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HYPOGLYCEMIC AND HYPOLIPIDEMIC PROPERTIES OF THREE PLANTS EXTRACT IN ALLOXAN INDUCED DIABETIC RATS

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Abstract

The aim of the current study was to investigate the potential mechanism of Hypoglycemic and hypolipidemic action of the mixture extract of three plants *(Artemisia sieberi, Nigella sativa and T. polium)* and its impact on some biochemical parameters in alloxan induced diabetic rats. Rats have been induced diabetic by injected with single dose of alloxan, all treatments were orally administered once day for four weeks. The long-term effects of mixture extract on some physiological parameters were investigated in normal and alloxan stimulate diabetic male rats. Biochemical tests were done such as glucose, lipid profile (cholesterol, triglyceride, LDL, HDL and VLDL), liver function tests (AST and ALT), kidney function tests (Blood Urea, serum creatinine) and oxidative stress biomarkers. Alloxan stimulate diabetic rats showed significant increases in the levels of blood glucose, triglycerides, cholesterol, low density lipoprotein (LDL-cholesterol), urea, creatinine, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) while high density lipoprotein (HDL-cholesterol) levels was significantly decreased compared to normal rats. Administration of mixture plants extract to diabetic rats resulted in a significant decrease in blood glucose, triglycerides, cholesterol, LDL–cholesterol, ALT, AST and urea, creatinine while HDL–cholesterol level was markedly increased in comparison with untreated diabetic rats after four weeks of treatment. To estimate changes in the cellular antioxidant defense system, we measured the activities of antioxidant enzymes, superoxide dismutase (SOD), catalase (CAT) and malondialdehyde (MDA) in serum.Mixture plants treatment has been shown to provide a protective effect by decreasing lipid peroxidation. The results of this study indicate that mixture plants extract possesses hypoglycemic, hypolipidemic and antioxidant effects in alloxan-induced diabetic rats and suggest that, this extract may be an excellent adjuvant support in the therapy of diabetes and its complications especially when it is used for a longer period.

***Keywords*:** Alloxan ; Diabetes rats *; Nigella sativa*, *Artemisia sieberia*, oxidative stress.

Introduction

Diabetes mellitus is a metabolic endocrine disorder that impairs many physiological functions of the body by a loss of glucose homeostasis, with disorder of carbohydrate, fat, and protein metabolism resulting from defects in insulin secretion, insulin action, or both [1]. Diabetes mellitus is represented by hyperglycemia, lipidaemia, and oxidative stress; it predisposes influance individuals to long term complications affecting the eyes, skin, kidneysand blood vessels [2] Despite considerable forward in the treatment of diabetes by oral hypoglycaemic agents, search for newer drugs continues because the coexistance synthetic drugs have several limitations and harmful effects [3]. Therefore, administration diabetes without any side effects is still a challenging task for health improvement providers [4]. Artemisia is awidespread and varied genus of the family Asteraceae was separately used medicinal plant in folk medicine, It also has other pharmacological actions, such as protecting liver, lowering the blood pressure and gastrointestinal ailments [5]. The plant has been reported to have antioxidant potential [6]. free radical scavenging and anti-inflammatory activity [7]. The active principlesin this plant are the terpenes, p-cymene,1,8-cineole ergostadien-3-ol,ludartintetramethoxyflavone(fromshoot) and trans-matricaria ester have been isolated[8], and Flavonoids that ranging from common flavone and flavonol glycosides to more unusual highly methylated flavonoids such as Hispidulin and Cirsilineol which possess an anti-proliferative activity against multiple types of cancer cells [9]. In studies of the leaves and stems of Artemisis a total of eight flavonoids O- and C-glycoside were isolated and identified [10]. *Nigella sativa*(*N. sativa*)commonly known as black seed or black cumin, is a grassy plant grows in temperate and cold climate areas and has green - blue flowers and small black seeds. It is an annual herbaceous plant native to Asia, and cultivated. *N. sativa* has been steadily increasing for the strong need to volatile oils for pharmaceutical purpose [11]. It has been traditionally used for culinary and medical purposes as a natural remedy for a number of diseases that include diuretic, hemorrhagic and anti-dandruff therapy, asthma, diabetes, inflammation, bronchitis, fever and influenza. The general chemical composition of the *N. sativa* seeds is fats (31-35.5%w/w), proteins (16-19.9%w/w),carbohydrates (33.9%),fibers (4.5-6.5%) and moisture (5-7%)[12]. *Teucrium polium*. (*T. polium*) has long been recognized in folk medicine in the treatment of many pathophysiological implications, such as gastrointestinal disorders, inflammations, diabetes and rheumatism. Several researches have shown that this plan has hypotensive(13),antiinflammatoryhyp[14].
hypoglycemic[15].Various compounds such as iridoids, flavonoids and cirsiliols are characterized in *T. polium* by phytochemical analyses [16],intra-peritoneal (ip) injection of *T. polium* extract could reduce blood glucose in rats after 4 and 24 hours In[17]. intra-esophageal administration of *T. polium* aqueous extract, after 24 h, resulted in a significant reduce in the serum glucose level, in streptozocin induced diabetic rats, which reached those of the normoglycemic animals in 8 days [18].

