Research Article

ANTIDIABETIC AND ANTIHYPELIPIDAEMIC ACTIVITY OF *CAPPARIS SPINOSA* EXTRACT

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ABSTRACT

In this study Male albino rats were randomly divided into four groups. Group I and II serves as vehicle control (Demineralized water) and triton control (Triton WR-1339 - 200 mg/kg; i.p.), Group III, IV were treated with atorvastatin (7.2 mg/kg) & test substance 400 mg/kg/day respectively as single dose for two days. In the second study animals were divided into four groups. The first group was normal control, second group was used as diabetic control group. The diabetic rats of third and fourth group were treated orally with *capparis spinosa* fruit extract (200mg/kg b.w. & 400mg/kgb.w.) for 28 days, fifth group was treated orally with 25mg/kgb.w. Gliclazide**.** In case of OGTT the extract OD, extract BD and Gliclazide treated groups, glucose level nonsignificantly decreases at 60 and 120 min giving the indication regarding the supportive action of *capparis spinosa* extract and also with STZ&NA induced rats significant blood glucose and lipid lowering was found with the same extract.

Keywords: Diabetes Mellitus, *Capparis Spinosa*, Streptozotocin, Albino Rats.

INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder affecting approximately 4% population worldwide and is expected to increase by 5.4% in 2025[1]. It is characterized by abnormalities in carbohydrate, lipid and lipoprotein metabolism, which not only leads to hyperglycemia but also cause many complications such as hyperlipidemia, hyperinsulinemia, hypertension and atherosclerosis[2,3] which results in decreased ability of insulin to stimulate glucose uptake in peripheral tissues, insulin resistance, and the inability of the pancreatic β-cells to secrete insulin adequately which ultimately leads to β-cell failure caused by a combination of genetic and environmental factors. The major sites of insulin resistance in type-2 diabetes are the liver, skeletal muscle and adipose tissue.[1]

Capparis spinosa is an evergreen Shrub growing to 1 m (3ft 3in) by 2 m (6ft), Family, the capparidaceae present in the Himalayan area. It grows on rocky cliffs and stone walls in the sea-spray zone. Leaves are alternate, round to ovate, thick, and glistening. It has beautiful flowers that are hermaphrodite. Flowers are about 2 inches in diameter, white with numerous violet stamens, and very pleasing in appearance. The first recorded use of the caper bush was for medicinal purposes in 2000 BC by the Sumerians. It has been suggested that capers have been used or are still being used in reducing flatulence, in the treatment of rheumatism, anemia and gout. Further medical uses include ingesting for improving liver functions, as diuretics, kidney disinfectants[4]. Infusions and decoctions from caper root bark have been traditionally used for dropsy, anemia, arthritis and gout[5-7]. The root-bark is analgesic, anthelmintic, antihaemorrhoidal, aperient, depurative, diuretic, emmenagogue, expectorant, hepatoprotective, tonic and vasoconstrictive[8-10]. Externally, it is used to treat skin conditions, capillary weakness and easy bruising[11]. The bark is harvested in the autumn and dried for later use[12]. Liver, an important organ actively involved in metabolic functions, is a frequent target of a number of toxicants[13]. The principal cause of carbon tetrachloride CCl4 induced hepatic damage is lipid peroxidation and decreased activities of antioxidant enzymes and generation of free radicals[14,15]. The resulting hepatic injury was characterized by leakage of cellular enzymes into the blood stream and by centrilobular necrosis[16,17]. The present study was undertaken to evaluate the antihyerglycemic and antihyperlipidemic activity of capparis spinosa fruit extract in experimental animals using Nicotinamide (NA) and Streptozotocin (STZ) induced diabetic rats and triton induced hyperlipidaemia.

