Comparative Physiological Study of the Protective Effects of Green Coffee and Berberine Extracts in Male Rats with Induced Diabetes

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***Abstract*—** Diabetes mellitus (DM) is a chronic disorder of carbohydrate metabolism characterized by abnormal persistent state of hyperglycemia which is associated with lipid metabolic disorders and oxidative stress.This study aimed to compare the effects of green coffee bean extract (GCBE) and berberine for the amelioration of STZ-induced hyperglycaemia in male adult rats. Thirty adult male rats were used and divided randomly into six experimental groups (5 rats/group) as follows: control, cloud of strep /streptozotocin-induced diabetes group, berberine treated group alone, green coffee-treated group alone, streptozotocin + berberine-treated group and streptozotocin + green coffee (Coffea arabica)-treated groups. Experimental diabetes was induced using streptozocin (45 mg/kg body weight). Diabetes was defined as fasting blood glucose ≥ 200 mg/dl after 48 hours. The oral treatment lasted for a period of 8 consecutive weeks.

The biochemical analysis included blood glucose, lipid profile parameters and oxidative stress biomarkers (malondialdehyde (MDA) & glutathione(GSH&& superoxide dismutase(SOD)). The findings revealed that diabetic rats induced by STZ showed increased hyperglycemia, dyslipidemia and oxidative stress as compared to control. The administration of GCBE and berberine also improved most of the biochemical parameters. Green coffee extract exhibited more pronounced antihyperglycemic and antioxidant activities as compared to the cholesterol-lowering effect of berberine.

***Keywords* —** green coffee, lipids, berberin, rats.

INTRODUCTION

Diabetes mellitus (DM) is, in fact, the third most common chronic metabolic disease globally (1), and health care challenge characterized by its increasing prevalence as well as serious complications over longer duration. Diabetes is a group of diseases that result in high blood sugar (too much glucose in the blood.) The cause of diabetes depends on the specific type. lipid and protein metabolism.Chronic hyperglycemia is associated with many chronic pathological complications (2).

Objective oxidative stress is an established pathogenetic mechanisms that are increasingly being recognized with the progression of diabetes mellitus and its complications. In a hyperglycaemic milieu, hyperglycemia causes overproduction of ROS (reactive oxygen species) which, in turn, leads to enhanced lipid peroxidation followed by mitochondrial dysfunction, cell injury (3), and the depletion of cellular antioxidant machinery (4). While malondialdehyde (MDA), a well-established marker of lipid peroxidation and oxidative tissue damage, is an exogenous mutagen(5).Glutathione (GSH) and superoxide dismutase (SOD), the principal free radical scavengers in biological systems maintaining cellular redox homeostasis from many pathological stresses, consist major endogenous antioxidant defenses (6).

Experimentally induced diabetes using streptozotocin (STZ) is established as one of the most reproducible experimental models for studying aspects of diabetic pathophysiology and testing antidiabetic drug candidates (7). Streptozotocin is a nitrosourea compound that specifically concentrates in pancreatic β-cells, through glucose transporter-2 (GLUT-2), and damages the cells resulting in loss of insulin-dependent hyperglycemia(8). In addition, dyslipidemia and an oxidative stress state changes as seen in human diabetes mellitus have also been indicated in STZ-induced diabetes (9).

Increased incidence of type 2 diabetes mellitus has gained more interest in natural products, with several plant derived compounds currently under development or approved as adjunctive therapies for glucose homeostasis regulation due to their antioxidant and metabolic regulatory activities. Green coffee bean extract (GCBE) attracts attention because of its high contents of chlorogenic acid, caffeine and polyphenolic compounds with possible antioxidant and metabolic activity(10). Many mechanisms have been proposed including inhibition of intestinal glucose absorption, reduction of hepatic gluconeogenesis and increases in glucose utilization(11). Moreover, it is also conceivable that the action of green coffee is due to its scavenging activity against free radicals and increase attainment of endogenous antioxidant(12).

Berberine (BBR), a bioactive isoquinoline alkaloid, can be extracted from over 20 traditional medicinal plants and

has been one of the most studied compounds with diabetic antihyperglycemic and hypolipidemic properties (13). In two of our recent studies, we demonstrated that berberine ameliorated dyslipidaemia and hyperglycemia through multiple mechanisms including the activation of AMP-activated protein kinase (AMPK) enhancement of glucose uptake in peripheral tissues suppression of hepatic glucose output, and modulation of lipo-metabolic pathways. Thus, the action of berberine might also be due to antioxidant and anti–inflammatory effects that potentially prevent diabetic complications (14,15).

