

Antioxidant and Antidiabetic effect of Quercetin in rats

Mohamed Ahmed Abdelmoaty^{a, c}, Mohamed A. Ibrahim^{b, d},
Nagwa S. Ahmed^{a, c} and Mohamed Anwar Abdelaziz^{a, d}

^a Departments of Biochemistry, and ^b Pharmaceutics,

^c Sohag Faculty of Medicine, Sohag University, and ^d El-Azhar Faculty of Pharmacy, El-Azhar University (Assiut)

ABSTRACT

Quercetin (QE), one of natural flavonoid group, was widely distributed as a secondary metabolite in plant kingdom and recognized as anti-inflammatory, antiallergic, antiviral, antibacterial and antitumor activity. It has been believed that oxidative stress plays a role in the pathogenesis of diabetes mellitus (DM). The aim of the present study was the evaluation of possible effects of QE on blood glucose and antioxidant enzymes in experimental streptozotocin (STZ)-induced diabetes in rats. STZ was injected intraperitoneally at a single dose of 50 mg kg⁻¹ for diabetes induction. QE (15 mg kg⁻¹ day, intraperitoneal (i.p.) injection) was injected for 3 days prior to STZ administration; these injections were continued to the end of the study (for 25 days). Glucose tolerance test and random plasma glucose were done for all animals. In order to determine the changes of cellular antioxidant defense system, antioxidant enzymes such as glutathione peroxidase (GSHPx), superoxide dismutase (SOD) and catalase (CAT) activities were measured in pancreatic homogenates. Quercetin had no effect on plasma glucose level of normal animals but its pre-treatment was able to prevent diabetes induced by single i.p. injection of streptozotocin-treated rats. Antioxidant enzyme activity significantly decreased ($P < 0.05$) in STZ induced diabetic group. QE treatment significantly increased the antioxidant enzyme activities ($P < 0.05$). It could be concluded that quercetin, a flavonoid with antioxidant properties, exerting its beneficial antidiabetic effects. However, it may be of little value in normoglycemic animals.

Abbreviation:

CAT (Catalase), GSHPx (Glutathione peroxidase), QE (Quercetin), SOD (Superoxide dismutase), and STZ (streptozotocin).

INTRODUCTION

Diabetes mellitus (DM) is a pathologic condition, resulting in severe metabolic imbalances and non-physiologic changes in many tissues, where oxidative stress plays an important role in the etiology⁽¹⁾. Diabetics and experimental animal

models exhibit high oxidative stress markers and reactive oxygen species (ROS) in pancreatic islets due to persistent and chronic hyperglycemia, thereby deplete the activity of the antioxidative defense system and thus promote free radical generation⁽²⁾. Such models include alloxan or streptozotocin (STZ) induced diabetic rats and mice⁽³⁾.

STZ, an antibiotic produced by *Streptomyces achromogenes*, is a common used agent in experimental diabetes by⁽³⁾. STZ induced type 1 diabetes, hyperglycemia and oxidative stress have been implicated in the etiology and pathology of disease complications⁽⁴⁾. The mechanism by which STZ destroys β -cells of the pancreas and induces hyperglycemia is still unclear. One of the actions which have been attributed to STZ is depletion of intracellular nicotinamide dinucleotide (NAD) in islet cells⁽⁵⁾. In addition, STZ has been shown to induce DNA strand breaks by methylation or alkylation in pancreatic islet cells⁽⁶⁾. Chemicals with antioxidant properties and free radical scavengers were shown to prevent pancreatic islets against cytotoxic effects of STZ or alloxan⁽⁷⁾. Calcium does not play a significant role in necrosis of β -cells by STZ since calcium channel antagonists do not protect β -cells against that drug⁽⁸⁾. Interestingly, STZ is not equally effective in all vertebrates and mechanisms of action may differ between groups^(9,10).

The cellular antioxidant status determines the susceptibility to oxidative damage and is usually altered in response to oxidative stress. Accordingly, interest has recently grown in the role and usage of natural antioxidants as means to prevent oxidative damage in diabetes with high oxidative stress. The antioxidants such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSHPx) are the initial step to protect the cells against lipid peroxidation^(11,12). Reduced antioxidant levels as a result

of increased free radical production in experimental diabetes have been reported by many authors^(13,14).

