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EVALUATION OF PLANT EXTRACTS ON INSULIN RESISTANCE PRODUCED BY DEXAMETHASONE IN EXPERIMENTAL ANIMALS

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ABSTRACT

In this current research work two plants collected, extracted and evaluate their antidiabetic activity. We conducted a study to examine the preventative impact of the hydroalcoholic extracts of *Adenium obesum* and *Gazania rigens* on insulin resistance caused by dexamethasone in experimental animals. The albino wistar rats were organized into seven groups. One group included of healthy animals, while the remaining six groups were utilized for generating diabetes. Following an 18-hour fasting period, the animals with diabetes were given the subsequent treatment. After a 6-day duration of administering dexamethasone, the animals with diabetes were later administered the same treatment. The standard drugs Glibenclamide (5 mg/kg) and Pioglitazone (2mg/kg) and test samples *Adenium obesum* and *Gazania rigens*, with a dose of 400 mg/kg body weight and combination of both extracts (400 mg/kg body weight) were administered orally in a single dose over a 15-day period via a gastric tube. The combination of hydroalcoholic extracts from *Adenium obesum* and *Gazania rigens* demonstrated a protective effect against insulin resistance induced by dexamethasone.

Keywords: *Adenium obesum*, *Gazania rigens*, insulin resistance, dexamethasone, Glibenclamide and Pioglitazone

INTRODUCTION

Diabetes is metabolic non-communicable disease which increases rapidly in India. The ICMR-INDIAB estimates for the prevalence of diabetes and prediabetes in India are significantly higher than previous reports.[1]

Herbal medications include a high concentration of phytochemicals, which are thought to have a significant impact on the treatment of chronic illnesses like cancer, diabetes, and coronary heart disorders.[2]

In this current research work two plants collected from Rajasthan and investigate Pharmacological profile. The current work will be helpful to identify new potential principles from ornamental plants and promote the use of herbals towards their medicinal principles. However, above claims demands further studies on complete plant with respective isolation of active constituent/s, responsible for activity. Further, detail pharmacological screening is necessary to pin point the further possible mechanism of action.

In current work an effort was made to extract both plants and evaluate their antidiabetic activity. The above mentioned postulate that plants have no or less side effects, they are easily available and no specific method necessary for their cultivation also.

Adenium obesum is a flowering plant species that is classified under the family Apocynaceae.[3, 4] *Adenium obesum* is utilized for the therapeutic management of several ailments. The root and bark extract is utilized to treat various skin ailments and to eradicate lice. The latex is used as a medicine for the recovery of deteriorating dental health and infected injuries, and the Somali people are utilizing it as nasal drops.[5] The bark of *A. obesum* is also utilized to induce abortion. In a therapeutic context, the Nigerian population is utilizing the entire plant for its medicinal properties in combating malaria, trypanosomiasis, and leishmaniasis.[6,7] The biochemical analysis of the chosen plant species revealed the presence of carbohydrate, cardiac glycoside, flavonoid, prenylated flavonoids, terpenoids, pregnanes, and various other minor chemical components.[8]

Gazania rigens exhibits a compact and upright growth pattern, characterized by many branches and moderate horizontal expansion. It belongs to the Asteraceae family.[9] The plant has been utilized for its emmenagogue, abortifacient, vermifuge, diuretic, and digestive properties. Additionally, it has been employed in the treatment of arthritis pain, rheumatism, and skin fungal infections. The leave preparations were used to treat head pain and scurvy because it contained rich amount of vitamin C.[10] Homoeopathic plant preparations are utilized to alleviate symptoms such as headaches, vertigo, emotional distress, restlessness, scalp itching, throat pain, stomach cramps, and breathing difficulties. The oil of plant is used in the treatment of anxiety, asthma, colds, congestion, acne and dandruff.[11] The chemical composition

analysis of *Gazania rigens* identified the presence of flavonoids, polyphenols, coumarins, sterols, and triterpenoids. Specifically, the compounds lupeol-3-O-stearate, costunolide, 11,13-dihydro-costunolide, santamarine, lupeol, β-amyrin, and β-sitosterol-3-O-β-D-glucopyranoside were detected.[12]

MATERIALS AND METHODS

Collection and extraction of Plant Materials

The aerial portions of *Adenium obesum* and *Gazania rigens* have been collected from various locations, namely Jodhpur and Jaipur. The identity of the collected desiccated aerial components of *Adenium obesum* and *Gazania rigens* were confirmed by Botanical Survey of India, Jodhpur with reference no. – BSI/AZRC/L12012/ Tech/2019-20 (Pl. Id).

