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Hypoglycemic, hypolipidemic and antioxidant activities of *Allium porrum* leaves extract in streptozotocin-induced diabetic rats

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Abstract : This study aims to investigate the antidiabetic, antihyperlipidemia and antioxidant activities of methanolic extract of *Allium porrum* leaves in streptozotocin‑induced diabetic rats.
Methods: methanolic extract at 200 and 400 mg/kg bw and glibenclamide (5 mg/kg) were evaluated in diabetic rats based on the analysis of biochemical parameters, such as glucose, cholesterol, triglycerides, HDL, LDL, AST, ALT, LDH, Urea, and creatinine levels. Enzymatic and non enzymatic antioxidant of MDA, GSH , CAT and SOD were also assessed.
Results: Oral administration of methanolic extract to diabetic rats caused significant decrease in the levels of serum glucose, ALT, AST, LDH. Moreover, the extract decreased MDA content and increased the levels of SOD, GSH and CAT compared with diabetic rats. Also, creatinine and urea were improved as a result of the treatment of the extract. The extract exhibited antidiabetic, antihyperlipidemia and antioxidant activities and consequently may alleviate liver and renal damage caused by STZ -induced diabetes this might be attributed to the presence of flavonoides, phenolics and sulphur compounds which may be acting as free radical scavenging effect, inhibiting lipid peroxidation and increasing antioxidant activities. *Allium porrum* has a potential and helpful to the prevention of diabetic and its complications.
Key words : *Allium porrum*, complications, antidiabetic, antihyperlipidemic, antioxidant.

Introduction

Allium porrum Synonyms: *Allium ampeloprasumporrum* Family: Alliaceae (Onion Family) common name leek, is a bulbous perennial plant is mostly grown as vegetable. Leeks are a good source of flavonoids, kaempferol derivatives or quercetin derivatives[1-2], malonyl flavonols[3],phenolic[4], sapogenins[5], steroidal saponin[6-7], essential oils[8], fatty acids[9].In addition to numerous volatile organosulfur compounds contributing to their rich flavor and other quality properties for leeks[10].

Allium porrum has been used for treatments hyperlipidemia[11]and hyperglycemic[12]. Ethanolic extracts from leaves and stems exhibited antioxidant activity[13-14], antimicrobial and cytotoxic activities[4], alcoholic extract showed promising protective effect against osteoporosis[15], pectic polysaccharides have immunostimulating activities[16]. The volatile sulphur compounds showed a good antimicrobial activity[8]and

antioxidant Activities[17] while phenolics as flavonoid glycosides exhibited platelet anti-aggregation activity[1]in addition to, aqueous extracts and pure compounds of quercetin, zalcitabine, allicin exhibited anti-adenovirus agents[18].Other bioactive components for example sapogenins, exhibited antiproliferative activity[5]aswell as steroidal saponins showed antifungal activity[6],haemolytic and immuno-modulatory properties[7] and gastroprotective property[19].

Diabetes mellitus is a metabolic disorder results in abnormally high blood sugar levels (hyperglycemia). The abnormal high blood sugar level is due to defects in either insulin secretion or insulin action in the body[20]. Diabetes mellitus is characterized by hyperglycemia, lipoprotein abnormalities, raised basal metabolic rate, defect in enzymes, and high oxidative stress which induced damage to pancreatic beta cells. It is the most common endocrine disorder that impairs glucose homeostasis resulting in severe diabetic complications including retinopathy, neuropathy, nephropathy, hyperlipidemia hypercholesterolemia, ketosis, atherosclerotic coronary artery and peripheral atherosclerotic vascular diseases and weight loss[21-22]due to disturbance in utilization of glucose[23]. Diabetes is associated with increased oxidative stress induced by generation of free radicals due to persistent hyperglycaemia[24] as well as inadequate antioxidant defences[25]. The diabetic state lipid peroxidation can be induced by protein glycation and glucose auto-oxidation that can lead to formation of free radicals. The main free radicals that occur in this state are superoxide hydroxyl and peroxyl radicals. All these free radicals might play a role in DNA damage, glycation, protein modification reactions, and in lipid oxidative modification in diabetes[26]. Oral synthetic antidiabetic agents drugs used for the treatment of diabetes and insulin are often associated with undesirable side-effects such as weight gain, acute hypoglycemia, edema, hepatic and cardiac defects, gastric and respiratory complications[27]or diminution in response after prolonged use[4]. Due to undesired side effects of insulin and oral hypoglycaemic, continuous efforts are being made to develop new compounds or combinations for treatment of diabetes, especially of herbal origin. Plant drugs are frequently considered to be less toxic and more free from side effects than synthetic ones[28-30].

Materials and Methods

Chemicals and apparatus

Kits were purchased from Biodiagnostics Company (Cairo, Egypt), Folin–Ciocalteu reagent (Sigma Chemical Co., St. Louis, Mo., U.S.A.) Folin–Ciocalteu's, Aluminum chloride, chlorogenic acid, rutin purchased from Sigma–Aldrich (USA). Streptozotocin, STZ was purchased from (Sigma–Aldrich, USA). was dissolved in fresh sodium citrate buffer (pH 4.5, 0.1 mol·L^{-1}), and in order to minimize the degradation, the obtained solution was immediately injected IP. Tablets Glibenclamide 5mg were obtained from (Aventis pharm., LtdAnkleswar). All solvents and chemicals were Fisher HPLC grade, (Fisher Scientific, USA).

Plant materials

Allium porrum was cultivated in Faculty of Agriculture, Farm, Cairo University, Giza, Egypt, and leaves were collected during December to January. The plant was kindly identified by, Mrs. TerseaLabib, taxonomist at Orman Botanical garden, Giza, Egypt and Dr. Mona Marzok, Researcher at the Herbarium of National Research Centre , Giza, Egypt. A voucher specimen was deposited at the Herbarium of the National Research Centre (NRC), Dokki, Giza, Egypt.

Extraction

The fresh leaves were dried at room temperature in shad and grinded to fine powder. Air dried fine powdered were extracted with methanol in percolator at room temperature till exhausted and concentrated under reduced pressure at 40 ºC at rotary evaporator till dryness, the extract yield was 17.20%.

Determination of total phenolics and total flavonoids and in the alcohol extract

Reagents:

Aluminum chloride was prepared by dissolving 2 g of aluminum chloride (Sigma) in 100 ml pure methanol. Foline reagent, saturated solution of sodium carbonate (20 gm /100 ml dist. Water).

Preparation of total phenolics and total flavonoids compounds

For determination of the total phenolic and flavonoid compounds in the extracts: known weight of the extract was dissolved in 80% methanol in measuring flask 100 ml. and completed to 100 ml.

Estimation of total phenolics

The total phenolics content (TPC) was determined by Folin–Ciocalteu according to the method described by[31-32] with some modification. Briefly, 1.0 ml. of the sample extract was added to 7.5 ml. of redistilled water and 0.5 ml. of Folin–Ciocalteu reagent (Sigma Chemical Co., St. Louis, Mo., U.S.A.) was added. After 15min equilibration, the mixture was neutralized with 1.0 ml. of 20% Na_2CO_3, mixed well by a vortex. After a 30-min reaction, the absorbance of the mixture was measured at 760 nm with a (UV–VIS spectrophotometer). Chlorogenic acid was used a standard curve, the mean of three readings were recorded and results were expressed as milligrams of chlorogenic acid equivalent per gram of the extract (mg /1 g extract).

