www.ThePharmaJournal.com

The Pharma Innovation

ISSN (E): 2277- 7695
ISSN (P): 2349-8242
NAAS Rating 2017: 5.03
TPI 2017; 6(8): 150-155

www.thepharmajournal.com
Received: 01-06-2017
Accepted: 02-07-2017

Chintu Kotadiya
Department of Veterinary Pharmacology and Toxicology, College of Veterinary Sciences and Animal Husbandry, Junagadh Agricultural University, Junagadh, Gujarat, India

UD Patel
Department of Veterinary Pharmacology and Toxicology, College of Veterinary Sciences and Animal Husbandry, Junagadh Agricultural University, Junagadh, Gujarat, India

CM Modi
Department of Veterinary Pharmacology and Toxicology, College of Veterinary Sciences and Animal Husbandry, Junagadh Agricultural University, Junagadh, Gujarat, India

HB Patel
Department of Veterinary Pharmacology and Toxicology, College of Veterinary Sciences and Animal Husbandry, Junagadh Agricultural University, Junagadh, Gujarat, India

VA Kalaria
Department of Veterinary Pharmacology and Toxicology, College of Veterinary Sciences and Animal Husbandry, Junagadh Agricultural University, Junagadh, Gujarat, India

VB Chauhan
Department of Veterinary Pharmacology and Toxicology, College of Veterinary Sciences and Animal Husbandry, Junagadh Agricultural University, Junagadh, Gujarat, India

Correspondence
UD Patel
Department of Veterinary Pharmacology and Toxicology, College of Veterinary Sciences and Animal Husbandry, Junagadh Agricultural University, Junagadh, Gujarat, India

Effect of *Opuntia elatior* fruit juice and quercetin administration on glucose level, lipid profile, hyperalgesic response and spontaneous motor activity in diabetic rats

Chintu Kotadiya, UD Patel, CM Modi, HB Patel, VA Kalaria and VB Chauhan

Abstract
The study was carried out to evaluate effect of *Opuntia elatior* fruit juice and quercetin administration on alteration of glucose level, lipid profile, hyperalgesic response and spontaneous motor activity in diabetic rats. Administration of *Opuntia elatior* and quercetin for 28 days has significantly lowered blood glucose level in diabetic rats. Upon glucose tolerance test, the glucose levels in rats of different treatment groups were significantly increased at 30 and 60 minutes after oral glucose load. However, glucose levels of diabetic rats treated with *Opuntia elatior* fruit juice and quercetin alone and in combination or Glibenclamide were significantly lowered at the end of 120 min. In lipid profile, levels of total cholesterol and triglyceride were significantly increased while levels of HDL-cholesterol and LDL-cholesterol were non-significantly higher in diabetic control group compared to other groups. The values of altered lipid profile were changed towards normal levels when rats treated with *Opuntia elatior* fruit juice along with quercetin. Treatment with glibenclamide, *Opuntia elatior* fruit juice and quercetin alone and in combination attenuated the hyperalgesic response in diabetic rats. There was significant reduction in locomotor activity of diabetic control rats compare to normal controls which was improved with treatment of *Opuntia elatior* fruit juice and quercetin alone and in combination. *Opuntia elatior* fruit juice and quercetin treatment has glucose lowering effect along with improvement in altered lipid profile and other pathophysiological alterations in diabetic rats.

Keywords: *Opuntia elatior*, quercetin, diabetic rats, glucose and lipid profile, hyperalgesia, spontaneous motor activity

1. Introduction
The term diabetes refers to a group of metabolic disorders characterized by high blood sugar (glucose) levels as a result of defects in insulin secretion, or action, or both. Diabetes mellitus is a syndrome, associated with hyperglycemia, polyurea, polyphagia, polydypsia, hyperlipidemia, oxidative stress, ketosis, nephropathy, neuropathy and cardiovascular disorders [1, 2]. Diabetes mellitus has become a growing problem in the contemporary world. It has been documented that the prevalence of diabetes has risen from 108 million in 1980 to 422 million in 2014 and is expected to increase up to 366 million people worldwide by 2030 [3]. In particular, data suggest that approximately 40.9 million Indian people are affected by diabetes and these numbers are expected to be 69.9 million by 2030, thus, India will become ‘‘Diabetes Capital of the World’’ [4].
Traditional Indian and ayurvedic medical system have been evolved during thousands of years. Many plants are believed to possess hypoglycemic activity [5]. At present many polyherbal formulations containing plant extracts are available in market for the treatment of diabetes. Herbal based formulation for the treatment of diabetes may be beneficial to patients of diabetes. The fruits of *Opuntia elatior* Mill (prickly pear) belongs to family Cactaceae, having antioxidant actions and used for treating diabetes, burns, bronchial asthma and indigestion in many countries over the world [6]. Large quantities of pectin and mucilage fibers are found in prickly pear cactus, increase the viscosity of food in the gut, and slowing or reducing sugar absorption, and lower blood glucose level [7]. Quercetin is a polyphenolic flavonoid compound found in many dietary sources like brassica, green vegetables, berries, onions, parsley, apple, legumes, green tea, citrus fruits and red grape. It also possesses multiple pharmacological effects such as antioxidant and anti-inflammatory activities [8].

