ANTIDIABETIC ACTIVITY OF AERIAL PARTS OF *ARGEMONE MEXICANA LINN.* IN ALLOXAN INDUCED HYPERGLYCAEMIC RATS

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Summary

Argemone mexicana L. (Papaveraceae), commonly known as prickly poppy, is an indigenous herb used as a medicinal plant in several countries. The present study was designed to investigate the possible actions of ethanolic and aqueous extract of aerial parts of *Argemone mexicana* Linn , on glucose homeostasis in acute normoglycemic and alloxan induced hyperglycemic rats, including oral glucose tolerance and up to 11-days of study in hyperglycaemic rats. The body weight measurement and certain serum biochemical estimation were undertaken in 11-days treated hyperglycemic rats. Both extracts were used at dose levels of 200 and 400 mg/kg each by oral route, keeping glibenclamide (5 mg/kg) as standard drug. The biochemical parameters used in the study are blood glucose concentration, urea, creatinine, triglyceride, cholesterol. The test result revealed that in normoglycemic rats

the decrease in blood glucose level lies between 3 to 12% in extract treated groups, while the hyperglycaemic rats showed a progressive fall of blood sugar level in a significant extent ($p<0.05$ to 0.001). The extract at the tested dose levels, significantly ($p<0.05$) decreases the elevated glucose in blood upon glucose ingestion in glucose tolerance test. The test extracts, significantly improve the level of serum urea, creatinine, triglyceride and cholesterol when compared to diabetic control. The effect on body weight on 11-days treated animal groups showed recovery of body weight while comparing with diabetic control group. It is concluded that, the extracts of the aerial parts of *Argemon mexicana*, endowed with potent antidiabetic activity, which might be contributed by pancreatic and or extra pancreatic action of the test extracts.

Keywords: *Argemone mexicana,* Diabetes mellitus, alloxan, antidiabetic.

Diabetes mellitus (DM) is a syndrome which affects more and more people in all countries over the world. It is well known that diabetes mellitus is the commonest endocrine disorder that, according to the World Health Organization (WHO, 2004), affects more than 176 million people world wide(1). From an ethnopharmacological perspective, it is important to understand that this disease is one at the interface of conventional biomedical and local (or traditional) treatment.

Diabetes mellitus (DM) which not only lead to hyperglycemia but also cause many complications, such as hyperlipidemia, hypertension and atherosclerosis (2-4). Many plant species are known in folk medicine of different cultures to be used for their hypoglycaemic properties and therefore used for treatment of DM (5,6). Despite this, few traditionally used antidiabetic plants have received proper scientific screening.

Argemone mexicana L. (Papaveraceae), commonly known as prickly poppy, is an indigenous herb used as a medicinal plant in several countries. In Mexico, the seeds are

considered as an antidote to snake venom. In India, the smokes of the seeds are used to relieve toothache. The fresh yellow, milky seed extract contains protein-dissolving substances, effective in the treatment of warts, cold sores, cutaneous infections, skin diseases, itches, and also dropsy and jaundice (7). The plant contains alkaloids as berberine, protopine, sarguinarine, optisine, chelerytherine etc. Medicinal plants being the effective source of both traditional and modern medicines, are genuinely useful for primary health care. Over the years, World Health Organization (WHO) advocated traditional medicines as safe remedies for ailments of both microbial and non-microbial origins (8). In USA, some plant based compounds as well as herbal remedies are used along with other medications. In some cases, patients used these treatments instead of conventional medications, and severe complications including increased hospitalizations, ketoacidosis, and acute hyperglycaemia occurred (9).

The present study has been designed to determine the role of extracts of aerial parts of *A. mexicana* for potential antidiabetic activity, if any, against normoglycemic and alloxan induced hyper glycemic rats.