MATERIALS AND METHODS

Animals

Male adult albino rats (200–225 g) bred in the animal house of the institute were used. A group of six animals in a cage were kept in controlled conditions, temperature 25–26°C, relative humidity 60–80% and 12/12 h light/dark cycle (light from 08:00 a.m. to 08:00 p.m.). The identification of animals has been done by cage card and corresponding colour body markings using picric acid. The animals were kept in polypropylene cages with stainless steel grill top, facilities for feed and water bottle and bedding of clean paddy husk, fed on standard pellet diet and U.V. purified and filtered water will be provided ad libitum in polypropylene bottles with stainless steel sipper tubes. The standard pellet diet (Protein: 20.12%, Total Oil: 4.38%, Dietary Fiber: 3.65%, Moisture: 8.0%)

was supplied by Rayan's biotechnologies Pvt. Ltd, Hyderabad, India. The Institutional Animal Ethical Committee has approved the experimental protocol (Approval No.29) prior to carry out the animal experimentation. The study design was in compliance with guidelines of Institutional Animal Ethical Committee (IAECRegd No: 926/ab/06/CPCSEA).

Preparation of extracts: Ethanolic extract of the plant *capparis spinosa* was purchased from cure herbs, New Delhi.

Acute Toxicity studies: Wistar rats weighing 150-175 g of either sex, maintained under standard husbandry conditions, were used for all sets of experiments in groups of six animals. The ethanolic extract was administered to different groups of rats in doses ranging from 100-2000 mg/kg. There is no lethality in any of the groups. One tenth of the maximum dose of the extract and its double dose, tested for acute toxicity, was selected for evaluation of antidiabetic, i.e., 200 mg/kg & 400mg/kg b.w. and the highest dose was selected for antihyperlipidaemic study (400mg/kgb.w.). The experiments were performed after the experimental protocol had been approved by the Institutional Animal Ethics Committee, Roland institute of pharmaceutical sciences, Berhampur.

Chemicals

Tyloxapol, Sodium chloride and Triton WR 1339 were purchased from HiMedia Laboratories Pvt. Ltd.; India. Atorvastatin was a gift from Ranbaxy Laboratories Ltd., India. Streptozotocin (STZ; Himedia Laboratories Pvt. Ltd. Mumbai), nicotinamide **(**NA; Himedia laboratories Pvt. Ltd. Mumbai), Gliclazide (Chemical Products, Mumbai), EDTA (Qualigens, Mumbai, India), Glucose (Nice chemicals Pvt. Ltd. Cochin), Citric acid (Nice chemicals Pvt. Ltd. Cochin), Sodium citrate 2-hydrate (Merk Specialities Pvt. Ltd. Mumbai)

Biochemical kits

All the kits were obtained from Crest Biosystems, a division of Coral Clinical Systems, Goa. The kits like Glucose, Triglycerides, Cholesterol, etc were used in Auto analyzer (3000 Evolution, BSI, Italy).

Experimental

Induction of Hyerlipidaemia in Triton model

Hyerlipidaemia was induced by a single intraperitoneal injection of Triton (Triton WR-1339 - 200 mg/kg; i.p.) in all the groups except vehicle control one.

Induction of type II diabetes mellitus

Type II diabetes mellitus was induced by a single intraperitoneal injection of 120 mg/kg of nicotinamide (NA) followed by STZ 50 mg/kg[18] intravenously 15 min afterwards. STZ was dissolved in citrate buffer (pH 4.5) and NA[18] was dissolved in normal saline[19]. The animals were made to fast for 12h before induction. The animals were allowed to drink 5%glucose solution overnight to overcome the drug-induced hyperglycemia. Diabetes was confirmed by the elevated glucose levels in the plasma of the rats, determined after 3 days of the induction. The threshold value of the fasting plasma glucose to diagnose diabetes, was taken as >200 mg/dl. Only those rats that were found to have plasma glucose level >200 mg/dl were used in the study.

Determination of plasma glucose and other biochemical parameters

Animals were fasted overnight. Blood (0.5 ml) was withdrawn from the sublingual vein under ether anesthesia and was collected in micro tubes previously filled with 10% EDTA solution (20 µl of 10% EDTA/ ml of blood). The micro tubes were centrifuged at 4000 rpm at 4°C for 20 min to obtain clear plasma. The plasma was then analyzed for glucose in the auto analyser (3000 Evolution, BSI Italy) using commercially available biochemical kits.

