State of the art paper

Research progress of typical flavonoids in improving insulin resistance

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Abstract

Flavonoids are a large class of compounds that are widely found in many plants, including plants used in Chinese herbal medicines. Previous studies have revealed that flavonoids possess biomedical activities, including anti-oxidant, anti-cancer, anti-viral, and anti-inflammatory properties. They also have the functions of lowering lipids, lowering blood sugar, and improving insulin resistance. This article selects four typical compounds of flavonoids, namely baicalin, baicalein, quercetin, and rutin, and reviews their effects and mechanisms of action in improving insulin resistance. With a view for future clinical research on flavonoids as antidiabetic drugs, we therefore provide the theoretical basis for the development and application of flavonoids.

Key words: flavonoids, insulin resistance, type 2 diabetes, baicalin, baicalein, quercetin, rutin.

Introduction

With rapid economic development and the improvement of living standards, the numbers of patients with type 2 diabetes (T2D) have increased worldwide. Globally, it is predicted that the prevalence of diabetes among adults aged 20 to 79 years old will reach up to 6.4% and will continue to increase up to 7.7% by 2030, reaching approximately 439 million adults. Between 2010 and 2030, the numbers of adults with diabetes in developing countries will increase by 69%, while in developed countries the cases of diabetes will increase by 20% [1].

Insulin resistance (IR) and impaired insulin secretion are the two major pathophysiological bases for the occurrence and development of T2D. There are many factors that lead to insulin resistance, such as obesity, hyperlipidemia, inflammation, increased oxidative stress, and mitochondrial dysfunction. To improve insulin resistance, the current treatment involves the administration of thiazolidinediones and biguanides. Although they can improve the sensitivity of peripheral tissues to insulin, they have large side effects that include increased bodyweight and edema. In severe cases, these drugs could increase the risk of fractures and heart failure, making their side effects even life-threatening. Therefore, finding both safe and effective alternatives for improving insulin resistance has become the focus of many researchers.

Currently, biomedical researchers and clinicians are looking for treatments to maintain normal blood sugar and improve insulin sensitivity. Among the alternative medicines, traditional Chinese medicine (TCM) is an ideal candidate as it shows multiple levels, multiple pathways, multiple targets, and multiple links in treating several health conditions, thereby offering unique advantages in managing metabolic diseases with complex pathogenesis. Therefore, current trends in diabetes treatment are focusing on TCM, which is considered as a natural approach with fewer side effects.

Flavonoids are a group of compounds with 2-phenylchromone as the basic core. They are widely found in natural plants and in many Chinese herbal medicine preparations. The main flavonoids are divided into isoflavones, flavonols, flavanones, flavanols, chalcones, and anthocyanins. Most of the flavonoids are combined with sugar to form glycosides, and the small parts are in free form [2]. Recent studies have shown that flavonoids have biological activities, such as anti-oxidation, anti-cancer, anti-viral, anti-inflammatory, lipid-lowering, hypoglycemic, and improving insulin resistance [3]. Our previous study confirmed that the total flavonoids of guava leaf can reduce blood sugar levels and improve the insulin signaling pathway in BALB/C mice [4]. In this paper, four typical flavonoids compounds, namely baicalin, baicalein, quercetin, and rutin, are selected for a thorough review to address future application in managing diabetes. This article summarizes their role in improving insulin resistance and its related mechanisms in recent years, thereby providing the theoretical basis for the development of antidiabetic drugs in the future (Table I).

Baicalin and insulin resistance

Baicalin is an important flavonoid extracted from the traditional Chinese herbal medicine *Scutellaria baicalensis* Georgi. Baicalin has been shown to have antioxidant, anti-tumor, and anti-inflammatory properties. It lowers blood sugar and lipid levels, thereby improving the metabolism [5,6]. It is also involved in detoxification and regulation of the immune system [7, 8].

Baicalin can exert antidiabetic activity by inhibiting reactive oxygen species (ROS)-mediated damage and preventing mitochondrial membrane polarization damage [9]. Administration of baicalin nanolipids resulted in the significant decrease of the total fasting blood glucose (FBG), triglyceride (TG), and total cholesterol (TC) in rats [10]. Xi *et al.* [7] found that baicalin can improve dyslipidemia and reduce hyperglycemia in insulin-resistant mice, thereby improving glucose and insulin tolerance.

