doi.org/10.36721/PJPS.2022.35.3.REG.769-775.1

Protective effect of rutin against diabetes-associated cognitive decline in rats

Liu Xianchu[1], Peng Huan[2], Liu Kang[1], Deng Beiwang[1] and Liu Ming[3*]
[1]Institute of Physical Culture, Hunan University of Arts and Science, Changde, Hunan, China
[2]Department of Hematology, Xiangya Changde Hospital, Changde, Hunan, China
[3]Faculty of Science, College of Furong, Hunan University of Arts and Science, Changde, Hunan, China

Abstract: Diabetes is a well-known risk factor for cognitive deficit. Rutin (RUT) possesses diverse pharmacological activities and is widely used in diabetic complication. The aim of this study is to assess the improvement of RUT on diabetes-associated cognitive decline (DACD). In our study, Morris water maze was examined to estimate cognitive function. In hippocampus tissue, spectrophotometer was performed to evaluate super oxide dismutase (SOD), catalase (CAT), reduced glutathione (GSH), malondialdehyde (MDA), acetyl cholinesterase (AChE) and choline acetyl transferase (ChAT) levels. Quantitative real-time polymerase chain reaction (qRT-PCR) and enzyme-linked immunosorbent assay (ELISA) were utilized to analyze Tumor necrosis factor-a (TNF-a) and interleukin-1β (IL-1β) contents. Western blot was used to detect the protein expressions of brain derived neurotrophic factor (BDNF), glial fibrillary acidic protein (GFAP), nuclear factor erythroid-2-related factor-2 (Nrf-2) and heme oxygenase-1 (HO-1). Our data revealed that RUT markedly improved learning and memory capacities in Morris water maze test. In hippocampus, RUT markedly inhibited AChE, GFAP MDA, TNF-a and IL-1β levels and augmented ChAT and BDNF, SOD, CAT, GSH, Nrf-2 and HO-1 levels. In conclusion, RUT may be involved in protection efficacy against STZ-induced cognitive deficits via improvement of oxidative stress, inflammatory response and Nrf-2/HO-1 pathway.

Keywords: DACD, Rutin, Oxidation, Inflammation, Nrf-2, HO-1

INTRODUCTION

Diabetes mellitus is one of metabolic diseases and is diagnosed by hyperglycemia (Harreiter and Roden, 2019). Long-term abnormally hyperglycemic circumstance is harmful for organ and tissue in human which ultimately stimulates many serious complications and disability. Cognitive defect is a severe complication of diabetes and affect life quality in patients, which has become a seriously health problem (van Duinkerken and Ryan, 2020). In contemporary world, an increasing number of people suffer from cognitive defect because of disturbance of carbohydrate metabolism. Hippocampus damage due to chronic high blood glucose is the main reason of learning and memory injury in patients diabetic. Hence, uncontrolled hyperglycemia influences hippocampus function and brings about a detrimental role in the occurrence of cognitive defect.

The clinical pathogenesis and mechanisms of DACD is variety and complexity (Kossler *et al.,* 2020). The abnormal homeostasis of oxidation and inflammation is a potentially motivational factor of DACD (Zhang *et al.,* 2020). In addition, chronic hyperglycemia restrains Nrf-2 and HO-1 expressions in hippocampus. In contrast, enhancements of Nrf-2 and HO-1 activities are beneficial to alleviation of cognitive decline in STZ-induced diabetes (Liang *et al.,* 2018). Moreover, Nrf-2/HO-1 pathway is considered as a crucial factor in the regulation of oxidative stress and inflammatory reaction. Studies have demonstrated that activation of Nrf-2/HO-1 pathway can promote antioxidant defense system by increasing SOD and CAT contents in diabetes (Wang *et al.,* 2019). In cognitive decline, activation of Nrf-2/HO-1 pathway has been proved to inhibit inflammation stimulation by preventing TNF-a, IL-1β and IL-6 activities (Xu *et al.,* 2019). Accordingly, improvement of DACD is closely related to Nrf-2 and HO-1 activities which attribute to its regulation function in oxidative stress and inflammatory response.

Rutin, as a flavonol glycoside, possesses diverse pharmacological activities, such as anti-inflammatory and anti-oxidant. Previous studies showed that RUT was beneficial for hippocampus damage to improve cognitive defect via modulating Nrf-2/HO-1 pathway (Woo *et al.,* 2020). Besides, it was also reported that RUT could retard diabetes in rat (Ganesan *et al.,* 2020). In this study, we hypothesized that RUT exerted inhibitory effect on DACD via ameliorating antioxidant and anti-inflammatory productions through regulating Nrf- 2/HO-1 *in vivo*.

