electrolyte concentrations in Pomegranate and/or ZnCL2 treated hypertensive rats. Pairwise multiple comparison tests were done using post-hoc Bonferroni t-test. Data are shown as mean±SEM.

***** This group is significantly different compared to control group.

4. DISCUSSION

This study was designed to examine the effects of pomegranate seed extract and $ZnCl_2$, individually and in combination, on the blood pressure, weight, haematological and biochemical parameters of rats. Hypertension in the rats was induced via synthetic glucocorticoid, Dexamethasone (DEX) ingestion in combination with NaCl. DEX induction of hypertension was previously reported (Soto-Piña et al., 2016, Dubey et al., 2017). Dexamethasone induces increased blood pressure as a result of enhancing blood vessels' reactivity (contraction) to vasopressin (Iijima and Malik, 1988). Moreover, dexamethasone reduces nitric oxide (NO) synthesis and impairs relaxation of endothelial cells (Yin et al., 1992, Ong et al., 2009).

Short period NaCl induced hypertension is a result of vasoconstrictor 20-hydroxyeicosatetraenoic acid (20-HETE) action, in response to high salt diet (Walkowska et al., 2015). High sodium diet, up to 8%, has been shown to increase superoxide formation, particularly in the kidney cortex. Superoxide radicals decrease NO bioavailability in the thick ascending loop; therefore, more NaCl reabsorption takes place which eventually causes high blood pressure in rats (Dobrian et al., 2003).

Our results show that each of pomegranate seed extracts and $ZnCl_2$ counteract the effects of Dexamethasone on blood pressure within two weeks of treatment. However, when a combination of both, pomegranate and $ZnCl_2$ were used, the hypertensive effect of Dexamethasone did not change, this might be due to the antagonistic effect of these two treatments together. It is possible that Na^+ ion increase we observed only in pomegranate seed extracts and $ZnCl_2$ combination group has caused a decrease in the bioavailability of NO to lower the blood pressure. In fact, the phenolic compounds in pomegranate was observed to decrease amount of the zinc in kidney and heart tissues in rats (Aksu et al., 2017).

Pomegranate has been reported to increase nitric oxide activity; therefore, it is possible that the reduction in the systolic blood pressure we observed might be due partly to the enhanced NO action. In addition, pomegranate lowers protein and lipid oxidation via increasing the antioxidant molecules such as glutathione (GSH)(Gbinigie et al., 2017). Other studies have reported a possible link between the reduction of blood pressure and pomegranate intake (Sahebkar et al., 2017, Achraf et al., 2018); however, the data still is not conclusive. To our best knowledge, there is limited data on how pomegranate consumption affects cell signalling pathways, and whether there is any variation on the effects of pomegranate juice, skin, aril or the seed extract on the blood pressure.

Dexamethasone-treated animals showed a significant decrease in the total body weight compared to the control group. Dexamethasone is reported to acts in the hypothalamus to induce rapid transport of Intracerebroventricular neuropeptide Y (NPY) from cell bodies within the arcuate nucleus to terminal regions including the dorsomedial and ventromedial hypothalamic regions, thus controlling appetite (Chen and Romsos, 1996). This result was most prominent in rats that were treated with a combination of $ZnCl_2$ and Dexamethasone. However, the decrease in total body weight did not appear to be affected by pomegranate seed extract when the pomegranate+DEX+ NaCl-treated animals were compared with DEX+NaCl treated animal group. Therefore, it is most likely that the decrease in total body weight is due to Dexamethasone. Correlation between total body weight loss and Dexamethasone treatment has been reported previously (Dubey et al., 2017).

Even though our results show no change in blood cell components, other studies have reported that pomegranate juice can increase platelet count in men after 15 days of intake(Achraf et al., 2018). Previous studies proposed that pomegranate peel can assist with type 2 diabetes, by lowering blood glucose (Banihani et al., 2013); our study shows no significant changes in the levels of glucose after consumption of pomegranate seed extract. We did not observe changes in the levels of serum electrolytes K^+, Ca^{2+}, and Cl^- or the haematological parameters (RBCs, HGB, HCT, and PLTs). A slight reduction of WBCs was observed in response to pomegranate seed extract treatments. A similar finding was detected in $ZnCl_2$ treatment group. In addition, serum Na^+ electrolyte was significantly increased when a combination of pomegranate seed extract and $ZnCl_2$ were used together.

