Antidiabetic and Hypolipidemic Effects of 5,7-Dimethoxyflavone in Streptozotocin-Induced Diabetic Rats

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Source of support: Departmental sources

Background: The flavones are considered as competent antidiabetic molecules due to their strong antioxidant activities and higher in vivo stability. The present study evaluated the antidiabetic and hypolipidemic effects of 5,7-dimethoxyflavone in streptozotocin (STZ)-induced diabetic rat models.

Material/Methods: The antidiabetic potential of 5,7-dimethoxyflavone was evaluated in streptozotocin-induced diabetic rats. The serum levels of triglyceride, total cholesterol, and high-density lipoprotein cholesterol were measured using the Randox assay kit. Histopathological examination was carried out by hematoxylin and eosin (HE) staining.

Results: Oral administration of 5,7-dimethoxyflavone significantly reduced STZ-induced enhancement in blood sugar and glycosylated hemoglobin, as well as significant increases in C-peptide, insulin, hemoglobin, and total protein content (p<0.05). Additionally, treatment with 5,7-dimethoxyflavone resulted in a remarkable increase in non-enzymic antioxidants. Administration of 5,7-dimethoxyflavone had a hypolipidemic effect by significantly reducing levels of serum triglycerides, total cholesterol, and low-density lipoproteins. The histopathological examination of rat pancreases revealed the beneficial effect of 5,7-dimethoxyflavone and protection of β cell integrity in STZ-induced diabetic rats.

Conclusions: These findings reflect the antidiabetic and hypolipidemic effects of 5,7-dimethoxyflavone, suggesting that 5,7-dimethoxyflavone may be a promising compound for use in development of new antidiabetic drugs.

MeSH Keywords: Diabetes Mellitus, Type 1 • Flavones • Hypoglycemic Agents

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/918794
Background

Diabetes mellitus (DM) is a severe metabolic pathological condition that results in non-physiological changes in many tissues and oxidative stress, which has a vital role in the progression of this disease [1]. DM results in micro- and macro-vascular complications that cause great loss of life. A constant increase in the elderly population, obesity, energy-rich diets, and sedentary lifestyles are responsible for the significant rise in diabetes globally [2]. The World Health Organization (WHO) reported that the number of diabetic patients is predicted to increase from 150 to 300 million by 2025 [3]. The available blood glucose-lowering agents and dietary measures only partially correct the multiple metabolic defects in non-insulin-dependent diabetes mellitus (NIDDM), with insulin resistance remaining relatively unresponsive to treatment [4]. Hypoglycemia and secondary organ failure are common problems associated with the currently-available sulphonylureas. Therefore, research seeks to develop new hypoglycemic drugs that can address these limitations.

Streptozotocin (STZ) is generally used to elicit DM condition in animal models owing to its effects on β cells in the pancreas. DM elicited by STZ is coupled with the formation of reactive oxygen species (ROS), which leads to oxidative stress and finally to oxidative damage [5]. Diabetic patients and experimental animals have high oxidative stress because of continuous and chronic hyperglycemic condition, which diminishes the activity of the oxidative stress scavenging system (anti-oxidative defense) resulting in generation of de novo free radicals [6]. Plant metabolites with oxidant-attenuating potential and ability to scavenge free radicals may facilitate the renewal of β cells and help in the protection of pancreatic islets of Langerhans against the toxic effects induced by STZ [7,8]. Physiologically, an array of oxidant-attenuating systems protects against free radical damage endogenously [9]. In DM, glycation of proteins and auto-oxidation of glucose may breed free radicals, which act as catalysts for peroxidation of lipid [6]. The disproportion of antioxidant-attenuating functions in DM, such as undesirable antioxidant-related enzymatic changes [10], low vitamin levels [11], and low ceruloplasmin levels [12], have been described. Reduction in peroxidation of lipids and enhancement of antioxidant functioning could be a way by which diet-based treatment reduces diabetic morbidity [13].