Flavonoids are a group of naturally occurring compounds widely distributed as secondary metabolites in the plants⁽¹⁵⁾. They have been recognized for having interesting clinical properties, such as anti-inflammatory, anti-allergic, anti-viral, anti-bacterial, and anti-tumor activities⁽¹⁶⁾. One of these flavonoids, quercetin (QE) (3,5,7,3',4'-pentahydroxyflavone), prevents oxidant injury and cell death by several mechanisms, such as scavenging oxygen radicals⁽¹⁷⁾ protecting against lipid peroxidation⁽¹⁸⁾ and chelating metal ions⁽¹⁹⁾. Pari and Saravanan⁽²⁰⁾ renew interest in the use of plant compounds as antidiabetic compounds⁽²⁰⁾. Due to the presence of aromatic hydroxyl groups, flavonoids have strong antioxidant properties⁽²¹⁾. They are scavengers of reactive oxygen and nitrogen species and, therefore, inhibit peroxidation reactions. They, also, protect macrophages from oxidative stress by keeping glutathione in its reduced form⁽²²⁾. Flavonoids have the capacity to inhibit enzymes such as cyclooxygenases and protein kinases involved in cell proliferation and apoptosis⁽²³⁾. They, also, protect normal rat islets from STZ, normalize blood glucose levels and promote β -cell regeneration in islets of STZ-treated rats⁽²⁴⁾. Tritiated thymidine incorporation into islet cell DNA was, also, enhanced by these flavonoids in an in vitro study⁽²⁵⁾. However, the beneficial effects of flavonoids in STZ-diabetic animals could not be

demonstrated⁽²⁶⁾. A different flavonoid, quercetin, used in doses of 15–50 mg/kg body mass was capable of normalizing blood glucose level, augmenting liver glycogen content and significantly reducing serum cholesterol and LDL concentration in alloxan–diabetic rats⁽²⁷⁾. Exposure of isolated rat islets to certain flavonoids such as quercetin enhances insulin release by 44–70% via alteration in calcium fluxes and in cyclic nucleotide metabolism⁽²⁸⁾.

The present study was undertaken to determine the effect of minimal dose of quercetin on antioxidant status and blood glucose concentration in normoglycemic and STZ induced diabetic rats.

MATERIALS & METHODS

Reagents

Quercetin was obtained from Sigma Chemical Company (USA) and dissolved in 0.5 ml of 60% ethanol just before injection. Streptozocin vials containing 1 g streptozocin and 220 mg citric acid was obtained from Upjohn Co. (USA). Streptozocin was reconstituted with 9.5 ml of 0.9% NaCl solution to pH 3.5–4.5 according to manufacturer's instructions. Furthermore, dilution of the drug was performed in 0.9% NaCl solution immediately before use. The enzymatic kits for the determination of glucose was supplied by Bicon, Co. Germany.

Animal experiments

Adult male albino rats bred and raised at the Assiut University animal quarters with a mass ranging from 200 to 250 g, and averaging 16 weeks

old were used and maintained at 20–22°C, light period 7.00a.m. to 7.00p.m., and relative humidity 55%. Five animals each were housed in a cage and were given a rat Purina chow diet, water and libitum. Diabetes was induced upon injection of streptozocin (50 mg/kg body mass) once intraperitoneal 3 days after the initiation of treatments. Blood was obtained from the tail vein using heparinized microhematocrit tubes. Plasma glucose of all groups was measured day after day. After one week, glucose tolerance test was done. Animals with plasma glucose level exceeding 16.6 mM were considered as diabetic. All normoglycemic and STZ diabetic rats were employed for the tests described below.

Effect of quercetin on plasma glucose level

The required amount of quercetin was dissolved in 0.5 ml of 60% ethanol prior to injection to rats. Four groups of rats including (five rats per group) were used: (1) normoglycemic control group receiving the vehicle as one intraperitoneal (i.p.) injection of 0.5 ml 60% ethanol per day; (2) normoglycemic rats receiving one i.p. injection of 15 mg quercetin per kg body mass per day; (3) diabetic control rats receiving one i.p. injection of 0.5 ml 60% ethanol per day; and (4) diabetic experimental animals receiving one i.p. injection of 15 mg quercetin per kg body mass per day. Such treatment was began 3 days prior to induction of diabetes and continued for 25 days at 13:00 h every day. Blood was collected from the tails using heparinized microhematocrit tubes and used for

plasma glucose determination on the day of intraperitoneal injection of STZ (day 0) and every other day thereafter.

Glucose tolerance test

Glucose tolerance test was performed according to the procedures of Young et al. (1995) on the four different groups mentioned above⁽²⁹⁾. Following quercetin treatment for 2 weeks, plasma glucose was determined, the animals were treated with another respective dose of quercetin and deprived of food for 24 h. After this period, blood was collected through heparinized tubes for plasma glucose (fasting glucose level). The fasting plasma glucose levels of the all diabetic and control rats groups were done. Fasted animals were fed 1 ml of a glucose solution containing 3 g/kg body weight glucose through a gavage. Tail blood were collected at 45, 90 and 135 min after glucose feeding and plasma glucose levels were determined and used for establishing glucose tolerance curves⁽²⁹⁾.

