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Original Article

A comparison between the effectiveness of quercetin and glibenclamide on β-cells of male mice under oxidative stress

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Abstract

Low levels of antioxidants in Langerhans' islets can lead to oxidative stress and damage to beta cells. Many of the symptoms of diabetes may occur as a natural response of the human body to defects in reactive oxygen species (ROS). Many commercially available drugs, such as glibenclamide, are now prescribed to increase insulin secretion. Available studies show that long-term use of glibenclamide as a drug may increase inflammatory factors in β-cells and insulin secretion, as well as underlying diseases due to toxic, mutagenic and carcinogenic effects. This paper presents a comparative study analyzing the detailed effects of glibenclamide *versus* quercetin (QE), an antioxidant with free radical scavenging activity and minimal negative side effects. In this experimental study, islets were divided into three groups, including control, treatment and comparison, isolated and divided to investigate the proposed drugs' effects based on the malondialdehyde (MDA) biomarkers, insulin secretion and total antioxidant capacity (TAC). The results of the study show that a high concentration of QE significantly improves insulin secretion in β-cells. In addition, QE has beneficial effects, including decreasing MDA levels and increasing TAC. In conclusion, quercetin can be used in conjunction with more conventional therapies, such as glibenclamide, to reduce oxidative stress and maintain beta-cell functionality for insulin secretion in diabetic patients.

Keywords: quercetin, insulin secretion, malondialdehyde, oxidative stress, glycemic conditions, total antioxidant capacity.

Introduction

Many scientific studies indicate that various tissues, such as the pancreas, may eventually be damaged by the disproportionate effects of Reactive Oxygen Species (ROS) produced as a result of a series of cascading reactions due to increased blood glucose [1]. As a natural response to ROS damage, the human body produces many antioxidants such as superoxide dismutase (SOD), glutathione (GSH), and catalase (CAT) to reduce the destructive effects of ROS in vulnerable areas of the body, such as the pancreas [2]. Oxidative stress is an imbalance between the generation of oxygen free radicals and the body's antioxidant defense capacity [3]. Furthermore, due to the weakness of the antioxidant system in the pancreas, oxidative stress damages β-cells and leads to early signs of diabetes, such as extreme fatigue, frequent and excessive urination, persistent hunger, severe thirst, blurred vision and weight loss [4]. However, it is important not to overlook the significant effect of antioxidant depletion in chronic disease [2]. The use of antioxidant compounds plays an essential role in maintaining the balance between the strength of the antioxidant system in the islets of Langerhans and the oxidative stress situation caused by the onset of diabetes. Therefore, enhancing the antioxidant defense system in islets of Langerhans leads to the prevention of the progression of diabetes and its complications [5]. This paper evaluates the administration of an active herbal ingredient as an alternative, naturally

derived treatment for maintaining β-cell function due to their minimal side effects [6]. Recent studies have shown that Quercetin (QE) has free radical scavenging activity, and its antioxidant activity can effectively protect against tissue damage induced by ROS [7]. QE is a flavonoid with potent antioxidant activity that is widely found in onions, green tea, red wine, grapefruit, apples, berries, and lettuce [8]. Because of its antioxidant properties, it was previously known as a superior plant phenolic compound with beneficial effects on cancer, viral infections and obesity [9]. QE has a protective effect on skeletal muscles, the nervous system and the heart [10, 11]. It is worth noting that flavonoids have proactive protective effects against aging, cardiovascular disease and diabetes [12, 13]. The neuroactive effect of QE has also triggered some protective activities against Antioxidants with phenolic or flavonoid components, which can make islets of Langerhans more resistant to oxidative stress, especially in diabetes [14]. Therefore, in this work, QE is used to develop a stepwise experimental procedure in islets of Langerhans.

Methylglyoxal (MG) is a highly reactive product [15] of glucose and fructose metabolism. MG increases due to hyperglycemia and aging, which can lead to a decrease in the mass and functional capacity of the animal's pancreatic β-cells [16]. MG is produced inside the body's cells, but even a small fraction of it leaking out results in a significant increase in the glycation of cellular and extracellular proteins by methylglyoxal [17]. Insulin secretion is the beginning of free radical-induced apoptosis [18] and DNA fragmentation [19], leading to a decrease in beta-cell mass. The formation of methylglyoxal-induced advanced glycation end-products (AGEs) leads to early diabetes-related changes, emphasizing the glycosylation of proteins by methylglyoxal [20]. Considering that no study has been done on the effect of QE on insulinotropic and antioxidant defense in islets of Langerhans exposed to methylglyoxal, this study was designed and conducted.