Fruit of *Opuntia* spp. and quercetin containing plants have been reported individually to be helpful for the treatment of diabetes mellitus. Looking to possible role of species of Opuntia available at Saurashtra region of Gujarat, India, the present study was planned to evaluate effect of *Opuntia elatior* fruit juice and quercetin administration on alteration of glucose level, lipid profile, hyperalgesic response and spontaneous motor activity in diabetic rats.

2. Materials and methods

2.1 Experimental animals

The present study was conducted on 42 male albino rats. The rats were obtained from Zydus Research Centre, Cadila Healthcare Pvt. Ltd., Ahmedabad, Gujarat. They were maintained as per the protocol outlined in publication of the Committee for the Purpose of Control and Supervision of Experiments on Animals standard guidelines [9]. The experimental protocol including number of rats and various procedures involved was approved by the Institutional Animal Ethics Committee (IAEC), College of Veterinary Science and Animal Husbandry, Junagadh Agricultural University, Junagadh, Gujarat (Protocol approval No. JAU/JVC/IAEC/SA/02/2015).

2.2 Animal husbandry

The rats were housed in standard polypropylene cages with stainless steel top grill. The cages were changed at least thrice in a week. During entire study period the animals were housed in the cool environmental temperature (23^0C to 26^0) with relative humidity ranged between 40 to 55%. Twelve hour dark and light cycle was maintained in animal room. Rat pelleted feed (VRK biological system, Vadodara, Gujarat, India) containing 18% protein was provided *ad libitum* to animals throughout the study period.

2.3 Plant materials and chemicals

Fruits of *Opuntia elatior* plant were collected from local market of Junagadh and authenticated by Botanist. Fruits were cleaned properly and seeds were removed and juice was made daily. The specimen is submitted for preservation in the Herbarium, Department of Veterinary Pharmacology and Toxicology, College of Veterinary Science and A.H., Junagadh Agricultural University, Junagadh, Gujarat (Specimen No. JVC/VPT/SP/02/2015). Quercetin (QCT), streptozotocin (STZ) and glibenclamide (GLB) were purchased from the Sigma Aldrich with lot No. SLBD8415V, SLBJ7785V and BCBN1690V, respectively.

2.4 Induction of diabetes

Streptozotocin was dissolved in citrate buffer previously adjusted to pH 4.5 with 0.1 mol citric acid. This solution was administered by intraperitoneal injection to rats at a dose of 50 mg/kg body weight in all animals except animals of normal control and vehicle control groups. Diabetes was confirmed after 48 h by measuring increased level of glucose using biochemical kit (Biosystems S.A., Barcelona). Rats with blood glucose level above >150-200 mg/dl were grouped for experiments with randomization procedure based on glucose and body weight.

2.5 Experimental design

Forty two albino rats were divided in seven groups (C1, C2, C3, C4, T1, T2 and T3). Rats of group C1, C2, and C3 were kept as normal, vehicle and diabetic control, respectively. Rats of group C4 were administrated with glibenclamide at dose rate of 5 mg/kg, P.O. for 28 days (Treatment control). Rats of group T1 and T2 were treated with *Opuntia Elatior* fruit juice (OEFJ) at dose rate of 4 mL/kg, P.O. and quercetin at dose rate of 50 mg/kg, P.O., respectively for 28 days. Rats of group T3 were administrated with OEFJ at dose rate of 4 mL/kg, P.O. along with quercetin at dose rate of 50 mg/kg, P.O. for 28 days.

2.6 Parameters studied

2.6.1 Physical and behavior examinations

All rats during the treatment period were examined daily for abnormal physical and behavioral changes.

2.6.2 Body weight and feed consumption

The body weight of individual rat was recorded daily during experimental period. The feed offered to each group was accurately recorded daily in the morning. The residual feed given day before, was accounted. Based on these data, amount of feed consumed by rats of each group was counted daily basis.

