

Uric acid is a key player in salt-induced endothelial dysfunction: the therapeutic role of *Stigma maydis* (corn silk) extract

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Abstract: Hyperuricemia has been implicated in the pathogenesis and complications of cardiovascular diseases with associated elevated oxidant events. There is evidence that excessive salt intake results in cardiometabolic disturbances but the mechanism is elusive. Also, *Stigma maydis* (corn silk) is noted for its antioxidant properties among other beneficial roles. This study, therefore, aimed to establish the effect of high-salt diet (SD) on uric acid (UA) production and the role of *S. maydis* in salt-induced phenotypes. Four groups of randomly selected rats ($n = 5$) were fed with normal rat feed, corn silk extract (500 mg/kg), SD (8%) and corn silk extract plus high-salt feed. After 6 weeks of the experimental procedure, each animal was anesthetized by exposure to chloroform vapor and blood samples collected by cardiac puncture. Data were expressed in means $\pm$ SEM and p values < 0.05 were accepted as significant. SD resulted in reduced plasma superoxide dismutase (SOD), nitric oxide (NO), and glutathione peroxidase (GPx) but not endothelial nitric oxide synthase. Also, plasma UA and vascular cell adhesion molecule-1 (VCAM-1) increased in the SD group compared with control. However, *S. maydis* extract in the SD-exposed group increased NO and GPx and not SOD. Also, *S. maydis* extract attenuated UA and VCAM-1. In conclusion, high-salt intake may initiate deleterious cardiovascular events through UA-dependent mechanism and *S. maydis* extract has therapeutic potential in high-salt-induced oxidative damage and/or UA-dependent endothelial pathologies.

Key words: hyperuricemia, corn silk, high salt, uric acid, Wistar rats, endothelial dysfunction.

Résumé : L'hyperuricémie est impliquée dans la pathogenèse et les complications de maladies cardiovasculaires associées à des événements présentant une augmentation des oxydants. D'après des données probantes, une consommation excessive de sel entraîne des troubles cardiométaboliques, mais le mécanisme est insaisissable. *Stigma maydis* (barbe de maïs) est entre autres également reconnu pour ses propriétés antioxydantes. Cette étude vise donc à établir l'effet d'un régime alimentaire riche en sel (« SD ») sur la production d'acide urique (« UA ») et le rôle de *S. maydis* dans les phénotypes induits par le sel. Quatre groupes de rats choisis aléatoirement ($n = 5$) prennent de la nourriture normale pour rat, de l'extrait de barbe de maïs (500 mg/kg), SD (8%), de l'extrait de barbe de maïs et de la nourriture riche en sel. Après six semaines d'expérimentation, chaque animal est anesthésié par exposition à des vapeurs de chloroforme et des échantillons de sang sont prélevés par ponction cardiaque. Les données sont exprimées en moyenne $\pm$ erreur type de la moyenne et les valeurs de $p < 0,05$ sont admises comme significatives. Un régime riche en sel engendre une diminution de la superoxyde dismutase plasmatique (« SOD »), de l'oxyde nitrique (« NO ») et de la glutathion peroxydase (« GPx »), mais pas de l'oxyde nitrique synthase endothéliale. Comparativement au groupe de contrôle, l'UA plasmatique et la molécule d'adhésion cellulaire vasculaire-1 (« VCAM-1 ») augmentent dans le groupe SD. Toutefois, l'extrait de *Stigma maydis* dans le groupe exposé au SD entraîne une augmentation de NO et de GPx mais pas de SOD. En outre, l'extrait de *S. maydis* atténue UA et VCAM-1. En conclusion, une consommation élevée de sel peut déclencher des événements cardiovasculaires nuisibles par le biais d'un mécanisme dépendant de l'UA et l'extrait de *S. maydis* présente un potentiel thérapeutique dans les dommages oxydatifs et/ou les pathologies endothéliales dépendantes de UA. [Traduit par la Rédaction]

Mots-clés : hyperuricémie, barbe de maïs, teneur élevée en sel, acide urique, rats Wistar, dysfonctionnement endothélial.

