ISSN 2616-5791 Vol.5, Issue 2: 15-21, DOI: 10.25236/AJMHS.2024.050203

Research progress of isoquercitrin in the treatment of diabetes and its complications

Sihua Lu[1,a], Guihong Huang[2,3,4,5,b,*]

[1]*Lingui Clinical College, Guilin Medical University, Guilin, Guangxi, 541199, China*
[2]*Department of Pharmacy, The Second Affiliated Hospital of Guilin Medical University, Guilin, Guangxi, 541199, China*
[3]*Guangxi Health Commission Key Laboratory of Glucose and Lipid Metabolism Disorders, Key Laboratory of Diabetic Systems Medicine, Guangxi Key Laboratory of Metabolic Reprogramming and Intelligent Medical Engineering for Chronic Diseases, Guilin, Guangxi, 541199, China.*
[4]*Guangxi Key Laboratory of Drug Discovery and Optimization, Guangxi Engineering Research Center for Pharmaceutical Molecular Screening and Druggability Evaluation, School of Pharmacy, Guilin Medical University, Guilin, Guangxi, 541199, China*
[5]*Guangxi Clinical Research Center for Diabetes and Metabolic Diseases, Guilin, Guangxi, 541199, China*
[a]*1656558308@qq.com,* [b]*guihonghuang666@163.com*
[*]*Corresponding author*

Abstract: *Diabetes mellitus (DM) is a group of multifactorial metabolic disorders characterized by chronic high blood glucose levels. It is often the result of impaired insulin secretion or insulin resistance.This article discusses the improvement of isoquercitrin on diabetes and its associated complications, including type 2 diabetes, hepatic gluconeogenesis, and diabetic neuropathy. We reviewed the published related papers in detail, analyzed the pathogenesis of diabetes from the perspective of its pathogenesis, and showed how isoquercitrin affects its key signaling pathways by regulating the levels of related factors, and ultimately improves the role of diabetes and its related complications.*

Keywords: *Diabetes; Isoquercetrin; Complications of diabetes; Oxidative stress; Liver gluconeogenesis*

1. Introduction

Globally, more than one in 10 adults are now living with diabetes. Moreover, there is a growing list of countries where one-in-five or even more of the adult population has diabetes. In 2021, the global prevalence of diabetes in people aged 20-79 is estimated to be 10.5% (536.6 million people), rising to 12.2% (783.2 million people) in 2045[1]. In addition, these statistics have been slowly increasing over the past few decades.Reducing the damage caused by diabetes has become a popular topic. It has become the primary goal of diabetes prevention or treatment to effectively prevent the onset of diabetes, control the progression of diabetes, improve the health of people around the world, and find new ways to improve insulin resistance and insulin sensitivity.

Recently, there has been increasing interest in hypoglycemic drugs derived from natural products, especially from plants, including natural flavonoids. Flavonoids are natural phenolic compounds which are widely distributed in plants. They have broad biological activities and their potential role in treating diabetes has been extensively studied [2].Studies have demonstrated hypoglycemic effects of flavonoids in various experimental models and treatments [3-5]. There is also evidence of inhibition of vitamin C and glucose transport and absorption [6].Isoquercitrin, the most abundant monomer glucoside of the natural flavonoid quercetin, holds promise for diabetes treatment and prevention. Isoquercetin was isolated for the first time by Douglas et al. from the seed pods of the Canadian Bauhinia [7]. In China, isoquercitrin is one of the major active ingredients in various medicinal herbs, such as Bidens pilosula, Huangkui, Apocynaceae asiatica, and Vitex negundo.According to the comprehensive research on the biological activity of isoquercitrin, in addition to lowering blood sugar, isoquercitrin also has anti-inflammatory, antioxidant, anti-virus, anti-tumor, anti-arteriosclerosis, blood pressure lowering and other biological activities.Therefore, isoquercitrin has become a breakthrough in researching and

ISSN 2616-5791 Vol.5, Issue 2: 15-21, DOI: 10.25236/AJMHS.2024.050203

developing natural drugs for diabetes. In order to lay a theoretical foundation for the follow-up research and development of isoquercitrin, this article reviewed the relevant role of isoquercitrin in diabetes and its complications and fully understood the research and development progress of isoquercitrin.