Estimation of total flavonoid

The total flavonoids content (TFC) was determined according to method as adopted[32-33]. Briefly, 3 ml. of the extract was mixed with 3 ml. of $AlCl_3$ (2 % in methanol) solution and the mixture was allowed to stand for 30 min. The absorbance was measured at 415 nm. bya spectrophotometer(UV-VIS, 2401 Shimadzue, Inc., Kyoto, Japan). Rutin was used as a standard curve and the mean of three readings were recorded, the total flavonoids was expressed in mg as rutin equivalent per 1g of the extract (mg /1g extract).

Animals

Adult male albino rats (Wister rat) weighing 140-190 g were obtained from Animal House, of National Research Center (NRC), Dokki, Giza, Egypt. Rats were kept in conventional cages with free access to water ad libitum and standard rat feed with rodent pellet diet. All animals received human care in compliance with guidelines of Ethical Committee of National Research Center and followed the recommendations of The National Institute of Health Guide for care and use of Laboratory animals (Eighth edition).

The animals were housed in polypropylene cages (each cage housing six animals) and allowed to acclimatize to laboratory conditions for seven days prior the experimental. Animals were maintained under controlled conditions of temperature ($25^oc\pm 1^oC$), humidity (50±15%) and normal photoperiod (12–12 h light-dark cycles). All the experiments were performed in accordance to the guide for the care and use of laboratory animals, as adopted by Medical Research Ethics Committee, National Research Centre, Dokki, Egypt (Ethical approval-No 16006).

Acute Oral Toxicity Study

Healthy male Swiss albino rats were used for the acute oral toxicity study. All rats were fasted overnight before treatment and were given food one hour after treatment. A single high dose, as recommended by Organization for Economic Co-operation and Development (***OECD* 1992**)[34] guidelines of 3000 mg/kg. Methanol extract was dissolved in water, by adding few drops of Tween-20 and with assistance of ultrasonic water bath. 100, and 1000 up to 3000 mg/kg bw. of the extract was administered by gavage to each group (10 male rats weighing between 150 and 200 g), and water was given to 10 male and as a control group. After a single administration, signs of possible toxicity were observed every hour for the first six hours and every day for 14 days. Surviving animals were observed for any signs or symptoms of toxicity and for mortality for up to 14 days as described previously[35-36]. The visual observations included changes in the skin and fur, eyes and mucous membranes, and behavioral pattern.

Induction of Diabetes

Diabetes in rats was induced with a single injection dose of STZ (50 mg/kg body weight) by intraperitoneal route. The STZ was freshly dissolved in fresh sodium citrate buffer (pH 4.5) solution as vehicle, the animals were allowed to fast for 24 hr before STZ injection. Diabetes was confirmed by the determination of fasting blood glucose concentration with the help of a glucometer (Behringer Mannheim, Eli Lilly Ltd., São Paulo, Brazil) after 48 h of administration. Rats exhibiting blood glucose levels 250 mg/dL or more were segregated and kept into cages marked and used for the experiment. The values of recorded glucose levels were considered for zero time.

The extract preparation (methanol extract was dissolved in distilled water, by adding few drops of Tween-20 and with assistance of ultrasonic water bath) were fed orally to diabetic rats after two days of STZ

administration by gastric intubation of respective groups once daily for 21 days. Control animals (groups I) received the same amount of distilled water, the animals were carefully monitored every day.

Experimental design

Group I: Control rats were injected with citrate buffer (pH 4.5), i.p.

Group II: Diabetic rats was injection by a single dose of STZ (50 mg/kg bw weight by intraperitoneal route.

Group III: Diabetic rats treated with methanol extract of *Allium porrum* leaves(200 mg/kg b.w.) daily by oral administration for 3 weeks.

Group IV: Diabetic rats treated with methanol extract of *Allium porrum* leaves(400 mg/kg b.w.) daily by oral administration for 3 weeks.

Group V: Diabetic rats treated with glibenclamide (0.6 mg/kg b.w.) daily by oral administration for 3 weeks[37].

Sampling

Blood samples were collected after 7, 14 and 21 days, the animals were allowed to fast overnight and blood samples were withdrawn from the retro-orbital venous plexus and immediately mixed with ethylene diamine tetra acetic acid (EDTA) as anticoagulant.

Blood samples were centrifuged at 4000 rpm for 20 min at 4 ^{o}C to obtain plasma for the determination of various biochemical parameters such as blood glucose, ALT, AST, urea and creatinine, triglycerides , cholesterol, LDL, HDL and total protein.

At the end of the experiment (21 days), the treated rats were fasted and killed, the liver was homogenized in chilled Tris-HCl buffer (0.025 M, pH 7.4) using potter- Elvehjem Homogenizer with Teflon. The homogenates were centrifuged at 4000 rpm for 20 min at 4°C. The supernatants were collected and stored at -80 ^{o}C for subsequent determinations of CAT, GSH, SOD and MAD.

Biochemical analysis

Aspartate and alanine aminotransferases (AST &ALT) were estimated by the method[38].
Blood glucose was determined by the method[39].
Cholesterol was determined by the method[40].
Triglycerides were determined according to the method[41].
LDLandHDLwere measured in blood serum according to the method[42].
Urea was estimated according to the method[43].
Total protein was estimated according to the method[44].
Creatinine was evaluated according to the method[45].
The activity of superoxide dismutase (SOD) was estimated according to the method[46].
Catalase activity was assayed in liver tissue homogenate according to the method [47].
Reduced glutathione (GSH) was colorimetrically determined according to the method [48].
Malondialdehyde (MAD) was determined in liver tissue homogenate according to the method[49].Statistical Analysis. All data were expressed as mean ± SD of six rats in each group. Statistical analysis was carried out by one-way analysis of variance (ANOVA), Costat Software Computer Program:

Results

Percentage of total phenolics and total flavonoids in the extracts

Table 1: Percentage of total phenolics and total flavonoids in the extract

Methanol extract	Percentage of total phenolic	Percentage of total flavonoids	Percentage of non flavonoids
Allium porrum leaves	6.84	3.75	1.87

Total phenolics content was determined from crude extract of *Allium porrum* leaves using Folin Ciocalteu reagent. The results are presented in (Table 1). The results obtained showed that the extract contains 6.84 % total phenolics and 3.75% total flavonoids.The total phenolic (TP) and total flavanoid (TF) content of

methanol extract were expressed as chemical equivalents of chlorogenic acid and rutin, respectively, since different phenolic compounds contribute differently to the readings using the Folin-Ciocalteau reagent. TP and TF values were 6.84 % and 3.75% respectively, indicating that the mean TF value corresponds to 54.82% of the mean TP value.

Acute toxicity

The alcoholic extract of *Allium porrum* leaves was found to be nontoxic up to the dose of 3000 mg/kg bw.and did not cause any behavioral changes or death of tested animals.

