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Original Article

Influence of Chamomile Leaves extract in Different Doses on Renal Functions and Diabetic indices in Streptozotocin – Induced Diabetic Rat

Mohamed Zaeim Hafez Ahmed[1]*, Muhammad Abdelbaeth Hassan Elfiky[1], Elsayed Elagamy Elsayed Mohamed[2], Ramadan Hassan Ibrahim Thabet[2], Ahmed Mohamed Gad Allah[3], Ahmed Abdrabo Elshenawy Elsisi[2], Ahmed Abdel Nasser Ahmed Mohamed[2], Tarek Shikhon[4], Mostafa Abo-akrab[4], Sayed A.M.Mahmoud[5], Mohamed AbdelAziz Doma[5], Wael Ahmed Mahmoud Khattab[6], Khaled Saleh Ali Elhamaky[7], Mohamed El-Salamoni[6], Fatma Mahmoud Abdelraheem[8], Mahmoud Ahmad Mohamed Azab[6], Ashraf Abdel Aty Elshenawy Emara[6], Mohamed E EL-Refaey[1], Ahmed A. Abd El-Rhman[1], Ahmed F. Abdel Ghany[1], Ghada Adel Hegazy[9]

Mohamed Zaeim Hafez Ahmed[1]*, Muhammad Abdelbaeth Hassan Elfiky[1], Elsayed Elagamy Elsayed Mohamed[2], Ramadan Hassan Ibrahim Thabet[2], Ahmed Mohamed Gad Allah[3], Ahmed Abdrabo Elshenawy Elsisi[2], Ahmed Abdel Nasser Ahmed Mohamed[2], Tarek Shikhon[4], Mostafa Abo-akrab[4], Sayed A.M.Mahmoud[5], Mohamed AbdelAziz Doma[5], Wael Ahmed Mahmoud Khattab[6], Khaled Saleh Ali Elhamaky[7], Mohamed El-Salamoni[6], Fatma Mahmoud Abdelraheem[8], Mahmoud Ahmad Mohamed Azab[6], Ashraf Abdel Aty Elshenawy Emara[6], Mohamed E EL-Refaey[1], Ahmed A. Abd El-Rhman[1], Ahmed F. Abdel Ghany[1], Ghada Adel

Correspondence

Mohamed Zaeim Hafez Ahmed

Physiology department, Faculty of Medicine, Al-Azhar University (Assiut), Assiut, EGYPT.

E-mail: dr.mohamedhafez20@gmail.com

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ABSTRACT

Background: The prevalence of diabetes among Egyptians is rising. Therefore, there is always a demand for innovative natural medicines. Medicinal plants have long been a significant source in search of novel, effective alternatives for human therapy. Chamomile is one of the most widely used medicinal plants, which may help hyperglycemic patients by lowering blood sugar levels. **Objectives:** To determine how chamomile extract affects the kidneys when albino male rats with chronic diabetes are induced by streptozotocin (STZ). **Methods:** The study was conducted in the Al-Azhar Faculty of Medicine (Assiut) pharmacology department animal laboratory. For this investigation, a local strain of fifty adult male albino rats was used as the animal model and weighed 120 to 150 g. In this study, rats were divided into five groups, body weight, and systolic blood pressure was measured, and blood samples were collected for measuring blood glucose and insulin level, HbA1c, Na, K, and renal function tests, and histopathological examination was done. **Results:** After the study, mean glucose levels, HbA1c, urea, creatinine, K, and systolic blood pressure were significantly decreased in group IV & group V compared to group III. In contrast, body weight serum insulin level and Na increased dramatically in group IV & group V compared to group III. **Conclusion:** The serum levels of urea and creatinine in diabetic patients may be positively affected by chamomile. Additionally, short-term chamomile uses benefits diabetic individuals by decreasing loss of body weight, lowering HbA1c, and increasing insulin levels.

Keywords: Chamomile leaves, Diabetes mellitus, Streptozotocin.