Materials and Methods

The plant material used in this study was aerial parts of *A. mexicana,* collected from road side area from khargone dist khargone M.P., India, during spring (mid-March to mid-April 2010) and was authenticated by the Taxonomist Dr. Pushpa Patel Taxonomist, department Botany, Government P G College Khargone M.P. The plant materials were initially rinsed with distilled water and dried on paper towel in laboratory at (37 ± 1) ^{o}C for 24 h. The plant materials were initially defatted with petroleum ether and then extracted with alcohol and water using soxhlet apparatus. The yield of the plant extracts ethanol and aqueous measured about 25g each after evaporating the solvent using water bath. The standard extracts obtained were then stored in a refrigerator at 4 ^{o}C for further use (10).

Preparation of the test samples

The test extract was suspended in 25% Tween 20 in distilled water prior to oral administration to the experimental

animals. Glibenclamide (5 mg/kg) was used as the reference control. Animals in the control group received only the 25% Tween 20 (2ml/kg). All the test samples were administered through oral route.

Animals

Male albino wistar rats, weighing 150–200 g and Swiss albino mice, weighing 20–25 g were used. Prior to the experiments, the selected animals were housed in acrylic cages in standard environmental conditions (20–25 ^{0}C), fed with standard rodent diet for 1 week in order to adapt to the laboratory conditions and water *ad libitum.* They were fasted overnight (12 h) before experiments, but were allowed free access to water. Six animals were used for each group of study. All the experiments on animals were conducted in accordance with the internationally accepted principles for laboratory animal use and as per the experimental protocols duly approved by the Institutional Ethical Committee (IAEC No. 1171/C/08/CPCSEA).

Determination of blood glucose levels

Fasting blood glucose concentration was determined using a Glucometer (Optium), based on the glucose oxidase method. Blood samples were collected from the tip of tail at the defined time patterns (11, 12).

Screening for antidiabetic activity

The Screening for antidiabetic activity was followed as per standard procedures (13). The test samples were suspended in 25% Tween 20 in distilled water. Glibenclamide (5 mg/kg) was used as reference control during the study. All the test samples were administered through oral route.

Single dose study

In normoglycaemic animals

The animals were fasted for 18 h, but were allowed free access to water before and throughout the duration of experiment. At the end of the fasting period, taken as zero time (0 h), blood was withdrawn (0.1 ml) from the tip of the tail of each rat under mild ether anaesthesia. Plasma was separated following centrifugation the glucose was estimated by

GOD/POD method using Glucose estimation kit from M/s. Sigma Diagnostics (India) Pvt. Ltd., Baroda, India. The normal rats were then divided into six groups of six animals each. Group I served as solvent control and received only vehicle (2 ml/kg) through oral route, Group II received glibenclamide (5 mg/kg) and served as reference control. Groups III to VI received the alcohol and aqueous extract at a dose of 200 and 400 mg/kg, respectively, through oral route. Blood glucose levels were examined after 1, 2, 4, 6, 8 and 10 h of administration of single dose of test and control samples (table 1)

In alloxan induced diabetic animals

The acclimatized animals were kept fasting for 24 h with water *ad libitum* and injected intraperitoneally a dose of 150 mg/kg of alloxan monohydrate in normal saline. After 1 h, the animals were provided feed *ad libitum*. The blood glucose level was checked before alloxanisation and 24 h after alloxanisation as above. Animals were considered diabetic when the blood glucose level was raised beyond 200 mg/100 ml of blood. This condition was observed at the end of 72 h after alloxanisation. The animals were segregated into six groups of six rats in each. Group I served as normal reference, Group II served as solvent control and received vehicle (2 ml/kg) through oral route. Group III received glibenclamide (5 mg/kg). Groups IV to VII received the test extract at doses of 200 and 400 mg/kg in a similar manner as per the above experiment. Blood glucose level of each rat was estimated at 1, 2, 4, 6, 8 and 10 h, respectively (table 2).

In glucose loaded hyperglycaemic animals

An oral glucose tolerance test (OGTT) was performed on diabetic rats by feeding glucose (5 g/kg) per os. Animals were deprived of food 18 h before and during the experiment but were allowed free access to water. They were divided into 7 groups of 6 rats each. Five groups received the plant extract at the doses of as per above experiment by os. One group received 5mg/kg of glibenclamide and the control group received the vehicle. The plant extract, glibenclamide and vehicle were orally administered 1 h before glucose administration. Blood glucose level was determined before drug and glucose administration (−1 and 0 h, respectively) and subsequently at 0.5, 1, 2 and 3h after (table 3).