Effect of *Allium porrum* leaves extract on body weight (g) of diabetic rats

Table 2. Effect of *Allium porrum* leaves extract on body weight (g) of diabetic rats

Treatment	Time in week			
	Zero	1	2	3
Normal control	207.1±8.65	216.54±10.00	221.9±12.34	233.36±11.78
Diabetic Control STZ diabetic rats	210.63±13.81	180.00±8.77	158.39±6.80^{G}	135.98±8.91^{G}
Diabetic ratstreated with *Allium porrum*leaves extract(200 mg/k.bw)	215.67±3.67	190.81±4.89*	177.21±10.34*	160.00±3.61*^{G}
Diabetic ratstreated with *Allium porrum*leaves extract (400 mg/k.bw)	204.00±10.34	188.21±2.69*	192.84±5.78*	190.44±9.27*
Diabetic ratstreated with Glibenclamide	198.11±3.67	187.55±6.45	183.43±4.32	192.56±4.11

Each value is the mean of body weight (g) ±SE, n= 8

Statistical analysis was carried out using one way ANOVA and Tukey's as post-hoc test.
*significantly different from corresponding zero time P < 0.01,
G significantly different from diabetic+ Glibenclamide group P< 0.01

Table 2 shows that the animals administrated by STZ-i.p caused a strong and progressive decrease the body weight by 14.2%,24.7% and 35.2% from the first (P < 0.001) and second (P < 0.001) to the third week comparedtoinitial time and normal control animals. Repeated administration of the extract (200 mg/kg bw.) to STZ-induced diabetic animals significantly (P<0.001) induced slight improvement the diminishing of the body weight by 2.6 %, 7.0 % and 9.6 % at 1st, 2nd and 3th week respectively compared to diabetic rats, whereas oral gavage of the extract (400 mg/kg bw.) restoring the body weight and the reduction were 7.8%, 5..9% and 6.9% at 1st, 2nd and 3th week respectively compared to diabetic control. Also, the body weight of diabetic rats treated with glibenclamide was declined by 5.8%, 7.6% and 3.00% at 1st, 2nd and 3th week. The results of the treatment at level 400 mg/kg bw.were similar to glibenclamide standard drug. The body weight either of treated animals with the extract at 400 mg/kg bw. orglibenclamide was recovered significantly but not to the control level (Table 2). After 21 days supplementation, the body weight of all the animals was insignificantly different from control level.

Effect of *Allium porrum* leaves extract on blood glucose level (mg/dl) of diabetic rat

Table 3. Effect of *Allium porrum* leaves extract on blood glucose level (mg/dl) of diabetic rats

	Time in week			
	Zero	1	2	3
Normal control	84.47±3.16	95.97±3.39	91.9±5.47	93.27±4.76
Diabetic Control STZ diabetic rats	378.43±16.57	390.40±21.90	367.33±26.54	340.34±17.88
Diabetic rats treated by *Allium porrum* leaves extract (200 mg/k.bw)	380.76±12.3	300.87±15.23*^{G}	269.87±11.56*^{G}	218.07±6.69*^{G}
Diabetic rats treated by *Allium porrum* leaves extract (400 mg/k.bw)	343.23±14.75	271.41±16.21*^{G}	190.63±10.68*^{G}	140.34±9.23*
Diabetic rats treated with Glibenclamide	390.43±21.50	250.34±11.89*	183.43±8.33*	120.51±8.92*

Each value is the mean of blood glucose (mg/dl) (g) ±SE, n= 8

Statistical analysis was carried out using one way ANOVA and Tukey's as post-hoc test.
*significantly different from corresponding zero time P < 0.01,
G significantly different from diabetic+ Glibenclamide group P< 0.01

As shown in Table 3 fasting blood glucose level of all animals before treatment were within the normal range and blood glucose level was significantly elevated after 48 h of streptozotocin injection with respect to control level. No reduction of blood glucose levels was observed in diabetic rats in all durations when compared with initial level and control. Supplementation of *Allium porrum* leaves extract for one, two and three weeks produced a significant reduction in blood glucose levels in all durations when compared with initial level and diabetic control. The blood glucose levels of diabetic rats treated with *Allium porrum*l eaves extract at doses of 200 and 400 mg/kg showed significant differences at 1, 2 and 3 weeks from initial levels($P < 0.001$) (Table 3). The reduction induced by 200 and 400 mg doses seemed to be greater by the end of 21 days' treatment. The hypoglycemic effect of extract was dose-dependent, so the extract at dose 400 mg/kg bw. showed a significant and pronounced reduction in blood glucose level than 200 mg/kg bw. Glibenclamide, a known hypoglycemic drug, caused a strong and progressive significant decrease ($P < 0.001$) in blood glucose levels after oral administration for 21 days when compared with initial level and diabetic control. The results of the treatment at level 400 mg/kg bw. were similar to glibenclamide standard antidiabetic drug.

Effect of *Allium porrum* on hepatic oxidative stress

Table 4.Effect of *Allium porrum* leaves extract for three weeks on hepatic oxidative stress parameters of diabetic rats

	MDA (nmol/ mg tissue	GSH (mg/ g) tissue	SOD (U/g tissue)	CAT (U/g tissue)
Normal control	1.32±0.13	7.96±0.28	450.97±24.18	0.97±0.06
Diabetic Control STZ diabetic rats	7.1±0.45*	3.17±0.22*^{G}	182.23±6.84*^{G}	0.54±0.04*
Diabetic ratstreated by *Allium porrum*leaves extract (200 mg/k.bw)	3.56±0.48*$^{@}$	5.03±0.35*$^{@G}$	312.95±16.28*$^{@G}$	0.83±0.05*$^{@}$
Diabetic ratstreated by *Allium porrum*leaves extract (400 mg/k.bw)	2.34±0.38*$^{@}$	6.31±0.31*$^{@G}$	391.71±16.36$^{@}$	0.91±0.05$^{@}$
Diabetic ratstreated by Glibenclamide	3.57±0.19*	9.34±0.35*$^{@}$	390.23±5.78*$^{@}$	0.94±0.02$^{@}$

Each value is the mean ±SE, n= 8

Statistical analysis was carried out using one way ANOVA and Tukey's as post-hoc test.
***significantly different from normal control P < 0.01,**
@significantly different from diabetic control P < 0.01

G significantly different from glibenclamidegroup P< 0.01

Table4illustrates that the level of MDA significantly($p< 0.001$) increased whereas concentrations of GSH, SOD and CAT significantly ($p< 0.001$) decreased in the STZ-diabetic ratsas compared to control. Treatment with the extracts (200mg/kg and 400mg/kg) were significantly ($P <0.001$) reduced MAD concentration and significantly ($P <0.001$) increased the activities of CAT, SOD and GSH in the liver tissues of STZ-diabetic rats compared to diabetic control rats.Oral administration of the extract (200 and 400 mg/kg) showed a significant and pronounced improvement of MAD, CAT, SOD and GSH toward normal control and similar to glibenclamide treatment. The extract (400 mg/kg) caused a strong and progressive significant decrease ($P < 0.001$) in MDA level and induced significant elevation on liver CAT, SOD and GSH concentrations after oral administration of the extract to the STZ-diabetic rats for 21 days when compared with diabetic control.

