COMPARATIVE ANTIDIABETIC ACTIVITY OF THREE SPECIES *OF SALACIA* AND TWO MARKET SAMPLES ON STREPTOZOTOCIN INDUCED DIABETIC RATS.

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ABSTRACT: Aqueous extracts of roots of *Salacia reticulata (Sr), Salacia macrosperma (Sc), Salacia chinensis (Sc)*, and two market samples (MS1, MS 2) sold under the traditional name-*Saptarangi* were used to compare their antidiabetic activity in Streptozotocin induced diabetic rats at the concentrations of 500 mg/kg in different groups of six diabetic rats each orally once a day for three days. Glibenclamide (Gleb), a known standard antidiabetic drug, was also given to one of the groups to support the result at the concentration of 500 µg /Kg body weight , orally once a day for three days. 72 hours post STZ treatment, the plasma samples were collected for its glucose levels at 0 Hrs, then at the intervals of 1Hr, 2 Hrs, 3Hrs, 4Hrs, 5 Hrs, 6 Hrs and 24 Hrs. At the termination of the study, Glucose level of the animals treated with *Sr* and *Sc* were significantly low at 4 Hrs, however the glucose level of the animals treated with (Gleb) showed a significant decrease at 3rd Hrs. Whereas the animals treated with MS1 and MS2 did not show any significant decrease even after 4Hrs.

Keywords: Antidiabetic activity, *Salacia reticulata, Salacia macrosperma, Salacia chinensis*, albino rats.

INTRODUCTION:

Diabetes mellitus is a complex and multifarious group of disorders that disturbs the metabolism of carbohydrates, fat and protein. It results from shortage or lack of insulin secretion or reduced sensitivity of the tissue to insulin. Several drugs such as biguanides and sulfonyurease are presently available to reduce hypoglycemia in diabetes mellitus. These drugs have side effects and thus searching for a new class of compounds is essential to overcome diabetic problems (Noor *et al*., 2008). Management of diabetes without any side effect is still a challenge to the medical community. There is continuous search for alternative drugs. Therefore it prudent to look for options in herbal medicines for diabetes as well, although, herbal medicines have long been used effectively in treating diseases in Asian communities and throughout the world. Many traditional plants treatments for diabetes are also used. But most of the evidence for their beneficial effects is anecdotal (Bailey and Day, 1989).

A wide range of medicinal plant parts are used in extraction as raw drugs and they possess varied medicinal properties. The raw druga rea collected in smaller quantities by the local communities and folk healers for local use (Jadhav *et al.* 2013). Traditional antidiabetic plants might provide new oral hypoglycemic compounds, which can counter the high cost and poor availability of the current medicines/ present day drugs for many rural populations in developing countries. India is well known for its herbal wealth. Medicinal plants like *Trigonella foenum, Allium sativum, Gymnema sylvestre* and *Syzigium cumini* have been studied (Grover *et al*., 2002) for treatment of diabetes mellitus. However, detailed studies on the efficacy, mechanism of action and safety of plant extract are needed.

Diabetes mellitus is a major endocrine disorder affecting nearly 10% of the population all over the world (Burke *et al*., 2003). Diabetes is one of the leading causes of death in humans and animals. In animals it occurs most frequently in the dog with an incidence of approximately 0.2%. In the Indigenous Indian system medicine good number of plants were mentioned for the cure of diabetes and some of them have been experimentally evaluated and active principles were isolated (Grover *et al*., 2002). WHO (1980) has also recommended the evaluation of the effective of plants in conditions where there are no safe modern drugs (Upadhya and Pandey, 1984). The ethnobotanical information reports state that about 800 plats may possess antidiabetic potential (Aguilara *et al*., 1998). Recently the medicinal values of various plants extracts have been studied by many scientists in the field of diabetic research (Daisy and Eliza, 2007; Noor *et al*., (2008). Various parts of herbs have been used for medicinal purposes including the treatment of diabetes mellitus.

Streptozotocin (STZ) is a naturally occurring nitrosourea product of *Streptomyces acromogenes.* Usually, the intraperitonial injection of a single dose (60mg/kg body weight) of it exerts direct toxicity on β cells resulting in necrosis within 48-72 hrs and causes a permanent hypoglycemia. STZ breaks nuclear DNA strand of the islet cells (Takasu *et al*., 1991).