Comparative studies comparing the physiological and biochemical effects of green coffee extract and berberine in diabetic conditions are scant even though several studies investigated the positive role of both on diabetes. Therefore the present study was performed to compare the modulatory effects of green coffee bean extract and berberine supplementation on serum blood glucose, lipid profile parameters and oxidative stress markers in streptozotocin diabetic male rats(16).

MATERIALS AND MTHODS

Experimental Animals and Ethical Considerations

After acclimatization, the animals were assigned randomly to six experimental groups (5 rats/group) as follows: control group: rats were administered with normal saline and served as negative control group; streptozotocin (STZ) group; STZ-induced diabetic rats; berberine group : non-diabetic rats received berberine; green Coffee group: non diabetic rats treated by green coffee bean extract; STZ + Berberine group: treated with berberine diabetic rats; STZ + Green Coffee group; STZ-induced diabetic rats administered with green coffee bean extract. all procedures must have been approved by the appropriate institutional animal care and ethics committee: UOK.VET.PH.2025.145.

Induction of Diabetes Mellitus

Diabetes was induced with a single intraperitoneal injection of streptozotocin (STZ) 45 mg/kg BW after an overnight fast. In order to keep the stability and effectiveness of stretzotocin, it was freshly prepared in chilled citrate buffer (pH 4.5) just prior to injection. The dose was selected according to previous reports of successful induction of diabetes mellitus in experimental rats (6).

Fasting blood glucose levels were assessed through tail vein blood samples collected 48 h after STZ administration. Diabetic rats were defined as those displaying fasting blood glucose levels 200 mg/dl or over and included in the experimental experiment (3).

Preparation and Administration of Treatments

Berberine was given orally at a total dose of 25 mg/kg body weight daily for the entire duration of study. An extract from green coffee bean (GCBE) was given orally at 400 mg/kg body weight/ day for 8 continuous weeks. The doses chosen were based on previous studies showing relevant antioxidant and antidiabetic activities (13).

The green coffee extract used in this study was prepared from unroasted coffee beans with high content of chlorogenic acid, caffeine and other polyphenolic compounds. The decoction was prepared using standardized laboratory planned cold water extraction methods and the other extract preparations, i.e., filtration through 90–120_ mm diameter filter papers, followed by concentration under pressure.

Sample Collection

Animals were allowed to fast overnight before blood collection at the end of the experimental period. They collected fasting blood samples in the morning under identical laboratory conditions. Blood samples were centrifuged to separate serum and stored at appropriate temperatures until biochemical examination.

Biochemical Parameters

Glucose metabolism was assessed by measuring serum glucose levels to evaluate hyperglycemia as well as the effect of treatment on improving glucose metabolism. The determination of lipid profile parameters;Total cholesterol;Triglycerides; Low-density lipoprotein cholesterol (LDL-C); High-density lipoprotein cholesterol (HDL-C).

Biomarkers of oxidative stress and antioxidants comprised:

Malondialdehyde (MDA) like marker for lipid peroxidation; GSH as an endogenous antioxidant; Superoxide dismutase (SOD) activity as a marker of antioxidant enzymatic defense

Statistical Analysis

The acquired data were represented as mean ± standard deviation (Mean ± SD). Statistical Package for Social Sciences [SPSS] version 26 was used to perform data analysis. Differences between experimental groups were evaluated using one-way analysis of variance (ANOVA) and, when appropriate, post hoc analyses. All differences were statistically significant at $p \leq 0.05$.

RESULT AND DISCUSSION

In the present study, streptozotocin treatment induced severe hyperglycemia during the 72 hour experimental period supporting a diabetic state. Table (1) shows that the blood glucose levels of diabetic rats were significantly higher than those of the controls at all experimental time intervals. Eight weeks later, blood glucose levels in the STZ group was 136.3 ± 13.01 mg/dl while 100.2 ± 4.43 mg/dl in the control group, denoting successful induction of pancreatic β-cell dysfunction and impairment of glucose homeostasis ($p < 0.05$).