INTRODUCTION

Insulin secretion, action, or both can be erratic, leading to diabetes mellitus (DM), an endocrine condition. In turn, inadequate or absent insulin causes persistently elevated blood sugar levels and glucose intolerance.[1] More than 3000 years ago, physicians in ancient India and Egypt became the first to recognize it as a disease entity.[2] In Egypt, diabetes is becoming a more serious public health issue. Because of rising rates of central obesity, sedentary lifestyles, dietary changes, and possibly more significant usage of unregulated pesticides, it is becoming more and more common. The likelihood of diabetic complications was raised by smoking, lack of health knowledge, and poor adherence to treatment.[3]

In 2013, there were 382 million diabetics globally, and by 2035, 592 million people are expected to have the condition.[4] One of the leading causes of premature death worldwide is DM.[5] Because DM can result in a variety of costly, hazardous, and stressful effects, such as cardiovascular disease, retinopathy, neuropathy, and nephropathy, it places a considerable burden on health systems and society.[6] DM has several costs for society, including direct costs for people with DM, their families, and the healthcare sector, as well as indirect costs for the government and society.[7]

Most diabetes-associated issues are brought on by hyperglycemia and an increase in the production of free radicals obtained from oxygen, which can result in vascular dysfunction.[8] A member of the Asteraceae family, chamomile is the scientific name for Matricaria chamomilla or Matricaria recutita. With a high concentration of phenolic chemicals and terpenoids, chamomile has a wide range of biological and pharmacological actions, including anti-inflammatory, antioxidant, antibacterial, anti-cancer, anti-spasmodic, and sedative characteristics.[9]

One of the oldest medicinal plants is chamomile, which has a long history of use. According to recent studies, chamomile may help reduce blood sugar levels in hyperglycemia.[10] Therefore, this study aimed to determine how the chamomile extract affected albino male rats with chronic streptozotocin-induced diabetes and their bodies' oxidative processes.

MATERIALS AND METHODS

Study design

Fifty adult male albino rats of a local strain, housed in the animal lab of the pharmacology department at the Al-Azhar Universty Faculty of Medicine (Assiut), served as study participants. They weighed between 120 and 150 g and were about eight weeks old. We purchased rats from the animal house at Assiut University. The animals were kept in suitable cages

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(20 x 32 x 20 cm for every three rats) at room temperature and with a natural light-dark cycle. The rats were given a standard diet consisting of tap water and store-bought rat chow. They were detained for two weeks before the experiment to get used to the new conditions.

The rats were divided into five groups (10 rats each).

Group I: included control received distilled water.

Group II: included normal received chamomile extract (150mg/kg)

Group III: included diabetic received distilled water

Group IV: included diabetic received chamomile extract (150mg/kg)

Group V: included diabetic received chamomile extract (300mg/kg)

Chemical reagents

The Egyptian Company for Biotechnology-Egypt provided blood glucose, serum urea, and HbA1c kits**.** Insulin was included in the kits that Immunospec Corporation, Canoga Park, California, provided. Biolabo Reagents Kits, France, supplied Creatinine, Na+, and K+ kits. The following parameters were measured after 6th week: Body weight and Systolic blood pressure.

Biochemical estimations included Serum glucose[12] and insulin[13], Serum creatinine[14], urea, Na+[15], K$^+$[15], and HbA1c.[16]

Induction of diabetes

Diabetes was developed in rats that had fasted overnight by giving them a single intraperitoneal injection of streptozotocin (60 mg/kg body weight) in a 0.1M sodium citrate buffer (pH 4.5).[17] The preparation of this material for injection was done away from light.[18] Streptozotocin (MP Biomedicals, France) injections can cause deadly hypoglycemia because they destroy beta cells, which triggers a massive release of pancreatic insulin.[19] To avoid hypoglycemia, the rats were on an oral 10% glucose solution for 48 hours after the injections. The onset of diabetes was identified after three days using a tail vein blood sample and an Accu-Chek glucometer (Roche, Germany). [20] The study included rats with chronic diabetes with blood glucose levels of 350 mg/dl or higher. [21]