MATERIALS AND METHODS

Animals and experimental design

Three-month-old Sprague-Dawley rats (male, 230±20g) were raised at standard laboratory environment with temperature (23±2℃), humidity (50±10 %), 12:12 h light-

**Corresponding author:* e-mail: liuming0206@huas.edu.cn

dark cycle. 45 rats were randomly divided into 3 groups: Control group (CON, n = 15); Diabetes mellitus (DM, n = 15); Diabetes mellitus treated with rutin (DM + RUT, n = 15). After acclimatization for one week, STZ was dissolved in citric acid buffer (pH 4.5) and intraperitoneally injected at the dose of 50 mg/kg body weight to constitute diabetic rat. Moreover, blood was acquired from caudal vein to measure glycemia concentration. The glycemia concentration was more than 16.7mM in rat, which could be identified as diabetic model. RUT was orally fed at 50mg/kg/day for 45 days (Hasanein *et al.,* 2020; Fernandes *et al.,* 2010). In this study, animal experiments were inspected according to the Ethics Committee of Hunan University of Arts and Science (No. HUAS-2021-TY-071).

Chemicals and reagents

Rutin (purity: ≥95%), streptozotocin (STZ) and qRT-PCR primer sequences were purchased from Sangon Biotech (shanghai, China). The assay kits of SOD, CAT, GSH, MDA, AChE and ChAT were purchased from Nanjing Jiancheng Biotechnology Institute (Nanjing, China). The ELISA kits of TNF-α and IL-1β were purchased from BOSTER Biological Technology (Wuhan, China). The antibodies of Nrf-2 and HO-1 were purchased from proteintech (Wuhan, China). The antibodies of BDNF and GFAP were purchased from servicebio (Wuhan, China).

Morris water maze

Rat was tested via Morris water maze after RUT treatments to evaluate memory and learning capabilities. At the beginning of tests, rat swam for 5 min/days to adapt water environment. In training period, rats were guided to seek for hidden platform. In escape latency test, the average time of locating the hidden platform was calculate in each experiment to assess learning ability for four consecutive days. In the fifth day, rats were measured by probe trial to seek for removed platform. The number times of crossing original platform were calculated to assess memory retention.

Biochemical assay

After memory and learning experiments, rats were anesthetized by chloral hydrate. Hippocampus was dissected rapidly, washed with PBS and stored at -80^{o}C. In biochemical assay, hippocampus was ground at a low temperature and centrifuged for protein extraction. The contents of SOD, CAT, GSH, MDA, AChE and ChAT were tested with commercially available kits, while TNF-α and IL-1β levels were measured by ELISA kits.

qRT-PCR analysis

Hippocampus was cut, homogenized and centrifuged to extract RNA by trizol reagent. Then, total RNA from supernatant was reverse transcribed into cDNA with MBI Revert Aid. The transcriptional expression was measured by qRT-PCR. qRT-PCR was performed with SYBR by Bio-Rad real-time PCR systems. The primer sequences were used as previously reported (table 1). TNF-α and IL-1β mRNA expressions were normalization to β-actin. The signal was represented by comparative CT methods.

Western blot

The hippocampus was homogenized and added with RIPA and proteinase inhibitor to obtain protein. Determination of protein content was performed according to BCA method. The extracted protein was boiled in water at 100^{o}C for 5 min to induce albuminous degeneration. The SDS-PAGE was used to separate different molecular weight of proteins. Then, proteins were transferred onto PVDF membranes by wet electro blotting systems. The membrane was incubated with 5% nonfat dry milk, suitable concentrations of primary antibodies and labeled non-specificity antibodies, respectively. The bands were observed by ECL system. The signal was analyzed by Image J. The protein relative expressions were exhibited via normalizing to β-actin.

STATISTICAL ANALYSIS

All data were showed as mean ± standard deviation (SD). The results were analyzed with SPSS 16.0 software. Statistical difference was demonstrated by one-way ANOVA test. $p<0.05$ was deemed statistically significant.

RESULTS

Properties of RUT on STZ-induced cognitive deficit

Morris water maze was used to estimate the improvements of RUT against STZ-induced learning and memory impairment. As shown in the fig. 1, the time of escape latency was remarkably increased in DM group, while treatment with RUT markedly decreased escape latency. In the probe experiment, the frequency of crossing removed platform was remarkably decreased in DM group. On the contrary, RUT markedly enhanced the frequency of platform crossings.