Study of blood glucose level on alloxan induced 11-days treated diabetic animals

The animals were kept fasting for 24 h with water *ad libitum* and injected alloxan monohydrate intraperitoneally at a dose of 150 mg/kg in normal saline. After 1 h, the animals were provided rodent-feed *ad libitum*. The blood glucose level was measured 72 h after administration of alloxan. The animals showing blood glucose level beyond 200 mg/dl were considered for the study. The diabetic animals were segregated into six groups of six rats each. Group II served as solvent control and received only vehicle (2 ml/kg) through oral route. Group III received glibenclamide (5 mg/kg); Groups IV and V received ethanol extract at doses of 200 and 400 mg/kg, similarly Group VI and VII received aqueous extract at same dose level respectively in a similar manner, for 11days. The Group I served as normal reference. The blood glucose level was measured on 0, 3, 7 and 11^{th} day of treatment (table 4).

Determination of body weight and serum biochemical of 11-days treated alloxan induced diabetic rats

The body weight of the 11-days treated animals comprised of similar group distribution as above was determined by simple weighing, using standard balance on 0, 3, 7 and 11 day of the study. The animals were sacrificed at the end of the study and blood samples were collected by standard method for estimation of serum urea, creatinine, triglycerides and cholesterol (table 5 & 6).

Results & Discussion

Alloxan-induced type 2 diabetes is a chemical model of experimental diabetes mellitus developing a severe hyperglycaemia and widely used in the diabetic studies. This model was used in our investigation to evaluate the effects of aerial parts of Argemone mexicana ethanolic and aqueous extracts on hyperglycaemia and some metabolic disorders related

to diabetic mellitus. The effects of ethanol and aqueous extracts of aerial parts of *Argemone mexicana* on fasting blood glucose levels of normal and diabetic rats are presented in table 1 and 2 respectively. The plant extracts induced 3-12% fall of fasting blood glucose which is not significant enough to interpret hypoglycemic effect on normal rats (table 1). Treatment of normal rats with glibenclamide produced a significant ($p<0.01$) hypoglycaemic effect from first to six hour, reaching a 40.15% maximum fall ($p<0.01$) in the blood glucose, as compared with the normal control group or with time 0. In alloxan induced diabetic rats, as shown in table 2, a dose dependent effect of the plant extract was observed. The test extracts showed a persistent decrease in blood glucose level till the end of 10 hr., with maximal decrease noted in aqueous extract at 400 mg/kg dose, reaching 70.25% ($p<0.01$), while the standard drug glibenclamide showed 66.65% decrease. The test result presented in table 3, indicates that, the test extracts induce reduction in hyperglycaemia during the glucose tolerance test in diabetic rats. As expected, glibenclamide produced a significant ($p<0.01$) inhibition of 30.10% glucose intake-induced hyperglycaemia when compared with solvent control group.

The alloxan-induced hyper glycaemia was significantly ($p<0.01$) corrected by the plant extract at the end of the treatment (11 days) in a sustained dose dependent manner, the result of which is presented in table 4. The maximal reduction 73.10% was observed with aqueous extract at high dose of 400 mg/kg. The potency of the extract in the light of fall of blood sugar level is dose dependent and in the order of aqueous extract followed by ethanol extract.

Argemone mexicana recover the body weight of treated diabetic group in a significant extent ($p<0.01$) when compared with diabetic control group and approach towards the untreated control normal animal group (table 5).

The biochemical parameters of plasma urea, creatinine, triglyceride, cholesterol values of treated diabetic groups at the end of the treatment (11 days) decreases in a significant extent ($p<0.001$) when compared with diabetic control group (table 6). The extent of decrease is in a dose dependent order and the potency rest first with aqueous extract followed by ethanolic extract.

