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Anti-Diabetic Effects of Pomegranate Peel Extract and L-Carnitine on Streptozotocin Induced Diabetes In Rats

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Type 2 diabetes mellitus is a far reaching ongoing metabolic problem portrayed by hyperglycemia and related with a few intricacies like hyperlipidemia. The current study aimed to study the anti-diabetic efficacy of pomegranate peel extract and L-carnitine on streptozotocin-induced diabetes mellitus in rats. A total of 70 male rats were divided into 7 groups (normal rats treated with the pomegranate peel extract and L-carnitine; rats given a high-fat diet to cause hyperlipidemia, this rats given low-dose intraperitoneal streptozotocin injections to cause type II diabetes; diabetic rats given PPE and L-carnitine orally every day for 12 weeks. Measurements of body mass, blood sugar, lipid profile and antioxidant enzyme activity were made. The treatment group that received PPE + L-carnitine showed a significant decrease in weight, blood glucose, cholesterol, triglycerides and low-density lipoprotein were significantly reduced, while high-density lipoprotein levels were significantly increased. Superoxide dismutase levels were increased, catalase and Nuclear Factor Erythroid-derived 2 (Nfe2) in diabetic rats treated with PPE and L-carnitine, while Malondialdehyde levels decreased significantly. According to the results of the study, PPE and L-carnitine had significant anti-hyperglycemic, hypolipidemic, and antioxidant benefits after 12 weeks of treatment in streptozotocin-induced diabetic rats.

Keywords: *Diabetic mellitus*, pomegranate peel extract, L-carnitine.

Diabetic mellitus (DM) is a chronic endocrine condition that affects protein, lipid, and glucose metabolism.[1] All forms of diabetes are characterized by decreased insulin levels in the blood (insulin deficit) and diminished ability of peripheral tissues to respond to (insulin resistance). The condition has pandemic proportions and poses a threat of spreading globally.[2]

The World Health Organization (WHO) estimates that there were around 285 million cases of illness in the globe in 2010; by 2030, 438 million people are anticipated to use this number by 2025.[3] With the biggest number of diabetic people worldwide and a steadily rising incidence of diabetes, India has earned the unsavory title of "Diabetes Capital of the World".[4] Hyperglycemia, or elevated blood glucose levels, is caused by an inability to make or utilize insulin.[5] Long-term elevated glucose levels are linked to the body being harmed and a number of organs and tissues failing.[6]

With different degrees of effectiveness, a wide variety of complementary and alternative therapies have been employed to treat DM.[7] Worldwide, medicinal plants continue to be very important in providing for people's health .[8]

Metformin is the drug of choice for treating type 2 diabetes T2DM and was originally regarded as complementary and alternative medicine.[4] Over 1200 plants and chemicals have been claimed to be treatments for the same disease,

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and over 400 have been tested for usage in type 2diabetic patients.[9] Hyperglycemia results in the constant production of reactive oxygen species (ROS), and research has shown that diabetes alters the activity of antioxidant enzymes in numerous organs.[10] Antioxidants are crucial for neutralizing free radicals and defending the organism against oxidative stress.[11]

Peel of pomegranate (PP) as a type of fruit, pomegranates are a Middle Eastern native plant that are now widely farmed and consumed on a global scale.[12] The (PP), which accounts for around 26% to 30% of the weight of the fruit, is distinguished by its high concentrations of antioxidants, such as phenolic chemicals and flavonoids compound and a range of minerals like potassium, magnesium, sodium, calcium, phosphorus, and complex sugars, it has been discovered that pomegranate peels may aid in promoting general health and treating specific diseases when consumed.[13] Therefore, supplements produced from Pomegranate Peel Extract (PPE) will be more beneficial than pomegranate pulp extract alone. In order to maintain the body's health and increase muscle mass, it is preferable to use pomegranate peels rather than other supplements since they are high in vitamin C, which is a crucial component of health .[14]