Chamomile extract preparation and administration

We bought fresh chamomile leaves from an Egyptian herbal market, Matricaria chamomilla L. Ten grams of chamomile plant leaves and one hundred milliliters of boiling water were combined in a glass container. The contents of the container periodically swirled and agitated for an hour, leaving them to stand at room temperature for the entire night. The extracts were then filtered using filter paper (Double Rings filter paper 102, 11.0 cm). Using a vacuum pump rotary evaporator, the filtrates were concentrated at 50°C under reduced pressure, yielding a greenish mass of leaf extracts. Every day at 11 a.m., chamomile was administered orally via gavage.

Collection of blood samples for laboratory assessment

Morning blood samples were obtained after a 12-hour fast and at 10 am from the retro-orbital venous plexus after the experiment. A heparinized capillary tube with an internal diameter of 0.75 to 1.0 mm was placed within the medial can reach the eye globe. After the blood was collected into a glass centrifuge tube that was dry, clean, and graded, the serum was separated by centrifuging at 5000 rpm for 10 minutes. The separated serum was aliquoted and frozen in an Epindorff tube at -20°C until it was time to measure specific biochemical characteristics.

Histopathological examination

The kidney and pancreas samples were quickly preserved in 10% neutral buffered formalin, embedded in paraffin, cut into 5-m-thick sections, and stained with hematoxylin and eosin (HE) to assess the histological analysis.

Systolic Blood Pressure Measurement Procedure

Rats were routinely trained to use the tail-cuff method to measure SBP. The rats spent two hours daily at nine in the morning in their maintenance cages. Then, the systolic blood pressure was measured in free-ranging animals. After it was established that the rats had had adequate training and were unlikely to be distressed by the tail-cuff method, systolic blood pressure values were obtained. Systolic blood pressure was measured simultaneously on two different days (11 AM) every two weeks. [22] Systolic blood pressure was measured using rat tail systolic blood pressure equipment (Harvard - USA):

Biochemical investigations

Blood glucose measurements

The blood glucose level was assessed using diamond diagnostics kits and an enzymatic colorimetric technique.[12]

Insulin Measurements

Enzymatic immunoassay was used to quantify insulin concentrations in serum by measuring serum insulin levels.[13] The assay technique uses two anti-insulin antibodies: one for immobilization in the solid phase (microtiter wells) and the other for the antibody-enzyme Horseradish peroxidase (HRP) conjugate solution. The microtiter wells coated with the insulin antibody received the standards and test samples (sera). Then, HRP (conjugate)-labeled anti-insulin antibodies were included. The wells were cleaned with water to eliminate unbound labeled antibodies following an hour of incubation at room temperature. Adding a TMB (tetramethylbenzidine) solution and subsequent incubation for 20 minutes caused the production of a blue color. With the use of a stop solution, color development was stopped. The addition of a stop solution halted the color development. At 450 nm, the hue shifted to yellow and was spectrophotometrically recorded. The relationship between the test sample's color intensity and insulin levels was direct.

Serum urea measurements

A urease colorimetric analysis was performed to measure the serum urea content. Urea hydrolyzes in the presence of urease and water to produce carbon dioxide and ammonia. When the pH is alkaline, free ammonia combines with an indicator to make a colored complex inversely proportional to the amount of urea in the sample.[23]

Sodium measurement

Sodium was assessed based on the reaction between a certain chromogen and a chromophore whose absorbance changes directly to the sodium content in the test substance. [15]

Potassium measurement

A modified version of Maruna and Trinder's first methods was used to determine potassium. By using these techniques, sodium is precipitated as sodium magnesium uranyl acetate or triple salt. The remaining uranium is then combined with ferrocyanide to form a chromophore, the absorbance of which changes in direct proportion to the amount of sodium present in the test sample.[15]