5. CONCLUSIONS AND SIGNIFICANCE

We conclude that pomegranate seed extract lowers systolic blood pressure (mmHg) in hypertensive rat models. In addition, the supplementary $ZnCl_2$ can significantly lower blood pressure as well. Whereas both treatments (pomegranate or $ZnCl_2$) do not cause any changes in blood glucose levels, RBCs, HGB, HCT, and PLT counts. They do not have any significant effect on body weight. However, there is a slight reduction in WBCs count in both pomegranate and $ZnCl_2$ treated groups. There were no significant differences in the levels of serum K^+, Ca^{2+}, and Cl^- among the treated groups. Nevertheless, serum Na^+ level in serum increased significantly when the rats ingested a combination of pomegranate and $ZnCl_2$ compared to serum Na^+ level of the control group. This has a counter effect on the reduction of blood pressure. Therefore, we recommend not to combine pomegranate seed extract and $ZnCl_2$ together as a dietary supplement. Our data shows that pomegranate has a potential therapeutic effect in lowering blood pressure in hypertensive subjects.

Acknowledgements

We express our gratitude to the staff of Advanced Animal Physiology lab and the staff of Animal House facility at the Department of Biology, College of Science.

Conflict of Interest

The authors declare no conflicts of interest.

6. REFERENCES

ACHRAF, A., HAMDI, C., TURKI, M., ABDELKARIM, O., AYADI, F., HOEKELMANN, A., YAICH, S. & SOUISSI, N. 2018. Natural pomegranate juice reduces inflammation, muscle damage and increase platelets blood levels in active healthy Tunisian aged men. *Alexandria Journal of Medicine,* 54**,** 45-48.

ADIGA, S., TRIVEDI, P., RAVICHANDRA, V., DEB, D. & MEHTA, F. 2010. Effect of Punica granatum peel extract on learning and memory in rats. *Asian Pacific Journal of Tropical Medicine,* 3**,** 687-690.

AHMED, H. H., EL-ABHAR, H. S., HASSANIN, E. A. K., ABDELKADER, N. F. & SHALABY, M. B. 2017. Punica granatum suppresses colon cancer through downregulation of Wnt/β-Catenin in rat model. *Revista Brasileira de Farmacognosia,* 27**,** 627-635.

AKSU DS, SAĞLAM YS, YILDIRIM S, AKSU T. 2017. Effect of pomegranate (*Punica granatum L.*) juice on kidney, liver, heart and testis histopathological changes, and the tissues lipid peroxidation and antioxidant status in lead acetate-treated rats.*Cell Mol Biol (Noisy-le-grand)*,63, 33-42.

AL-MEGRIN, W. A. 2017. In vivo study of pomegranate (Punica granatum) peel extract efficacy against Giardia lamblia in infected experimental mice. *Asian Pacific Journal of Tropical Biomedicine,* 7**,** 59-63.

AMBARWATI, D., FATMAWATI, F., NOORYANTO, M., SANTOSO, S., WINDU BAKTIYANI, S. C. & NURDIANA, N. *Punica granatum* fruit extract inhibits the production of pro-inflammatory cytokines and angiogenic factors of HUVEC cells induced by plasma from patients with pre-eclampsia. *Clinical Nutrition Experimental,* 15**,** 9-14.

AN, J., GUO, Y., WANG, T., PANTUCK, A. J. & RETTIG, M. B. 2015. Pomegranate extract inhibits EMT in clear cell renal cell carcinoma in a NF-κB and JNK dependent manner. *Asian Journal of Urology,* 2**,** 38-45.

BANIHANI, S., SWEDAN, S. & ALGURAAN, Z. 2013. Pomegranate and type 2 diabetes. *Nutrition Research,* 33**,** 341-348.

BAO, B., PRASAD, A. S., BECK, F. W. J. & GODMERE, M. 2003. Zinc modulates mRNA levels of cytokines. *American Journal of Physiology-Endocrinology and Metabolism,* 285**,** E1095-E1102.

