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Research Article

Investigation of the Anti-diabetic and Anti-lipid Peroxidative Properties of Gallic Acid in Diabetic Rats

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Abstract
Diabetes mellitus is a chronic non-communicable disease that occurs due to insulin deficiency or reduced function in the body. Therefore, the scientific investigation of herbal plants and their effectiveness is essential. It has been shown that gallic acid has hypoglycemic properties. In this study, the anti-diabetic and anti-lipid peroxidation properties of gallic acid were investigated. For this purpose, Streptozotocin was injected intraperitoneally into male rats at a dose of 60 mg/kg to induce type I diabetes. Seven days after Streptozotocin injection, blood samples were taken and rats with serum glucose levels higher than 250 mg/dL were considered diabetic. The rats were divided into 4 groups. Two groups of diabetic rats received either water or gallic acid at a dose of 40 mg/kg, and two groups of normal rats received either water or gallic acid at 40 mg/kg dose. The treatment period for all groups was 8 weeks. After the end of the period, blood samples were taken from the rats under fasting conditions. The collected blood samples were analyzed for serum biochemical factors (glucose, cholesterol, triglycerides, High-density lipoprotein, and creatinine) using spectrophotometry with the respective kits, and the level of lipid peroxidation in red blood cells was measured. The administration of gallic acid at a dose of 40 mg/kg (8 weeks) significantly reduced serum levels of glucose, triglycerides, cholesterol, alanine aminotransferase, aspartate aminotransferase, very low-density lipoprotein, low-density lipoprotein, and creatinine, while significantly increasing serum levels of high-density lipoprotein. Additionally, the level of Malondialdehyde in red blood cells was decreased in the diabetic group receiving gallic acid compared to the diabetic control group, and in normal rats receiving gallic acid at a dose of 40 mg/kg (8 weeks), it had no significant effect on serum factors and had no toxicity.

Keywords: diabetes mellitus, lipid peroxidation, gallic acid, serum factors, rat

1. INTRODUCTION

Diabetes mellitus is one of the most common non-communicable diseases worldwide and is a serious and potentially devastating condition that affects all age groups globally. In Iran, there are nearly 6.3 million diabetic patients and approximately 7.7 million individuals with impaired glucose tolerance (elevated fasting blood sugar or 2 h after a meal or both above normal levels but not in the diabetic range) [1]. There are 2 common types of diabetes known as type I and II diabetes. Type I diabetes is an autoimmune disease that affects individuals at a young age. This type of disease is caused by the destruction of beta cells in the pancreas, which are responsible for insulin production [2]. Currently, the common treatment for type I diabetes is insulin therapy, but this method only provides partial control of blood sugar and can lead to various long-term complications such as cardiovascular diseases, blindness, kidney failure, and peripheral neuropathy [3]. Unlike type I diabetes, type II diabetes is associated with metabolic disorders that include impaired beta cell function, insulin resistance, and beta cell destruction. It is worth mentioning that most diabetic patients are affected by type II diabetes [4].

There is a real need for new methodologies and strategies to improve the biological sciences [5]. Medicinal plants and their extracted compounds are helpful in the treatment of various diseases [6]-[10]. The World Health Organization (WHO) has identified 21,000 plant species that are used for medicinal purposes worldwide. Among these plant species, 150 species are commercially used on a relatively large scale [6]. Pomegranate, scientifically known as *Punica granatum*, belongs to the family Punicaceae, and its ancient Latin name is "pumum" meaning apple, and "granatum" meaning seed. It originated in Iran and gradually spread from the Mediterranean to northern India [11]. It is a natural source rich in phenolic compounds, including antioxidants such as tannins, polyphenols, flavonoids, vitamin C, tocopherols, and anthocyanins, and their preventive and therapeutic properties have been proven in numerous studies. The biochemical properties of

