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Hepato-renal protective effects of gallic acid and *p*-coumaric acid in nicotinamide/streptozotocin-induced diabetic rats

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Abstract: The goal of diabetes treatment is primarily to save life and alleviate symptoms and secondary to prevent long-term diabetic complications resulting from hyperglycemia. Thus, our present investigation was designed to evaluate the hepato-renal protective effects of gallic acid and *p*-coumaric acid in nicotinamide/streptozotocin (NA/STZ)-induced diabetic rats. Experimental type 2 diabetes was induced by a single intraperitoneal (i.p.) injection of STZ (65 mg/kg b.wt.), after 15 min of i.p. injection of NA (120 mg/kg b.wt.). Gallic acid and *p*-coumaric acid were orally administered to diabetic rats at a dose of 20, 40 mg/kg b.wt./day, respectively, for 6 weeks. Body weight, serum glucose, protein profile, liver function enzymes and kidney function indicators was assayed. Treatment with either gallic acid or *p*-coumaric acid significantly ameliorated the elevated levels of glucose, alanine aminotransferase (ALT), aspartate aminotransferase (AST), urea and uric acid. Both compounds were also found to restore total protein, albumin, and globulin as well as body weight of diabetic rats to near normal values. It can conclude that both gallic acid and *p*-coumaric acid have potent hypoglycemic and hepato-renal protective effects in diabetic rats. Therefore, our results suggest promising hypoglycemic agents that can attenuate the progression of diabetic hepatopathy and nephropathy.

Key words: Gallic acid; *p*-coumaric acid; liver function; kidney function; diabetes

Introduction

Diabetes mellitus (DM) is a complex metabolic syndrome of multiple etiologies characterized by chronic hyperglycemia with impaired metabolism of carbohydrate, fat and protein resulting from deficiency in insulin secretion and/or insulin action. Untreated or poorly controlled hyperglycemia of diabetes can cause long-term damage, dysfunction, and failure of various organs (1). Hyperglycemia enhances biochemical abnormalities such as formation of advanced glycation end products (AGE), antioxidant enzyme inactivation, over activity of polyol pathway and protein kinase C activation and cytokine production, leading to increase of oxidative stress induced injury and development of diabetic complications (2,3).

Hyperglycemia is considered an important factor in the development of many complications in diabetics such as hepatopathy and nephropathy (4). The prevalence of hepatopathy among diabetics is estimated to be between 17% and 100% (5). Diabetic hepatopathy is a type of advanced liver disease which is characterized by liver cirrhosis, liver failure or the need for a liver transplant (6). Further, Arkkila *et al.,* (7) reported that the activities of liver damage markers including, serum alanine aminotransferase (ALT) and aspartate transaminase (AST) are elevated in the untreated diabetic patients. Particularly, diabetic nephropathy is a major cause of end-stage renal disease worldwide, affects 20-40% of all patients with diabetes (type 1 and type 2) (8). The diabetic hyperglycemia induces the elevation of plasma levels of urea acid and creatinine, which are considered as the significant markers of renal dysfunction (9). For these reasons, it is essential to discover not only a cure for diabetes but also for its complications to improve the quality of life and decrease the rate of mortality (10).

Although, several therapies are used for diabetes mellitus treatment, there are certain limitations due to high cost and side effects such as hypoglycemia, weight gain, gastrointestinal disturbances, and liver toxicity (11). Therefore, the field of herbal medicines research has been gaining significant importance in the last few decades and the demand to use natural products in the treatment of diabetes is increasing worldwide (12). Among the known natural bioactive components and phytochemicals, recently phenolic compounds are very popular because of their safety and efficacy (13).

Gallic acid (GA) (3,4,5-trihydroxybenzoic acid), a naturally occurring polyphenol, is abundantly present in many fruits, vegetables and derivative products (tea, wines, etc.) (14). Especially, tea is an important source of GA and contains up to 4.5 g/kg of fresh weight (15). GA has multiple biological activities such as antibacterial, antiviral, anti-inflammatory, antioxidant, antitumor (16), and reduces heart infarction incidence and oxidative liver damage (17). This polyphenol is even more effective than ascorbic acid to prevent lipid peroxidation (15). Also, it was reported that GA shows antihyperglycemic and antihyperlipidemic activities (18).