Flavonoids are a group of bioactive polyphenols with a wide distribution in plants, especially in fruits and vegetables [14]. Flavonoids are becoming an attractive subject for medical research and have been found to possess many pharmacological properties, including anti-inflammatory, estrogenic, antimicrobial, and enzyme inhibition activities [15,16], and antioxidant and allergenic activities [17]. Flavonoids or even crude extracts rich in flavonoids exhibit the capacity to decrease blood glucose levels [18]. It is believed that the methylated flavones have the benefit of increasing metabolic stability and may prove more beneficial as antidiabetic agents. With this background, the present study therefore evaluated the antidiabetic activity of 5,7-dimethoxyflavone in streptozotocin-induced diabetic rats.

Material and Methods

Experimental animals

Male albino Wistar rats weighing about 160±10 g were used in this study. Pellet-based diet and water were available to animals throughout the study. Animals were maintained in ventilated rooms with controlled photoperiod and temperature (28±2°C). The Animal Ethics Committee approved the animal experimental procedures (approval number JPPH/32C, Dec 2018). All the procedures were carried out according to standard animal ethics guidelines [19].

Induction of experimental diabetes

Diabetes was induced in overnight (O/N) fasted rats by intraperitoneal injection (1 ml/rat) of STZ at the dosage of 90 mg/kg solubilized in citrate buffer (pH 4.5) [20], while the normal control animals were intraperitoneally administered citrate buffer alone. Subsequently, blood was collected from O/N-fasted animals via sinuscular puncture 72 h after STZ injection. Rats showing levels of fasting plasma glucose >270 mg/dl were used for experiments [21].

After STZ treatment, rats were randomly grouped, with 10 animals/group. Out of the 3 diabetic animal groups, 2 diabetic animal groups were given 5,7-dimethoxyflavone at the dosage of 50 and 100 mg/kg daily as a suspension in 4% Tween 80 by oral gavage, and the third group was used as a diabetic control. An untreated normal control group was administered daily O/N-fasted animals via sinuscular puncture 72 h after STZ injection. Rats showing levels of fasting plasma glucose >270 mg/dl were used for experiments [21].

The blood pressure (BP) of each rat was assessed 12 h after the last dose, and then the rats were anesthetized. Blood samples from each animal were withdrawn via sinusicular puncture at the beginning, middle (1 month), and end (2 month) of the study. Blood samples were allowed to clot for 1 h at 25°C. Subsequently, the samples were centrifugated at 3000 rpm for 20 min for the preparation of the serum and stored at −70°C until use. Various biochemical tests were performed using the serum and plasma samples.
Biochemical analysis

The serum levels of the triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-c), and serum glucose (Glc) were measured using the Randox assay kit (Randox Laboratories, Ltd., UK). Low-density lipoprotein cholesterol (LDL-c) was then calculated according to the Friedewald equation: TC-(HDL-C+1/5 TGs). The serum insulin and C-peptide levels were compared by ELISA (enzyme-linked immunosorbent assay) method using a rat insulin kit (Mercodia, Uppsala, Sweden). Total hemoglobin total proteins and glycosylated hemoglobin was estimated using a procedure described previously [22].

Estimation of reduced glutathione, vitamin E, and vitamin C

The levels of glutathione (GSH) were examined by slight modification of a procedure reported earlier [23]. Briefly, aliquots (0.5 ml) of collected blood were precipitated with 2.0 ml of 5% trichloroacetic acid. After centrifugation, supernatant (1.0 ml), Ellman’s reagent (0.5 ml), and phosphate buffer (3.0 ml, 0.2 M, pH 8.0) were added. The color developed was spectrophotometrically interpreted at 412 nm. A number of standard samples were also included in the assay and treated in the same way along with blank (3.5 ml) buffer. The vitamin E and C levels in plasma were measured by standard protocols as described previously [24,25].

Estimation of ceruloplasmin

The levels of ceruloplasmin in plasma were assessed by slight modification of a procedure reported earlier [26]. We added acetate buffer (8.0 ml, 0.4 M, pH 5.5) and 0.5% p-phenylenediamine hydrochloride (1.0 ml) to plasma (0.05 ml), followed by incubation at 37°C for 60 min. Subsequently, 1.0 ml of 0.5% sodium azide was added, followed by incubation at 4°C for 30 min. The control group in which the sodium azide was added prior to addition of p-phenylenediamine hydrochloride was also included in the assay. The development of color was examined spectrophotometrically at 540 nm.

