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#### **Research Article**

# Investigation of Anti-diabetic potential of the Flowers of *Hibiscus syriacus* L. Plant

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#### ABSTRACT

The present study was carried out to identify the phytochemicals and evaluate the anti-diabetic activity of *Hibiscus syriacus* L. Ethanol and aqueous extracts were studied for the Oral Glucose Tolerance Test (OGTT) study and sub-acute effects on alloxan-induced diabetic rats. Blood glucose levels, serum lipid profiles and histopathological study of the pancreas were performed. Alloxan induced diabetes in rats by damaging the beta cells of the pancreas. After *H. syriacus* L. treatment blood glucose, TC, TG, LDL and VLDL of all tested rats were significantly decreased and at the same time HDL was increased in alloxan-induced diabetic rats. However, the ethanolic extract of *H. syriacus* showed more significant anti-diabetic activity than the aqueous extract. The results reveal that *H. syriacus* L. flowers extract may have potent anti-diabetic activity, justifying the use of the drug for the treatment of diabetes mellitus.

#### INTRODUCTION

Diabetes mellitus (DM) is a combination of heterogeneous disorders commonly presenting with episodes of hyperglycaemia and glucose intolerance due to lack of insulin, defective insulin action, or both. [1] Untreated diabetes can eventually lead to CVS disorder, stroke, kidney disease, blindness, and damage to the nerves of feet. [2] The number of people living with diabetes is expected to rise from 366 million in 2011 to 552 million by 2030. [3] Diabetes mellitus is categorized into 2 types. Type 1 DM results from the body's failure to produce enough insulin and is referred to as "insulin-dependent diabetes mellitus" or "juvenile diabetes". Type 2 DM begins with insulin resistance, a condition in which cells fail to respond to insulin properly and the condition is referred to as "non-insulin-dependent diabetes mellitus" or "adult onset diabetes". [4]

P. Swaroopa *et al.* have mentioned in their review about various plant species such as *Acorus calamus, Aegle marmelos, Afzelia Africana, Alstonia scholaris, Azadirachta indica, Caesalpinia bonducella, Lantana camara, Ficus benghalensis, Gymnema sylvestre along with thirty plant species reported for their hypoglycemic properties.<sup>[5]</sup> The <i>Hibiscus syriacus* Linn. is a shrub belonging to Malvaceae family, distributed in most of Eastern and Southern Asia. The flower, fruit, root, stem, and skin of *H. syriacus* share various pharmacological activities and have been widely used as a traditional Chinese medicine ingredients.<sup>[6]</sup> The genus Hibiscus is widely distributed over Korea, China, India and Siberia.

Its name indicates that it was first identified in Syria.<sup>[7]</sup> The dried flower of H. syriacus L. is used commercially as a tea in Europe. Different species of the plant Hibiscus

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already reported for their Anti Diabetic properties and the water-soluble mucilage's extracted from the leaves of H. syriacus L. also exhibits hypoglycemic activity. [8-10] However, the aqueous extract of the leaves has antimycobacterial activity. The root bark of H. syriacus L. is used in folk medicine as an anti-pyretic, anthelmintic, wound healing, fungicide, and hematochezia treatment. Furthermore, its root bark exhibits antioxidant and significant cytotoxic activities. [11-16]

The present study was undertaken to identify phytochemicals and evaluate the anti-diabetic activity of H. syriacus L. flowers to develop a natural anti-diabetic drug.

## MATERIALS AND METHODS

#### **Plant Material**

Hibiscus syriacus L. flowers were collected from August to September from the garden of G.R.Y. Institute of Pharmacy, Vidya Vihar Borawan, Khargone (M.P.)

#### **Identification and Authentication of Plant**

The plant *Hibiscus syriacus* L. was identified and authenticated by Dr. S.K. Mahajan, (Retd) Botanist from Government College, Khargone, Madhya Pradesh. The herbarium of the plant specimens was prepared and deposited in the Department of Pharmacognosy, G.R.Y. Institute of Pharmacy, Vidya Vihar Borawan district Khargone Madhya Pradesh, India, under voucher no. G.R.Y.I.P. 43.

### **Preparation of Extract**

The flowers were shade dried, grounded into coarse powder, and passed through the seive. The dried flowers powder (1000g) was extracted at room temperature with petroleum ether for defating for 7 days with occasional shaking followed by re-maceration with ethanol and water. The macerates were filtered and concentrated to dry residue. The dry extracts were kept in a vacuum desiccator until use.