Effect of *Allium porrum* on liver and kidney functions

Table 5 Effect of *Allium porrum*l eaves extract for three weeks on liver and kidney parameters of diabetic rats

Treatment	AST (U/l)	ALT (U/l)	LDH(IU/l)	Protein (g/dl)	Creatinine (mg/dl)	Urea(mg/dl)
Normal control	40.48±1.00	23.78±1.12	285.63±34.16	7.88±0.18	0.57±0.04	35.76±1.07
Diabetic Control STZ diabetic rats	71.15±1.56*^{G}	43.20±1.50*	1668.84±108.57*^{G}	3.55±0.18*^{G}	0.91±0.09*^{G}	82.66±2.89*^{G}
Diabetic rats treated by *Allium porrum* leaves extract (200 mg/k.bw)	54.88±0.95*$^{@G}$	32.94±1.78*$^{@}$	259.54±24.27$^{@}$	5.86±0.16$^{*@G}$	0.78±0.05$^{@}$*^{G}	56.92±2.05*$^{@G}$
Diabetic rats treated *Allium porrum l*eaves extract (400 mg/k.bw)	41.64±1.32$^{@}$	24.00±0.81$^{@G}$	248.78±14.1$^{@}$	8.16±0.25$^{@}$	0.64±0.05$^{@}$	40.12±3.45$^{@}$
Diabetic ratstreated Glibenclamids	44.43±1.09$^{@}$	37.98±2.65	270.56±8.65	7.50±1.77	0.55±0.02	37.82±1.85

Each value is the mean ±SE, n= 8
Statistical analysis was carried out using one way ANOVA and Tukey's as post-hoc test.
*significantly different from normal control P < 0.01,
@significantly different from diabetic control P < 0.01
G significantly different from glibenclamide group P< 0.01

Table 5 shows the level of hepatic and renal markers, urea, creatinine, ALT, AST, and LDH were significantly ($p < 0.001$) increased while total protein significantly ($p < 0.001$) decreased in diabetic groups. Treatment with *Allium porrum* leaves extract (200 and 400mg/k.bw)for 21 days significantly reversed these values as compared to diabetic control. Similar effect was observed in glibenclamide treated group. Administration of leaves extract at doses (200 and 400mg/k.bw)for 21 days significantly elevated the concentration of protein, the activities of plasma AST, ALT, LDH, urea and creatinine were significantly ($p < 0.001$) decreased relative to their normal levels (Table 5). However, treatment of STZ-diabetic rats with the extract at 400 mg/kg bw. produced progressive and strong reduction the level of hepatic and renal markers , urea, creatinine, ALT, AST, and LDH, on the other hand, total protein was also increased compared with the diabetic group. Furthermore, the extract at 400 mg/kg bw. restored all values in diabetic rats to near normal range and similar to glibenclamide treatment.

Effect of *Allium porrum* extract on lipid profile

Table 6. Effect of *Allium porrum* leaves extract for three weeks on lipid profile parameters of diabetic rats

Treatment	Cholesterol (mg/dl)	Triglycerides(mg/dl)	HDL(mg/dl)	LDL (mg/dl)
Normal control	65.92±1.83	51.83±3.30	35.69±1.45	44.99±3.78
Diabetic Control STZ diabetic rats	122.78±2.74*	127.56±3.97*	24.03±1.42*	106.62±3.31^{G}
Diabetic rats treated by *Allium porrum* leaves extract (200 mg/k.bw)	66.52±4.77$^{@G}$	83.39±2.95*$^{@G}$	32.87±0.80$^{@}$	71.30±5.38$^{@}$
Diabetic rats treated *Allium porrum l*eaves extract (400 mg/k.bw)	46.94±1.53$^{@}$	52.33±2.25$^{@}$	39.41±1.38$^{@}$	44.76±3.75$^{@}$
Diabetic rats treated Glibenclamids	40.42±1.50$^{@}$	45.96±1.08$^{@}$	38.40±2.12$^{@}$	39.66±1.77

Each value is the mean ±SE, n= 8
Statistical analysis was carried out using one way ANOVA and Tukey's as post-hoc test.
*significantly different from normal control P < 0.01,
@significantly different from diabetic control P < 0.01
G significantly different from glibenclamidegroup P< 0.01

Table 6 shows that the effect of the *Allium porrum* extract on serum HDL, LDL, triglycerides and total cholesterol in diabetic rats. The results showed that the levels of LDL, cholesterol andtriglycerides in diabetic rats were significantly ($p < 0.001$) increased following treating with streptozotocin while HDL levels significantly ($p < 0.001$) decreased when compared with normal control. The administration of *Allium porrum* leaves extract at doses of 200 and 400 mg/kg bw. significantly reduced serum triglycerides, total cholesterol and LDL whereas HDL elevated when compared with diabetic control rats. Treatment with standard drugs glibenclamide produced significant ($p< 0.001$) decrease in LDL, cholesterol and triglycerides, but a significant ($p < 0.001$) increase in HDL levels, compared to diabetic control group. *Allium porrum* extract at dose of 400 mg/kg bw. was found was significantly better than its lower dose and to be effective as glibenclamide.

Discussion

The alcoholic extract of *Allium porrum* leaves was found to be nontoxic up to the dose of 3000 mg/kg bw.and did not cause any behavioral changes or death of tested animals.

The body weight either of treated animals with the extract at 400 mg/kg bw. orglibenclamide was recovered significantly but not to the control level. After 21 days supplementation, the body weight of all the animals was insignificantly different from control level. Generally, the body weight was reduced in STZ-induced diabetic rats,this characteristic weight loss in diabetic rats could be due to degradation and catabolism of fats and proteins [50]. Thus, increased catabolic reactions leads to muscle wasting which may be the major cause of weight loss in diabetic rats [51]. However, extract treated groups showed a sign of recovery in the body weight which suggest the protective effect of the extract by preventing it from muscle wastage and other macromolecular degradations and this was confirmed with other data [52-54].

The effect of STZ which causes tissue damage of cells of islets of pancreas that destroy*β* cells and result in insulin deficiency. Insulin deficiency ultimately causes increased blood glucose[55]. In diabetic control rats, there is significant elevation of glucose level [56].The hypoglycaemic potency of *Allium porrum* may be attributed to the presence sulphur compound [10] as well as flavonoids [1-2]. The mechanism of hypoglycaemic action probably involves direct or indirect stimulation of insulin secretion [57]**.** On the other hand, this effect may occur due to a reduction in intestinal glucose absorption or induction of glycogenic process along with reduction in glycogenolysis and glyconeogenesis[58].The results of plasma glucose are consistent with the finding of other *Allium* species which exhibited antidiabetic effects [59-62].

The possible sources of oxidative stress in the pathogenesis of diabetes and diabetic complications have been extensively studied for many years based on in animal models and in patients. Diabetics exhibit high oxidative stress due to persistent and chronic hyperglycemia, which thereby depletes the activity of antioxidative defense system and thus promotes novo freeradicals generation[63-64.]

Numerous studies have found increased lipid peroxides or ROS and oxidative stress (or both) in different animal models of diabetes[65-66].Oxidative stress has been shown to be responsible, at least in part, for the β-cell dysfunction caused by glucose toxicity. Under hyperglycemia, production of various reducing sugars such as glucose-6-phosphate and fructose increases through glycolysis and the polyol pathway. During this process, ROS are produced and cause tissue damage[67].In vitro and in vivo studies have suggested the implication of oxidative stress in the progression of β -cell dysfunction in type 2 diabetes[68].STZ has a β -cell cytotoxic and itis not fully understood, it is thought to be mediated by the inhibition of free radical scavenger-enzymes thereby enhancing the production of the superoxide radical. Eventually, STZ causes diabetes and it is associated with the generation of ROS causing oxidative damage[69].