2. Isoquercitrin and diabetes

2.1. Isoquercitrin and type 2 diabetes

Type 2 diabetes mellitus (T2DM) has become an epidemic disease, and the pathogenesis of T2DM is still unclear. It has been reported that insulin insensitivity is an early phenomenon, partly related to obesity, but before the development of pancreatic hyperglycemia, pancreatic cell function progressively decreases over time.Several related mechanisms have been proposed, including an increase in unesterified fatty acids, mitochondrial dysfunction in inflammation, adiposity, and insulin resistance, and amyloid protein formation in glycotoxicity, adiposity, and cellular disorders [8]. It is reported that isoquercitrin regulates blood glucose and lipids, improves pancreatic islet function, and suggests that isoquercitrin can be used to treat type 2 diabetes [9].From a molecular structural point of view, studies have shown that the flavonoid molecule isoquercetin forms a new complex with alpha-glucosidase, indicating that isoquercetin may act as an alpha-glucosidase inhibitor used to control glycemic control [10].

2.1.1. Isoquercitrin and obesity

Insulin resistance refers to a pathological state in which insulin secretion is normal or even above normal, but the patient's body is insensitive to insulin action, so the secreted insulin cannot regulate the body's blood glucose to normal levels. It is considered the main mechanism in T2DM.Based on current genetic evidence, β-catenin is a particularly important regulator of fat formation [11]. Small molecules that regulate the Wnt/β-catenin pathway may control obesity-related fat production.Growing evidence suggests that high sugar levels can activate the Wnt/β-catenin pathway. Through the research of Kahkashan Resham, et al, it was shown that diabetes hyperglycemia can increase the binding of Wnt ligand to curl receptor and co receptor LRP5/6, which in turn increases β-catenin expression [12]. Isoquercetin can specifically block the Wnt pathway, prevent the differentiation of 3T3-L1 preadipocytes into adipocytes, and thus combat obesity.Therefore, Isoquercitrin has a certain significant role in preventing and treating obesity, reducing the occurrence of insulin resistance and diabetes risk.

2.1.2. Isoquercitrin and oxidative stress

Oxidative stress (OS) is a state of imbalance between oxidative and antioxidant effects in the body. When cellular redox balance is disturbed, oxidative stress results in damage to cell membranes and key biomolecules including DNA, proteins, and lipids [13-15]. In addition, it was demonstrated that oxidative stress impairs insulin secretion and insulin function in diabetes[16-17]. Reported molecular pathways involved in diabetic oxidative stress include: (1) the glucose oxidation pathway (glycolysis); (2) the advanced glycation end product (AGE) pathway; (3) the diacylglycerol formation and PKC activation pathway; (4) the hexosamine pathway; (5) the polyols pathway; and (6) the insulin signaling pathway. In treating oxidative stress, Fe2+ chelation has become a method to treat many diseases related to reactive oxygen species (ROS) [18]. In an analysis based on an oxidative damage model of mesenchymal stem cells (MSCs), isoquercetin as a cell protective agent may indirectly or directly participate in the scavenging of ROS and protect MSCs from ROS-induced oxidative damage. The 6"-OH group in isoquercitrin enhances Fe^{2+} chelating ability, reduces its hydrogen donating ability by steric hindrance or H-bonding, and increases its protection against ROS-induced oxidative damage [19]. Meanwhile, isoquercitrin has been shown to reduce hyperglycemia and oxidative stress by regulating several genes in the Nrf2 pathway that inhibit oxidative stress, as demonstrated by Muthukumaran et al [20]. Nrf2 regulates redox, protein and metabolic balance and is a central and multitasking regulator. A number of antioxidant genes and proteins involved in managing oxidative stress are regulated by this pathway [21]. However, its potent inhibitory effect on oxidative stress cannot be overlooked, and isoquercitrin offers greater development space for the treatment of oxidative stress-related diseases in the future.