Materials and Methods

In current study, 50 albino male rats, weighing 160-180 g were utilized and divided in to four groups (10 rats for each group), group 1 consisted of rats as control, group 2 consisted of alloxan –induced diabetic rats, group3 consisted of alloxan

–induced diabetic rats that received aqueous mixture extract(150mg\kg b.weight) gave to the rats for four weeks with free access to food and water ad libitum and group4 is diabetic reference control, that is, glibenclamide was given at a dose of 5mg/kg of body weight [19].The animals were kept in individual propylene cages under standard laboratory conditions. Rats were maintained on a 12 hour light/dark cycle at a stable temperature 25± 2°C. and fed with standard rat diet and water ad libitum. [20]. In overnight-fasted rats, diabetes was induced by a single intraperitoneal (i.p.) injection of alloxanmonohydrate (120mg/kg, (was purchased from Sigma chemical Co). Rats were confirmed diabetic by measuring the fasting blood glucose level with a One Touch Glucometer (Life scan; Johnson & Johnso, New Brunswick, NJ, USA), two days after injection of alloxan, Animals were included in the experiment with a blood glucose level collected from tail of rats above 250 mg/dl were considered diabetic and selected for further study. The oral administration of mix crude extracts of three plants continued once daily at the same time for four weeks. blood glucose levels were estimated every week [21].

Acute toxicity test

For acute toxicity test, mixture extract was administer at different doses, ranging from (100, 200, 400, 800 mg/kg), the extract was administered orally. Another control group received (distilled water) and kept under the same conditions. The rats were observed continuously for 24 for behavioral and any adverse change and thereafter for any lethality [22]. Acute oral toxicity study was performed according to the guidelines of the Organisation for Economic Cooperation and Development (OECD) [23].

Assessment of extracts effects on biochemical parameters

Oral administration with mix plants extract was started24h after alloxan injection in diabetic rats while normal and diabetic groups were administered only distill water. All rats were maintained in these treatment regimens for four weeks with easy access to food and water. At on the termination day of the experimental period, blood samples were collected after 12 hours period of fasting by heart puncture. Serum was collected and analyzed for Lipid profile (total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) ,were estimated using the procedure of commercially available kit (Spinreact Spain). creatinine, and blood urea(by using the colorimetric method and used Human kit (Human Gasellschaft fur Biochemica And DiagnosticambH, Germany[24].

Statistical Analysis

The Statistical analysis system- SAS (2012) program was used to effect of difference factors in study parameters. Least significant difference –LSD test (ANOVA) was used to significant compare between means [25].

Results and Discussion

Table1 shows highly significant decrease in glucose concentration in animal treated with three plant extract (100.21± 8.2) mg/dl after three weeks, compare to other groups and control (113.20± 4.2) mg/dl.

Table 1 : Glucose concentration in diabetic rates treated with mixture extract of three plants and glibenclamide at different weeks of treatment.