Introduction

Oxidative stress is involved in the advancement of endothelial dysfunction (Silva et al. 2012) and vascular oxidative stress is usually triggered by many pathways, including the xanthine oxidase pathway (Kelley et al. 2010). Xanthine oxidase catalyzes the production of uric acid (UA) during purine catabolism and generates reactive oxygen species (ROS) in the process (Saugstad 1996). The UA status of a biological system can be used to reflect the level of

oxidative stress and is also a strong predictor of macrovascular complications (Bos et al. 2006). The mechanism(s) by which UA may engender organ damage is still partly understood, but there is growing evidence that an endothelial dysfunction is a fundamental event and in association with UA affects cardiovascular function and structure (Johnson et al. 2003). An array of experiments in rats demonstrated that elevated plasma UA elicited by uricase inhibition triggers hypertension and disrupts nitric oxide

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(NO) production in the macula densa, which is a point on the distal end of the thick ascending limb containing densely packed granules, while treatment with NO precursor (L-arginine) reduces hypertension and renal injury (Mazzali et al. 2001; Sánchez-Lozada et al. 2005).

Exposure of the cells to excess oxidants damage the cell proteins, provokes inflammation, and promotes apoptosis (Dröge 2002). Although oxidants are required for immune response signaling, cellular antioxidant molecules play a vital role in maintaining physiological redox status. Superoxide dismutase (SOD) plays a key antioxidant role in nearly all living cells exposed to oxygen as singlet oxygen is one of the main ROS in the cell. Also, glutathione peroxidase (GPx) is a selenium-containing antioxidant enzyme that effectively reduces H_2O_2 and lipid peroxides to water and lipid alcohols, respectively, and in turn oxidizes glutathione to glutathione disulfide (Hecker et al. 2013). Reduced glutathione has also been shown to play a major role in the regulation of intracellular redox reactions (Hecker et al. 2013).

Corn belongs to the grass family Graminae (*Zea mays*). It is a highly successful cereal grass among others in the equatorial region. Corn silk (CS; *Stigma maydis*) is made from stigmas, the yellowish thread like strands from the female inflorescence of maize. CS is an important herb used traditionally by the Chinese and Native Americans to treat many diseases. It is also used as traditional medicine in many parts of the world such as Turkey, United States, and France (Hasanudin et al. 2012). CS is a waste material from corn cultivation and is in abundant supply (Maksimović et al. 2005). It has been consumed for a long time as a therapeutic remedy for various illnesses and is important as an alternative natural-based treatment. Other beneficial treatments of CS include anti-fatigue activity, anti-depressant activity, and diuretic activity (Hu et al. 2010). In addition, it possesses an excellent antioxidant capacity (Ebrahimzadeh et al. 2008) and demonstrates protective effects in radiation and nephrotoxicity (Bai et al. 2010; Sepehri et al. 2011).

High-salt diet (SD), on the other hand, is a diet that comprises high sodium content. Estimates indicate that 8% salt diet in rats is equivalent to 40 g/day in humans, an intake that is significantly higher than what is obtainable in the normal human diet (Luft et al. 1990). There is growing evidence that excessive dietary salt promotes the development of not only insulin resistance but also hypertension in humans and animal models (Donovan et al. 1993; Ogihara et al. 2001, 2002). Furthermore, an SD in Sprague-Dawley rats led to insulin resistance, decreased glucose utility in skeletal muscle, and elevated blood pressure (Ogihara et al. 2002). Therefore, this study aimed at testing the hypothesis that UA-led oxidative events are involved in salt-induced endothelial derangements and *S. maydis* extract has therapeutic potential to resolve this salt-engendered condition.

Materials and methods

Animals

Twenty female Wistar rats with a mean weight of 135 ± 1 g were acclimatized for 1 week and randomly allotted into 4 groups of 5 rats each. They were maintained at a standard temperature (28°C) in a well-controlled lit room with food and water provided ad libitum. The number and suffering of animals were reduced to the barest minimum. The study was carried out in line with the National Institutes of Health's *Guide for the Care and Use of Laboratory Animals* and was ratified by the ethical review committee, University of Ilorin, Ilorin, Nigeria.

Extract preparation

Approximately 50 g of freshly collected *S. maydis* (Fig. 1) was thoroughly washed with distilled water, cut into shreds, and air-dried at room temperature for 7 days and then dissolved in 200 mL of 100% methanol in a conical flask. This was then placed in a

Fig. 1. A diagram showing the identification of *Stigma maydis* (corn silk) on a corn plant. [Color online.]



shaker for approximately 120 h at $28 \pm 2^\circ\text{C}$. The resulting extracts were then transferred to clean vessels, evaporated to dryness, and re-dissolved in dimethyl sulfoxide according to the methods of Larson et al. 2016 to yield a stock concentration of approximately 200 mg/mL. The stock concentration was filtered with a membrane filter and stored in an amber bottle at room temperature. Extracts were administered at a dose of 500 mg/kg body weight of rats in distilled water (orally). (Ha et al. 2018).