Grouping of Animals in Triton model[20-22]

The animals were randomly divided into four groups. Groups I and II serves as vehicle control (Demineralized water) and triton control (Triton WR-1339 - 200 mg/kg; i.p.), respectively[17]. Group III was treated with atorvastatin (7.2 mg/kg). Groups IV, was treated with the test substance *capparis spinosa* extract, at the dose of 400 mg/kg respectively after the intra-peritoneal administration of Triton WR-1339 at the dose of 200 mg/kg. The vehicle, reference standard or test substance will be administered orally as a single dose. The blood samples of each animal will be collected at 0, 18, 24, 40 and 48 h post treatments and serum will be separated for estimation of cholesterol and triglycerides.

Grouping of Animals in STZ&NA model for blood glucose estimation.

They were divided into 4 experimental groups, each group containing six animals in it. Twenty four rats of body weight range 150-200g were selected from the stock of animal house. Six animals were not treated with NA and STZ and kept as non-diabetic control. Diabetes was induced in rest of 18 rats. Rats that showed blood glucose level more than 200mg/dl were selected for further grouping. The experimental groups are

Group 1: Non-diabetic control, treated with normal saline daily.

Group 2: Diabetic control (STZ+ NA), treated with normal saline.

Group 3: Diabetic (STZ+ NA), treated with *capparis spinosa* (200 mg/kg b.w.) once a day.

Group 4: Diabetic (STZ+ NA), treated with *capparis spinosa* (400 mg/kg b.w.) once a day.

Group 5: Diabetic (STZ+ NA), treated with 25mg/kgb.w. of Gliclazide.

Oral glucose tolerance test[23]

Oral glucose tolerance test (OGTT) was carried out in overnight fasted rats, which were equally divided into four groups of six rats each. Group of normal control (Gr II & positive control) received only vehicle (1 ml of 0.3% CMC; p.o.) and standard group (111) received 1 ml of reference drug (Gliclazide 25mg/kg b.w.).[22] Suspended in the vehicle while group IV and V were administered with *capparis spinosa* extract (200& 400mg/kg, p.o.) respectively. Thereafter, following 30 min post extract, all the animals were administered with glucose (2 g/kg). Blood samples were collected from sublingual vein prior to dosing and then at 30, 60 and 120 min after glucose administration. The fasting blood glucose level was analyzed using auto analyzer using sugar testing kits.

Statistical analysis: The data obtained in the studies were subjected to one way analysis of variance (ANOVA) for determining the significant difference. The intergroup significance was analyzed using Dennett's t test. P values <0.05 were considered to be significant. All the values were expressed as mean ± SEM.

RESULTS

Triton model - Body weight

The mean body weight of each group is presented in table 1 and fig. 1. There is no significant difference in the mean body weight of vehicle control and Triton control group throughout the experiment period. Also, the treated groups did not show any significant body weight change when compared to Triton control.

Table 1: Effect of different extracts on body weight in triton-induced hyperlipidaemic rats

Treatment groups	Body weight (g)		
	Day 0	Day 1	Day 2
I - Vehicle control (Demineralised water; 10 ml/kg)	239.17 ± 4.21	261.33 ± 4.30	259.83 ± 5.52
II - Triton control (200 mg/kg; *i.p.*)	237.80 ± 1.88	253.40 ± 2.58	260. 00 ± 3.21
III - Atorvastatin (7.2 mg/kg)	241.00 ± 2.86	255.67 ± 3.03	259.67 ± 4.92
IV - Extract C (400 mg/kg)	238.83 ± 3.77	252.67 ± 4.54	258.83 ± 4.03

Values are expressed as mean ± SEM, n=6, except for groups II and V where n=5; Here extract C is *capparis spinosa*