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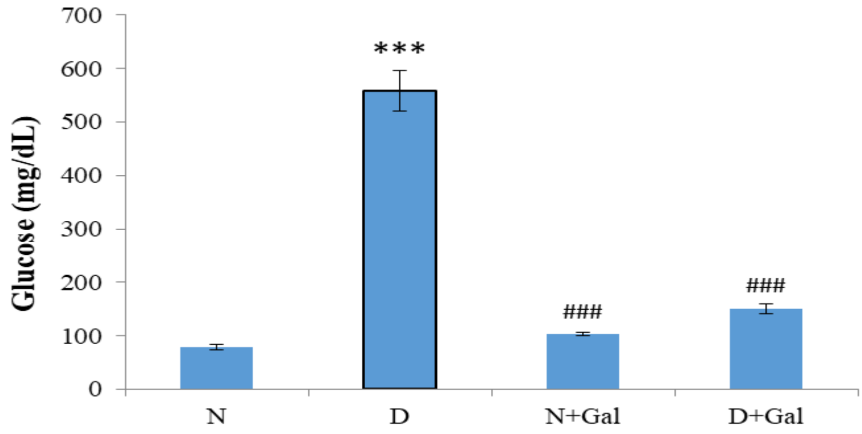

Figure 1. Effect of gallic acid administration for 8 weeks on serum glucose levels in normal and diabetic rats. Results are shown as mean±S.E.M. (n=6).

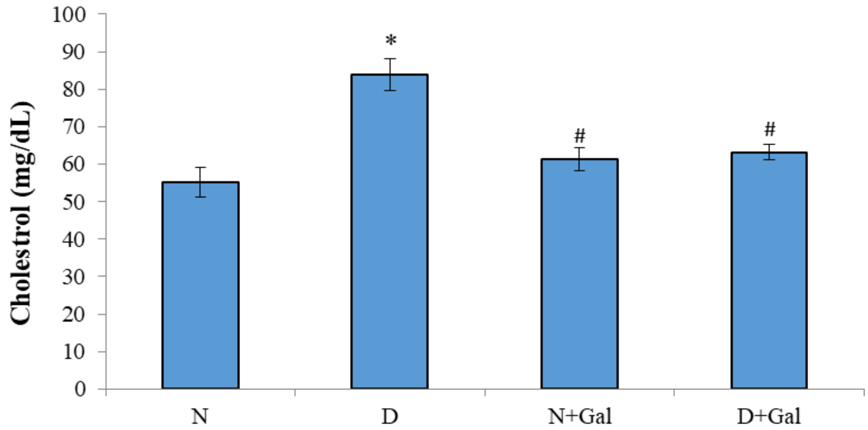

Figure 2. The effect of gallic acid administration for 8 weeks on serum cholesterol levels in normal and diabetic rats. The results are presented as mean±S.E.M. (n=6).

*D: Diabetic group without drug administration (Negative control); N+Gal: Normal group receiving gallic acid at a dose of 40 mg/kg; D+Gal: Diabetic group receiving gallic acid at a dose of 40 mg/kg; *** p<0.001 significant difference compared to the normal group; ###p<0.001: significant difference compared to the diabetic group.*

these mentioned compounds are mainly due to their antioxidant properties. The antioxidant property (or in other words, free radical scavenging) of pomegranate fruit peel is comparable to other parts of the fruit, including petals, flags, and calyxes, but it is lower in leaves [12].

Research has shown that pomegranate fruit peel extract has the highest antimicrobial activity compared to other parts of the plant. Other studies have shown that the antibacterial property of pomegranate fruit extract is more effective against Gram-positive bacteria [13]. The results of studies indicate that different parts of the pomegranate plant can inhibit the growth of certain tumor cells [14]. Polyphenols extracted from pomegranate fruit juice have shown significant anticancer effects on breast cancer cells under *in vitro* conditions [15]. Recently, its antioxidant and analgesic effects on diabetic rats have been identified and received attention [16]. Preclinical studies on animal models have shown that extracts obtained from the flower [17], seed [18], seed oil [19], and compounds such as gallic acid, ellagic acid, quercetin, and punicalagin have anti-diabetic properties [20]. In addition to the mentioned cases, it has also been shown that pomegranate juice improves hyperlipidemia caused by diabetes and prevents some other secondary complications related to diabetes [21]. This study investigates the effect of gallic acid on the level of lipid peroxidation, certain lipids, and blood creatinine in diabetic rats.