Treatment

After a week of acclimatization, groups were fed with normal rat chow (CTR), extract of CS, SD, and SD with CS extract (SD+CS). After 6 weeks of the experimental procedure, the animals were anesthetized with chloroform by inhalation and blood samples were collected by cardiac puncture and dispensed into lithium heparinized sample bottles. The blood was then centrifuged at 5000 rpm at 10°C for 15 min to separate the plasma from the cells.

Determination of sodium ion content in feed

Atomic emission spectroscopy method was used to determine the Na^+ content of the feed sample. High-salt feed comprising 8% NaCl (Sofola et al. 2002) was prepared and fed to the SD group instead of 0.3% NaCl found in the normal rat chow.

Phytochemical analysis

Phytochemical screening (PS) of the local CS with voucher number UILH/001/1219 was done for this study by standard photochemical screening according to the methods of Latimer 2016 and the proximate compositions of the extract obtained. PS of the CS reflected that alkaloids contain the highest percentage by weight/kg (115.69 mg/log) followed by terpenoids (90.36 mg/log).

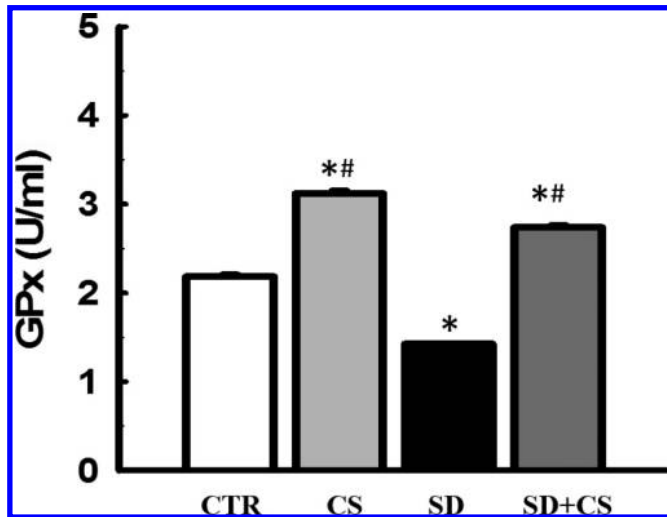
Biochemical assay

Plasma vascular cell adhesion molecule-1 (VCAM-1), NO, and UA were determined by using ELISA kit (E-EL-R2434) from Elabscience (Wuhan, China). GPx, SOD, and endothelial nitric oxide synthase (eNOS) were measured by the standardized enzymatic colorimetric method using assay kit obtained from Fortress diagnostics (Antrim, UK).

Statistical analysis

Results were presented as means $\pm$ SEM. The test for significance was done using 1-way ANOVA and Least Significant Difference post hoc test. $P < 0.05$ was accepted as significant. All statistical comparisons and test were done using version 20 of the Statistical Package for Social Sciences (SPSS).

Fig. 2. Effect of corn silk (CS) with high-salt diet (SD) on glutathione peroxidase (GPx). The animals were fed with normal chow (CTR group), high-salt (8%) feed (SD group), CS extract (500 mg/kg; CS group), and both high-salt (8%) and CS extract (500 mg/kg; SD+CS group). CS extract increased GPx singly or in combination with SD. Data were analyzed by 1-way ANOVA followed by Bonferroni post hoc test. Values are expressed as means $\pm$ SEM of 5 rats per group (*, $p < 0.05$ vs CTR group; #, $p < 0.05$ vs SD group).



Results

S. maydis extract heightens circulating GPx in high-salt-fed rats

Plasma GPx was significantly reduced compared with control in the SD group. However, *S. maydis* extract treatment with or without salt diet led to elevated plasma GPx compared with CTR and SD groups (Fig. 2).

S. maydis extract without an SD increases plasma SOD

Plasma SOD did not change compared with CTR in SD and SD+CS groups but significantly increased in CS when compared with CTR. The impact of high-salt intake on redox activities revealed was independent of superoxide dismutase (Fig. 3).

S. maydis extract increased NO synthesis in high-salt-fed rats

In the SD group, NO but not eNOS reduced significantly compared with CTR. Nevertheless, NO and eNOS increased in the CS group compared with CTR and SD groups. However, both NO and eNOS in the plasma were augmented and normalized in the SD+CS groups (Fig. 4a and 4b).

S. maydis extract attenuated VCAM-1 in high-salt-fed rats

Plasma VCAM-1 increased significantly in the SD group, whereas it was attenuated significantly in both CS and SD+CS groups (Fig. 5).