## **Physicochemical Analysis**

For physicochemical analysis, flowers of *H. syriacus* L. were collected and shade dried. Physical constants were determined following the Indian Pharmacopoeia. It includes ash value, extractive value, and moisture content.

## **Preliminary Phytochemical Analysis**

The ethanolic and the aqueous extract were tested qualitatively for the presence of various phytoconstituents such as flavonoids, phenolic acids, anthocyanins, quinones, alkaloids, tannins, and saponins using standard phytochemical methods. Phytochemical tests were carried out following Shah and Quadry and Kokate  $et\ al.^{[17,18]}$ 

## PHARMACOLOGICAL STUDY

## **Experimental Animals**

Healthy albino rats of either sex weighing about 150–200 g were used during the study. The animals were obtained from the G.R.Y. Institute of Pharmacy, Borawan, dist. Khargone (Madhya Pradesh). Before the initiation of the experiment, the rats were acclimatized for a period of 5 days. Standard environmental conditions such as temperature ranging from 18 to 32°C, relative humidity (70%), and 12 hours dark/light cycles were maintained in the quarantine. All the animals were fed with rodent pellet diet and water under strict hygienic conditions. The experiment was carried out according to the guidelines of the Committee for the Purpose of Control and Supervision of Experimental on Animals, New Delhi, India, and the research protocol was approved by the Institute animal ethical committee (1151/ac/07/CPCSEA).

### **Experimental Design**

Screening of *Hibiscus syriacus* L. ethanol and aqueous extract for anti-diabetic action was done in rats by conducting glucose tolerance test (GTT) study and evaluating their effects (Multi dose treatment study) on blood glucose level, Serum lipid profiles and histopathology of pancreas in alloxan diabetic rats.

## **Acute Oral Toxicity Study**

An acute oral toxicity study was carried out as per OECD - 423 guidelines to determine the minimum lethal dose of ethanolic and aqueous flowers extract of *H. syriacus* L. Wistar albino rats of either sex weighing 150–200 gm were used. The experimental animals were kept fasting overnight, providing only water, after which the extracts were administered orally at 2000 mg/kg. They were observed continuously for any behavioral changes and toxic manifestations like hyperactivity, changes in the skin, fur, convulsions, excretion, pupil dilation, sedation, hypothermia, and mortality during the first 4 hours, periodically during the first 24 hours. After that the animals were continuously monitored at regular intervals for 7 days. No deaths or hazardous signs were detected in the rats during the 7 days of observation. Hence 400mg/kg dose of the extracts was taken for the following experiment.

#### **Induction of Diabetes**

The rats were randomly divided into 5 groups containing 6 animals in each group. To induce diabetes, a freshly prepared solution of alloxan (120 mg/kg body weight) dissolved in sterile normal saline, was administered intraperitoneally (i.p.) to group II, III, IV & V. The fasting blood glucose was determined after 72 hours to confirm the induction of diabetes. The diabetic rats were stabilized for 5 days and the next day (Day 0) experiment was started. Rats showing a blood glucose level above 230 mg/dl were taken for the study. [19]

## **Oral Glucose Tolerance Test (OGTT)**

Fasting blood glucose level of each rat was determined at zero time after overnight fasting with free access to water. Rats were divided into four groups containing six rats each. The first group of animals received 1 mL of 1% gum acacia suspension orally (Control animals). The remaining groups received Metformin (150 mg/kg/p.o Standard) and H. syriacus L. ethanol and aqueous extracts (400 mg/kg), by oral route using an orogastric tube. Glucose (2 gm/kg) was orally administered 30 min. after the administration of extract or Metformin or gum acacia suspension. Blood samples were collected from the tail vein under ether anesthesia just prior to and 30, 60, 120 and 240 min after glucose loading. Glucose levels were estimated by commercially available glucose strips using One Touch Glucometer.

## Effect of *H. syriacus L.* Ethanol and Aqueous Extracts on Blood Glucose Levels and Serum Lipid Profiles in Alloxan-induced Diabetic Rats [Multi Dose (sub acute) Treatment]<sup>[20]</sup>

A single intraperitoneal injection of 120 mg/kg of alloxan monohydrate was employed to induce diabetes in overnight fasted male Wistar albino rats weighing 150-200 gm. After 72 hr animals with blood glucose levels higher than 250 mg/dl were considered diabetic and were included in the study. Animals were divided into five groups containing six animals in each.

*Group I:* Normal control rats received 1 ml of 1% gum acacia suspension.