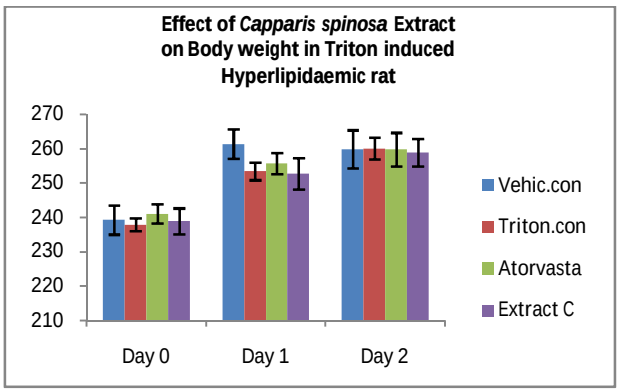

Figure 1: Effect of *Capparis spinosa* extract on Body weight

Lipid profile

Serum cholesterol

The mean serum total cholesterol level of each group is presented in table 2 and fig. 2. At hour 0, there is no significant change in the serum total cholesterol levels between all the groups. After induction of Triton, the vehicle control group showed a significant increase in serum total cholesterol level at Hour 18 and 24 when compared with Triton control group. Treatment with Atorvastatin showed a significant decrease in serum total cholesterol level when compared with Triton control group. *Capparis spinosa* extract treated group shows non significant decrease in serum total cholesterol level when compared to Triton control.

Table 2: Effect of different extracts on serum total cholesterol in triton-induced hyperlipidaemic rats

Treatment groups	Serum total cholesterol (mg/dl)				
	Hour 0	Hour 18	Hour 24	Hour 40	Hour 48
I - Vehicle control (Demineralised water; 10 ml/kg)	62.48 ± 3.45	38.12 ± 4.88	40.91 ± 2.25	50.70 ± 2.28	47.22 ± 1.93
II - Triton control (200 mg/kg; *i.p.*)	66.44 ± 5.21	258.85 ± 29.47*	210.72 ± 29.81*	60.79 ± 3.33	54.14 ± 3.16
III - Atorvastatin (7.2 mg/kg)	65.44 ± 5.22	125.80 ± 15.46#	112.80 ± 18.27#	60.85 ± 5.06	60.86 ± 4.27
IV Extract C (400 mg/kg)	65.56 ± 2.71	190.73 ± 18.98	144.50 ± 12.87	59.37 ± 3.90	54.34 ± 2.36

Values are expressed as mean ± SEM, n=6, except for groups II where n=5, Here extract C is *Capparis spinosa*

*p ≤ 0.05, Vehicle control Vs Triton control

#p ≤ 0.05, Triton control Vs Treated groups

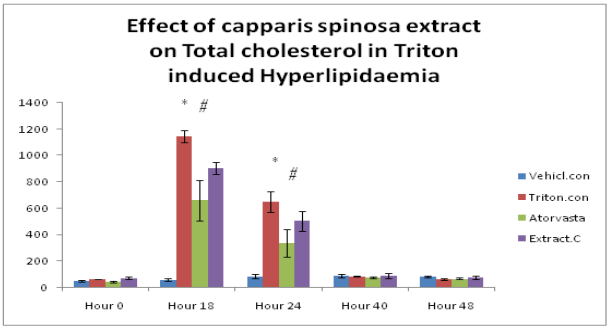

Figure 2: Effect of *Capparis spinosa* extract on serum total cholesterol

Serum total triglycerides

The mean serum triglycerides level of each group is presented in table 3 and fig. 3. At hour 0, there is no significant change in the serum triglycerides level between all the groups. After induction of Triton, the vehicle control group showed a non-significant increase in serum triglycerides level at Hour 18 and 24 when compared with Triton control group. Treatment with Atorvastatin showed a non-significant decrease in serum triglycerides level when compared with Triton control group. *Capparis spinosa* extract treated group shows non significant decrease in serum triglycerides level when compared to Triton control group.