Serum HbA1c Measurements

Serum HbA1c was measured, and its quantities were quantitatively determined using an enzymatic immunoassay.[16] This assay employs the competitive inhibition enzyme immunoassay technique. A microplate has been pre-coated with an anti-HbA1c monoclonal

antibody. A competitive inhibitory process is initiated between biotin-labeled HbA1c and unlabeled HbA1c (Standards or samples) using the pre-coated antibody specific to HbA1c. After incubation, the unbound conjugate is eliminated. Following that, avidin conjugated to horseradish peroxidase (HRP) is added to each microplate well, and the mixture is then incubated. The level of HbA1c in the sample is inversely linked with the amount of bound HRP conjugate. The color that results from adding the substrate solution has an inverse relationship with the HbA1c level of the sample.

Statistical analysis

The statistical analysis was carried out using the software program (SPSS). The quantifiable data was displayed as mean± standard error (S.E.). The statistical analysis of the differences between the groups was conducted using a one-way analysis of variance (ANOVA) and the Tukey-Kramer test to determine differences in means. The cutoff point for statistical significance is set at $P < 0.05$.

RESULTS

In comparison to the control groups GI and GII, the mean body weight in group IV dramatically dropped after the eighth week, according to the current study. Compared to the diabetes control group GIII, the mean body weight in group IV increased very little. When GV was compared to the diabetic control group GIII, mean body weight increased significantly; however, there was a significant decline when GV was compared to the control group GI and GII. No discernible differences were found when GIV and GV were compared (Table 1).

At the end of the eighth week, the mean systolic blood pressure in both G_{IV} and G_V decreased significantly compared to GIII, and the mean systolic blood pressure in GV decreased considerably compared to G_{IV}. However, there were no significant differences between GIV and GV and G_I and G_{II} (Table 2).

Furthermore, by the conclusion of the eighth week, group IV's mean glucose had considerably increased compared to the control groups, GI and GII. On the other hand, it dropped substantially in contrast to group III. The GV level significantly increased compared to the control groups GI and GII and dramatically decreased compared to GIII. In addition, the GV group's performance declined significantly compared to the GIV group. Nonetheless, the mean insulin levels of GIV & GV significantly increased compared to GIII but dramatically dropped compared to the control groups, GI & GII. There was a noticeable increase in GV relative to GIV. On the other hand, the mean Hba1c in GIV and GV significantly dropped from GIII. When compared to G_{IV}, the mean Hba1c in G_V was reduced considerably. Compared to both G_I and G_{II}, there was a discernible rise in the mean Hba1c in both G_{IV} and G_V. (Table 3).

Furthermore, after the eighth week, GIV & GV had considerably lower mean urea and creatinine levels than GIII. Urea levels in GV substantially decreased in comparison to GIV. In terms of creatinine,

Table 1. Effects of different doses of chamomile extract on mean body weight in diabetic male albino rats after 8th weeks in the studied groups.

	Group I	Group II	Group III	Group IV	Group V
Body weight/g	212.3± 2.37	211.9± 1.45	160.6± 2.77*	174.8± 3.71**	181.1± 4.20**

* Significant decrease when compared with both G_I &G_{II}.
** significant increase when compared with G_{III}.

Table 2. Effects of intake of chamomile extract on mean Systolic blood pressure in diabetic male albino rats after 8th weeks in the studied groups.

	Group I	Group II	Group III	Group IV	Group V
Sys. BP/ mm Hg	119.2± 2.03	117± 2.49	141.4 ± 4.1*	124.9± 0.97**	113.2± 1.64#**

* Significant increase when compared with both G_I & G_{II}.
** significant decrease when compared with G_{III}.
# significant decrease when compared with GIV.

Table 3. Effects of intake of chamomile extract on mean glucose, insulin, and Hba1c in diabetic male albino rats after 8th weeks in the studied groups.