The results described here of the extract at two doses 200 and 400 mg/kg bw. enhanced and restored the endogenous antioxidant defense system, and reversed lipid peroxidation in the liver, thereby increasing transcription of CAT and GSH and reducing cell damage which may play an important role in liver protection. Lipid peroxidation may bring about protein damage and inactivation of membrane bound enzymes either through direct attack by free radicals or through chemical modification of its end products, such as MDA[70]. Thereby, the antioxidant property of the extract may be due to the presence of phenolics as well as flavonoids such as quercetin. The results are in agreement with previously reported[67, 71-74].Also, Pedraza-Chaverri*et al*. (2000)[75] reported that onion and garlic were effective in preventing or ameliorating oxidative stress.

Complication of diabetes induces elevation of plasma levels of urea and creatinine as significant markers of renal dysfunction [76]. However, the significant elevation in the serum concentrations of urea and serum creatinine were reduced by the oral administration of the *Allium porrum* extract in a dose dependent manner. Elevation in plasma creatinine and urea levels reveals the development of diabetic nephropathy in diabetic rats andthe reduction of these biochemical parameters by *Allium porrum* herb elucidates its protective effect.

Normal liver functions are characterized by balanced activities of the enzymes AST, ALT, and ALP (used as serum marker enzymes), which are found in high concentrations in the cytoplasm of liver cells. An increase in these enzyme activities reflects active liver damage. Inflammatoryhepatocellular disorders result in extremely elevated transaminase levels and indicates that diabetes may be induced hepatic dysfunction [77-78].

In the present study significant increased in the serum marker enzymes, AST, ALT, LDH, and decreased in the level of total protein was observed in streptozotocin treated rats, this is may be due to leakage of these enzymes into the blood stream as a result of streptozotocin toxicity which leads to the liver damage. However, treatment of STZ diabetic groups with alcohol extract of *Allium porrum* leaves at doses 200 and 400 mg/ kg bw. for 21 consecutive days could restore the activities of AST, ALT, LDH enzymes and total protein to their normal levels. A dose of 200 mg/kg was sufficient to protect liver damage as judged from serum marker enzyme levels. A possible explanation for the differential effects of *Allium porrum* on the activities of AST, ALT, LDH, and total protein may be inhibited the liver damage induced by STZ. In addition, preliminary phytochemical studies suggest that the flavonoids present in the plant could be responsible for the hepatoprotective activity.

Supporting our finding it has been found by Larcan *et al*. (1979)[79] that liver was necrotized in diabetic patients. Therefore, the increment of the activities of AST, ALT, LDH, in plasma may be mainly due to the leakage of these enzymes from the liver cytosol into the blood stream [80], which gives an indication of the hepatotoxic effect of STZ. On the other hand, treatment of the diabetic rats with of *Allium porrum* leaves at doses 200 and 400 mg/ kg bw. caused reduction in the activity of these enzymes in plasma compared to the mean values of diabetic group. These results are in agreement with those obtained [81-82].

Hyperlipidemia is a metabolic complication of diabetes and abnormality of the high concentration of serum lipids in diabetes mellitus due to an increase in the mobilization of free fatty acids from the peripheral fat deposits under utilization of the glucose[83]**.**

In the present study, LDL, total cholesterol and triglycerides were significantly decreased whereas HDL elevated in diabetic rats treated by methanolic extract of *Allium porrum* leaves as compared to diabetic controls. Theextract at dose of 400 mg/kg bw. was found as effective as glibenclamide. The reduction in cholesterol level may be due to effects of methanolic extract by stimulating effect of glucose utilization by peripheral tissues [84].This may be due to the increase in insulin secretion by the extractwhich decreases the total cholesterol and total triglycerides and increases HDL level. In addition to the hypoglycaemic effect of *A. porrum* leaves extract it may be able to improve some lipid metabolites including TG, HDL, LDL and cholesterol levels in diabetic rats. It is reported that diabetes are associated with profound alterations in lipid and lipoprotein profile[85-86]. Regulating the plasma or tissue lipid levels leads to a decrease in the risk of micro- or macro vascular disease and related complications[87]. Regarding to the mechanism of action of methanolic extract it may be enhanced the activity of enzymes involved in bile acid synthesis and its excretion and this may be have decreased in serum cholesterol and triglycerides. The lipid lowering effect of the extract might be due to the action of flavanoids and other phenolic compounds which normalized rate of lipogenesis or activating normoglycemia by the insulinotropic effect of flavanoids[88]or the lipid lowering property of phenolic compounds [89].Thus, this result suggested that the extract of *Allium porrum* leaves would be helpful for the prevention of diabetic complications through improving dyslipidaemia.

This is in agreement with other workers who reported that garlic extracts was shown to improve lipid profile, reducing serum cholesterol levels[90], lipid lowering effect [91]. According to these investigators, the triglycerides lowering effect due to inhibition of fatty acid synthesis suggesting that some constituents of garlic may act as inhibitors for some enzymes such as hydroxy methyl glutaryl CoA reductase, which participates in cholesterol synthesis [92-92]. Accumulation of triglycerides is one of the risk factors in coronary heart disease. The significant increase in the level of triglyceride of diabetic control rats may be due to the lack of insulin. Since

under normal condition, insulin activates the enzyme lipoprotein lipase and hydrolysis triglyceride[94].However, in diabetic state lipoprotein lipase is not activated due to insulin deficiency resulting in hypertriglyceridemia. Methanolic extract of *Allium porrum* leaves reduces triglycerides in tissues of STZ-induced diabetic rats and may prevent the progression of coronary heart disease.

During diabetic conditions lipogenesis is decreased while lipolysis is increased in the hepatic tissue. The increment of cholesterol in tissues is due to the decreased level of high density lipoprotein (HDL) cholesterol. The observed hypolipidemic effect may be due to decreased cholesterogenesis and fatty acid synthesis[95]. Hence the increase in the level of tissue lipids may be the result of an increased uptake and mobilization of lipids from the portal system[96].

Conclusions

The finding of this study evidently indicates that oral treatment of diabetic rats with a methanolic extract of *Allium porrum* leaves (200 and 400, mg/kg body weight) and glibenclamide showed beneficial effects on blood glucose level ($P<0.01$) as well as improving liver, kidney functions and due to diabetes. *Allium porrum* leaves exerted antioxidant, hyperlipidaemia and antihyperglycemic effects and consequently may alleviate liver and renal damage caused by STZ -induced diabetes. It could be speculated that the observed anti-hyperglycaemic activity of *Allium porrum* leaves might be related to the presence of flavonoides, phenolic and sulphur compounds. Antioxidant status of the extract might also be responsible for antidiabetic action .Thus, this result suggested that the extract of *Allium porrum* leaves would be helpful for the prevention of diabetic and its complications.