2.6.3 Glucose and lipid profile estimation

During 28 days of experiment approximately 0.2 ml blood samples from all rats were collected from retro-orbital plexus under light anaesthesia on day 0, 7, 14, 21, 28 for glucose estimation after induction of diabetes. Oral glucose tolerance test (OGTT) was also carried out on day 15 of experimental period. Overnight fasted animals of all groups were administered with glucose (2 g/kg) orally. Control animals were administered with equal volume of distilled water only. Blood samples were obtained after glucose administration at 0, 30, 60, 90 and 120 min for the assay of glucose [10]. At the end of 28 days, blood samples were collected from retro-orbital plexus from all animals for lipid profiling. Blood glucose, total cholesterol, HDL cholesterol, LDL cholesterol and triglyceride were estimated by using standard kit (Biosystems S.A., Barcelona Spain) on semi-automatic biochemistry analyzer (Microlab-300, ELI Tech Group, France).

2.6.4 Hyperalgesic response

The hyperalgesic response was evaluated at day 14 and 28 of experiment by analgesiometer (Eddy's Hot plate method) after drug administration on that day [11]. The animals were individually placed on an Eddy's Hot plate having temperature of 55 ± 1°. The latency to the first sign of paw licking or jump response to avoid the heat was taken as an index of the pain threshold; the cutoff time was 10 seconds in order to avoid damage to the paw.

2.6.5 Spontaneous motor activity

Spontaneous motor activity was evaluated at day 14 and 28 of experiment by using actophotometer [12]. The animals were individually placed in actophotometer and the basal activity score of all animals were recorded after drug administration to assess the effect of drug treatment on spontaneous motor activity. Each animal was observed for a period of 5 min in a square closed field area (30×30×30 cm) equipped with six photocells in the outer wall. Interruptions of photocell beam (locomotor/exploratory action) were recorded by means of digital counter.

2.7 Statistical analysis
All the data obtained were presented as means ± standard error (SE). Data were analyzed statistically by one way ANOVA and different treatment group means were compared by Duncan's multiple range tests to observe difference among the treatments [13].

3. Results and Discussion
The mean values of glucose levels at day 0, 7, 14, 21 and 28 of experiment after daily oral administration of OEFJ and quercetin in animals of different groups are presented in Table 1. The mean glucose levels in Oral glucose tolerance test (OGTT) at day 15th of experiment in animals of different groups are shoen in Table 2. Effect of daily oral administration of OEFJ and quercetin on lipid profilein all animals of different groups is presented in Table 3. The data of average feed consumption (g/day/rat) and body weight (g) of experimental animals of different groups are graphically depicted in fig. 1 and fig. 2, respectively. Effect of daily oral administration of OEFJ and quercetin on hyperalgesic and spontaneous motor activity at day 14th and 28th of experiment in animals of different groups are graphically presented in fig. 3 and fig. 4, respectively.

After induction of diabetes, clinical symptoms like dullness, sluggish movement, weight loss, polyuria, polydipsia, and polyphagia were observed in rats of diabetic control group. One animal of diabetic control group after administration of streptozotocin (STZ) shown sign of polyuria and progressive reduction in body weight. These symptoms were mild to moderate in all other treatment group except normal and vehicle control groups. Reduction in body weight in diabetes might be due to breakdown of tissue proteins in diabetic rats [14].

In the present study, feed consumption in diabetic control rats was significantly increased ($P<0.05$) at 4th week of experiment. OEFJ treatment in diabetic rats had no significant effect on feed consumption. The results of present study are in agreement with previous report that *Opuntia elatior* fruit juice treatment in diabetic mice had no effect on feed intake [15]. Quercetin alone and along with OEFJ treated rats showed significantly ($P<0.05$) higher feed consumption compared to normal control group. In contrast, other findings suggested quercetin had no significant effect on feed consumption in mice [16].

Significantly ($P<0.05$) decrease in body weight of diabetic animals was observed after one week of treatment compared to the other groups. In support of our findings other researchers also have reported, decreased body weight in streptozotocin-induced hyperglycemic rats [17, 18]. The body weight of diabetic rats treated with glibenclamide, OEFJ and quercetin were significantly ($P<0.05$) restored near to its normal level. Rats treated with OEFJ along with quercetin also shown significantly ($P<0.05$) higher body weight. OEFJ administration to diabetic rats improved the body weight which might be due to a better control of the hyperglycemic state in diabetic rats. Similar to *Opuntia elatior* in the present study, administration of *Opuntia dillenii Haw* fruit juice shown to improve body weight in streptozotocin induced diabetic rats [19]. Restoration of body weight in streptozotocin–induced diabetic mice by polysaccharides from *Opuntia dillenii* was also reported earlier [20]. The body weight restoration in diabetic rats treated with quercetin alone as well as *Opuntia elatior* along with quercetin fruit juice might be due to interactive effect of both treatments.