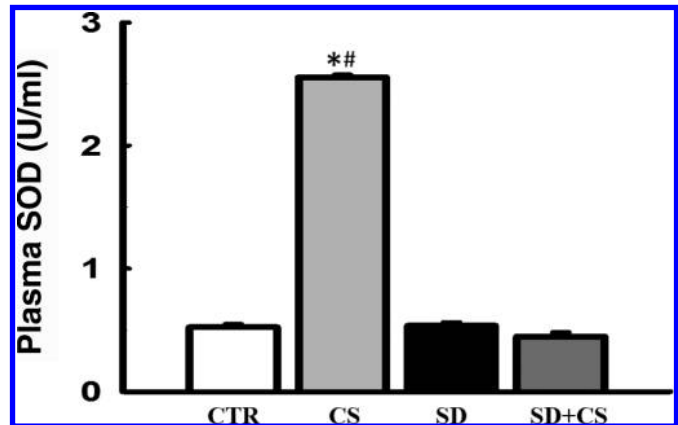
S. maydis extract suppressed plasma UA in high-salt-fed rats

Plasma UA was elevated in the SD group and was reduced in the CS group compared with CTR. However, the plasma UA in SD+CS group was reduced and was comparable to the CTR group (Fig. 6).

Discussion

The links between high-salt intake and cardiometabolic disturbances are still being investigated. The present study probed the possible relationship between high-salt intake and markers of endothelial dysfunction and antioxidant capacity. In this study, high-salt intake disrupts markers of the endothelial function indicated by a reduction in plasma NO but not eNOS and elevation of plasma VCAM-1. This disruption is associated with elevated

Fig. 3. Effect of corn silk (CS) with high-salt diet (SD) on plasma superoxide dismutase (SOD). The animals were fed with normal chow (CTR group), high-salt (8%) feed (SD group), CS extract (500 mg/kg; CS group), and both high-salt (8%) and CS extract (500 mg/kg; SD+CS group). CS extract increased SOD singly but not in combination with SD. Data were analyzed by 1-way ANOVA followed by Bonferroni post hoc test. Values are expressed as means $\pm$ SEM of 5 rats per group (*, $p < 0.05$ vs CTR group; #, $p < 0.05$ vs SD group).



plasma UA and deteriorated systemic antioxidant defense. NO is a vasodilator that augments blood flow. Adequate perfusion of organs plays a pivotal role in their function and sustenance. The expression of adhesion molecules (VCAM-1 and ICAM-1) has been shown to be negatively regulated by NO through the suppression of superoxides and downregulation of inflammatory factors (Space et al. 2000). Data here showed that high-salt intake raised the blood level of VCAM-1, a molecule known to increase in non-quiescent inflamed endothelium. Increased inflammatory and proliferative activities in the endothelium is a strong risk factor for atherosclerosis and heart failure. Hence, high salt may induce endothelial dysfunction through dysregulated inflammatory response, leading to adverse events such as macrovascular diseases, which are associated with high mortality.

Oxidative stress has been implicated in cardiometabolic disturbances and usually causes damage to cellular structures resulting in loss of functionality. Despite the fact that these oxidants have physiological signaling roles, a cellular antioxidant defense is paramount in regulating the amount of oxidant present in the cell. Depressed antioxidant capacity of the cell will make the cell more susceptible to oxidative damage. In this study, high-salt intake caused depression in circulating GPx and SOD. These 2 enzymes reduce superoxides and ROS protecting the cell from redox imbalance and cell damage (Matés and Sánchez-Jiménez 1999). The reduction in these enzymes might be as a result of overwhelming excessive ROS and superoxides generation.

Among the processes that liberate ROS, UA production via xanthine oxidase activity is very important. Studies have shown that inhibition of xanthine oxidase with allopurinol reduced UA levels and improved renal derangements (Kosugi et al. 2009). Also, hyperuricemia has been implicated in inflammatory and cardiometabolic diseases (Johnson et al. 2005; Leyva et al. 1998). Despite the fact that uric acid agreeably functions as an anti-inflammatory molecule, previous studies have shown the relationship between UA and surrogate markers of cardiometabolic diseases, such as endothelial dysfunction (Khosla et al. 2005). This study, however, is the first to show that high-salt intake increased UA production with concomitant depression of antioxidant defense systems (G6PD-dependent GPx and SOD) and NO synthesis with evidence of increased endothelial adhesion to inflammatory cells. Therefore, it shows that salt-induced derangement might be UA/oxidative stress-dependent. UA has been shown to augment arginase activity thereby