Groups	Week-0 Mean ± SE.	Week-1 Mean ± SE.	Week-2 Mean ± SE.	Week-3 Mean ± SE.
control	18.80 ± 2.6 A	130.42± 4.3 A	124.30 ± 7.2 A	113.20± 4.2 A
Diabetic	300.30± 3.4 B	290.70± 6.2 B	305.12 ± 3.5 B	280.00 ± 5.6 B
Diabetic + Mix Extracts 150mg\kg	209.50± 3.9 A	190. 10± 6.3 B	173.62± 8.3 C	153.63± 4.3 D
diabetic glibenclamide 5mg/kg	269.43±4.23 A	247.54±2.55 B	163.35±3.43 C	142.72±1.67 D

The extracts can decrease blood glucose in diabetic animals, serum glucose decreased significantly in diabetic rats after receiving 50 mg/kg *T. polium* for a month [26]. Other study reported that aqueous extract of *T. polium* aerial parts caused significant reduce in blood glucose concentration 4 h after intravenous administration and 24h after i.p. administration in both the normoglycemic and STZ-hyperglycemicrats, an other study reported a reduction in blood glucose concentrations of streptozotocin hyperglycemic rats after treatment by a single oral dose of *T. polium* aqueous decoction[27].Significant decrease in blood concentration of glucose in streptozotocin induced hyperglycemic rats after six weeks of consecutive oral treatment with aqueous extract of T. *polium* via a relatively potent insulin tropic action[28]. These findings also support the traditional use of this plant as a hypoglycemic agent [29]. phytochemical investigations on *Teucrium* spp have shown the presence of bioactive compounds such as diterpene derivatives[30].fatty acid esters flavon[31], irloids and steroids [32]. It has been suggested that hypoglycemic effect of aqueous *T. polium* extract may be attributed to its constituents such as iridoids, flavonoids and cirsiliol [33]. Several studies will probably show the role of each of these components in reducing blood glucose level. *Artemisia* genus, have active anti-diabetic properties [34]. This property may be due to flavonoids components that have high efficiency against α-amylase and α-glucosidase enzymes [35, 36].

The changes in the levels of serum lipids in control and experimental groups are illustrated in Table2. There was a significantlly increase in the level of Cholesterol in diabetec groups (162.34± 4.6) mg\dl as compared to the control (73.23± 2.7) mg\dl and significant decrease (120.22±1.65) mg\dl in Diabetic+ Mix extracts compared to diabetic group. The level of Triglyceride obtained significant increase in diabetic group(120.35± 5.6) mg\dl compared to the control group(76.94± 3.8)mg\dl. While the results show significant decrease in Triglyceride (86.32± 2.1) mg\dl in Diabetic+ Mix extracts compared to diabetic group. Also the results revealed

significant improvement in C- HDL level in diabetic+ mix extracts (40±2.56)mg\dl compared to the diabetic group (30±1. 98) mg\dl treated. While the results show significant increase in level of C-LDL in diabetic group (118.34±4.71) mg\dl compared with control group (43.22±3.67)mg\dl, also the results obtained significant reduce in C-LDL level in diabetic animals treated with mixture extract(73.22±3.92)mg\dl compared with diabetic group. Finally, the results illustrated a significant increase in C-VLDL level in the diabetic (24.33±2.41)mg\dl compared with control group (15.00±.95)mg\dl. The diabetic group treated with mixture extract showed significant decrease in C- VLDL level(17.24±0.95) mg\dl compared with diabetic group. As well as serum activities of AST enzyme was significantly increased in diabetic group ((123.42 ± 1.9) U/L as compared to the control group (69.92± 0.6) U/L. On the other hand, the results showed significant increase in serum activities of ALT in diabetic group(84.60± 5.3) U/L as compared to the control(40.20± 2.4) U/L and. While the diabetic group that treated with mixture extract obtained significantly reduce in serum activities of ALT (56.20± 3) U/L.

Table 2 : Glucose concentration, lipid profile and ALT,AST level in diabetic albino rats treated with mixture extract of three plants.

