Advances in Tea and its Bioactive Components Against Diabetic Nephropathy

Junru Yin

Mercyhurst preparatory school, Erie, 16441, US

Abstract. Diabetic nephropathy has become a serious and growing public health problem. Experimental studies have shown that tea is protective against diabetic nephropathy. Possible mechanisms include enhanced insulin action, improved insulin resistance, activation of insulin signaling pathways, protection of islet β-cells, free radical scavenging, and reduction of inflammation. In addition, clinical trials have confirmed that tea intervention is effective in patients with diabetic nephropathy. Thus, to highlight the importance of tea in the prevention and treatment of diabetic nephropathy, this review summarizes and discusses the effect of tea on diabetic nephropathy based on the results of experimental and clinical studies and pays special attention to its mechanism of action.

Keywords: Diabetic Nephropathy; Tea; Bioactive Components.

1. Introduction

Diabetic nephropathy (DN) is one of the main complications of diabetes and has become one of the main causes of chronic kidney failure. The occurrence of DN is associated with multiple mechanisms, including impairment of renal function caused by hyperglycemia and oxidative stress. Numerous studies have demonstrated that DN is the major cause of its morbidity and mortality. For this reason, finding effective strategies for DN prevention and management is essential.

As a popular global beverage, tea has a variety of biological activities and health effects, such as antioxidation, anticancer, liver protection, heart protection, antiobesity, intestinal flora improvement, and antidiabetic effects. At present, an increasing number of studies have paid attention to the protective effect of tea and its bioactive components, such as green tea and active ingredient tea polyphenols, on diabetic nephropathy. This suggests to us that tea and its bioactive ingredients are promising materials for the clinical treatment of diabetic nephropathy.

To provide an updated understanding of tea targeting DN, we reviewed and discussed the protective effects of tea against DN and emphasized the related molecular mechanisms.

2. The Effect of the Bioactive Components of Tea on Diabetic Nephropathy

2.1 Tea Polyphenols (TP)

TP is the general name of polyphenols in tea, including flavanols, flavonoids and phenolic acids, mainly flavanols named epigallocatechin gallate (EGCG). Because tea polyphenols have antioxidant effects and reduce blood sugar, it is speculated that tea polyphenols have a relevant preventive and therapeutic effect on diabetic nephropathy.

Lu Ying et al. used intraperitoneal streptozotocin (STZ) to induce DN in rats [1]. The results showed that tea polyphenols could reduce increased urine volume and increased endogenous creatinine clearance and the endogenous creatinine clearance rate ($P < 0.001$), reduce urinary protein excretion ($P < 0.01$), reduce blood serum/urinary endothelin endothelin-1 (ET-1) levels ($P < 0.01$), and reduce blood triglyceride levels in DN rats. Although a hypoglycemic effect of TP and its main component catechin has previously been reported [2], the data do not find this action, suggesting that the preventative effect of tea polyphenols on DN is not achieved by hypoglycemic oxidation, enhancing the removal of reactive oxygen radicals and hydroxyl radicals, regulating lipid metabolism disorders and anti-lipid peroxidation and improving blood rheology all contribute to delaying the progression of DN [3]. Another study also found that green tea polyphenols could attenuate urinary

protein excretion and the characteristic morphological changes in urinary protein excretion and diabetic nephropathy by lowering blood glucose levels [4]. Furthermore, green tea catechins can inhibit the production of superoxidative radicals, oxidized proteins, lipids, and leukotriene B-4 by regulating 5′-lipooxygenase activity in diabetic rats, thereby reducing kidney oxidative damage and the inflammatory response.

Later, researchers conducted further research on tea polyphenols. Hong Deng and her colleagues [5] used human glomerular mesangial cells to observe the effect of high sugar on reactive oxygen species production and the expression of transformed growth factor-β1 (TGF-β1) in mesangial cells and the intervention effect of tea polyphenols. This study showed that TGF-β1 plays a role in regulating the oxidative balance of mesangial cells in high-glucose culture and can inhibit the elevated TP expression of mesangial cells at high glucose, showing the protective effect of TPs on human mesangial cells at high glucose. It may be an important mechanism for TPs to be further studied against diabetic nephropathy. On this basis, in 2018, researchers studied the effect and mechanism of TP on high glucose-induced human glomerular mesangial cell (HGMC) aging and tested the relevant signaling molecule protein expression level of the telomere-p53-p21-Rb pathway [6]. The results showed that mannitol had no significant effect on the telomere length of HGMCs; the telomere length of HGMCs in the high-dose D-glucose group was significantly shortened. These results suggest that the telomere-p53-p21-Rb signaling pathway is involved in the high glucose-induced senescence process of HGMCs. TP intervention has been able to delay high glucose-induced HGMC senescence by a mechanism related to the inhibition of telomere-p53-p21-Rb signaling pathway activity.