Fig. 4. Effect of corn silk (CS) with high-salt diet (SD) on (A) plasma nitric oxide (NO) and (B) endothelial nitric oxide synthase (eNOS). The animals were fed with normal chow (CTR group), high-salt (8%) feed (SD group), CS extract (500 mg/kg; CS group), and both high-salt (8%) and CS extract (500 mg/kg; SD+CS group). CS extract increased NO singly and maintained NO at normal levels in combination with high salt. CS extract increased eNOS singly or in combination with SD. Data were analyzed by 1-way ANOVA followed by Bonferroni post hoc test. Values are expressed as means $\pm$ SEM of 5 rats per group (*, $p < 0.05$ vs control; #, $p < 0.05$ vs SD).

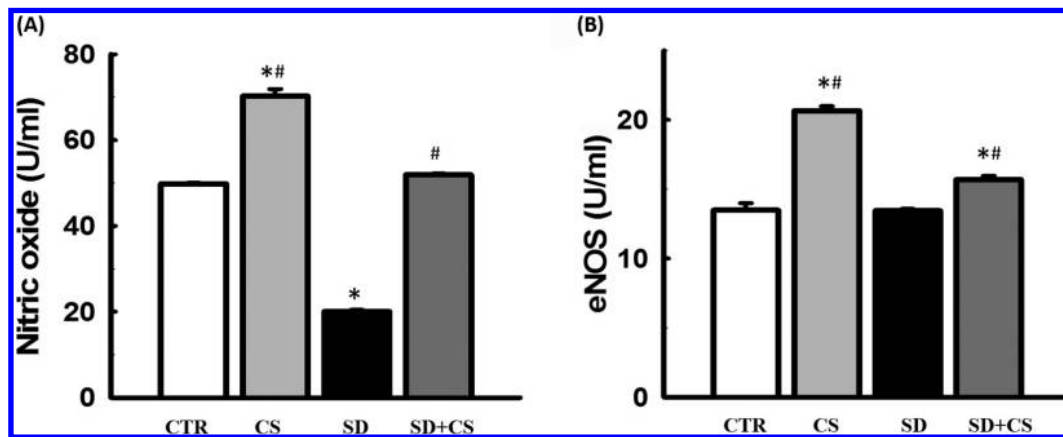


Fig. 5. Effect of corn silk (CS) with high-salt diet (SD) on plasma vascular cell adhesion molecule-1 (VCAM-1). The animals were fed with normal chow (CTR group), high-salt (8%) feed (SD group), CS extract (500 mg/kg; CS group), and both high-salt (8%) and CS extract (500 mg/kg; SD+CS group). CS extract reduced VCAM-1 singly but not in combination with SD. Data were analyzed by 1-way ANOVA followed by Bonferroni post hoc test. Values are expressed as means $\pm$ SEM of 5 rats per group (*, $p < 0.05$ vs control; #, $p < 0.05$ vs SD).

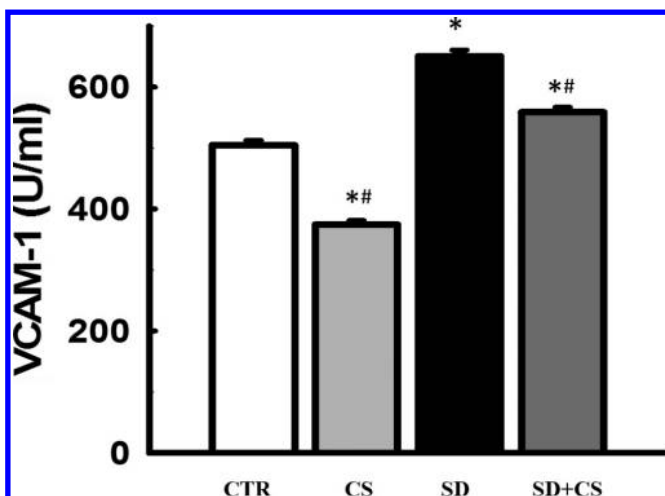
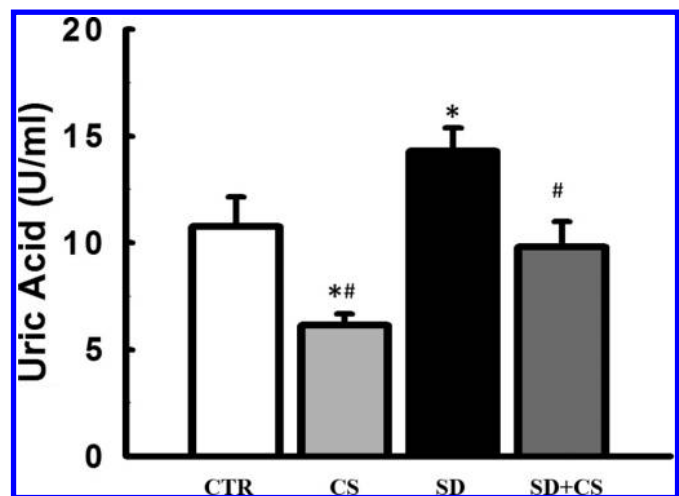