Parameters\groups	Control	Diabetic	Diabetic+ Mix Extracts 150 mg\kg	Diabetic + glibenclamide 5mg/kg
Glucose(mg\dl)	96.25.13± 4.5 A	293.75 ± 7.3 A	181.32± 2.9 B	150.44±2.54 C
Cholesterol (mg\dl)	83.23± 2.7 A E	162.34± 4.6 B	116.33± 2.9 C	120.22±1.65 A
Triglyceride (mg\dl)	76.94± 3.8 C	120.35± 5.6 A	86.32± 2.1 B	90.52±3.33 B
VLDL	15.00±.95 B	24.33±2.41 A	17.24±0.95 B	18.37±1.69 B
LDL	43.22±3.67 C	118.34±4.71 A	73.22±3.92 B	77.37±2.09 B
HDL	25.32±1.45 A	20.63±2.72B	26.25±1.98 A	25.44±1.37 A
AST (U\L)	69.92± 0.6 C	123.42 ± 1.9 A	80.22 ± 3.3 B	78.32± 2.66 B
ALT(U\L)	40.20± 2.4 D	84.60± 5.3 A	56.20± 3.1 B	54.73±4.38 B

These findings support the previous report by [38]. who indicated an antilipidemic effect for *T. polium* extract, antidiabetic agent. *T. polium* crude extract is able to enhance insulin secretion after a single dose of the plant extract at high glucose concentration. These results clearly indicated for the first time that *T. polium* crude extract is able to produce a dose-dependent stimulation of basal insulin release and also to potentiate the glucose-stimulated production of insulin in rat islets with no significant and detectable effects on the time pattern of insulin secretion [39].

The study conducted by [40] found that the aqueous extract of *T. polium* aerial parts, given intraperitoneally at doses of 50 to 150 mg/kg for 10 days, reduced significantly the serum levels of cholesterol and triglycerides among the hyperlipidemic rats, also [41] evaluated the effect of an aqueous extract *T. polium* on serum lipids and glucose in diabetic male rats. It has been reported that some flavonoids have antihyperlipidemic properties and the presence of these classes of constituents in *T. polium* may play an important role in the observed hypolipidemic effects. Many species of genus Artemisia have been reported to have antidiabetic activity. In *Artemisia indica* the hydromethanolic crude extract at a dose of 200 and 400 mg/kg b. w and chloroform fraction 200mg/kg b. w administered orally for 15 days showed a significant reduction in blood glucose level [42]. Similar results were observed in our study that was carried out *on Artemisia amygdalina* where hydroethanolic and methanolic extract produced a significant decrease in the serum glucose level at a dose of 500mg/kg. The extracts also showed increased dose-dependent anti-hyperglycaemic effect. The results also match with the study carried on *Artemisia judaica*, where the bioactive principles found were the flavonoids [43]. The effect of lowering blood glucose levels ,may be due to the increased efficiency of the peripheral tissues for the uptake of glucose from blood. Thus the extracts can also be useful in patients with type II diabetes and need further detailed studies for the validation of these results, others believe that the aqueous extract and/or decoction of the whole plant possess a hypoglycemic effect in normal and diabetic animals .The aqueous extract from its aerial parts at 0.39 g/kg (equivalent to2.3 g/kg as crude plant) orally seem to have minimum adverse effect and showed significant decrease in plasma glucose levels of both the normoglycemic and the alloxanized rabbits timedependently. The aqueous extract of A. sieberi had been significant reduction in blood glucose level in diabetic rats [44].

Table 3 shows that the values of blood urea significantly increase in diabetic group (50.42 ± 2.1) as compared with control (25.12± 0.7) mg\dl. Also the results revealed significant decrease in blood urea in Diabetic+ Mix Extract group (29.14 ± 2. 2) mg\dl compared to diabetic group ((50.42 ± 2.1) mg\dl. The values of Creatinine of diabetic group showed high significant increase in (1.6 6± 0.02) mg\dl as compared with control group (0.45 ± 0.04)mg\dl and significant decrease Diabetic+ Mix Extract group (0.5 1 ± 0.02).