*Group II:* Diabetic control rats received 1 ml of 1% gum acacia suspension.

 $\it Group~III:$  Diabetic rats received standard drug Metformin 150 mg/kg.

*Group IV:* Diabetic rats received ethanolic extract of *H. syriacus* L. (EEHS) 400 mg/kg.

*Group V:* Diabetic rats received aqueous extract of *H. syriacus* L. (AEHS) 400 mg/kg.

In this study, these rats were given the same doses of the extract once daily for 21 days. Blood samples were collected from the tail vein of non-fasted rats on days 0, 7, 14 and 21<sup>st</sup> day of extract administration and blood

 $\textbf{Table 1:} \ \textbf{Qualitative phytochemicals screening of} \ \textit{H. syriacus flowers} \\ \textbf{extracts}$ 

S.No.	Phytochemical constituents	Pet. Ether extract	Ethanolic extract	Aqueous extract
1	Carbohydrate	-	+	+
2	Glycoside	-	+	+
3	Proteins	-	+	-
4	Flavonoids	-	+	+
5	Tannins	+	+	+
6	Alkaloids	-	-	+

**Key**: Present phytochemicals are represented by (+) sign, absent phytochemicals are represented by (-) sign.

glucose levels were estimated using glucometer. Serum lipid profiles on day 21 were measured by an autoanalyzer.

#### **Blood Glucose Estimation**

Animals were kept fasted overnight. Blood sampling was done by sterilizing the tail with 10% alcohol and then nibbling the tail at the start of the experiment. After the operation, the tips of the tails were sterilized by swabbing with 70% ethanol. Fasting blood glucose was estimated by commercially available glucose strips using One Touch Glucometer and repeated on 0<sup>th</sup> day, 7<sup>th</sup>, 14th, and 21<sup>st</sup> day.

# Histopathological Studies<sup>[21]</sup>

Pancreatic tissues from rats of all groups of Multi-dose (Sub acute) treatment were subjected to histopathological studies. The whole pancreas from each animal was removed after sacrificing the animal under anesthesia and was collected in 10% formalin solution and immediately processed by the paraffin technique. Sections of 3-5  $\mu m$  thickness were cut and stained by hematoxylin and eosin for histological examination.

## **Statistical Analysis**

All the data were expressed as mean  $\pm$  S.E.M for 6 rats in each group. Statistical analysis was carried out using Student's t-test to analyze the significance between the groups. A value of p < 0.05 was considered to be significant.

#### RESULTS

## **Physicochemical Parameters**

After estimating physical constants, the results obtained were total ash 10% w/w, Acid Insoluble ash 0.24% w/w, water soluble ash 6.5% w/w, water soluble extractive value 30.4% w/w, Alcohol soluble extractive 14.4% w/w and moisture content 9.8% w/w.

#### **Phytochemical Investigation**

Successful evaluation of botanical phytocompounds from plant material largely depends on the type of solvent used in the extraction procedure. The result of the phytochemical screen showed the presence of tannins, glycosides, protein, flavonoids, carbohydrates, and alkaloids in flowers of *H. syriacus* L. (Table 1).

## **Acute Toxicity Study**

Acute toxicity study revealed no mortality or any toxic reactions with oral administration of ethanol and aqueous extracts of flowers of H. syriacus L. even at the highest dose (4000 mg/kg). The biological evaluation of extracts are carried out at 1/10 doses of  $LD_{50}$ .

## **Oral Glucose Tolerance Test (OGTT)**

Ethanol and Aqueous extracts of flowers of *H. syriacus* L. significantly improved the glucose tolerance test up to 4 h (Table 2 and Fig. 1). Approximately 18 and 7% reduction in blood glucose level was observed in control values at the



2 and 4 hours, respectively. The Metformin also improved the glucose tolerance test up to 4 hours.

## Anti-diabetic Effect of H. syriacus

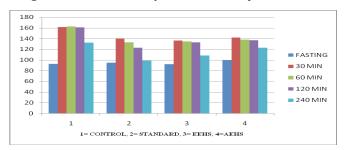
The anti-diabetic effect of different extracts of *H. syriacus* L. flowers on fasting blood glucose level is presented in Table 3 and Fig. 2. Alloxan-induced diabetic rats showed significant (p < 0.001) difference in blood glucose level compared to normal control. The blood glucose level of diabetic rats was estimated before and after 1st, 7th and 14th days of treatment. Continuous administration of EEHS and AEHS significantly (p < 0.05) reduced the blood glucose levels to 152 and 173 mg/dL, respectively. till 21st day (Table-3 and Fig. 1). However, the ethanolic extract of H. syriacus L. with dose of 400 mg/kg body weight had a greater reduction in Blood glucose level than the aqueous extract after 21 days of treatment administration. Similarly, the metformin-treated group revealed significant (p < 0.05) reduction in BGL on the 7<sup>th</sup>, 14<sup>th</sup> and 21<sup>st</sup> days. There is also a statistically significant (p < 0.05) difference between the activity of the aqueous extract and the ethanolic extract.

