SHORT COMMUNICATION

Hypoglycemic activity and mechanisms of myricetin

Junqing Qian¹, Jinqiu Zhang¹, Yan Chen², Chengen Dai³, Jing Fan² and Hui Guo¹

¹College of Pharmaceutical Sciences, Zhejiang University of Technology, Hangzhou, China; ²WuXi AppTec, Shanghai, China; ³Research Institute of Subtropical Forestry, Chinese Academy of Forestry, Hangzhou, China

ABSTRACT
Myricetin has been reported to have a wide variety of beneficial physiological functions. The present study was designed to investigate the mechanism of high purity myricetin, as a hypoglycemic functional component on high fat diet (HFD) fed streptozotocin (STZ) induced diabetic rats. Four-week antihyperglycemic effects of myricetin were assayed. The results showed that continuous administration of myricetin (50 and 200 mg/kg body weight) in HFD/STZ induced diabetic rats dose-dependently reduced the body serum glucose and insulin. Furthermore, administrations of myricetin significantly increased the expression of insulin receptor (InsR) and glucose transporter 4 (GLUT4) gene and increased the expression of glucose-6-phosphatase (G-6-Pase) and phosphoenolpyruvate carboxykinase (PEPCK) gene. Moreover, myricetin protected pancreatic tissue from HFD fed STZ induced apoptosis through regulation of Bcl-2 associated X (Bax) gene and B-cell lymphoma-2 (Bcl-2) gene. The experimental results show that myricetin has significant health benefits and can be explored as a potentially promising dietary supplement for auxiliary hypoglycemic.

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1. Introduction
Hyperglycemia is a complex chronic metabolic disorder characterised by the destruction of pancreatic β-cells leading to the lack of insulin production, or the resistance of...
cells to insulin, or both (Sharma et al. 2014). The hyperglycemia control and complications trial also proved that even the optimal control of blood glucose could not prevent complications, thus alternative/complementary treatment strategies are required (Pareek et al. 2019). Currently, natural products have gained considerable attention worldwide to take advantage of nutrition and functional properties. Xu et al. (2018) investigated the anti-diabetic activities of Leucaena leucocephala. Meng et al. (2016) found that Hovenia flavonoids exerted promising inhibition effect on two major hydrolactic enzymes, \( \alpha \)-amylase and \( \alpha \)-glucosidase, and they were effective and promising functional foods in alleviating type 2 diabetes. Yan et al. (2016) purified four flavonoid glycosides from BQ pulp. And the flavonoids extracts showed strong \( \alpha \)-glucosidase inhibitory activities.

Myricetin (3,3',4',5,5',7-hexahydroxyflavone), is a member of the class of flavonoids called flavonols. The compound exhibits a wide range of activities, including strong anti-oxidant, anti-cancer, improve hyperlipidemia and insulin resistance, anti-inflammatory activity (Choi et al. 2014; Singh and Bast 2015; Semwal et al. 2016). Myricetin reduces insulin resistance and blood sugar levels by increasing the production of endogenous beta-endorphins and activating opioid receptors (Liu et al. 2006; Semwal et al. 2016; Imran et al. 2021). And it can significantly improve hyperlipidemia (Park et al. 2016). Myricetin may protect human umbilical vein endothelial cells from high glucose-induced apoptosis by increasing total antioxidant capacity of the cells, and reduce toxicity to kidney (Kandasamy and Ashokkumar 2014; Gupta et al. 2020). However, the hypoglycemic action of myricetin at the molecular level remains to be elucidated (Hwang et al. 2009).

Hence, the present study was designed to investigate the possible mechanisms potentially contributing to the hypoglycemic effect of myricetin in high fat diet (HFD) fed streptozotocin (STZ) induced type 2 diabetic rats, which provides the basis for the development of the hypoglycemia. It heightens the natural products, myricetin, fall blood sugar function research.

2. Results and discussion

2.1. Nuclear magnetic detection of myricetin

Myricetin was detected by HPLC, quantitative control with standard substance, purity is 98.1\% (The HPLC spectra is shown in Figure S1). Nuclear Magnetic Detection \(^{13}\)C NMR and \(^1\)H NMR was detected by Fourier transform NMR spectroscopy (Bruker AVANCE III500 spectrometer, Bruker, Switzerland). Results were shown in Figure S2A, S2B. The peaks around the \( \delta \)40 of the chemical shift are solvent DMSO-d\(_6\) peaks, \( \delta \)93.1 to 175.7 represent 15 carbons with 13 different chemical shifts. \( \delta \)2.51 and 3.36 in Figure S2 B are solvent DMSO-d6 and water peaks, respectively. \( \delta \)6.18 to 12.51 represent 10 hydrogen with 8 different chemical shifts, respectively.

The molecular formula of myricetin is \( \text{C}_{15}\text{H}_{10}\text{O}_6 \). And the molecular structure is 3,5,7,3',4',5' hydrogen atoms at the aromatic ring skeleton formed by hydroxyl substituted. The nuclear magnetic spectra of the sample and the standard nuclear magnetic data (Devi et al. 2015) were compared and the structure of myricetin was qualitatively analysed to confirm the molecular structure of myricetin sample.
2.2. Oral glucose tolerance test

The response to an oral glucose tolerance test on day 28 is shown in Figure S4. After the rats received a glucose load orally, serum glucose levels increased to a peak at 30 min. The glucose levels of diabetic group were higher than those in the normal group at all the tested points throughout the OGTT study. All the myricetin-treated rats showed significantly lower glucose levels than the diabetic group (Figure S4A). The area under the curve (AUC) in the myricetin-treated group also decreased significantly (Figure S4B). Moreover, the improvement in oral glucose tolerance in diabetic rats treated with myricetin was dose-dependent. Metformin also improved oral glucose tolerance of diabetic rats.

