Original Article
Food Science and Technology

ISSN 0101-2061 (Print)
ISSN 1678-457X (Online)

DOI: https://doi.org/10.1590/fst.116621

Extraction of lycopene from tomato pomace and its protective effects on renal injury in diabetic rats

Rong XIE[1], Heping ZHANG[1]*, Xiaohui LIU[1], Jiali LIU[2], Qinyun LI[1]

Abstract

The aim of this study was to investigate the protective effects of lycopene from tomato pomace on renal injury in diabetic rats. Lycopene was extracted from tomato pomace. The rats were divided into control, model and 10, 20 and mg/kg lycopene groups. The diabetic nephropathy model was constructed in the latter four groups. Then, the latter three groups were treated with 10, 20 and mg/kg lycopene, respectively. After four weeks of treatment, compared with the model group, in 20 and 40 mg/kg lycopene groups the serum fasting plasma glucose level was decreased ($P < 0.05$), the fasting insulin level was increased ($P < 0.05$), the renal index and 24-h urinary protein level were decreased ($P < 0.05$), the blood urea nitrogen and serum creatinine levels were decreased ($P < 0.05$), the renal tissue superoxide dismutase and glutathione peroxidase levels were increased ($P < 0.05$), the renal tissue malondialdehyde level was decreased ($P < 0.05$), and the serum tumor necrosis factor α, interleukin 6 and hypersensitive C-reactive protein levels were decreased ($P < 0.05$). In conclusion, lycopene from tomato pomace can alleviate renal injury in diabetic rats. The mechanism may be related to the resistance of oxidative stress and inflammatory response.

Keywords: lycopene; diabetes; renal injury; oxidative stress; inflammatory response.

Practical Application: Lycopene from tomato pomace has the protective effects on renal injury in diabetic rats, and may be clinically applied for prevention and treatment of diabetic nephropathy.

1 Introduction

Lycopene is a kind of natural carotenoids. It mainly exists in tomato, watermelon, red grapefruit, papaya and other foods, and has the highest content in tomato (Vieira et al., 2020; Li et al., 2021). Tomato pomace is a byproduct of industrial tomato processing, and contents abundant lycopene (Perretti et al., 2013; Pellicanò et al., 2020). Lycopene has strong antioxidant activity (Müller et al., 2016; Zheng et al., 2020). In addition, lycopene has a variety of biological effects such as anti-inflammation (Chen et al., 2019), anti-tumor (Mirahmadi et al., 2020), cardiovascular protection (Cheng et al., 2019) and immunity enhancement (Eze et al., 2019), so it has the functions of preventing cancer (Chen et al., 2015), delaying aging (Petyaev, 2016) and protecting skin (Chernyshova et al., 2019). The development and application of lycopene in food, medicine, cosmetics and other fields has become a research hotspot.

Diabetes is a chronic endocrine and metabolic disease with genetic characteristics. With the improvement of people's living standard and changes of diet structure, the incidence of diabetes has increased year by year, which seriously endangers the health and life quality of people (Xia et al., 2019). The diabetic patients with poor long-term glycemic control often suffer from the complications in multiple organs and tissues, which are the main cause of disability or even death of diabetic patients (Cole & Florez, 2020). Renal injury, namely the diabetic nephropathy, is a common complication of diabetes, and it is a lesion with high incidence rate and mortality rate (Wang et al., 2018). The pathological changes of diabetic nephropathy include glomerular and tubular hypertrophy, basement membrane thickening and mesangial hyperplasia, which finally progress to glomerulosclerosis and tubulointerstitial fibrosis (Ji et al., 2019). Due to the complex pathogenesis, the diabetic nephropathy is currently treated mainly using the hypoglycemic drugs and renin-angiotensin system blocking drugs, but they have varying degrees of side effects on the body. Therefore, it is significant to develop new drugs for treatment of diabetic nephropathy. The pathogenesis of diabetic nephropathy is complex, involving a variety of factors and signal pathways. Studies have confirmed that the oxidative stress and inflammatory response play a key role in the occurrence and development of diabetic nephropathy (Elmarakby & Sullivan, 2012; Bao et al., 2018). Studies have shown that some herbal supplementation and herbal extracts have the alleviative effect on diabetes (Yan et al., 2020; Rehman et al., 2021). This study aimed to extract lycopene from tomato pomace, and investigate its protective effects on renal injury in diabetic rats, for providing an experimental basis for clinical application of lycopene to prevention and treatment of diabetic nephropathy.