Table 3: Effect of different extracts on serum triglycerides in triton-induced hyperlipidaemic rats

Treatment groups	Serum triglycerides (mg/dl)				
	Hour 0	Hour 18	Hour 24	Hour 40	Hour 48
I - Vehicle control (Demineralised water; 10 ml/kg)	51.14 ± 5.05	59.67 ± 10.56	86.65 ± 16.65	91.33 ± 13.27	81.91 ± 6.99
II - Triton control (200 mg/kg; *i.p.*)	62.42 ± 2.16	1144.36 ± 45.85	648.78 ± 75.40	87.89 ± 4.29	63.02 ± 4.51
III - Atorvastatin (7.2 mg/kg)	42.68 ± 5.75	661.72 ± 153.31	337.34 ± 105.01	75.86 ± 7.18	67.50 ± 5.95
IV - Extract C (400 mg/kg)	71.25 ± 10.33	903.83 ± 44.36	505.04 ± 74.82	90.78 ± 20.52	75.01 ± 13.70

Values are expressed as mean ± SEM; n=6, except for groups II where n=5, Here extract C is *Capparis spinosa*

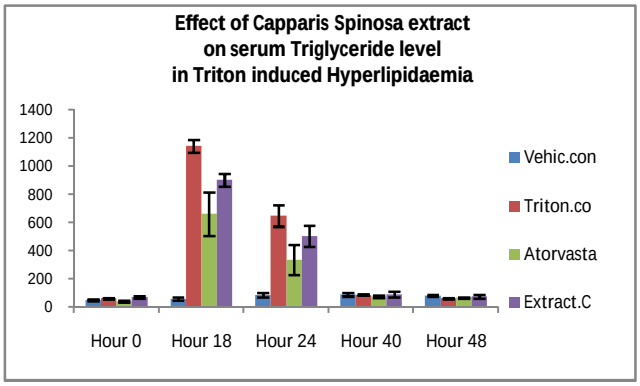

Figure 3: Effect of *Capparis spinosa* extract on serum triglyceride

Blood glucose level (STZ & NA model)

In STZ induced diabetic rats, the blood glucose levels were in the range of 234-296 mg/dl, which were considered as severe diabetes. In the gliclazide (50mg/kg) and *capparis spinosa* extract (200mg/kg & 400mg/kgb.w) groups, the peak values of blood sugar significantly decreased from198±10.89 to 145±3.43 in case of Gliclazide, 241.5±7.9mg/dl to 209.83±1.7mg/dl in case of *capparis spinosa* extract OD and from 229.8±7.46mg/dl to 202±4.33mg/dl in case of *capparis spinosa* BD on the 28th day, respectively (Table-4 & Fig-4). Hence, *capparis spinosa* extract (OD &BD) reduced the blood glucose levels in diabetic rats but values did not return to those of normal controls. Therefore, *capparis spinosa* extract possess statistically significant (P<0.01) antidiabetic activity, when compared with diabetic control. There was a marked reduction in blood glucose level (28days) in STZ – diabetic animals.

Oral glucose tolerance test

The effect of *capparis spinosa* extract (200mg/kg & 400mg/kgb.w) groups, at different time points revealed no significant difference among the groups at 0 min & 30min. However, at 60 min & 120 min, significant difference was observed between the groups (Table-5 & Fig-5). Hence, gliclazide (50mg/kg) and *capparis spinosa* extract (200mg/kg & 400mg/kgb.w) groups, the peak values of blood sugar significantly decreased from 88.5±6.86 to 74.16±4.02 in case of Gliclazide between 60 min to 120 min, from 124±5.09mg/dl to 115.83±4.2mg/dl in case of *capparis spinosa* OD and from 109±2.6mg/dl to 81.6± 4.2mg/dl in case of *capparis spinosa* BD extract on the 28th day, respectively possess statistically significant (P<0.01) antidiabetic activity, when compared with diabetic control. Hence, *capparis spinosa* ethanolic extract (OD &BD) reduced the blood glucose levels in diabetic rats non significantly but values did not return to those of normal controls.

