REVIEW ARTICLE

Role of Quercetin Flavonoid as Antidiabetic: A Review

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Received: 8th September, 2021; Revised: 5th October, 2021; Accepted: 25th November, 2021; Available Online: 25th December, 2021

ABSTRACT

Today hypoglycemia, kidney problem and hepatotoxicity became the main complication of diabetes mellitus (DM) and real challenges to modern medical research. New trials afford the use of herbal products obtained from plant sources considered more affordable and effective and show less adverse effects as an alternative cure for DM. Natural products like secondary metabolites have many different biological activities and attention is received to developing an anti-diabetic medication from a flavonoid compound. Numerous studies have highlighted not only the flavonoids have hypoglycemics effects, but it's also important in managing DM complications. DM and its numerous complications are now becoming one of the serious threats to human health and also, the current available synthetic drugs used for the management of DM are neither cheap nor entirely effective. Unfortunately, these current drugs do not restore regular glucose homeostasis over a prolonged period and they are not free from side effects.

Quercetin shows a good anti-oxidant activity and may improve beta-cell functions and increase insulin secretion from the Langerhans islets in pancreas, which can be considered a good alternative medical treatment for diabetic patients. The present review is an attempt to understand the biological activity, therapeutic activity and mechanism of quercetin and its eventual clinical results in field of medicine development in the diabetes mellitus management as an alternative treatment.

Keywords: Diabetes mellitus, Flavonoid, *In-vitro* and *in-vivo* evidence, Quercetin.

International Journal of Drug Delivery Technology (2021); DOI: 10.25258/ijddt.11.4.65

How to cite this article: Hamid HK, Obaid MA. Role of Quercetin Flavonoid as Antidiabetic: A Review. International Journal of Drug Delivery Technology. 2021;11(4):1495-1500.

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

DM can be defined a metabolic disorder described by high level of glucose in blood (hyperglycemia) that result either from defects in insulin activity or insulin release from pancreatic beta cells or both. Also, Diabetes mellitus is a disease that the chronic hyperglycemia has identified as a result of the deficiency of insulin action which is one of the common bases of diabetes leading to characteristic carbohydrates,lipid and protein metabolism abnormalities.[1] DM can be identified as one of the universal epidemic diseases. WHO data report stated that this disease affected about 285 million people worldwide in 2010 and expected to be increased to 439 million by the year of 2030.[2]

It was determined that 1 out of 2 patients who have diabetes mellitus isn't familiar with this disease. Which is highly significant in the patients who have type 2 diabetes mellitus (T2DM) as a result of the extended asymptomatic period that has raised risks of the micro-vascular and macro-vascular complications, and increased death rates in comparison to the normoglycemic persons, complications that are associated with diabetes have been reduced considerably in the last years all over the world. It is possible as a result of considerable enhancement in the programs of the preventive care for the adults who have diabetes as well as the massive use of the drugs that control blood glucose, dyslipidemia and hypertension. None-the-less, a significant disease burden is persisting as a result of continuous increases in diabetes prevalence, fundamentally as a result of risks of increasing obesity, aging and world overpopulation.[3]

There are 3 major DM types, which are: type 1 (insulin-dependent), type 2 (insulin resistance), and type 3 (gestational diabetes). T2DM represents for 90 to 95% of diabetes cases. The major problem in T2DM is insulin resistance.long-term damages, failure and malfunction of different organs such as the eyes, nerves, kidneys, blood vessels and heart have been related to the chronic hyperglycemia. Although patients who have type I diabetes can be treated by administering exogenous insulin. In general, for type II diabetic patients, changing their lifestyle (such as exercise and diet) and oral hypoglycaemic agents are recommended.[4]

Currently, the available anti-diabetic medications focus upon eliminating the increase in the glucose from blood, only giving symptomatic relief from this disorder. The anti-diabetic medications must be administered lifelong and despite this, diabetic complications, particularly neuropathy, keep steadily and slowly progressing, moreover, the additional side effect