Received 07 Nov., 2021
Accepted 17 Dec., 2021
[1]*Department of Nephrology, Affiliated Hospital of North Sichuan Medical College, Shunqing District, Nanchong, China*
[2]*Department of Clinical Medicine, North Sichuan Medical College, Nanchong, China*
*Corresponding author: zhanghepingnc1@163.com

2 Materials and methods

2.1 Extraction of lycopene from tomato pomace

Crude tomato pomace was washed, seed-removed and dehydrated. After drying, it was crushed and screened. A certain quality of dry tomato pomace powder was placed in the supercritical CO_2 extraction. The extraction was performed under the optimal conditions as follows: extraction temperature, 52 °C; extraction time, 2 h; extraction pressure, 35 MPa; CO_2 flow rate, 22 kg/h, entrainer (ethanol) volume fraction, 90%. Under these conditions, the final lycopene product was obtained, with purity of 36.48%.

2.2 Construction of diabetic nephropathy model

Male SD rats (180-220 g) were adaptively fed for 1 week under conditions of condition of temperature of 22 ± 2 °C, humidity of 50 ± 5% and 12 h/12 h light/dark cycle. Then, the rats were fed with high-fat and high-glucose diet for 8 weeks. Then, the rats were treated with 30 mg/kg streptozotocin by single sterile intraperitoneal injection for two days, once per day. After 72 h, the fasting blood glucose (FBG) and 24-h urinary protein (24h UP) levels were detected. The FBG > 16.7 mmol/L and 24h UP > 20 mg indicated the successful modeling of diabetic nephropathy. The rats with failed modeling were eliminated.

2.3 Grouping of rats and treatment

Forty-eight rats with successful modeling of diabetic nephropathy were randomly divided into model group and 10, 20 and mg/kg lycopene groups, with 12 rats in each group. Other 12 rats with normal feeding were selected as control group. The rats in 10, 20 and mg/kg lycopene groups were treated with 10, 20 and mg/kg lycopene by gavage, respectively. The rats in control and model groups were treated with equal volume of normal saline by gavage. The treatment was performed once per day, for 4 successive weeks. No rat died during the treatment in each group.

2.4 Determination of urine and blood indexes

At the end of experiments, the rats in each group were fasted for 12 h, with free drinking. The rats were weighed for obtain the body mass. The 24 h urine sample was collected with metabolic cage. The 24h UP was determined by sulfosalicylic acid method. The rats were anesthetized with chloral hydrate. The blood was collected from the abdominal aorta. After centrifuging at 3000 r/min for 10 min, the serum was obtained. The serum FGB and fasting insulin (FINS) levels were detected using the corresponding kits. The blood urea nitrogen (BUN) and serum creatinine (Scr) levels were measured by automatic biochemical analyzer. The inflammatory response indexes including tumor necrosis factor α (TNF-α), interleukin 6 (IL-6) and hypersensitive C-reactive protein (hs-CRP) levels were determined using enzyme-linked immunosorbent assay. The procedures were in accordance to the instructions of kits.

2.5 Determination of renal index

The kidneys of rats were taken. The left and right kidneys were separated. After washing with normal saline and sucking dry with filter paper, the left kidney was weighed to obtain the left kidney mass. The renal index (left kidney mass / body mass, mg/g) was calculated.

