Antihyperglycemic and Antihyperlipidemic Effects of Hesperidin and Naringin in High Fat Diet/Streptozotocin Type 2 Diabetic Rats

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Abstract: The purpose of this study was to investigate the effect of hesperidin and naringin on blood glucose, glycosylated hemoglobin and serum insulin levels in high fat fed/streptozotocin-induced type 2 diabetic rats. Also this study evaluated effects of the tested compounds on lipid profile, serum adiponectin and resistin levels, serum cardiac function parameters and liver and muscle glycogen contents. An oral dose of 50 mg/kg b.wt. hesperidin or naringin was given continually for 30 days after diabetes induction. In the diabetic control group, levels of glucose, glycosylated hemoglobin, AST, LDH and CK-MB were significantly increased, while serum insulin level and hepatic and muscle glycogen were decreased. Both hesperidin and naringin supplementation significantly reversed these parameters. In addition, both compounds were found to alleviate lipid profile and serum adiponectin and resistin levels. These results showed that hesperidin and naringin have potential antihyperglycemic and antidyslipidemic activities in high fat fed/STZ-induced type 2 diabetic rats.
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1. Introduction

Diabetes mellitus, a pervasive and multifactorial metabolic syndrome, is characterized by imperfection in insulin secretion and insulin receptor or postreceptor events with derangement in carbohydrate, protein and lipid metabolism and results in chronic hyperglycemia, a clinical hallmark of diabetes (1). Hyperglycemia and hyperlipidemia, as the most common features of diabetes mellitus, contribute to the development of microvascular and macrovascular complications of diabetes, which cause the morbidity and mortality of diabetes (2). In addition, hyperglycemia in diabetic patients is associated with alteration in glucose and lipid metabolism and modification in liver enzyme levels (3). Diabetes mellitus is recognized as a major risk factor for cardiovascular diseases (CVD) such as atherosclerosis, heart attack, stroke etc. About 75% of deaths among men with diabetes and 57% among women with diabetes are attributable to CVD (4).

Adiponectin is a peptide hormone predominantly synthesized and secreted from adipose tissue that modulates a number of metabolic processes, including glucose regulation, fatty acid catabolism, and vascular biology (5,6). In contrast to other adipokines, adiponectin is underexpressed in obese patients with insulin resistance or type 2 diabetes mellitus (T2DM) (7,8), and in patients with coronary heart disease (8). In human subjects, circulating levels of adiponectin are positively correlated with insulin sensitivity (9). Low plasma levels of adiponectin (hypoadiponectinemia) have been observed in several forms of diabetes with insulin resistance, including T2DM, gestational diabetes, and diabetes associated with lipodystrophy (9). Resistin belongs to a family of cysteine-rich secretory proteins called resistin-like molecules (10,11). In rodents, resistin is derived almost exclusively from adipose tissue, and serum resistin is elevated in animal models of obesity and insulin resistance (12,13). Plasma resistin levels were highly positively correlated with TG and apoA-I/apoB ratio, whereas they were inversely correlated with high density lipoprotein (HDL) and apoA-I levels (14). Moreover, the insulin-resistant effects of resistin are thought to account for the activation of glucose 6-phosphotase, which subsequently prevents glycogen synthesis and increases the rate of glucose production (15). These findings suggest that resistin contributes to the development of insulin resistance and atherosclerosis, and thereby is linked to clinical vascular events (16,17).

Nowadays the agents used as the main means for diabetes treatment are synthetic drugs and insulin. However, these drugs usually come with considerable side effects, such as hypoglycemia, drug-resistance, dropsy, and weight gain (18). In contrast, hundreds of traditional folk medicines have demonstrated potential for the treatment of diabetes with less tolerability and side effects. Thus, there is an

increasing need to search for more natural antidiabetic agents from the traditional medicine. Currently, there is much interest in the usefulness of citrus fruits because of their intake appears to be associated with reduced risk of certain chronic diseases and increased survival as reported by **Chen *et al*.** (19). Thus, the present study was designed to evaluate the efficacy of the citrus flavonoids, hesperidin and naringin, on the impaired glucose tolerance, insulin resistance and some biochemical parameters of high-fat diet/streptozotocin induced-diabetic albino rats and to suggest their probable hypoglycemic and hypolipidemic mechanisms of action.