Histopathological examination

Pancreatic tissue sections were fixed in formaldehyde (4 g/L) and then embedded in paraffin. The paraffin-embedded sections were subsequently stained with HE. Histopathological examination was done by 2 pathologists who were blinded to the treatment design used in the experiment. The criteria chosen for scoring the degree of injury to islet cells of the pancreas was according to a procedure discussed previously [27]. Scores of 0, I, II, III, and IV were used to score the number and cell morphology of islet cells. A score of 0 indicates normal cells (normal cell morphology and number of the islets cells). A score of I indicate less cell injury (the number of cells were reduced to less extent and the islet cells were slightly swollen). A score of II indicates modest injury (the cell volume and number of islet cells were decreased to a moderate extent). A score of III indicates noticeable injury (islet cells were evidently swelled and the number of cells were evidently decreased). A score of IV indicates extreme injury (islet cells were also extremely swollen and the numbers of islet cells were extremely reduced). The degree of injuries was expressed as the average of 10 different fields in each sample slide.

Statistical analysis

Statistical analysis was done by one-way ANOVA and Duncan’s multiple range test performed using the SPSS software package, version 9.05. Final values were presented as average±SD for 10 rats in each sampling group. A p value <0.05 was regarded as indicating a statistically significant difference.

Results

Effect of the 5,7-dimethoxyflavone on blood glucose levels

Fasting levels of plasma glucose of the rats at the termination of the experiment (day 60) in the diabetic control group treated with the highest tested dose of the 5,7-dimethoxyflavone raised as high as 22.01 mm/L±1.98 mmol/L in comparison to the normal control group rats (3.88±0.23 mmol/L). The 5,7-dimethoxyflavone given at 2 doses (50 and 100 mg/kg body weight) to diabetic rats lead to considerable (p<0.05) reduction in the blood glucose levels (52.61% and 64.01%, respectively) compared to the rats in the diabetic group on day 60. However, 5,7-dimethoxyflavone at the highest tested dose (100 mg/kg body weight) given to normal control rats did not exhibit any significant (p<0.05) effect on fasting blood glucose levels (Table 1). 5,7-dimethoxyflavone administered at 100 mg/kg showed the greatest effect on lowering plasma glucose levels (64.01%) in the diabetic group compared to 50 mg/kg body weight of the 5,7-dimethoxyflavone.

Effect of 5,7-dimethoxyflavone on reduced glutathione, Vitamin C, Vitamin E, and ceruloplasmin levels

The non-enzymic antioxidant levels in different rat groups are shown in Table 2. The levels of GSH (40.29%), vitamin E (41.18%), vitamin C (65%), and ceruloplasmin (34.29%) levels decreased to a significant (p<0.05) extent in the diabetic control group in comparison to rats in the normal control group. Treatment with 5,7-dimethoxyflavone in the diabetic groups caused a significant (p<0.05) rise in the plasma levels of GSH (12.5%), vitamin E (25%), vitamin C (90%), and ceruloplasmin (33%) relative to the rats in the diabetic control group. The increase
in the plasma levels of non-enzymatic antioxidants was observed to be dose-dependent as there was an obvious increase in these parameters with increase in dose administration from 50 to 100 mg/kg body weight (Table 2).

### Table 1. Effect of 5,7-dimethoxyflavone on plasma glucose levels (mmol/L) in normal and diabetic rats on day 0, day 30, and day 60.

| Group                               | Glucose (mmol/L) |
|-------------------------------------|------------------|
| Normal control                      | Day 0            | Day 30          | Day 60          |
|                                     | 3.98±0.22        | 4.38±0.11       | 3.92±0.34       |
| Normal+5,7-dimethoxyflavone (100 mg/kg) | 3.88±0.23        | 4.11±0.25       | 3.84±0.20       |
| Diabetic Control                    | 16.2±1.33        | 20.43±1.44      | 22.01±1.98      |
| Diabetic+5,7-dimethoxyflavone (50 mg/kg) | 14.45±1.15       | 12.56±1.54      | 10.43±0.66      |
| Diabetic+5,7-dimethoxyflavone (100 mg/kg) | 13.60±1.22       | 10.46±0.52      | 7.92±0.60       |

Each value is mean±S.D. for 8 rats in each group (n=10). Values that have a different superscript letter (a, b, c, d, e) differ significantly with each other (p<0.05, Duncan’s multiple range test).

