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Antioxidant and Antihyperlipidemic Effect of *Solanum Nigrum* Extract in Experimental Diabetes Model

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ABSTRACT Diabetes mellitus (DM) is a chronic metabolic non-communicable disease; it is globally considered the fifth cause of death and it has attained worldwide epidemic proportions. In our study, we aimed to investigate the diabetic effects of *Solanum nigrum* extract using the control group (C), diabetes group (D), groups given the *Solanum nigrum* extract (SN) and diabetes group + *Solanum nigrum* extract (D+SN). Our results observed the biological effectiveness of *Solanum nigrum* extract on glucose levels, significant increase serum glucose level group (D) (663±21.8 mg/dL) in comparison with C (131±9.8 mg/dL) were recorded. However, there were no significant difference in glucose level between C group (131±9.8 mg/dl) and SN group (196.14±12.1 mg/dL). Moreover, glucose level of D+SN group (484.8±40.0 mg/dL) was significantly higher than C (131±9.8 mg/dl), D (663±21.8 mg/dl) and SN groups (196.14±12.1 mg/dL). Total antioxidant status (TAS) level in D group (1.85±0.15.7) was significant when compared C group (1.28±0.17). Significant differences were observed between D group and D+SN group (1.54±0.07). However, TAS levels showed no significant difference in both SN (1.27±0.10) and D+SN (1.54±0.07) groups in comparison to the control group. Total oxidant status (TOS) level in D group (6.30±1.41) was given significant differences in comparison with control C (3.87±0.34), SN (4.87±0.80) group and D+SN (4.14±0.34) groups. In contrary, there were no significant differences between all of C, SN, D+SN groups. As a result, we can say that the *Solanum nigrum* plant extract is effective on diabetes, but it cannot lower the glucose level to normal levels, it needs to be investigated in future studies and its effects at different doses by different extraction methods.

Keywords: *Hypolipidemica agent, Streptozocin, Oxidative stress.*

ÖZ

Deneysel Diyabet Modelinde *Solanum nigrum* Ekstraktının Antioksidan ve Antihiperlipidemik Etkisi

Diabetes mellitus (DM), kronik, metabolik, bulaşıcı olmayan bir hastalıktır, dünya çapında beşinci ölüm nedeni olarak kabul edilir ve dünya çapında epidemik oranlara ulaşmıştır. Çalışmamızda kontrol grubu (K), diyabet grubu (D), *Solanum nigrum* özü (SN) ve diyabet + *Solanum nigrum* özü (D+SN) verilen gruplar kullanılarak *Solanum nigrum* ekstraktının diyabetik etkilerini araştırmayı amaçladık. Sonuçlarımız, *Solanum nigrum* ekstraktının glukoz seviyeleri üzerinde biyolojik etkinliği gözlenirken, serum glukoz seviyesinde (D) (663±21.8 mg/dL) C'ye (131±9.8 mg/dL) kıyasla anlamlı artış kaydedildi. Ancak C grubu (131±9.8 mg/dl) ve SN grubu (196.14±12.1 mg/dL) arasında glukoz düzeyi açısından anlamlı fark yoktu. Ayrıca D + SN grubunun glukoz düzeyi (484.8±40.0 mg/dL), C (131±9.8 mg/dl), D (663±21.8 mg/dl) ve SN gruplarına (196.14±12.1 mg/dL) göre anlamlı olarak yüksekti). D grubunda (1,85±0,15,7) toplam antioksidan durum (TAS) düzeyi, C grubu (1.28±0.17) ile karşılaştırıldığında anlamlıydı. D grubu ile D+SN grubu arasında anlamlı farklar gözlendi (154±007). Ancak TAS düzeyleri hem SN (1.27±0.10) hem de D+SN (1.54±0.07) gruplarında kontrole göre anlamlı farklılık göstermedi. D grubunda (6.30±1.41) toplam oksidan durum (TOS) düzeyi, kontrol C (3.87±0.34), SN (4.87±0,80) grubu ve D+SN (4.14±0.34) gruplarına göre anlamlı farklılık gösterdi. Aksine, tüm C, SN, D+SN grupları arasında anlamlı bir fark yoktu. Sonuç olarak *Solanum nigrum* bitki ekstraktının diyabet üzerinde etkili olduğunu ancak glikoz seviyesini normal seviyelere indiremediğini, farklı dozlarda ve farklı ekstraksiyon yöntemleri ile etkilerinin ileriki çalışmalarda araştırılması gerektiğini söyleyebiliriz.