2.1.3. Isoquercitrin and inflammatory factors

Inflammation is the body's defensive response to stimuli. It's most often manifested as redness, swelling, heat, pain, and dysfunction. It can be inflammation caused by infection or inflammation caused by noninfection. IL-8, IL-6, IL-1, as well as the inflammatory mediator NO are known products or effectors of the immune system [22]. They can directly inhibit insulin action in insulin targets such as

ISSN 2616-5791 Vol.5, Issue 2: 15-21, DOI: 10.25236/AJMHS.2024.050203

liver, muscle and adipocytes via paracrine pathways [23-24]. Through endocrine effects, these tissue cytokines can also be released into the systemic circulation, where they can cause insulin resistance.By decreasing the expression levels of key insulin signaling molecules, cytokines can also inhibit insulin action through transcriptional mechanisms [25]. Population-based studies show [26] that inflammatory markers are closely related to metabolic disorders, obesity and atherosclerosis, and inflammation is considered the "common ground" between these conditions and type 2 diabetes.Quercitrin's anti-inflammatory effects have long been confirmed. However, later studies found that it and its glycosides act to inhibit inflammatory cells that produce inflammatory mediators. Its anti-inflammatory effects are thought to target neutrophils and monocytes [27]. The anti-inflammatory mechanism of isoquerctin was further investigated by decreasing the production of TNF-alpha, NO, iNOS and COX-2. All of the above evidence indicates that isoquercitrin has anti-inflammatory effects and to some extent reduces the development of diabetes.

2.2. Isoquercitrin and gluconeogenesis in the liver

Glycogenesis is the process of converting various non-sugars (lactic acid, glycogenic amino acids, glycerol, etc.) into glucose. However, the liver is the main source of gluconeogenesis, and renal gluconeogenesis is only one tenth of liver gluconeogenesis [28]. During fasting, noncarbohydrate sources of glucose and glycogen provide glucose to starving tissues through hepatic gluconeogenesis to maintain glycemia. Impaired cell function, insulin resistance, and increased glucagon secretion promote increased hepatic gluconeogenesis, leading to increased hepatic glucose output and impaired hepatic glucose control, followed by hyperglycemia [29-30]. The key to the treatment of diabetes is to reduce the occurrence of abnormal activity of hepatic glucose abnormalities.

Gluconeogenesis relies on PEPCK, fructose-1, 6-diphosphatase, and glucose-6-phosphatase (G6Pase) to avoid irreversible glycolytic reactions. The time required to transcribe the two rate-limiting enzymes, PEPCK and G6Pase, determines the rate of hepatic gluconeogenesis [31]. Transcription of PEPCKs and G6Pase genes is regulated by multiple factors and cytokines, and one of its key ways is to change activity of different metabolic factors by activating adenosine activated protein kinase (AMPK). Experimental studies have shown that AMPK activation inhibits gluconeogenesis, endogenous glucose output, and fasting glucose [32]. After phosphorylating threonine 172 (Thr172), AMPK may suppress the effective expression of gluconeogenic enzymes and associated transcription factors, thereby inhibiting the occurrence of gluconeogenic reactions in the liver and lowering glucose [33].Based on this, Zhou et al. found that isoquercitrin can enhance phosphorylating AMPK. In subsequent studies, Xie Xiuying et al. experimentally demonstrated the effects of okra alcohol isoquercitrin on hepatocyte gluconeogenesis, PEPCK, and G6Pase [34]. Isoquercitrin can promote the regulation of AMPK phosphorylation in hepatocytes, significantly reduce PEPCK and G6Pase expression, and verify this effect is dose-dependent.