p-Coumaric acid (PCA) (4-hydroxyphenyl-2-propenoic acid) is a phenolic acid widely distributed in plants and form a part of human diet (19). It is widely present in apples, pears, and vegetables and plant products, such as beans, potatoes, tomatoes, and tea. PCA has attracted substantial attention due

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to its several pharmacological and biological actions, such as antioxidant (radical scavenging) (20), chemoprotective (21), neuroprotective (22), cardioprotective (23), anti-microbial (24), anti-cancer (25), anti-ulcer activity (26), anti-inflammatory activity (27), and hepatoprotective activity (28). In addition, PCA is able to reduce plasma cholesterol levels (29), prevent HFD-induced obesity (30), and improve insulin resistance (31). Since hyperglycemia is accompanied by complications in liver and kidney, the present study was designed to investigate the hepato-renal protective effects of gallic acid and *p*-coumaric acid in NA/STZ-induced diabetic rats.

Materials and Methods

Chemicals

Streptozotocin, nicotinamide and gallic acid were purchased from Sigma Chemical Co., St Louis, MO, USA. *p*-Coumaric acid was purchased from Santa Cruz Biotechnology Inc., Santa Cruz, CA, USA. All other chemicals were of analytical grade and were obtained from standard commercial supplies.

Experimental animals

Adult male albino rats (*Rattus norvegicus*) weighing about 130±10 g were used in the present study. They were obtained from National Research Center (NRC), Doki, Giza, Egypt. They were kept under observation for two weeks before the onset of the experiment to exclude any intercurrent infection. The chosen animals were housed in plastic good aerated cages at normal atmospheric temperature (25±5°C), humidity (55±5%) and normal 12 hours' light/dark cycle. During the entire period of study, the rats were provided with water and normal basal diet with known composition *ad libitum*. The animal procedures were conducted according to the principles and guidelines of the Canadian Council on Animal Care (CCAC), 1993.

Induction of diabetes

Experimental type 2 diabetes was induced in overnight fasted rats by single intraperitoneal (i.p.) injection of streptozotocin (65 mg/kg b.wt.), freshly dissolved in cold citrate buffer, pH 4.5 after 15 min of i.p. injection of nicotinamide (120 mg/kg b.wt.) prepared in normal physiological saline (32). Seven days after streptozotocin injection, rats were deprived of food (8-10 hours), blood samples were taken from lateral tail vein after 2 hours of oral glucose administration (3 g/kg b.wt.) and plasma glucose concentration was measured. Rats with a 2-hour plasma glucose level ranging from 180-300 mg/dl were considered mildly diabetic and included in the experiment.

Experimental design and treatment schedule

The experimental animals were divided into four groups of six rats each (n = 6) as follows:

- **Group I:** Served as normal control and were orally administered an equivalent volume of vehicle.
- **Group II:** Served as diabetic control and were orally administered an equivalent volume of vehicle.
- **Group III:** Diabetic rats were orally treated with gallic acid (20 mg/kg b.wt.) (18).
- **Group IV:** Diabetic rats were orally treated with *p*-coumaric acid (40 mg/kg b.wt.) (33).

All treatments were dissolved in 0.5% carboxymethylcellulose (CMC) and given daily for 6 weeks by gastric intubation. The dose was regulated 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. Furthermore, body weight of experimental groups was recorded at the beginning (initial) and at the end (final) of the treatment period.

Sample collection

By the end of the experimental period, the animals were fasted for 12 hours, and then sacrificed under diethyl ether anesthesia. Blood was allowed to coagulate at room temperature and centrifuged at 3000 r.p.m. for 30 minutes. The clear, non-hemolysed supernatant sera were quickly removed, divided into three portions for each individual animal, and kept at -20ºC for subsequent analysis.

Biochemical analysis

Determination of serum glucose: On the day before sacrifice at the end of sixth week, fasting blood samples were taken from lateral tail vein of overnight fasted rats (8-10 hours). Another blood samples were taken after two hours of oral administration of glucose solution (3 g / kg b.wt.) through gastric intubation. Sera were separated and used for glucose estimation spectrophotometrically according to the method of Trinder (34) using reagent kit purchased from Spinreact Co. (Spain).