Anahtar Kelimeler: *Hipolipidemik ajan, Oksidatif stres, Streptozosin.*

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INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic non-communicable disease; it is globally considered as the fifth cause of death and it has attained worldwide epidemic proportions. As of 2015, more than 415 million adults were investigated to have DM, and this number is predicted to elevate to 642 million by 2040 (Domingueti et al. 2016; Unnikrishnan et al. 2016). DM is a group of metabolic disorders of carbohydrate, protein and fat which can be recognized by chronic hyperglycemia (the elevation of glucose level in blood) following defects in secretion and/or action of insulin, a protein (hormone)is produced in β-cells of the pancreas (Patel et al. 2012; Ahmet et al. 2019; Söğütlü et al. 2019). Hyperglycemia is also followed by the generation of reactive species (ROS) which subsequently leads to lipid peroxidation and membrane damage and thus, plays an important role in the production of secondary complications in diabetes mellitus such as kidney, eye, blood vessel, and nerve damage. The inhibition of peroxidation chain reaction through antioxidants protect β-cells from oxidation and consequently play important roles in regulating related-metabolic activities in diabetes. Such antioxidants including phenolic compounds (tannins, flavonoids and stilbenes) and vitamin C and vitamin E can naturally be found from plant extracts preserving functions of β-cells and also preventing diabetes-induced formation of ROS (Patel et al. 2011).

In addition, extracts of several herbal medicines have been used and recommended to have potential therapeutic effects on diabetes and its complications (Tiwari and Rao 2002; Mukherjee et al. 2006). *S. nigrum* is a herb that belongs to the Solanaceae family and includes in a class of Dicotyledonae. *S. nigrum* is also known as black nightshade, garden nightshade, or blackberry nightshade (Zaidi et al. 2019; Alam et al. 2022). Extracts from *Solanum nigrum Linn* (European black nightshade) which belongs to the *Solanum* genus and Solanaceae family (Mani et al. 2022) have been reported to exhibit anti-tumor activity against different types of cancers (Xiang et al. 2016) and significant antidiabetic activities against diabetes (Poongothai et al. 2010). Due to its antipyretic - diuretic activities, this plant is extensively used as Chinese folk medicine. Recent studies revealed that extracts of *S. nigrum* exhibit antioxidant (Saibu et al. 2020), hepatoprotective (Hsu et al. 2009), antihyperlipidemic, antidiabetic (Hou et al. 2013; Sohrabipour et al. 2013) and anti-inflammatory activities (Wang et al. 2017).

The present study is carried out to evaluate the antioxidant and antihyperlipidemic activities of the extract of *S. nigrum Linn* grown in southern Iraq on the rate of diabetes in rats.

MATERIAL AND METHODS

Experimental Animals

Twenty-eight male rats weighing 200-250 g were obtained from the Experimental Medical Applicated and Research Center of Van Yuzuncu Yil University, Medical Faculty. Subjects randomly composed of seven rats each; control (C), Diabetes Mellitus without SN (D), Diabetes Mellitus with SN group given and SN given. This study was performed with Van YYU Animal Experiments Local Ethics Committee (VAN YUHADYEK) (Approval no: 2016/02, date: 25.02.2016).

Preparation of Plant Extract

Solanum nigrum L. plant was collected from northern Iraq. It has been confirmed in the herbarium of Van YYU Faculty of Science, Department of Biology (*S. nigrum L.,* Sp. PI. 186). Plant samples of Solanum nigrum were thoroughly washed under tap water, and then dried in the shade. The dried samples were finely pulverized to a powder sample. 100 g of powder was suspended in 250 ml of water for two hours and then heated to 60-65 °C for 30 minutes. The extract was collected by the separation process and this process was repeated three times. The collected extracts were put together and passed through a swab. The filtrate was evaporated at 40-50 °C in rot vapor under reduced pressure. The obtained dark semi-solid material (yield 14%) was maintained at 0-4 °C until using. A known amount of residual extract was then suspended in distilled water and administered to animals via oral (Umamageswari et al. 2017).

