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EVALUATION OF HYPOGLYCEMIC POTENTIAL OF THREE ETHNO-HERBS IN STREPTOZOTOCIN – INDUCED DIABETIC RATS

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ABSTRACT:

Catharanthus roseus (L.) G. Don (Apocyanaceae), *Momordica charantia* L. (Cucurbitaceae) and *Syzygium cumini* (L) Skeels (Myrtaceae) has been documented as an ethno-hypoglycemic herbs from south-east Rajasthan. Therefore, to evaluate their potential an oral administration of the aqueous extract was administered for 15 days at the concentration of 500 mg /kg body weight in STZ induced hyperglycemic activity. GBC was used in another group to support the results at the concentration of 0.25 mg /kg body weight orally once a day for 15 days. Hypoglycemic activity was observed in all the treated groups revealing significant reduction in blood glucose levels. The results were also found akin to urino-analysis and the body weight tendencies. The performance of *Catharanthus roseus* was found better as compared to other two and is quite comparable with GBC. Results indicate presence of insulin mimicking natural products in all 3 plants which may contribute for the exploration of new safer drugs.

KEY WORD: *Diabetes mellitus, streptozotocin (STZ), Glibenclamide, Catharanthus roseus, Momordica charantia, Syzygium cumini.*

INTRODUCTION:

Diabetes dates back synonymous to the ages of man. Before the introduction of insulin in 1922, treatment of diabetes mellitus (DM) relied heavily on dietary measures which included the use of ethno-traditional plant therapies. Ethno-herbs provide better health coverage for 80% of the world population,

especially in the developing countries (Srinivasan, 2005). Unfortunately with the onset of modern voyage the DM is hiking and the traditional systems of therapies are becoming hypogean. Depending on synthetic drug system has led to the curse of side effects bursting into severe complications leading to the series of medication. This phase can be checked by utilizing hypoglycemic plants which are safer and cheaper (Kamboj, 2000). Modern pharmaceutical companies have revealed their significance which has resulted about 90% of new drugs to be derived from already established medicinal plants (Mosh, 2005). Furthermore, after the recommendation made by WHO on DM, investigations on hypoglycemic agents from plants have become more important (Kumar, 2010).

Rajasthan is an enriched state of traditional systems and proceedings. It also hugs a vast knowledge in this field, which has been documented time to time. A number of plants have shown varying degrees of hypoglycemic and antidiabetic activities (Grover *et al*., 2002, Katewa and Jain 2006 and Sharma *et al*., 2007).

DM is characterized by metabolic dysfunction that results in elevated blood and tissue concentrations of many metabolites namely – glucose, cholesterol, triglycerades, fatty acids and ketone bodies (*Onoaghe et al*., 2010). Over production of glucose and decreased utilization by the tissues form the fundamental basis of hypoglycemic conditions in DM (Shirwaikar *et al*., 2005). The marked hyperlipaemia that characterizes the diabetic state is a consequence of the uninhibited actions of lipolytic enzymes on the fat depots (Abubakar *et al*., 2009). For the evaluation of hypoglycemic activity, DM induction is an initial step which can be carried out using Streptozotocin. STZ enters the β-cells via. a glucose transporter (GLUT 2) and causes alkylation of DNA. DNA damage induces activation of poly ADP-ribosylation, a process that is more important for the diabetogenicity of Streptozotocin (Szkudelski, 2001). It is also associated with a characteristic loss of body weight, which is due to muscle wasting and loss of tissue proteins (Chatterjee *et al*., 2002). Treatment with antidiabetic plant checks weight loss and regains *i.e.* by reversal of antagonizing (Barik *et al*., 2008). It also enhances insulin secretion and / or improves / mimic's insulin action.

Therefore, an attempt was made to evaluate the potential of three ethno-medicinal plants viz. seeds of *Syzygium cumini* (L) Skeels (Jamun, Myrtaceae), flowers of *Catharanthus roseus* (L.) G. Don (Sadabahar, Apocyanaceae) and fruits *of Momordica charantia* L. (Karela, Cucurbitaceae) in Streptozotocin induced DM in Swiss Albino Rats of Wistar strains. Utilization of plant part and mode of administration was followed as per ethno-medicinal reporting's from south-east Rajasthan and dose was calibrated accordingly in preliminary screening of blood glucose levels (Katewa and Arora, 1997).