Previous studies have shown that the hypoglycemic and lipid-lowering effects of baicalin may be related to the activation of adenylate activated protein kinase (AMPK) [11]. Liu [12] found that baicalin can improve insulin resistance and islet function in a T2D mouse model by promoting the sensitivity of liver and skeletal muscle to insulin and stimulating insulin secretion. Hence, the mechanism may be related to regulating the liver and skeletal muscle AMPK/protein kinase B (Akt)/ glycogen synthase kinase-3 (GSK-3β) signaling pathway. Moreover, baicalin has been shown to improve insulin resistance in a T2D rat model by regulating the liver calcium/calmodulin-dependent protein kinase, specifically the calcium/calmodulin-dependent protein kinase kinase β (CaMKKβ)/ AMPK/acetyl-CoA carboxylase (ACC). The pathway is related to the de novo synthesis pathway of AMPK/ACC fatty acid in skeletal muscle.

In addition, *in vitro* cell studies revealed that baicalin increases glucose uptake by affecting glucose transporters (GLUTs), enhances glycogen synthesis, and accelerates sugar consumption, thereby improving the liver insulin resistance [13, 14]. Using a BRL-3A cell model, baicalin can also increase the uptake and utilization of glucose while reducing lipid metabolism disorders, thereby

Table I. Mechanisms of four typical flavonoids to improve insulin resistance

Flavonoid name	Mechanism to improve insulin resistance
Baicalin	Hypoglycemic (GLUT4), lowers lipids, lowers insulin, anti-inflammatory (IL-1β, TNF-α, IL-6), anti-oxidative (GSH, SOD), improves skeletal muscle IR (AMPK/Akt/GSK-3β), liver IR (CaMKKβ/AMPK/ACC, PPAR-γ), induces autophagy
Baicalein	Lowers blood sugar, lowers lipids (cleaves caspase-3), protects pancreatic β-cells and promotes secretion, anti-inflammatory (TNF-α, IL-1β, IL-6), inhibits SOCS3 and GSK3β, increases IRS1 and AKT1, regulates MAPK/PI3K/AKT signaling pathway
Quercetin	Reduces blood sugar and lipids, anti-inflammatory (TLR4/NF-κB, TNF-α, IL-1β, IL-6), improves liver IR (PI3K/AKT/NF-κB, ADPN, AdipoR2)
Rutin	Anti-oxidative (SOD, GSH-Px, MDA, CAT), anti-inflammatory (TNF-α), affects insulin signaling pathway (PFK, PDH, Akt, GLUT4), improves endoplasmic reticulum stress (PDI, IRE1α), improves liver IR (PEPCK, PGC-1α), improves fat IR (P-Aktser473, P-AMPK), improves liver cells (PPAR-α, DGAT)

improving insulin resistance. The specific mechanism of action may be related to its induction of autophagy [15]. Animal experiments further confirmed that when the body has insulin resistance, autophagy is inhibited. After increasing the liver autophagy level in obese mice, insulin resistance can be significantly improved, indicating that the mechanism of baicalin in improving insulin resistance is related to the induction of autophagy [16].

Increased interleukin-1β (IL-1β) increases insulin resistance by inducing fatty degeneration of liver cells and promoting inflammation [17]. Baicalin can reduce the production of inflammatory factors, such as tumor necrosis factor α (TNFα), IL-1β, and IL-6, with a mechanism of action related to the enhancement of glutathione (GSH) and superoxide dismutase (SOD) activity. These chemicals improve steatosis and inflammation in non-alcoholic fatty liver model rats, thus exerting their anti-inflammatory effect and improving insulin resistance [18].

Past studies have revealed that peroxisome proliferators-activated receptor-γ (PPAR-γ) is the target of Gegen Qinlian Decoction in the treatment of T2D, thus significantly improving insulin resistance [14]. Modern Chinese medicine research shows that baicalin is one of the very important active ingredients in Gegen Qinlian Decoction [19].