Experimental Design

Diabetes-induced D and DSN group rats were administered intraperitoneally (i.p.) by dissolving 45 mg/kg single dose streptozocin (STZ) (Sigma, USA) in citrate buffer at pH 4.5 (0,1 M) (Bloch and Vardi, 2005). The same amount of saline was injected into the control group. D and DSN group, 72 hours after injection of STZ, blood glucose levels were determined by means of Plus MED Accuro biosensor screener and striplines in the blood samples taken from the tail of the rats. Blood sugar levels higer than or equal to 270 mg / dl were included in the study. The rats in the SN and D+SN groups were orally administered with 250 mg/kg/day gavage of SN extract dissolved in distilled water every day (Umamageswari et al. 2017).

Control Group: Seven randomly selected rats were divided into control groups.

Group 1: Seven rats STZ solutions in this group were given 45 mg/kg IP route. (D)

Group 2: Seven rats in this group were dissolved in distilled water and the SN solution was administered orally for 25 days at 250 mg/kg/day. (SN)

Group 3: Seven rats in this group were treated with STZ solution 45 mg / kg IP, followed by 72 hours after the glucose measurement was performed. Water was added to the rinsed aqueous solution at a dose of 250 mg/kg/day for 28 days. (D+SN)

Collection of Samples

Blood samples were drawn from the left ventricle of the hearts of the animals to the glazed glass serum tubes under ketamine and rompun anesthesia after a twenty-eight-day trial. The blood samples were centrifuged at 3000 rpm for 10 minutes at + 4 °C. TAS, TOS and biochemical parameter analyzes were obtained in these samples.

Preparation of Samples

Blood samples were carefully collected from the heart. About 5 mL blood samples from each rat were withdrawn into vacutainer tubes with gel and centrifuged to (3000 rpm in 4°C) for ten minutes to separate serum, the serum was transferred to eppendorf tubes for biochemistry tests, TAS, and TOS all samples were stored at -20 ºC prior to analysis. Biochemical parameters including (glucose, high density lipoprotein (HDL), low density lipoprotein (LDL), total cholesterol, triglyceride, very low-density lipoprotein (VLDL-cholesterol) were determined using kits (Architect

Plus, ci16200, by Abbott Company, USA) and biochemical auto analyzers (Cobas C311, Roche- Germany).

Statistical Analysis

The results obtained in the study were assessed using (SPSS 22.0). The results were analyzed for statistical significance using one-way ANOVA. Multiple comparisons to compare the data of groups 1-3, Raw values from all analyzes were presented as the mean±standard error of respective groups ($p<0.05$).

RESULTS

The present study was investigated to study the effect of *Solanum nigrum* extract on glucose level, total cholesterol, triglyceride, HDL, LDL, TAS and TOS on blood samples of rats. The levels of those parameters belonging to the experimental groups are shown in Table 1.

Glucose Levels

Results from table 1 represent significant increasing of serum glucose level ($p<0.05$) in diabetes group (D) in comparison with control group (C). However, there were no significant differences ($p>0.05$) in glucose level between C group and *Solanum nigrum* extract group (SN). Moreover, in regards to glucose level, results from table 1 demonstrated that (D+SN) group was significantly higher than results from all of C, and SN groups and lower than D groups.

Cholesterol Levels

In return to table 1, results showed that there were no significant differences ($p>0.05$) in cholesterol levels between C group and SN group, D group and D+SN group (Table 1). Diabetes caused significant increase ($p<0.05$) in triglycerides (Tg) level in D group in comparison to both C and SN group. In contrast, no significant differences were found between D group and D+SN group, Furthermore, triglyceride (Tg) levels showed no significant differences ($p>0.05$) between SN, D+SN and C group (Table 1). Despite recording higher levels of HDL-cholesterol in D, SN and D+SN groups in comparison to control (C group), these levels showed no significant differences ($p>0.05$) in C group compared to SN group, D group and D+SN group (Table 1). LDL-cholesterol levels demonstrated no significant difference ($p>0.05$) in C group compared to D group, SN group and D+SN group (Table 1). Results from table 1 observe that the diabetes resulted in significant increase ($p<0.05$) in VLDL-cholesterol levels in D group in comparison with control C. Whereas, SN group observed lower level of VLDL-cholesterol in comparison to control C group, this change was not significant. Similarly, the level of VLDL-cholesterol in D+SN was not significantly higher in comparison with control (Table 1).