It is generally accepted that alloxan treatment causes permanent destruction of β-cells and impairment of renal function; and sulfonylureas are known to lower the blood glucose level by stimulating β-cells to release insulin (14). The hypoglycemic effect comparable to glibenclamide suggested that the extract may act by regenerating the β-cells in alloxan-induced diabetes (15). And the decreased activity in glucose level in OGTT might be, due to a decrease in the rate of initial glucose absorption when plant fiber is given orally with glucose (16). Diabetes mellitus causes failure to use of glucose for energy which leads to increased utilization and decrease storage of protein responsible for reduction of body weight essentially by depletion of body proteins (17). It has been reported that the increase in glycaemia in alloxan or streptozotocin-induced diabetic rats was associated with dislipidoemia characterized by elevated serum triglycerides total cholesterol levels (18). The improvement of blood glucose level induced by most hypoglycaemic treatment is associated with a reduction of serum triglycerides and total cholesterol.

Conclusion

The study shows that the aerial parts of Argemone mexicana had an anti-diabetic effect. Further pharmacological, biological and biochemical investigations are required to elucidate the mechanism of action and the active principles of Argemone mexicana in the said activity.

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Table 1: Effect of ethanolic and aqueous extracts of *Argemone mexicana* on blood glucose level in normoglycemic rats.

Groups & Treatment and dose	Blood Glucose Levels(mg/dl)							% decrease at 10 hrs
	0 hr	1 hr	2 hrs	4 hrs	6 hrs	8 hrs	10 hrs	
I. Diabetic Control (Tween + Water)	94.6 ± 1.1	87.2 ± 4.62	91.43 ±1.86	89.56 ± 0.81	91.58 ±2.23	89.66 ± 0.46	92.67 ±3.22	--
II. Glibenclamide (5mg/kg)	91.43 ± 1.31	81.22 ± 2.63	67.53 ±2.34*	58.12 ± 2.61**	54.72±2.44***	73.83 ± 1.42***	71.63±2.81***	21.65
III. Et. Ext. (200mg/kg)	89.13 ± 1.2	87.8 ± 1.1	86.93 ±2.65	86.73 ± 1.46	86.57 ±1.43	86.29 ± 0.89*	85.83 ±1.51	3.70
IV. Et. Ext. (400mg/kg)	88.4 ± 2.43	87.31 ± 2.16	86.13 ±1.87	85.78 ± 1.67	84.97 ±2.69	84.11 ± 1.43**	82.21 ±2.49*	7.0
V. Aq. Ext. (200mg/kg)	92.53 ± 1.27	91.46 ± 1.68	89.88 ±1.09	87.19 ± 0.91	86.07 ±2.13	85.78 ± 1.18**	83.66 ±1.89**	9.58
VI. Aq. Ext. (400mg/kg)	91.18 ± 0.93	87.19 ± 0.78	85.71 ±2.61	85.23 ± 1.37	84.83 ±2.38*	83.11 ± 1.21***	79.87 ±2.73***	12.40

Values are expressed in MEAN ± S.E.M of six animals. One Way ANOVA followed by Dunnet's t-test (t-value denotes statistical significance at $^{*}p<0.05$, $^{**}p<0.01$ and $^{***}p<0.001$ respectively, in comparison to group-I).

Table 2: Effect of ethanolic and aqueous extracts of *Argemone mexicana* on blood glucose level in single dose treated alloxan induced hyperglycemic rats.