2. Material and Methods:

Chemicals

Hesperidin, naringin and streptozotocin, were purchased from Sigma Chemicals Co., St. Louis, MO, USA, stored at 2-4 °C and protected from sunlight. All other chemicals were of analytical grade and were obtained from standard commercial supplies.

Experimental animals

White male albino rats (*Rattus norvegicus*) weighting about 190±10 g were used as experimental animals in the present investigation. The animals were housed in standard polypropylene cages and maintained under controlled room temperature (22±2 ◦C) and humidity (55±5%) with 12 h light and 12 h dark cycle and were fed a standard diet of known composition, and water *ad libitum*. The animals used in the present study were maintained in accordance with the principles and guidelines of the Canadian Council on Animal Care as outlined in "Guide for the Care and Use of Laboratory Animals" (20).

Development of HFD-fed low dose STZ-treated type 2 diabetic rats

The rats were allocated into two dietary regimens by feeding either normal or high fat diet (HFD) *ad libitum*, for the initial period of 2 weeks (21). The composition and preparation of HFD were described elsewhere (22). After the 2 weeks of dietary manipulation, the group of rats fed by HFD were injected intraperitoneally (i.p.) with low dose of STZ (35 mg/kg b.wt.), while the respective control rats were given vehicle citrate buffer (pH 4.5) in a dose volume of 1 ml/kg, i.p. Seven days after STZ injection, rats were screened for blood glucose levels. Overnight fasted (10-12 hours) animals were given glucose (3 g/kg b.wt.) by gastric intubation. After 2 hours of oral administration, blood samples were taken from lateral tail vein, left to coagulate and centrifuged then serum glucose concentration was measured. Rats having serum glucose ≥ 300 mg/dl, after 2 hours of glucose intake, were considered diabetic and selected for further pharmacological studies. The rats were allowed to continue to feed on their respective diets until the end of the study.

Experimental design

The experimental animals were divided into four groups, each group comprising six rats as detailed follows. Group 1 served as control rats; Group 2 served as diabetic control rats; Group 3 served as diabetic rats administered with hesperidin (50 mg/kg b.wt.) in aqueous suspension orally for 30 days, and Group 4 served as diabetic rats administered with naringin (50 mg/kg b.wt.) in aqueous suspension orally for 30 days. The dosage was adjusted every week according to any change in body weight to maintain similar dose per kg body weight of rat over the entire period of study for each group. By the end of the experiment, animals were sacrificed and blood samples, muscle and liver were obtained.

Biochemical study

On the day before sacrifice, oral glucose tolerance test (OGTT) was performed in normal, diabetic control and diabetic rats treated with hesperidin and naringin. Blood samples were obtained from lateral tail vein of rats deprived of food overnight (10-12 hours). Successive blood samples were then taken at 0, 30, 60, 90 and 120 minutes following the administration of glucose solution (3 g/kg b.w.) through gastric intubation. Blood samples were left to coagulate, centrifuged, and clear non-hemolyzed serum was obtained for determination of glucose concentration according to the method of Trinder (23), using commercial diagnostic kit (Randox laboratories, UK). Serum insulin level was assayed by Sandwich ELISA using kits purchased from Linco Research, USA. Blood glycated Hb was determined according to the method of Little *et al*. (24) using Helena GLYCO-Tek affinity column method (Helena Laboratories, USA). Liver and muscle glycogen contents were assayed according to the method of Seifter *et al*. (25). Serum adiponectin was assayed by Sandwich ELISA using kits of purchased from Linco Research (USA) and serum resistin was assayed using ELISA kits purchased from Biovendor (USA).

Because abnormalities in insulin action are poorly detected by a single determination of glucose or insulin levels (26,27), the insulin resistance was evaluated by homeostasis model assessment estimate of insulin resistance (28) as follows:

HOMA-IR = Fasting insulin level (μU/ml) x Fasting blood glucose (mmol/l)/22.5.

Serum cholesterol (29), triglycerides (30), HDL-cholesterol (29), free fatty acids (31), and liver hydroxymethylglutaryl-CoA reductase activity (32) were estimated. Serum LDL-cholesterol level was calculated from Friedewald (33) formula (LDL-cholesterol = total cholesterol – triglycerides/5 – HDL-cholesterol). Serum vLDL-cholesterol concentration was calculated according to Nobert (34) formula (vLDL-cholesterol = triglycerides/5). Serum aspartate aminotransferase (AST) (35), lactate dehydrogenase (LDH) (36), and Creatine kinase (CK-MB) (37) activities were also estimated. Cardiovascular indices were calculated according to Ross formula (38) as the following: Cardiovascular index 1 = total cholesterol/HDL-cholesterol and Cardiovascular index 2= LDL-cholesterol/HDL-cholesterol.