Table 1. Effect of Green Coffee and Berberine on Blood Glucose levels

Groups	Blood Glucose(mg/dl) after 2 days of treatment Mean ±SD	Blood Glucose(mg/dl) after 4 weeks of treatment Mean ±SD	Blood Glucose(mg/dl) after 8 weeks of treatment Mean ±SD
Control	108.6 ±14.05 b	102.8±6.01 7 b	100.2±4.43 8 b
Streptozotocin	147.6±14.2 6 a	143.7±4.50 9 a	136.3±13.0 1 a
Berberine	122.8±7.26 b	102.2±12.2 8 b	109.0±7.34 8 b
Streptozotocin+	148.2±26.4 7 a	126.8±13.0 5 a	120.0±13.8 3 a

Berberine			
Green Coffee	104.0±7.550 b	86.20±5.070 b	84.60±9.182 b
Streptozotocin+ Green Coffee	157.8 ± 8.139 a	121.3±2.082 b	112.3±5.859 b

The hyperglycemia found after STZ administration can be explained by a selective cytotoxic effect towards pancreatic β-cells on the part of streptozotocin. Streptozotocin (STZ) selectively enters the β-cells via glut-2 transporters and induces DNA alkylation, oxidative stress, mitochondrial dysfunction, and necrotic cell death ultimately causing insulin deficiency and sustained hyperglycemia (3,8). This result were in agreement with other reports showing a marked increase in blood sugar level after STZ -induced diabetes in experimental rats (16).

Interestingly, the nontreated STZ group experienced a gradual decline in glucose levels across the experimental period. This observation could be attributed to some degree of pancreatic adaptation, residual β-cell activity or metabolic compensatory response seen sporadically in experimental diabetic models. Analogous observations have previously been documented in STZ-diabetic rats and may results from heterogeneity in the extent of pancreatic damage produced by streptozotocin (17).

Both green coffee bean extract and berberine treatment led to significant improvements in blood glucose levels, but the effects were not identical for each of these treatments. The most potent antihyperglycemic effect was observed with green coffee extract, especially in GCBE-administered diabetic rats where blood glucose levels were reduced to approximately 112.3 ± 5.85 mg/dl by the end of eight weeks.

Green coffee extract has been reported to show antihyperglycemic activity possibly due to its high content of chlorogenic acid, caffeine and polyphenolic compounds. According to previous studies, chlorogenic acid reduces intestinal glucose absorption, suppresses hepatic gluconeogenesis and other processes by producing neuroprotective effects (18). Furthermore, caffeine may modulate glucose metabolism via effects on energy expenditure and antioxidant activity, while polyphenolic compounds are also thought to contribute by direct quenching of reactive oxygen species that can stimulate oxidative stress-induced pancreatic injury (5). Furthermore, the antioxidant features of inexperienced espresso might also additionally shield leftover pancreatic β-cell feature underneath diabetic conditions.

Berberine has been shown to lower blood glucose in diabetic rats as well, though it was clearly less effective than green coffee extract. BER works as an effective treatment for diabetic rats which had glucose levels of 120.0 ± 13.83 mg/dl after eight weeks. The mechanisms behind the antidiabetic activity of berberine likely result from activation of AMP-activated protein kinase (AMPK), a central regulator in glucose uptake, cellular energy metabolism and hepatic glucose production (5,19).

The more potent antihyperglycemic effect resulted from green coffee extract in this study may be due to its strong antioxidant property as it, in turn, reduced oxidative damage caused by hyperglycemia. Because oxidative stress depletes glucose metabolism and damages the pancreas, antioxidant-rich compounds can offer more protection against diabetic conditions [22,24].Current work is in line with Chen et al. (14) that showed green coffee supplementation significantly improved blood glucose regulation via modulation of glucose metabolism. Similarly, Xie et al. One recent study (15) documented that berberine has glucose lowering properties through the activation of AMPK-dependent pathways and regulation of glucose metabolic homeostasis.

In the current study, it was shown that streptozotocin-induced diabetes led to obvious disturbances of lipid metabolism which are indicated by increased levels of serum cholesterol, triglycerides and LDL-C, while HDL-C level was decreased compared with control values. These results validate the onset of diabetic dyslipidemia, one of the predominant metabolic disorders seen with diabetes mellitus.
STZ treated group revealed a marked rise ($p < 0.01$) of serum cholesterol level at week eight (211.3 ± 18.42 mg/dl) compared to control group (167.2 ± 9.67 mg/dl). In diabetic rats, triglyceride values were also significantly higher than in the control animals (222.3 ± 9.92 mg/dl vs 199.3 ± 3.92 mg/dl). The concentration of LDL-C increased significantly, but HDL-C levels were decreased significantly in the diabetic group.

Table 2. Effect of Green Coffee and Berberine on lipid profile Levels in Diabetic Rats.