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of actual drugs.[5] The negative impacts of the hypoglycaemic medications and insulin and high costs of those drugs are usually stated as some issues considering the treatment of diabetes, stimulating search for the new therapeutic agents that try at presenting effectiveness, safety, and low price. Presently, there is huge movement in complementary and conventional medicine to use herbal preparations and/or derivatives to treat diabetes symptoms. In this way, the interest of current ethno pharmacological research has been crescent in investigating the plant species with anti-hyperglycemic effects, according to evaluations of safety and efficacy of the plant preparations for the management of diabetes to mechanisms of action, clarifying their anti diabetic actions.[6]

Since old ages, the natural compounds from a variety of the plants and a number of the other dietary compounds have been in practice, some of them were stated to be possessing important anti-diabetic characteristics. Using those plant based components for preventing or managing the diabetes was documented in a variety of the countries (such as India, China and America) all over the world. Those active ingredients from the herbal sources have therapeutic advantages, suchas the hypoglycemic activities, anti-oxidant characteristics, and might easily overcome the hyper-glycemia and other health issues that are safely related to diabetes. One of the effective regulations of blood sugar level is the fundamental step for preventing or reversing the complications related to diabetes in type 1 and type 2 diabetes patients, thereby enhancing the quality of life. Which is why, the focus was shifted toward the herbal medications as a more sufficient alternative method, resulting in the creation of minimum or no side effect in the clinical practices in cost-effective way in comparison with synthetic oral hypoglycemic medications.[7]

One of the most researched natural products has been flavonoids, mainly present as a part of daily food consumption in several comestible fruits. These polyphenolic compounds have been commonly researched in the past years due to their advantageous characteristics in cardio-vascular diseases amongst their pharmacological impacts as anti-inflammatory, anti-oxidant, anti-viral and anti-carcinogenic agents. It was suggested with these reports that flavonoids can be described as molecules that can interact with more than a single target, allowing them to be described as privileged structures following the definition of Patchett. Furthermore, recent researches have shown that flavonoids are highly effective anti-diabetic agents. The National Institutes of Health Clinical Centre is currently researching the uses of quercetin on the absorption of glucose in obesity and obesity with patients who have T2DM on the oral test of glucose tolerance.[8] This review will focus and demonstrate the main activity of quercetin toward diabetic disease.

Historical Review of Quercetin (Flavonoid Compound)

Quercetin is a main member of the flavonoids family, derived from various vegetables and fruits, such as onions, apples, berries, multiple nuts, seeds, barks, flowers, and tea. Current pharmacological studies have shown that quercetin has varied biological functions for human health, including cardiovascular defense, antiulcer, antiallergic, anticancer, anti-inflammatory, antidiabetes and cataract prohibition. Developing *in vivo* studies have shown that quercetin could also be considered an anti-oxidant due to its ability to inhibit xanthine oxidase by diminishing free radical formation, altering anti-oxidant defenses, and inhibiting lipid peroxidation.[9]

Moreover, it has become increasingly evident that quercetin could improve diabetic complications through different signal pathways and is a most promising compound for preventing and managing these diseases nutritionally.[10] Quercetin has been reported to interact with various molecular targets in small intestine, pancreas, skeletal muscle, adipose tissue, and liver to regulate haemostasis of whole-body glucose.[11]

What are the Issues in the Current Diabetic Therapy that Made Quercetin a Good Substitute Medical Option?