	Group I	Group II	Group III	Group IV	Group V
Glucose (Mg/dl)	105± 3.59	106.9± 2.29	406.1± 10.73*	284.6 ± 14.31**	251.1± 2.37$**
Insulin (µU/ml)	31.29±0.59	29.99± 0.61	4.71± 0.45#	8.51± 0.64##	16.96± 0.49φ##
HbA1c%	6.033± 0.21	5.81± 0.35	13.79± 0.7&*	9.89± 0.57**	7.9 ± 0.31***

* Significant increase when compared with both G_I & G_{II}, ** Significant decrease when compared with G_{III},
$ Significant decrease ($P < 0.05$) in mean Hba1c in G_V when compared with G_{IV}.
# Significant decrease when compared with both G_I &G_{II}, ##Significant increase when compared with G_{III}, φ Significant increase when compared with both G_{IV}.

Table 4. Effects of intake of chamomile extract on renal functions in diabetic male albino rats after 8th weeks in the studied groups.

Renal functions	Group I	Group II	Group III	Group IV	Group V
Urea (Mg/dl)	22.3 ±1.08	19.5± 0.91	53.7± 2.9*	36.4± 2.89**	25.2 ± 2.61**
Creatinine (Mg/dl)	0.65± 0.061	0.603± 0.052	1.31± 0.078*	0.77± 0.09**	0.69 ± 0.069**

* Significant increase when compared with both G_I & G_{II}.
** Significant decrease when compared with G_{III}.

Table 5. Effects of intake of chamomile extract on electrolytes in diabetic male albino rats after 8th weeks in the studied groups.

Electrolytes	Group I	Group II	Group III	Group IV	Group V
Na (Meq/L)	146.9± 1.11	144.1± 1.13	140.3± 0.64*	145.8± 0.72**	147.1± 1.078**
K (Meq/L)	4.49± 0.18	4.51± 0.19	5.59± 0.024#	4.61± 0.219##	4.6± 0.22##

* Significant decrease when compared with both G_I & G_{II}, ** Significant increase when compared with G_{III}. # Significant increase when compared with both G_I & G_{II}, ## Significant decrease when compared with G_{III}. Significant change = P value < 0.05.