Statistical analysis

The data were analyzed using the one-way analysis of variance (ANOVA) (39) (PC-STAT, University of Georgia, 1985) followed by LSD test to compare various groups with each others. Results were expressed as mean ± SE and values of $P>0.05$ were considered non-significantly different, while those of $P<0.05$ and $P<0.01$ were considered significant and highly significant, respectively.

Results

The OGTT of diabetic rats showed a highly significant elevation at fasting state and at 30, 60, 90 and 120 min after oral glucose loading as compared to normal animals. The treatment of diabetic animals with hesperidin and naringin induced a potential improvement of elevated values at all points of OGTT curve (Fig. 1).

Table 1 shows the effect of hesperidin and naringin on the levels of fasting serum insulin and blood glycosylated hemoglobin (HbA1c%) in the control and experimental groups of rats. Diabetic group of rats have highly significantly ($p<0.01$; LSD) elevated HbA1c% as compared with normal control group of rats. Oral administration of hesperidin as well as naringin to diabetic rats significantly ($p<0.01$; LSD) improved the altered level. Serum insulin level exhibited an opposite pattern; it was significantly ($p<0.01$; LSD) decreased in diabetic rats as compared to normal ones and was significantly increased as a result of treatment with both hesperidin and naringin. Liver and muscle glycogen contents of HFD/STZ diabetic control rats showed a highly significant decrease (LSD; $P< 0.01$) as compared to normal control. Both treatment agents showed a detectable amelioration of liver and muscle glycogen contents of diabetic rats (Table 1).

HOMA-IR of normal, diabetic and diabetic treated with hesperidin and naringin is depicted in figure 2. Diabetic rats showed a significant ($p<0.01$; LSD) elevation of HOMA-IR that was decreased significantly upon administration of either hesperidin or naringin. However, while both hesperidin and naringin have more or less similar effects, hesperidin seemed to be more effective on serum insulin, blood HbA1c% and HOMA-IR.

Data on the effect of hesperidin and naringin on lipid profile of diabetic rats are presented in Table 2. Diabetic rats exhibited a highly significant increase ($P<0.01$; LSD) in serum cholesterol, triglycerides, LDL- and vLDL-cholesterol and FFAs as compared with the non-diabetic group. Moreover, HDL-cholesterol was affected in an opposite manner, as it was decreased ($P<0.01$; LSD) in diabetic rats and significantly increased ($P<0.01$; LSD) in response to both treatment agents. The administration of both hesperidin and naringin led to marked amelioration of all parameters of the altered lipid profile. Liver HMG-CoA reductase activity, expressed as a ratio of HMG-CoA to mevalonate, was significantly (LSD; $P<0.01$) increased in diabetic rats as compared with the normal control rats. Administration of the two tested agents produced a highly significant (LSD; $P<0.01$) decrease in the enzyme activity as compared with the diabetic group as illustrated in figure 3.

Table 3 depicts the effect of hesperidin and naringin administration on some cardiac function biomarkers in serum of diabetic rats. Serum CK-MB, AST and LDH activities were deleteriously increased (LSD; $P<0.01$) in the diabetic control rats. Moreover, treatment of diabetic animals with both hesperidin and naringin induced a potential alleviation (LSD; $P<0.01$) of these altered parameters; hesperidin seemed to be more effective than naringin in improving serum AST and LDH activities, while the latter showed more potent effect on CK-MB activity. Cardiovascular risk indices 1 and 2 exhibited the same behavioral pattern; they were highly significantly (LSD; $P< 0.01$) increased in HFD/STZ diabetic rats as compared to normal control group. Hesperidin as well as naringin produced remarkable amelioration on these altered parameters (Fig. 4).

Diabetic rats exhibited a highly significant (LSD; $P< 0.01$) decrease in fasting serum adiponectin level as compared with the normal control rats. The administration of both agents showed a marked improvement (LSD; $P< 0.01$) of serum adiponectin concentration (Fig. 5). Administration of HFD and STZ produced a highly significant elevation ($P<0.01$; LSD) of serum resistin as compared with normal rats. The treatment of HFD/STZ diabetic rats with hesperidin and naringin induced a highly significant

amelioration (P<0.01; LSD) of the elevated serum resistin (Fig. 6).