The results in the present study showed that administration of OEFJ and quercetin to diabetic rats significantly ($P<0.05$) prevented a steep onset of hyperglycemia after STZ administration compared to diabetic control rats. However, glibenclamide produced better effect than OEFJ and quercetin in decreasing the blood glucose level. In line of our findings, potent hypoglycemic activity of purified extract (1 mg/kg body weight per day) of prickly pear cactus (*Opuntia fuliginosa*) in rats was observed [21]. Single or repeated dose of cactus fruit juice treatment in alloxan-induced diabetic rats had significantly ($P<0.05$) decreased the blood glucose levels [22]. Similarly, fruit juice of *Opuntia ficus indica* at the dose rate of 3 ml/day showed good hypoglycemic effect in rats [23].

The data in the present study indicted significant hypoglycemic effect of quercetin in diabetic rats which were in line of previous report on the effect of quercetin on alloxan-induced diabetes mellitus [24] and streptozotocin induced diabetes mellitus in rats [25,26]. Quercetin has ability to facilitate insulin secretion in diabetic rats [27]. It probably acting either by the insulin mimetic activity or increasing the insulin secretion.

The hypoglycemic effect of OEFJ might be due to soluble fibers present in it along with quercetin. Soluble fibers from fruit have been reported to reduce blood glucose level by absorbing sugar molecules from the intestine and prevent to enter in to systemic circulation [28]. Simultaneously, antioxidant effect of quercetin on β-cell of langarhance in pancreas protects against the harmful effect of streptozotocin. This concurrent effect of fruit juice and quercetin might be responsible for the maintaining blood glucose level to normal during the treatment.

In OGTT the glucose levels in rats of different treatment groups were significantly ($P<0.05$) increased in all groups at 30 and 60 minutes after oral glucose administration at dose of 2 g/kg. The values of glucose levels decreased at 90 minutes and found significantly ($P<0.05$) lowered at 120 minutes after glucose load which were comparable to the value at pre-glucose administration in all groups except diabetic control group. Glucose levels of diabetic rats treated with OEFJ and quercetin alone and in combination or Glibenclamide were significantly decreased at the end of 120 min when compared with the diabetic control. Similar to our findings, other scientists reported the hypoglycemic effect of *Opuntia streptacantha* as it containing dietary fiber which decrease the intestinal glucose absorption [29]. This might be the result of lower glucose level when the plant preparation is administered before or during food intake or oral/gastric glucose load. Quercetin has significantly reduced the fasting glucose with producing significant changes in the insulin levels of diabetic rats. The results of the oral glucose tolerance test (OGTT) indicated that quercetin reduced streptozotocin (STZ) induced increases in both area under curve glucose (AUC glucose) and area under curve insulin (AUC insulin) in high fat feed type 2 diabetic rats [30].

In lipid profile, mean levels of total cholesterol and triglyceride were significantly increased while levels of HDL-cholesterol and LDL-cholesterol were non-significantly higher in diabetic control group compared to other groups. The mean levels of total cholesterol, HDL-cholesterol and LDL-cholesterol in rats treated with OEFJ along with quercetin were found comparable to normal control rats. Similar effect of Prickly pear (*Opuntia robusta*) intake (25 g/day) on altered lipid metabolism in rats was observed. It decreased total cholesterol (12%), LDL- cholesterol (15%)

and triglycerides (12%), while HDL-cholesterol remained unchanged [28]. Similarly, previous study [31] has shown, a decrease in total and LDL-cholesterol in rats fed prickly pear seed oil, exceptionally rich in linoleic acid, while HDL remained unchanged. A beneficial effect of *Opuntia* spp. on total- and LDL-cholesterol might be due to an increase in hepatic LDL-binding and a decreased absorption. Beneficial effect of Opuntia powder was observed, as it has decreased total cholesterol, LDL, triglycerides and malondialdehyde in wistar rat [32]. In guinea pigs, the addition of prickly pear pectin decreases LDL-cholesterol by increasing the expression of hepatic apo-B and apo-E receptors [33]. Quercetin has reduced the de novo fatty acid and triglycerides synthesis and acetyl-CoA carboxylase (ACC) activity in rat hepatocytes [34]. Some investigations have suggested that LDL-cholesterol is lowered by quercetin in hyperlipidemic patients; otherwise, quercetin inhibits LDL oxidation [35]. Japanese study reported an inverse correlation between quercetin intake and total plasma cholesterol concentration [36]. However, several studies have illustrated quercetin's ability to inhibit LDL oxidation. Similarly, other researchers also reported that 21 % reduction in cardiovascular disease mortality when the intake of quercetin was greater than 4 mg/dl [37].

In diabetic rats, hyperalgesic response (second) was significantly faster than other groups at 14th and 28th day of experimental period. This is in agreement with recent findings that significant reduction in paw withdrawal threshold in diabetic rats [38]. Treatment with OEFJ and quercetin alone and in combination attenuated the hyperalgesic response due to diabetes in rats. Quercetin has also been recorded to attenuate the thermal hyperalgesia in STZ-induced diabetic rats [39].