2.6 Determination of renal tissue indexes

The right kidney of rats was taken. The 10% renal tissue homogenate was prepared using 5 mL Tris-HCl solution (pH 7.4). After centrifugation at 3000 r/min for 10 min, the supernatant was obtained. The superoxide dismutase (SOD), glutathione peroxidase (GSH-Px) and malondialdehyde (MDA) levels were determined using the corresponding kits. The procedures were in accordance to the instructions of kits.

2.7 Statistical analysis

SPSS 18.0 software was used for statistical analysis. The data were presented as mean ± standard deviation. The differences among five groups were analyzed using one-way analysis of variance, followed by SNK-q test. A $P < 0.05$ was regarded as statistically significant.

3 Results and discussion

3.1 Comparison of FBG and FINS among five groups

FBG and FINS levels are the gold indexes of diabetes (Qu et al., 2014). In this study, after four weeks of treatment, compared with control group, in model group and three lycopene groups the serum FBG level was significantly increased ($P < 0.05$), and the FINS level was significantly decreased ($P < 0.05$). Compared with the model group, in 20 and 40 mg/kg lycopene groups the serum FBG level was significantly decreased ($P < 0.05$), and the FINS level was significantly increased ($P < 0.05$) (Table 1). Zheng et al. (2019) have found that lycopene can decrease the FBG level in type 2 diabetic rats. In the study of Ozmen et al. (2016), lycopene can increase the insulin level in rats with experimentally induced diabetes mellitus. These findings are basically consistent with the results of our study.

3.2 Comparison of renal index and 24h UP level among five groups

Previous study (Hussien et al., 2020) has shown that, lycopene has the nephroprotective effect in mice. Renal index and 24h UP level are the indexes reflecting the renal injury (Zhu et al., 2018).

Table 1. Comparison of FBG and FINS among five groups.

Group	n	FBG (mmol/L)	FINS (mIU/L)
Control	12	5.47 ± 1.67	33.17 ± 5.36
Model	12	24.90 ± 4.89[a]	19.69 ± 2.81[a]
10 mg/kg lycopene	12	22.19 ± 3.15[a]	22.11 ± 3.30[a]
20 mg/kg lycopene	12	15.32 ± 3.05[abc]	25.16 ± 3.99[ab]
40 mg/kg lycopene	12	11.89 ± 2.62[abcd]	28.66 ± 2.81[abcd]
F		58.003	23.940
P		0.000	0.000

[a]$P < 0.05$ compared with control group; [b]$P < 0.05$ compared with model group; [c]$P < 0.05$ compared with 10 mg/kg lycopene group; [d]$P < 0.05$ compared with 10 mg/kg lycopene group. FBG, fasting plasma glucose; FINS, fasting insulin.

Table 2. Comparison of renal index and 24h UP level among five groups.

Group	n	Renal index (mg/g)	24h UP (mg)
Control	12	2.83 ± 0.21	8.82 ± 1.56
Model	12	4.66 ± 0.65[a]	28.05 ± 5.19[a]
10 mg/kg lycopene	12	4.28 ± 0.53[a]	24.40 ± 3.28[a]
20 mg/kg lycopene	12	3.84 ± 0.43[ab]	20.64 ± 4.06[ab]
40 mg/kg lycopene	12	3.37 ± 0.42[abcd]	11.78 ± 1.60[abcd]
F		26.792	58.917
P		0.000	0.000

[a]P < 0.05 compared with control group; [b]P < 0.05 compared with model group; [c]P < 0.05 compared with 10 mg/kg lycopene group; [d]P < 0.05 compared with 10 mg/kg lycopene group. 24h UP, 24-h urinary protein.

Table 3. Comparison of BUN and Scr levels among five groups.