2. MATERIALS AND METHODS

2.1. Experimental Design

The study population consisted of 32 male rats weighing between 270-290 g. They were divided into 4 groups and observed for 2 months. The control group received no medication, the negative control group consisted of diabetic rats without medication, experimental group 1 received a daily dose of 40 mg/kg gallic acid via gastric gavage, and experimental group 2 consisted of diabetic rats receiving a daily dose of 40 mg/kg gallic acid via gastric gavage .At the end of the 8 weeks, all rats were fasted and anesthetized with ketamine (50 mg/kg) and xylazine (20 mg/kg). Blood samples were collected from the heart to measure lipid peroxidation in red blood cells and levels of glucose, cholesterol, triglycerides, high-density lipoprotein (HDL), creatinine, and malondialdehyde (MDA).

2.2. Serum Factor Measurement

The serum was separated from the blood samples by centrifugation at 3200 rpm for 15 min. Glucose, creatinine, cholesterol, triglycerides, and HDL levels were measured using spectrophotometry with kits from Koushan Zist Azma company.

2.3. Lipid Peroxidation Measurement in Red Blood Cells

For the measurement of lipid peroxidation in red blood cells, 5 mL of blood was collected in EDTA-containing tubes. The tubes were centrifuged at 3,000 rpm for 15 min to separate the plasma. The red blood cells were washed three times with 0.1 M PBS and a 50% suspension of red blood cells was prepared. A specific volume of the suspension was mixed with a specific volume of PBS, followed by the addition of 0.4 M H_2O_2 and TCA containing meta-arsenite. The suspension was then centrifuged at 1500 g for 10 min at 4 °C, and 1 mL of the supernatant was mixed with TBA 1% containing NaOH 50 mM. The mixture was heated at 95 °C for 15 min and the optical absorption at 532 nm was measured against a blank to calculate the MDA level.

2.4. Statistical Analysis

The data obtained in this study were analyzed using SPSS software. One-way ANOVA and Tukey's post hoc test were used to compare the differences between the different groups. A significance level of $p < 0.05$ was considered statistically significant. The data were plotted using Excel software.

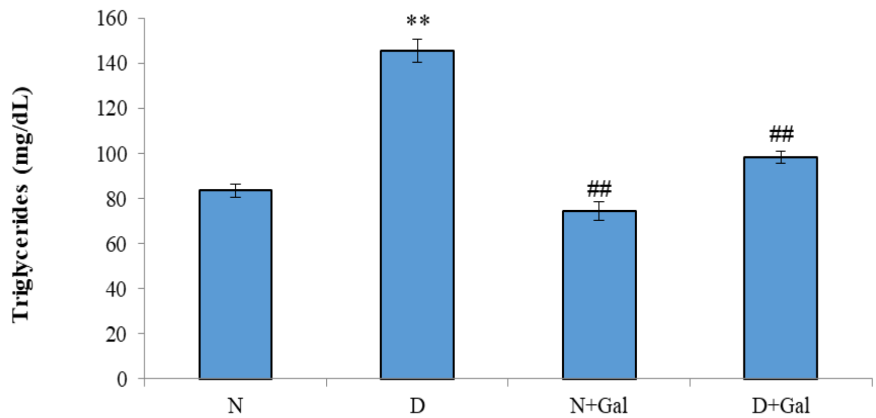

Figure 3. The effect of administering gallic acid for 8 weeks on serum triglyceride levels in normal and diabetic rats. The results are presented as mean±S.E.M. (n=6).