Data in present study indicated significant reduction in locomotor activity of diabetic rats which was improved with treatment of OEFJ and quercetin alone and in combination. Neuroprotective role of quercetin in locomotor activities was also evaluated [40] and they reported that the quercetin promotes locomotor recovery in rats experimentally demyelinated with ethidium bromide. This suggesting that there was demyelination prevention or further remyelination velocity as well as it was able to prevent the inhibition of AChE activity and the increase of lipidic peroxidation, suggesting that quercetin can protect cholinergic neurotransmission.

In conclusion, routine administration of *Opuntia elatior* fruit juice and quercetin can improve glucose and lipid profile, hyperalgesic response and spontaneous motor activity in diabetic rats. Though the findings of this short term study are encouraging, still further detail investigation is required to explore the therapeutic effects of long term administration of *Opuntia elatior* fruit juice and quercetin in diabetic rats.

Table 1: Effect of 28 days daily oral administration of *Opuntia elatior* fruit juice and quercetin on blood glucose level in diabetic rats

Groups	Blood glucose level (mg/dl)				
	Day 0 (Mean ± SE)	Day 7 (Mean ± SE)	Day 14 (Mean ± SE)	Day 21 (Mean ± SE)	Day 28 (Mean ± SE)
C1	111.22 ± 3.69^{a}	105.83 ± 4.57	93.58 ± 4.35^{a}	104.53 ± 2.75^{ab}	96.62 ± 5.18^{a}
C2	108.97 ± 4.39^{a}	111.08 ± 9.0	81.43 ± 2.95^{a}	88.90 ± 2.36^{a}	91.95 ± 9.34^{a}
C3	275.78 ± 59.81^{b}	245.60 ± 52.53	249.37 ± 67.15^{b}	224.92 ± 63.88^{c}	229.25 ± 54.58^{b}
C4	268.63 ± 58.58^{b}	184.82 ± 33.83	144.87 ±28.68^{ab}	116.10 ± 6.65^{abc}	147.58 ±31.81^{ab}
T1	269.37 ± 41.79^{b}	214.78 ± 59.57	203.93 ±39.55^{ab}	191.33 ± 37.10^{abc}	188.55 ±38.34^{ab}
T2	258.35 ± 44.84^{b}	225.48 ± 60.59	224.73 ±54.29^{ab}	205.93 ± 42.94^{bc}	180.70 ±38.09^{ab}
T3	262.88 ± 46.99^{b}	232.07 ± 54.53	201.22 ±36.50^{ab}	195.13 ± 35.35^{abc}	159.95±17.88 ^{ab}

Table 2: Effect of daily oral administration of *Opuntia elatior* fruit juice and quercetin on oral glucose tolerance test (OGTT) at day 15th of experiment in diabetic rats

Groups	Blood glucose level (mg/dl) on 15th day at different time intervals				
	0 Minute (Mean ± SE)	30 Minute (Mean ± SE)	60 Minute (Mean ± SE)	90 Minute (Mean ± SE)	120 Minute (Mean ± SE)
C1	93.55 ± 4.38^{ab}	140.95±13.96^{ab}	113.33 ±2.79^{ab}	104.48±3.14^{ab}	96.63 ±4.88^{ab}
C2	81.50 ±2.90^{a}	97.05 ±6.30^{a}	90.43 ± 2.38^{a}	85.10 ± 3.29^{a}	81.82 ±3.53^{a}
C3	249.50 ± 67.23^{c}	394.23 ± 76.69^{bc}	284.22 ± 70.97^{c}	272.13 ± 67.75^{c}	267.23 ± 62.50^{d}
C4	144.72 ± 28.74^{abc}	235.30 ± 52.31^{abc}	245.48 ± 72.55^{abc}	200.98 ± 46.01^{abc}	166.48 ± 35.19^{abcd}
T1	203.82 ± 39.66^{bc}	237.85 ±42.91^{abc}	224.65 ± 37.08^{abc}	218.83 ± 38.26^{bc}	214.90 ± 7.94^{bcd}
T2	224.82 ± 54.27^{c}	329.00 ± 78.83^{c}	268.23 ± 68.25^{bc}	244.82 ± 59.14^{c}	245.05 ± 62.04^{cd}
T3	131.17 ± 18.06^{abc}	251.68 ± 37.26^{abc}	214.13 ± 35.09^{abc}	168.37 ± 24.66^{abc}	131.50± 17.08^{abc}

Table 3: Effect of 28 days daily oral administration of *Opuntia elatior* fruit juice and quercetin on lipid profile in diabetic rats