Determination of protein profile: Serum total proteins concentration was determined according to the method of Peters (35) using reagent kits purchased from Spinreact Company (Spain). Serum albumin concentration was determined according to the method of Doumas *et al.,* (36) using reagent kits purchased from Human Diagnostics (Germany). Serum globulin concentration and albumin/globulin ratio were calculated according to Doumas *et al.,* (36) from the following equations:

Globulin (g/dl) = Total proteins (g/dl) - Albumin (g/dl).

Albumin/Globulin (A/G) ratio = Albumin (g/dl) / [Total proteins (g/dl) - Albumin (g/dl)]

Determination of liver function enzymes: The activities of serum ALT and AST were estimated according to the kinetic method of Gella *et al.,* (37) using reagent kits purchased from Biosystems Company (Spain).

Determination of kidney function indicators: Urea concentration was estimated according to the method of Fawcett and Scott (38) using reagent kits purchased from Diamond Diagnostic Chemical Company (Egypt). Serum uric acid concentration was measured based on the method of Barham and Trinder (39) using reagent kits obtained from Spinreact Company (Spain).

Statistical analysis

The experimental results were expressed as mean ± standard error (SE) and subjected to One-Way Analysis of Variance (ANOVA), using a computer software package (SPSS version 20, IBM Corp., 2011) and followed by Duncan's Multiple Range Test (DMRT) to determine the significant differences between groups, at $P < 0.05$.

Results

Effect of gallic acid and *p*-coumaric acid on body weight

Initial and final body weights of normal control, diabetic control, and diabetic treated rats are represented in figure 1. At the end of experiment, the diabetic control rats exhibited a significant decrease (P<0.05) of body weight as compared to normal ones. The treatment of diabetic rats with either gallic acid or *p*-coumaric acid showed a significant (P<0.05) protection against body weight loss.

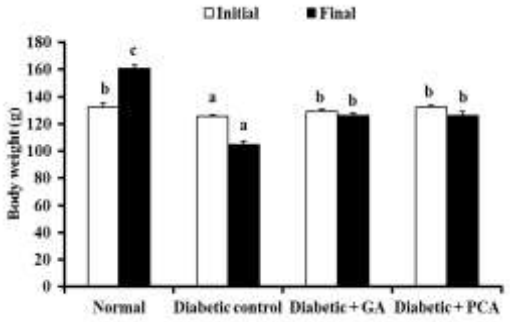

Figure 1: Body weight changes of normal, diabetic control and diabetic rats treated with gallic acid and *p*-coumaric acid.

Effect of gallic acid and *p*-coumaric acid on serum glucose level

As indicated in figure 2, diabetic control rats exhibited significant (P<0.05) increase in serum glucose levels at fasting state and at 2 hours post-glucose loading as compared to normal ones. Treated diabetic rats with gallic acid or *p*-coumaric showed a significant (P<0.05) decrease of glucose levels at fasting state and at 2 hours post-glucose loading as compared to their corresponding diabetic controls.

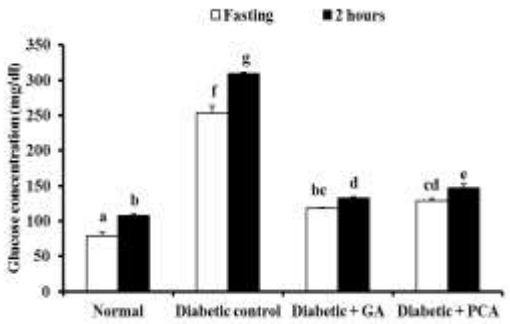

Figure 2: Serum glucose levels at fasting state and 2 hours post-glucose loading of normal, diabetic control and diabetic rats treated with gallic acid and *p*-coumaric acid.

Effect of gallic acid and *p*-coumaric acid on protein profile parameters

Data describing the effect of treatments on protein profile parameters in the different groups are showed in figure 3. The recorded values of the diabetic control group indicated that serum total protein concentration was significantly (P<0.05) decreased as compared to normal control group. Oral administration of gallic acid and *p*-coumaric acid significantly (P<0.05) increased the level of total protein in diabetic rats. Serum albumin and globulin levels showed similar manner as total proteins with significant (P<0.05) changes in albumin and globulin concentrations between groups. Furthermore, albumin/globulin (A/G) ratio showed non-significant (P>0.05) increase between diabetic control and normal ones but treated groups exhibited slight decrease as compared to diabetic control group.