### Table 2. Effect of 5,7-dimethoxyflavone on plasma glutathione, vitamin E, vitamin C, and ceruloplasmin in normal and diabetic rats.

| Group                               | Glutathione | Vitamin E | Vitamin C | Ceruloplasmin |
|-------------------------------------|-------------|-----------|-----------|---------------|
| Normal control                      | 0.67±0.05   | 0.034±0.002 | 0.12±0.01 | 1.40±0.10     |
| Normal+5,7-dimethoxyflavone (100 mg/kg) | 0.65±0.03   | 0.034±0.002 | 0.13±0.01 | 1.37±0.10     |
| Diabetic control                    | 0.4±0.02    | 0.020±0.001 | 0.042±0.01 | 0.92±0.06     |
| Diabetic+5,7-dimethoxyflavone (50 mg/kg) | 0.45±0.02   | 0.025±0.002 | 0.08±0.02 | 1.23±0.08     |
| Diabetic+5,7-dimethoxyflavone (100 mg/kg) | 0.59±0.02   | 0.030±0.002 | 0.09±0.01 | 1.30±0.06     |

Values that have a different superscript letter (a, b, c) differ significantly with each other (p<0.05), Duncan’s multiple range test.

### Table 3. Effect of 5,7-dimethoxyflavone on plasma insulin, total hemoglobin, C-peptide, glycosylated hemoglobin, and total protein levels in normal and diabetic rats. Each value is average±S.D. for 10 rats in each group (n=10).

| Group                               | Insulin µU/mL | C-peptide ng/mL | Total hemoglobin (g%) | Glycosylated hemoglobin (mg/dL) | Total protein g/dL |
|-------------------------------------|---------------|-----------------|-----------------------|---------------------------------|-------------------|
| Normal control                      | 13.14±1.22    | 22.86±1.71      | 10.25±0.37            | 0.44±0.034                      | 10.55±0.44        |
| Normal+5,7-dimethoxyflavone (100 mg/kg) | 13.77±1.22    | 22.67±0.89      | 10.78±0.89            | 0.42±0.20                       | 10.60±0.78        |
| Diabetic control                    | 6.88±0.66     | 12.12±1.58      | 6.56±0.64             | 0.84±0.02                       | 7.01±0.82         |
| Diabetic+5,7-dimethoxyflavone (50 mg/kg) | 8.44±1.25     | 15.76±1.15      | 8.44±0.64             | 0.42±0.04                       | 8.01±0.34         |
| Diabetic+5,7-dimethoxyflavone (100 mg/kg) | 11.22±1.33    | 19.46±1.88      | 9.92±0.43             | 0.52±0.06                       | 9.80±0.50         |

Values that have a different superscript letter (a, b, c) differ significantly with each other (p<0.05, Duncan’s multiple range test).

### Effect on insulin and other plasma proteins

The significant (p<0.05) reduction in plasma concentration of insulin (47.64%), total proteins (33.55%), C-peptide (46.98%), and total hemoglobin (17.65%) and increase in the concentration of glycosylated hemoglobin (90.90%) were detected in
diabetic control group rats relative to the normal control group (Table 3). Administration of 5,7-dimethoxyflavone in the diabetic group at both the test doses led to increases in these values at both doses. When 5,7-dimethoxyflavone was administered at 50 mg/kg, we found a remarkable improvement in plasma insulin (22.67%), total proteins (14.26%), C-peptide (30.03%), and total hemoglobin (29.85%) and reduction in glycosylated hemoglobin (50%) relative to the diabetic control rats. 5,7-dimethoxyflavone at 100 mg/kg led to a significant rise in the levels of these biochemical parameters with 63.08%, 60.56%, 49.17%, and 39.80 increase in insulin, C-peptide, total hemoglobin, and total protein levels, respectively, and a considerable decrease (49.17%) in the level glycosylated hemoglobin.