In addition, studies have shown [35] that isoquercitrin inhibits gluconeogenesis in liver cells and promotes AMPK α Thr172 and TORC2 Ser171 are phosphorylated and act in a similar way to metformin. TORC2 is a regulatory protein of the transcription factor cyclic adenosine responsive element binding protein (CREB) in the nucleus of the liver. Upon AMPK activation, TORC2 is phosphorylated and cytoplasmically sequestered, leading to decreased CREB transcription and inhibition of PEPCK and G6Pase expression, controlling hepatic gluconeogenesis [36]. Overexpressing TORC2 Serl71 was reported to increase the expression of genes coding for enzymes involved in gluconeogenesis and liver glucose output [37]. Therefore, promoting TORC2 Serl71 phosphorylation may become a targeted therapy for inhibiting liver glucose. Metformin, a common clinical antihyperglycemic agent, also reduces hepatic glucose production through a similar AMPK pathway activation mechanism. AMPK inactivation and elevation of fasting plasma glucose were observed [38]. Metformin does not improve glycemia in LKB1 knockout mice. This suggests that LKB1 is also an important target for the inhibition of hepatic gluconeogenesis. Recent studies have found that isoquercitrin can pass through LKB1-AMPKα pathway to inhibit liver gluconeogenesis [39], experiment found its total AMPKα . There was no significant change in gene level, whereas isoquercitrin was mainly regulated at the protein level through AMPK regulation of LKB1.

ISSN 2616-5791 Vol.5, Issue 2: 15-21, DOI: 10.25236/AJMHS.2024.050203

3. Isoquercitrin and complications of diabetes mellitus

3.1. Isoquercitrin and diabetic neuropathies

Diabetes neuropathy is a disease of the peripheral nervous system. It affects the somatic and autonomic components of the nervous system. Diabetic neuropathies are one of the most common chronic complications of diabetes. The incidence rate in patients with type 1 diabetes is approximately 54%-59%. The incidence rate in patients with type 2 diabetes is approximately 45%[40-41]. It has been found that isoquercitrin can largely ameliorate streptozotocin (STZ)-induced apoptosis, mitochondrial dysfunction and oxidative stress, promote the differentiation and neurite outgrowth of N2a cells, and protect hippocampal neurons from STZ-induced neurotoxicity.Finally, it has been proposed that isoquercitrin is one of the flavonoid compounds that has the best anti-cytotoxic activity [42].Neuroinflammation is also associated with abnormal Wnt signaling. The Wnt signaling protein has been shown to be important in the development of neurons and can trigger neuropathic pain in hyperglycemia [43]. Recently, it has been reported [44] that isoquercitrin can reduce the abnormal expression of Wnt target proteins (c-myc and MMP2), which leads to behavioral pain and attenuates neurological parameters in diabetic neuropathy mice.

3.2. Isoquercitrin and nonalcoholic fatty liver disease

Nonalcoholic fatty liver disease (NAFLD) is a clinicopathologic syndrome considered one of the most common causes of liver damage, including steatosis [45]. Alterations in hepatic metabolism lead to excessive production of sugars and lipids, which promote the development of glucose intolerance and dyslipidemia, inducing T2DM. T2DM has become a powerful predictor of NAFLD, and more than 70% of diabetic patients suffer from NAFLD [46]. In some studies, isoquercitrin has a protective effect on liver injury in type 2 diabetic rats, and the ALT and AST of mice in the isoquercitrin-treated group are significantly decreased. Coincidentally, other studies have shown that isoquercitrin can activate the AMPK and TGF-β signaling pathways to improve lipid accumulation, reduce inflammation and oxidative stress, and thereby ameliorate NAFLD.

3.3. Isoquercitrin and Cancer

With nearly one-sixth of all deaths, cancer is the second leading cause of death worldwide. Approximately 9.6 million people will die from cancer in the year 2018. Diabetes is strongly associated with developing cancer. The risk of cancer is 20% higher in diabetic patients than in healthy individuals [47]. Studies suggest that hyperglycemia may lead to tumor proliferation and invasion [48]. According to the report [49], hyperglycemia or diabetes-induced cancer cell proliferation occurs indirectly through: (1) insulin and insulin-like growth factor 1 (IGF-1), (2) leptin/adiponectin secretion, (3) inflammatory response, (4) reactive oxygen species (ROS) production, (5) immune abnormalities (platelet activation). Isoquercitrin was confirmed to reduce the viability and colony growth of cancer cells and to activate apoptotic pathways in cancer cells. In one study, HepG2 and Huh7 human liver cancer cells were exposed to isoquercitrin and autophagy and cell apoptosis were examined. Finally, it was confirmed that isoquercitrin can induce apoptosis and autophagy of liver cancer cells through the AMPK/mTOR/p70S6K signaling pathway [50].