Group	n	BUN (mmol/L)	Scr (μmol/L)
Control	12	5.82 ± 0.78	23.34 ± 2.05
Model	12	18.94 ± 2.54[a]	42.90 ± 4.65[a]
10 mg/kg lycopene	12	15.43 ± 2.87[ab]	40.12 ± 5.90[a]
20 mg/kg lycopene	12	12.17 ± 2.04[abc]	34.47 ± 4.98[ab]
40 mg/kg lycopene	12	9.84 ± 1.56[abcd]	30.27 ± 4.04[abcd]
F		79.160	36.651
P		0.000	0.000

[a]P < 0.05 compared with control group; [b]P < 0.05 compared with model group; [c]P < 0.05 compared with 10 mg/kg lycopene group; [d]P < 0.05 compared with 10 mg/kg lycopene group. BUN, blood urea nitrogen; Scr, serum creatinine.

Yang et al. (2011) have found that, lycopene can decrease the serum and urinary protein levels in rats with mercuric chloride renal damage. In this study, after treatment, the renal index and 24h UP level in model group and three lycopene groups were significantly higher than those in control group, respectively (P < 0.05). Compared with the model group, each indexes in 20 and 40 mg/kg lycopene groups was significantly decreased (P < 0.05) (Table 2). This suggests that, besides lowering blood glucose, lycopene can alleviate the renal injury of diabetic rats.

3.3 Comparison of BUN and Scr among five groups

BUN and Scr are also the indexes reflecting the renal injury (Li et al., 2020). Mahmoodnia et al. (2017) have found that lycopene can reduce the BUN and Scr levels in patients with cisplatin-induced nephropathy. Results of this study showed that, after treatment, compared with control group, in model group and three lycopene groups the BUN and Scr levels were significantly increased, respectively (P < 0.05). Compared with the model group, the BUN level in 10, 20 and 40 mg/kg lycopene groups and the Scr level in 20 and 40 mg/kg lycopene groups were significantly decreased, respectively (P < 0.05) (Table 3). This further confirms that, lycopene has the nephroprotective effect in diabetes rats.

3.4 Comparison of renal tissue SOD, GSH-Px and MDA levels among five groups

It is found that, under the condition of long-term hyperglycemia, the levels of polyol oxidation, protein glycosylation and glucose autoxidation are significantly increased (Hammes, 2018). Oxidative stress is closely related to renal injury caused by diabetes (Jha et al., 2016; Gong et al., 2019). SOD, GSH-Px and MDA are the main indexes to evaluate the level of oxidative stress. Lycopene has strong antioxidant activit (Müller et al., 2016; Zheng et al., 2020). Results of this study showed that, after treatment, compared with control group, in model group and three lycopene groups the renal tissue SOD and GSH-Px levels were significantly decreased (P < 0.05), and the MDA level was significantly increased (P < 0.05). Compared with the model group, in 20 and 40 mg/kg lycopene groups the SOD and GSH-Px levels were significantly increased (P < 0.05), and the MDA level was significantly decreased (P < 0.05). This indicates that, lycopene may alleviate the renal injury of diabetic rats by resisting the oxidative stress (Table 4).

Table 4. Comparison of renal tissue SOD, GSH-Px and MDA levels among five groups.

Group	n	SOD (U/mg prot)	GSH-Px (U/mg prot)	MDA (nmol/mg prot)
Control	12	55.37 ± 8.04	48.09 ± 7.37	2.82 ± 0.43
Model	12	25.94 ± 4.33[a]	18.49 ± 3.41[a]	13.30 ± 2.87[a]
10 mg/kg lycopene	12	30.20 ± 6.28[a]	22.37 ± 4.37[a]	11.38 ± 3.29[a]
20 mg/kg lycopene	12	36.73 ± 3.17[ab]	26.18 ± 5.59[ab]	6.52 ± 1.66[abc]
40 mg/kg lycopene	12	40.17 ± 5.50[abc]	33.26 ± 6.84[abcd]	5.09 ± 1.04[abc]
F		44.148	41.206	59.485
P		0.000	0.000	0.000

[a]P < 0.05 compared with control group; [b]P < 0.05 compared with model group; [c]P < 0.05 compared with 10 mg/kg lycopene group; [d]P < 0.05 compared with 10 mg/kg lycopene group. SOD, superoxide dismutase; GSH-Px, glutathione peroxidase; MDA, malondialdehyde.