In the present investigation, three species of *Salacia, Salacia reticulata (Sr), Salacia macrosperma (Sc), Salacia chinensis (Sc)*, belonging to the family Hippocrataceae (Yadav, 2002), earlier known as Celastraceae were selected. Roots of above three plants were used in the present study to clarify their effect in the treatment of STZ induced diabetes. A comparison was made with the Glibenclamide, a standard drug used in treating diabetes mellitus.

MATERIALS AND METHODS :

Adult albino Wister rats weighing about 150-200 g were used in the present investigation. All the rats were given a period of acclimatization for 15 days before starting the experiment. They were fed *ad libitum* on commercially available mice feed. Animals were given free access to water.

Streptozotocin was purchased from Sisco Research laboratory Pvt. Ltd. Mumbai and was freshly dissolved in 0.2 ml of 0.1M citrate buffer pH=4.5 (Prakasam *et al*.,2008) at the dose of 50mg/kg body weight and injected intraperitonially within 15 min of dissolution in a vehicle volume of 0.2 mL with 1 mL tuberculin syringe fitted with 24 gauge needle. Diabetes was confirmed by the determination of fasting glucose concentration on the third day (72 Hrs) post administration of streptozotocin.

Dried Root powder of *Salacia reticulata, Salacia macrosperma, Salacia chinensis* and two market samples, sold

under the name- *Saptarangi*, was made, sieved through BSS 85 sieve and were stored in airtight perlpet jar, with proper labeling.

A single dose of Glibenclamide provokes a brisk release of insulin from pancreas. It acts on β cell membrane leading to enhance calcium flux across it, hence degranulation. Daonil (glibenclamide) manufactured by Aventis Pharma Ltd. was collected from market and preserved at room temperature.

Diabetes was induced in all the experimental rats by giving a single dose of 50mg/kg body weight of Streptozotocin. The animals were allowed to drink 5% glucose solution overnight to overcome drug-induced hypoglycemia (Bhandari *et al*. 2008). STZ-induced animals exhibit massive glycosuria and hyperglycemia (Prakasam *et al*. 2008). After three days (72 hours), animals with marked hyperglycemia (blood glucose level above 200mg %) were selected and were used for the efficacy evaluation (Bhandari *et al*,. 2008).

The diabetic, Albino Wistar Rats were divided into the following groups.

Group I consisted of 6 STZ induced diabetic rats and served as diabetic controlled and were given distilled water only.

Group II consisted of 6 STZ induced diabetic rats and were given glibenclamide (modern antidiabetic drug) at the dose of 500 µg/kg body weight for 3 days once a day.

Group III consisted of 6 STZ induced diabetic rats and were given aqueous root powder of *Salacia reticulata* at the dose of 500mg/kg body weight for three days, once a day.

Group IV consisted of 6 STZ induced diabetic rats and were given aqueous root powder of *Salacia macrosperma* at the dose of 500mg/kg body weight for three days, once a day.

Group V consisted of 6 STZ induced diabetic rats and were given aqueous root powder of *Salacia chinensis* at the dose of 500mg/kg body weight for three days, once a day.

Group VI consisted of 6 STZ induced diabetic rats and were given aqueous root powder of market sample (MS1) at the dose of 500mg/kg body weight for three days, once a day.

Group VII consisted of 6 STZ induced diabetic rats and were given aqueous root powder of market sample (MS2) at the dose of 500mg/kg body weight for three days, once a day.

After three days (72 Hrs post treatment) of herbal treatment, the experiment was terminated and observations were made by collecting the blood from the retro-orbital plexus method (Waynforth, 1980) in heparinized 1ml syringes. Blood samples were collected at 0, 1, 2, 3,4,5,6, and 24 hours post herbal dose. The blood samples were immediately centrifuged and the clear plasma was separated. The plasma so obtained was further analyzed for glucose concentrations.

Plasma glucose was determined by the GOD-POD method (Trinder, 1969). Glucose estimation is carried out using SPAN diagnostic kits.

RESULTS AND DISCUSSIONS :

Streptozotocin (the drug that induces diabete in rats) causes selective destruction of β cells of Islets of Langerhans and brings an increased glucose levels. It is evident from the present investigation that the streptozotocin administration at the dose of 50 mg/kg body weight causes significant diabetogenic response in albino rats.