In summary, baicalin has an excellent effect in improving insulin resistance of cells. Its mode of action is related to the following properties: antioxidant, anti-inflammatory, hypoglycemic, lipid-lowering, autophagy inducing, and glucose regulation. However, most of these studies only focus on liver cells and little is known about its effects in other organs and tissues, including skeletal muscle, fat, pancreas, and intestines. Therefore, the mechanism of baicalin in improving insulin resistant in other organs should be further studied to provide detailed scientific knowledge for the development of clinical antidiabetic drugs.

Baicalein and insulin resistance

Baicalein is one of the flavonoids with the highest content in the traditional Chinese medicine *Scutellaria baicalensis* Georgi. Numerous studies have shown that baicalein has antidiabetic and insulin resistance effects. In a nutritionally obese rat model (fed with a high-fat diet), baicalein was shown to reduce FBG, pancreatic β-cell apoptosis, and pancreatic β-cell dysfunction. It also improves glucose tolerance and insulin levels. Similarly, baicalein can protect the vitality of INS382/13 cells and human pancreatic islets, thereby promoting its secretory function [20, 21]. Baicalein can also improve insulin resistance in type 2 diabetic SD rats by lowering blood sugar and blood lipids [22].

Baicalein can also inhibit the activation of cell pathways induced by high glucose and down-regulate the expression of downstream inflammatory molecules. It is suggested that the improvement of insulin resistance by baicalein is closely related to inhibition of the inflammatory signaling pathway [23]. Further investigation revealed that baicalein has a significant protective effect on liver steatosis caused by high fat content. This effect could be related to its inhibition of large release of free fatty acids and inflammatory factors (e.g., TNF-α, IL-1β, IL-6) associated with liver steatosis. Moreover, its effect could also be related to promoting the synthesis and secretion of protective adiponectin [24], thereby regulating blood lipids and liver lipids and inhibiting the production of lipid peroxidation products. Hence, this improves the body's ability to scavenge free radicals [25]. Baicalein is also linked to the final inhibition of cleaved caspase-3 expression [26].

Baicalein has a good weight loss effect on a nutritionally obese rat model, with a significant improvement effect on the leptin resistance induced by diet. This effect increases the sensitivity of the target organs to insulin and thus improves insulin resistance [27]. In addition, baicalein can reduce the expression of cytokine signaling 3 (SOCS3). It increases the phosphorylation level of insulin receptor substrate 1 (IRS1) and AKT1, but reduces the phosphorylation of GSK3β [28]. Modern animal experiments showed that baicalein-rich *Scutellaria baicalensis*-Coptis can improve glucose and fat metabolism in T2D rats by regulating the MAPK/PI3K/AKT signaling pathway, thereby improving insulin resistance [29].

In summary, baicalein can improve insulin resistance by lowering blood sugar and lipids, protecting pancreatic β cells, and increasing the sensitivity of target organs to insulin. It can also reduce the insulin resistance index through its anti-inflammatory and antioxidant properties, mainly by regulating the MAPK/PI3K/AKT signal pathway. Whether baicalein has a regulatory effect on PPAR-γ, endoplasmic reticulum stress and autophagy should be explored in future research. Moreover, the effective concentration and effective dose of baicalein in patients with clinical T2D need to be further studied.

Quercetin and insulin resistance

Quercetin is a pentahydroxyflavone found in the leaves, flowers, and fruits of many plants, such as aloe vera, which is one of the plants used in Chinese herbal medicine. Quercetin has antioxidant and anti-inflammatory properties. It can also reduce lipid synthesis and inhibit inflammation [30].

Quercetin can significantly reduce fasting hyperglycemia and the HOMA-IR index, thereby im-

proving liver IR [31]. Studies *in vitro* have shown that quercetin can inhibit LPS-induced inflammation in mouse RAW264.7 cells, and its mechanism is potentially related to regulation of the toll-like receptor-4 (TLR4)/NF-κB signaling pathway, which is responsible for regulating cellular inflammatory responses involving inflammatory cytokines (TNF-α, IL-1β, IL-6) and chemokines [32]. In animal experiments, quercetin can improve the degree of liver tissue steatosis in rats with non-alcoholic steatohepatitis. It reduces liver inflammation and improves liver IR by regulating the PI3K/AKT/NF-κB signaling pathway. Quercetin also increases liver adiponectin (ADPN) and adiponectin receptor 2 (AdipoR2) expression levels, which indicate improved liver functions [33].