Dried powdered aerial parts of *Adenium obesum* and *Gazania rigens* (250 gm each) were separately extracting exhaustively with mixture of ethanol and water (1:1) in a Soxhlet apparatus to obtain hydroalcoholic extracts. The hydroalcoholic extracts were concentrated using rotary vacuum evaporator and all hydroalcoholic extracts were preserved for anti-diabetic activity in a vacuum desiccator. [13, 14]

Acute oral toxicity study of hydroalcoholic extracts of aerial portions of *Adenium obesum* and *Gazania rigens* was followed according to Organization for Economic Cooperation and Development guidelines-423. Six male rats were utilized in the study, with each rat receiving a single oral dose of 2000 mg/kg, p.o. The animals had an overnight fasting period before receiving the medication, and their food intake was restricted for an additional 3-4 hours.[15] Observations encompass a comprehensive assessment of the skin and fur, eyes, respiration, somatomotor activity, and behavior pattern. Special focus was given to the observation of tremors, convulsions, salivation, diarrhea, and coma. Both extracts showed low toxicity profile with high safety margin up to 2000 mg/kg. The experimental methodology received approval from the institutional animal ethical committee, and the animals were cared for in accordance with the rules set by the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), 1737/PO/Rc/S/14/CPCSEA by Institute of Biomedical and Industrial Research, Jaipur.

Dexamethasone Induced Diabetes

Glucocorticoids hinder the process of insulin-mediated glucose uptake by directly interfering with key components of the insulin signaling cascade, including glycogen synthase kinase-3, glycogen synthase, and GLUT4 translocation.[16, 17]

Drugs and Chemicals

Two dose levels were selected, with one dose being around one-tenth of the highest dose administered during the acute toxicity tests, and the second dose being twice that of the one-tenth dose i.e., 200mg/kg, 400mg/kg/body weight, respectively. A solution consisting of distilled water and 2% Tween 80 (0.5 ml/kg) was utilized as

a medium for creating test doses of hydroalcoholic extracts from the aerial portions of *Adenium obesum* and *Gazania rigens*, with a dose of 400 mg/kg body weight. Glibenclamide (5 mg/kg) [18] and Pioglitazone (2mg/kg) [19] were used as standard antidiabetic drug. Rats were orally given test samples and standard medications. Dexamethasone (8 mg/kg, i.p.)[20] was administered to induce diabetes in rats over a period of six days.

Experimental Setup

The fastest rats were grouped into seven groups, each consisting of six animals. One group consisted of normal animals, while the other six groups were used for inducing diabetes. After a period of 18 hours of fasting, the animals with diabetes were administered the following pharmacological treatment. After 6 days of administering dexamethasone, the animals with diabetes received same treatment. The medications and test samples were given in a single dose over a period of 15 days using a stomach tube. [21] The recommended daily dose of the standard medications Glibenclamide and Pioglitazone was determined using the extrapolation method, based on the human dose adjusted for surface area.

Experimental Protocol

There were a total of seven groups of animals, with each group consisting of six experimental animals. The drugs and test extracts were given to diabetic rats orally once a day at 9:00 AM for duration of 15 days. The blood glucose concentration was measured in cohorts of experimental animals administered with test and standard on day 0 and day 15.

Groups, Induction of insulin resistance and treatment with test and standard:

Dexamethasone was used in this experiment and dissolved in normal saline. A total of 42 albino wistar rats were used. They were divided into seven groups of six animals each:

I Normal control (untreated) rats, receiving by gavage distilled water

II Control group received dexamethasone (8mg/kg/i.p.) for 15 days.

III Hydroalcoholic extract of *Adenium obesum* (400mg/kg, p.o.) + treated with dexamethasone (8 mg/kg/i.p.) for 15 days.

IV Hydroalcoholic extract of *Gazania rigens* (400mg/kg, p.o.) + treated with dexamethasone (8 mg/kg/i.p.) for 15 days.

V Hydroalcoholic extract of *Adenium obesum* + *Gazania rigens* (400mg/kg, p.o.)+ treated with dexamethasone (8 mg/kg/i.p.) for 15 days.