Material and methods

Preparation of animals

The animals used in this study were 30 male NMARI mice weighing 25 to 35 grams obtained from Ahvaz Jundishapur University of Medical Sciences (AJUMS). The animals were maintained at a temperature of 20–24°C under a predetermined light cycle (12 hours of darkness followed by 12 hours of light) according to the ethical rules and principles of animal care (IR.AJUMS.ABHC.REC.1400.103). The animals had access to tap water and commercial chow ad libitum.

Mice Langerhans islets isolation procedure

Islets of Langerhans were isolated according to the procedure established by O'Dowd JF [21] for isolation of islets from rodent pancreas by collagenase digestion method. Animals were first anesthetized with ketamine/xylazine (10/1 mg/kg, IP). The pancreas was separated and transferred to a petri dish containing Krebs bicarbonate buffer solution (Merck, Germany) and cut into 1 mm pieces. The pancreatic islets were selected under a stereomicroscope. Finally, the islets were transferred to a petri dish containing a different dose of glucose (2.8, 5.6, and 16.7 mM) and centrifuged at 3000×g for 5 minutes [22].

Study grouping

Control groups

The positive control groups were defined as the first group based on three levels of glycemic effect with 1ml of Hanks buffer containing different concentrations of glucose, i.e., hypoglycemia (HOC): 2.8 mM, normal glycemic (NGC): 5.6 mM, and hyperglycemia (HEC): 16.7 mM.

Secondly, the negative control group was developed by exposing the isolated Langerhans islets to a 300 mM dose of MG in 1 ml of Hanks' buffer containing the three glucose concentrations (i.e., HOC, NGC and HEC) for 2 hours to generate a reactive oxygen species-environment.

The third control group was considered based on the solo effects of dimethyl sulfoxide (DMSO) on the previously defined glucose concentration, i.e., HOC, NGC, and HEC. It is worth mentioning that DMSO has served as a QE solvent to enable the proactive protection effects of QE on isolated Langerhans islets [23].

Treatment groups

The fourth, fifth and sixth test groups were defined based on the effects of three doses of QE on the scavenging of free oxidative radicals. In this study, three different dosages of QE (i.e., 15, 30, and 60 mM) [24] were tested under oxidative stress conditions with a 300 mM concentration of MG [25] in 1 ml Hanks buffer at the proposed three levels of glycemic state (HOC, NGC, and HEC).

The development of these groups aimed to assess the impact of different doses of QE on strengthening the antioxidant system in the islets of Langerhans and improving diabetes symptoms. This is a key focus of the current study, providing new insights into the effective dose of QE.

The comparison group

Finally, The seventh group in this study serves as a comparison group to evaluate the effectiveness of QE in reducing oxidative stress in β-cells compared to 10 mM glibenclamide [26], a well-known commercial drug that has been used for many years to treat diabetes.

Oxidative stress in islet cells and treatment

To induce oxidative stress in isolated islets of Langerhans, a dose of 300 mM MG was added to each islet sample and incubated for 30 minutes, followed by centrifugation at 3000×g for 5 minutes. To reduce oxidative stress, doses of 15, 30, and 60 mM QE were added to the islet samples and incubated at 37°C for 2 hours. After incubation, the oxidative-induced protocol was repeated with 300 mM MG. The supernatant from each microtube was then stored at -70°C for later measurement of malondialdehyde (MDA), total antioxidant capacity (TAC), and insulin levels. Each microtube contained seven islets, and the experiment was repeated six times for each.

Antioxidant measurements

The levels of MDA, TAC, and insulin secretion in the isolated islets of Langerhans were measured using the ELISA method and a specific commercial kit from Teb Pazhouhan Razi, Iran and Monobind Inc, USA respectively.