Parameters	Treatment groups						
	C1	C2	C3	C4	T1	T2	T3
Total cholesterol (mg/dL)	59.17 ± 0.79^{a}	57.17 ± 2.12^{a}	65.67 ± 2.09^{b}	57.33 ± 1.73^{a}	58.33 ± 1.54a	57.33 ± 2.06^{a}	59.33 ± 1.69^{a}
Triglycerides (mg/dL)	99.67 ± 6.25^{a}	111.50 ± 7.27^{ab}	142.6± 13.08^{bc}	141.83 ± 13.15^{bc}	131.83 ± 11.78^{bc}	162.0 ± 9.61^{c}	149.83 ± 8.84^{c}
HDL–cholesterol (mg/dL)	15.50 ± 1.31	16.00 ± 2.13	12.67 ± 1.91	14.17 ± 1.87	19.83 ± 1.17	18.50 ± 1.34	17.50 ± 1.45
LDL – cholesterol (mg/dL)	36.33 ± 4.21	36.33 ± 2.59	41.83 ± 3.12	37.00 ± 2.50	40.00 ± 3.15	40.50 ± 1.80	38.17 ± 2.20

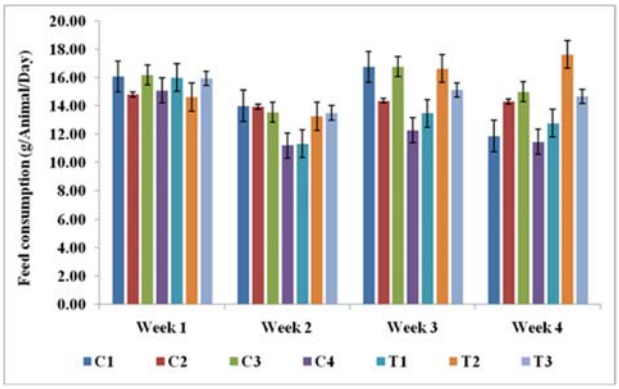

Fig 1: The average feed consumption (g/day/rat) of experimental animals of different groups

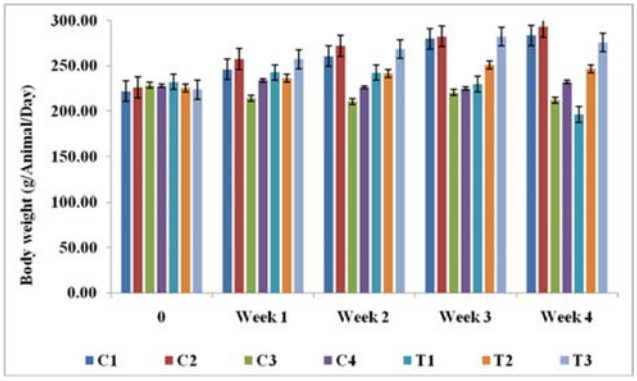

Fig 2: Body weight (g) in experimental animals of different groups.

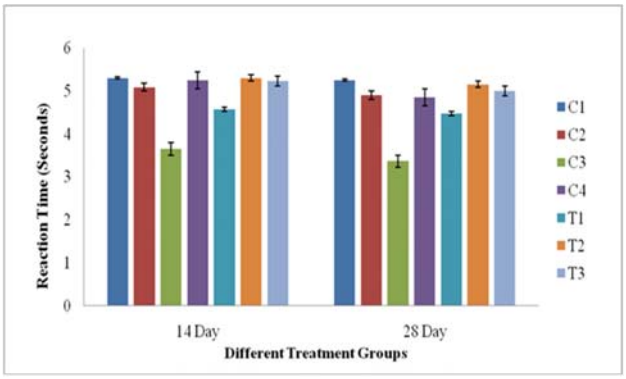

Fig 3: Effect of daily oral administration of *Opuntia elatior* fruit juice and quercetin on hyperalgesic activity at day 14th and 28th of study in experimental animals of different groups

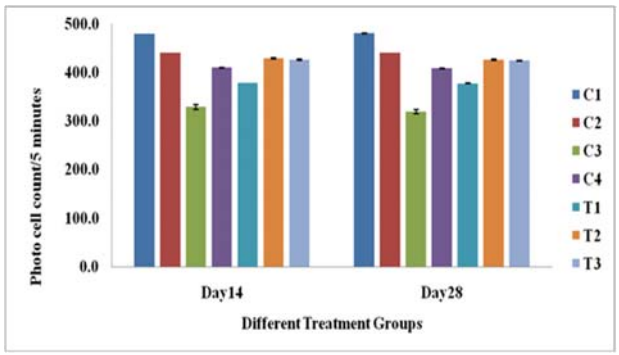

Fig 4: Effect of daily oral administration of *Opuntia elatior* fruit juice and quercetin on Spontaneous motor activity at day 14th and 28th of study in experimental animals of different groups