The physiologically active version of the non-essential amino acid carnitine is called L-carnitine .[15] Methionine and lysine, two amino acids, are used by your body to make carnitine, which is also present in foods like dairy, meat, and avocados. Carnitine, or L â hydroxy ã N trimethyl aminobutyric acid, is synthesized primarily in the liver and kidneys. There is experimental evidence that l-carnitine stimulates the activity of the pyruvate dehydrogenase complex by decreasing the intra-mitochondrial acetyl CoA/CoA ratio through the trapping of acetyl groups .[16] The simultaneous reduction in acetyl CoA levels in the cytosol further contributes to activate the glycolytic pathway, that is why l-carnitine covers a role in the glucose metabolism and assists in fuel sensing .[17] L-carnitine covers also an important role in lipid metabolism, acting as an obligatory cofactor for â-oxidation of fatty acids by facilitating the transport of long-chain fatty acids across the mitochondrial inner membrane as acylcarnitine esters. Its lack impairs the ability to use fat as fuel; this can result in an acute metabolic decompensation, most often early in life, with hepatic encephalopathy and hypoketotic hypoglycemia .[18]

The amino acid L-carnitine, which is a protein building block and aids in energy production, is also crucial for healthy heart and brain function, muscular movement, and a variety of other bodily functions .[19]

L-carnitine supplements can help those whose genetic condition causes their levels of natural l-carnitine to be too low. Having a medical procedure (hemodialysis for renal illness) or using some medications (such as valproic acid for seizures) that deplete the body's L-carnitine levels .[20] Supplementation with L-carnitine under medical supervision may benefit diabetic patients, the effectiveness of the supplement as a replacement, however, requires further study, it is also given to dieters, severe vegetarians, and babies who are underweight or born prematurely. Certain fatty acids are transported into cells via L-carnitine, where they undergo oxidation.[21] Energy is released as a result of this process. L-carnitine supplements improve the body's capacity to utilize fat as a source of energy, lower cholesterol and triglyceride levels, and may minimize the risk of health issues in diabetics who have impaired fat metabolism .[15] Since diabetes raises the chance of developing cardiac issues, L-carnitine has a preventive impact on the muscles and function of the heart. Review the pharmacological effects and clinical applications of L-carnitine as cardioprotective and antioxidant involving also the liver respiration chain activity, prevention and treatment of heart metabolic disturbances in cardiovascular, obese diabetic cardiomyopathy (considering the fibrosis, cardiac subcellular function, heart-rate variability, and cardiac autonomic function), hyperlipidemia, and dilated cardiomyopathy diseases.

Therefore the current study aimed to evaluate the anti-diabetic efficacy of pomegranate peel extract and L-carnitine on streptozotocin-induced diabetes mellitus in rats.

MATERIALS AND PROCEDURES

Chemical

The Sigma Chemical Company provided L-carnitine and streptozotocin, as well as other high analytical grade chemicals and solvents.

Medicinal plants

Getting PPE produced and administered Fresh pomegranate fruit was purchased at the neighborhood market in Tanta, Egypt, and its peel was removed before being first dried in the shade for ten days. Using a grinder, the powdered dry plant ingredients were created. A total of 100 g of dried plant material that had been ground up was submerged in methanol for one day at room temperature before being filtered through Whatman filter paper. After the filtrate was centrifuged at 8000 rpm for 15 minutes, the methanol was evaporated at 45 °C under reduced pressure. [22]

Animal

A total of 70 mature male albino wistar rats (297-350g) were purchased from the Egyptian Stock Holding Company for Biological Products of Vaccines, Sera, and Drugs (VACSERA, Alexandria, Egypt). Our study approved for animal care and use ethical committee by our university (IACUC-SCI-TU-0292). Before the trial began, rats were kept at our Faculty's animal house for a week. They were kept in conventional circumstances with a standard rodent feed, unlimited access to water, a standard temperature of 25 °C, and a relative humidity of at least 40%.