Oxidative Stress Analysis

As a consequence of diabetes, results showed significant increase ($p<0.05$) in TAS level in D group compared to control group (C). However, results determined from respective samples observed no significant differences between D group and D+SN group. Moreover, TAS levels showed no significant difference ($p>0.05$) in both SN and D+SN groups in comparison to control, when SN administrated to diabetes rats (Table 1). Diabetes resulted in significant increase ($p<0.05$) in total oxidant status (TOS) in D group in comparison with control C, SN group and D+SN groups. In contrary, there were no significant differences ($p>0.05$) between all of C, SN D+SN groups (Table 1).

Table 1: The level of serum biochemical parameters in experimental groups.

Parameters	Control (C)	Diabetes (D)	*S. nigrum* (SN)	Diabetes + *S.nigrum* (EX) D+SN
Glucose (mg/dL)	131±9.80^{a}	663±21.80^{c}	196.14±12.10^{a}	484.80±40.00^{b}
T. Cholesterol (mg/dL)	51.50 ±1.90^{a}	59.40±3.60^{a}	53.28±2.50^{a}	60.06±3.60^{a}
Triglyceride (mg/dL)	54.66±7.10^{a}	73.57±12.70^{b}	41.42±3.60^{a}	59.66±7.80^{ab}
HDL Cholesterol (mg/dL)	38.60±2.60^{a}	41.62±3.10^{a}	42.48±1.40^{a}	45.81±3.50^{a}
LDL Cholesterol (mg/dL)	4.10±0.20^{a}	4.10±0.80^{a}	6.00±1.10^{a}	5.70±0.07^{a}
VLDL Cholesterol (mg/dL)	10.93±1.42^{a}	14.71 ±2.42^{b}	8.28±0.72^{a}	11.93±1.56^{ab}
TAS (µmol H_2O_2 Equiv/L)	1.28±0.17^{a}	1.85±0.15^{b}	1.27±0.10^{a}	1.54±0.07^{ab}
TOS (µmol H_2O_2 Equiv/L)	3.87±0.34^{a}	6.30±1.41^{b}	4.87±0.80^{a}	4.14±0.34^{a}

HDL: High density lipoprotein, LDL: Low density lipoprotein, VLDL: Very low-density lipoprotein, TAS: Total antioxidant status, TOS: Total oxidant status.

* Different letters between the lines is statistically significant ($p<0.05$). X=mean, SE=Standard error.

DISCUSSION AND CONCLUSION

High concentrations of plasma glucose lead to metabolic disorders and glucose intolerance, this metabolic abnormality is characterized by hyperglycemia (Taylor et al. 2021; Al-kuraishy et al. 2021). This condition is associated with the increase of metabolic disturbance of carbohydrate, fat, and protein enhancing the production of free radicals that follow by oxidative stress, renal failure, neurodegeneration, cardiovascular abnormalities and immune dysfunction (Hung et al. 2012).

As shown in table 1, glucose level in diabetes group (D) was significantly increased in comparison with control group (C). This result agrees with previous studies by Hung et al. (2012) which they stated that the concentrations of plasma glucose are increased in DM patients following significant deficiency in insulin. However, results showed no significant differences in glucose level between control group and *Solanum nigrum* extract group (SN). In this context, extracts of *Solanum nigrum* had no significant effect in decreasing glucose level in normal rats.

Poongothai et al. (2010) which they determined significant reduction in glucose level after administration of the aqueous extract of *Solanum nigrum* to induced diabetic rats. In addition, a relevant study considering antidiabetic activity of *Solanum nigrum* in Alloxan Induced diabetic rats by Umamageswari et al. (2017) indicated that aqueous extract of berries of this plant at 200 mg/kg/day observed significant reduction in blood glucose by 7 days, they finally concluded effective roles of berries extracts of *Solanum nigrum* as an antidiabetic activity. Tiwari and Jain (2017) studied hypoglycemic activity of *Solanum nigrum* on alloxan Induced DM in rats. In this study alcoholic extracts of leaves of this plant were used at different doses 50, 100, 200, 400 mg/kg of body weight. Their results indicated significant hypoglycemic role of this plant. Our results are in line with previous studies regarding antidiabetic activities of *Solanum nigrum*, in this context, aqueous extracts from the respective plant seems to have effective roles in regulating blood glucose levels and possesses therapeutic characteristics against hyperglycemic activities.