4. Discussion

Type 2 diabetes develops primarily due to insulin resistance and insulin producing pancreatic β-cell dysfunction, leading to insufficient insulin secretion (40-42). The rats fed HFD can result in insulin-resistance mainly through Randle or glucose–fatty acid cycle (43,44). In our study, HFD/STZ diabetic control rats exhibited significantly elevated fasting blood glucose and HOMA-IR, accompanied with diminished serum insulin levels. Hence, it is suggested that insulin resistance has been developed in these animals. Therefore, this rat model exhibits hyperglycemia and insulin resistance that would closely reflect the natural history and metabolic characteristics of humans, and it is further sensitive to pharmacological testing.

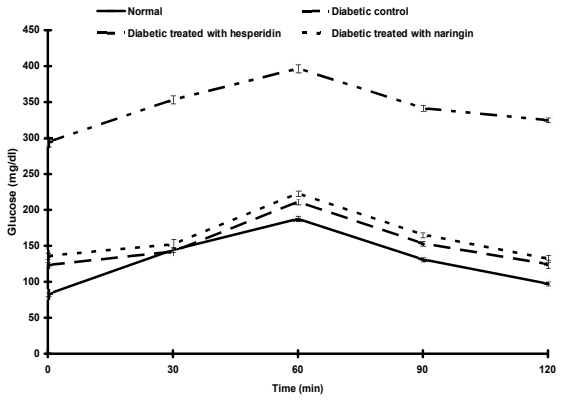

Fig. 1: OGTT of normal, diabetic control and diabetic rats treated with hesperidin and naringin.

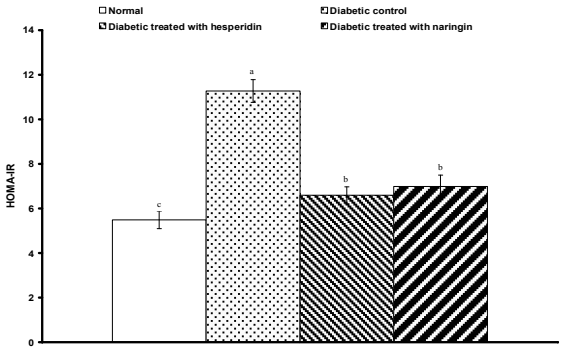

Fig. 2: HOMA-IR index of normal, diabetic control and diabetic rats treated with hesperidin and naringin.

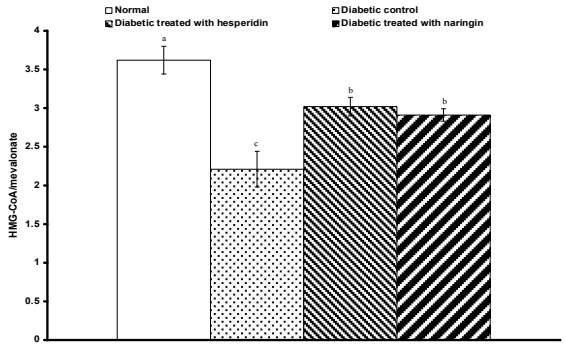

Fig. 3: Liver hydroxymethylglutaryl-CoA reductase activity of normal, diabetic control and diabetic rats treated with hesperidin and naringin.

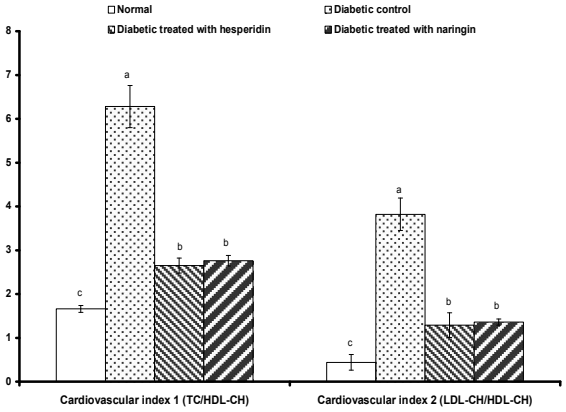

Fig. 4: Cardiovascular risk indices 1 and 2 of normal, diabetic control and diabetic rats treated with hesperidin and naringin.