VI Rats were treated with a standard drug Pioglitazone (2mg/kg/p.o/15days)

VII Rats were treated with a standard drug Glibenclamide (5mg/kg/p.o/15days)

RESULTS

The results hydroalcoholic extract of *Adenium obesum* and *Gazania rigens* aerial parts were investigated against Dexamethasone induced diabetic are presented.

Table 1: Effect of hydroalcoholic extracts of *Adenium obesum* and *Gazania rigens* aerial parts on body weight.

S.No.	GROUP	Body weight (g) Day 0	Body weight (g) Day 15	Change in Body weight (%)
1.	Normal control	250	255	+2%
2.	Dexamethasone control (8mg/kg/i.p.)	250	195*a	-22%
3.	*A. obesum* (400 mg/kg, p.o.) + Dexamethasone	250	230*a	-8%
4.	*G. rigens* (400 mg/kg, p.o.) + Dexamethasone	255	220*a	-13.7%
5.	*A. obesum* + *G. rigens* (400 mg/kg, p.o.) + Dexamethasone	250	235**a	-6%
6.	Pioglitazone (2mg/kg, p.o.) + Dexamethasone	255	235**a	-7.8%
7.	Glibenclamide(5mg/kg/p.o.) + Dexamethasone	250	240**a	-4%

The values are expressed as Mean ± SEM (n=6) and were analyzed using a one-way ANOVA followed by Dunnett's test. Statistical significance is indicated by **$p<0.01$ and *$p<0.05$ (a - compared to the Normal control group).

Table 2: Effect of hydroalcoholic extracts of *Adenium obesum* and *Gazania rigens* aerial parts on fasting blood glucose.

S.No.	GROUP	Fasting Blood glucose (mg/dl) (DAY 0)	Fasting Blood glucose (mg/dl) (DAY 15)
1.	Normal control	93.13±1.72	98.43±1.43
2.	Dexamethasone control (8mg/kg/i.p.)	272.35±1.82	277.16±1.22**a
3.	*A. obesum* (400 mg/kg, p.o.)	266.20 ±3.16	133.20 ±1.26**a

	+ Dexamethasone		
4.	*G. rigens* (400 mg/kg, p.o.) + Dexamethasone	268.82 ±2.41	140.11 ±2.23**a
5.	*A. obesum* + *G. rigens* (400 mg/kg, p.o.) + Dexamethasone	270.20 ±1.36	125.39±5.16**a
6.	Pioglitazone (2mg/kg, p.o.) + Dexamethasone	269.54±2.23	115.30 ±1.46**a
7.	Glibenclamide(5mg/kg/p.o.) + Dexamethasone	271.54±2.23	108.60 ±1.12**a

The values are expressed as Mean ± SEM (n=6) and were analyzed using a one-way ANOVA followed by Dunnett's test. Statistical significance is indicated by **p<0.01 and *p<0.05 (a - compared to the Normal control group).

Table 3: Effect of hydroalcoholic extracts of *Adenium obesum* and *Gazania rigens* aerial parts on plasma insulin and HOMA-IR.

S.No.	**GROUP**	**Fasting Insulin level (µIU/L)**	**HOMA- IR**
1.	Normal control	4.9±0.28	0.94±0.02
2.	Dexamethasone control (8mg/kg/i.p.)	18.89±0.65*a	12.92±0.38*a
3.	*A. obesum* (400 mg/kg, p.o.) + Dexamethasone	9.37 ±0.49*a	2.42±0.08**a
4.	*G. rigens* (400 mg/kg, p.o.) + Dexamethasone	11.45± 0.23*a	2.92±0.05**a
5.	*A. obesum* + *G. rigens* (400 mg/kg, p.o.) + Dexamethasone	8.22 ±0.82*a	1.92±0.04**a
6.	Pioglitazone (2mg/kg, p.o.) + Dexamethasone	6.91± 0.31**a	1.68±0.11**a
7.	Glibenclamide(5mg/kg/p.o.) + Dexamethasone	5.17± 0.21**a	0.85±0.02**a

The values are expressed as Mean ± SEM (n=6) and were analyzed using a one-way ANOVA followed by Dunnett's test. Statistical significance is indicated by **p<0.01 and *p<0.05 (a - compared to the Normal control group).