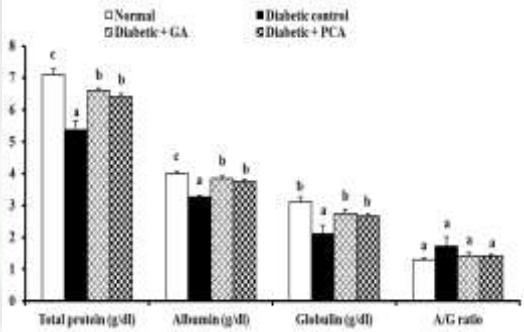

Figure 3: Protein profile of normal, diabetic control and diabetic rats treated with gallic acid and p-coumaric acid.

Effect of gallic acid and *p*-coumaric acid on liver function enzymes

Diabetic rats exhibited a significant (P<0.05) elevation of both serum ALT and AST activities as compared to normal rats. On the other hand, oral treatment with either gallic acid or *p*-coumaric acid caused significant (P<0.05) decrease of both enzymes activities as compared to diabetic rats. The preceding data are represented in figures 4 and 5.

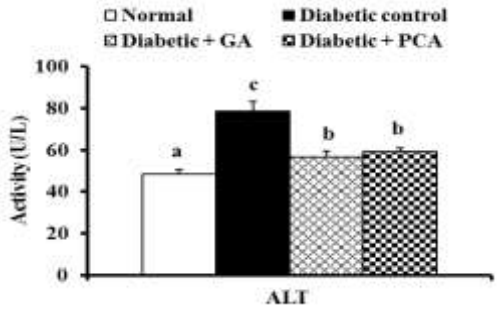

Figure 4: Serum ALT activity of normal, diabetic control and diabetic rats treated with gallic acid and *p*-coumaric acid.

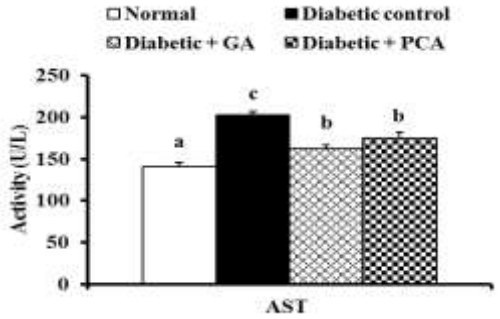

Figure 5: Serum AST activity of normal, diabetic control and diabetic rats treated with gallic acid and *p*-coumaric acid.

Effect of gallic acid and *p*-coumaric acid on kidney function indicators

The levels of kidney function indicators are showed in figures 6 and 7. Serum urea and uric acid of diabetic control rats exhibited a significant ($P<0.05$) increase as compared to normal ones. Gallic acid or *p*-coumaric acid treatment of diabetic rats produced a significant ($P<0.05$) decrease in urea and uric acid concentrations as compared to diabetic control ones.

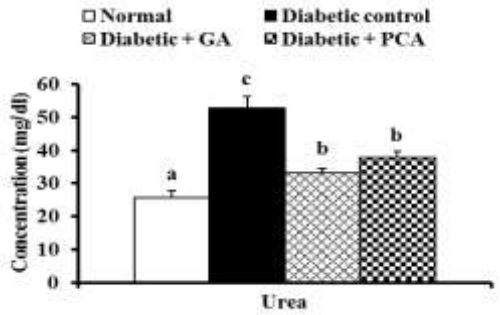

Figure 6: Serum urea concentration of normal, diabetic control and diabetic rats treated with gallic acid and *p*-coumaric acid.

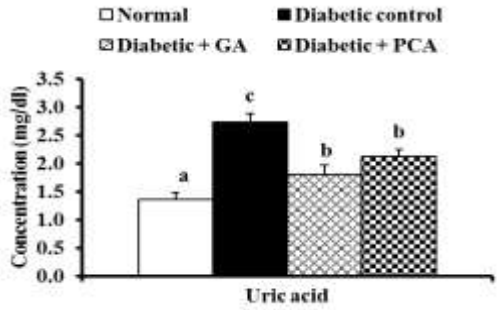

Figure 7: Serum uric acid concentration of normal, diabetic control and diabetic rats treated with gallic acid and *p*-coumaric acid.