Groups	**Cholesterol level (mg/d) Mean ±SD**	**Triglyceride levels(mg/dl) Mean ±SD**	**LDL-C (mg/d) Mean ± SD**	**HDL-C (mg/d) Mean ± SD**
Control	167.2±9.676 b	199.3±3.921b	36.26±1.873 b	111.1±6.848 a
Streptozotocin	211.3±18.42 a	222.3±9.923 a	50.98±6.832 a	83.94±3.590 b
Berberine	145.9±6.353 c	186.4±4.299 c	32.33±2.257 b	111.6±5.497 a
Streptozotocin+ Berberine	171.8±9.030 b	206.3±1.219 b	37.16±1.379 b	98.58±3.310 a
Green Coffee	145.0±7.824 c	183.7±11.03 c	29.72±1.331 c	108.2±8.420 a
Streptozotocin+ Green	172.5±5.620 b	204.8±1.611 b	36.18±2.239 b	99.47±3.201 a

Coffee				

The dyslipidemia that was seen might be due to either insulin deficiency or impaired glucose metabolism induced by streptozotocin administration. Insulin typically balances lipid metabolism by activating lipoprotein lipase and inhibiting hormone-sensitive lipase. Consequently, insulin deficiency promotes lipolysis and release of free fatty acids from adipose tissue to liver increasing hepatic triglycerides and cholesterol synthesis(1,17). In addition, oxidative stress associated with hyperglycemia can further damage lipid metabolism and strengthen lipid peroxidation, so that LDL-C level was increased, while HDL-C level was decreased.

Both green coffee bean extract and berberine treatment significantly improved the profiles of several lipid profile parameters in diabetic rats as well as non-diabetic rats, suggesting that lipids are potential therapeutic targets for this supplement. Hypolipidemic potentialGreen coffee extract showed significant hypolipidemic activity (with respect to LDL-C) as it decreased the levels of LDL-C to 36.18 ± 2.239 mg/dl in the STZ + Green Coffee group compared with 50.98 ± 6.832 mg/dl in untreated diabetic group (12). Likewise, green coffee treatment significantly reduced serum cholesterol and triglyceride levels.

The lipid-lowering activities of green coffee extract are likely linked to chlorogenic acid, caffeine and antioxidant polyphenols found in green coffee beans. Chlorogenic acid has been shown to inhibit liver lipid formation and stimulate fatty acid degradation, thus leading to improvement of lipid metabolism (14,16). The results of the studies indicate that coffee polyphenols have antioxidant activities, and reduce oxidative modification of lipoproteins, therefore improving hepatic metabolic function. Caffeine is also associated with an improvement in lipid oxidation and energy expenditure (12).

Treatment with berberine also showed significant improvement in lipid profile parameters. In diabetic rats, berberine-treated groups showed below normal serum cholesterol, triglycerides and LDL-C levels while HDL-C concentration increased partially. These results are in accordance with previous studies, which showed that berberine had hypolipidemic effects (20).

The lipid-lowering effects of berberine have been attributed primarily to the activation of AMP-activated protein kinase (AMPK), an important regulator of lipid metabolism, which inhibits hepatic lipogenesis and stimulates fatty acid oxidation (5). Berberine has also been shown to increase hepatic LDL receptor expression, which clears LDL from circulation and decreases serum LDL-C (16). In addition, under the diabetic condition, it has also been shown that berberine could decrease cholesterol absorption in the intestine and restore glucose and lipid homeostasis .Specifically, the present results suggest that green coffee extract has a somewhat stronger effect on lowering LDL-C than berberine, but that berberine broader modulated general lipid metabolism. Such differences are possibly related to the different mechanisms of action and antioxidant capacities of these two vitamins. The activity of green coffee is mainly through antioxidant and polyphenolic pathways, while berberine has a wider intracellular metabolic regulatory effect (involving AMPK signaling pathways) compared with green coffee (21)

Potential mechanism for the decrease of HDL-C in diabetic rats is related with oxidative stress and altered lipoprotein metabolism which accompanies diabetes mellitus. The increase of HDL-C levels after treatment can reflect improvement in lipid transport and antioxidant defense mechanisms. HDL particles with their antioxidant and anti-inflammatory properties may impair diabetic processes responsible for resultant cardiovascular complications (22).

These findings are consistent with the previous study by AlAmri et al. (16),who found that green coffee extract had serious improvements in terms of lipid metabolism and oxidative stress on diabetic rats. Similarly, Utami et al. (5) and Xie et al. Berberine has also been shown to modulate lipid metabolic pathways resulting in decreased cholesterol and triglyceride levels (15).

In this work, the data showed that streptozotocin-induced diabetes produced dose-dependent oxidative stress as indicated by increased malondialdehyde (MDA) levels and decreased glutathione (GSH) concentration and superoxide dismutase (SOD) activity relative to control group. These changes are associated with overproduction of reactive oxygen species (ROS) and/or impairment of antioxidant defence systems in diabetes rats.