Statistical analysis

Data were analyzed using the Statistical Package for Social Sciences Software (SPSS). A one-way analysis of variance (ANOVA) was performed, followed by post hoc

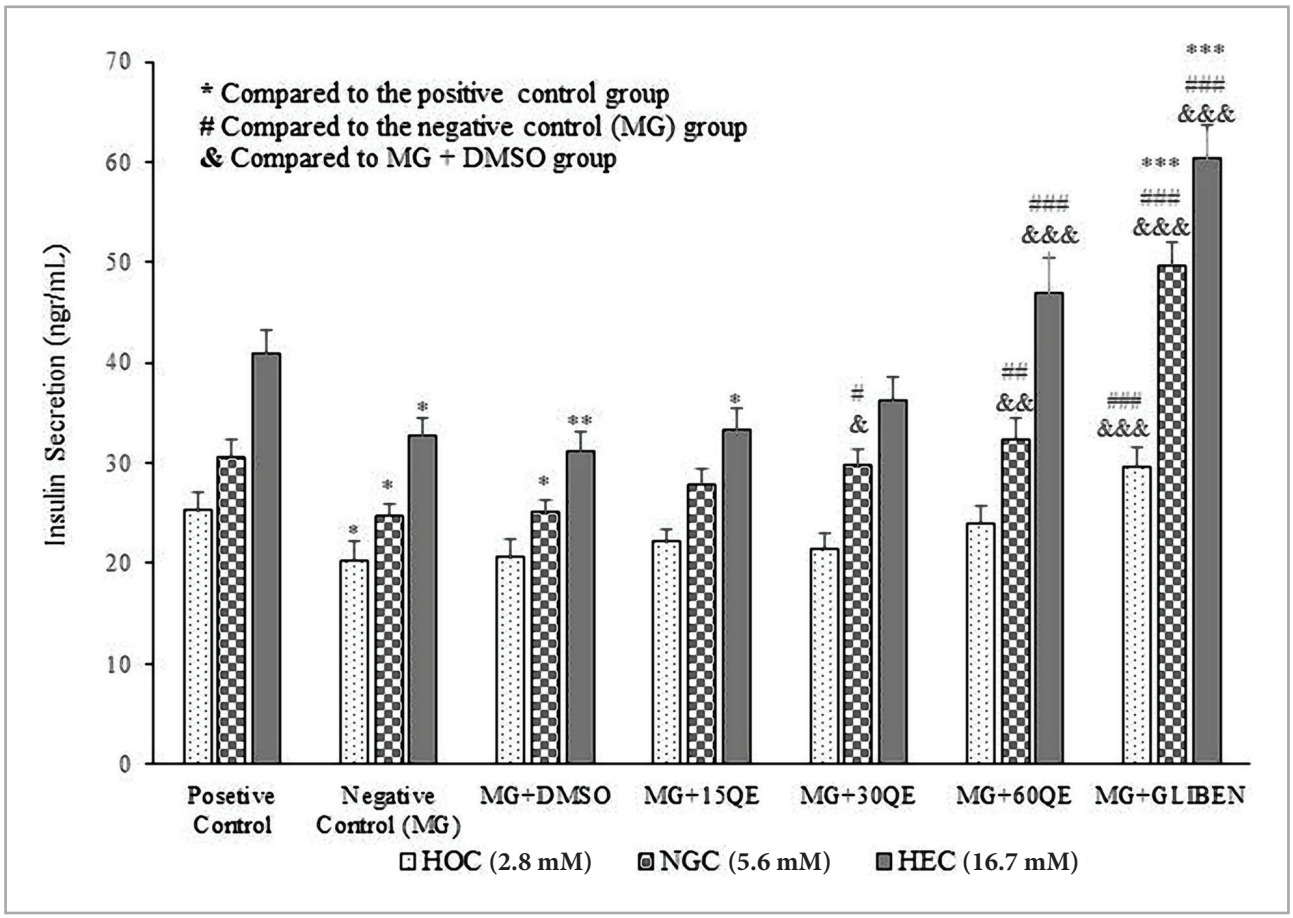

Figure 1: Effects of glibenclamide and QE on insulin secretion level of islets of Langerhans. Data are expressed as the mean±SE, n=6 (7 islets in each sample). Three symbols denote significantly correlated variables (p-value <0.05); two symbols denote strong correlation (p-value <0.01); and one symbol denotes weak correlation with the positive control group. (GLIBEN: glibenclamide).

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least significant difference (LSD) tests to determine statistical significance. Results are presented as mean±standard error (SE), with a P-value of less than 0.05 considered statistically significant in all experiments.