MATERIALS AND METHODS:

- Experimental animals: White albino rats of Wistar strain weighing 100-150g were used for the present study. They were acclimatized for 15 days (Rthymic light and dark period of 12 h, 25 ± 5°C, 35-60% humidity) and were fed *ad libitum*. During fasting course they were deprived of food for atleast 12 h but were allowed free access to drinking water.
- Extract preparation: Aqueous extract was prepared by cold maceration of respective shade dried parts by soaking 100 g in 500 ml of distill water for 5 days and followed up by filtration. The extract was stored at 5-8°C.
- Induction of diabetes: Streptozotocin (STZ) in physiological saline was injected intraperitoneal as 50 mg /kg body weight.
- Glibenclamide (GBS): It acts on β-cells membrane enhancing calcium flux hence helps in provoking brisk release of insulin. Therefore, GBS will be utilized to compare with aqueous extract treatment.

Blood glucose concentration is analyzed utilizing glucose oxidase-peroxidase reactive strips with the help of glucometer. Urinary glucose and ketone is evaluated through keto-diastix strips. Body weight of anesthetize rats was taken with the help of single pan balance.

- Experimental design:

Group No.	Treatment
I	Control
II	Streptozotocin (STZ)
III*	STZ + Aqueous seed extract of *Syzygium cumini*
IV*	STZ + Aqueous floral extract of *Catharanthus roseus*
V*	STZ + Aqueous fruit extract of *Momordica charnatia*
VI**	STZ + Glibenclamide (GBC)

* In Group III, IV and V extract was administered as 500 mg /kg body weight per day for fifteen days.

* GBC was administered as 0.25 mg /kg per day for fifteen days.

RESULTS AND DISCUSSION:

Swiss Albino rats of Wistar strains treated with STZ revealed 2-3 folds increase in blood glucose levels as compared to control i.e. non-diabetic revealing hyperglycemic or diabetic phase. Continuous oral administration of aqueous extract of *Syzygium* seeds, *Catharanthus* flowers and *Momordica* fruits has shown a decremental trend after 24 h which was highest in Group IV *i.e.* treated with *Catharanthus*

flowers. During Urinanalysis ketone bodies were observed in traces which signify the state of ketoacidosis. These bodies were again restored by experimental rats after the phase of hypoglycemia was attained. Urine glucose was found to be in between 100-1000 mg /dL in diabetic rats but the quantity declined as treated by aqueous extract of three plants. In case where group was treated with *Cathranthus* flowers urine glucose concentration was comparable to STZ + GBS treated mice (Group VI). Same trend was also observed when body weight was measured for different groups, which can be related to other parameters leading to hypoglycemic conditions.

In case of *Syzygium* seeds hypoglycemic activity can be conferred due to the presence of mycaminose which triggers flow of insulin (Kumar *et al.*, 2008 and Pepato *et al.*, 2001 and 2005). STZ-induced diabetes has been shown to produce a partial or total deficiency of insulin that causes decrease in concentration of glycolytic enzymes. Oral administration of an aqueous extract of *Catharanthus roseus* (flower), *Momordica charantia* (fruits) and *Syzygium cumini* (seeds) decreased the elevated blood glucose levels within 15 days. There prolonged administration might have stimulated that β-cells of Islets of Langerhens to produce insulin (Gray and Flatt, 1999 & Mahalingam and Kannabiran, 2008). Insulin has been shown to be potentiator of hexokinase and glucokinase. The decreased levels of glycogen synthase, glucokinase, lactate dehydrogenase, succinate dehydrogenase and malate dehydrogenase may be due to decreased insulin levels in diabetic rats. (Prasad *et al.*, 2009). Metabolic restoration and insulin-mimic action of these plants are quite comparable with GBC. Therefore, in future a dose and time mediated findings will open a path for the formulation of new herbal drugs against the silent killer "diabetes mellitus".