Up until now, the insulin has been found as the most effective diabetes treatment despite the availability of a variety of the oral anti-diabetic agents such as the sulfonylureas, biguanides, α-glucosidase inhibitors, glinides as well as others, often utilized as monotherapy or combined for the achievement of enhanced glycemic regulations. The parenteral insulin therapy has insufficient patient compliance due to the needle phobia, skin bulges, pain, common infections, allergic reactions, and stress that results from the long term and difficult insulin therapy regimen.[12,13]

Those have been defined as the most direct causing factors resulting in the patients who have poor compliance to the treatment. In addition to that, hypoglycemia is defined as the most severe and common insulin therapy side effect that could not be disregarded. The rate of diabetic complications has been found greater amongst groups with low income, possibly due to insulin therapy costs. Moreover, most other hypoglycaemic medications also have noticeable side effects and lack of capability to prevent diabetic complications, which is why the currently available therapies are not always acceptable to patients concerning the later diabetic complication stages. All over the world, pharmacologists are devoting their efforts to searching for substitute therapeutic methods or synergetic therapies to prevent those metabolic illnesses.[14] The general scenario urges implementing efficient and cost-effective preventive measures for combating diabetes and reducing the high mortality and morbidity rates.[7] The ethnobotanical information reported approximately 800 plants, which could be possessing anti-diabetic potential.[15] A wide range of conventional herbal treatment methods has been found as possibly beneficial bio-products that are increasingly sought to manage or control diabetes.[16]

It could be mentioned in this regard, the fact that was discovering widely utilized hypoglycemic drugs as metformin has come from the conventional method of utilizing *Galega officinalis.*[17]

Flavonoids have gained a greater deal of attention by the scientific community due to their structural diversities, abundance in nature, powerful pharmacological activities with low adverse reactions,[18] a rising number of flavonoids has been confirmed to be having possible anti-hyperglycemic impacts, like the quercetin.[17] Quercetin that has low molecular weight and possesses anti-diabetic activity was well studied as a promising and highly interesting herbal substance for safely enriching current diabetes therapy.[7]

Can Flavonoids Like Quercetin be used to Treat Diabetes Mellitus as a Main Treatment? And What is the Mechanism of Action of this Herbal Drug as Anti-Diabetic Agent?

Many studies have been done to explore the likely role of flavonoids in the treatment of diabetics patients. Many studies show that the flavonoid, especially quercetin is essential in preventing the complications of diabetes mellitus more than any other drugs that use now to treat this disease.[17]

Because quercetin has a wide variety of physiological and bio-chemical actions, which include the oestrogenic, antiplatelet, anti-oxidant and anti inflammatory characteristics, all of these features gave it an effective role in diminishes hyperglycemia and reducing the severity of this disease that affects millions of people.[7] Where dietary quercetin was observed with a small percentage in fruits and vegetables was sufficient to reduce increased fasting blood glucose levels and glucose in the urine.[19] In addition, quercetin also have been effective role in treat obesity that considered the risk factor to develop T2DM in people who suffer from overweight.[19]

During the past few years, many methods were made to use flavonoids, specifically, quercetin in vivo and *in vitro* models through the incorporation of some innovative approaches for the improvement of its anti-diabetic activities and this can be done through several mechanisms that make it effective in reducing the level of glucose in the blood, but it was not at the required level. Therefore, we cannot consider it a main treatment for this disease until some problems related to the bioavailability, poor solubility, and pharmacokinetics are solved.[7]

Mechanisms of Action of Quercetine as Anti-diabetic Agent

Quercetin showing numerous pharmacological effects and acceptable results in treating diabetes through different mechanisms.

Action of Quercetin on Islet β-cells

When blood sugar concentration rises, low viability and defect pancreatic beta cells (β cell) lead to emergence DM as a critical metabolic disorder.[20] As quercetin is used, it promotes the proliferation of the pancreatic beta cell and increases the metabolism of glucose and insulin secretion by giving superior hypoglycaemic effect and insulin-sensitizing operation.[21]

In addition, quercetin decreases:

- plasma cholesterol.
- fasting plasma insulin.
- Glucose postprandial.

Quercetin play important role in increasing activity of β cell via

- Elevation insulin secretion.
- Protection the β cell from damage.
- Increase islet β cell proliferation.