Table 1 shows mean plasma glucose levels (mg/dl) of the animals of different groups. Diabetic animals treated with Glibenclamide (GrpII), showed a significant decrease in the plasma glucose level (343.528dL) P<0.0001 at 3 hrs after 72 hours post Streptozotocin treatment. The diabetic rats treated with the root extract of *Salacia reticulata*, (Grp III), a crude antidiabetic drug, showed a significant decrease in the plasma glucose level at 4hours (325.078 mg/dL) P<0.00001 at 4 hours after 72 hours post Streptozotocin treatment. Plasma glucose level of the animal of Grp IV , treated with root extract of *Salacia macrosperma*, showed less significance (390.763 mg/dL) P<0.025. More interestingly, the animals of Grp V, treated with root extract of *Salacia chinensis* showed a significant decrease in the plasma glucose level at 4 hours after 72 hours post Streptozotocin treatment. (333.201mg/dL) P<0.0001. However the animals treated with two market samples, MS1 and MS2, of group VI and VII, did not show any significant decrease in the plasma glucose level, at 4 hours after 72 hours post Streptozotocin treatment. **Graph 1** indicates the efficacy of three species of *Salacia* and two market samples at 4th hour post dose treatment, while the animals treated with Glibenclamide- a modern antidiabetic drug, (Grp II) showed a significant decrease in the plasma glucose level at 3 hrs after 72 hours post Streptozotocin treatment

Various fractions of the alcoholic extracts of the roots of *S. macrosperma* were evaluated for their antidiabetic activity in alloxan diabetic rats by estimating various biochemical parameters in blood i.e. glucose, proteins, lipids, cholesterol and free fatty acids, after oral administration for 8 days. The alcoholic extract exhibited significant antidiabetic activity. (Venkateshvarlu *et.al,* 1994).

17 fractions of extracts obtained from 11 Tanzanian medicinal plants administered orally to the mice (500mg/kg body weight/day) produced a significant reduction of parasitaemia. It included petroleum ether fraction of the roots of *S. madagascariensis* by (Gessler *et.al,* 1996).

The ethanolic extract of *S. macrosperma* showed a significant hypoglycemic activity in fasted rabbits by Venkateshvarlu *et. al,* (1991). According to Wolf and Weisbrode (2003) the salacinol extract did not show any histopathological indication of toxic effects in male Sprague- Dawley rats. Petroleum ether extract of the root bark of *S. oblonga* (Wall). was studied in STZ diabetic rats and antilipid peroxidative activity of the same was studied in the cardiac tissue. The results suggest that *S.oblonga* possess antidiabetic and antioxidative activity by Krishnakumar *et,al.* (1999).

A change in the body weight is an important factor to monitor the health of the animals. Loss of body weight is frequently the first indication of the onset of the adverse effect. The dose at which the bodies weight loss is 10% or more is considered to be a toxic dose irrespective of whether or not, it is accompanied by any other changes. Animal from all dosage groups did not show decrease in body weight, greater than 10%. Food consumption can indicate an adverse effect of a drug at an early stage. Measurement of water consumption is carried out in studies of diuretic compounds that are known to affect the kidneys. Mortality is a main criterion in accessing the acute toxicity (LD_{50}) of any drug. There was no mortality recorded even at the highest dose levels i.e. 2.0g/kg body weight.

From the results of this study, it is observed that there are no significant changes in body weight, food and water consumption by the animal from all dosage groups. (0.5 g/Kg body weight to 2.0 g/Kg body weight). There is no mortality recorded even at the highest dose level i.e. 2.0g/Kg body weight, which proves that the plants *S. reticulata. S.macrosperma* and S. *chinensis* root extract has no significant

toxic effect in mice.

The limitations of currently available oral anti-diabetic agents either in terms of efficacy/safety coupled with the emergence of the disease into a global epidemic have encouraged a concerned effort the world over to discover drugs that can manage diabetes more efficiently (Chakraborti and Rajgopalan, 2002). This study tries to assess antidiabetic property of three species of *Salacia* and two market samples of *Salacia*, which are sold for the treatment of diabetes. Streptozotocin is the most extensively used model and is relatively the easiest. Besides, it is a well-described model to study the effect of the antidiabetogenic agent (Mallick *et. al*, 2006).