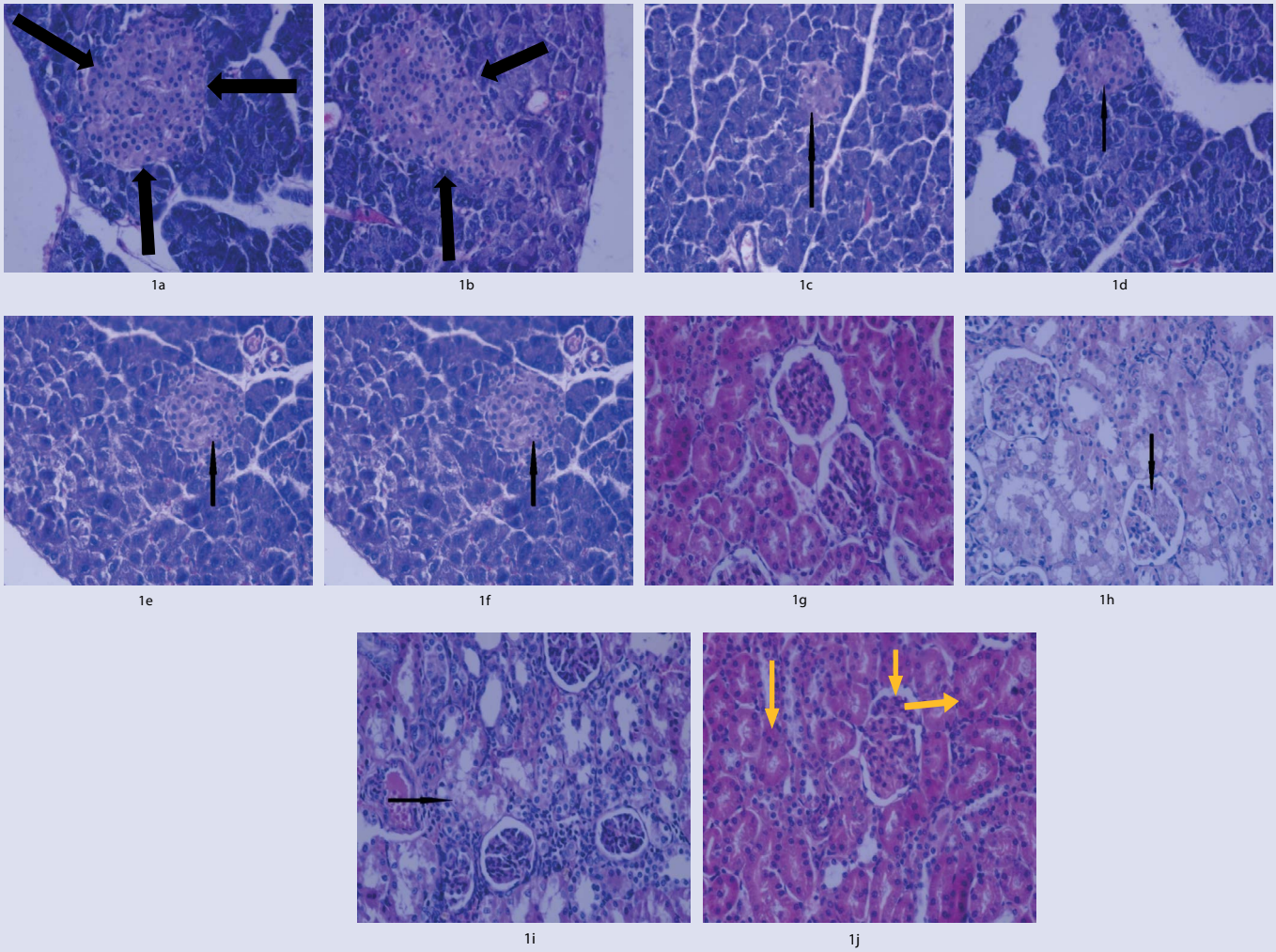

Figure 1a. Pancreas of normal rats that received distilled water (G_I) (H & E stain x 400).
Figure 1b. Pancreas of normal rats that received chamomile extract (150 mg/kg) (G_{II}) (H & E stain x 400).
Figure 1c. Pancreas of diabetic rats received distilled water (G_{III}) (H & E stain x 400)
Figure 1d. Pancreas of diabetic rats that received chamomile extract (150 mg/kg) (G_{IV}) (H & E stain x 400).
Figure 1e. Pancreas of diabetic rats that received chamomile extract (300 mg/kg) (G_V) (H & E stain x 400).
Figure 1f. Kidney of normal rats that received distilled water (G_I) (H & E stain x 400).
Figure 1g. Kidney of normal rats that received chamomile extract (150 mg/kg) (G_{II}) (H & E stain x 400).
Figure 1h. Kidney of diabetic rats received distilled water (G_{III}) (H & E stain x 400).
Figure 1i. Kidney of diabetic rats that received chamomile extract (150 mg/kg) (G_{IV}) (H & E stain x 400).
Figure 1j. Kidney of diabetic rats that received chamomile extract (300 mg/kg) (G_V) (H & E stain x 400).

there was no difference between GIV and GV, although there was a difference between GI and GII (Table 4). Furthermore, after the eighth week, the mean Na in GIV & GV increased dramatically compared to GIII. On the other hand, the mean k in GIV and GV declined markedly in comparison to GIII. However, there was no appreciable variation in mean Na or K between GIV and GV. There were no discernible differences between GIV and GV compared to GI and GII (Table 5).