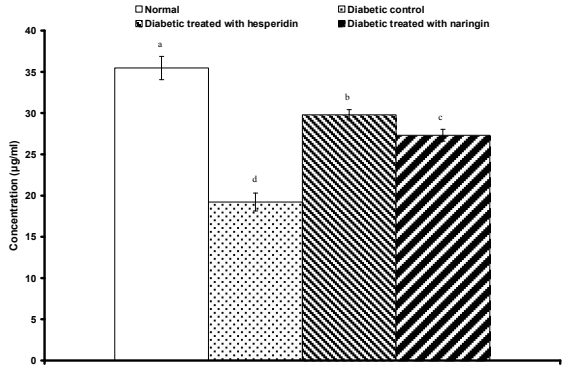

Fig. 5: Serum adiponectin of normal, diabetic control and diabetic rats treated with hesperidin and naringin.

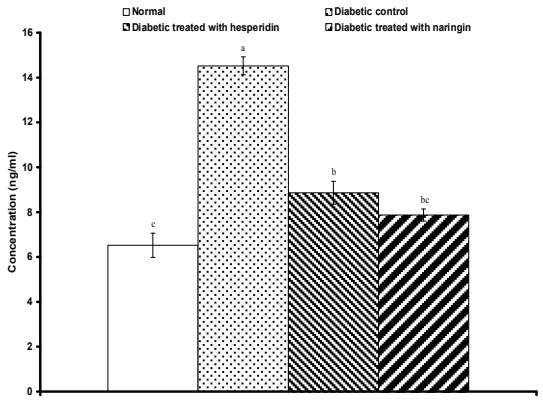

Fig. 6: Serum resistin of normal, diabetic control and diabetic rats treated with hesperidin and naringin.

Table 1: Serum insulin, blood glycosylaed hemoglobin (HbA1c %), and liver and muscle glycogen content of normal, diabetic control and diabetic rats treated with hesperidin and naringin.

Parameter / Group	Insulin (µU/ml)	HbA1c%	Liver glycogen (mg/g tissue)	Muscle glycogen (mg/g tissue)
Normal	26.84 ± 1.40[a]	4.71 ± 0.18[d]	22.81 ± 1.86[a]	4.98 ± 0.22[a]
Diabetic control	15.50 ± 0.76[c]	8.96 ± 0.23[a]	11.95 ± 0.77[c]	2.03 ± 0.22[c]
Diabetic treated with hesperidin	21.55 ± 1.13[b]	5.85 ± 0.18[c]	19.33 ± 1.25[b]	3.49 ± 0.18[b]
Diabetic treated with naringin	20.67 ± 1.08[b]	6.26 ± 0.17[b]	17.38 ± 1.14[b]	3.49 ± 0.36[b]
F- prob	P< 0.001	P< 0.001	P< 0.001	P< 0.001
LSD at 5%	2.32	0.40	2.74	0.53
LSD at 1%	3.17	0.54	3.73	0.72

- Data are expressed as Mean ± SE. Number of animals in each group is six.
- Means which share the same superscript symbol (s) are not significantly different.

Table 2: Lipid profile of normal, diabetic control and diabetic rats treated with hesperidin and naringin.

Parameter / Group	Total Cholesterol (mg/dl)	Triglycerides (mg/dl)	HDL-cholesterol (mg/dl)	LDL-cholesterol (mg/dl)	vLDL-cholesterol (mg/dl)	Free fatty acids (mmol/L)
Normal	67.92±3.35[c]	56.84±2.51[c]	39.18±1.37[a]	17.38±1.77[c]	11.03±0.80[c]	0.57±0.07[c]
Diabetic control	199.90±5.05[a]	193.17±3.28[a]	26.87±1.71[c]	101.19±5.43[a]	38.50±1.79[a]	1.68±0.06[a]
Diabetic treated with hesperidin	93.10±2.38[b]	82.68±2.58[b]	33.19±1.65[b]	42.77±1.71[b]	15.97±1.22[b]	0.92±0.10[b]
Diabetic treated with naringin	98.34±3.77[b]	85.71±2.96[b]	33.77±1.53[b]	46.16±3.14[b]	16.24±1.72[b]	1.04±0.12[b]
F- prob	P< 0.001	P< 0.001	P< 0.001	P< 0.001	P< 0.001	P< 0.001
LSD at 5%	7.84	5.93	3.27	7.02	3.00	0.18
LSD at 1%	10.69	8.09	4.46	9.57	4.09	0.25

- Data are expressed as Mean ± SE. Number of animals in each group is six.
- Means which share the same superscript symbol (s) are not significantly different.