The STZ- induced diabetes is regarded as a meaningful model of type 1 diabetes and also resembles many of the features of human Diabetes mellitus (Senthikumar and Subramanium,2008; Senthikumar *et. al*, 2006).

Streptozotocin is more selective for beta cells with less general toxicity than of alloxan. STZ induces oxidative stress. Oxidative stress is caused by a relative overload of oxidants i.e. reactive oxygen species. Once, STZ enters inside the cell, it is able to spontaneously decompose to form an isocyanate compound and a methyldiazohydroxide. Isocyanate compound and methyldiazohydroxide undergoes intramolecular carboxylation and alkylation of cellular components respectively. The DNA damage of β cells of pancreas mainly by alkylation with carbonium ion produced by methyldiazohydroxide (Selvan *et.al,* 2008).

Streptozotocin also depresses the hepatic NAD levels, while alloxan does not (Hoftiezer and Carpenter, 2003),

Maximum reduction in blood glucose was observed after three hours of administration of aqueous decoction of *Salacia reticulata*, which persisted up to 5 Hrs, suggesting its antidiabetic potential (Karunayaka, *et al*. 1984).

When 0.5 g/Kg,1.0g/Kg and 5g/kg doses of *S. reticulata* were dosed to the rats, reduced the plasma glucose levels by 42.8%; and 87.5% respectively.(Serasinghe *et,al*.1990).

Randomized double blind clinical trial to investigate the effect of an herbal tea containing *S.reticulata* in patients with type II Diabetes mellitus as assessed by HbA1C, A statistically significant fall in HbA1C was seen with tea, compared to a rise in HbA1C with the placebo group which concluded that the tea is an effective and safe treatment for type II diabetes. (Jayawardena *et al* 2005).

A study on hydroalcoholic extract of S.reticulata at the dose of 500mg/kg P.O. reduced significantly the serum glucose level when compared to the control group in hydrocortisone induced hypoglycemia model (Rabbani *et, al*. 2006).

A water soluble fraction (25-100mg/Kg per orally) prepared from roots and stems of *S,reticulata* strongly inhibited elevated serum glucose level after the administration of sucrose or maltose. (Yoshikawa *et, al*.2001).

In an animal model of type II diabetes, magniferin and its glucosides lowered its blood glucose levels at a dose of 30mg/Kg P.O. for two weeks and significantly improved hyperinsulenemia, which concluded that magniferin probably decreases blood sugar level through decreasing insulin resistance. (Ichiki *et,al.*1998).

The study on antidiabetic activity of various fractions of the alcoholic extract of roots of *S.macrosperma* in alloxan-diabetic rats, showed that the methanolic fraction followed by residual fractionation of the alcoholic extract exhibited significant antidiabetic activity. (Venkateshwarlu *et, al*. 1991).

The hypoglycemic activity of root bark of *S.prenoides* againsed alloxan induced diabetes in the rats proved its potential as antidiabetic plant. (Pillai *et,al.* 1979).

The studies on two compounds from the root bark of S.oblonga from chloroform eluted fraction of the petroleum ether extract which demonstrated about 60% and 76% hypoglycemic activity in albino rats. This indicate the therapeutic importance of *S.oblonga* . (Augusti *et, al.* 1995).

The antidiabetigenic activity of mehanolic extract from the stem of *S.chinensis* showed its potent anti-hyperglycemic effect in oral sucrose or maltose loaded rats. (Yoshikawa *et, al.* 2003).