3.5 Comparison of serum TNF-α, IL-6 and hs-CRP levels among five groups

Inflammation plays an important role in the process of renal injury caused by diabetes (Pérez-Morales et al., 2019). Study has shown that the serum TNF-α, IL-6 and hs-CRP levels are increased in patients with diabetic nephropathy (Aly et al., 2020). Lycopene has good anti-inflammatory effect (Jiang et al., 2018). Results of our study showed that, after treatment, compared with control group, in model group and three lycopene groups the serum TNF-α, IL-6 and hs-CRP levels were significantly increased, respectively (P < 0.05). Compared with the model group, the IL-6 level in 10, 20 and 40 mg/kg lycopene groups and the TNF-α and hs-CRP levels in 20 and 40 mg/kg lycopene groups were significantly decreased, respectively (P < 0.05) (Table 5). This confirms that, lycopene can reduce the inflammatory response in diabetic rats, thus alleviating the renal injury.

Table 5. Comparison of serum TNF-α, IL-6 and hs-CRP levels among five groups.

Group	n	TNF-α (ng/L)	IL-6 (ng/L)	hs-CRP (mg/L)
Control	12	11.05 ± 1.67	12.19 ± 1.38	2.41 ± 0.43
Model	12	18.21 ± 2.44[a]	21.43 ± 2.06[a]	5.67 ± 0.58[a]
10 mg/kg lycopene	12	17.36 ± 3.05[a]	18.63 ± 1.34[ab]	5.03 ± 0.78[a]
20 mg/kg lycopene	12	15.73 ± 2.89[ab]	16.30 ± 1.06[ab]	4.34 ± 0.31[abc]
40 mg/kg lycopene	12	14.88 ± 3.05[ab]	15.18 ± 1.62[abc]	3.98 ± 0.29[abcd]
F		12.328	55.327	89.699
P		0.000	0.000	0.000

[a]P < 0.05 compared with control group; [b]P < 0.05 compared with model group; [c]P < 0.05 compared with 10 mg/kg lycopene group; [d]P < 0.05 compared with 10 mg/kg lycopene group. TNF-α, tumor necrosis factor α; IL-6, interleukin 6; hs-CRP, hypersensitive C-reactive protein.

4 Conclusions

In conclusion, lycopene from tomato pomace can alleviate renal injury in diabetic rats. These protective effects may be related to the resistance of oxidative stress and inflammatory response, but the specific mechanisms remain to be further explored. This study has provided some experimental evidence for the application of lycopene to clinical prevention and treatment of diabetic nephropathy.

Conflict of interest

The authors declare that there is no conflict of interest.

Acknowledgements

This work was supported by the Key Research Projects of Scientific Research Projects of Sichuan Provincial Health Commission in 2019 (No. 19ZD006).

References

Aly, R. H., Ahmed, A. E., Hozayen, W. G., Rabea, A. M., Ali, T. M., El Askary, A., & Ahmed, O. M. (2020). Patterns of Toll-like receptor expressions and inflammatory cytokine levels and their implications in the progress of insulin resistance and diabetic nephropathy in type 2 diabetic patients. *Frontiers in Physiology*, 11, 609223. http://dx.doi.org/10.3389/fphys.2020.609223. PMid:33442388.

Bao, L., Li, J., Zha, D., Zhang, L., Gao, P., Yao, T., & Wu, X. (2018). Chlorogenic acid prevents diabetic nephropathy by inhibiting oxidative stress and inflammation through modulation of the Nrf2/HO-1 and NF-κB pathways. *International Immunopharmacology*, 54, 245-253. http://dx.doi.org/10.1016/j.intimp.2017.11.021. PMid:29161661.