Properties of RUT on STZ-induced cholinergic dysfunction

As shown in the fig. 2, the AChE activity was remarkably enhanced, while ChAT activity was remarkably decreased in DM group. Treatment with RUT observably reversed these changes in hippocampus, which could provide a positive defense from cholinergic dysfunction induced by hyperglycemia.

Properties of RUT on BDNF and GFAP expressions in diabetic rat

As shown in the fig. 3, hyperglycemia remarkably decreased BDNF expression and enhanced GFAP expression in DM group, respectively. While treatment with RUT markedly attenuate these changes in hippocampus, suggesting that RUT might be effective in

STZ-induced nervous system disorder.

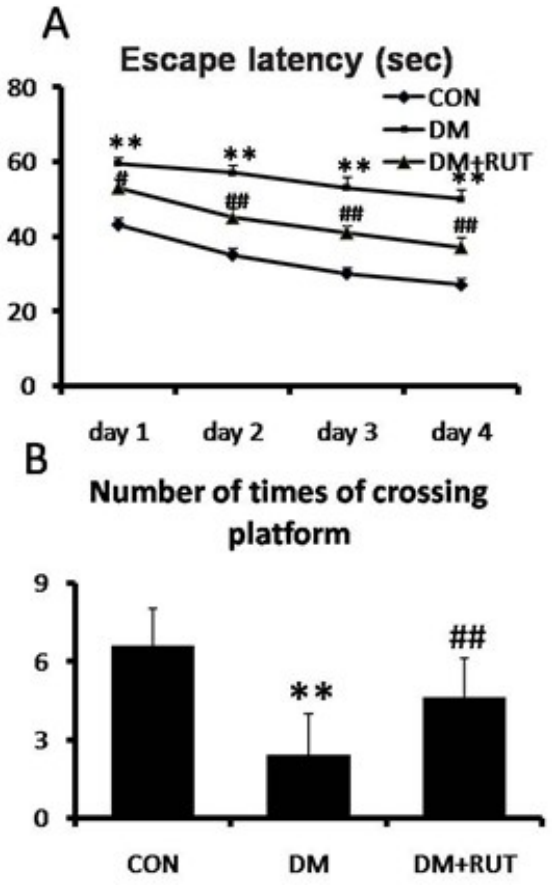

Fig. 1: Properties of RUT on escape latency (A) and frequency of platform crossings (B) in diabetic rat. n = 10/group. **p<0.01 compared with CON group; # p< 0.05, ## p<0.01 compared with DM group.

Properties of RUT on STZ-induced oxidative stress

To estimate oxidation resistance of RUT in STZ-induced diabetes model, the concentrations of SOD, CAT, GSH and MDA were detected in hippocampus. As shown in fig. 4, hyperglycemic remarkably decreased SOD, CAT and GSH levels, but increased MDA content. Treatment with RUT observably increased antioxidant enzyme activities in hippocampus. Likewise, RUT observably augmented GSH level in hippocampus. On the contrary, RUT observably mitigated STZ-induced MDA content in hippocampus.

Properties of RUT on STZ-induced inflammatory response

To estimate improvement of RUT on STZ-induced inflammatory response, the levels of TNF-α and IL-1β were detected in hippocampus. As shown in fig. 5, the protein and mRNA levels of TNF-α and IL-1β were remarkably increased in DM group. On the contrary, treatment with RUT markedly restrained generation of proinflammatory mediators in hippocampus.