Table 3. Effect of Green Coffee and Berberine on Oxidative Stress Levels in Diabetic Rats

Groups	GSH (ng/ml) Mean ±SD	SOD(U/ml) Mean ±SD	MDA (nmol/ml) Mean ±SD
Control	423.9±44.81 a	3917±318.6 a	87.35±16.21 c
Streptozotocin	167.2±32.46 c	830.4±349.3 c	281.3±40.72 a
Berberine	433.1±55.52 a	4045±518.0 a	88.28±8.426 c
Streptozotocin+ Berberine	289.3±63.02 b	2245±737.6 b	187.9±34.56 b
Green Coffee	453.2±61.85 a	4221±617.0 a	77.74±21.06 c
Streptozotocin +Green Coffee	326.5±27.44 b	2548±606.7 b	187.3±31.50 b

Malondialdehyde is one of the principal end-products of lipid peroxidation in aa a significant biomarker for oxidative cellular injury. As the STZ-treated group showed marked increase in malondialdehyde (MDA) levels (281.3 ± 40.72 nmol/ml, $P < 0.05$) as compared to MDA level of the control group (87.35 ± 16.21 nmol/ml), this indicates increased lipid peroxidation and oxidative tissue damage during STZ induced diabetes .

Increased MDA levels after STZ treatment may also be due to hyperglycemia induced excessive generation of free radicals. Chronic hyperglycemia drives glucose autooxidation, mitochondrial dysfunction, glycation of proteins and activation of oxidative metabolic pathways leading to the production of excessive free radicals and destruction of

membrane lipids (9). An increase of MDA was previously observed in the STZ-induced diabetic animal models (22).
Diabetic rats, on the other hand, showed significant decreases in antioxidant biomarkers such as GSH and SOD (17). Glutathione is one of the main intracellular antioxidants for detoxifying reactive oxygen species and needs to maintain cellular redox balance, while superoxide dismutase plays a primary enzymatic antioxidant defense system. Thus, lowering of GSH and the decrease in catalase activity could be an early event that reflects exhaustion of endogenous antioxidant defense mechanisms to cope with oxidative stress induced by free radical generation (22)

Both green coffee bean extract and berberine treatments reduced oxidative stress marker levels. The highest antioxidant acti-vity was presented by green coffee extract, which significantly decreased the concentration of MDA as well as improved the levels of GSH and SOD to normal. Diabetic rats received green coffee extract, and levels of MDA in plasma fell to 187.3 ± 31.50 nmol/ml, but GSH and SOD levels were markedly better than those in untreated diabetic rats.

This high concentration in chlorogenic acid, caffeine, and polyphenolic compounds likely explains the strong antioxidant activity of green coffee extract. Chlorogenic acid is a potent free radical scavenger, which has the ability to neutralize reactive oxygen species and inhibit lipid peroxidation Moreover, caffeine may play a role in antioxidant defense by modulation of oxidative metabolic pathways and reduction of oxidative cellular injury (7). In addition, polyphenol compounds of green coffee might enhance endogenous antioxidant enzyme activities and maintain cellular antioxidant capacity against oxidative stress.

Berberine treatment also improved markers of oxidative stress, but this effect was somewhat smaller than the effect found following green coffee extract. Berberine-treated diabetic rats showed lower levels of MDA and some correction of GSH and SOD activities. These results are consistent with previous observations which showed that berberine exerts antioxidant and cytoprotective effects (20).

Antioxidant functions of berberine might include the suppression of oxidative stress signaling pathways, the inhibition of generation of reactive oxygen species, upregulation in expression and activity levels of antioxidant enzymes as well as improvement in mitochondrial function. Moreover, it is believed that berberine also reduces oxidative damage associated with inflammation by regulating metabolic regulatory pathways and inflammatory mediators (23).
Green coffee extract demonstrated significantly stronger antioxidant activity in the present study, possibly related to direct radical scavenging effects from chlorogenic acid and polyphenolic compounds that provide fast protection against oxidative damage. By contrast, berberine is mainly exerting antioxidant action through intracellular metabolism and signaling pathways (7).

Additionally, improvement in oxidative stress biomarkers after treatment probably indirectly also improved glucose metabolism and lipid profile parameters. Oxidative stress is related to pancreatic β-cell dysfunction and disorganized glucose metabolism, as well as lipid abnormalities in strain of diabetes mellitus. Accordingly, the lowering of oxidative stress may compensate in maintaining metabolic homeostasis and improving diabetic complications (24).

These current findings are in agreement with those of Al-Brakati et al. including (22), which showed that green coffee extract markedly decreased oxidative stress and boosted antioxidant status in diabetic rats. In agreement, previous reports demonstrated that berberine increased antioxidant defenses and decreased lipid peroxidation levels in diabetes (2,25).

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