References

1. Georg P, Ludvik B. Lipids and Diabetes. Journal of Clinical and Basic Cardiology 2000; 3:159-62.
2. Gandjbakhch I, Leprince P, D'Alessandro C, Ouattara A, Bonnet N, Varvous S *et al*. Coronary artery bypass graft surgery in patients with diabetes. Bulletin de L'Académie Nationale de Médecine. 2005; 189:257-266.
3. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care. 2004; 27:1047-1053.
4. Mohan V, Sudha V, Radhika G, Radha V, Rema M, Deepa R. Gene-environment interactions and the diabetes epidemic in India. Forum of Nutrition. 2007; 60:118-126.
5. Lamba SS, Buch KY, Lewis H, Lamba HJ. Photochemical as potential hypoglycemic agents. Journal of Natural Products chemistry. 2000; 21:457-495.
6. Kim JH, Park SM, Ha HJ, Moon CJ, Shin TK, Kim JM. *et al*. *Opuntia ficus-indica* attenuates neuronal injury in *in vitro* and *in vivo* models of cerebral ischemia. Journal of Ethnopharmacology. 2006; 104(1-2):257-262.
7. Lopez JL. Use of *Opuntia cactus* as a hypoglycemic agent in managing type 2 diabetes mellitus among Mexican American patients. Nutrition Bytes. 2007; 12(1):1-6.
8. Terao J. Dietary flavonoids as antioxidants. Forum of Nutrition. 2009; 61:87-94.
9. Committee for the Purpose of Control and Supervision on Experiments on Animals. CPCSEA guidelines for laboratory animal facility. Indian Journal of Pharmacology. 2003; 35:257-274.
10. Hepcy KD, Dinakar A, Senthil KN. Antidiabetic activity of ethanolic extracts of *Alangium salvifolium* and *Pavonia zeylanica* in streptozotocin induced diabetic rats. International Journal of Pharmacy and Pharmaceutical Science. 2012; 4:337-339.
11. Kanaan SA, Saadé NE, Haddad JJ, Abdelnoor AM, Atweh SF, Jabbur SJ. *et al*. Endotoxin-induced local inflammation and hyperalgesia in rats and mice: a new model for inflammatory pain. Pain. 1996; 66(2-3):373-379.
12. Goddard M, Zheng Y, Darlington CL, Smith PF. Locomotor and exploratory behavior in the rat following bilateral vestibular differentiation. Behaviour Neuroscience. 2008; 122:448-459.
13. Snedecor GW, Cochran WG. Statistical methods. 7th ed. Iowa (USA): Iowa State University Press, Ames, 1980.
14. Andulla B, Varadacharyulu NCH. Antioxidant role of mulberry leaves in streptozotocin-diabetic rats. Clinical Chimica Acta. 2003; 338:3-10.
15. Hahm HW, Park J, Son YS. *Opuntia homifusa* stems lower blood glucose and cholesterol levels in streptozotocin induced diabetes rats. Nutrition Research. 2011; 31:479-487.
16. Le NH, Kim CS, Park T, Park JHY, Sung K, Lee DG *et al*. Quercetin protects against obesity-induced skeletal muscle inflammation and atrophy. Mediators of Inflammation. 2014, 1-10.
17. Mallick C, Maiti R, Ghosh D. Comparative study on antihyperglycemic and antihyperlipidemic effects of separate and composite extract of seed of *Eugenia jambolana* and root of *Musa paradisiaca* in streptozotocin-induced diabetic male albino rat. Iranian Journal of Pharmacology Therapeutics. 2006; 5:27-33.
18. Oyedemi SO, Adewusi EA, Aiyegoro, Akinpelu DA.