Experimental Induction of Diabetes

After a 12-hour fast, high-fat diet rats were given a single, freshly-made intraperitoneal (ip) injection of streptozotocin (STZ), 55 mg/kg body weight, which was promptly dissolved in 1 ml of sodium citrate buffer, pH 4.5.[23] To reverse drug-induced hypoglycemia, the STZ-treated rats were given access to 5% glucose solution overnight. On the third day following infusion of STZ, rats were declared diabetic if they had persistent glycosuria, hyperglycemia, and is it measured in blood levels greater than 250 mg/dl.

Design of Experiments

A total number of 70 rats were separated into seven groups, each made up of a maximum of ten rats: Group 1 normal rats were given a standard diet, Group 2 normal rats were given PPE 200mg/kg per day over the course of 12 weeks [12], and Group 3 normal rats were given L-carnitine 100 mg/kg per day over the course of 12 weeks [24]; Group (4) diabetic control (rats were given a high-fat diet to induce hyperlipidemia, and rats were given STZ to induce T2DM; Group (5) diabetic rats received PPE 200mg/kg orally every day for 12 weeks [12]; Group (6) diabetic rats, which received L-carnitine 100 mg/kg orally every day for 12 weeks [24]; and Group (7) diabetic rats, which received PPE 200mg/kg and L-carnitine 100mg/kg orally every day for 12 weeks, respectively.

METHODS

Measurement of Body Weight

After a 12-week experiment, the weights for each rats in each group were recorded

Preparing blood

After a 12-week treatment period, rats were fasted for 8 hours in preparation for blood serum analysis. Before taking blood samples from the orbital venous plexus, the rats were sedated with diethyl ether. For 10 minutes, blood serum was centrifuged at 2000 rpm while being chilled to measure the amounts of several biochemical markers..

Blood Parameter Analysis

Serum glucose was performed using a kit purchased from human Diagnostics in Cairo City High density lipoprotein (HDL), and Low density lipoprotein (LDL) levels were assessed enzymatically using a kit purchased from human diagnostics, Cairo City, Egypt, in accordance with the method described by Burtis[25].

Tissue samples

Following scarification, the rats' livers were instantly removed and cooled saline washed. Each slice of the ten liver from each group was homogenized individually with cooled glass-Teflon porter-Elvheim to estimate total Superoxide dismutase (SOD) , catalase (CAT), malondialdehyde (MDA)and nuclear factor erythroid related factor 2 (Nrf2) activity.

Biochemical marker tests and ntioxidantsenzyme activity

SOD activity was measured using the Paoletti[26] method, CAT activity was measured using method Buege[27],using a kit from Bio Diagnostics, (Cairo City, Egypt), MDA level was measured using method Buege[27],using a kit from Bio Diagnostics, (Cairo City, Egypt), and Nfe2 was measured. following a kit purchased from Bio Diagnostics (Cairo City, Egypt), the activity was assessed following the method Theodore.[28]

Statistical analysis

The statistical analysis of the data

resulted in the presentation of means and standard deviations (SD). Using one-way analysis of variance (ANOVA), all data were statistically analyzed, and then all diabetic groups were compared using the Student's t test utilizing computer software (Graphpad In State Software, Inc.). P-values less than p= 0.05were considered as statistically significant.

RESULTS

Treatments' impact on body weight

In contrast to normal animals, diabetic animals had significantly lower body weights, which may have been improved by better glycemic control after receiving PPE and L-carnitine treatment. Table 1 shows that after the 12th week of treatment, there was a substantial rise in body weight across all groups (p= 0.01). Biomedical analysis

Blood glucose levels

Table 2 demonstrates that there was no significant difference in serum glucose levels between the control group (G1) and group (G2) in any of the groups after the 12-week. The levels of serum glucose in the diabetic group (G4) are noticeably greater than those in the control group (G4). In contrast, diabetic rats treated with PPE + L-carnitine (G5, G6, and G7) groups demonstrated a significant (p0.01) decrease in serum glucose levels when compared to the diabetic group (G4); the decrease was more significant in the PPE and L-carnitine (G7) treatment than in the PPE (G5) or L-carnitine (G6) group.