Additionally, all the pancreatic cells were present in the correct proportions, and the cells of the islets of Langerhans (arrow) showed no histological changes. In addition, the cells of the islets of Langerhans experience necrosis and atrophy when exposed to distilled water (arrow). Furthermore, the cells of the islets of Langerhans (arrow) experienced modest necrosis and shrinking due to the usage of chamomile extract. In generally healthy islets of Langerhans, there was a slight lymphocytic infiltration during the consumption of honey plus canagliflozin (arrow), (Figure 1 a-e). The glomeruli and tubules were also visible in a typical way. There was also tubular degeneration, glomerulosclerosis (arrow), and mononuclear cell infiltration. Modest lymphocytic infiltration in the tubal epithelium (arrow), although the glomerular tufts were standard. In usually healthy kidney tissue, there was a slight thickening of the glomerular basement membrane (arrow), (Figure 1 f-j).

DISCUSSION

Our results showed a significant increase in body weight (BW) in diabetic rats treated with chamomile extract compared to diabetic rats not receiving treatment. Chamomile extract's antioxidant properties may cause diabetic rats to increase body weight after receiving honey treatment. Because antioxidants have anti-catabolic qualities, they can stop protein catabolism. As a result, refraining from drastic weight loss. [24]

The results of our investigation showed that chamomile extract significantly reduced the systolic blood pressure of diabetic rats as compared to control diabetic rats. These results corroborated Awaad et al. [25], who found that supplementing with chamomile extract has an antihypertensive effect. Oxidative stress is also suggested to play a role in the development of hypertension. [26] The notion that oxidative stress leads to hypertension is further supported by the benefits of antioxidants in treating oxidative stress and regulating or lowering high blood pressure in both experimental and clinical studies. [27]

The results of our study indicate that chamomile extract is an excellent way to lower blood sugar levels in rats with diabetes caused by STZ. These results corroborated those of Cemek et al. [28] and Zemestani et al.[29] who found that chamomile extracts lowered blood glucose levels in rats with diabetes induced by streptozotocin. By decreasing the levels of fibrinogen (FBG), glycated hemoglobin, glucose tolerance, and glycated serum protein (GSP) in diabetic mice and raising insulin secretion and glucose tolerance, the total flavonoids in this plant also have a hypoglycemic effect.[30]

This study demonstrated that in diabetic rats, chamomile extract considerably increases insulin levels. This relates to the study of Prasanna et al.[31] which discovered that administering chamomile extract raised insulin levels. Our results showed that chamomile extract-treated diabetic rats had significantly greater blood Na+ levels and considerably reduced urea, creatinine, and K+ serum levels. The potential of a chamomile extract to shield organs from harm caused by chemical assaults is supported by two previous studies.[31,32] This damage is assumed to be caused by increased oxidative stress. The improvement in renal functions in diabetic rats treated with chamomile extract may be related to the extract's hypoglycemic and antioxidant effects, according to El-shaer and Nofal's [33] findings that chamomile extract demonstrated protective and enhancing effects against STZ-induced diabetes in rats. In a different study, Hajizadeh-Sharafabad et al.[9] , Perestrelo et al.[34] reported that chamomile helps with oxidative stress indicators, glycemic and lipid profiles, and diabetes mellitus-related issues. Supplementation may lessen the progressive end-organ damage caused by long-term hyperglycemia in diabetes mellitus since it has been demonstrated to reduce oxidative stress and shield against organ damage in animals with experimentally generated diabetes.