*D: Diabetic group without drug administration (Negative control); N+Gal: Normal group receiving gallic acid at a dose of 40 mg/kg; D+Gal: Diabetic group receiving gallic acid at a dose of 40 mg/kg; *** p<0.001 significant difference compared to the normal group; ###p<0.001: significant difference compared to the diabetic group.*

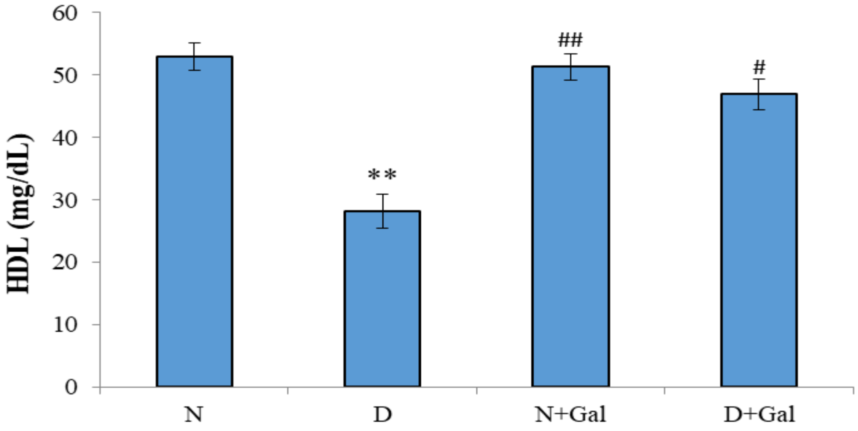

Figure 4. Effect of gallic acid administration for 8 weeks on serum HDL levels in normal and diabetic rats. The results are presented as mean±S.E.M. (n=6).

*D: Diabetic group without drug administration (Negative control); N+Gal: Normal group receiving gallic acid at a dose of 40 mg/kg; D+Gal: Diabetic group receiving gallic acid at a dose of 40 mg/kg; *** p<0.001 significant difference compared to the normal group; ###p<0.001: significant difference compared to the diabetic group.*

3. RESULTS AND DISCUSSIONS

3.1. Effect of Oral Administration of 40 mg/kg Gallic Acid on Serum Levels of Certain Biochemical Factors in Different Groups

The results showed that in healthy rats receiving a daily dose of 40 mg/kg gallic acid for 8 weeks, there were no significant changes in serum levels of glucose, cholesterol, triglycerides, HDL, creatinine, and MDA compared to healthy rats (positive control). However, the comparison of serum levels of glucose, cholesterol, triglycerides, HDL, creatinine, and MDA in diabetic rats with healthy rats showed a significant increase in glucose, cholesterol, triglycerides, creatinine, and MDA, and a significant decrease in HDL after the induction of diabetes. However, the administration of 40 mg/kg gallic acid for 8 weeks to diabetic rats resulted in a significant decrease in serum levels of cholesterol, triglycerides, creatinine, and MDA, while significantly increasing HDL.

3.2. Effect of Oral Administration of 40 mg/kg Gallic Acid on Serum Glucose Levels in Different Groups

The comparison of serum glucose levels in diabetic rats with healthy rats showed a significant increase in glucose after the induction of diabetes ($p < 0.001$), 558.75±37.50 vs. 78.50±5.72. However, the administration of 40 mg/kg gallic acid to diabetic rats for 8 weeks resulted in a significant decrease in serum glucose levels compared to diabetic rats (negative control) ($p < 0.001$), 151.12±9.43 vs. 558.75±37.50 (Figure 1).