Table 4: Effect of *Capparis spinosa* extract on Blood sugar level (STZ & NA MODEL)

	Nondiabetic control	Diabetic control	Gliclazide	*Capparis Spinosa* (200 mg/ kgb.w.)	*Capparis spinosa* (400mg/kg b.w.)
Week 0	89.66±6.8	257± 4.289	198± 10.89**	241.5 ± 7.89*	229.8± 7.46**
Week 2	96.5± 5.31	277.5± 2.16	163± 2.33**	218.3 ± 2.13*	219.66± 6.7**
Week 4	96.16± 5.45	297.5± 6.56	145± 3.43**	209.83 ± 1.7*	202± 4.33**

*p ≤ 0.05, Vehicle control Vs Diabetic control

**p ≤ 0.05, Diabetic control Vs Treated groups

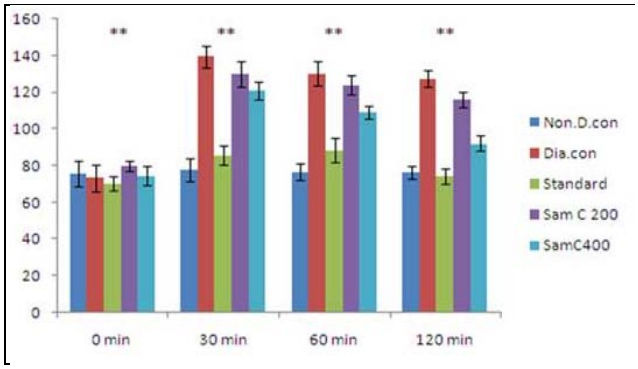

Figure 4: Effect of *Capparis spinosa* extract Blood sugar level (STZ&NA MODEL) in Oral glucose tolerance test

Table 5: Effect of *Capparis spinosa* fruit extract on oral glucose tolerance test in STZ & NA Model

	Non-diabetic control	Diabetic control	Standard	*Capparis spinosa* 200mg/kgb.w.	*Capparis spinosa* 400mg/kgb.w
0min	75.83±7.11	73.5 ±7.34	70.33 ±3.88**	79.83±3.12	73.1± 3.4
30 min	77.66±6.15	139.5 ± 6.09	85.8 ±5.11**	130±7.09	117± 4.2
60 min	76.5±4.46	130.3 ±6.6	88.5 ±6.86**	124±5.09	109±2.6
120 min	76.33±3.72	127.5 ± 4.23	74.16 ±4.02**	115.83±4.2	81.6± 4.2

Values are expressed as mean ± SEM, n=6; *p ≤ 0.05, Vehicle control Vs Diabetic control; **p ≤ 0.05, Diabetic control Vs Treated groups

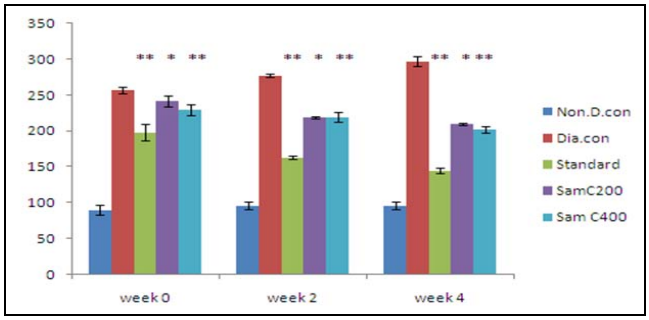

Figure 5: Effect of *Capparis spinosa* fruit extract on oral glucose tolerance test in STZ & NA Model