Results and discussion

The efficacy of QE in reducing oxidative stress in β-cells was evaluated by comparing the results of three different doses of QE (15, 30, and 60 mM) in three different glycemic conditions: HEC, NGC, and HOC. The results for insulin secretion, MDA, and TAC measurements are discussed below.

The effect of QE on insulin secretion

The results show that glibenclamide is more than 200% more effective than QE in increasing insulin secretion in the negative control groups. This may be due to the strong effect of glibenclamide, a well-known drug for neutralizing oxidative stress in β-cells, compared to the low concentration of QE. At first glance, this might seem to be an advantage for glibenclamide. However, other factors related to the inflammatory oxidative stress response of β-cells may affect the long-term use of glibenclamide as a drug. Long-term clinical studies [27] have shown that β-cells function can gradually deteriorate due to adverse effects such as islet inflammation [28], hypersecretion of islet amyloid polypeptide (IAPP) followed by amyloid deposition [29], and other destructive mechanisms. For this reason, other biological markers of oxidative stress, such as MDA secretion and TAC, have been used to compare the potential adverse effects of glibenclamide and QE [30].

Figure 1 shows that while glibenclamide is more effective in increasing insulin secretion in all three glycemic conditions, a significant increase in insulin secretion was observed with increasing doses of QE. This suggests that although insulin secretion increases with higher concentrations of QE, a higher dose of QE is required to reduce oxidative stress compared to glibenclamide.

The effect of QE on MDA secretion

MDA, or malondialdehyde, is an organic compound with the formula CH2(CHO)2 and is a byproduct of the peroxidation of polyunsaturated fatty acid (PUFA). It is found in vegetable oils and at high levels in rancid foods and has been proposed as a biological marker of oxidative stress [31]. MDA has also been shown to