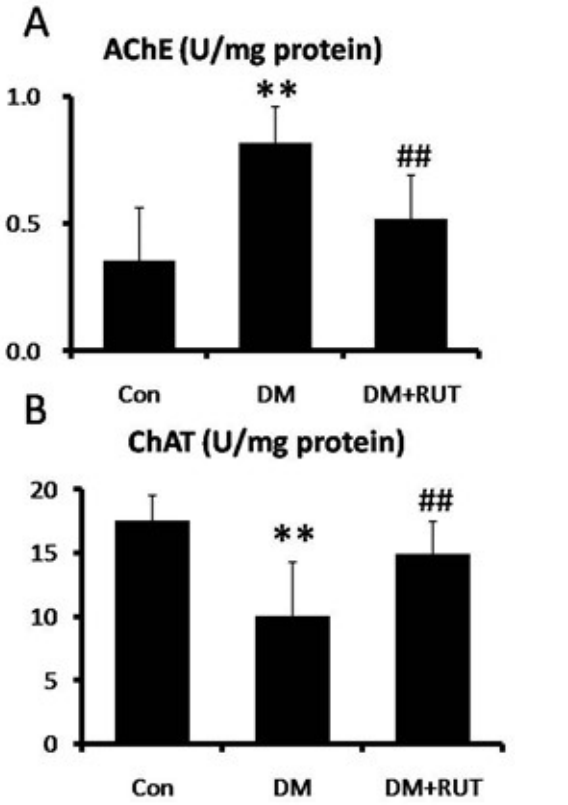

Fig. 2: Properties of RUT on the activities of AChE (A) and ChAT (B) in hippocampus. n=5/group. **p<0.01 compared with CON group; ## p<0.01 compared with DM group.

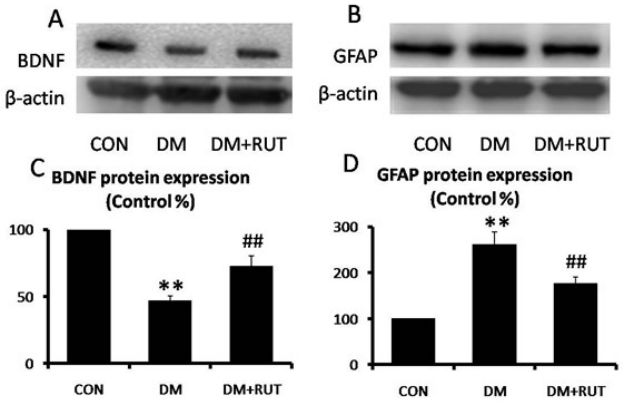

Fig. 3: Properties of RUT on the expressions of BDNF (A and C) and GFAP (B and D) in hippocampus. n = 5/group. **p<0.01 compared with CON group; ## p<0.01 compared with DM group.

Properties of RUT on regulation of Nrf-2/HO-1 pathway in diabetic rat

According to the results given in fig. 6, Nrf-2 and HO-1 expressions were remarkably inhibited in DM group. Treatment with RUT could significantly enhanced Nrf-2 and HO-1 expressions in hippocampus. These results indicated that the RUT modulated Nrf-2/HO-1 pathway to inhibit hyperglycemic-induced cognitive deficits.

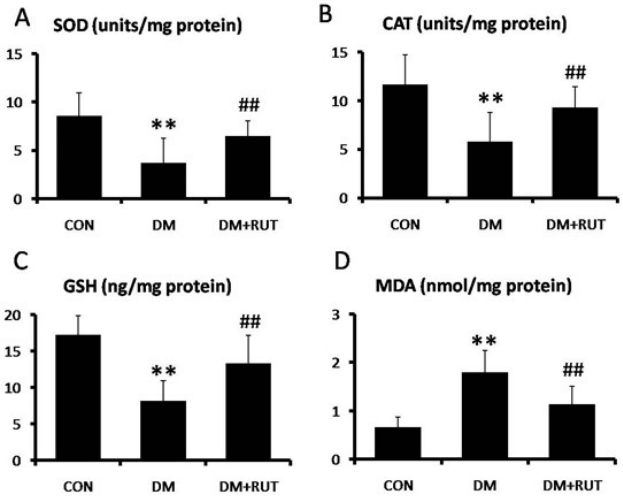

Fig. 4: Properties of RUT on SOD (A) and CAT (B) activities, GSH (C) and MDA (D) contents in hippocampus. n=5/group. **p<0.01 compared with CON group; ## p<0.01 compared with DM group.

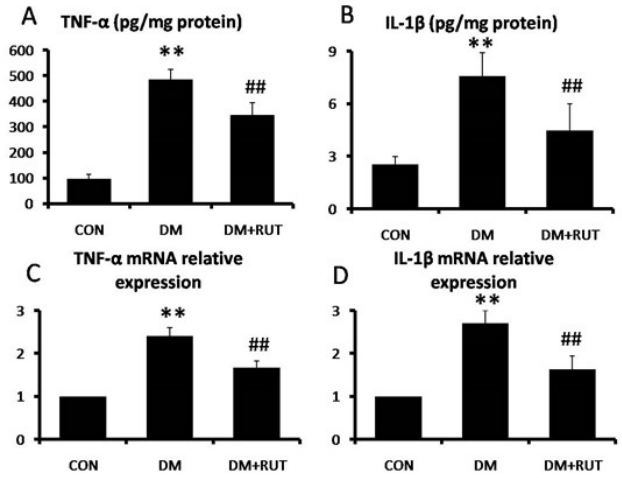

Fig. 5: Properties of RUT on TNF-α (A, C) and IL-1β (B, D) levels in hippocampus. n=5/group. **p<0.01 compared with CON group; ## p<0.01 compared with DM group.