3.3. The Effect of Oral Administration of Gallic Acid at a Dose of 40 mg/kg on Serum Cholesterol Levels in Different Groups

Comparison of serum cholesterol levels in diabetic rats with healthy rats indicates a significant increase in cholesterol after diabetes induction ($p < 0.05$), 83.87±4.37 vs. 55.26±3.94). Administration of gallic acid at a dose of 40 mg/kg to diabetic rats for 8 weeks resulted in a significant decrease in serum cholesterol levels compared to healthy rats (negative control group) ($p < 0.05$), 63.17±2.13 vs. 83.87±4.37 (Figure 2).

3.4. The Effect of Oral Administration of Gallic Acid at a Dose of 40 mg/kg on Serum Triglyceride Levels in Different Groups

Comparison of serum triglyceride levels in diabetic rats with healthy rats indicates a significant increase in triglyceride levels after diabetes induction ($p < 0.01$), 145.51±5.05 vs. 83.57±2.82. Administration of gallic acid at a dose of 40 mg/kg for eight weeks in diabetic rats resulted in a significant decrease in serum triglyceride levels compared to diabetic rats (negative control group) ($p < 0.01$), 98.51±2.73 vs. 145.51±5.05 (Figure 3).

3.5. The Effect of Oral Administration of Gallic Acid at a Dose of 40 mg/kg on Serum HDL Levels

Comparison of serum HDL levels in diabetic rats with healthy rats indicates a significant decrease in HDL after the onset of diabetes ($p < 0.01$), 52.99±2.21 vs. 28.19±2.79. Administration of gallic acid at a dose of 40 mg/kg to diabetic rats for eight weeks resulted in a significant increase in serum HDL levels compared to diabetic rats (negative control group) ($p < 0.05$), 28.19±2.79 vs. 46.94±2.43 (Figure 4).

3.6. The Effect of Oral Administration of Gallic Acid at a Dose of 40 mg/kg on Serum Creatinine Levels in Different Groups

Comparison of serum creatinine levels in diabetic rats with healthy rats indicates a significant increase in creatinine after diabetes induction ($p < 0.01$), 0.94±0.03 vs 1.45±0.06). Administration of gallic acid at a dose of 40 mg/kg to diabetic rats for eight weeks resulted in a significant decrease in serum creatinine levels compared to diabetic rats (negative control group) ($p < 0.01$), 1.45±0.06 vs. 0.98±0.03 (Figure 5).

3.7. The Effect of Oral Administration of Gallic Acid at a Dose of 40 mg/kg on The Level of Lipid Peroxidation in Red Blood Cells in Different Groups

Comparison of serum MDA levels in diabetic rats with healthy rats indicates a significant increase in MDA after diabetes induction ($p < 0.01$), 2.66±0.01 vs. 4.84±0.13). The administration of gallic acid at a dose of 40 mg/kg to diabetic rats for 8 weeks resulted in a significant decrease in serum MDA levels compared to diabetic rats (negative control group) ($p < 0.01$), 4.84±0.13 vs. 3.05±0.15 (Figure 6).

3.8. Discussion

Diabetes mellitus is one of the chronic metabolic diseases. Due to its prevalence, complications, and heavy treatment costs associated with this disease, it is considered one of the most important priorities in healthcare and treatment in today's world, especially in Iran. One of the reasons for the reduced lifespan of these patients is the lack of continuous and sufficient care. It should be noted that drug consumption alone cannot be as effective as proper nutrition and exercise in controlling diabetes [22].The incidence of diabetes is rapidly increasing worldwide, particularly in developing countries, where the residents have adopted a diet rich in sugar and starch, which has been a problem for developed countries for years. According to the