Chen, G., Ni, Y., Nagata, N., Zhuge, F., Xu, L., Nagashimada, M., Yamamoto, S., Ushida, Y., Fuke, N., Suganuma, H., Kaneko, S., & Ota, T. (2019). Lycopene alleviates obesity-induced inflammation and insulin resistance by regulating M1/M2 status of macrophages. *Molecular Nutrition & Food Research*, 63(21), e1900602. http://dx.doi.org/10.1002/mnfr.201900602. PMid:31408586.

Chen, P., Zhang, W., Wang, X., Zhao, K., Negi, D. S., Zhuo, L., Qi, M., Wang, X., & Zhang, X. (2015). Lycopene and risk of prostate cancer: a systematic review and meta-analysis. *Medicine*, 94(33), e1260. http://dx.doi.org/10.1097/MD.0000000000001260. PMid:26287411.

Cheng, H. M., Koutsidis, G., Lodge, J. K., Ashor, A. W., Siervo, M., & Lara, J. (2019). Lycopene and tomato and risk of cardiovascular diseases: A systematic review and meta-analysis of epidemiological evidence. *Critical Reviews in Food Science and Nutrition*, 59(1), 141-158. http://dx.doi.org/10.1080/10408398.2017.1362630. PMid:28799780.

Chernyshova, M. P., Pristenskiy, D. V., Lozbiakova, M. V., Chalyk, N. E., Bandaletova, T. Y., & Petyaev, I. M. (2019). Systemic and skin-targeting beneficial effects of lycopene-enriched ice cream: A pilot study. *Journal of Dairy Science*, 102(1), 14-25. http://dx.doi.org/10.3168/jds.2018-15282. PMid:30447975.

Cole, J. B., & Florez, J. C. (2020). Genetics of diabetes mellitus and diabetes complications. *Nature Reviews. Nephrology*, 16(7), 377-390. http://dx.doi.org/10.1038/s41581-020-0278-5. PMid:32398868.

Elmarakby, A. A., & Sullivan, J. C. (2012). Relationship between oxidative stress and inflammatory cytokines in diabetic nephropathy. *Cardiovascular Therapeutics*, 30(1), 49-59. http://dx.doi.org/10.1111/j.1755-5922.2010.00218.x. PMid:20718759.

Eze, E. D., Afodun, A. M., Kasolo, J., & Kasozi, K. I. (2019). Lycopene improves on basic hematological and immunological parameters in diabetes mellitus. *BMC Research Notes*, 12(1), 805. http://dx.doi.org/10.1186/s13104-019-4841-8. PMid:31831054.

Gong, D. J., Wang, L., Yang, Y. Y., Zhang, J. J., & Liu, X. H. (2019). Diabetes aggravates renal ischemia and reperfusion injury in rats by exacerbating oxidative stress, inflammation, and apoptosis. *Renal Failure*, 41(1), 750-761. http://dx.doi.org/10.1080/0886022X.2019.1643737. PMid:31441362.

Hammes, H. P. (2018). Diabetic retinopathy: hyperglycaemia, oxidative stress and beyond. *Diabetologia*, 61(1), 29-38. http://dx.doi.org/10.1007/s00125-017-4435-8. PMid:28942458.

Hussien, Y. A., Abdalkadim, H., Mahbuba, W., Hadi, N. R., Jamil, D. A., & Al-Aubaidy, H. A. (2020). The nephroprotective effect of lycopene on renal ischemic reperfusion injury: a mouse model. *Indian Journal of Clinical Biochemistry*, 35(4), 474-481. http://dx.doi.org/10.1007/s12291-019-00848-7. PMid:33013018.