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References

1. Fattorusso E, Lanzotti V, Taglialatela-Scafati O, Cicala C. The flavonoids of leek, *Allium porrum.* Phytochem., 2001, 57: 565-569.
2. Soininen TH, Jukarainen N, Soininen P, Auriola SOK, Julkunen-Tiitto R, Oleszek W, Stochmal A, Karjalainene RO, Vepsäläinena JJ. Metabolite Profiling of Leek (*Allium porrum*L) Cultivars by ^{1}H NMR and HPLC–MS. Phytochem. Anal., 2014, 25: 220–228.
3. Di Donna L, Mazzotti F, Taverna D, Napoli A, Sindona G. Structural Characterisation of MalonylFlavonolsinLeek (*Allium porrum*L.) Using High-performance Liquid Chromatography and Mass Spectrometry. Phytochem. Anal., 2014, 25: 207–212.
4. Radovanović B, Mladenović J, Radovanović A, Pavlović R, Nikolić V. Phenolic Composition, Antioxidant,Antimicrobial and Cytotoxic Activites of *Allium porrum*L. (Serbia) Extracts. Journal of Food and Nutrition Research,2015, 3(9): 564-569.
5. Carotenuto A, Fattorusso E, Lanzotti V, Magno S, Carnuccio R, D'Acquisto F. Keto-Porrigenin and the Unique 2,3-Seco-Porrigenin, New AntiproliferativeSapogenins from *Allium porrum.* Tetrahedron,1997, 53(9): 3401-3406.
6. Carotenuto A, Fattorusso E, Lanzotti V, Magno S. Spirostanolsaponins of *Allium porrum*L. Phytochemistry, 1999, 51: 1077-1082.
7. Ada˜o CR, da Silva BP, Tinoco LW, Parente JP. Haemolytic activity and immunological adjuvant effect of a new steroidal saponin from *Allium ampeloprasum var. porrum*. Chemistry & Biodiversity, 2012, 9: 58-67.
8. CasellaS, Leonardi M, Melai B, Fratini F, Pistelli L. The Role of Diallyl Sulfides and Dipropyl Sulfides in the In Vitro Antimicrobial Activity of the Essential Oil of Garlic, *Allium sativum* L. and Leek, *Allium porrum*L. Phytotherapy Research, 2013, 27(3): 380–383.

9. Tsiaganis CM, Laskari K, Melissari E. Fatty acid composition of Allium species lipids. Journal of Food Composition and Analysis, 2006,19: 620–627.
10. Mondy N, Duplat D, Christides JP, Arnault I, Auger J. Aroma analysis of fresh and preserved onions and leek by dual solidphase micro extraction-liquid extraction and gas chromatography mass spectrometry. J. Chromatogr. A, 2002, 963: 89-93.
11. Movahedian A, Sadeghi H, Ghannadi A, Gharavi M, Azarpajooh S. Hypolipidemic activity of *Allium porrum*L. in cholesterol-fed rabbits. Journal Of Medicinal Food, 2006, 9 (1): 98–101.
12. Aslan M, Orhan N, Orhan DD, Ergun F. Hypoglycemic activity and antioxidant potential of some medicinal plants traditionally used in Turkey for diabetes. Journal of Ethnopharmacology, 2010, 128: 384–389.
13. Mladenović JD, Mašković PZ, Pavlović RM, Radovanović BC, Aćamović-Đoković G, Cvijović MS. Antioxidant activity of ultrasonic extracts of leek *Allium porrum*L. HemijskaIndustrija, 2011, 65(4): 473–477.
14. Vishwakarma S, Chandan K, Jeba RC, Khushbu S. Comparative study of Qualitative Phytochemical screening and antioxidant activity of *Mentha arvensis, Elettaria cardamomum* and *Allium porrum.* Indo American Journal Of Pharm Research., 2014, 4(05): 2538-2556.
15. El-Shenawy SMA, Yassin NAZ,,Badary OA, Abd EL-Moneem M, AL-Shafeiy HM. Study of the effect of *Allium porrum*on osteoporosis induced in rats. Der Pharmacia Lettre, 2013, 5(1): 188-198.
16. Kratchanova M, Nikolova M, Pavlpova E, Zanakieva I, Kussovski V. Composition and properties of biologically active pectic polysaccharides from leek (*Allium porum*). Journal of the Science of Food and Agriculture,2010, 90: 2046–2051.
17. Mnayer D, Tixier ASF, Petitcolas E, Hamieh T, Nehme N, Ferrant C, Fernandez X, Chemat F. Chemical Composition, Antibacterial and Antioxidant Activities of Six Essentials Oils from the *Alliaceae*Family. Molecules,2014, 19: 20034-20053.
18. Chen CH, Chou TW, Cheng LH, Ho CW. In vitro anti-adenoviral activity of five *Allium* plants, Journal of the Taiwan Institute of Chemical Engineers, 2011, 42: 228–232.
19. Malafaia.CRA, da Silva BP, Tinoc LW, Parente JP. Structural characterization and gastroprotective property of a novel glucofructan from *Allium ampeloprasum* var. *porrum*. Carbohydrate Research, 2015, 402: 44–49.
20. Gotep J. "Glycosides fraction extracted from fruit pulp of *Cucumis metuliferus* E. Meyer has antihyperglycemic effect in rats with alloxan-induced diabetes,". Journal of Natural Pharmaceuticals, 2011, 2(2),:48–51.
21. Ugochukwu NH, Babady NE, Cobourne M, Gasset SR. The effect of *Gongronema latifolium* extracts on serum lipid profile and oxidative stress in hepatocytes of diabetic rats. Journal of Bioscience, 2003, 28: 1–5.
22. Dewanjee S, Bose SK, Sahu R, Mandal SC. Antidiabetic effect of matured fruits of *Diospyrosperegrina*in alloxan induced diabetic rats. International Journal of Green Pharmacy, 2008, 95–9.
23. Sharma VK, Kumar S, Patel HJ, Hugar S. "Hypoglycemic activity of *Ficus Glomerata*in alloxan induced diabetic rats." International Journal of Pharmaceutical Sciences Review and Research, 2010, 1(2): 18–22.
24. Rolo AP, Palmeira CM. Diabetes and mitochondrial function: Role of hyperglycemia and oxidative stress. Toxicol Appl. Pharmacol., 2006, 212: 167-78.
25. Noiri E, Tsukahara H. Parameters for measurement of oxidative stress in diabetes mellitus: Applicability of enzyme-linked immuno sorbent assay for clinical evaluation. J. Investig. Med., 2005, 53:167-75.
26. Sies H. Oxidative stress: Oxidants and antioxidant. Exp. Physiol., 1997, 82:291-295.
27. Akash MSH, Shen Q, Rehman K, Chen S. Interleukin-1 receptor antagonist: a new therapy for type 2 diabetes mellitus. J. Pharm. Sci., 2012, 101: 1647–58.
28. Pari L, Umamaheswari J. Antihyperglycaemic activity of *Musa sapientum* flowers: effect on lipid peroxidation in alloxan diabetic rats. Phytother. Res., 2000, 14: 1–3.
29. Rajan M, Kumar KV, Kumar PS, Ramaniyam RT, Kumar NS. Antidiabetic activity of ethanolic extract on *Albizia odoratissima* benth in alloxan induced diabetic rats. Int. J. Pharm. Sci., 2010, 2: 786–91.
30. Romila Y, Mazumder PB, Choudhury MD. A review on antidiabetic plants used by the people of Manipur characterized by hypoglycemic activity. Assam Uni. J. Sci. Tech. Bio. Environ. Sci., 2010, 6: 167–75.