DISCUSSION

Type II diabetes was induced by administration of NA followed by STZ. STZ produces the chronic diabetic condition in which function of many organs is altered. In type II diabetes, blood glucose level and lipid profile are significantly altered. In our study, after treating with *capparis spinosa* extract, the biochemical abnormalities were significantly improved and extract decreased the blood glucose level. Action of STZ in β-cells is accompanied by characteristic alterations in blood insulin and glucose concentrations. Two hours after injection, hyperglycemia was observed with a concomitant drop in blood insulin[24]. STZ damages pancreatic β –cells, possibly by generating excess reactive oxygen species, and thus widely used for the induction of experimental diabetes mellitus[25]. Recent experiments have proved that the main reason for the STZ-induced β- cell death is alkylation of DNA. The alkylating activity of STZ is related to its nitrosourea moiety, especially at the O_6 position of guanine. Since STZ is a nitric oxide (NO) donor and NO was found to bring about the destruction of pancreatic islet cells, it was proposed that this molecule contributes to STZ-induced DNA damage. It can be stated that potent alkylating properties of STZ are the main reason of its toxicity. However, the synergistic action of both NO and reactive oxygen species may also contribute to DNA fragmentation and other deleterious changes caused by STZ. NO and reactive oxygen species can act separately or form the highly toxic peroxynitrate. Therefore, intracellular antioxidants or NO scavengers substantially attenuate STZ toxicity. STZ-induced DNA damage activates poly ADP ribosylation. This process leads to depletion of cellular NAD+, further reduction of the ATP content and subsequent inhibition of insulin synthesis and secretion[24]. The rats administered with NA 15 min before STZ has been shown to develop moderate and stable non-fasting hyperglycaemia without any significant change in plasma insulin level. As NA is an antioxidant which exerts protective effect on the cytotoxic action of STZ by scavenging free radicals and causes only minor damage to pancreatic beta cell mass producing type II diabetes[26].

Blood glucose level

The fundamental mechanism underlying hyperglycemia in diabetes mellitus involves overproduction (excessive hepatic glycogenolysis and gluconeogenesis) and decreased utilization of glucose by the tissues[26]. Diabetic rats showed high glucose level (200-300 mg/dl) throughout the experiment compared to non diabetic rats. The diabetic rats treated with *capparis spinosa* extract and gliclazide showed significantly decreased glucose level as compared to diabetic control group. The possible mechanism by which *capparis spinosa* extract brings about its antihyperglycemic action is due to the elevated plasma insulin level.[26]

Biochemical parameters

Diabetic rats showed high cholesterol and triglyceride level. Increased levels of serum triglycerides and cholesterol observed in streptozotocin-induced diabetic rats were in accord with other studies. The abnormal high concentrations of serum lipids in diabetic animals are due mainly to an increase in the mobilization of free fatty acids from the peripheral fat depots, since insulin inhibits the hormone-sensitive lipase. Excess fatty acids in the serum of diabetic rats are converted into phospholipids and cholesterol in the liver. These two substances along with excess triglycerides formed at the same time in the liver may be discharged into the blood in the form of lipoproteins. *capparis spinosa* extract and gliclaziide treated rats showed non-significant decrease in plasma cholesterol and triglyceride level as compared to diabetic control group.

OGTT[27]

In the OGTT or glucose loaded hyperglycemic model, the *capparis spinosa* ethanolic extract tested for antihyperglycemic activity exhibited significant antihyperglycemic activity at a dose level of 400mg/kgb.w. Excessive amount of glucose in the blood induces the insulin secretion. This secreted insulin will stimulate peripheral glucose consumption and control the production of glucose through different mechanisms. However, from the study (glucose control), it was clear that the secreted insulin requires 2-3 h to bring back the glucose level to normal.[27] In case of the *capparis spinosa* extract OD, *capparis spinosa* extract BD and gliclazide treated groups, the glucose levels significantly decreased at 60 min and at 120 min and reached at the normal level compared to diabetic group giving the indication regarding the supportive action of extract and gliclazide.

Capparis spinosa fruit extract contains important constituents like rutin, Phenolic compounds, Tocopherols, carotenoids, glycosides, capparic acid, flavonoids and several of these constituents are responsible for having antidiabetic and antihyperlipidaemic activity. Flavonoids are potent antioxidants and are known to modulate the activities of various enzymes due to their interaction with various biomolecules.[29] Flavonoids, alkaloids, tannins and phenolics as bioactive antidiabetic principles are also reported.[30] Flavonoids regenerate the damaged ß-cells in alloxan diabetic rats.[31] Therefore it was concluded that the effectiveness of this extract against metabolic disorders lies in its constituent. Further isolation of the extract will prove its exact mechanism of action.

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