**Lipid profile**

The changes in the serum lipids levels after completion (day 60) of the study are depicted in Figure 1A–1D. It was observed that the TG level increased to a significant (p<0.001) extent in the diabetic group, the TC-lowering effect became apparent. The TC-reduction was observed after the treatment of rats with both test doses of 5,7-dimethoxyflavone (Figure 1C). In the diabetic group, the levels of HDL-c were lowered significantly (p<0.001) in comparison to the normal control group (Figure 1B); however, the concentrations of TC in diabetic groups receiving 5,7-dimethoxyflavone at 2 different doses was significantly reduced (p<0.001). No significant effects of 5,7-dimethoxyflavone were observed on cholesterol levels in the normal control rats. After 30 days of treatment with 5,7-dimethoxyflavone in diabetic group, the TC-lowering effect became apparent. The TC-lowering effects of 5,7-dimethoxyflavone were also observed in the normal control group (p<0.05). At the termination of the study, a significant (p<0.05) increase in TC was revealed in diabetic rats relative to the values obtained at the start of the study. A significant (p<0.001) rise in LDL-c levels at day 60 of the study was seen in the diabetic group, but a significant (p<0.001) reduction was observed after the treatment of rats with both test doses of 5,7-dimethoxyflavone (Figure 1C). In the diabetic group, the levels of HDL-c were lowered significantly (p<0.001) in comparison to the normal control group (Figure 2D). However, HDL-c increased to a significant (p<0.001) extent in diabetic rats after the oral administration of 5,7-dimethoxyflavone at both

**Figure 1.** Effect of 5,7-dimethoxyflavone on lipid profile (A), triglycerides (B), TC (C), low-density lipoproteins (LDL), and (D) high-density lipoproteins (HDL). All experiments were carried out in triplicate and results are expressed as mean±S.D.
doses. The differences in HDL-c concentrations were observed to be significant ($p < 0.05$) on day 30 and day 60 of the investigation in the diabetic and control groups compared with the concentrations obtained on day 0 of the study.

**Histological results**

The examination of HE-stained sections revealed that vehicle (4% Tween 80) administration alone did not lead to any significant changes in pancreas histology throughout the 2-month study (Figure 2A). In contrast, treatment of STZ-induced rats caused severe pancreas injury, decreasing the numbers of islets cells and reducing the volume of pancreatic islands. Islets of Langerhans were severely reduced in diameter in the diabetic control group relative to the normal control group (Figure 2B). Oral administration of 5,7-dimethoxyflavone (100 mg/kg body weight) led to a moderate expansion of islets of Langerhans, and scores and the degree of the injuries

Figure 2. Histopathological changes of pancreas. (A) Normal control. (B) Normal control with 5,7-dimethoxyflavone (100 mg/kg). (C) Diabetic rats plus streptozotocin. (D) Diabetic rats with 5,7-dimethoxyflavone (50 mg/kg). (E) Diabetic rats with 5,7-dimethoxyflavone (100 mg/kg). These images are representative of several replicates.
It has also been reported that in STZ-induced diabetic rats, the secretion of insulin and the decline in blood glucose levels are inhibited and thereby protecting the pancreas against oxidative stress and preventing STZ-induced oxidative peroxidation of lipids, preventing STZ-induced oxidative stress in diabetic rats, resulting in renewal of GSH [32]. The availability of mRNA [36]. It was also reported that there is a reduction in the protein concentration in serum of diabetic rats treated with 5,7-dimethoxyflavone [34]. In DM, an array of proteins is made to glycate in a non-enzymatic manner and are believed to induce severe disease complications [35]. We observed that the total plasma proteins were reduced, which may be due to enhanced peroxidation of lipids in the diabetic animal models. The reduction in the total protein counts in the diabetic group may also be attributed to: (i) decrease in uptake of amino acids, (ii) higher transformation of glycogenic amino acids to CO$_2$, (iii) reduction of essential amino acids, and (iv) decrease in the synthesis of proteins due to limited availability of mRNA [36]. It was also reported that there is a reduction in the protein concentration in serum of diabetic subjects [37], indicative of increased peroxidation of lipids and reduction in the antioxidant defensive system.