Discussion

Diabetes mellitus is the most prevalent metabolic disorder. If it is not duly treated, it will lead to serious complications such as hepatopathy, nephropathy, neuropathy, retinopathy, etc., which are the main causes of morbidities and mortalities (5,40). Chemically induced diabetes in rodents using streptozotocin (STZ) is the most common animal model for understanding the molecular basis and pathogenesis of diabetes and its related complications (41). STZ selectively destroys insulin producing β-cells of pancreas by inducting DNA alkylation, causing activation of poly (ADP-ribose) polymerase (PARP), resulting in depletion of cytosolic NAD^+ and ATP. Finally, STZ action leads to necrosis of pancreatic β-cells (42). As a result of β-cells necrosis, insulin deficiency predominates resulting in repression of glycolytic enzyme and expression of gluconeogenic enzyme which promotes gluconeogenesis in liver and decreased utilization of glucose by the peripheral tissues contributes to hyperglycemia (43). The nicotinamide/streptozotocin (NA/STZ) rat model of type 2 diabetes used in this study is based on the protective effects of NA against β-cytotoxic effects of STZ (44). This model, as a model for non-obese type 2 diabetes, is reported to be more suitable for both biochemical and pharmacological researches testing potential antidiabetic effects of natural compounds on the course of diabetes in addition to studies focused on diabetic complications (45,46).

In the present investigation, the diabetic animals exhibited a marked increase in serum glucose levels at fasting state and at 2 hours post-glucose loading as compared to their corresponding normal ones. These results run parallel with the studies of Pierre *et al.,* (47), Saini and Sharma (48) and Mahmoud *et al.,* (49). Elevation of blood glucose may be attributed to the reduced entry of glucose to peripheral tissues, muscle and adipose tissue (50), increased glycogen breakdown (51) and increased gluconeogenesis and hepatic glucose production (52). After treatment with either gallic acid or *p*-coumaric acid, diabetic rats showed significant decrease of glucose concentration at fasting state and at 2 hours post-glucose loading.

Our results are in agreement with those of Latha and Daisy (18) and Punithavathi *et al.,* (53) who found that gallic acid significantly lowered blood glucose via potentiation of insulin secretion from regenerated β-cells in STZ-induced diabetic. Moreover, Ambika *et al.,* (33) and Relaxin-Shairibha *et al.,* (54) reported the hypoglycemic effect of *p*-coumaric acid in STZ-induced diabetic rats. Previous studies showed that phenolic compounds acted on ATP sensitive K^+ channels and regulated blood glucose (55). Consequently, our phenolic compounds, gallic acid and *p*-coumaric acid, may exhibit the hypoglycemic effect via stimulation of insulin secretion.

With regards to body weight, diabetic rats showed significant decrease in the body weight. This could be due to dehydration, increase in muscle wasting (56) and catabolism of fats and proteins (57). These results run parallel with the studies of Pierre *et al.,* (47) and Sharma *et al.,* (58). Oral administration of gallic acid and *p*-coumaric acid to diabetic rats improved body weight and this could be due to a better control of hyperglycemic state in the diabetic rats. This agrees well with observation of Latha and Daisy (18) who demonstrated that gallic acid treatment of STZ-induced diabetic rats increases the body weight. Furthermore, Amalan and Vijayakumar (59) demonstrated that *p*-coumaric acid administration increases body weight of STZ-induced diabetic rats. According to Punithavathi *et al.,* (53), decreased levels of blood glucose could improve body weight in STZ-induced diabetic rats. Moreover, Insulin generally has an anabolic effect on protein metabolism in that it stimulates protein synthesis and retards protein degradation (59). Therefore, the ability of treatments to protect body weight loss in diabetic rats seems to be as a result of improving insulin secretion and glycemic control.