Based on previous studies, some scholars began to conduct a clinical trial [7] and selected 61 cases of diabetic nephropathy. In the combination group, high-throughput hemodialysis (HFHD) and tea polyphenols for 3 and 6 months, the MDA levels were significantly lower than those of the control group, and the SOD and T-AOC levels were significantly higher than those of the control group. This result showed that tea polyphenols could further improve the oxidative stress status in MHD patients, reduce the chronic inflammatory state of the patients' body, and thus reduce the loss of nutrients and improve their nutritional status.

2.2 Tea Pigment

Tea pigment is extracted from the tea mainly through catecholamine polyphenols through the transformation of chemical structure and the mixture of theaflavins and thearubigins in tea, with dilated blood vessels, improved microcirculation, increased renal blood flow, reduced plasma viscosity, red blood cell aggregation, reduced blood high coagulation state, eliminated oxygen free radicals, and prevented biofilm lipid peroxidation [8].

As early as 1997, there was a group intervention of tea pigment to study [9], indicating that the efficacy of tea pigment was recognized very early. In 2003, Xia Chengyun et al. [10] tested 68 outpatients in a type 2 diabetic nephropathy department. Patients were divided into two groups according to the principle of randomization. The treatment group included 18 men and 14 women. The age ranged from 35 to 64 years. Course duration between 2 and 13 years (8.19 ± 3.11) years. The treatment group added a tea pigment capsule to the conventional treatment of DM. Both courses of 0.24 g oral administration 3 times daily were for 8 weeks. The decrease in plasma ET and UAER of urinary albumin excretion at 24 h in the treatment group ($P < 0.05$), while the decrease in plasma α-granule membrane protein GMP-140 showed no correlation with UAER ($P > 0.05$). The results suggested that tea pigment could significantly reduce the plasma GMP-140 and plasma ET levels in DN patients. Meanwhile, the 24-h UAER was also significantly decreased, and reduced plasma ET was significantly positively associated with the 24-h UAER. Therefore, the study concluded that the mechanism of the better therapeutic effect on IDN may be related to reducing plasma ET levels and inhibiting platelet activity. In summary, the experiment is only a short-term experiment of tea pigment on diabetic nephropathy. If further results are obtained, long-term experimental research and observation will be needed.

In 2009, Li Cailand et al. [11] specifically studied prevention and treatment by using theophylavin and rat renal bulb mesangial cells for diabetic nephropathy. Teaflavin is a golden yellow pigment found in yellow tea and black tea and is the product of tea fermentation. Biochemically, theaflavin is a class of polyphenol hydroxy groups with the structure of teparenone. Teafflavin was the first to find exact pharmacological compounds from tea, with strong antioxidant, anti-inflammatory, antitumour, anti-cardiovascular and cerebrovascular effects [12]. The experiment found that high glucose (HG), glycosylated end product (AGE) and H2O2 can be used as independent factors to activate p38 mitogen-activated protein kinase (p38 MAPK) and TGF-β, significantly increasing the activity of phosphorylated p38 MAPK and TGF-β protein expression, suggesting that the p38 MAPK pathway may be involved in the pathological process of stimulating extracellular matrix (ECM) secretion in mesangial cells. In addition, the contents of fibronectin (FN), collagen type (Col), and laminin (LN) were significantly increased under HG, AGE, and H2O2 conditions.

2.3 Tea Polysaccharide

Tea polysaccharide is a complex compound composed of sugars, proteins, pectin and ash that cannot be digested and absorbed by the human gastrointestinal tract. Its chemical essence is acid polysaccharide or acid glycoprotein, among which acid glycoprotein is an important component to promote the promotion of insulin activity.

In 2018, Jia Liangliang et al. [13] used intraperitoneal injection of streptozotocin to establish a mouse model of diabetic nephropathy. The experimental data indicated that urinary protein, blood creatinine and blood urea nitrogen were decreased significantly at 24 h compared with the model group. At the same time, the tea polysaccharide administration group also significantly improved the activity of superoxide dismutase (SOD) and glutathione peroxidase (GPX) in the kidney, reduced malondialdehyde (MDA) content, and upregulated the expression of SOD1 and GPX1 mRNA in kidney tissue. Therefore, tea polysaccharide delays the development of diabetic nephropathy in mice, which may be related to its upregulation of SOD1 and GPX1 mRNA expression, the improvement of SOD and GPX activity in kidney tissues, reduced MDA content, and regulation of the balance of the oxidation-antioxidant system.