The STZ-induced diabetic rats showed a notable rise in plasma TGs and reduction of HDL cholesterol level on day 30 (middle) and day 60 (end) of the experiment (Figure 1A, 1D). This hypertriglyceridemia could be attributed either to VLDL overproduction by the liver or defects in removal of TG-rich lipoprotein (LPL) from the circulation, or both. The latter is explained in pancreative tissue damage was repaired in diabetic rat groups treated with 5,7-dimethoxyflavone at 50 and 100 mg/kg (Figure 2D, 2E, respectively). Treatment with 100 mg/kg 5,7-dimethoxyflavone showed no significant effect on pancreas histology in normal control rats (Figure 2C).

### Discussion

It has been suggested that severe oxidative stress can contribute to onset of diabetic complications [28]. Increased oxidative stress in the diabetic state is due to increased free radical generation or reduced antioxidant defensive responses [29]. Oxidative stress either leads to adaptation or cell injury resulting in DNA damage, along with the degradation of proteins and lipids, the build-up of undesirable molecules, and disturbances in homeostasis at the cellular level [30]. The administration of certain polyphenols and flavonoids in experimental animal diabetic models has been demonstrated to cause a significant reduction in oxidative stress [31]. The substantial production of reactive oxygen species (ROS) lowers the protective physiological moieties such as the reduced form of GSH, ceruloplasmin, vitamin C, and vitamin E in diabetic animals. Treatment of diabetic rats with 5,7-dimethoxyflavone led to an increase in the non-enzymic antioxidants levels and therefore reduction in oxidative stress in diabetic rats, resulting in renewal of GSH levels in the plasma. Non-enzymatic antioxidants like vitamin C and vitamin E that are oxidized get recycled via a substantial reducing capacity contributed to by GSH [32].

The administration of STZ led to a remarkable rise in blood glucose and the reduced insulin and C-peptide levels. Also, 5,7-dimethoxyflavone caused a reduction in blood glucose and a rise in insulin and C-peptide in diabetic rats. 5,7-dimethoxyflavone demonstrated a strong potential to scavenge free radicals and inhibit peroxidation of lipids, preventing STZ-induced oxidative stress and thereby protecting β cells against the ensuing increased secretion of insulin and decline in blood glucose levels. It has also been reported that in STZ-induced diabetic rats, quercetin (a flavonoid) decreases oxidative stress and protects pancreatic β cells by maintaining the membrane integrity of these cells [8]. Increased insulin may also be attributed to the stimulating effect of 5,7-dimethoxyflavone, thereby activating the existing β cells of Langerhans in diabetic rats to secrete increased insulin. C-peptide is synthesized during insulin biosynthesis, and both the peptides (insulin and C-peptide) are then secreted in equimolar ratios to the blood circulation [33]. Thus, an elevation in the levels of C-peptide in STZ-induced diabetic animal models treated with 5,7-dimethoxyflavone show a similar trend as is the case with the enhanced insulin release, thereby possibly restoring the β cells of islets of Langerhans.
by the fact that LPL, a key enzyme for TG removal, is an insulin-dependent enzyme [37,38]. LPL plays a key role in generating HDL cholesterol. Results also indicated that increase in lipolysis of TG-rich lipoproteins increased HDL cholesterol levels, thereby confirming that the relationship between the two is a precursor-product [39,40]. In our study, we observed that 5,7-dimethoxyflavone prevented the rise in serum TGs, TC, and LDL-C. Moreover, 5,7-dimethoxyflavone at both the doses also reduced the hyperlipidemia associated with DM. This effect of the compound was more significant after 1 month and at the end (day 60) of the experiment. Treatment with 5,7-dimethoxyflavone modified the undesirable changes in serum TG, TC, and LDL-C to a significant (P<0.05) extent. Additionally, treatment with 5,7-dimethoxyflavone showed a significant potential to decrease the serum levels of TGs (P<0.05) and LDL-C (P<0.05) and to increase HDL-C (P<0.001) in normal control rats. From the above discussion it can be concluded that the lipid profile, even in the normal control rats, can be normalized by treatment with 5,7-dimethoxyflavone.