Changes in lipid profiles

Cholesterol and triglycerides levels in the control group (G1) and group (G6) did not significantly differ, as shown in Table 1 of the study. In comparison to the control group (G4), the diabetic group (G4) has significantly higher levels of HDL-C, triglycerides, and cholesterol. A significant (p0.01) reduction in cholesterol, triglycerides, and LDL-C levels was observed in diabetic rats treated with PPE or/and L-carnitine (G5, G6, and G7) groups when compared to the diabetic group (G4); the reduction was more pronounced in the PPE + L-carnitine (G7) treatment group than in the PPE (G5) or L-carnitine (G6) groups.

Antioxidative enzyme activity and the biomarker are affected by the treatment

According to Table 2, neither the control group (G3) nor the group (G6) had significantly different levels of SOD or CAT activity. In the diabetic group (G4) compared to the control group (G4), there is a discernible decline in the activity of (SOD and CAT). However, diabetic rats treated with PPE and L-carnitine (G5, G6, and G7) groups showed a significant (p= 0.01) increase in (SOD and CAT) activity when compared to the diabetic group (G4); the increase was more pronounced in the PPE + L-carnitine (G7) treatment than in the PPE (G5) or L-carnitine (G6) groups.

Malondialdehyde level in liver

The levels of MDA in the control group (G1) and group (G3) did not significantly differ, as shown in Table (2). Compared to the control group (G4), the levels of (MDA) are significantly higher in the diabetes group (G4). However, compared to the control group (G4), diabetic rats treated with PPE and L-carnitine (G5, G6, and G7) showed a significant (p0.01) decrease in MDA levels; the decrease was more pronounced in the PPE + L-carnitine (G7) treatment group than in the PPE (G5) or L-carnitine (G6) groups.

liver (Nrf2) activity (ng/mg protein)

In the control group (G3) and group (G6), the levels of (Nrf2) did not significantly

Table 1. The impact of PPE + L-carnitine's on weight Serum glucose, lipid profile in different groups

	G1	G2	G3	G4	G5	G6	G7
Weight (g) after the 12th week	361*±5.4	306±2.1	310*±1.37	297.0±3.3	318*±4.1	314.5*±2.9	324*±2.5
Glucose(mg/d) after the 12th week	88.5±1.4	80±1.1	83*±1.45	517±22.4	225.5*±5.8	226.5*±8.7	221*±3.7
Cholesterol (mg/dl)	80.0±6.2	77±4.2	77.5*±5.2	87.5±5.6	75.0*±2.4	79.5*±2.8	72.5*±1.9
Triglycerides (mg/dl)	80.5±2.9	74.5±2.4	78.5±2.3	97.5±2.8	74.0*±0.9	76.0*±1.3	72.5*±2.9
HDL-c (mg/dl)	41.0*±1.4	37.5±1.3	40*±3.4	32.0±1.4	44.5*±2.3	42.5±1.6	47.0*±1.5
LDL-c (mg/dl)	22.5*±7.4	23.5±4.7	23±6.6	37.5±6.02	16.0*±3.4	20.5±3.4	12.0*±1.9

Table 2. The impact of PPE + L-carnitine's on activity of (SOD, CAT, MDA and Nrf2) (wet weight tissue) of liver in different groups

	G1	G2	G3	G4	G5	G6	G7
SOD (U/gm/wet weight tissue)	155.5*±6.1	163*±2.7	160±2.9	129±1.9	155*±7.30	140±9.8	174.5*±5.0
CAT(U/gm/wet weight tissue)	2.07*±0.2	2.66*±0.2	2.1±0.3	1.82±0.3	2.14*±0.4	2.17±0.1	3.97*±0.3
MDA(nmol/gm/wet weight tissue)	2.84±0.13	2.75*±0.2	2.8±0.3	3.74±0.2	3.03*±0.3	3.14±0.2	2.88*±0.3
Nrf2 (ng/mg protein)	116*±4.5	128*±2.2	124±2.2	107.5±5.8	126.5*±2.3	123.5*±1.9	145.5*±5.5

differ, as shown in Table 2. When compared to the control group (G4), the levels of (Nrf2) are significantly lower in the diabetes group (G4). In contrast, diabetic rats treated with PPE and L-carnitine (G5, G6, and G7) groups showed a significant (p0.01) increase in (Nrf2)levels when compared to the diabetic group (G4); the increase was more pronounced in the PPE + L-carnitine (G7) treatment than in the PPE (G5) or L-carnitine (G6) groups.