Due to its ability to induce autophagy and apoptosis in cancer cells, it was reported to be a potential chemopreventive therapy for melanoma cells. Studies have shown that isoquercitrin inhibits the survival of SK melanoma cells and enhances mitochondrial apoptosis through activation of caspase-dependent and -independent pathways and downregulation of PI3K/AKT pathway. The results of a phase II clinical trial, in addition to demonstrating that plasma PDI may be a viable therapeutic target for anticoagulation therapy in cancer populations considered to be at high risk for thrombosis and hemorrhage, also confirmed that isoquercitrin inhibited PDI activity and significantly reduced plasma D-dimer levels, soluble P-selectin, and thrombin production [51].

4. Conclusions

Although there is more and more promising evidence that isoquercitrin plays a very significant role in diabetes and its complications, which provides a new direction for treating and preventing diabetes, considering that most studies are conducted in vitro and in vivo, more human clinical trials are needed to determine the real potential of isoquercitrin in treating diabetes and its related diseases. Finally,

ISSN 2616-5791 Vol.5, Issue 2: 15-21, DOI: 10.25236/AJMHS.2024.050203

through this review, we may conclude that isoquercitrine shows promise as a new treatment for diabetes and its complications, with great potential for delaying the progression of diabetes complications and improving the clinical value of patients' quality of life.

Acknowledgements

This study was supported by the National Natural Science Foundation of China (NO.82160701); Guilin scientific research and technology development plan project (NO.20210227-5); Medical Science Research Fund of Beijing Health Alliance Charitable Foundation (No.KM226002).

References

[1] Sun H, Saeedi P, Karuranga S, Pinkepank M, Ogurtsova K, Duncan BB, Stein C, Basit A, Chan JCN, Mbanya JC, Pavkov ME, Ramachandaran A, Wild SH, James S, Herman WH, Zhang P, Bommer C, Kuo S, Boyko EJ, Magliano DJ. IDF Diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. Diabetes Res Clin Pract. 2022 Jan; 183:109119. doi: 10.1016/j.diabres.2021.109119. Epub 2021 Dec 6. Erratum in: Diabetes Res Clin Pract. 2023 Oct;204:110945. PMID: 34879977.

[2] Ong KC, Khoo HE. Effects of myricetin on glycemia and glycogen metabolism in diabetic rats. Life Sci. 2000 Aug 25;67(14):1695-705. doi: 10.1016/s0024-3205(00)00758-x. PMID: 11021354.

[3] Kao YH, Hiipakka RA, Liao S. Modulation of endocrine systems and food intake by green tea epigallocatechin gallate. Endocrinology. 2000 Mar;141(3):980-7. doi: 10.1210/endo.141.3.7368. PMID: 10698173.

[4] Tsuneki H, Ishizuka M, Terasawa M, Wu JB, Sasaoka T, Kimura I. Effect of green tea on blood glucose levels and serum proteomic patterns in diabetic (db/db) mice and on glucose metabolism in healthy humans. BMC Pharmacol. 2004 Aug 26;4:18. doi: 10.1186/1471-2210-4-18. PMID: 15331020; PMCID: PMC517497.

[5] Sabu MC, Smitha K, Kuttan R. Anti-diabetic activity of green tea polyphenols and their role in reducing oxidative stress in experimental diabetes. J Ethnopharmacol. 2002 Nov;83(1-2):109-16. doi: 10.1016/s0378-8741(02)00217-9. PMID: 12413715.

[6] Song, J., Kwon, O., Chen, S., Daruwala, R., Eck, P., Park, J. B., and Levine, M. Flavonoid inhibition of sodium-dependent vitamin C transporter 1 (SVCT1) and glucose transporter isoform 2 (GLUT2), intestinal transporters for vitamin C and glucose. J. Biol. Chem. 2002, 277, 15252–15260.