Conclusions

5,7-dimethoxyflavone exhibits remarkable anti-diabetic and hypolipidemic effects and may be useful for the management of diabetes. However, more studies are required for further confirmation.

Conflict of interest

None.

References:

1. Dai Ly L, Xu S, Choi SK et al: Oxidative stress and calcium dysregulation by palmitate in type 2 diabetes. Exp Mol Med, 2018; 49(2): e291
2. Zheng Y, Ley SH, Hu FB: Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. Nat Rev Endocrinol, 2018; 14(2): 88
3. World Health Organization: Diabetes mellitus Fact Sheet No. 138, Geneva, Switzerland, WHO. 2002
4. Freund P, Wolff HP, Kühnle HF: (-)-BM 13.0913: A new oral antidiabetic agent that improves insulin sensitivity in animal models of type II (non-insulin-dependent) diabetes mellitus. Metabolism, 1995; 44: 570–76
5. Mans K, Aburjai T: Accessing the hypoglycemic effects of seed extract from Aegle marmelos in alloxan-induced diabetic rats. J Pharm Res Int, 2019; 26: 1–10
6. Ligouri I, Russo G, Curcio F et al: Oxidative stress, aging, and diseases. Clin Interv Aging, 2018; 13: 757–72
7. Fernandez-Alvarez J, Barbera A, Nadal B et al: Stable and functional regeneration of pancreatic beta-cell population in nSTZ-rats treated with tungstate. Diabetologia, 2004; 47: 470–77
8. Coskun O, Kanter M, Korkmaz A, Oter S: Quercetin, a flavonoid antioxidant, prevents and protects streptozotocin-induced oxidative stress and β-cell damage in rat pancreas. Pharmacol Res, 2005; 51: 117–23
9. Talluri MR, Ketha A, Battu GR et al: Protective effect of Aurelia aurita against free radicals and streptozotocin-induced diabetes. Bangladesh Journal of Pharmacology, 2018; 13(3): 287–95
10. Marltim AC, Sanders RA, Watkins J: Effects of α-lipoic acid on biomarkers of oxidative stress in streptozotocin-induced diabetic rats. J Nutr Biochem, 2003; 14: 286–94
11. Thakur P, Kumar A, Kumar A: Targeting oxidative stress through antioxidants in diabetes mellitus. J Drug Target, 2018; 26(9): 766–76
12. Anwar MM, Meki AR: Oxidative stress in streptozotocin-induced diabetic rats: Effects of garlic oil and melatonin. Comp Biochem Physiol Part A Mol Integr Physiol, 2003; 135: 539–47
13. Armstrong AM, Chestnutt JE, Gormley MJ, Young IS: The effect of dietary treatment on lipid peroxidation and antioxidant status in newly diagnosed non-insulin dependent diabetics. Free Radic Biol Med, 1996; 21: 719–26
14. Boege G, Weinstein SF, Albano D et al: Flavonoid intake and risk of pancreatic cancer in male smokers (Finland). Can Epidemiol Biomark Prev, 2008; 17: 553–62
15. Havsteen B: Flavonoids, a class of natural products of high pharmacological potency. Biochem Pharmacol, 1983; 32: 1141–48
16. Harborne JB, Baxter H: The handbook of natural flavonoids. Chichester, UK: John Wiley and Sons, 1999; 1 and 2
17. Juca MM, Cysne Filho FM, de Almeida IC et al: Flavonoids: biological activities and therapeutic potential. Nat Prod Res, 2018 [Epub ahead of print]
18. Li HT, Wu XD, Davey AK, Wang J: Antihyperglycemic effects of baicalin on streptozotocin-nicotinamide induced diabetic rats. Phytother Res, 2011; 25: 189–94
19. Kilkenny C, Browne WJ, Cuthill IC et al: Improving bioscience research reporting: The ARRIVE guidelines for reporting animal research. PLoS Biol, 2010; 8(6): e1000412
20. Park HS, Kim SH, Kim YS et al: Luteolin inhibits adipogenic differentiation by regulating PPARgamma activation. Biofactors, 2009; 35: 373–79
21. Morakinyo AO, Samuel TA, Adekunbi DA: Magnesium upregulates insulin receptor and glucose transporter-4 in streptozotocin-nicotinamide-induced type-2 diabetic rats. Endocr Regul, 2018; 52(1): 6–16
22. Bannon, P: Effect of pH on the elimination of the labile fraction of glycosylated haemoglobin. Clin Chem, 1982; 28: 2183
23. Ellman GL: Tissue sulphydryl groups. Arch Biochem Biophys, 1959; 82: 70–77
24. Baker H, Frank O, DeAngelis B, Feingold S: Plasma tocopherol in man at various times after ingesting free or acetylated tocopherol. Nut Rep Int, 1980; 21: 531–36
25. Omaye ST, Turnbull JD, Sauberlich HE: Selected methods for the determination of ascorbic acid in animal cells, tissues, and fluids. Methods Enzymol, 1979; 62: 3–11
26. Ravin HA: An improved colorimetric enzymatic assay of ceruloplasmin. Trans Res, 1961; 58: 161–68
27. Taghizadeh M, Rashidi AA, Taherian AA et al: The protective effect of hydroalcoholic extract of rosa canina (Dog Rose) fruit on liver function and structure in streptozotocin-induced diabetes in rats. J Diet Suppl, 2018; 15(5): 624–35
28. de Bem GF, Costa CA, Santos IB et al: Antidiabetic effect of Euterpe oleracea Mart. (açai) extract and exercise training on high-fat diet and streptozotocin–nicotinamide induced diabetic rats. Biofactors, 2009; 35: 373–79
29. Xue Y et al.: Anti-diabetic and hypolipidemic effects of 5,7-dimethoxyflavone... © Med Sci Monit, 2019; 25: 9893-9901