Mechanisms of Quercetin on Eenhancing the Uptake of Glucose in the Organs and Tissues

Glucose uptake by many organs and tissues needed cellular glucose transporter type 4 [GLUT4], for instance, this [GLUT4] is found in skeletal muscle and adipocyte, carries glucose by signaling pathway involves insulin receptor tyrosine kinase.[22] Defective [GLUT4] translocation and abnormal insulin signal transduction will impair diabetic patient glucose utilization. Quercetine control blood glucose level through elevation of the expression of GLUT-4 and enhances the uptake of glucose on skeletal muscle cell surface through the stimulation of the adenosine monophosphate activated protein kinase (AMPK) pathway.[23]

Reduction Glycogen Breakdown

Glucose undergoes the phosphorylation by the glucokinase to glucose 6-phosphate followed by glycolysis. Insulin hormone cause suppression of gluconeogenesis and glycogenolysis because it affects on the regulation of transcriptions of the genes encoding hepatic and muscular enzymes such as the glucose 6-phosphatase and phosphor-enolpyruvate carboxykinase.[24,25]

Quercetin has been found to result in increasing the level of the glucokinase so that it promotes glycogen synthesis that reduces the expression of glucose 6-phosphatase and phospho-enolpyruvate carboxy-kinase gene expression, thereby resulting in the inhibition of the gluconeogenesis and/or glycol-genolysis.[26,27]

Inhibition of A-Glucosidase to Reduce Intestinal Glucose Absorption

Carbohydrates can be defined as hydrolyzed by intestinal brush-border enzymes before the absorption to their analogous monosaccharides. One such enzyme is α-glucosidase which is essential in the digestion of carbohydrate. Therefore the effect of carbohydrates on blood sugar is reduce by α-glucosidase inhibitors. Acarbose is an α-glucosidase inhibitor capable of markedly decreasing the postprandial blood glucose, glycosylated haemoglobin (HbA1c) and effectively enhancing insulin sensitivity in and among people with diabetes with type 2 mellitus.[28]

Quercetin also has as α-glucosidase inhibitory activity like Acarbose, and they can delay glucose absorption and prevent the digestion of carbohydrates; besides being inhibitors of sucrase, maltase and α-amylase, it exhibits as well, hypoglycemic potentials for the DM treatments.[19,29]

Quercetin Role in Diabetic Complications

Quercetin reduces insulin resistance and intensifies glucose uptake through raising the expressions of the silent mating type information regulation 2 homolog (SIRT-1) protein and PPAR-γ and stimulating AMPK. Oxidative stress increases

insulin resistance and ruins insulin secretion as a result of exacerbating diabetic complications. As quercetin possesses an anti-oxidant property, it can hinder oxidative stress and prevent the incidence of complications related to diabetes. The immune system produces inflammation in beta islet cells and causing insulin resistance through producing chemokines and cytokines. In this regard, the specific therapeutic effect of quercetin is thought to block the release of these inflammatory agents. Diabetic complications including retinopathy, nephropathy and neuropathy are thought to be caused by inflammation and oxidative stress. Quercetin can prevents these two leading causes of diabetic complications by blocking NF-κB cells, monocyte chemoattractant protein 1 (MCP-1) and intercellular adhesion molecule 1 (ICAM1) in the patients suffering from diabetic retinopathy. Furthermore, quercetin is reported to reduce the levels of biomarkers indicating nephropathy, including creatinine, blood urea nitrogen (BUN), and 8-hydroxydeoxyguanosine.[30]

What Are the Problems that make Quercetin Less Potent as Monotherapy for Diabetes? Moreover, What are the Methods have been Suggested to Make it More Effective in the Future?

Quercetin has bad pharmacokinetic properties since it has insufficient bioavailability, short half-life, and low aqueous solubility if taken orally. All of these obstacles make it less effective. As a result, polymeric carrier systems (nano or micro particles) have been widely applied to control release of compound in the biological system and improve quercetin bio-availability. Natural polymers have been used in such manner, e.g., pectin, alginate, guar gum, and others. Moreover, the solubility, molecular weight, and structure of polymers also affect drug delivery and bioavailability.