Table 3: Heart function variables of normal, diabetic control and diabetic rats treated with hesperidin and naringin.

Parameter / Group	AST (U/L)	LDH (U/L)	CK-MB (U/L)
Normal	33.62 ± 1.49[c]	171.86 ± 5.71[d]	111.74 ± 4.52[d]
Diabetic control	95.03 ± 5.24[a]	276.74 ± 7.96[a]	262.24 ± 5.24[a]
Diabetic treated with hesperidin	45.07 ± 1.60[b]	196.05 ± 3.84[c]	180.65 ± 5.08[b]
Diabetic treated with naringin	46.79 ± 2.20[b]	210.66 ± 6.43[b]	168.63 ± 4.45[c]
F- prob	P< 0.001	P< 0.001	P< 0.001
LSD at 5%	6.35	13.52	10.25
LSD at 1%	8.66	18.44	13.98

- Data are expressed as Mean ± SE. Number of animals in each group is six.
- Means which share the same superscript symbol (s) are not significantly different

In the diabetic animals, the present data indicate a marked increase in serum glucose levels as compared to normal rats. These results run parallel with the studies of Schalaan *et al*. (45) and Ahmed *et al*. (46). Administration of STZ caused rapid destruction of pancreatic β-cells in rats, which led to impaired glucose stimulated insulin release and insulin resistance, both of which are marked features of T2DM (47). Elevation of blood glucose may be attributed to reduced entry of glucose to peripheral tissues, muscle and adipose tissue (48), increased glycogen breakdown (49) and increased gluconeogenesis and hepatic glucose production (50). Furthermore, Powers (51) stated that insulin resistance in T2DM causes elevation in blood glucose due to the same reasons. From another point of view, the hyperglycemia observed in our study could be explained through glucose–fatty acid cycle (52), where the high FFAs reduce the glucose uptake and utilization, through the increased endogenous glucose production (53). The present data demonstrated that the treatment of diabetic rats with either hesperidin or naringin caused a potential amelioration of glucose tolerance. Decrease in the elevated serum glucose levels is in agreement with the results of Jung *et al*. (54) who recorded the hypoglycemic effect of hesperidin and naringin in C57BL/KsJ-db/db mice. Moreover, Pari and Suman (55) reported the hypoglycemic effect of naringin in STZ/nicotinamide diabetic rats and Akiyama *et al*. (56) showed the glucose lowering effect of hesperidin in type 1 diabetic rats.

The observed increase in the levels of glycosylated hemoglobin in diabetic control group rats is due to the presence of excessive amounts of blood glucose. During diabetes the excess of glucose present in blood reacts with hemoglobin to form glycosylated hemoglobin (57). Estimation of HbA1c has been found to be particularly useful in monitoring the effectiveness of therapy in diabetes (58). In our study, oral administration of hesperidin and naringin significantly decreased the levels of fasting blood glucose and HbA1c. These results indicated the beneficial effects of both hesperidin and naringin in preventing the pathogenesis of diabetic complications caused by impaired glucose metabolism.

In comparison with the normal control rats, the present study revealed a highly significant decrease in fasting insulin level of HFD/STZ diabetic rats. We hypothesize that the possible mechanism of hesperidin and naringin on hypoglycemic action may be through potentiating pancreatic secretion of insulin from β-cell of islets and/or due to enhanced transport of blood glucose to the peripheral tissue or by other mechanisms such as stimulation of glucose uptake by peripheral tissue, inhibition of endogenous glucose production or activation of gluconeogenesis in liver and muscles. By their ability to scavenge free radicals hesperidin (59) and naringin (60) prevent STZ-induced oxidative stress and protects β-cells resulting in increased insulin secretion and decrease in the elevated blood glucose levels. In this context, research by Pari and Suman (55), have shown that, naringin decreased the elevated blood glucose concentration and increased the insulin release in STZ-induced diabetic rats. Also, Akiyama *et al*. (56) reported that, in STZ-induced diabetic rats, hesperidin decreased blood glucose and increased serum insulin levels.