2.4 Tetramethyl Uric Acid

In 2019, Gong Bin et al. [14] extracted tetramethyluric acid from Yunnan bitter tea for further research. Yunnan bitter tea is well known as the dicotyledaceae plant of both medicine and food. It is recorded as bitter and slightly sweet, which is cool. Therefore, Yunnan bitter tea is a good product for the treatment of hypertension and diuresis. Tetrasmethyluric acid (1,3,4,9-tetramethylethyl uric acid, TC) has antioxidant pharmacological activity. TC is a purine alkaloid with a structure similar to caffeine but with much stronger effects than caffeine. 1,3,4,9-The anti-inflammatory and analgesic effects of tetramethyluric acid have been found. The protective effect of long-term oral terophylline monomers on oxidative damage in rats can also be studied [15].

The experimental results indicated that the serum TG, TT, ALT and LDL-C levels were decreased compared with those in the damage group, and MDA, PCO and the antioxidant indexes CAT, SOD and GSH were significantly increased compared with those in the injury group. This shows that TC enhances the activity of antioxidant enzymes, enhances the antioxidant capacity of the antioxidant system, and jointly protects the kidney through an oxidative stress response and anti-inflammatory effect**.**

3. The Effect of Individual Tea Species on Diabetic Nephropathy

3.1 Green Tea

In diabetic spontaneously hypertensive rats (SHRs), green tea prevented podocyte apoptosis and albuminuria by enhancing the expression of p-LDL-lipoprotein receptor-associated protein 6 (p-LRP6) and blocking the interaction of glycogen synthase kinase 3 and p53 (GSK3-p53) [16].

3.2 Black Tea

Pu'er tea can reduce R AGE expression and glomerular IgG deposition by inhibiting AGE accumulation to improve diabetic nephropathy [17]. Jade tea (a dark tea) polypeptide can activate the PKCζ/JNK/nuclear factor-κB (NF-κB)/THF-α/iNOS, late glycosylation end products AGEs/ RAGE/ TGF-1 pathway, regulate podocin expression in glomeruli, and reduce the release of proinflammatory cytokines to improve diabetic nephropathy [18].

Oolong tea polysaccharide can improve renal tissue inflammation and advance the glomerular vascular permeability of glutathione peroxidase (GSH-PX) by enhancing the activity of superoxide dismutase and GSH-PX.

4. The Effect of Compound Tea on Diabetic Nephropathy

In 2017, people began to study a compound tea called Huangjing tea [19]. It tastes sweet and flat, invigorating the spleen, lung and kidney, and can regulate immunity, reduce lipids and sugar, delay ageing and protect the kidney [20]. Yellow essence tea is used for diabetes complications, and the health tea is made with green money willow, orange dulvenia, mulberry leaf, pueraria root, yam, barbary wolfberry, poria cocos and other food ingredients. In a rat model of STZ- and high-fat high-glucose diet-induced type 2 diabetic nephropathy, compared with the model group, yellow tea extract significantly improved glucose and lipid metabolism, glucose tolerance, and insulin resistance in the diabetic rats and reduced urea nitrogen and muscle liver. Pathological histological examination also suggested that yellow tea extract improved the degree of kidney pathological histological damage. The experimental results preliminarily reveal that a certain concentration of yellow tea extract has a good effect in improving renal function in rats with diabetic nephropathy, which provides an experimental basis for the application of yellow tea tea in assisting diabetes with glucose reduction and improving complications. Whether the dose range of Huangjing tea extract for better protection in type 2 diabetic nephropathy rats is dose-dependent remains to be further studied.

5. Conclusion

In conclusion, tea has a good therapeutic effect on diabetic nephropathy in vitro and in vivo. Experimental studies have shown that tea can prevent DN by improving insulin resistance, activating the insulin signaling pathway, exerting insulin-like effects, improving oxidative stress and alleviating the inflammatory response. In addition, clinical trials have shown that tea has positive effects in preventing and treating diabetes and its complications. The molecular mechanism of tea and its active components needs to be further studied. In addition, it is difficult to conclude whether the effective doses in animal studies are beneficial to humans because of the differences in the doses and effects of tea in experimental and clinical studies. Therefore, the protective effect of tea on diabetes and its complications needs further clinical studies. In addition, special attention should be given to the safety of tea and tea products.