To overcome problems of quercetin absorption and many other obstacles, encapsulation of quercetin is recommended. Furthermore, novel techniques incorporation leads to improved utilization of quercetin.[7]

Quercetin bio-availability is, in general, poor, and it's bioavailability varies widely between individuals.

There are several factors affect the bioavailability of quercetin:

- A small number of the researches that look for vitamin C status and age effects on quercetin supplements' bio-availability; however, there are not any researches that seek for vitamin C status and age effects upon the bio-availability food-derived quercetin.
- Onion-derived quercetin, mainly quercetin glucoside, has a higher bio-availability than apple-derived quercetin, containing quercetin galactoside and quercetin rhamnoside.
- The existence of the sugar moieties results in increasing the bio-availability, and the differences in the quercetin conjugated glycosides impact the bio-availability.
- Non-digestible fibres could result in improving quercetin's bio-availability.
- The bio-availability of the quercetin is higher in the case where it is taken as one of the integral food components.[31]

Are There Any available Pharmaceutical Dosage Forms of Quercetin as Antidiabetes Drug present in the Market or is it Still Just Under Laboratory Research?

Presently, the most available dosage form about quercetin in the market is anti-oxidant formula and energetic capsules like Gingo bilba which contain a high percentage of quercetin flavonoids and many other dosage forms that improve hepatic function. Also, quercetin with a bromeline (protein digesting enzyme mix derived from fruit, juice and stem, of pineapple plant) can work synergistically to support body immunity levels, and this combination presents as a capsule in the market. Unfortunately, no dosage form contains quercetin as anti-diabetic approved by the Food and Drug Administration (FDA) is available in the pharmacy until now.

One of the latest systematic reviews and meta-analyses of the animal studies has shown that the quercetin decreases the levels of the serum of glucose at 10, 25, and 50 mg/kg doses of body weight. Another review published in phytotherapy research found that taking 500 mg or more quercetin daily for eight weeks lowered blood glucose levels in individuals with metabolic syndrome and increased risk of diabetes.[32]

Dose Quercetin has Synergistic Effect When Combined with Oral Sulphonylurea Drug?

Some studies have found that the synergistic role shown by this two combination therapy is very effective towards diabetes mellitus especially in streptozocin (STZ)-induced diabetic during the experience on the rats. Treatment with the gliclazide only lowered the serum glucose, while raised serum C-peptide, superoxide dismutase, reduced levels of adiponectin and glutathione. However, combined quercetin administration with the gliclazide has resulted in clearly increasing the serum superoxide dismutase and reduced glutathione more compared to the gliclazide alone.

Depending upon the above mentioned results, such combination might be considered prospective concerning DM.[33]

Other combination therapy has shown effectiveness in the treatment of diabetes mellitus is a quercetin plus sitagliptin had shown an enhancement in the inflammatory and oxidative status, glycemic regulation, metabolic rate, β-cells activity, and islet structure in STZ- induced diabetes mellitus in rats.[34]

CONCLUSION AND FUTURE PERSPECTIVE

The current review discussed the activity of quercetin and also the molecular mechanisms of it as anti-diabetic agent, also the possibility of improving the pharmacokinetics of this herbal drug such bio-availability and absorption to make it more effective against diabetes mellitus depending on recently relevant published articles, there is extensive evidence of an anti-diabetic effect of quercetin. This is because it has impressive characterize as an anti-oxidant to reduce oxidative stress, which increases the incidence of diabetes after randomized controlling studies. A combination of quercetin

with current anti-diabetic drugs shows good effectiveness as an adjunctive rather than a primary therapy when treating rat after induction of diabetes by STZ. Finally, in our opinion, this herbal drug in the future may be considered a drug of choice as antidiabetics, but this requires much modern research and available studies.

ACKNOWLEDGEMENT

I would like to express my deepest gratitude to all teaching staff and students of College of pharmacy, National university of science and technology especially assist. Prof. Dr. Abdul Razzaq Al Rubaie, Chief of University and Assist. Prof. Dr. Muhammad Sabbar, dean of our college.

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