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]
31. Kidd PM: Glutathione: Systemic protectant against oxidative and free radical damage. Altern Med Rev, 2007; 2: 155–76
32. Garfinkel AS, Nilsson-Ehle P, Schotz MC: Regulation of lipoprotein lipase: Induction by insulin. Biochim Biophys Acta, 2016; 424: 264–73
33. Wahren J, Ekberg K, Samnegård B, Johansson BL: C-peptide: A new potential in the treatment of diabetic nephropathy. Curr Diab Rep, 2011; 1: 261–66
34. Gumieniczek A: Effects of repaglinide on oxidative stress in tissues of diabetic rabbits. Diabetes Res Clinic Pract, 2005; 68: 89–95
35. Vlassara H, Browne M, Cerami A: Nonenzymatic glycosylation of peripheral nerve protein in diabetes mellitus. Proc Nat Acad Sci USA, 2018; 78: 5190–92
36. Ahmed RG: The physiological and biochemical effects of diabetes on the balance between oxidative stress and antioxidant defense system. Med J Islamic World Acad Sci, 2005; 15: 31–42
37. Mahboob M, Rahman MF, Grover P: Serum lipid peroxidation and antioxidant enzyme levels in male and female diabetic patients. Sing Med J, 2005; 46: 322–24
38. Bellamkonda R, Karuna R, Rao BS et al: Beneficiary effect of Commiphora mukul ethanolic extract against high fructose diet induced abnormalities in carbohydrate and lipid metabolism in Wistar rats. J Tradit Complement Med, 2018; 8(1): 203–11
39. Kshatriya D, Li X, Giunta GM et al: Phenolic-enriched raspberry fruit extract (Rubus idaeus) resulted in lower weight gain, increased ambulatory activity, and elevated hepatic lipoprotein lipase and heme oxygenase-1 expression in male mice fed a high-fat diet. Nutr Res, 2019; 68: 19–33
40. Patsch JR, Gottlo AM, Olivercrona T, Eisenberg S: Formation of high-density lipoprotein2-like particles during lipolysis of very low-density lipoproteins in vitro. Proc Nat Acad Sci USA, 2008; 75: 4519–23

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