DISCUSSION

Rutin is widely present in flowers and fruits. RUT has been used as a medicine and possesses various therapeutic actions in many diseases because of its multiple biological efficacies including antioxidant and anti-inflammatory. In experimental diabetes, RUT was confirmed to enhance body weight gain, decrease blood glucose and improve biochemical parameters (Fernandes *et al.,* 2010; Sun *et al.,* 2020). In hyperglycemia, RUT can alleviate STZ-induced tissue damage, such as kidney, retina, heart and nerves (Ghorbani, 2017). In addition, RUT also has a protective property against cognitive defect in many experimental models. Previous research showed RUT enhanced sevoflurane or propofol-induced memory and cognitive capacities in neonatal mice (Man *et al.,* 2015). In beta-amyloid induced neurotoxicity, RUT activated MAPK pathway to enhance memory retrieval in rats (Moghbelinejad *et al.,* 2014). In ovariectomized rats, RUT relieved ischemia/reperfusion damage to ameliorative recognition memory (Liu *et al.,* 2018). All these studies showed that RUT possessed feasible treatment effect both in diabetes and cognitive impairment. In this study, our results demonstrated RUT exhibited its protective effect against STZ-induced cognitive deficits, as represented by mitigating escape latency and increasing frequency of platform crossings.

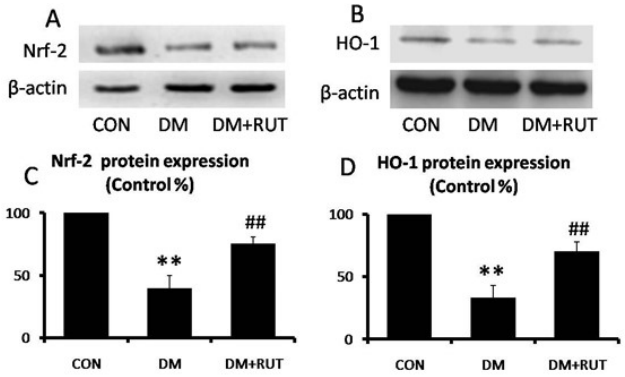

Fig. 6: Properties of RUT on regulation of Nrf-2 (A, C) and HO-1 (B, D) expressions in hippocampus. n= 5/group. **p<0.01 compared with CON group; ## p<0.01 compared with DM group.

Chronic hyperglycemia is a crucial indicator in the development of cholinergic dysfunction. AChE and ChAT, as key enzymes in nerve conduction, are involved in the modulation of the cholinergic system. There are multiple researches illustrating the associations between cholinergic dysfunction and cognitive defect. In diabetes, the activity of AChE was increased, while the activity of ChAT was decreased in hippocampus. Previous research showed puerarin exhibited remarkable increase in AChE accompanied with reduction in ChAT to ameliorate STZ-induced learning and memory impairment (Liu *et al.,* 2016). In addition, RUT inhibited AChE activity to improve neurobehavioral deficits in NaF-induced toxicity (Nkpaa and Onyeso, 2018). We found that RUT exhibited its modulation mechanism on cholinergic system against hyperglycemia-induced cognitive impairments by decreasing AChE activity and increasing ChAT activity in hippocampus.

BDNF and GFAP possess vital functions both in cognitive defect and diabetes. BDNF, as a neurotrophin, is involved in survival and growth of neurons. GFAP, as an astrocyte marker, is closely linked to neuroinflammation and neuronal injury. In diabetes mellitus, irisin played an important role in the upregulation of BDNF protein and suppression of GFAP protein (Wang *et al.,* 2019; Huang *et al.,* 2019). Previous study showed that RUT enhanced BDNF gene expression against beta-amyloid relevant

memory anomalies (Moghbelinejad *et al.,* 2014). In Huntington's disease, RUT inhibited GFAP level to improve memory retrieval (Suganya and Sumathi, 2017). In our finding, RUT exhibited its neuroprotective effect against hyperglycemia-induced cognitive dysfunctions by increasing BDNF expression and decreasing GFAP expression in hippocampus.