Groups & Treatment	Blood Glucose Levels(mg/dl)							%age decrease at 10hrs
	0 hr	1 hr	2 hrs	4 hrs	6 hrs	8 hrs	10 hrs	
I. Normal Control	93.09±1.38	89.50 ± 0.64	88.50 ±0.64	90.50±0.64	87.59 ±0.64	88.67±2.14	89.76±2.33	--
II. Diabetic Control (Tween + Water)	307.5 ± 4.341	297.63±4.93$^{###}$	301.81±2.89$^{###}$	291.88±3.51$^{###}$	287.89±3.67$^{###}$	303.77±4.29$^{###}$	279.61±2.71$^{###}$	--
III.Glibencamide (5mg/kg)	295.7 ± 2.17	258.62±3.21***	198.31±2.89***	139.21±2.63***	126.31±3.28***	118.91±2.96***	98.59±2.87***	66.65
IV. Et. Extract (200mg/kg)	363.2 ± 3.98	348.38±3.26	307.53±3.24	240.79±3.81***	211.44±2.59***	163.53±4.28***	149.36±3.71***	58.87
V. Et. Ext. (400mg/kg)	382.7 ± 4.15	369.68±2.88	309.81±2.36*	222.37±3.77***	153.69±3.91***	141.84±3.28***	132.59±2.93***	65.35
VI. Aq. Ext. (200 mg/kg)	371.09± 5.22	352.23±3.91	292.62±3.11**	246.59±4.12***	167.84±3.86***	158.63±3.57***	141.32±2.98***	61.91
VII. Aq. Ext. (400 mg/kg)	378.7 ± 7.25	312.33±	259.36±2.47	176.34±4.26***	143.76±3.51***	127.34±2.15***	112.64±2.38***	70.25

Data represented as mean ± SEM, (n=6). p<0, 0.05 $^{#}$significant, $^{##}$very significant, $^{###}$highly significant as compare to normal control group. p<0.05 *significant, **very significant, ***highly significant as compare to diabetic control group. (One way analysis of variance (ANOVA) followed by Dunnett's t-test).

Table 3: Effect of ethanolic and aqueous extracts of *Argemone mexicana* on oral glucose tolerance in normal rats

Group	Treatment and dose	Blood glucose concentration (mg/dl)					% decrease at end of 4hr
		0 min	30 min	60 min	120 min	180 min	
I	Normal Control	83.75 ± 0.47	86.50 ± 0.64	88.50 ±0.64	83.50 ±0.64	86.50 ±0.64	--
II	Solvent control	90.50±0.64	135.52±0.64$^{###}$	118.83±0.85$^{###}$	98.50±0.64$^{###}$	91.50±0.64$^{###}$	--
III	Glibenclamide (5mg/kg)	89.43 ± 0.40	95.50±1.04***	81.53±0.91***	72.50±0.64***	62.51±0.64***	30.10
IV	Et. Ext. (200mg/kg)	83.62±0.40	98.25±0.85***	97.61±0.91***	93.50±0.64***	92.13 ± 0.64	6.22
V	Et. Ext. (400mg/kg)	87.50 ± 0.64	107.31±1.37***	102.32±1.10***	94.50±0.64**	91.50 ± 0.64	14.73
VI	Aq. Ext. (200mg/kg)	91.50 ± 0.64	116.84±1.10***	109.83±0.85***	102.65 ± 0.91*	95.50 ±0.64**	18.26
VII	Aq. Ext. (400mg/kg)	84.87 ±0.91	128.36±0.85***	117.36 ±1.10	103.51±0.64***	96.53±0.64***	24.79

Data represented as mean ± SEM, (n=6). $p<0.05$ $^{#}$significant, $^{##}$very significant, $^{###}$highly significant as compare to normal control group. $p<0.05$ *significant, **very significant, ***highly significant as compare to solvent control group. (One way analysis of variance (ANOVA) followed by Dunnett's t-test).

Table 4: Effect of ethanolic and aqueous extract of *Argemone mexicana* on blood glucose level in alloxan induced diabetic rats.

Groups	Treatment	Blood glucose concentration (mg/dl)				%decrease at 11 day
		0 day	3 day	7 day	11 day	
I	Normal Control	88.33 ± 2.155	89.33 ± 1.745	89.33 ± 1.820	90.33 1.687	--
II	Diabetic control	407.5 ± 4.341	407.7 ± 6.458$^{\#\#\#}$	419.5 ± 5.708$^{\#\#\#}$	452.7 ± 10.53$^{\#\#\#}$	--
III	Glibenclamide (5mg/kg)	395.7 ± 27.17	212.3 ± 3.603***	173.5 ± 3.630***	101.8 ± 4.90***	74.27
IV	Et. Ext. (200mg/kg)	413.2 ± 7.998	327.8 ± 8.080***	143.2 ± 11.57***	174.5 ± 5.97***	57.76
V	Et. Ext. (400mg/kg)	422.7 ± 15.15	346.7 ± 7.360***	214.8 ± 5.081***	146.3 ± 4.787***	65.38
VI	Aq. Ext. (200mg/kg)	431.0 ± 21.22	323.8 ± 12.16***	241.3 ± 12.44***	136.3 ± 3.921***	68.37
VII	Aq. Ext. (400mg/kg)	448.7 ± 18.25	324.3 ± 9.330***	216.2 ± 2.770***	120.7 ± 5.207***	73.10