CHANOIT, G., LEE, S., XI, J., ZHU, M., MCINTOSH, R. A., MUELLER, R. A., NORFLEET, E. A. & XU, Z. 2008. Exogenous zinc protects cardiac cells from reperfusion injury by targeting mitochondrial permeability transition pore through inactivation of glycogen synthase kinase-3β. *American Journal of Physiology - Heart and Circulatory Physiology,* 295**,** H1227-H1233.

CHEN, H. L. & ROMSOS, D. R. 1996. Dexamethasone rapidly increases hypothalamic neuropeptide Y secretion in adrenalectomized ob/ob mice. *American Journal of Physiology-Endocrinology and Metabolism,* 271**,** E151-E158.

CHEN, T.-I. & CHEN, M. Y.-C. 2016. Zinc Is Indispensable in Exercise-Induced Cardioprotection against Intermittent Hypoxia-Induced Left Ventricular Function Impairment in Rats. *PLOS ONE,* 11**,** e0168600.

DOBRIAN, A. D., SCHRIVER, S. D., LYNCH, T. & PREWITT, R. L. 2003. Effect of salt on hypertension and oxidative stress in a rat model of diet-induced obesity. *American Journal of Physiology-Renal Physiology,* 285**,** F619-F628.

DUBEY, H., SINGH, A., PATOLE, A. M. & TENPE, C. R. 2017. Antihypertensive effect of allicin in dexamethasone-induced hypertensive rats. *Integrative Medicine Research,* 6**,** 60-65.

EL GHAZZAWY, I. F., MELEIS, A. E., FARGHALY, E. F. & SOLAIMAN, A. 2011. Histological study of the possible protective effect of pomegranate juice on bisphenol-A induced changes of the caput epididymal epithelium and sperms of adult albino rats. *Alexandria Journal of Medicine,* 47**,** 125-137.

FAHMY, Z., EL-SHENNAWY, A., EL-KOMY, W., ALI, E. & ABD EL-HAMED, S. PP-195 Potential antiparasitic activity of pomegranate extracts against schistosomules and mature worms of *Schistosoma mansoni:* in vitro and in vivo study. *International Journal of Infectious Diseases,* 14**,** S84.

FAWOLE, O. A. & OPARA, U. L. 2013. Effects of maturity status on biochemical content, polyphenol composition and antioxidant capacity of pomegranate fruit arils (cv. 'Bhagwa'). *South African Journal of Botany,* 85**,** 23-31.

GBINIGIE, O. A., ONAKPOYA, I. J. & SPENCER, E. A. 2017. Evidence for the effectiveness of pomegranate supplementation for blood pressure management is weak: A systematic review of randomized clinical trials. *Nutrition Research,* 46**,** 38-48.

HMID, I., HANINE, H., ELOTHMANI, D. & OUKABLI, A. 2016. The physico-chemical characteristics of Morrocan pomegranate and evaluation of the antioxidant activity for their juices. *Journal of the Saudi Society of Agricultural Sciences*.

IIJIMA, F. & MALIK, K. U. 1988. Contribution of vasopressin in dexamethasone-induced hypertension in rats. *Hypertension,* 11**,** I42.

JING, P., YE, T., SHI, H., SHENG, Y., SLAVIN, M., GAO, B., LIU, L. & YU, L. 2012. Antioxidant properties and phytochemical composition of China-grown pomegranate seeds. *Food Chemistry,* 132**,** 1457-1464.

KALAYCIOĞLU, Z. & ERIM, F. B. 2017. Total phenolic contents, antioxidant activities, and bioactive ingredients of juices from pomegranate cultivars worldwide. *Food Chemistry,* 221**,** 496-507.

KAMBE, T., TSUJI, T., HASHIMOTO, A. & ITSUMURA, N. 2015. The Physiological, Biochemical, and Molecular Roles of Zinc Transporters in Zinc Homeostasis and Metabolism. *Physiological Reviews,* 95**,** 749-784.

LABSI, M., KHELIFI, L., MEZIOUG, D., SOUFLI, I. & TOUIL-BOUKOFFA, C. 2016. Antihydatic and immunomodulatory effects of Punica granatum peel aqueous extract in a murine model of echinococcosis. *Asian Pacific Journal of Tropical Medicine,* 9**,** 211-220.

LEE, S., CHANOIT, G., MCINTOSH, R., ZVARA, D. A. & XU, Z. 2009. Molecular mechanism underlying Akt activation in zinc-induced cardioprotection. *American Journal of Physiology-Heart and Circulatory Physiology,* 297**,** H569-H575.