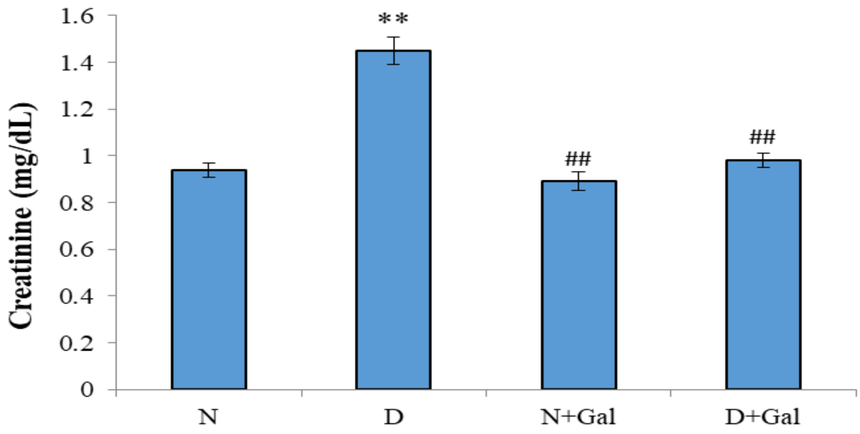

Figure 5. The effect of gallic acid administration for 8 weeks on serum creatinine levels in normal and diabetic rats. The results are presented as mean±S.E.M. (n=6).

*D: Diabetic group without drug administration (Negative control); N+Gal: Normal group receiving gallic acid at a dose of 40 mg/kg; D+Gal: Diabetic group receiving gallic acid at a dose of 40 mg/kg; *** p<0.001 significant difference compared to the normal group; ###p<0.001: significant difference compared to the diabetic group.*

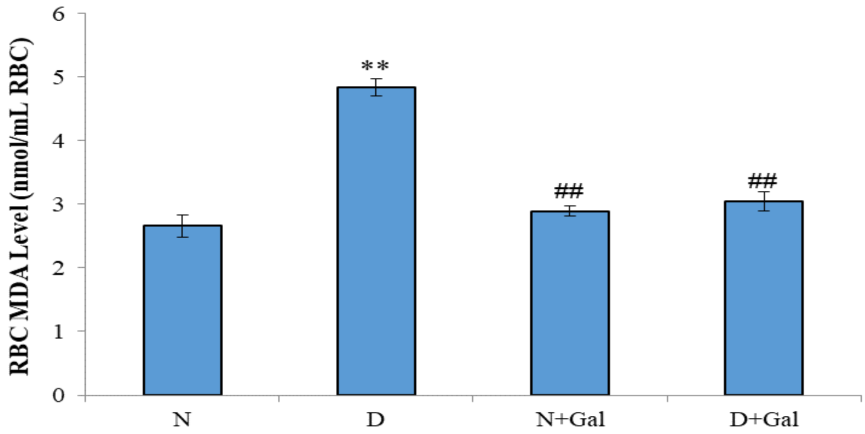

Figure 6. The effect of gallic acid administration for 8 weeks on the level of MDA in red blood cells taken from normal and diabetic male rats. The results are presented as mean±S.E.M. (n=6).

*D: Diabetic group without drug administration (Negative control); N+Gal: Normal group receiving gallic acid at a dose of 40 mg/kg; D+Gal: Diabetic group receiving gallic acid at a dose of 40 mg/kg; *** p<0.001 significant difference compared to the normal group; ###p<0.001: significant difference compared to the diabetic group.*