Our findings showed that chamomile extract significantly reduced the HbA1c levels of diabetic rats compared to the control group. A positive correlation exists between the reduction of HbA1c levels in treated diabetic rats and their improved glycemic condition. These results corroborated Rafraf et al.[35] who discovered that chamomile extract consumption dramatically reduced HbA1c and blood glucose levels. Rats treated with 300 mg/kg of chamomile extract showed a more significant improvement in serum levels of HbA1c, insulin, blood urea, and glucose than diabetic rats given 150 mg/kg of the extract. These rats also showed a considerable drop in their systolic blood pressure. These findings corroborated those of Cemek et al.[28] who demonstrated that in STZ-diabetic mice, chamomile dramatically decreased the oxidative stress caused by hyperglycemia and protected cells dose-dependently. Our analysis revealed that the controls' Langerhans were within the standard size range, in contrast to the diabetic untreated group, which displayed necrosis and atrophy of the islets of Langerhans cells. Our results were consistent with those of Kulkarni et al. [36] who reported that the mean-cell number of STZ diabetic rats significantly decreased. Furthermore, the pancreatic islets' necrosis resulted in a discernible reduction in size and degradation of the -cells. According to the study's findings, diabetic rats given chamomile extract (150 mg/kg) had their islets of Langerhans cells somewhat shrink and barely necrose. According to our findings, El-shaer and Nofal demonstrated an enhanced ameliorative impact of chamomile, as the positively stained cells for the insulin marker in most of the studied sections ranged from 85 to 90%HPF cells, with a small number of cells. In 10- 15%/HPF cells, the staining or positivity was only marginal.[33]

In the current investigation, in otherwise healthy islets of Langerhans, the pancreas of diabetic rats given 300 mg/kg of chamomile extract showed a slight lymphocytic infiltration. Given chamomile extract (300 mg/kg), diabetic rats showed a higher improvement in their pancreas histology. This improvement may have been caused by an enhanced antioxidant defense system and decreased oxidative stress from hyperglycemia. The kidney sections of normal rats given saline in the current study showed normal morphology in their glomeruli and tubules. The kidneys of diabetic rats left untreated showed signs of tubular deterioration, glomerulosclerosis, and mononuclear cell infiltration. Our results agreed with those of Razdan and Minaz, [37].

A histological examination was performed on kidney tissue from normal rats based on their findings. On the other hand, the kidney tissue of diabetic control rats underwent the same analysis, identifying thickening of the glomerular basement membrane, glomerulosclerosis, tubular degeneration, and infiltration of mononuclear cells. Additionally, the diabetic group's kidneys showed thicker basement membranes, nodular sclerosis, and mesangial expansion, according to Abdel-Wahab et al.[38] The kidneys of diabetic rats administered 150 mg/kg of chamomile extract displayed typical glomerular tufts, minimal tubal epithelium vacuolization, and modest lymphocytic infiltration in the current study. According to Alahmadi et al. [32], chamomile has a preventive effect against renal injury.

The present study is in line with Abou Galala et al 39 who elucidate the protective effect of chamomile extract (300mg/kg) on renal functions and diabetic indices. In the other hand our study interpretate chamomile extract protective effect which is dose dependent Cemek et al 28 in two doses 150mg/kg and 300mg/kg with relatively larger number of samples (50 rats) with 8 weeks experimental period.

Improvements were made to the effects of chamomile on cell death. Previous studies have also demonstrated the preventative benefit of chamomile against a few kidney injury models due to its antioxidant and anti-apoptotic capabilities. Our results indicate that there was a slight thickening of the glomerular basement membrane in the kidney tissue of diabetic rats treated with both chamomile extract (300 mg/kg) and chamomile extract. The increased improvement in kidney histology in diabetic rats treated with 300 mg/kg of chamomile extract may be attributed to a reduced level of oxidative stress brought on by hyperglycemia and an enhanced antioxidant defense system.

CONCLUSION

Our findings suggest that chamomile may benefit the serum creatinine and urea levels of diabetes patients. Additionally, using chamomile briefly helps diabetic people lose weight, increase their insulin levels, and lower their HbA1c.

ETHICAL ISSUES

The research and the protocol of this study were based on the guidelines of animal studies. They were approved by the Ethics Committee of Al-Azhar University of Medical (Assiut), (REC ID, AZAST/Research/35/11/2023). Accordingly, we tried to follow the guidelines related to animal experiments, which were approved by the United States National Institutes of Health. The supplier of the streptozotocin was MP Biomedicals in France. Additionally, chamomile was bought at a nearby herbal Egyptian market.

CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

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