Table 4: Effect of hydroalcoholic extracts of *Adenium obesum* and *Gazania rigens* aerial parts on oral glucose tolerance test (OGTT)

S.No.	GROUP	0 min	30 min	60 min	90 min	120 min
1.	Normal control	90	125	140	115	95
2.	Dexamethasone control (8mg/kg/i.p.)	250	270	288	261	255
3.	*A. obesum* (400 mg/kg, p.o.) + Dexamethasone	135	160	188	150	133
4.	*G. rigens* (400 mg/kg, p.o.) + Dexamethasone	144	175	198	158	147
5.	*A. obesum* + *G. rigens* (400 mg/kg, p.o.) + Dexamethasone	130	155	170	135	125
6.	Pioglitazone (2mg/kg, p.o.) + Dexamethasone	125	160	178	145	120
7.	Glibenclamide(5mg/kg/p.o.) + Dexamethasone	120	148	167	130	110

Table 5: Effect of hydroalcoholic extracts of *Adenium obesum* and *Gazania rigens* aerial parts on lipid profile:

S.No.	GROUP	Total CH	Total TG	LDL	VLDL	HDL
1.	Normal control	92.13± 1.25	52.39± 1.96	43.35± 1.87	12.27± 0.25	46.50± 1.63

2.	Dexamethasone control (8mg/kg/i.p.)	188.6± 1.71 *a	158.3± 1.19 *a	92.48± 1.27*a	35.67± 0.36*a	19.67± 1.30*a
3.	*A. obesum* (400 mg/kg, p.o.) + Dexamethasone	117.55 ±1.54** *a	66.93± 1.89**a	54.34± 2.14** a	15.48± 0.77** a	32.76± 1.93**a
4.	*G. rigens* (400 mg/kg, p.o.) + Dexamethasone	121.63 ±2.36** *a	69.0± 3.11**a	58.31± 2.65** a	17.79± 0.64** a	29.1± 1.20**a
5.	*A. obesum* + *G. rigens* (400 mg/kg, p.o.) + Dexamethasone	106.44 ±1.66** *a	62.50± 3.11**a	51.22± 1.89** a	14.87± 0.68** a	35.61± 1.55**a
6.	Pioglitazone (2mg/kg, p.o.) + Dexamethasone	101.89 ±2.58** *a	59.45± 2.74**a	42.73± 2.27** a	12.55± 0.50** a	44.01± 1.46**a
7.	Glibenclamide(5mg/kg/ p.o.) + Dexamethasone	89.39± 1.75**a	58.76± 2.52**a	45.85± 3.34** a	13.45± 0.50** a	45.08± 1.32**a

The values are expressed as Mean ± SEM (n=6) and were analyzed using a one-way ANOVA followed by Dunnett's test. Statistical significance is indicated by **$p<0.01$ and *$p<0.05$ (a - compared to the Normal control group).

Table 6: Effect of hydroalcoholic extracts of *Adenium obesum* and *Gazania rigens* aerial parts on hepatic enzymes:

S.No.	**GROUP**	**ALT (U/L)**	**AST (U/L)**	**ALP (U/L)**	**Bilirubin (mg/dl)**
1.	Normal control	44.70±1.08	34.90± 0.17	26.70± 1.67	0.57± 2.11
2.	Dexamethasone control (8mg/kg/i.p.)	140.89± 0.67*a	127.0± 0.55*a	90.69± 0.21*a	7.11±1.14*a
3.	*A. obesum* (400 mg/kg, p.o.) + Dexamethasone	58.08± 1.80**a	65.44± 2.81**a	40.21± 2.11**a	2.76± 1.33**a
4.	*G. rigens* (400 mg/kg,	62.74±	70.12±	44.18±	3.87±

	p.o.) + Dexamethasone	2.95**a	4.79**a	2.44**a	2.77**a
5.	*A. obesum* + *G. rigens* (400 mg/kg, p.o.) + Dexamethasone	54.08± 1.42**a	55.21± 2.19**a	35.10± 1.84**a	1.16± 1.43**a
6.	Pioglitazone (2mg/kg, p.o.) + Dexamethasone	48.28± 0.04**a	40.5± 1.45**a	30.21± 2.33**a	0.98± 2.76**a
7.	Glibenclamide(5mg/kg/ p.o.) + Dexamethasone	46.29± 0.05**a	38.53± 0.15**a	28.44± 2.72**a	0.82± 2.44**a

The values are expressed as Mean ± SEM (n=6) and were analyzed using a one-way ANOVA followed by Dunnett's test. Statistical significance is indicated by **p<0.01 and *p<0.05 (a - compared to the Normal control group).