Tissue homogenization and antioxidant enzymes assay

At killing time (25 days after quercetin treatment), rats were anaesthetized with sodium pentobarbital (63 mg/kg body weight, intraperitoneally). Blood was collected by cardiac puncture. Pancreas of each rat was removed, cleaned of fatty tissue, blotted dry and weighed. Each pancreas was homogenized in 10 vol. of 50 mM sodium phosphate buffer (pH 7.4) for 30 sec. using a Glas-Col (TURBAX-Germany) homogenizer. The homogenate was filtered through gauze and the filtrate was centrifuged

at 1088×g for 5 min in a refrigerated centrifuge. The resultant supernatant was used for measurement of antioxidant enzymes⁽³⁰⁾.

Superoxide dismutase

SOD activity was measured depending on its antagonizing effect on autooxidation of epinephrine of epinephrine (colourless) into adrenochrome (chromogen) by superoxide anion generated in alkaline condition. Therefore, the optical density was inversely proportionate with the enzyme activity⁽³¹⁾.

Glutathione peroxidase (GSHPx)

Measurement of GSHPx activity depended on its ability in destruction of H₂O₂ in present of reduced glutathione and NADPH. The released NADP was measured at ΔOD₃₄₀ compared to supernatant protein content⁽³²⁾.

Catalase

Catalase activity was measured and depended on its ability to decrease added hydrogen peroxide in supernatant solution so, the read at OD₂₄₀ was decreased after 2 minutes of incubation compared to supernatant protein content⁽³³⁾.

Statistics

Using SPSS version 10 software, the data were statistically analyzed by one-way ANOVA and Duncan test. The level of statistical significance was set at $P < 0.05$.

RESULTS

Quercetin significantly increased the pancreatic activity of SOD enzyme threefold within 25 days after its injection (group 2) compared to that control normoglycemic group

(group 1). STZ had an opposite effect on the activity of pancreatic SOD (group 3), but that effect was ameliorated by pretreatment with quercetin prior to STZ injection (group 4) (table 1).

Quercetin produced a significant double increase the activity of pancreatic GSHPX after 25 days of administration compared to normoglycemic control group. STZ decreased pancreatic GSHPX and this was antagonized by pretreatment with quercetin (table 1).

Similar effect could be observed in pancreatic CAT, the activity of

pancreatic CAT after quercetin treatment was significantly greater (three times) than the normoglycemic control group, but, STZ had an opposite effect. This activity was significantly higher in quercetin + STZ group than STZ diabetic group (table 1).

The current results suggested that STZ could decrease pancreatic SOD, GSHPX and CAT but, quercetin could enhance the activity of these enzymes and consequently antagonize STZ effect on these antioxidant enzymes.

Table (1): Antioxidant effect of quercetine on normoglycemic and streptozocin-diabetic rats

	Group 1	Group 2	Group 3	Group 4
SOD (U/mg protein)	26.54 ±1.73	77.28±5.87*	6.62±1.61*	17.14±2.74 [#]
GSHPx (µM/min./ mg protein)	0.03±0.01	0.06±0.01*	0.01±0.01*	0.03±0.01 [#]
CAT (µM/sec./ mg protein)	0.03±0.002	0.06±0.01*	0.01±0.01*	0.04±0.004 [#]

Data are expressed as mean ±SD. of 5 rats in each group. In each column, figures bearing *is a significantly different at $P<0.05$ between group 1 and 2, * is a significantly different between group 1 and 3, and [#] is a significantly different between group 3 and 4. Group 1 is normoglycemic control; group 2 is normoglycemic + 15 mg quercetin per kg; group 3 is diabetic control and group 4 is 50 mg/kg STZ + 15 mg quercetin per kg. Pancreatic SOD (superoxide dismutase) expressed in U/mg protein, GSHPx (glutathione peroxidase) expressed in µM/min./mg protein and CAT

(catalase) expressed in µM/sec./mg protein.

Intraperitoneal injection of STZ increased plasma glucose level gradually to reach its maximum level up to 35.8 ±3.4 mM within 14 days. Quercetin had no effect on plasma glucose concentration of normoglycemic animals, but significantly maintained blood glucose level and antagonizing the effect of STZ on diabetes induction in experimental rats for 3 subsequent doses of quercetin prior to STZ injection. The range of blood glucose level of the diabetic animals treated with quercetin was 4.5 to 7-9 mM but in STZ injected group was 4.6 to 35.8 mM allover the period of experiment (Fig.1).