Table 3 : Concentration of blood urea and createnine in diabetic albino rats treated with aqueous mixture extract of three plants.

Parameters\group	Control	Diabetic	Diabetic + Mix Extracts 150 mg\kg	Diabetic + glibenclamide 5mg/kg
B. Urea (mg\dl)	25.12± 0.7 C	50.42 ± 2.1 A	29.14 ± 2.2D B	31.18 ± 1.9 B
Creatinine (mg\dl)	0.45 ± 0.04 B	1.6 6± 0.02 A	0.5 1 ± 0.02 B	0.40 ± 0.09 B

Serum urea and creatinine levels are indicators of kidney disfunction. *A.sieberi* decrease the kidney problems and cardiovascular diseases by lowering serum urea, uric acid, creatinine as well as improving lipid profile by its antioxidant activity. Therefore oral administration of *A. sieberi* oil exhibit cardio protective, nephro protective and hepato protective activities in alloxan induced diabetic rats[45]. *N. sativa*extract has a significant nephroprotective activity for paracetamol-induced nephrotoxicity as confirmed by reduced serum urea and creatinine [46].

As can be seen in Table 4 the mean values of SOD significantly increase in diabetic group (2.95 ± 0.11) U/ml as compared with the control group(1.05± 0.43) U/ml and decrease in Diabetic+ Mix Extracts group (1.53 ±0.2) U/ml compared to diabetic group(2.95 ± 0.11)U/ml ,also the value of CAT revealed significantly increase in diabetic group (2.06±0.41) U/ml as compared to control(0.8 5 ±0.05) U/ml ,whereas the results were obtained significantly decrease in CAT level in Diabetic+ Mix Extracts (1.27 ±0.06) U/ml. Our current study indicate that, the diabetic group observed significantly increase in MDA (4.5 0± 0.9 40) and decrease in Diabetic+ Mix Extracts 2.1 3± 0. 6

Table 4 : Level of Superoxide dismutase, Catalase and Malondialdyhid in diabetic albino rats treated with aqueous mixture extract of three plants.

Groups	SOD (U/ml) Mean ±SE.	CAT(U/ml) Mean ± SE.	MDA Mean± SE.
control	1.05± 0.43 A	0.8 5 ±0.05B	1.08± 0.09 A
Diabetic	2.95 ± 0.11 B	2.06±0.41 B	4.50± 0.94 A
Diabetic+ Mix Extracts 150 mg\kg	1.53 ±0.22 B	1.27 ±0.06 B	2.13± 0. **6** A
Diabetic + glibenclamide 5mg/kg	1.90±0.12 B	1.9±0.04 B	2.96±**0.9** A

In recent years, oxidative stress has been implicated in a variety of degenerative processes and diseases; these include acute and chronic inflammatory conditions [47]. *Nigella sativa* was observed to also have potent antioxidant component such as flavonoid [48,49], and Administration of *N. sativa* extract caused significant decreases of MDA and increases of antioxidant activity. Thymohydroquinone and thymoquinone are the most important constituents of *N. sativa* that has antioxidant and cytoprotective effect by increasingantioxidant enzymes (SOD and CAT) and inhibite *in vitro* non-enzymatic lipid peroxidation (MDA) [50].

It has been determined that, the antioxidant effect of plant extract is mainly related to phenolic compounds, such as tannins, phenolic diterpenes and flavonoids [52]. The antioxidant activity of flavonoids is related to their structure especially the hydroxy substitution of the aromatic A and B rings and the C-ring substitution pattern [52]. Many studies reported that phenolic compounds display antioxidant activity, as a result of their capacity to scavenge free-radicals. Phenolic compounds can also act as antioxidants by chelating metal ions, preventing radical formation and improving the antioxidant endogenous system [53, 54]. Different mechanisms have been attributed to explain the antioxidant activities of phenolic compounds, including scavenging of free radical, prevention of chain initiation, binding of transition metal ion catalysts, decomposition of peroxides and prevention of continued hydrogen abstraction [55].

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