Jha, J. C., Banal, C., Chow, B. S., Cooper, M. E., & Jandeleit-Dahm, K. (2016). Diabetes and kidney disease: role of oxidative stress. *Antioxidants & Redox Signalling*, 25(12), 657-684. http://dx.doi.org/10.1089/ars.2016.6664. PMid:26906673.

Ji, L., Wang, Q., Huang, F., An, T., Guo, F., Zhao, Y., Liu, Y., He, Y., Song, Y., & Qin, G. (2019). FOXO1 Overexpression attenuates tubulointerstitial fibrosis and apoptosis in diabetic kidneys by ameliorating oxidative injury via TXNIP-TRX. *Oxidative Medicine and Cellular Longevity*, 2019, 3286928. http://dx.doi.org/10.1155/2019/3286928. PMid:30962862.

Jiang, L. N., Liu, Y. B., & Li, B. H. (2018). Lycopene exerts anti-inflammatory effect to inhibit prostate cancer progression. *Asian Journal of Andrology*, 21, 80-85. PMid:30198495.

Li, N., Wu, X., Zhuang, W., Xia, L., Chen, Y., Wu, C., Rao, Z., Du, L., Zhao, R., Yi, M., Wan, Q., & Zhou, Y. (2021). Tomato and lycopene and multiple health outcomes: Umbrella review. *Food Chemistry*, 343, 128396. http://dx.doi.org/10.1016/j.foodchem.2020.128396. PMid:33131949.

Li, X., Liao, J., Su, X., Li, W., Bi, Z., Wang, J., Su, Q., Huang, H., Wei, Y., Gao, Y., Li, J., Liu, L., & Wang, C. (2020). Human urine-derived stem cells protect against renal ischemia/reperfusion injury in a rat model via exosomal miR-146a-5p which targets IRAK1. *Theranostics*, 10(21), 9561-9578. http://dx.doi.org/10.7150/thno.42153. PMid:32863945.

Mahmoodnia, L., Mohammadi, K., & Masumi, R. (2017). Ameliorative effect of lycopene effect on cisplatin-induced nephropathy in patient. *Journal of Nephropathology*, 6(3), 144-149. http://dx.doi.org/10.15171/jnp.2017.25. PMid:28975094.

Mirahmadi, M., Azimi-Hashemi, S., Saburi, E., Kamali, H., Pishbin, M., & Hadizadeh, F. (2020). Potential inhibitory effect of lycopene on prostate cancer. *Biomedicine and Pharmacotherapy*, 129, 110459. http://dx.doi.org/10.1016/j.biopha.2020.110459. PMid:32768949.

Müller, L., Caris-Veyrat, C., Lowe, G., & Böhm, V. (2016). Lycopene and its antioxidant role in the prevention of cardiovascular diseases-a critical review. *Critical Reviews in Food Science and Nutrition*, 56(11), 1868-1879. http://dx.doi.org/10.1080/10408398.2013.801827. PMid:25675359.

Ozmen, O., Topsakal, S., Haligur, M., Aydogan, A., & Dincoglu, D. (2016). Effects of caffeine and lycopene in experimentally induced diabetes mellitus. *Pancreas*, 45(4), 579-583. http://dx.doi.org/10.1097/MPA.0000000000000489. PMid:26418913.

Pellicanò, T. M., Sicari, V., Loizzo, M. R., Leporini, M., Falco, T., & Poiana, M. (2020). Optimizing the supercritical fluid extraction process of bioactive compounds from processed tomato skin by-products. *Food Sci Technol.*, 40(3), 692-697. http://dx.doi.org/10.1590/fst.16619.

Pérez-Morales, R. E., Del Pino, M. D., Valdivielso, J. M., Ortiz, A., Mora-Fernández, C., & Navarro-González, J. F. (2019). Inflammation in diabetic kidney disease. *Nephron*, 143(1), 12-16. http://dx.doi.org/10.1159/000493278. PMid:30273931.