Fig. 6. Effect of corn silk (CS) with high-salt diet (SD) on plasma uric acid (UA). The animals were fed with normal chow (CTR group), high-salt (8%) feed (SD group), CS extract (500 mg/kg; CS group), and both high-salt (8%) and CS extract (500 mg/kg; SD+CS group). CS extract reduced UA singly or in combination with SD. Data were analyzed by 1-way ANOVA followed by Bonferroni post hoc test. Values are expressed as means $\pm$ SEM of 5 rats per group (*, $p < 0.05$ vs control; #, $p < 0.05$ vs SD).



increasing the clearance of L-arginine, which is the substrate for eNOS. This status reduces NO synthesis and may contribute to endothelial dysfunction (Zharikov et al. 2008). Taken together, salt-induced elevated UA indirectly (through oxidative stress) or directly (through increased arginase activity) can modulate NO synthesis, which eventually determines the inflammatory or proliferative status of the endothelium through regulation of adhesion molecules. This study shows that NO reduced in SD-fed rats without a corresponding reduction in eNOS. This status shows that UA might have reduced NO by reducing eNOS substrate L-arginine. Conversely, CS extract treatment in this study showed significant antioxidant potentiating capacity and elicited attenuation of salt-induced deleterious alterations. This study, however, showed that the therapeutic effect of the extract might be mediated by its suppression of circulating UA levels (Fig. 6). In summary, the model presented in this study demonstrates that salt-induced cardiometabolic disruption might be indicated by both endothelial dysfunction and depressed

antioxidant capacity. Nevertheless, since an array of literature supports the antioxidant potentiating effect of *S. maydis* extract (Ebrahimzadeh et al. 2008), among other reportedly therapeutic effects (Hu et al. 2010), we administered the extract as a therapeutic intervention in salt-induced derangement of endothelial dysfunction mediators. Considering the dearth of information in the effect of *S. maydis* on UA production, this study also investigated the effect of the extract on plasma UA. It was found that CS extract ameliorated salt-induced elevated endothelial dysfunction markers and buffered redox status in high-salt-fed rats. These effects were accompanied by suppression of plasma UA:

1. UA was significantly reduced in rats treated with the extract alone compared with the CTR group (Fig. 6). This shows that the extract has a UA-lowering capacity at least in healthy rats but the mechanism remains elusive. However, we propose enhanced uricase activity, inhibition of xanthine oxidase, and

increased UA excretion/clearance since reports indicate that the extract has diuretic property (Hu et al. 2010).

2. The extract reduced plasma UA to levels comparable to the CTR group from the elevated salt-induced levels in high-salt-fed rats (Fig. 5). This advances the therapeutic potential of the extract in conditions characterized by hyperuricemia. The therapeutic potential is hence affirmed by the reversal of endothelial dysfunction markers and improved antioxidant capacity in rats fed with SD and treated with the extract.

Conclusion

In conclusion, this study demonstrates that UA production is involved in the pathogenesis of salt-induced elevated endothelial dysfunction markers and that CS extract has therapeutic potential in UA heightening conditions. Therefore, it is recommended that the mechanism of these striking findings and the link between the extract's phytochemicals and anti-UA effect should be studied towards characterizing novel pharmacologic and therapeutic candidates in the treatment of cardiometabolic diseases.

Conflict of interest statement

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no financial support for this work that could have affected its outcome.