Data represented as mean ± SEM, (n=6). p<0, 0.05 $^{\#}$significant, $^{\#\#}$very significant, $^{\#\#\#}$highly significant as compare to normal control group. p<0.05 *significant, **very significant, ***highly significant as compare to diabetic control group. (One way analysis of variance (ANOVA) followed by Dunnett's t-test).

Table 5: Effect of ethanolic and aqueous extract of *Argemone mexicana* on body weight on treated alloxan induced diabetic rats.

Groups	Treatment	Body weight in (gm)			
		0 day	3 day	7 day	11 day
I	Normal Control	185.3 ± 4.2	188.34±3.93	193.22±4.38	199.8 2± 6.8
II	Diabetic control	188.8 ± 3.8	182.56±4.61	173.36±3.28##	164.74 ± 7.2###
III	Glibenclamide (5mg/kg)	178.5 ± 4.9	182.31±3.72	187.74±2.89**	194.56 ± 6.1**
IV	Et. Extract (200mg/kg)	183.6 ± 4.6	186.53±3.77	190.87±3.44**	194.53 ± 6.1**
V	Et. Extract (400mg/kg)	178.2 ± 5.1	187.59±3.46	191.82±4.68**	195. 3 3± 5.8**
VI	Aq. Extract (200mg/kg)	182.4 ± 4.4	188.37±2.86	192.91±3.73**	195.54 ± 6.0**
VII	Aq. Extract (400mg/kg)	181.3 ± 4.2	184.73±3.41	189.39±3.66**	194.62 ± 5.1**

Data represented as mean ± SEM, (n=6). $p<0.05$ $^{\#}$significant, $^{\#\#}$very significant, $^{\#\#\#}$highly significant as compare to normal control group. $p<0.05$ *significant, **very significant, ***highly significant as compare to diabetic control group. (One way analysis of variance (ANOVA) followed by Dunnett's t-test).

Table 6: Effect of ethanolic and aqueous extract of *Argemone mexicana* on some serum biochemical parameters on treated alloxan induced diabetic rats.

Groups	Treatments	Urea mg/dl	Creatinine mg/dl	Triglycerides mg/dl	Cholesterol mg/dl
I	Control	42.25±0.47	0.83±0.004	84.25±0.47	63.25±0.75
II	Diabetic control	183±0.64$^{###}$	1.53±0.008$^{###}$	145.5±0.64$^{###}$	172.8±1.10$^{###}$
III	Glibenclamide (5mg/kg)	89±0.40***	1.13±0.006***	104.8±0.85***	85±0.91***
IV	Et. Ext. (200mg/kg)	143.8±0.47***	1.29±0.006***	138.3±0.85***	128.5±1.04***
V	Et. Ext. (400mg/kg)	109±0.40***	1.27±0.004***	132.5±1.19***	114.5±1.32***
VI	Aq. Ext. (200mg/kg)	92.50±0.64***	1.17±0.006***	115.0±1.08***	96.75±1.31***
VII	Aq. Ext. (400mg/kg)	89±0.40***	1.15±0.006***	108.3±0.85***	94.25±1.10***

Data represented as mean ± SEM, (n=6). $p<0.05$ $^{#}$significant, $^{##}$very significant, $^{###}$highly significant as compare to control group. $p<0.05$ *significant, **very significant, ***highly significant as compare to negative control group. (Analysis of Variance (ANOVA) followed by dunnett's test).

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