In summary, quercetin improves IR by lowering blood sugar levels, reducing blood lipid levels, and mediating anti-inflammatory responses. However, in vivo studies on quercetin are limited, with a few reports focusing on the liver.

Rutin and insulin resistance

Rutin is a glycoside made of the flavonol quercetin and disaccharide rutinose. It is widely found in the plant kingdom, such as *Sophora japonica* and other medicinal plants. It has antioxidant and regulating properties. The role of glucose and lipid metabolism and vascular protection also has a therapeutic effect on inflammation [34, 35].

Veerapur *et al.* [36] showed that the extract of *Cassia glauca* Lamk is rich in rutin and can improve the insulin resistance of streptozotocin-induced diabetic rats. Rutin reduces insulin resistance by reducing antioxidative stress and inflammatory responses. Oxidative stress and inflammation are triggering factors of insulin resistance [37].

Rutin improves IR

Previous studies showed that the total flavonoids of *Potentilla chinensis* are mainly composed of rutin, which is involved in improving insulin resistance by increasing superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) activity, hence reducing malondialdehyde (MDA) levels [38]. The therapeutic mechanism of Chinese herbal medicine is multiple in action due to its different components. Sophorutin was shown to enhance the antioxidant capacity of T2D mice, thereby improving IR. It was also reported to reduce the blood sugar levels, lower the body weight, reduce serum TC and TG contents, and inhibit glycolipid in diabetic mice [39].

Rutin and metformin can reduce the levels of MDA and inflammatory factors. Both can significantly increase the antioxidant enzyme activities, including the catalase hydrogen peroxidase (CAT), GPX, and SOD, indicating that rutin has the same antioxidant effects as metformin [40]. Meng *et al.* also found that rutin can greatly increase the SOD activity in T2D rats, reduce MDA content, relieve oxidative stress, and protect diabetic rats [41]. Troxerutin shows some antioxidant effects by removing excessive free radicals and superoxide ions generated by oxidative stress and lipid peroxidation [42].

Rutin and its anti-inflammatory effects

Rutin can improve IR and treat diabetes mellitus (DM) by inhibiting the release of inflammatory responses associated with DM. Gao *et al.* found that rutin can improve the inflammatory response of mouse adipocytes induced by a high-fat diet and promote the browning of white adipose tissue, thereby improving IR [43]. Rutin can reduce the expression of TNF-α protein. It also improves the liver morphology of rats, indicating that rutin can improve the pathological state of diabetes by reducing the number of inflammatory factors.

Other mechanisms of rutin

In addition to improving IR through its antioxidant and anti-inflammatory activities, rutin can also affect the insulin signaling pathway, promote adipocyte differentiation, and improve endoplasmic reticulum stress. Yang *et al.* found that Sophorutin can regulate the expression of proteins related to the insulin signaling pathway in diabetic db/db mice and reduce liver IR in mice [44]. Rutin administration improved glucose tolerance in db/db mice and strengthened the activities of glucose metabolizing enzymes phosphofructokinase (PFK) and pyruvate dehydrogenase (PDH). On this basis, Akt (Ser 473) and Akt (Thr 308) phosphorylation levels increased significantly, improving the level of glucose utilization. Hsu *et al.* also suggested that rutin can activate the insulin signaling pathway in skeletal muscle cells to increase the uptake of sugar by GLUT4 [45].

Existing research results suggest that endoplasmic reticulum stress is one of the important mechanisms leading to chronic metabolic diseases [46]. Exercise combined with rutin intervention can reduce the expression of protein disulfide isomerase (PDI) and inositol-requiring enzyme 1α (IRE1α), which is a marker of endoplasmic reticulum stress, and improve high-fat diet The induced increase in the expression level of phosphoenolpyruvate carboxykinase (PEPCK), and can increase the peroxisome proliferator-activated receptor co-stimulatory factor-1α (PGC-1α) expression level. Improve IR caused by non-alcoholic fatty liver disease [47].