2.3. Effects of myricetin on gene expressions

Figure S5A and S5B showed the expression of G-6-Pase and PEPCK gene in normal and diabetic rats. G-6-Pase and PEPCK were significantly increased in the diabetic group compared with the normal control group. Myricetin at doses of 50 and 200 mg/kg markedly reduced G-6-Pase and PEPCK gene expression compared with the diabetic group. Our data showed that myricetin dose-dependently decreased Bax and increased Bcl-2 expression levels in the pancreas (Figure S5C, S5D). Moreover, Bcl-2/Bax ratio, a main index of apoptotic cell death, were significantly increased in the myricetin groups (Figure S5E). There was a clear increase in GLUT 4 expression in the myricetin groups (Figure S5F). Furthermore, compared with diabetic rats, the myricetin groups demonstrated a clear increase of more than 50% in the expression level of insulin receptor (InsR) gene, a tyrosine kinase receptor which plays a key role in the regulation of glucose homeostasis (Figure S5G).

3 Conclusion

The present study has demonstrated the potency of myricetin to ameliorate hyperglycemia and insulin resistance in diabetic rats. The myricetin modulates glucose uptake and metabolism in peripheral tissues via InsR and GLUT4 gene expression in skeletal muscle, and regulates gluconeogenesis via G6Pase and PEPCK in liver. Furthermore, myricetin protect pancreatic β-islet cells from STZ-induced apoptosis through regulating gene expression of Bax and Bcl-2. The findings provided a basis for the application of myricetin hypoglycemic functional food. At the same time, it also deepened the research on the hypoglycemic function of natural products.

Disclosure statement

No potential conflict of interest was reported by the authors.

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References

Choi HN, Kang MJ, Lee SJ, Kim Ji. 2014. Ameliorative effect of myricetin on insulin resistance in mice fed a high-fat, high-sucrose diet. Nutr Res Pract. 8(5):544–549.

Devi KP, Rajavel T, Habtemariam S, Nabavi SF, Nabavi SM. 2015. Molecular mechanisms underlying anticancer effects of myricetin. Life Sci. 142:19–25.

Gupta G, Siddiqui MA, Khan MM, Ajmal M, Ahsan R, Rahaman MA, Ahmad MA, Arshad M, Khushar M. 2020. Current pharmacological trends on myricetin. Drug Res (Stuttg). 70(10):448–454.

Hwang HJ, Kim SW, Baek YM, Lee SH, Hwang HS, Yun JW. 2009. Gene expression profiling in streptozotocin-induced diabetic rat liver in response to fungal polysaccharide treatment. Korean J Chem Eng. 26(1):115–126.

Imran M, Saeed F, Hussain G, Imran A, Mehmood Z, Gondal TA, El-Ghorab A, Ahmad I, Pezzani R, Arshad MU, et al. 2021. Myricetin: A comprehensive review on its biological potentials. Food Sci Nutr. 9(10):5854–5868.

Kandasamy N, Ashokkumar N. 2014. Protective effect of bioflavonoid myricetin enhances carbohydrate metabolic enzymes and insulin signaling molecules in streptozotocin-cadmium induced diabetic nephrotoxic rats. Toxicol Appl Pharmacol. 279(2):173–185.

Liu IM, Liou SS, Cheng JT. 2006. Mediation of beta-endorphin by myricetin to lower plasma glucose in streptozotocin-induced diabetic rats. J Ethnopharmacol. 104(1-2):199–206.

Meng YH, Su AP, Yuan S, Zhao HG, Tan SY, Hu CY, Deng H, Guo YR. 2016. Evaluation of total flavonoids, myricetin, and quer cetin from Hovenia dulcis Thunb. as inhibitors of \( \alpha \)-amylase and \( \alpha \)-glucosidase. Plant Foods Hum Nutr. 71(4):444–449.

Pareek H, Sharma S, Khajja BS, Jain K, Jain GC. 2009. Evaluation of hypoglycemic and anti-hyperglycemic potential of Tridax procumbens (Linn.). BMC Complement Altern. Med. 9 (1):48

Park K-S, Chong Y, Kim MK. 2016. Myricetin: biological activity related to human health. Appl Biol Chem. 59(2):259–269.

Semwal DK, Semwal RB, Combrinck S, Viljoen A. 2016. Myricetin: a dietary molecule with diverse biological activities. Nutrients. 8(2):90.

Sharma S, Choudhary M, Bhardwaj S, Choudhary N, Rana AC. 2014. Hypoglycemic potential of alcoholic root extract of Cassia occidentalis L. in streptozotocin induced diabetes in albino mice. Bull Fac Pharm Cairo Univ. 52:211–217.

Singh P, Bast F. 2015. Screening and biological evaluation of myricetin as a multiple target inhibitor insulin, epidermal growth factor, and androgen receptor; in silico and in vitro 33. Invest New Drugs. 33(3):575–593.

Xu YC, Tao ZR, Jin Y, Yuan YF, Dong Tina TX, Tsim Karl WK, Zhou ZY. 2018. Flavonoids, a Potential New Insight of Leucaena leucocephala Foliage in Ruminant Health. J Agric Food Chem. 66(29):7616–7626.

Yan S, Zhang X, Wen X, Lv Q, Xu C, Sun C, Li X. 2016. Purification of Flavonoids from Chinese Bayberry (Morella rubra Sieb. et Zucc.) Fruit Extracts and \( \alpha \)-Glucosidase Inhibitory Activities of Different Fractionations. Molecules. 21(9):1148.