Hyperlipidemia can be found as a major risk factor of cardiovascular pathologies. It is confirmed that the *Solanum nigrum* plays effective roles in inhibiting H^+K^+ATPase which might subsequently serve as cardio protective regimen (Atanu et al. 2011). Lee et al. (2005) on the effect of aqueous extract of *Solanum nigrum* glycoprotein on levels of plasma lipid including total cholesterol in mice. They found the administration of this plant (20 and 40 g head body weight g^{-1}) were significantly decreased total cholesterol levels. Some researchers assessed antihyperglycaemic and antioxidant effects of leaves extract of *Solanum nigrum* in alloxan induced-diabetic rats, they found that leaves extract at 100 mg/kg was not significantly reduced the amount of VLDL in comparison to its level in normal rats (Maharana et al. 2011).

Arulmozhi et al. (2010), found that the use of the fruit extract of *Solanum nigrum* was not significantly reduced the level of triglyceride when rats treated with 250 mg/kg b.wt of this plant. A similar result was found by Gupta et al. (2009), they demonstrated that despite the reduction of triglyceride level of rats received high cholesterol diet and exposed to saponins of *Solanum nigrum* (100 mg/kg body weight p.o.), this reduction was not significant in comparison to triglyceride level in rats received normal diet. Our results showed that despite some reductions in the level of triglyceride in SN group in comparison to control C group, and in D+SN in comparison to D group, this result was not significant. In this study, the administrations of the extract of *Solanum nigrum* to respective rats were not significantly effective against those biochemical parameters in the present study.

Important oxidative parameters including Total oxidant status (TOS) and all serum antioxidants which are known as total antioxidant status (TAS). These parameters are used to monitor the progression and range of damages that resulted from oxidative stress in rat blood serum (Turkez et al. 2012). In the current study, we analyzed both TAS and TOS levels of serum in diabetic rats and we found significant differences in both parameters when compared to non-diabetic rats.

Important oxidative parameters including TOS and TAS were used to monitor the progression and range of damage results from oxidative stress in rat blood serum (Turkez et al. 2012). TAS levels were reduced, while TOS levels were increased in diabetic group. These results suggest an imbalance between antioxidant defense and free radical generation which has an important role in the progression of diabetic complication. However, TAS levels were reduced, while TOS levels were increased in diabetic group in response to administrations of *Solanum nigrum* extract. It is concluded that treatment of diabetic rats with *Solanum nigrum* decreased antioxidant factors and supported antioxidant factors. These results might improve reproductive complications as a consequence to diabetes (Beyazyıldız et al. 2013).

Due to the significant effects of our extracts on TAS and TOS, it appears that respective *Solanum nigrum* might associates with pathological states encompassing both communicable and non-communicable diseases. This indicates the need for components of this plant in our diet as potent antioxidants (Atanu et al. 2011). Based on our results, it is suggested that *Solanum nigrum* leaves glycoprotein might contributes in the regulation of radical scavenging activities including 1, 1-diphenyl-2-picrylhydrazyl radicals, hydroxyl radical, and superoxide anion (Adebooye et al. 2008).

Results from the present study reflect the contribution of *Solanum nigrum* extracts in the regulation of oxidant and antioxidant capacity and subsequently the oxidative stress harmony of diabetic rats. Moreover, the present results suggest that *Solanum nigrum* exerts its chemotherapeutic effects by modulating the antioxidant status during hyperglycemic infection.

In conclusion, the biological effectiveness of this extract can be limited at a particular level of blood glucose and might be effective when glucose level becomes out of normal range which subsequently shows medicinal contribution of *Solanum nigrum* in patients with DM. Thus, it might be worthy to conclude the anti- diabetic property of *Solanum nigrum*. This protective role might result from antioxidant and detoxifying effects of this plant as consequences of containing steroidal saponins including namely nigrumin I and II (Aali et al. 2010). Further studies elucidating mechanisms of action and exploring medicinal value of respective components of this extract can be of value. As a result, it was determined that the SN plant was statistically significant on the shaped diabetes and that the experimental diabetes level was lowered but the developing diabetes and the rising sugar could not be reduced to normal levels.

CONFLICTS OF INTEREST

The authors report no conflicts of interest.

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AUTHOR CONTRIBUTIONS

Idea / Concept: FY
Supervision / Consultancy: ACÖ
Data Collection and / or Processing: MNF
Analysis and / or Interpretation: FY, ACÖ
Writing the Article: ACÖ, MNF
Critical Review: FY

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