Perretti, G., Troilo, A., Bravi, E., Marconi, O., Galgano, F., & Fantozzi, P. (2013). Production of a lycopene-enriched fraction from tomato pomace using supercritical carbon dioxide. *The Journal of Supercritical Fluids*, 82, 177-182. http://dx.doi.org/10.1016/j.supflu.2013.07.011.

Petyaev, I. M. (2016). Lycopene deficiency in ageing and cardiovascular disease. *Oxidative Medicine and Cellular Longevity*, 2016, 3218605. http://dx.doi.org/10.1155/2016/3218605. PMid:26881023.

Qu, X., Huang, Z., Meng, X., Zhang, X., Dong, L., & Zhao, X. (2014). Prostate volume correlates with diabetes in elderly benign prostatic hyperplasia patients. *International Urology and Nephrology*, 46(3), 499-504. http://dx.doi.org/10.1007/s11255-013-0555-3. PMid:24022843.

Rehman, M. H. U., Ahmad, A., Amir, R. M., Ameer, K., Ali, S. W., Siddique, F., Hayat, I., Ahmad, Z., & Faiz, F. (2021). Ameliorative effects of fenugreek (Trigonella foenum-graecum) seed on type 2 diabetes. *Food Sci Technol.*, 41(2), 349-354. http://dx.doi.org/10.1590/fst.03520.

Vieira, D. A. D., Caliari, M., Souza, E. R. B., & Soares, M. S. Jr. (2020). Methods for and pigments extration and determination of color in tomato for processing cultivars. *Food Science and Technology*, 40(1), 11-17. http://dx.doi.org/10.1590/fst.42217.

Wang, Q., Guo, C., Zhang, L., Zhang, R., Wang, Z., Xu, Y., & Xiao, W. (2018). BOLD MRI to evaluate early development of renal injury in a rat model of diabetes. *The Journal of International Medical Research*, 46(4), 1391-1403. http://dx.doi.org/10.1177/0300060517743826. PMid:29446322.

Xia, Y., Xie, Z., Huang, G., & Zhou, Z. (2019). Incidence and trend of type 1 diabetes and the underlying environmental determinants. *Diabetes/Metabolism Research and Reviews*, 35(1), e3075. http://dx.doi.org/10.1002/dmrr.3075. PMid:30207035.

Yan, W. S., Jiang, L. J., & Xu, J. F. (2020). Cyclocarya paliurus (Batal.) Iljinskaja polysaccharides alleviate type 2 diabetes mellitus in rats by resisting inflammatory response and oxidative stress. *Food Sci Technol.*, 40(Suppl.), 158-162. http://dx.doi.org/10.1590/fst.06619.

Yang, H., Xu, Z., Liu, W., Deng, Y., & Xu, B. (2011). The protective role of procyanidins and lycopene against mercuric chloride renal damage in rats. *Biomedical and Environmental Sciences*, 24(5), 550-559. PMid:22108423.

Zheng, S., Deng, Z., Chen, F., Zheng, L., Pan, Y., Xing, Q., Tsao, R., & Li, H. (2020). Synergistic antioxidant effects of petunidin and lycopene in H9c2 cells submitted to hydrogen peroxide: Role of Akt/Nrf2 pathway. *Journal of Food Science*, 85(6), 1752-1763. http://dx.doi.org/10.1111/1750-3841.15153. PMid:32476138.

Zheng, Z., Yin, Y., Lu, R., & Jiang, Z. (2019). Lycopene ameliorated oxidative stress and inflammation in type 2 diabetic rats. *Journal of Food Science*, 84(5), 1194-1200. http://dx.doi.org/10.1111/1750-3841.14505. PMid:31012961.

Zhu, L., Han, J., Yuan, R., Xue, L., & Pang, W. (2018). Berberine ameliorates diabetic nephropathy by inhibiting TLR4/NF-κB pathway. *Biological Research*, 51(1), 9. http://dx.doi.org/10.1186/s40659-018-0157-8. PMid:29604956.