Data were expressed as men± SD of 10 rats per group. One-way ANOVA, which compares all diabetes group members, was used to determine the significance of the difference. As mean ±SD, values are expressed. P 0.001 was the significance level for the one-way ANOVA. Where, G1 represents the normal Control group, G2 represents the normal Control treated with PPE, and G3 represents the normal Control treated with L-carnitine group. G4, the group with diabetes; G5, the group receiving PPE treatment; G6, the group receiving L-carnitine treatment; and G7, the group receiving PPE and L-carnitine treatment

Data were expressed as men ± SD of 10 rats per group. By comparing all diabetic group members, a one-way ANOVA was used to determine the significance of the difference. The formula for values is mean ± SD. P 0.001 was considered significant for one-way ANOVA. Where, G1, the untreated Control group; G2, the untreated Control group treated with PPE; and G3, the untreated Control group treated with L-carnitine; G4, the diabetic group; G5, the diabetic receiving PPE treatment; G6, the diabetic receiving L-carnitine treatment; and G7, the diabetic receiving PPE plus L-carnitine treatment

DISCUSSION

In diabetic humans, hyperglycemia was linked to a number of metabolic abnormalities. A key element of glucose balance is insulin's capacity to control tissue glucose absorption. It is critical to switch out the currently used, side-effect-prone hypoglycemic drugs with innovative, highly effective, safe, and reasonably priced ones for the treatment of DM.[29-31] The goal of the current investigation was to determine how PPE and L-carnitine affected male albino wistar rats that had been given STZ to induce DM. The results showed that streptozotocin at a low dose and a high fat diet caused hyperglycemia in the experimental rats. In the current study, it was clear that rats with diabetes lost weight. While improvements were seen in the body weights of the diabetic group receiving PPE. PPE's antidiabetic activity appears to be what gives it the ability to stop body weight loss.

The current findings concur with earlier study .[32] According to the study, weight increased in the PPE and L-carnitine treated group compared to the diabetic group. Our findings agree with earlier research .[33] Due to the antidiabetic effect of L-carnitine, weight rose compared to the diabetes group; these findings are in line with the research .[1,34] PPE's phenolic content is responsible for its anti-diabetic effects. PPE reduces lipid peroxidation and oxidative stress, which is one important mechanism by which it ameliorates the effects of diabetic problems. The neutralization of reactive oxygen species produced may have this impact.[35,36]

In the results presented here, a rise in lipid peroxidation related with diabetes mellitus was

noted. Lipid peroxidation was seen to diminish after PPE and L-carnitine were administered. This may be because it actively transports fatty acids for use in energy production[18] according to previous studies [18,37] and the current study, oral administration of L-carnitine for a 12-week period improves the improvement of several features of diabetes, such as body weight reduction and glycemic level after fasting. The results of the current study showed that the glucose level was elevated in the diabetic group, which is in line. [1,18] The diabetic group's glucose level rose in comparison to the control group. Compared to the diabetic group, the groups receiving PPE had lower glucose levels.[12] Earlier research is compatible with the findings of the current study. Because of L-Carnitine's antidiabetic effect, glucose levels reduced in both those receiving treatment and those who were not, and these findings are in line with a study .[35]

Numerous research have demonstrated the hypoglycemic and antioxidant benefits of PPE. The suppression of enzymes that break down carbohydrates is another benefit of pomegranate products. *Punica granatum* (PG) flower and peel contain phenols, which may also have an antihyperglycemic effect. PPE likely regulates lipid metabolism by reducing oxidative and inflammatory damage and enhancing mitochondrial metabolism. [38,39]