[7] Douglass, C.D., Howard, W.L., Wender, S.H., 1949. The isolation of isoquercitrin from the seed pods of Cercis canadensis. J. Am. Chem. Soc. 71, 2658–2659.

[8] Stumvoll M, Goldstein BJ, van Haeften TW. Type 2 diabetes: principles of pathogenesis and therapy. Lancet. 2005 Apr 9-15;365(9467):1333-1346. doi: 10.1016/S0140-6736(05)61032-X. PMID: 15823385.

[9] Zhang R, Yao Y, Wang Y, Ren G. Antidiabetic activity of isoquercetin in diabetic KK - Ay mice. Nutr Metab (Lond). 2011 Dec 2;8:85.

[10] Li YQ, Zhou FC, Gao F, Bian JS, Shan F. Comparative evaluation of quercetin, isoquercetin and rutin as inhibitors of alpha-glucosidase. J Agric Food Chem. 2009 Dec 23;57(24):11463-11468. doi: 10.1021/jf903083h. PMID: 19938837.

[11] Arango NA, Szotek PP, Manganaro TF, Oliva E, Donahoe PK, Teixeira J.2005. Conditional deletion of [beta]-catenin in the mesenchyme of the developing mouse uterus results in a switch to adipogenesis in the myometrium. Dev Biol 288: 276–283.

[12] Resham K, Khare P, Bishnoi M, Sharma SS. Neuroprotective effects of isoquercitrin in diabetic neuropathy via Wnt/β-catenin signaling pathway inhibition. Biofactors. 2020 May;46(3):411-420.

[13] D. Wu, A.I. Cederbaum, Alcohol, oxidative stress, and free radical damage, Alcohol Res. Health (December (27)) (2003) 277–284.

[14] H. Bartsch, J. Nair, Oxidative stress and lipid peroxidation-derived DNA-lesions in inflammation driven carcinogenesis, Cancer Detect. Prev. 28 (December (6)) (2004)385–391.

[15] J.R. Speakman, C. Selman, The free-radical damage theory: accumulating evidence against a simple link of oxidative stress to ageing and lifespan, Bioessays 33 (April(4)) (2011) 255–259.

[16] F. Giacco, M. Brownlee, Oxidative stress and diabetic complications, Circ. Res. 107(October (9)) (2010) 1058–1070.

[17] J.L. Evans, I.D. Goldfine, B.A. Maddux, G.M. Grodsky, Are oxidative stress− activated signaling pathways mediators of insulin resistance and β-cell dysfunction? Diabetes 52 (January (1)) (2003) 1–8.

[18] Devos, D.; Moreau, C.; Devedjian, J.C.; Kluza, J.; Petrault, M.; Laloux, C.; Jonneaux, A.;