American Medical Association, body fat measurement technology shows that Asians, compared to Europeans with an equal body mass index (BMI), have more accumulated fat in their abdomen, which increases their risk of developing diabetes [23]. The results of the present study showed that an 8-week treatment of diabetic rats with gallic acid at a dose of 40 mg/kg significantly reduced glucose, cholesterol, triglycerides, and creatinine levels, while increasing HDL levels. Additionally, gallic acid led to a decrease in lipid peroxidation levels in red blood cells of diabetic rats. Based on previous research findings, an increase in blood glucose levels is usually accompanied by an increase in serum levels of cholesterol, triglycerides, low-density lipoprotein (LDL), very low-density lipoprotein (VLDL), and a decrease in HDL plasma levels [24]. Hyperglycemia leads to an increase in sterol regulatory element-binding proteins (SREBPs) in hepatocyte cells. SREBPs are transcription factors that activate the expression of more than 30 genes involved in the synthesis and uptake of cholesterol, fatty acids, triglycerides, and phospholipids. SREBP-1C is also essential for the expression of glucokinases.This enzyme participates in the expression of lipogenic genes (LPK), fatty acid synthesis (FAS), and acetyl-CoA carboxylase (ACC) in the presence of high levels of glucose and in coordination with another transcription factor called ChREBP. ACC converts phosphoenolpyruvate to pyruvate, which is the main source of acetyl-CoA for fatty acid synthesis and can also convert acetyl-CoA to malonyl-CoA. This compound inhibits carnitine palmitoyltransferase, which is responsible for the transport of fatty acids into the mitochondria, and ultimately reduces beta-oxidation of fatty acids by the mitochondria [25]. Therefore, blood lipid levels increase in patients with type I diabetes who have insulin secretion defects, leading to the progression of diabetes complications, including nephropathy [26]. In this study, the peel of *Punica granatum*, commonly known as pomegranate was used. In traditional medicine in many countries, various parts of the pomegranate tree, including the fruit, leaves, roots, and flowers, are used [27]. The extracted compounds from pomegranate peel include phenolic compounds and anthocyanins, including gallic acid, ellagic acid, punicalin, punicalagin, caffeic acid, ellagitannins, punicic acid, camphorol, and quercetin [28]. It has been reported that pomegranate peel can exhibit anti-inflammatory [29], analgesic, and wound-healing effects [30]. According to previous studies, gallic acid, ellagic acid, and punicalagin are responsible for the anti-inflammatory effects of *P. granatum* [31] and a recent study on diabetic rats has shown that gallic acid (a phenolic compound) can exhibit hypoglycemic, antioxidant, and analgesic effects

[16]. It has been reported in research studies that the hypoglycemic effect of gallic acid is related to the inhibition of α-amylase by this compound [15], and therefore, it is consistent with the results of this study regarding the blood glucose-lowering effect of this compound. Furthermore, phenolic compounds have been shown to have the ability to reduce blood cholesterol and triglyceride levels [32], In addition to the mentioned cases, phenolic compounds are known as protective factors in diseases related to oxidative stress due to their capacity to increase antioxidant activities and reduce the formation of free radicals have reported that phenolic compounds are capable of reducing plasma lipid levels, except for HDL [33]-[36]. Therefore, the beneficial effects of gallic acid on serum lipids and improvement in kidney and liver function can be attributed specifically to the phenolic nature of this compound. In this study, an increase in the level of malondialdehyde (MDA) in red blood cells was observed in diabetic rats compared to normal rats, which is consistent with the findings of other researchers. Reports indicate that phenolic compounds inhibit lipid peroxidation [37][38]. These compounds have been introduced as potent antioxidants against free radicals and as scavengers of free radicals, which appears to be related to their ability to donate hydrogen atoms. The phenolic group donates this hydrogen atom [39]. Therefore, the anti-lipid peroxidation property of gallic acid can be attributed to the phenolic nature of this compound.

4. CONCLUSIONS

The findings of the current research show that an 8-week treatment of diabetic mice with 40 mg/kg gallic acid resulted in a notable decrease in blood glucose, cholesterol, triglycerides, and creatinine levels. Furthermore, gallic acid elevated HDL levels. Moreover, gallic acid led to a reduction in lipid peroxidation levels in the red blood cells of diabetic mice. Additionally, this study observed an increase in MDA levels in the red blood cells of diabetic rats compared to normal rats, aligning with the discoveries of other researchers.

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Author Contributions

M. A., M. A., and M. K. did conceptualization, wrote the original draft, did funding acquisition, provided resources, performed methodology, did investigation, and analysed the data; S. T. J. did conceptualization, provided resources, did investigation, and analysed the data; H. A. and H. K. did manuscript preparation, methodology, review, editing, and proofreading.

Conflicts of Interest

The authors declare no conflict of interest.

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