Diabetes mellitus plays a central role in the initiation and progression of liver injury and this progressive disease is an independent risk factor for the development of chronic liver diseases (60). Protein profile parameters are used to ascertain the state of the liver's synthetic function (61). Our results showed that diabetic group exhibited significant decrease in serum total proteins, albumin and globulin along with non-significant change in albumin/globulin ratio (A/G ratio). This might be attributed to several reasons like increased gluconeogenesis and increased rate of amino acid conversion to glucose (62), decreased amino acid uptake (63), disturbance of amino acid levels (64), increased hepatocyte transport membrane (65) increased conversion rate of glycogenic amino acids to CO_2 and H_2O (66). Also, may be due to the structural distortion and the functional impairment of the hepatic cells which associated with low serum protein and albumin levels (67). Treatment of diabetic rats with either gallic acid or *p*-coumaric acid significantly elevated the levels of total protein, albumin and globulin near to normal levels. These results in accordance to Latha and Daisy (18) who demonstrated that gallic acid administration to diabetic rats led to significant increase in total protein and albumin as compared to diabetic control rats.

Liver enzymes such as AST and ALT are marker enzymes for liver function (68). These enzymes are transaminase enzymes that catalyse amino transfer reactions and play an important role in amino acids catabolism and biosynthesis (69). Thus, these enzymes are used as markers to assess the extent of liver damage in STZ-induced diabetic rats (70). Our data showed that serum ALT and AST were significantly increased in diabetic rats that agree with the finding of Abdel-Moneim *et al.,* (71). The serum elevation of liver damage biomarkers may occur as a result of deleterious effect of hyperglycemia in the liver of diabetic rats. Increasing the activities of these enzymes may due to leakage of the enzymes from the liver into the blood stream as a result of STZ toxicity which leads to the liver damage (72). These results are in line with Arkkila *et al.,* (7) who reported that elevated activities of serum AST and ALT is a common sign of liver diseases and observed frequently among people with diabetes than in the general population. Oral administration of gallic acid or *p*-coumaric acid significantly decreased the activities of ALT and AST in treated diabetic rats as compared to normal ones. These results are in agreement with those of (73) who showed that gallic acid decreases the activities of ALT and AST in hepatic ischemia and reperfusion injury in rats. Our results are also in agreement with those of Vandana *et al.,* (74) who demonstrated the hepatoprotective effects of phenolic acids, ferulic acid and p-coumaric acid, in ant-tubercular drug induced liver injury in rats. As a result, gallic acid and *p*-coumaric acid are considered potent hepatoprotective agents against liver injury associated with diabetes.

Diabetes is also associated with long-term complication in the renal system called diabetic nephropathy (4). The level of hyperglycemia in diabetic patients seems to be quantitatively linked to risk of developing renal lesions. Hyperglycemia-induced secondary mediators, such as protein kinase C and mitogen-activated protein kinase, and cytokine production are responsible for oxidative stress induced renal injury in the diabetic condition (75). Our results revealed a significant increase in serum urea and uric acid concentrations in non-treated diabetic rats. These results are in accordance with that of Mirmohammadlu *et al.,* (72) and Hu *et al.,* (76). The increased concentration of these metabolites in blood is due to metabolic disturbances observed in renal diseases associated with uncontrolled diabetes mellitus (77). The metabolic disturbances in diabetes are reflected in high activities of xanthine oxidase, lipid peroxidation, and increased triacylglycerol and cholesterol levels. Moreover, protein glycation in diabetes may lead to muscle wasting and increased release of purine, the

main source of uric acid (78). The present results revealed that the treatment of diabetic rats with either gallic acid or *p*-coumaric acid caused a significant decrease in urea and uric acid concentrations. These findings are in agreement with Latha and Daisy (18) who reported that urea and uric acid levels were significantly decreased in STZ-induced diabetic rats treated with gallic acid. Our results are also in agreement with those of Wilson *et al.,* (79) and Nasry *et al.,* (80) who demonstrated similar effects of phenolic acids, sinapic acid and caffeic acid, on kidney function parameters. The significant reductions in urea and uric acid in diabetic rats after administration of treatments indicate the renoprotective role of gallic acid and *p*-coumaric acid in preventing diabetic nephropathy.

Conclusion

Our results clearly indicate that both phenolic acids, gallic acid and *p*-coumaric acid, have hypoglycemic and hepato-renal protective effects in NA/STZ-induced diabetic rats, which may be mediated via potentiation of insulin secretion from β-cells resulting in better control of hyperglycemia and its related abnormalities in liver and kidney functions. Therefore, we can conclude that both compounds are potent hypoglycemic agents that can prevent the development of diabetic complications such as hepatopathy and nephropathy and pending further investigations to trace out the exact mechanistic pathways.

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