ISSN 2616-5791 Vol.5, Issue 2: 15-21, DOI: 10.25236/AJMHS.2024.050203

Ryckewaert, G.;Garçon, G.; Rouaix, N.; et al. Targeting chelatable Iron as a therapeutic modality in Parkinson's disease.Antioxid. Redox Signal. 2014, 21, 195–210.
[19] Li X, Jiang Q, Wang T, Liu J, Chen D. Comparison of the Antioxidant Effects of Quercitrin and Isoquercitrin: Understanding the Role of the 6"-OH Group. Molecules. 2016 Sep 19;21(9):1246.
[20] Jayachandran M, Wu Z, Ganesan K, Khalid S, Chung SM, Xu B. Isoquercetin upregulates antioxidant genes, suppresses inflammatory cytokines and regulates AMPK pathway in streptozotocin -induced diabetic rats. Chem Biol Interact. 2019 Apr 25;303:62-69.
[21] J.A. David, W.J. Rifkin, P.S. Rabbani, D.J. Ceradini, The Nrf2/Keap1/ARE pathway and oxidative stress as a therapeutic target in type II diabetes mellitus. J. Diab. Res.4826724 (2017) 1–15.
[22] COPPACK, S.W. 2001. Pro-inflammatory cytokines and adipose tissue. Proc. Nutr.Soc. 60: 349–356.
[23] Fève B, Bastard JP. The role of interleukins in insulin resistance and type 2 diabetes mellitus. Nat Rev Endocrinol. 2009 Jun;5(6):305-311. doi: 10.1038/nrendo.2009.62. PMID: 19399017.
[24] Hotamisligil GS. Mechanisms of TNF-alpha-induced insulin resistance. Exp Clin Endocrinol Diabetes. 1999;107(2):119-125. doi: 10.1055/s-0029-1212086. PMID: 10320052.
[25] Stephens JM, Pekala PH. Transcriptional repression of the C/EBP-alpha and GLUT4 genes in 3T3-L1 adipocytes by tumor necrosis factor-alpha. Regulations is coordinate and independent of protein synthesis. J Biol Chem. 1992 Jul 5;267(19):13580-13584. PMID: 1618860.
[26] STERN, M.P. 1995. Diabetes and cardiovascular disease. The "common soil" hypothesis. Diabetes 44: 369–374.
[27] Morikawa K, Nonaka M, Narahara M, Torii I, Kawaguchi K, Yoshikawa T, Kumazawa Y, Morikawa S. Inhibitory effect of quercetin on carrageenan-induced inflammation in rats. Life Sci. 2003 Dec 26;74(6):709-721. doi: 10.1016/j.lfs.2003.06.036. PMID: 14654164.
[28] Radziuk J. Tracer studies of liver metabolism. Horm Metab Res Suppl. 1990;24:31-40. PMID: 2272624.
[29] Bonner C,Kerr-Conte J,Gmyr V,et al. Inhibition of the glucose transporter SGLT2 with dapagliflozin in pancreatic alpha cells triggers glucagon secretion[J]. Nat Med,2015,21(5) : 512-517.
[30] WEI S, LI W, YU Y, et al. Ginsenoside compound K suppresses the hepatic gluconeogenesis via activating adenosine-5'monophosphate kinase: A study in vitro and in vivo [J]. Life Sci, 2015(139): 8-15.
[31] Xie Xiuying, Chen Lin, Lei Tao, Lu Ming, Shen Tian, Xu Bilin. The effects of two components in the alcohol extract of okra on gluconeogenesis and AMPK in liver cells α Effect of phosphorylation [J].Traditional Chinese patent medicines and simple preparations, 2018,40 (05): 1167-1170.
[32] Chen Lin, Lu Ming, Shen Tian, Xie Xiuying, Xu Bilin, Lei Tao. Research on the effect of isoquercitrin on hepatocyte gluconeogenesis by regulating AMPK-TORC2 phosphorylation [J]. Chinese Journal of Diabetes, 2019,27 (01): 62-68.
[33] MONTMINY M, KOO S H, ZHANG X. The CREB family: key regulators of hepatic metabolism [J]. Ann Endocrinol(Paris), 2004, 65(1): 73-75.
[34] Yoon S,Lee W,Ryu D,et a1. Suppressor of MEK null(SMEK),proteinphosphatase 4 catalytic subunit(PP4C)is a key regulator of hepatic gluconeogenesis.Proc Nad Acad Sci USA, 2010, 107:17704-17709.
[35] Wang Fei The effect of metformin on AMPK and PPARs activity in the liver of high-fat fed rats - a possible mechanism for improving fatty liver [D] Jinan: Shandong University, 2008.
[36] XIE M, ZHANG D, DYCK J R, et al. Apivotal role for endogenous TGF-β-activated kinase-1 in the LKB1/AMPactivated protein kinase energy-sensor pathway [J]. PNAS, 2006, 1039(46): 17378-17383.
[37] Chen L, Shen T, Zhang CP, Xu BL, Qiu YY, Xie XY, Wang Q, Lei T. Quercetin and Isoquercitrin Inhibiting Hepatic Gluconeogenesis Through LKB1-AMPKα Pathway. Acta Endocrinol (Buchar). 2020 Jan-Mar; 16(1):9-14.
[38] Zilliox L, Peltier AC, Wren PA, et al. Assessing autonomic dysfunction in early diabetic neuropathy: The survey of autonomic symptoms. Neurology. 2011;76:1099–1105.
[39] Sloan G, Shillo P, Selvarajah D, et al. A new look at painful diabetic neuropathy. Diabetes Res Clin Pract. 2018;144:177–191.
[40] Chen L, Feng P, Peng A, Qiu X, Lai W, Zhang L, Li W. Protective effects of isoquercitrin on streptozotocin-induced neurotoxicity. J Cell Mol Med. 2020 Sep;24(18):10458-10467.
[41] Ji RR, Xu ZZ, Gao YJ. Emerging targets in neuroinflammationdriven chronic pain. Nat Rev Drug Discov. 2014;13:533–548.
[42] Resham K, Khare P, Bishnoi M, Sharma SS. Neuroprotective effects of isoquercitrin in diabetic neuropathy via Wnt/β-catenin signaling pathway inhibition. Biofactors. 2020 May;46(3):411-420.
[43] Feldstein AE, Canbay A, Angulo P, Taniai M, Burgart LJ, Lindor KD, Gores GJ. Hepatocyte