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References

- Bai, H., Hai, C., Xi, M., Liang, X., and Liu, R. 2010. Protective effect of maize silks (*Maydis stigma*) ethanol extract on radiation-induced oxidative stress in mice. *Plant Foods Hum. Nutr.* **65**(3): 271–276. doi:10.1007/s11130-010-0172-6. PMID: 20526679.
- Bos, M.J., Koudstaal, P.J., Hofman, A., Witteman, J.C., and Breteler, M.M. 2006. Uric acid is a risk factor for myocardial infarction and stroke: the Rotterdam study. *Stroke*, **37**: 1503–1507. doi:10.1161/01.STR.0000221716.55088.d4. PMID: 16675740.
- Donovan, D.S., Solomon, C.G., Seely, E.W., Williams, G.H., and Simonson, D.C. 1993. Effect of sodium intake on insulin sensitivity. *Am. J. Physiol.* **264**: E730–E734. doi:10.1152/ajpendo.1993.264.5.E730. PMID: 8498495.
- Dröge, W. 2002. Free radicals in the physiological control of cell function. *Physiol. Rev.* **82**(1): 47–95. doi:10.1152/physrev.00018.2001. PMID: 11773609.
- Ebrahimzadeh, M.A., Pourmorad, F., and Hafe, S. 2008. Antioxidant activities of Iranian corn silk. *Turk. J. Biol.* **32**: 43–49.
- Ha, A.W., Kang, H.J., Kim, S.L., Kim, M.H., and Kim, W.K. 2018. Acute and sub-acute toxicity evaluation of corn silk extract. *Prev. Nutr. Food Sci.* **23**(1): 70–76. doi:10.3746/pnf.2018.23.1.70. PMID: 29662850.
- Hasanudin, K., Hashim, P., and Mustafa, S. 2012. Corn Silk (Stigma Maydis) in Healthcare: A Phytochemical and Pharmacological Review. *Molecules*, **17**: 9697–9715. doi:10.3390/molecules17089697. PMID: 22890173.
- Hecker, P.A., Leopold, J.A., Gupta, S.A., Recchia, F.A., and Stanley, W.C. 2013. Impact of glucose-6 phosphate dehydrogenase deficiency on the pathophysiology of cardiovascular disease. *Am. J. Physiol. Heart Circ. Physiol.* **304**: H491–H500. doi:10.1152/ajpheart.00721.2012. PMID: 23241320.
- Hu, Q.L., Zhang, L.J., Li, Y.N., Ding, Y.J., and Li, F.L. 2010. Purification and anti-fatigue activity of flavonoids from cornsilk. *Int. J. Phys. Sci.* **5**: 321–326.
- Johnson, R.J., Kang, D.H., Feig, D., Kivlighn, S., Kanellis, J., Watanabe, S., et al. 2003. Is there a pathogenetic role for uric acid in hypertension and cardiovascular and renal disease? *Hypertension*, **41**: 1183–1190. doi:10.1161/01.HYP.0000069700.62727.C5. PMID: 12707287.
- Johnson, R.J., Rodriguez-Iturbe, B., Kang, D.H., Feig, D.I., and Herrera-Acosta, J.A. 2005. Unifying pathway for essential hypertension. *Am. J. Hypertens.* **18**: 431–440. doi:10.1016/j.amjhyper.2004.08.035. PMID: 15797666.
- Kelley, E.E., Khoo, N.K., Hundley, N.J., Malik, U.Z., Freeman, B.A., and Tarpey, M.M. 2010. Hydrogen peroxide is the major oxidant product of xanthine oxidase. *Free Radic. Biol. Med.* **48**: 493–498. doi:10.1016/j.freeradbiomed.2009.11.012. PMID: 19941951.
- Khosla, U.M., Zharikov, S., Finch, J.L., Nakagawa, T., Roncal, C., Mu, W., et al. 2005. Hyperuricemia induces endothelial dysfunction. *Kidney Int.* **67**: 1739–1742. doi:10.1111/j.1523-1755.2005.00273.x. PMID: 15840020.
- Kosugi, T., Nakayama, T., Heinig, M., Zhang, L., Yuzawa, Y., Sanchez-Lozada, L.G., et al. 2009. Effect of lowering uric acid on renal disease in the type 2 diabetic db/db mice. *Am. J. Physiol. Renal Physiol.* **297**: F481–F488. doi:10.1152/ajprenal.00092.2009. PMID: 19458127.
- Larson, E.C., Pond, C.D., Rai, P.P., Matainaho, T.K., Piskaut, P., Franklin, M.R., and Barrows, L.R. 2016. Traditional preparations and methanol extracts of Medicinal plants from Papua New Guinea exhibit similar cytochrome p450 inhibition. *Evid. Based Complement. Alternat. Med.* **2016**: 7869710. doi:10.1155/2016/7869710. PMID: 27642356.