Oxidative stress is known to play a vital role in modulating progression of cognitive impairment. In chronic hyperglycemia, the activities of antioxidant enzymes such as SOD and CAT were decreased. Meanwhile, GSH, as an important reductive agent, participates in a variety of redox reactions in vivo. Various lines of demonstration have illustrated that GSH level is significantly reduced in diabetes. Moreover, MDA, as an advanced lipoxidation product, is overproduced which may aggravate oxidative stress in hippocampus of diabetic rats (Moldogazieva *et al.,* 2019). Previous research showed RUT facilitated SOD and CAT activities in rat model of cadmium-induced cognitive impairment (Oboh *et al.,* 2019). In diabetes atherosclerosis, RUT relieved premature senescence of VSMCs by attenuating oxidative stress (Li *et al.,* 2018). In addition, RUT improved STZ-induced decreasing of GSH, SOD, CAT, GPx and GRx in rat tissue (Kamalakkannan and Stanely, 2006). In diabetic retinopathy, RUT possessed neuroprotective effects by enhancing GSH level (Ola *et al.,* 2015). In this study, RUT showed its oxidation resistance against STZ-induced cognitive deficit by accelerating SOD and CAT activity, promoting GSH level and mitigating MDA content in hippocampus.

Uncontrolled hyperglycemia is also a crucial mediator of inflammatory response. The levels of inflammatory cytokines, including TNF-a and IL-1β, were increased in STZ-induced diabetes (Liu *et al.,* 2014). The experiment manifestation of excessive levels of inflammatory cytokines in hippocampus is closely related to the occurrence of cognitive dysfunction. Previous research showed RUT protected against head trauma-induced cognitive decline by reducing TNF-α level in hippocampus (Kumar *et al.,* 2014). In diabetes, RUT also inhibited the expressions of these inflammatory cytokines to ameliorate STZ-induced complications (Saklani *et al.,* 2016). In this study, RUT revealed its anti-inflammatory effect against STZ-induced cognitive deficits via relieving TNF-α and IL-1β levels in hippocampus.

The mechanism of DACD is variety and complexity. It is noteworthy that Nrf-2/HO-1 pathway plays a vital role in the prevention and treatment of STZ-induced cognitive deficits (Ma *et al.,* 2021). Nrf-2, as a ubiquitously transcriptional activator, is associated with oxidation resistance because it prompts expression of multiple antioxidant elements (Cui *et al.,* 2017). HO-1, which is regulated by Nrf-2, exhibits anti-inflammatory effect owing to its suppression in production of proinflammatory factors. In addition, HO-1 is also involved in modulation of oxidative reactions (Song *et al.,* 2021). In vancomycin-induced nephrotoxicity, the protective effect of RUT against oxidative stress and inflammatory response was associated with up regulation expressions of Nrf-2 and HO-1 (Qu *et al.,* 2018). It was proposed that RUT increased expression of Nrf-2 and HO-1 to alleviate sciatic neuropathy in STZ-treated rats (Mittal *et al.,* 2018). Our results showed RUT enhanced Nrf-2 and HO-1 expressions in hippocampus of diabetic rats, which suggested its suppression of oxidative stress and inflammation is closely related to Nrf-2 and HO-1 expressions.

CONCLUSION

Our research demonstrated that RUT with its improvement of learning and memory impairment was relevant to suppression of oxidative stress and inflammation via Nrf-2/HO-1 pathway in STZ-induced diabetic rat. These results indicated RUT may be an available therapeutic pharmaceutical to alleviate cognitive decline in diabetes.

ACKNOWLEDGEMENTS

This study was supported in part by a project supported by Hunan Provincial Natural Science Foundation of China (Grant No. 2020JJ5391 & 2021JJ40376).

REFERENCES

Cui W, Min X, Xu X, Du B and Luo P (2017). Role of Nuclear Factor Erythroid 2-Related Factor 2 in Diabetic Nephropathy. *J. Diabetes. Res.,* 3797802.

Fernandes AA, Novelli EL, Okoshi K, Okoshi MP, Di Muzio BP, Guimarães JF and Fernandes Junior A (2010). Influence of rutin treatment on biochemical alterations in experimental diabetes. *Biomed. Pharmacothe.,* **64**(3): 214-219.

Ganesan D, Albert A, Paul E, Ananthapadmanabhan K, Andiappan R and Sadasivam SG (2020). Rutin ameliorates metabolic acidosis and fibrosis in alloxan induced diabetic nephropathy and cardiomyopathy in experimental rats. *Mol. Cell. Biochem.,* **471**(1-2): 41-50.