Liver glycogen level may be considered as the best marker for assessing antihyperglycemic activity of any drug (61). The increased hepatic glucose output in diabetes may be derived from glycogenolysis and/or gluconeogenesis as reported by Raju *et al*. (50). In general, increased hepatic glucose production, plus decreased hepatic glycogen synthesis and glycolysis, are the major symptoms in type 2 diabetes that result in hyperglycemia (54). Our results revealed an enormous depletion in hepatic and muscle glycogen contents. These results are in accordance with those of Lavoie and Van de Werve (62) and Ahmed *et al*. (46) who found that STZ-induced diabetes reduced hepatic glycogen content and increased glucose-6-phosphatase activity in diabetic rats. These results are also in agreement with the work of Grover *et al*. (61) and Pari and Suman (55) who demonstrated that decreased enzymatic activity of hexokinase has also been reported in diabetic animals, resulting in depletion of liver glycogen. These changes are obviously due to insulin deficiency, which in turn results in the activation of glycogenolytic and gluconeogenic pathways (63). The elevation of liver glycogen content in the present investigation after treatment with hesperidin and naringin is due to ameliorations of these altered enzyme activities secondary to the increase of insulin levels in the blood.

It is reported that diabetes is associated with profound alterations in lipid and lipoprotein profile (64). Changes in concentrations of plasma lipids including cholesterol and lipoprotein are complications frequently observed in patients with diabetes mellitus and certainly contributes to the development of coronary heart disease (CHD) in these patients (65). In addition, Keenoy *et al*. (66) and Ravi *et al*. (67) revealed that the abnormalities in lipid metabolism generally lead to elevation in the levels of serum lipids and lipoproteins that in turn play an important role in the occurrence of premature and severe atherosclerosis, which affects patients

with diabetes. In the present study, the rise in blood glucose was accompanied with a marked increase in TC, LDL-C, TG and reduction in HDL-C in HFD/STZ diabetic rats. These results are in agreement with the findings of Tan *et al*. (68) and Zhang *et al*. (69) who reported increased serum TG, TC and LDL-C in HFD fed STZ-induced diabetic rats. On the other hand, HDL-C revealed a different behavioral pattern where it was detectably lowered in the diabetic rats. Serum HDL-C was found to be declined in HFD/STZ type 2 diabetic rats as reported by Tan *et al*. (68) and Schalaan *et al*. (45) and in STZ/NA type 2 daibetic rats as showed by Ahmed *et al*. (46). Treatment of HFD/STZ diabetic rats with hesperidin and naringin produced great improvement of the altered serum lipid variables. These results are in agreement with the work of Gorinstein *et al*. (70) who found that hesperidin and naringin supplementation significantly increased HDL and lowers TC, LDL, total lipids and TG plasma levels in rats fed a cholesterol-containing diet. The decrease of LDL levels may occur due to the reduction of vLDL and the increase of hepatic depuration of LDL precursors (71). Both hesperidin and naringin significantly ameliorated serum HDL-C in HFD/STZ diabetic rats. That is an advantage, since HDL-C is responsible for the transportation of cholesterol from peripheral tissues to the liver for metabolization. Both agents thus have the potential to prevent the formation of atherosclerosis and coronary heart disease which are the secondary diabetic complications of severe diabetes mellitus.

In the HFD/STZ diabetic group, the elevated serum FFA level obtained in this work is in agreement with that estimated in many previous studies (72,73). Several mechanisms of how elevated FFA levels decrease insulin sensitivity have been proposed, including the Randle hypothesis concerning inhibition of insulin-stimulated glucose transport. It also should be noted that FFAs regulate gene expression, especially those involved in lipid and carbohydrate metabolism (74). Chronically elevated FFAs may also impair insulin secretory function through toxic effects on pancreatic β-cells as predicted by the "lipotoxicity hypothesis" (75). Finally, increased flux of FFAs from adipose tissue due to lipolysis of visceral adipose depots to the non-adipose tissue (e.g., liver, skeletal muscle) may lead to excessive endogenous glucose production and progression to frank type 2 diabetes (76). Therefore, decreasing plasma FFA level is proposed as a strategy for prevention and treatment of insulin resistance as stated by Na *et al*. (77). Upon treatment of the diabetic animals with hesperidin and naringin there was a decreased level of serum FFA which may participate in the insulin sensitizing effects of both tested compounds. Also, the ability of scavenging free radicals and antioxidant properties of both agents may also participates in the hypolipidemic activity of both treatments by inactivating hepatic HMG-CoA reductase, a key enzyme, in cholesterol synthesis according to Raz *et al*. (78) who stated that inhibitors of hepatic HMG-CoA reductase are well established drugs for the treatment of hypercholesterolemia and decrease the incidence of dyslipidemia in diabetic subjects.