The results of this investigation support PPE therapy. In this study, HDL-C decreased in the diabetes group compared to the normal control group, whereas lipid levels (TG, TC, and LDL-C) increased in the diabetic group. The findings from our study concur with those from [40]. In agreement with [36,38], diabetics. Moreover L-carnitine is an important cofactor for the -oxidation of fatty acids and is involved in lipid metabolism. It accomplishes this by facilitating the passage of acylcarnitine esters, which are long-chain fatty acids, over the inner mitochondrial membrane. Its absence affects the body's capacity to use fat as fuel, which can cause an abrupt metabolic decompensation, most frequently in infancy, characterized by hepatic encephalopathy and hypoketotic hypoglycemia [21,22]. Increased ROS production and/or a depleted antioxidant enzyme system, which includes SOD, catalase, and MDA, can also contribute to oxidative stress. These anti-oxidant enzymes guard cells against cytotoxic ROS.

Additionally MDA, use glutathione's capacity to decrease thiols to lessen ROS targets like oxidized lipids and proteins. Lipid peroxidation in the cellular and subcellular membranes is the unavoidable result of ROS injury under the situation of inactive antioxidant enzymes [41,42].We measured the concentrations of SOD, CAT, and MDA in liver homogenates. In the model group, elevated MDA levels coincided with a decline in SOD and CAT antioxidant levels. PPE and L-carnitine therapy raised SOD levels and lowered MDA levels.

This study revealed that (SOD and CAT) were depleted in a diabetic group, and these results were consistent with Muhammad *et al*., Cerda *et al*., [43,44] However, the current study also revealed that PPE increased the activity of antioxidant enzyme (SOD and CAT), and these results are consistent with studies .[45.46] In this study, PPE and L-carnitine both increased SOD and CAT activity. These results are consistent with studies .[47] On the other hand, the current study found that PPE decreased the activity of antioxidant enzyme activities MDA, these results being consistent with a study.[46,47] This investigation revealed that MDA was raised in a diabetic group, and these results are consistent.[45] PPE and L-carnitine had lower antioxidant enzyme activity MDA in this investigation. [48,43]

Through Nrf2 controls the expression of detoxifying and antioxidant enzymes. Kelch-like ECH-associated protein 1(Keap1), an actin-binding repressor protein, locks down Nrf2 under normal circumstances and keeps it in the cytoplasm. Through this mechanism, Keap1 increases oxidative stress by inhibiting Nrf2 and ARE/EpRE activation. Diabetes has been linked to decreased Nrf2 expression and increased oxidative stress .[47,49] Although the precise mechanism of Nrf2 downregulation is still unknown, increasing (Keap1) and phosphorylating ERK both lower Nrf2 levels. Additionally, Nrf2 transcription factor is activated in hepatic cells by PPE and L-carnitine. In the current work, PPE and L-carnitine prevented the hyperglycemia-induced downregulation of Nrf2, a downstream gene product of the Nrf2-Keap1 pathway. [50] Therefore it is expected that regulating

Nrf2 expression will be essential in preventing oxidative damage caused by hyperglycemia in diabetic rats by PPE and L-carnitine. On the one hand, the current study revealed that PPE boosted the activity of antioxidant enzyme activities (Nrf2); these results are compatible with a study Liu *et al.*,.[48] This study shown that (Nrf2) was low in a diabetic group. L-Carnitine demonstrated higher antioxidant enzyme (Nrf2) activity in this study. [50,51] In order to control the adaptive response to oxidants and electrophiles, Nrf2 performs as a xenobiotic-activated receptor. [52]

CONCLUSION

The PPE and L-Carnitine are effective in preventing diabetes because they lower blood glucose, body weight, and elevated lipids caused by T2DM. Our results show the efficacy of oral PPE and L-Carnitine in the management of type 2 diabetes-related obesity. Also PPE and L-Carnitine play a significant part in functioning as a supplemental therapy in diabetes treatment protocols, with the goal of reducing diabetes progression and fat gain in diabetics.

Recommendation

Finally, we propose that PPE and L-Carnitine exhibit an intriguing anti-diabetic efficacy in this study and may be of significant use a remedy for T2DM. These nutrients are also good for lowering body weight, enhancing the lipid profile, and antioxidant enzymes.

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