Ghorbani A (2017). Mechanisms of antidiabetic effects of flavonoid rutin. *Biomed. Pharmacother.,* **96**: 305-312.

Harreiter J and Roden M (2019). Diabetes mellitus-definition, klassifikation, diagnose, screening und prävention (update 2019). *Wien. Klin. Wochenschr.,* **131**(Suppl 1): 6-15.

Hasanein P, Emamjomeh A, Chenarani N, Bohlooli M (2020). Beneficial effects of rutin in diabetes-induced deficits in acquisition learning, retention memory and pain perception in rats. *Nutr. Neurosci.,* **23**(7): 563-574.

Huang L, Yan S, Luo L and Yang L (2019). Irisin regulates the expression of BDNF and glycol-

metabolism in diabetic rats. *Mol. Med. Rep.,* **19**(2): 1074-1082.

Kamalakkannan N and Stanely Mainzen Prince P (2006). Rutin improves the antioxidant status in streptozotocin-induced diabetic rat tissues. *Mol. Cell. Biochem.,* **293**(1-2): 211-219.

Kaur H, Patro I, Tikoo K and Sandhir R (2015). Curcumin attenuates inflammatory response and cognitive deficits in experimental model of chronic epilepsy. *Neurochem. Int.,* **89**: 40-50.

Kössler T, Weber KS, Wölwer W, Hoyer A, Strassburger K, Burkart V, Szendroedi J, Roden M, Müssig K and GDS Group (2020). Associations between cognitive performance and Mediterranean dietary pattern in patients with type 1 or type 2 diabetes mellitus. *Nutr. Diabetes,* **10**(1): 10.

Kumar A, Rinwa P and Dhar H (2014). Possible nitric oxide modulation in the protective effects of rutin against experimental head trauma-induced cognitive deficits: behavioral, biochemical, and molecular correlates. *J. Surg. Res.,* **188**(1): 268-279.

Li Y, Qin R, Yan H, Wang F, Huang S, Zhang Y, Zhong M, Zhang W and Wang Z (2018). Inhibition of vascular smooth muscle cells premature senescence with rutin attenuates and stabilizes diabetic atherosclerosis. *J. Nutr. Biochem.,* **51**: 91-98.

Liang E, Ma M, Wang L, Liu X, Xu J, Zhang M, Yang R and Zhao Y (2018). The BET/BRD inhibitor JQ1 attenuates diabetes-induced cognitive impairment in rats by targeting Nox4-Nrf-2 redox imbalance. *Biochem. Biophys. Res. Commun.,* **495**(1): 204-211.

Liu C, Feng X, Li Q, Wang Y, Li Q and Hua M (2016). Adiponectin, TNF-α and inflammatory cytokines and risk of type 2 diabetes: A systematic review and meta-analysis. *Cytokine.,* **86**: 100-109.

Liu H, Zhong L, Zhang Y, Liu X and Li J (2018). Rutin attenuates cerebral ischemia-reperfusion injury in ovariectomized rats via estrogen-receptor-mediated BDNF-TrkB and NGF-TrkA signaling. *Biochem. Cell. Biol.,* **96**(5): 672-681.

Liu X, Mo Y, Gong J, Li Z, Peng H, Chen J, Wang Q, Ke Z and Xie J (2016). Puerarin ameliorates cognitive deficits in streptozotocin-induced diabetic rats. *Metab. Brain. Dis.,* **31**(2): 417-423.

Ma X, Song M, Yan Y, Ren G, Hou J, Qin G, Wang W, Li Z (2021). Albiflorin alleviates cognitive dysfunction in STZ-induced rats. *Aging*., **13**(14): 18287-18297.

Man YG, Zhou RG and Zhao B (2015). Efficacy of rutin in inhibiting neuronal apoptosis and cognitive disturbances in sevoflurane or propofol exposed neonatal mice. *Int. J. Clin. Exp. Med.,* **8**(8): 14397-14409.

Mittal R, Kumar A, Singh DP, Bishnoi M and Nag TC (2018). Ameliorative potential of rutin in combination with nimesulide in STZ model of diabetic neuropathy: targeting Nrf-2/HO-1/NF-kB and COX signalling pathway. *Inflammopharmacology.,* **26**(3): 755-768.

Moghbelinejad S, Nassiri-Asl M, Farivar TN, Abbasi E, Sheikhi M, Taghiloo M, Farsad F, Samimi A and Hajiali F (2014). Rutin activates the MAPK pathway and BDNF gene expression on beta-amyloid induced neurotoxicity in rats. *Toxicol. Lett.,* **224**(1): 108-113.