- Latimer, G.W. 2016. Official Methods of Analysis of AOAC International, 20th edition. Association of Official Analytical Chemists, Washington, DC, USA, pp. 598–590.
- Leyva, F., Anker, S.D., Godsland, I.F., Teixeira, M., Hellewell, P.G., Kox, W.J., et al. 1998. Uric acid in chronic heart failure: a marker of chronic inflammation. *Eur. Heart J.* **19**: 1814–1822. doi:10.1053/eurhj.1998.1188. PMID: 9886724.
- Luft, F.C., Zemel, M.B., Sowers, J.A., Fineberg, N.S., and Weinberger, M.H. 1990. Sodium bicarbonate and sodium chloride: effects on blood pressure and electrolyte homeostasis in normal and hypertensive man. *J. Hypertens.* **8**: 663–670. doi:10.1097/00004872-199007000-00010. PMID: 2168457.
- Maksimović, Z., Malenčić, Đ., and Kovačević, N. 2005. Polyphenol contents and antioxidant activity of Maydis stigma extracts. *Bioresour. Technol.* **96**: 873–877. doi:10.1016/j.biortech.2004.09.006. PMID: 15627557.
- Matés, J.M., and Sánchez-Jiménez, F. 1999. Antioxidant enzymes and their implications in pathophysiological processes. *Front. Biosci.* **4**: D339–D345. doi:10.2741/mates. PMID: 10077544.
- Mazzali, M., Hughes, J., Kim, Y.G., Jefferson, J.A., Kang, D.H., Gordon, K.L., et al. 2001. Elevated uric acid increases blood pressure in the rat by a novel crystal-independent mechanism. *Hypertension*, **38**: 1101–1106. doi:10.1161/hy1101.092839. PMID: 11711505.
- Ogihara, T., Asano, T., Ando, K., Chiba, Y., Sekine, N., Sakoda, H., et al. 2001. Insulin resistance with enhanced insulin signaling in high-salt diet-fed rats. *Diabetes*, **50**: 573–583. doi:10.2337/diabetes.50.3.573. PMID: 11246877.
- Ogihara, T., Asano, T., Ando, K., Sakoda, H., Anai, M., Shojima, N., et al. 2002. High-salt diet enhances insulin signaling and induces insulin resistance in Dahl salt-sensitive rats. *Hypertension*, **40**: 83–89. doi:10.1161/01.HYP.0000022880.45113.C9. PMID: 12105143.
- Sánchez-Lozada, L.G., Tapia, E., Santamaria, J., Avila-Casado, C., Soto, V., Nepomuceno, T., et al. 2005. Mild hyperuricemia induces vasoconstriction and maintains glomerular hypertension in normal and remnant kidney rats. *Kidney Int.* **67**: 237–247. doi:10.1111/j.1523-1755.2005.00074.x. PMID: 15610247.
- Saugstad, O.D. 1996. Role of xanthine oxidase and its inhibitor in hypoxia: reoxygenation injury. *Pediatrics*, **98**: 103–107. PMID: 8668378.
- Sepehri, G., Derakhshanfar, A., and Zade, F.Y. 2011. Protective effects of corn silk extract administration on gentamicin-induced nephrotoxicity in rat. *Comp. Clin. Pathol.* **20**: 89–94. doi:10.1007/s00580-009-0943-3.
- Silva, B.R., Pernomain, L., and Bendhack, L.M. 2012. Contribution of oxidative stress to endothelial dysfunction in hypertension. *Front. Physiol.* **3**: 441. doi: 10.3389/fphys.2012.00441.
- Sofola, O.A., Knill, A., Hainsworth, R., and Drinkhill, M. 2002. Change in endothelial function in mesenteric arteries of Sprague-Dawley rats fed a high salt diet. *J. Physiol.* **543**: 255–260. doi:10.1113/jphysiol.2002.022277. PMID: 12181296.
- Space, S.L., Lane, P.A., Pickett, C.K., and Weil, J.V. 2000. Nitric oxide attenuates normal and sickle red blood cell adherence to pulmonary endothelium. *Am. J. Hematol.* **63**: 200–204. doi:10.1002/(SICI)1096-8652(200004)63:4<200::AID-AJH7>3.0.CO;2-Q. PMID: 10706764.
- Zharikov, S.I., Krotova, K., Hu, H., Baylis, C., Johnson, R.J., Block, E.R., et al. 2008. Uric acid decreases NO production and increases arginase activity in cultured pulmonary artery endothelial cells. *Am. J. Physiol. Cell Physiol.* **295**: 1183–1190. doi:10.1152/ajpcell.00075.2008.

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