MATTHAIOU, C. M., GOUTZOURELAS, N., STAGOS, D., SARAFOGLOU, E., JAMURTAS, A., KOULOCHERI, S. D., HAROUTOUNIAN, S. A., TSATSAKIS, A. M. & KOURETAS, D. 2014. Pomegranate juice consumption increases GSH levels and reduces lipid and protein oxidation in human blood. *Food and Chemical Toxicology,* 73**,** 1-6.

MESTRY, S. N., DHODI, J. B., KUMBHAR, S. B. & JUVEKAR, A. R. 2017. Attenuation of diabetic nephropathy in streptozotocin-induced diabetic rats by Punica granatum Linn. leaves extract. *Journal of Traditional and Complementary Medicine,* 7**,** 273-280.

ONG, S. L. H., ZHANG, Y. & WHITWORTH, J. A. 2009. Mechanisms of Dexamethasone-Induced Hypertension. *Current Hypertension Reviews,* 5**,** 61-74.

SAHEBKAR, A., FERRI, C., GIORGINI, P., BO, S., NACHTIGAL, P. & GRASSI, D. 2017. Effects of pomegranate juice on blood pressure: A systematic review and meta-analysis of randomized controlled trials. *Pharmacological Research,* 115**,** 149-161.

SAHEBKAR, A., SIMENTAL-MENDÍA, L. E., GIORGINI, P., FERRI, C. & GRASSI, D. 2016. Lipid profile changes after pomegranate consumption: A systematic review and meta-analysis of randomized controlled trials. *Phytomedicine,* 23**,** 1103-1112.

SILVA, P. M., NAPOLEÃO, T. H., SILVA, L. C. P. B. B., FORTES, D. T. O., LIMA, T. A., ZINGALI, R. B., PONTUAL, E. V., ARAÚJO, J. M., MEDEIROS, P. L., RODRIGUES, C. G., GOMES, F. S. & PAIVA, P. M. G. 2016. The juicy sarcotesta of Punica granatum contains a lectin that affects growth, survival as well as adherence and invasive capacities of human pathogenic bacteria. *Journal of Functional Foods,* 27**,** 695-702.

SOTO-PIÑA, A. E., FRANKLIN, C., RANI, C. S. S., GOTTLIEB, H., HINOJOSA-LABORDE, C. & STRONG, R. 2016. A Novel Model of Dexamethasone-Induced Hypertension: Use in Investigating the Role of Tyrosine Hydroxylase. *Journal of Pharmacology and Experimental Therapeutics,* 358**,** 528-536.

TANG, Z.-L., WASSERLOOS, K., CROIX, C. M. S. & PITT, B. R. 2001. Role of zinc in pulmonary endothelial cell response to oxidative stress. *American Journal of Physiology-Lung Cellular and Molecular Physiology,* 281**,** L243-L249.

TEIXEIRA DA SILVA, J. A., RANA, T. S., NARZARY, D., VERMA, N., MESHRAM, D. T. & RANADE, S. A. 2013. Pomegranate biology and biotechnology: A review. *Scientia Horticulturae,* 160**,** 85-107.

VERARDO, V., GARCIA-SALAS, P., BALDI, E., SEGURA-CARRETERO, A., FERNANDEZ-GUTIERREZ, A. & CABONI, M. F. 2014. Pomegranate seeds as a source of nutraceutical oil naturally rich in bioactive lipids. *Food Research International,* 65**,** 445-452.

WALKOWSKA, A., KUCZERISZKA, M., SADOWSKI, J., OLSZYŃSKI, K. H., DOBROWOLSKI, L., ČERVENKA, L., HAMMOCK, B. D. & KOMPANOWSKA-JEZIERSKA, E. 2015. High Salt Intake Increases Blood Pressure in Normal Rats: Putative Role of 20-HETE and No Evidence

on Changes in Renal Vascular Reactivity. *Kidney & blood pressure research,* 40**,** 323-334.

YIN, K., CHU, Z. M. & BEILIN, L. J. 1992. Study of mechanisms of glucocorticoid hypertension in rats: endothelial related changes and their amelioration by dietary fish oils. *British Journal of Pharmacology,* 106**,** 435-442.