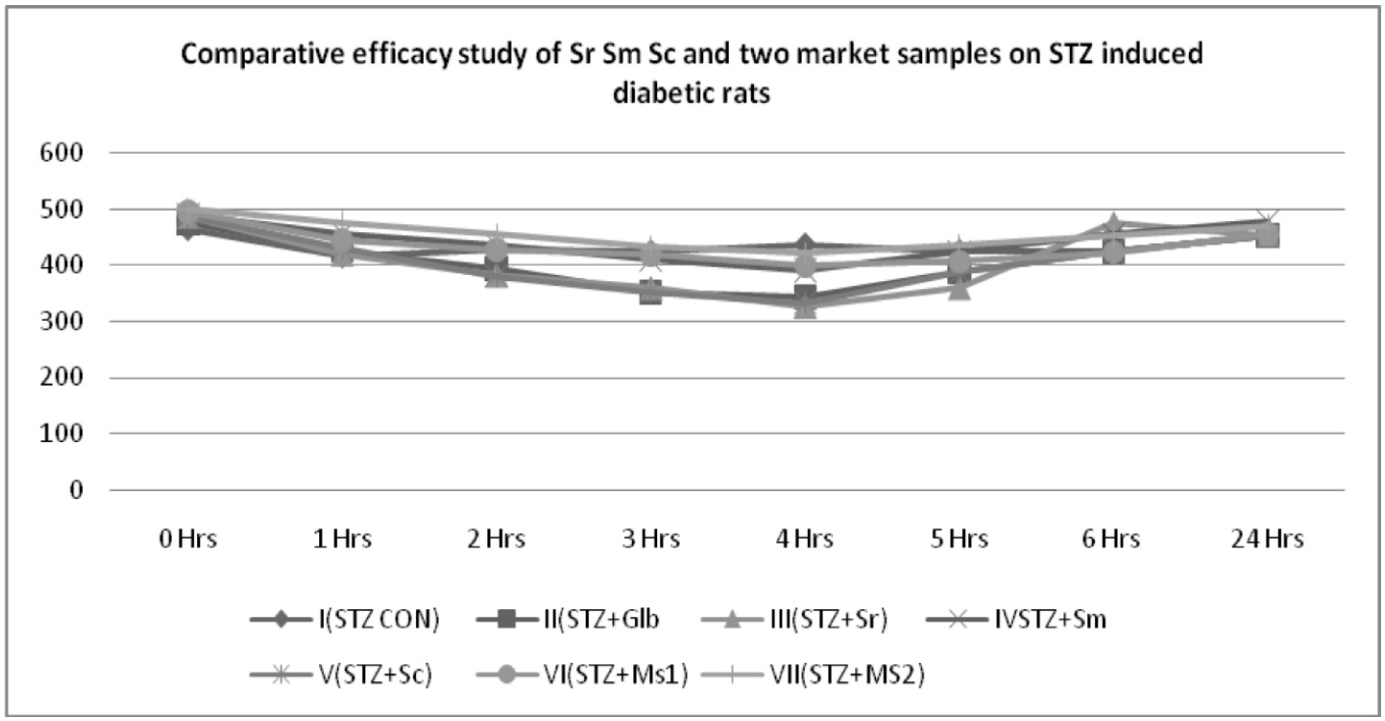
In the present study, antidiabetic properties of *S.macrosperma*, *S. chinensis* and two market samples of *S. reticulata*, sold in the market under the commercial name, Saptarangi, were compared with *S. reticulata* a crude antidiabetic drug,.

Table 1:-Mean Plasma glucose levels (mg/dl) of the animals of different groups. (72 hours post Streptozotocin treatment)

Group	0 Hrs	1 Hrs	2 Hrs	3 Hrs	4 Hrs	5 Hrs	6 Hrs	24 Hrs
I (STZ CON)	463.401	414.933	426.336	423.581	435.966	424.726	423.763	453.11
II (STZ+Glb	475.818	426.163 NS	394.778 ***	343.528 *******	351.786 ****	388.338	425.381	452.77
III (STZ+Sr)	485.628	418.143 NS	381.025	358.111	325.078 *******	358.343	473.12	452.596
IV (STZ+Sm)	488.326	454.538 NS	434.343	409.523	390.763 ***	422.851	453.538	477.16
V (STZ+Sc)	485.301	429.915 NS	381.311	351.786	333.201 ******	387.338	425.378	452.673
VI (STZ+Ms1)	495.013	444.425 NS	427.326	418.18	398.425 ***	406.378	422.535	455.783
VII (STZ+MS2)	499.523	475.513 NS	454.835	431.81	421.153 NS	435.135	452.223	470.081

******* p<0.0001,**** p<0.0050.,*** p<0.025.,** p<0.050.,N.S- Not significant

Graph 1:- Graph showing Comparative efficacy study of three species of *Salacia* species.



CONCLUSION:-

Results of efficacy studies conclusively prove the antidiabetic potential of genus *Salacia*, *Salacia reticulata* in particular. Therefore *S. chinensis* can be a good substitute for *S. reticulata,* as *S. reticulata* is rare, endemic and endangered.

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