In vitro studies demonstrated that rutin can promote the differentiation of 3T3-L1 preadipocytes and the absorption of glucose by differen-

tiated adipocytes [48]. Using an animal model, rutin was shown to improve the impaired insulin tolerance of SAMP8 mice fed with a high fat diet. Moreover, rutin intervention can increase the expression of P-Aktser473 and P-AMPK protein in adipose tissue, which may be another mechanism involved in improving IR [49]. Another cell experiment showed that rutin can reduce the TG content of steatosis HepG2 cells and increase the expression of PPAR-α in cells at the transcription and translation levels. It also inhibits the expression of diacylglycerol acyltransferase (acyl CoA: diacylglycerol acyltransferase, DGAT) in the pathway of TG synthesis [50].

Altogether, rutin is implicated in the improvement of IR by targeting different pathways, such as those involved in anti-inflammatory responses and anti-oxidation. It also affects the insulin signaling pathways and could improve the endoplasmic reticulum stress. However, studies on PPAR, a key target in the study of lipid metabolism in DM, are very limited. While participating in the regulation of blood glucose balance in the body, PPAR promotes the differentiation and adipogenesis of adipocytes and increases the body's sensitivity to insulin. It is a key target to improve IR and treat type 2 diabetes. Future research should focus on the regulatory effect of rutin on PPAR, and actively explore the mechanism of action of monomer components based on the rich theories of Chinese medicine.

Summary and outlook

The pathogenesis of insulin resistance and T2D has not been fully clarified yet, hindering the development of its therapeutic drugs. Due to the long treatment cycle of diabetic patients, most of them need life-long medication. Therefore, antidiabetic drug development should not only focus on the therapeutic effects of the drugs, but also on its side effects on various organs, as shown by several western medicine products.

Flavonoids have a clear antidiabetic effect with limited side effects and are found in many different sources, including natural ingredients (many edible and medicinal). It has multi-level, multi-pathway, and multi-target pharmacological activities that are favorable in managing diabetes. The four flavonoids have significant curative effects in improving insulin resistance and treating T2D by lowering blood sugar and lipids, as well as exerting anti-inflammatory and antioxidant activities, thus affecting the insulin signaling pathways and improving endoplasmic reticulum stress. Early studies revealed that total flavonoids in guava leaf can significantly improve blood sugar levels in diabetic mice. The mechanisms involved may be related to the influence of hepatic insulin sig-

naling pathways (glucokinase, glucokinase regulatory protein, insulin receptor substrate 1 and glucose transporter 4, and others) and the key enzymes of gluconeogenesis (glucose-6-phosphatase and phosphoenolpyruvate carboxylase) [4]. Our previous clinical research and basic research (*in vivo* and *in vitro* studies) showed that the empirical prescription "Hua Zhuo Jiedu Fang" has the effects of lowering blood sugar, lowering lipids, and improving insulin resistance [51, 52]. The prescriptions include Scutellaria baicalensis Georgi, Coptis chinensis, Chai Hu, and other Chinese herbal medicines that contain flavonoids, such as baicalein, baicalin, and quercetin. It is very likely that these active ingredients have played a role in improving insulin resistance and treating T2D, with the mechanism of action related to its influence on the expression of PPARγ and DGAT2. We also found that this formula can improve insulin resistance in rats exposed to PCBs [53], and can detoxify "environmental pollution", although the specific mechanism is under investigation.