Moldogazieva NT, Mokhosoev IM, Mel'nikova TI, Porozov YB and Terentiev AA (2019). Oxidative stress and advanced lipoxidation and glycation end products (ALEs and AGEs) in aging and age-related diseases. *Oxid. Med. Cell. Longev.,* 3085756.

Nkpaa KW and Onyeso GI (2018). Rutin attenuates neurobehavioral deficits, oxidative stress, neuro-inflammation and apoptosis in fluoride treated rats. *Neurosci. Lett.,* **682**: 92-99.

Oboh G, Adebayo AA, Ademosun AO and Olowokere OG (2019). Rutin alleviates cadmium-induced neurotoxicity in Wistar rats: Involvement of modulation of nucleotide-degrading enzymes and monoamine oxidase. *Metab. Brain. Dis.,* **34**(4): 1181-1190.

Ola MS, Ahmed MM, Ahmad R, Abuohashish HM, Al-Rejaie SS and Alhomida AS (2015). Neuroprotective effects of rutin in streptozotocin-induced diabetic rat retina. *J. Mol. Neurosci.,* **56**(2): 440-448.

Qu S, Dai C, Lang F, Hu L, Tang Q, Wang, H, Zhang Y and Hao Z (2018). Rutin attenuates vancomycin-induced nephrotoxicity by ameliorating oxidative stress, apoptosis and inflammation in rats. *Antimicrob. Agents. Chemother.,* **63**: e01545-18.

Saklani R, Gupta SK, Mohanty IR, Kumar B, Srivastava S and Mathur R (2016). Cardioprotective effects of rutin via alteration in TNF-α, CRP, and BNP levels coupled with antioxidant effect in STZ-induced diabetic rats. *Mol. Cell. Biochem.,* **420**(1-2): 65-72.

Song Y, Huang L and Yu J (2016). Effects of blueberry anthocyanins on retinal oxidative stress and inflammation in diabetes through Nrf-2/HO-1 signaling. *J. Neuroimmunol.,* **301**: 1-6.

Song J, Du G, Wu H, Gao X, Yang Z, Liu B and Cui S (2021). Protective effects of quercetin on traumatic brain injury induced inflammation and oxidative stress in cortex through activating Nrf2/HO-1 pathway. Restor. *Neurol. Neurosci.,* **39**(1): 73-84.

Suganya SN and Sumathi T (2017). Effect of rutin against a mitochondrial toxin, 3-nitropropionicacid induced biochemical, behavioral and histological alterations-a pilot study on Huntington's disease model in rats. *Metab. Brain. Dis.*, **32**(2): 471-481.

Sun C, Wang L, Sun J, Wang Z and Tang Z (2020). Hypoglycemic and hypolipidemic effects of rutin on hyperglycemic rats. *J. Tradit. Chin. Med.,* **40**(4): 640-645.

van Duinkerken E and Ryan CM (2020). Diabetes mellitus in the young and the old: Effects on cognitive functioning across the life span. *Neurobiol. Dis.,* **134**: 104608.

Wang J, De-Qiong X, Hong DQ, Zhang QQ and Zhang J

(2019). Attenuation of myocardial ischemia reperfusion injury by Geniposide preconditioning in diabetic rats. *Curr. Res. Transl. Med.,* **67**(2): 35-40.

Wang K, Song F, Xu K, Liu Z, Han S, Li F and Sun Y (2019). Irisin attenuates neuroinflammation and prevents the memory and cognitive deterioration in streptozotocin-induced diabetic mice. *Mediators. Inflamm.,* 1567179.

Woo Y, Lim JS, Oh J, Lee JS and Kim JS (2020). Neuroprotective effects of *Euonymus alatus* extract on scopolamine-induced memory deficits in mice. *Antioxidants.,* **9**(5): 449.

Xu N, Huang F, Jian C, Qin L, Lu F, Wang Y, Zhang Z and Zhang Q (2019). Neuroprotective effect of salidroside against central nervous system inflammation-induced cognitive deficits: A pivotal role of sirtuin 1-dependent Nrf-2/HO-1/NF-κB pathway. *Phytother. Res.,* **33**(5): 1438-1447.

Zhang S, Xue R and Hu R (2020). The neuroprotective effect and action mechanism of polyphenols in diabetes mellitus-related cognitive dysfunction. *Eur. J. Nutr.,* **59**(4): 1295-1311.