ISSN 2616-5791 Vol.5, Issue 2: 15-21, DOI: 10.25236/AJMHS.2024.050203

apoptosis and fas expression are prominent features of human nonalcoholic steatohepatitis. Gastroenterology. 2003 Aug;125(2):437-443. doi: 10.1016/s0016-5085(03)00907-7. PMID: 12891546.
[44] Hazlehurst JM, Woods C, Marjot T, Cobbold JF, Tomlinson JW. Non-alcoholic fatty liver disease and diabetes. Metabolism. 2016 Aug;65(8):1096-1108. doi: 10.1016/j.metabol.2016.01.001. Epub 2016 Jan 11. PMID: 26856933; PMCID: PMC4943559.
[45] Valenti L, Bugianesi E, Pajvani U, Targher G. Nonalcoholic fatty liver disease: cause or consequence of type 2 diabetes? Liver Int. 2016 Nov;36(11):1563-1579. doi: 10.1111/liv.13185. Epub 2016 Jun 30. PMID: 27276701.
[46] Villarreal-Garza, C.; Shaw-Dulin, R.; Lara-Medina, F.; Bacon, L.; Rivera, D.; Urzua, L.; Aguila, C.; Ramirez-Morales, R.; Santamaria,J.; Bargallo, E. Impact of diabetes and hyperglycemia on survival in advanced breast cancer patients. Exp. Diabetes Res. 2012, 2012,732027.
[47] Srivastava, S.P.; Goodwin, J.E. Cancer biology and prevention in diabetes. Cells 2020, 9, 1380.
[48] Ferroni P, Riondino S, Buonomo O, Palmirotta R, Guadagni F, Roselli M. Type 2 Diabetes and Breast Cancer: The Interplay between Impaired Glucose Metabolism and Oxidant Stress. Oxid Med Cell Longev. 2015;2015:183928. doi: 10.1155/2015/183928. Epub 2015 Jun 11. PMID: 26171112; PMCID: PMC4480937.
[49] Shui L, Wang W, Xie M, Ye B, Li X, Liu Y, Zheng M. Isoquercitrin induces apoptosis and autophagy in hepatocellular carcinoma cells via AMPK/mTOR/p70S6K signaling pathway. Aging (Albany NY). 2020 Nov 29;12(23):24318-24332.
[50] Won YS, Kim JH, Lizardo RCM, Min HJ, Cho HD, Hong SM, Seo KI. The Flavonol Isoquercitrin Promotes Mitochondrial-Dependent Apoptosis in SK-Mel-2 Melanoma Cell via the PI3K/AKT/mTOR Pathway. Nutrients. 2020 Nov 29;12(12):3683.
[51] Zwicker JI, Schlechter BL, Stopa JD, Liebman HA, Aggarwal A, Puligandla M, Caughey T, Bauer KA, Kuemmerle N, Wong E, Wun T, McLaughlin M, Hidalgo M, Neuberg D, Furie B, Flaumenhaft R; CATIQ Investigators11. Targeting protein disulfide isomerase with the flavonoid isoquercetin to improve hypercoagulability in advanced cancer. JCI Insight. 2019 Feb 21; 4(4):e125851.