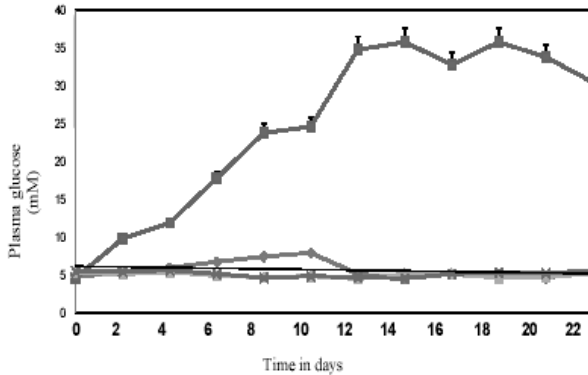


Fig. 1. Time Profile of Random plasma glucose concentration day after day in normoglycemic and streptozocin—diabetic rats after i.p. administration of streptozocin. Each point represents the mean \pm SD. of five rats \times , Normoglycemic control; \blacktriangle , normoglycemic + 15 mg quercetin per kg; \blacksquare , STZ control; \clubsuit , STZ + 15 mg quercetin per kg.

Glucose tolerance curve was done one week after STZ injection, and reached its peak (15.2 ± 1.59 mM) within 45 min. after oral glucose intake and returned to its fasting level within 135 min. in normoglycemic control rats. Quercetin exerted no different effect on the glucose tolerance curve. But, STZ impaired glucose tolerance curve where fasting

plasma glucose level was 15.4 ± 2 , reached its peak 30.3 ± 4 within 45 min. and did not returned back within 135 min. of oral glucose intake. Intraperitoneal injection of 10 mg quercetin/kg body weight prior to STZ was able to normalize glucose tolerance curves in experimental rats (Fig. 2).

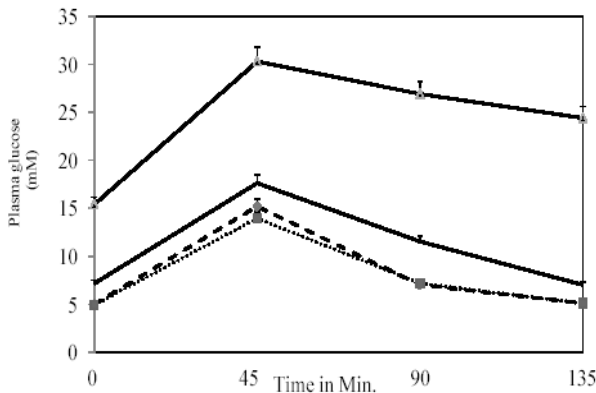


Fig. 2. Glucose tolerance curves of normoglycemic and streptozocin diabetic rats with or without i.p. administration of quercetin. Each point represents the mean \pm SD. of five rats \square , normoglycemic control; \blacksquare , normoglycemic + 15 mg quercetin per kg; \blacktriangle , diabetic control; \bullet , diabetic + 15 mg quercetin per kg.

DISCUSSION

STZ has a β -cell cytotoxic and a slight carcinogenic effect⁽²⁾. Although the β -cell cytotoxic effect of STZ is not fully understood, it is thought to be mediated by the inhibition of free radical scavenger-enzymes thereby enhancing the production of the superoxide radical⁽⁵⁾. Eventually, STZ causes diabetes mellitus and diabetes is associated with oxidative damage⁽⁴⁾. Diabetics and experimental animal models exhibit high oxidative stress due to persistent and chronic hyperglycemia, which thereby depletes the activity of antioxidative defense system and thus promotes de novo free radicals generation^(1,2). Oxidative stress has been shown to be responsible, at least in part, for tissue damage and β -cell dysfunction⁽³⁰⁾. Damaged β -cells often display extensive degranulation and necrosis when examined histologically, and are clinically associated with the development of diabetes⁽³⁴⁾. In vitro and in vivo studies have suggested the implication of oxidative stress in the progression of β -cell dysfunction in type 2 diabetes, too⁽²⁾. In the present study, STZ was associated not only with hyperglycemia and impaired glucose tolerance but also, with low antioxidant enzymes activity.

Srinivasan and Menon reported that the antioxidant drug bis-o-hydroxycinnamoylmethane used for protection of β -cells against reactive oxygen species (ROS) mediated damage by enhancing antioxidants and reduces hyperglycemia in STZ-induced diabetes⁽³⁵⁾. In the present study, we examined possible usefulness of QE to protect the rat

against diabetic effect of STZ and its effect on some antioxidant enzymes (SOD, GSHPX and CAT) which can protect β -cell against oxidative stress in type □ diabetes.