Diabetic dyslipidemia has long been shown to have a strong relation with CHD (65) which is the most dangerous and life threatening complication of diabetes and the risk for CHD in diabetes increases two or more folds (79). Increased TG and TC levels and decreased HDL-C represent a displayed lipid profile known as atherogenic profile which leads to the development of CHD (80). As favorable effect on lipid profile was observed following treatment with both hesperidin and naringin, this indicated that both agents might help to prevent the progression of cardiovascular diseases. In addition, several atherogenic indices such as TC/HDL-C and LDL-C/HDL-C have been used to predict CHD risk (81). Reduction of these indices in hesperidin and naringin supplemented diabetic rats strongly supported the notion that dietary supplementation with either hesperidin or naringin may lead to reduction in the risk of developing heart diseases. Also, there is some evidence to suggest that flavonoids can be incorporated into lipoprotein within the liver or intestine and subsequently be transported within the lipoproteins particle. Therefore flavonoids may be ideally located for protecting LDL from oxidation (54). Moreover, flavonoid consumption was inversely associated with mortality from CHD. Relative risks for CHD mortality and first myocardial infarction were approximately 50% lower in the highest tertile of flavonoid intake (82).

Our study revealed a significant increase in serum resistin level in HFD/STZ diabetic group in comparison with that of controls, which runs parallel to serum glucose levels, insulin levels and HOMA-IR index. The findings of this study are in line with that of Kushiyama *et al*. (83), who found that transgenic mice with hepatic resistin overexpression exhibit significant hyperglycemia, hyperlipidemia, fatty liver, and pancreatic islet enlargement, when fed a HFD. These effects may be due to resistin-induced impairment of glucose homeostasis and insulin action, thus modulating one or more steps in the insulin signaling pathway and possibly playing a role in the pathogenesis of insulin resistance (84).

The mechanism whereby resistin decreases insulin sensitivity involves several impacts. First, resistin reduces adenosine 5′-monophosphate

activated protein kinase activity in skeletal muscle, adipose tissue, and liver. These alterations decrease tissue insulin sensitivity that results in glucose intolerance, elevated FFA levels, and hypertriglyceridemia (15). Secondly, the resistin-induced reduction in IRS-1 and IRS-2 elevates mRNA levels of gluconeogenetic enzymes, such as glucose-6- phosphatase and phosphoenolpyruvate carboxykinase, thus suggesting a direct resistin induction of insulin resistance in the liver (85). Thirdly, resistin decreased glycogen synthase (GS) activity both in the presence or absence of insulin; this suggests that resistin directly down-regulates GS activity (86). Furthermore, it was reported that resistin promotes lipid accumulation in human macrophages by up-regulating CD36 cell surface expression, which is one of the scavenger receptors in macrophages involved in the uptake of modified LDL (87). Based on the current data, the resistin lowering effect of hesperidin and naringin may directly participate to their hypoglycemic and hypolipidemic effects.

In contrast to resistin, HFD/STZ diabetic rats exhibited diminished serum adiponectin level and treatment with either hesperidin or naringin significantly alleviated serum adiponectin. Serum levels of adiponectin are found to be in agreement with insulin sensitivity and the reduced levels of which are associated with the etiology of T2DM and obesity (88). Also, adiponectin has been reported to sensitize the body tissues toward actions of insulin. The proposed mechanism of action for adiponectin include [1] its insulin sensitizing effect which in turn regulates glucose metabolism through stimulation of AMPK (89) [2] enhanced oxidation of muscle fat and glucose transport mediated through AMPK activation and acetyl-CoA carboxylase inhibition (90) [3] inhibition of hepatic gluconeogenesis through decrease in the expression of phosphoenolpyruvate carboxylase and glucose-6-phosphatase (89), and [4] increased fatty acid combustion and energy consumption, partly through peroxisome proliferator activated receptor-α activation, leading to decreased TG content in skeletal muscles and liver (5). Moreover, it has been shown that mice lacking adiponectin expression have reduced insulin sensitivity or are more likely to suffer from insulin resistance (91). Though, the insulin sensitizing effects of the tested flavonoids are mediated partly via increasing serum adiponectin level.

Taken together, it can be concluded that the ameliorative effect of hesperidin and naringin on carbohydrate and lipid variables may be attributed to their insulin releasing capacity, lipid lowering effect, and ameliorating the altered adiponectin and resistin levels.

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