Antidiabetic and haematological effect of aqueous extract of stem bark of *Afzelia Africana* (Smith) on streptozotocin-induced diabetic wistar rats. Asian Pacific Journal of Tropical Biomedicine. 2011; 1(5):353-358.
19. Abdallah Inas ZA. Evaluation of hypoglycemic activity of *Opuntia dillenii* Haw fruit juice in streptozotocin-induced diabetic rats. The Egyptian Journal of Hospital Medicine. 2008; 33:544-558.
20. Zhao LY, Huang W, Yuan QX, Cheng J, Huang ZC, Ouyang LJ *et al*. Hypolipidaemic effects and mechanisms of the main component of *Opuntia dillenii* Haw polysaccharides in high-fat emulsion induced hyperlipidemic rats. Food Chemistry 2012; 134:964-971.
21. Trejo-Gonzalez A, Gabriel-Ortiz G, Puebla-Perez AM, Huizar-Contreras MD. A purified extract from prickly pear cactus (*Opuntia fuliginosa*) controls experimentally induced diabetes in rats. Journal of Ethnopharmacology 1996; 55(1):27-33.
22. Hassan F, El-Razek A, Hassan AA. Nutritional value and hypoglycemic effect of prickly cactus pear (*Opuntia Ficus Indica)* fruit juice in alloxan-induced diabetic rats. Australian Journal of Basic and Applied Science. 2011; 5(10):356-377.
23. Abd El-Razek FH, El-Metwally EM, Shehab GM, Hassan AA, Gomaa AM. Effects of cactus pear (*Opuntia ficus indica*) juice on oxidative stress in diabetic cataract rats. Saudi Journal of Health Science. 2012; 1:23-29.
24. Nuraliev I, Avezov GA. The efficacy of quercetin in alloxan diabetes. Eksperimental'naia I Klinicheskaia Farmakologiia. 1992; 55:42-44.
25. Mahesh T, Menon VP. Quercetin alleviates oxidative stress in streptozotocin-induced diabetic rats. Phytotherapy Research. 2004; 18:123-127.
26. 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.
27. Vessal M, Hemmati M, Vasei M. Antidiabetic effects of quercetin in streptozocin-induced diabetic rats. Comparative Biochemistry and Physiology Part C: Pharmacology, Toxicology and Endocrinology 2003, 2004; 135C(3):357-364.
28. Wolfram R, Kritz H, Efthimiou Y, Stomatopoulos J, Sinzinger H. Effect of prickly pear (*Opuntia robusta*) on glucose- and lipid-metabolism in non-diabetics with hyperlipidemia--a pilot study. The Wiener klinische Wochenschrift. 2002; 114(19-20):840-846.
29. Frati-Munari AC, Gordillo BE, Altamirano P, Ariza CR. Hypoglycemic effect of *Opuntia streptacantha* Lemaire in NIDDM. Diabetes Care 1988; 11(1):63-66.
30. Shao Y, Yu Y, Li C, Yu J, Zongc R, Pei C. Synergistic effect of quercetin and 6-gingerol treatment in streptozotocin induced type 2 diabetic rats and poloxamer P-407 induced hyperlipidemia. Monatshefte für Chemie - Chemical Monthly. 2016; 6(16):12235-12242.
31. Ennouri M, Evelyne B, Laurence M, Hamadi A. Fatty acid composition and rheological behaviour of prickly pear seed oils. Food Chemistry. 2005; 93:431-437.
32. Li CY, Cheng XS, Cui MZ, Yan YG. Regulative effects of Opuntia powder on blood lipids in rats and its mechanism. Journal of Chinese Materia Medica. 2005; 30: 694-696.
33. Fernandez ML, Lin EC, Trejo A, McNamara DJ. Prickly pear (*Opunti*a spp.) pectin reverses low density lipoprotein receptor suppression induced by a hypercholesterolemic diet in guinea pigs. Journal of Nutrition 1992;122: 2330-2340.
34. Gnoni GV, Paglialonga G, Siculella L. Quercetin inhibits fatty acid and triacylglycerol synthesis in rat-liver cells. European Journal of Clinical Investigation 2009;39**:**761–768.
35. Chopra M. Non alcoholic red wine extract and quercetin inhibit LDL oxidation without affecting plasma antioxidant vitamin and carotenoid concentrations. Clinical Chemistry 2000; 46:1162-1170.
36. Arai Y, Watanabe S, Kimira M. Dietary intakes of flavonols, flavones and isoflavones by Japanese women and the inverse correlation between quercetin intake and plasma LDL cholesterol concentration. Journal of Nutrition. 2000; 130:2243-2250.
37. Graf B. Flavonols, flavones, flavanones, and human health: epidemiological evidence**.** Journal of Medicinal Food. 2005; 8:281-290.
38. Solanki ND, Bhavsar SK. An evaluation of the protective role of *Ficus racemosa* Linn. In streptozotocin-induced diabetic neuropathy with neurodegeneration. Indian Journal of Pharmacology. 2016; 47(6):610-615.
39. Anjaneyulu M, Chopra K. Quercetin, an anti-oxidant bioflavonoid, attenuates diabetic nephropathy in rats. Clinical and Experimental Pharmacology and Physiology. 2004; 31(4):244-8.
40. Beckmann DV, Carvalho FB, Mazzanti CM, Dos Santos RP, Andrades AO, Aiello G *et al*. Neuroprotective role of quercetin in locomotor activities and cholinergic neurotransmission in rats experimentally demyelinated with ethidium bromide. Life Science 2014; 103(2):79-87.