References

[1] Lu Y, Yang R, Hu Y, et al. Preventive effect of tea polyphenols on streptozotocin induced renal injury in diabetic rats. Chinese Journal of Basic Medicine of Traditional Chinese Medicine. 2000(07):15-19.

[2] Cao D, Zhao M, Wan C, et al. Role of tea polyphenols in delaying hyperglycemia-induced senescence in human glomerular mesangial cells via miR-126/Akt-p53-p21 pathways. Int Urol Nephrol. 2019;51 (6): 1071-1078.

[3] Chen Y, Zheng Y. Antioxidant effect of tea polyphenols on oxygen free radicals. Chinese Journal of Nephrology. 1998(01):66-68.

[4] Deng H, Cao J. Effects of tea and tea polyphenols on blood lipid levels. Foreign Medical Sciences (Medical Geography). 2004(03):101-104+139.

[5] Li Q, Li H, Deng H, et al. Effect of tea polyphenols on the expression of intercellular adhesion molecule-1 in human mesangial cells under high glucose. Journal of Nanjing Medical University (Natural Science). 2007(04):295-298+290.

[6] Cao D, Han W, He J, et al. Tea polyphenols inhibit high glucose-induced senescence of human mesangial cells by regulating STAT3/miR-126/telomere signaling pathway activity. Chinese Journal of Traditional Chinese Medicine. 2018;43(23):4678-4684.

[7] Yang K. Effect of high-throughput hemodialysis combined with tea polyphenols on oxidative stress and nutritional status in patients with diabetic nephropathy undergoing maintenance hemodialysis. New clinical medicine in China. 2018;11(04):359-362.

[8] Liu Qin, Liao Bin, Xie Qi. Effect of tea pigment on blood lipid and fibrinogen in patients with hyperlipidemia. Journal of University of South China (Medical Edition). 2001(04):391-392.

[9] Fang C, Cui Y, Niu Y, et al. Clinical study of tea pigment in the treatment of diabetic nephropathy. Anhui Clinical Journal of Traditional Chinese Medicine. 1997(04):175-177.

[10] Xia C, Zhou J, Kang H, et al. Effect of tea pigment on plasma GMP-140 and plasma endothelin in patients with early diabetic nephropathy. Chinese Journal of Modern Medicine. 2003(17):36-38+41.

[11] Li C, Cai F, Zhao X, et al. Effects of theaflavin on the synthesis of p38 mitogen-activated protein kinase and extracellular matrix in diabetic rat glomerular mesangial cells. The tea science. 2009;29(06):470-474.

[12] Cai F, Li C, Wu J, et al. Modulation of the oxidative stress and nuclear factor kappaB activation by theaflavin 3,3'-gallate in the rats exposed to cerebral ischaemia–reperfusion. Folia Biol (Praha). 2007; 53 (5): 164-172.

[13] Jia L, Jin G, Peng G, et al. Protective effect of tea polysaccharide on oxidative stress injury of kidney in diabetic nephropathy mice. Central pharmacy. 2018;16(10):1388-1392.

[14] Gong P, Shi F, Chen F, et al. The protective effect of Yunnan bitter tea extract against oxidative stress on diabetic nephropathy induced by cadmium in mice. Modern food technology. 2019;35(08):6-12.

[15] Wang W, Su C, Liao H. Effect of tea pigment on insulin receptor in insulin resistant rats. Tea Science. 2008 (06):455-458.

[16] Peixoto EB, Papadimitriou A, Teixeira DA, et al. Reduced LRP6 expression and increase in the interaction of GSK3β with p53 contribute to podocyte apoptosis in diabetes mellitus and are prevented by green tea. J Nutr Biochem. 2015;26(4):416-430.

[17] Yan SJ, Wang L, Li Z, et al. Inhibition of advanced glycation end product formation by Pu-erh tea ameliorates progression of experimental diabetic nephropathy. J Agric Food Chem. 2012;60(16):4102-4110.

[18] Deng X, Sun L, Lai X, et al. Tea Polypeptide Ameliorates Diabetic Nephropathy through RAGE and NF-κB Signaling Pathway in Type 2 Diabetes Mice. J Agric Food Chem. 2018;66(45):11957-11967.

[19] Wang J, Liu S, Li J, et al. Protective effect of Huangjing tea extract on type 2 diabetic nephropathy rats. Central pharmacy. 2017;15(08):1061-1064.

[20] Li WX, Li YF, Zhai YJ, Chen WM, Kurihara H, He RR. Theacrine, a purine alkaloid obtained from Camellia assamica var. kucha, attenuates restraint stress-provoked liver damage in mice. J Agric Food Chem. 2013;61(26):6328-6335.