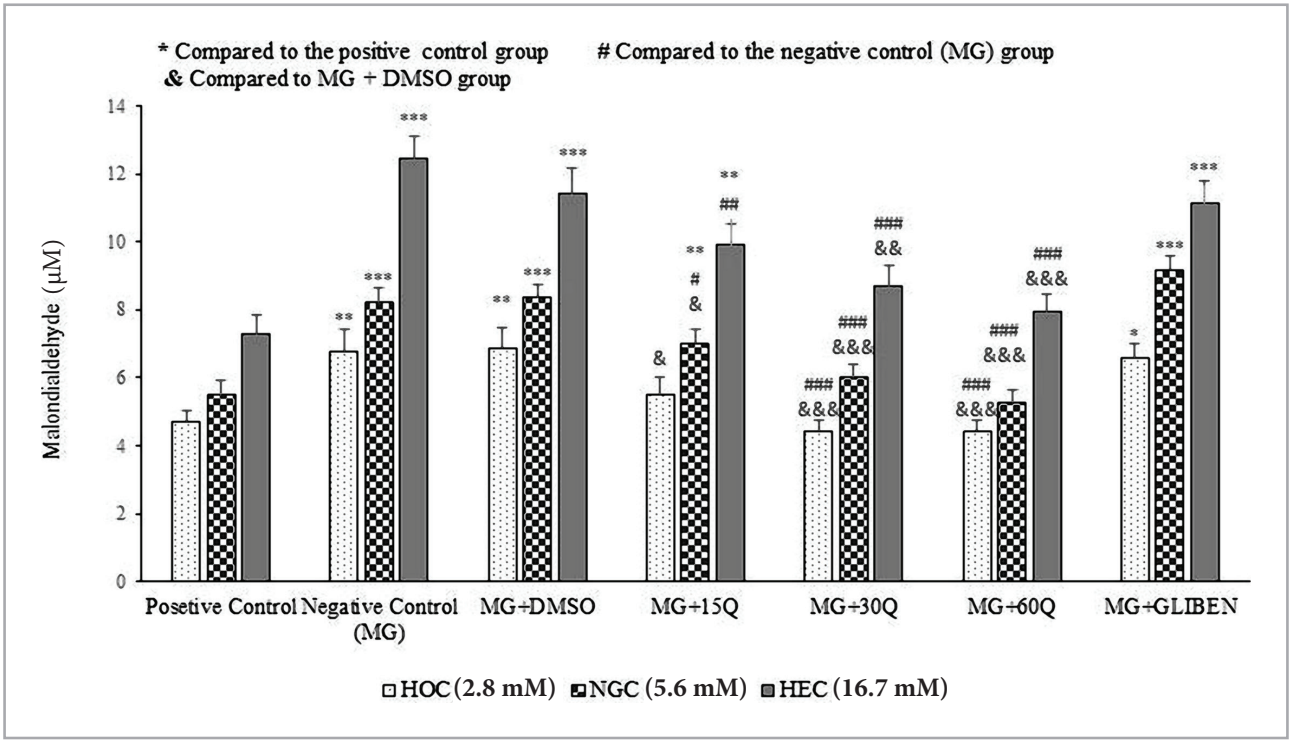

Figure 2: Effects of glibenclamide and QE on the MDA secretion level of islets of Langerhans. Data are expressed as the mean±SE, n=6 (7 islets in each sample). Three symbols denote significantly correlated variables (p-value <0.05); two symbols denote strong correlation (p-value <0.01); and one symbol denotes weak correlation with the positive control group. (GLIBEN: glibenclamide).

be toxic, mutagenic, and carcinogenic [32], and some studies have demonstrated that it can induce cytotoxicity and vascular endothelial growth factor (VEGF) expression in the rate of perceived exertion (RPE) cells *in vitro*. Due to lipid peroxidation and free radical scavenging by drugs, MDA can accumulate in β-cells and cause the aforementioned defects, especially over long periods of time [33]. In this study, MDA secretion was used as a marker to compare the effects of QE and glibenclamide on reducing the destructive effects of ROS and to identify the best drug with minimal side effects for long-term use.

The results show that QE decreased MDA secretion by approximately 29% in the NGC group compared to the negative control group, while glibenclamide increased MDA secretion by about 11% in this glycemic condition. In other conditions, glibenclamide did not show a significant correlation with the negative control group based on the calculated p-value. Additionally, as shown in Figure 2, increasing the dosage of QE resulted in a significant reduction in MDA secretion. This suggests that, unlike glibenclamide, higher doses of QE have a greater ability to reduce MDA secretion and consequently decrease the associated toxicity and mutagenic and carcinogenic side effects [34].

The effect of QE on total antioxidant capacity

In this study, total antioxidant capacity (TAC) was measured to assess the antioxidant status in the islets of Langerhans and evaluate the antioxidant response of glibenclamide and QE against free radicals remaining in diabetic β-cells.

The findings suggest that while QE is significantly more effective in increasing TAC in both positive and negative control groups, its effectiveness in negative control groups has increased by approximately 86% for a dosage of 60 mM compared to 30 mM (from an average of 17.7 times to 33 times). This indicates that the effective dose of QE in diabetic conditions is higher than 60 mM.

As shown in Figure 3, increasing the concentration of QE has resulted in a significant increase in TAC compared to glibenclamide. This suggests that the antioxidant activity of QE may gradually restore damaged β-cells by neutralizing oxidative stress over time with a high concentration of QE [35]. However, according to the calculated p-value, glibenclamide showed no significant effects in some conditions.

It is important to note that DMSO was used as a solvent for QE, as previously mentioned. According to the results shown in Figures, DMSO appears to have no