Quercetin, a flavonoid, used in low dose (15 mg kg body mass) was shown to be capable of preventing induced hyperglycemia by STZ and normalizing blood glucose level in rats. Hii and Howell reported that exposure of isolated rat islets to certain flavonoids such epicatechin or quercetin enhances insulin release by 44–70%⁽²⁸⁾. They argue that such flavonoids may act on islet function, at least in part, via alteration in Ca^{2+} fluxes and cyclic nucleotide metabolism⁽²⁸⁾. Vessal et al. suggested that QE supplementation has proven to be beneficial in decreasing blood glucose concentration, promoting regeneration of the pancreatic islets and increasing insulin release in STZ-induced diabetic rats; thus exerting its beneficial antidiabetic effects⁽³⁶⁾. The role and usage of natural antioxidants for preventing oxidative damage in diabetes has been grown^(11,13,18,28). Quercetin had no significant hypoglycemic effect on normoglycemic rats, but, antagonizing the raising in blood sugar induced by STZ treated rats and this effect might be secondary to its antioxidant activity.

Quercetin, a flavonoid found in many plants, is widely distributed in edible fruits and vegetables. When quercetin was administered orally, it was poorly absorbed from digestive tract and did not have a great influence on the organs⁽¹⁵⁾. Quercetin is the major flavonoid in the human diet and its daily intake with foods is

estimated to be 50–500 mg⁽¹⁷⁾. The injected intraperitoneally of a single dose of 15 mg kg⁻¹ to rat is equivalent of about 1000 to a 70 kg human person. Normalization of glucose tolerance curves in diabetic animals treated with 50 mg quercetin /kg body mass⁽²⁴⁾. Normalization of plasma glucose in quercetin in STZ-induced diabetic rats and its lack of effects on plasma glucose level of normoglycemic animals is in agreement with previously reported effects of epicatechin⁽²⁸⁾, and quercetin⁽³⁷⁾ in alloxan-diabetic animals.

The current result is consistent with the results of Wolf⁽³⁸⁾ and El-Missiry⁽³⁹⁾, who indicated an increase in lipid peroxides and a decrease in antioxidant enzymes in DM. Namely, the present results indicate that the preventive effects of QE may be due to inhibition of lipid peroxidation by its antioxidant nature.

In conclusion, it seems that quercetin could prevent hyperglycemia induced by STZ in rats. It was suggested that this effect was owing to its antagonistic effect to prevent a decrease of pancreatic activity of antioxidant enzymes induced by STZ. But to elucidate the exact mechanism of that modulatory effect, and to examine its potential therapeutic effects further studies are essential.

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تأثير الكراستين كمضاد للأكسدة لمرض البوال السكري في الفئران

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قسمي الكيمياء الحيوية الطبية* و علوم الصيدلة**

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يعتبر الكراستين اوجدا من مجموعة الفلافينويد الطبيعية الأكثر انتشارا في عالم النباتات المعروفة كمضادات للفيروسات والبكتريا والأورام وحيث أن هناك علاقة بين زيادة الأكسدة و مرض البوال السكري لذا فقد تم عمل هذه الدراسة علي مجموعة من فئران التجارب لدراسة تأثير الكراستين كمضاد للأكسدة ولمنع ارتفاع معدل الجلوكوز في البلازما وذلك بعد حقن الفئران بتجوييف البطن بمادة الاستيبتروتوسن التي تعمل علي حدوث مرض البوال السكوفيك بعد حقن بعض الفئران بتجوييف البطن بجرعة صغيرة من ماده الكراستين يوميا قبل ثلاث أيام من حقنه بمادة الاستيبتروتوسن ولمده خمسه وعشرون يوما ومتابعة معدل تغير الجلوكوز في البلازما بقياسه عشوائيا وعمل منحني الجلوكوز. وقد تم أيضا قياس بعض الإنزيمات المضادة للأكسدة في خلايا البنكرياسوقد أظهرت نتائج البحث غياب تأثير الكراستين علي تغير المعدل الطبيعي للجلوكوز في البلازما رغم أن له تأثيرا علي منع حدوث ارتفاعا في معدل الجلوكوز في البلازما في الفئران التي تم حقنها بمادة الاستيبتروتوسوقد وجد أيضا أن للكراستين تأثيرا علي ارتفاع نشاط إنزيمات مضادات الأكسدة في خلايا البنكرياس التي لها دورا في منع حدوث مرض البوال السكري.