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Table I: Effect of Aqueous extract of *S. cumini* (seeds), *C. roseus* (flowers) and *M. charantia* (fruits) on Blood glucose concentration in STZ induced diabetic rats

Time Interval	Blood Glucose Concentration (mg /100 ml)					
	Group I (C)	Group II (D)	Group III	Group IV	Group V	Group VI
Initial day	70.25 ± 6.01	243 ± 6.04	242.00 ± 7.44	243.10 ± 5.82	243.0 ± 5.00	243.33 ± 7.8
Day 1	68.03 ± 6.40	249.75 ± 7.14	200.40 ± 6.44a^{NS}	210.75 ± 6.80a^{NS}	210.0 ± 8.75a^{NS}	136 ± 9.45a^{NS}
Day 5	66.0 ± 7.48	260.8 ± 8.25	170.45 ± 6.45a^{NS}b*	160.5 ± 7.55a*b*	180 ± 9.33a^{NS}b*	95.1 ± 9.50a*b*
Day 10	67.05 ± 5.20	284 ± 7.45	140.55 ± 4.55 a*b*	110.45 ± 9.45a*b*	135.45 ± 9.55a*b*	80.75 ± 4.55a*b*
Day 15	67.07 ± 5.45	310.25 ± 7.00	130.65 ± 9.55 a*b*	80.45 ± 6.50a*b*	125.65 ± 4.55a*b*	77.50 ± 6.50a*b*

Values are mean ± SD of respective groups. (NS – Non significant)

* P < 0.05 Comparison were made: a – Initial Vs day 1, day 5, day 10 and day 15 of respective groups, b – Group II Vs Group III, IV, V and VI.

Table II: Effect of Aqueous extract of *S. cumini* (seeds), *C. roseus* (flowers) and *M. charantia* (fruits) on Urine glucose and Urine ketone bodies in STZ induced diabetic rats

Time Interval	Group I (C)		Group II (D)	Group III		Group IV	Group V	Group VI				
	U.G. %	U.K.	U.G%	U.K	U.G %	U.K	U.G.%	U.K	U.G. %	U.K	U.G. %	U.K.
Initial day	—	—	1/10	—	1/10	—	1/10	—	1/10	—	1/10	—
Day 1	—	—	1/2	T	1/2	T	1/4	T	1/2	T	1/10	—
Day 5	—	—	1/2	M	1/2	T	1/10	—	1/2	T	—	—
Day 10	—	—	1	M	1/4	—	1/10	—	1/4	T	—	—
Day 15	—	—	1	L	1/10	—	—	—	1/10	—	—	—

Ketone = – Absence of Ketone bodies, Trace (T) = 5 mg /dL, Small (S) = 15 mg /dL, Moderate (M) = 40 mg /dL and Large (L) = 80 mg /dL

Glucose = – Absence of Glucose, 1/10 = 100 mg /dL, 1/4 = 250 mg /dL, 1/2 = 500 mg/dL, 1 = 1000 mg/ dL and 2 or more 2000 mg /dL

Table III: Effect of Aqueous extract of *S. cumini* (seeds), *C. roseus* (flowers) and *M. charantia* (fruits) on Body weight in STZ induced diabetic rats

Time Interval	Body Weight (g)					
	Group I (C)	Group II (D)	Group III	Group IV	Group V	Group VI
Initial day	127 ± 2.0	128 ± 2.1	127 ± 3.2	126 ± 2.4	129 ± 2.4	128 ± 2.6
Day 1	128 ± 1.2	127 ± 2.6	127 ± 2.8	126 ± 3.1	128 ± 3.1	128 ± 3.2
Day 5	127 ± 1.8	120 ± 3.6	126 ± 3.2	124 ± 2.5	126 ± 2.0	128 ± 1.9
Day 10	127 ± 1.7	120 ± 2.5	127 ± 2.5	124 ± 4.5	126 ± 3.2	127 ± 1.5
Day 15	128 ± 1.6	119 ± 4.3	126 ± 2.8	126 ± 0.8	127 ± 3.0	127 ± 1.5

Data is mean ± SD

* P < 0.01 as compared to control.