The global population experiencing insulin resistance and T2D is increasing across the years. The four typical flavonoid compounds improve insulin resistance and anti-diabetic activity; their mechanisms of action have therefore opened up a new avenue for studying active ingredients in natural medicines. With the development of new separation technologies and the application of modern research methods, the research and development prospects for anti-diabetic active ingredients of natural medicines have broadened. Presently, although the research is still in the laboratory stages, some drug targets have been identified and have the potential for further development. On the one hand, attention should be given to the problem of reduced bioavailability caused by metabolism and transformation; on the other hand, attention should also be paid to the combined application of drugs. Diabetes, as a chronic disease, requires long-term medication, which may cause side effects such as drug resistance or liver damage. Flavonoids, combined with clinical first-line drugs, could be used to reduce toxicity and increase efficacy, making this an attractive direction for development. Again, attention must be paid to issues such as dosage, dosage form, pH, and medication safety. At the moment, the research available regarding the mechanisms of flavonoids is not thorough enough. In the later stages, integration of various disciplines and the use of modern molecular biology methods may assist with clarifying the targets and regulatory pathways of the activity, thus providing a theoretical basis for the development of natural pharmaceutical ingredients. In addition, multi-target drug development is expected to be able to treat complex diseases. The multi-component and multi-target

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action characteristics of flavonoids are expected to become important choices in the treatment of chronic and complex diseases. Target-based drug discovery requires cooperation from many different fields, from basic research through to target verification, biomarker development, bridging research and drug development; these fields need to work together in order to complete the research and development of new drugs.

In drug development research, a key issue that cannot be ignored is drug safety. At present, there are very few studies available reporting the toxicity of flavonoids. In recent years, adverse events of traditional Chinese medicine have frequently occurred; these are mainly related to the following aspects: 1) Weak awareness of the safe use of traditional Chinese medicine. Many people believe that traditional Chinese medicine is non-toxic and use it indiscriminately; 2) Quality control problems including the processing of traditional Chinese medicine materials including environmental pollution (soil, industrial "three wastes" pollution, pesticide and fertilizer pollution, etc.) which can cause heavy metals to be present in these traditional medicines and to exceed the standard limits; 3) Unreasonable clinical use such as non-differential treatment, overdoses, over-indication of medication, and combination medication; 4) The market supervision of Chinese medicinal materials is weak. Therefore, to develop flavonoids as active ingredients of natural medicines, it is necessary to strengthen early toxicity discovery research and remove the poisons from within the raw materials in advance. Improvement and appropriate treatment of Chinese medicinal materials, planting soil and environment, scientific and rational use of pesticides and fertilizers, and improvements in processing and processing methods are required, as is a strengthened research program in preclinical toxicology. In addition, Academician Zhang Boli pointed out: "The key to the safety of traditional Chinese medicine lies in its reasonable clinical application" [54]. Therefore, focusing on the quantity-time-toxicity-effect, the research strategy needed for guiding clinical rational use of drugs based on the safety research of traditional Chinese medicine, "starts from the basics, based on the clinical, and finally applied". In addition, drug toxicity is divided into two types: intrinsic toxicity and idiosyncratic toxicity. The former can be understood mostly via routine toxicology experiments in the preclinical safety evaluation stages, whilst the latter is more often found in the clinical evaluation stages. Evaluating and predicting the idiosyncratic toxicity of drugs is a challenging international problem, and an inevitable requirement for the development of translational toxicology and precision medicine. Therefore, safety evaluation systems of these traditional Chinese medicines, based in the real world and associated clinical syndromes, has been established [55]. Establishing the integrated management of "clinical monitoring-scientific evaluation-risk prevention and control", perfecting the scientific safety evaluations and supervision systems of traditional Chinese medicines, and improving the pertinence, accuracy and transformability of these safety evaluations are inevitable requirements in modernizing development of traditional medicines. They are also inevitable requirements in order to improve the safety of traditional Chinese medicine.

At this point in time, the research on flavonoids is not in-depth enough, and the research is mostly fragmented, lacks systematic studies and reviews, lacks continuity, and is out of touch with the clinic. Many research results are difficult to both translate and apply in clinical practice, and it is also difficult to supervise. The decision-making has formed strong scientific support, and the clinical adverse effects of traditional Chinese medicines have ranged from "unclear" to basically clear. In the future, the mechanism needs to be discussed in a comprehensive and systematic manner. Modern research methods such as pharmacology, pharmacodynamics, toxicology, and pharmacovigilance should all be introduced in order to study the safety of flavonoids. These will provide a stronger evidence base for the development of natural medicines and potentially bring new hope to diabetics worldwide.

Acknowledgments

Conflict of interest

The authors declare no conflict of interest.

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