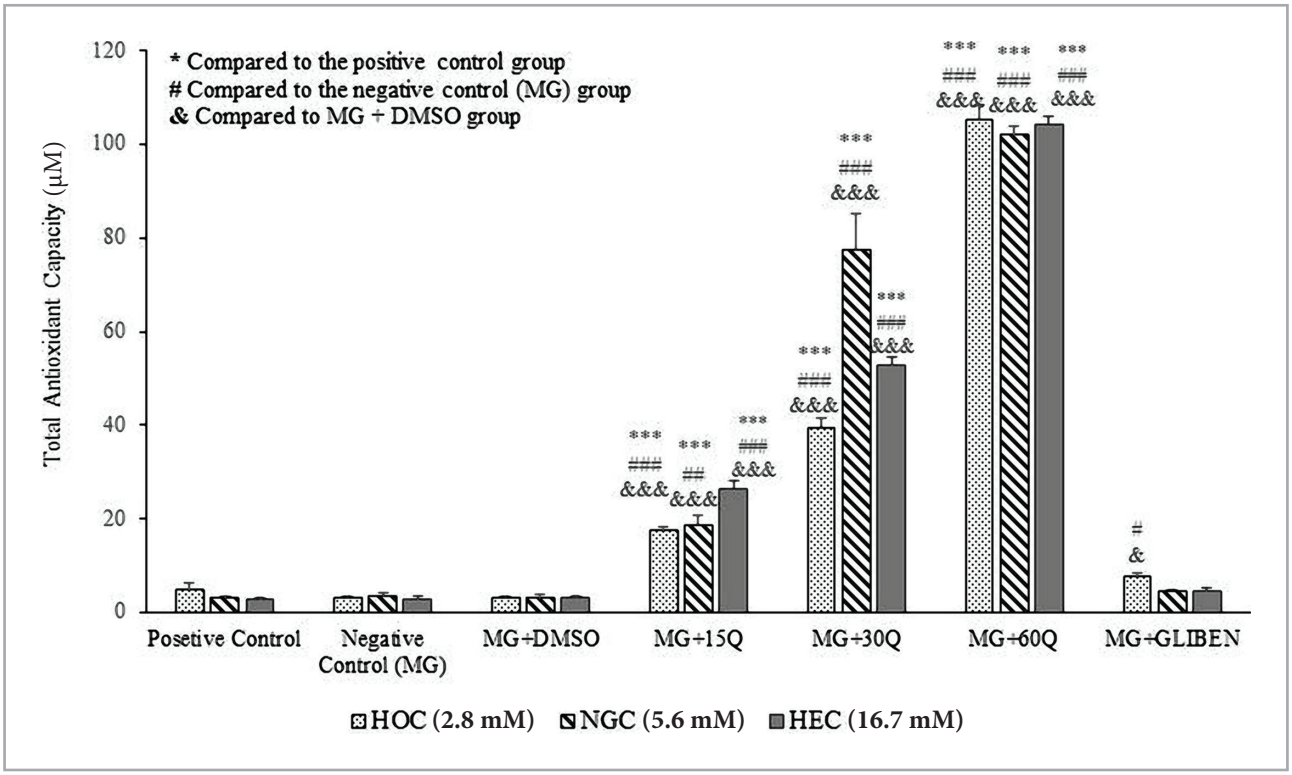

Figure 3: Effects of glibenclamide and QE on the TAC of islets of Langerhans. Data are expressed as the mean±SE, n=6 (7 islets in each sample). Three symbols denote significantly correlated variables (p-value <0.05); two symbols denote strong correlation (p-value <0.01); and one symbol denotes weak correlation with the positive control group. (GLIBEN: glibenclamide).

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effect on the effectiveness of QE on insulin secretion, MDA, and TAC.

Conclusion

In this study, the effects of glibenclamide, a traditional medication, and QE were assessed and compared through three grouping stages (test control, treatment, and comparison groups) by measuring the levels of insulin secretion, TAC, and MDA secretion as biomarkers. The results indicate that while a high concentration of QE is required for significant effectiveness in insulin secretion, its positive effects, such as reduced MDA secretion and increased TAC, demonstrate its potential as a supportive medication in reducing oxidative stress in β-cells. The superiority of QE is evident as it not only stimulates β-cells in the pancreas to secrete more insulin, but its long-term positive effects can also reduce the inflammatory defects caused by traditional treatments such as glibenclamide and insulin, which can deteriorate the health and functionality of β-cells.

According to the authors' knowledge, while the relationship between the long-term effectiveness of quercetin and the statistically significant decrease in MDA levels has been established, more extensive and comprehensive long-term clinical studies are needed to determine the extent of QE's contribution to both its effectiveness in insulin secretion and its ability to reduce oxidative stress in β-cells, in order to maintain their functionality during long-term treatment with glibenclamide. This could be a future line of research. Additionally, this study's limitations in the use of glycemic conditions and biomarkers require further investigation and experimentation due to the limited long-term monitoring of QE's detailed response in reducing oxidative stress in β-cells. Finally, the protective use of QE is raised, based on the positive effect of QE to maintain the long-term functionality of β-cells by scavenging the oxidative stress situation induced by existing commercial treatments such as glibenclamide and insulin.

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Conflict of interest

The authors declare no conflict of interest.

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