31. Singleton VL, Orthofer R, Lamuela-Raventos RM. Analysis of total phenols and other oxidation substrates and antioxidants by means of Folin–Ciocalteu reagent. Methods in Enzymology, 1999, 299: 152–178.
32. Meda A, Lamien CE, Romito M, Jeanne Millogo J, Nacoulma OG. Determination of the total phenolic, flavonoid and proline contents in *Burkina Fasan*honey, as well as their radical scavenging activity. Food Chemistry, 2005, 91: 571–577.
33. Arvouet-Grand A, Vennat B, Pourrat A, Legret P. Standardization of a propolis extract and identification of the main constituents. *Journal de Pharmacie de Belgique*. 1994, 49: 462–468.
34. OECD Guidelines for Testing of Chemicals. No 420: Acute Oral Toxicity-fixed Dose Method, Organisation for Economic Co-operation and Development: Paris, France, 1992.
35. Lee JN, Park CS, Kim HP, Hwang SY, Chung WG. Single dose toxicity study of Hwangjaegongjinbo, an invigorator, in mice and rats. J. Toxicol. Pub. Health., 2002, 18(1): 73-77.
36. Ryu SD, Park CS, Baek HM, Baek SH, Hwang SY, Chung WG.Anti-diarrheal and spasmolytic activities and acute toxicity study of Soonkijangquebo, a herbal anti-diarrheal formula. J. Ethnopharmacology, 2004, 91(1): 75-80.
37. Erejuwa OO, Sulaiman SA, Wahab MS, Salam SK, Salleh MS, Gurtu S. Comparison of antioxidant effects of honey, glibenclamide, metformin, and their combinations in the kidneys of streptozotocin-induced diabetic rats. Int. J. Mol. Sci., 2011, 12(1): 829-43.
38. Reitman S , Frankel S. A colorimetric method for the determination of serum glutamic oxalacetic and glutamic pyruvic transaminases. Amer. J. Clin. Pathol., 1957, 28: 56-63.
39. Trinder, P. Determination of glucose in blood using glucose oxidase with an alternative oxygen receptor. Ann. Clin. Biochem., 1969, 6: 24-27.
40. Abei H, Levy BB, Brodie BB, Kendall FE. A simplified method for the estimation of total cholesterol in serum and demonstration of its specificity. J. Biol. Chem., 1952, 195: 357-366.
41. Fossati P, Prencipe L. Serum triglycerides determined colorimetrically with an enzyme that produce hydrogen peroxide. Clin.Chem., 1982, 28 :2077-2080.
42. Lopez-Virella MF, Stone P, Collwell J. Cholesterol determination in high density lipoprotein by three different methods. Clin. Chem., 1977, 23(5): 882-884.
43. Fawcett JK, Scott JE. A rapid and precise method for the determination of urea. Journal of clinical pathology, 1960, 13: 156-159.
44. PetersT. Determination of total proteins. *Clinical Chemistry*. 1968, 14: 1147-1159.
45. Larsen K. Creatinine assay by a reaction-kinetic principle. Clin. Chem. Acta., 1972, 41: 209.
46. Nishikimi M, Appaji N, Yagi K. The occurrence of superoxide anion in the reaction of reduced phenazinemethosulfate and molecular oxygen.Biochm. Biophys. Res. Communication., 1972, 46: 849-854.
47. AebiH.. Catalase in vitro. Methods in Enzymology, 1984, 105: 121-126.
48. Beutler E, Durgun O, Kelly BM . Improved method for the determination of blood glutathione. J. Lab. Clin. Med., 1963, 51: 882-8.
49. Uchiyama M ,Mihara M. Determination of malonaldehyde precursor in tissues by thiobarbituric acid test. Anal. Biochem., 1978, 86: 271- 278.
50. Mc-Nurlan MA, Garlick PJ. Rates of Protein synthesis in rat liver and small intestine in protein deprivation and diabetes. Proc. Nut. Soc., 1979, 38: 7-11.
51. Rajkumar L, Srinivasan N, Balasubramanian K, Govindarajulu P. Increased degradation of dermal collagen in diabetic rats. Int. J. Exp. Biol., 1991, 29: 1081-1083.
52. Jariyah, Widjanarko SB, Yunianta, Estiasih T. Hypoglycemic effect of Pedada (*Sonneratia caseolaris*) Fruit Flour (PFF) in alloxan-induced diabetic rats. International Journal of PharmTech Research, 2015, 7(1): 31-40.
53. Kim DH, Yang BK, Jeong SC, Hur NJ, Das S, Yun JW, Choi, JW, Lee YS, Song CH. A preliminary study on the hypoglycemic effect of the exo-polymers produced by five different medicinal mushrooms. Journal of Microbiology and Biotechnology, 2001, 11: 167–171.
54. Devi MN, Singh Kh.B, Singh SR, Singh CB, Lukesh D, Amitabh D. Antihyperglycemic effect of Aqueous and Ethanol extract of Aerial part of *Osbeckia nepalensis* Hook in Alloxan induced Diabetic rats. International Journal of PharmTech Research, 2012,4(1):233-244.
55. DeFronzo RA, Tripathy D. "Skeletal muscle insulin resistance is the primary defect in type 2 diabetes," Diabetes care, 2009, 32(2): S157–S163.