Table 7: Effect of hydroalcoholic extracts of *Adenium obesum* and *Gazania rigens* aerial parts on Kidney:

S.No.	**GROUP**	**Albumin (g/dl)**	**Total protein (g/dl)**	**BUN (mg/dl)**	**Creatinine (mg/dl)**
1.	Normal control	3.5± 2.14	6.35 ± 2.23	12.10 ± 1.54	0.34±0.02
2.	Dexamethasone control (8mg/kg/i.p.)	8.9± 1.25*a	9.5 ± 4.67*a	40.64± 1.82*a	0.93±0.13 *a
3.	*A. obesum* (400 mg/kg, p.o.) + Dexamethasone	5.5± 3.21**a	7.9 ± 3.24**a	29.87 ± 0.63**a	0.57±0.09** a
4.	*G. rigens* (400 mg/kg, p.o.) + Dexamethasone	6.23± 3.26**a	8.85 ± 1.22**a	35.76± 0.63**a	0.69±0.01** a
5.	*A. obesum* + *G. rigens* (400 mg/kg, p.o.) + Dexamethasone	5.0± 2.11**a	7.3 ± 1.28**a	25.16± 0.66**a	0.44±0.08** a
6.	Pioglitazone (2mg/kg, p.o.) + Dexamethasone	4.5±3.26 **a	7.0 ± 3.23**a	16.54± 0.89**a	0.50±0.05** a

7.	Glibenclamide (5mg/kg/p.o.) + Dexamethasone	3.9± 2.76**a	6.5 ± 2.56**a	13.24± 2.10**a	0.39±0.03** *a

The values are expressed as Mean ± SEM (n=6) and were analyzed using a one-way ANOVA followed by Dunnett's test. Statistical significance is indicated by **p<0.01 and *p<0.05 (a - compared to the Normal control group).

DISCUSSION

Dexamethasone has commonly been employed to develop insulin resistance in experimental animals.[22]. The current study has demonstrated statistically significant (p>0.05) findings on the effects of dexamethasone on body weight loss, increased blood glucose levels, fasting insulin levels, triglyceride levels, total cholesterol levels, LDL, VLDL, hepatic enzyme, protein, and insulin resistance index. This could be attributed to the depletion of muscle and adipose tissue caused by excessive protein breakdown in the body. The data strongly indicate the development of insulin resistance in a living organism. The hydroalcoholic extracts of *Adenium obesum* and *Gazania rigens* were effective in preventing the development of insulin resistance caused by the injection of dexamethasone. Treatment with the plant extracts and standard drugs prevented the body weight loss. *Adenium obesum* and *Gazania rigens* may enhance the effectiveness of insulin in muscles and/or adipose tissue. This can also be attributed to the substantial rise in blood insulin levels, resulting in a high index of insulin resistance as indicated by HOMA-IR. Combination of hydroalcoholic extracts of *Adenium obesum* and *Gazania rigens* significantly prevented the rise in blood glucose, blood insulin and insulin resistance. Moreover, based on the results of the oral glucose tolerance test, it may be inferred that the plant extracts exhibited enhanced glucose tolerance compared to normal control group. The hydroalcoholic extract of Adenium obesum exhibits action that may be attributed to the presence of bioactive components, including polyphenols, flavonoids, triterpenes, and glycosides. These substances have been documented to effectively lower blood glucose levels.[23] Certain polyphenols in *Gazania rigens* has been shown to significantly reduce blood glucose levels.[24] So the mixture of hydroalcoholic extracts of *Adenium obesum* and *Gazania rigens* showed highly statistical significant (p>0.01) results on blood glucose, fasting insulin, triglycerides, total-cholesterol, LDL, VLDL, hepatic enzymes, protein level and insulin resistance index.

CONCLUSION

As per the results obtained from the respective study it is being shown that treatment with combination of hydroalcoholic extracts of *Adenium obesum* and

Gazania rigens exhibited protective effect against insulin resistance so produced by dexamethasone.

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