56. Konwar M, Das S. Comparative Study of Antidiabetic and Antioxidant Activities of the Ethanolic Extracts of Leaves and Bark of *Acacia Farnesiana* (L.)Willd. In Streptozocin Induced Type 1 Diabetic Experimental Animal Models. International Journal of PharmTech Research, 2015, 7(4): 591-600.
57. Carson JF. Chemistry and biological properties of onion and garlic. Food Rev. Internat., 1987, 3: 71–103.
58. Anusooriya P, Malarvizhi D, Gopalakrishnan VK, Devaki K. Antioxidant and Antidiabetic Effect of Aqueous Fruit Extract of *Passiflora ligularis* Juss. On Streptozotocin Induced Diabetic Rats. International Scholarly Research Notices, 2014, 1-10.
59. El-Demerdash FM, Yousef MI, Abou El-Naga NI. Biochemical study on the hypoglycemic effects of onion and garlic in alloxan-induced diabetic rats. Food and Chemical Toxicology, 2005, 43: 57–63.
60. Eidi A, Eidi M, Esmaeili E. Antidiabetic effect of garlic (Allium sativum L.) in normal and streptozotocin-induced diabetic rats. Phytomedicine, 2006, 13: 624–629.
61. Eyo JE, Ozougwu JC, Echi PC. Hypoglycemic effects of *Allium cepa*, *Allium sativum* and *Zingiber officinale* aqueous extract on alloxane induced diabetic rattus novergicus. Med. J. Islam. World Acad. Sci., 2011, 19:121-6.
62. Akash MSH, Rehman K, Chen S. Spice plant *Allium cepa*: Dietary supplement for treatment of type 2 diabetes mellitus. Nutrition, 2014, 30:1128–1137.
63. Baynes JW, Thorpe SR. The role of oxidative stress in diabetic complications. CurrOpinEndocrinol, 1996, 3:277–84.
64. Ihara Y, Toyokuni S, Uchida K, Odaka H, Tanaka T, Ikeda H, et al. Hyperglycemia causes oxidative stress in pancreatic beta-cells of GK rats a model of type 2 diabetes. Diabetes, 1999, 48:927–32.
65. Friedman J, Peleg E, Kagan T, Shnizer S, Rosenthal T. Oxidative stress in hypertensive, diabetic, and diabetic hypertensive rats. Am. J. Hypertens, 2003, 16:1049–52.
66. Laight DW, Carrier MJ, Anggard EE. Antioxidant, diabetes and endothelial dysfunction. Cardiovasc. Res., 2000, 47: 457–64.
67. EeShian T, Aminah A, NurKartinee K, ShahrulHisham ZA. Antioxidant and hypoglycaemic effects of local bitter gourd fruit (*Momordica charantia*) International Journal of PharmTech Research, 2015, 8(1): 46-52.
68. Kaneto H, Kajimoto Y, Miyagawa J, Matsuoka T, Fujitani Y, Umayahara Y. Beneficial effects of antioxidants in diabetes: possible protection of pancreatic beta-cells against glucose toxicity. Diabetes, 1999, 48: 2398–406.
69. Evans JS, Gerritsen GC, Mann K, Owen SP. Antitumor and hyperglycemic activity of streptozotocin (NSC-37917) and its cofactor, U-15,774. Cancer Chemother. Rep., 1965, 48: 1–6.
70. Coskun O, Kanter M, Korkmaz A, Oter S. Quercetin, a flavonoid antioxidant, prevents and protects streptozotocin-induced oxidative stress and β-cell damage in rat pancreas. Pharmacological Research, 2005, 51: 117–123.
71. Kumari K, Augusti KT. Antidiabetic and antioxidant effects of S-methyl cysteine sulfoxide isolated from onions (Allium cepa Linn) as compared to standard drugs in alloxan diabetic rats. Indian Journal of Experimental Biology,2002, 40: 1005–1009.
72. Sheweita SA, Newairy AA, Mansour HA, Yousef MI. Effect of some hypoglycemic herbs on the activity of phase I and II drug-metabolizing enzymes in alloxan-induced diabetic rats. Toxicology, 2002, 174: 131–139.
73. Anwar MM, Meki AR. Oxidative stress in streptozotocin induced diabetic rats: effects of garlic oil and melatonin. *Comparative Biochemistry and Physiology, Part A.* Molecular and Integrative Physiology, 2003, 135: 347–539.
74. Campos KE, Diniz YS, Cataneo AC, Faine LA, Alves MJ, Novelli, E.L. Hypoglycaemic and antioxidant effects of onion, *Allium cepa*: dietary onion addition, antioxidant activity and hypoglycaemic effects on diabetic rats. International Journal of Food Science and Nutrition, 2003, 54 (3): 241–246.
75. Pedraza-Chaverri J, Maldonado PD, Medina-Campos ON, Olivares-Corichi IM, Granados-Silvestre MA, Hernandez-Pando R, Ibarra-Rubio ME. Garlic ameliorates gentamicin nephrotoxicity: relation to antioxidant enzymes. Free Radicals in Biology and Medicine, 2000, 29,: 602–611.
76. Almadal TP, Vilstrup H. Strict insulin treatment normalizes the organic nitrogen contents and the capacity of urea–N synthesis in experimental diabetes in rats. Diabetologica, 1988, 31: 114–118.
77. Foreston WC, Tedesco FJ, Starnes EC. Marked elevation of serum transaminase activity associated with extrahepatic biliary tract disease. J. Clin. Gastroenterol., 1985, 76: 502–505.

78. Hultcrantz R, Glaumann H, Lindberg G. Liver investigation in 149 asymptomatic patients with moderately elevated activities of serum amnotransferases. Scand. J. Gastroenterol., 1986, 21: 109–113.
79. Larcan A, Lambert H, Laprevote-Heully MC, Delorme N. Light and electron microscopic study of hepatic lesions in the course of hyperlactatemia in diabetic patients. Diabetes Metabolism, 1979, 5: 103–112.
80. Navarro CM, Montilla PM, Martin A, Jimenez J, Utrilla PM. Free radicals scavenger and antihepatotoxic activity of Rosmarinus. Plant Medicine, 1993, 59: 312–314.
81. Ohaeri OC. Effect of garlic oil on the levels of various enzyme in the serum and tissue of streptozotocin diabetic rats. Bioscience and Reproduction, 2001, 21: 19–24.
82. Varadharaj V, Janarthanan UDK, Krishnamurthy V. Protective role of Ethanolic Leaf Extract of *Anonna squamosa* (L.) on Experimentally Induced Hepatocellular Carcinoma. International Journal of ChemTech Research, 2015, 8(1): 282-292.
83. Krisnakumar K, Augustti KT, Vijayammal PL. Hypolipidemic effect of *Solaciaoblanga* wall root bark in streptozotocin diabetic rats. Med. Sci., 2000, 28: 65-67.
84. Kamanyi A, Njamen D, Nikeh B. Hypoglycemic properties of aqueous root extracts of *Morindalucida* (Benth) (Rubiaceae) studies in mouse. Phytother Res., 1994, 8: 369e371.
85. Sharma SB, Nasir A, Prabhu KM, Murthy PS, Dev G. Hypoglycaemic and hypolipidemic effect of ethanolic extract of seeds of *Eugenia jambolana* in alloxan-induced diabetic rabbits. J. Ethnopharmacol., 2003, 85:201-6.
86. Pushparaj PN, Low HK, Manikandan J, Tan BK, Tan CH. Anti-diabetic effects of *Cichoriumintybus*in streptozotocin-induced diabetic rats. J. Ethnopharmacol., 2007, 111: 430-4.
87. Sakatani T, Shirayama T, Suzaki Y, Yamamoto T, Mani H, Kawasaki T, *et al*. The association between cholesterol and mortality in heart failure. Comparison between patients with and without coronary artery disease. Int. Heart J., 2005, 46:619-29.
88. Pinent M, Castall A, Biages I, Montagut G, Arola L, Ardevol A. Bioactivity of flavanoids on insulin secreting cells. Compr. Rev. Food Sci. Food Saf., 2008, 7: 2299.
89. Akhtar A, Rashid M, Wahed MII, et al. Comparison of long term antihyperglycemic and hypolipidemic effects of *Coccinia cordifolia* (Linn) and *Catharanthu sroseus* (Linn) in alloxan induced diabetic rats. Res. J. Med. Med. Sci.,2007, 2:29.
90. Knipschild JK, Ter-Riet G,. Garlic, onions and cardiovascular risk factors. A review of the evidence from human experiments. Emphasis on commercially available preparations. Br. J. Clin. Pharmacol., 1989, 28: 535–544.
91. Yeh YY, Yeh SM. Garlic reduces plasma lipids by inhibiting hepatic cholesterol and triacyglycerol synthesis. Lipids, 1994, 29: 189–193.
92. Gebhardt R. Inhibition of cholesterol biosynthesis by a water soluble garlic extract in primary cultures of rat hepatocytes. Arzneimittelforschung, 1991, 41: 800–804.
93. Gebhardt R, Beck H. Differential inhibitory effects of garlic-derived organosulfur compounds on cholesterol biosynthesis in primary rat hepatocyte cultures. Lipids, 1996, 1269–1276.
94. Frayn KN. Insulin resistance and lipid metabolism. *Curr. Opin.* Lipidol., 1993, 4: 197-204.
95. Bopanna KN, Kannan J, Sushma G, Balaraman ER, Rathore SP. Antidiabetic and antihyperglycemic effects of neem seed kernel powder on alloxan diabetic rabbits. Ind. J. Pharmacol., 1997, 29: 126-167.
96. Yadav UC, Moorthy K, Baquer NZ. Combined treatment of sodium orthovanadate and*Momordica charantia* fruit extract prevents alterations in lipid profile and lipogenic enzymes in alloxan diabetic rats. Mol. Cells Biochem., 2005, 268: 111-120.

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