In serum lipid profiles study on day 21, diabetes induced by alloxan lead to significant changes in levels of Serum cholesterol, triglyceride, LDL, VLDL, and HDL. When compared to Normal control, serum total cholesterol (TC), triglyceride (TG), low-density lipoprotein (LDL) and Very low-density lipoprotein (VLDL) increased and high-density lipoprotein cholesterol (HDL) decreased clearly in Diabetic rats. After the treatment of ethanol and aqueous extracts of flowers of *H. syriacus* L. (400 mg/kg) and metformin in hyperlipidemic rats for 21 consecutive days, there was a significant decrease in serum lipids (TC,

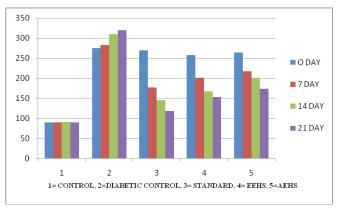
TG, LDL and VLDL), while there was marked increase in HDL.

## **Histopathological Studies**

Histopathological examination of pancreas of these animals showed comparable regeneration of Islets of Langerhans and ß cells by ethanol and aqueous extracts



**Fig. 1:** Effect of *H. syriacus* Flower extracts on the blood glucose levels in glucose loaded rats



**Fig. 2:** Effect of *H. syriacus* extracts on the blood glucose levels in Alloxan induced diabetic rats (Multi dose treatment/sub acute study)

Table 2: Effect of *H. syriacus* Flower Extracts on the blood glucose levels in glucose loaded rats

Ехр		Blood glucose concentration (mg/dL) (mean ± S.E.M.)				
Groups	Treatment	Fasting	30 min	60min	120 min	240 min
1	Normal control	92.8 ± 2.9	161.6 ± 4.1	162.7 ± 2.6	161.2 ± 3.5	132.6 ± 3.2
2	Metformin (150 mg/kg)	95.0 ± 3.8	140.0 ± 2.6*	132.7 ± 1.9*	122.8 ± 1.6*	98.6 ± 3.1*
3	Hibiscus syriacus Ethanol extract (400 mg/kg)	92.0 ± 5.2	136.0 ± 3.2*	134.5 ± 2.3*	133.0 ± 4.2*	108.03 ± 2.5*
4	Hibiscus syriacus Aqueous extract (400 mg/kg)	99.5±3.7	142.0±3.6	138.1±4.2*	136.8±2.5	122.7±3.2*

Significantly different from control: \* p < 0.05

Table 3: Effect of *H. syriacus* Extracts on the blood glucose levels in alloxan-diabetic rats (Multidose treatment /sub acute study)

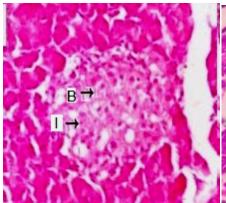
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Groups	0th Day	7th Day	14th Day	21st Day
Control	89.33 ± 1.85	89.83 ± 1.72	90.00 ± 1.86	89.16 ± 1.81
Diabetic Control	275.16 ± 1.40	282.16 ± 2.05	309.16 ±1.01	319.50 ± 1.68
Standard	269.66 ± 1.38	176.50± 1.33	144.50 ± 2.48	118.16 ± 1.92 5
EEHS	256.83 ± 1.19**	200.16± 1.95**	167.16 ± 2.02**	152.50 ± 2.06**
AEHS	263.33± 1.99*	216.66 ± 1.76*	200.66 ± 2.20*	173.66 ± 1.58

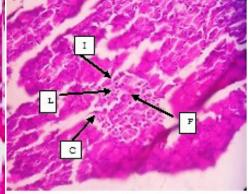
Data represent means  $\pm$  S.E.M.; P values were analyzed using Student's t-test, \*p < 0.05 (less significant), \*\*p < 0.05 (more significant), When groups IV and V compared with diabetic control i.e. group II.

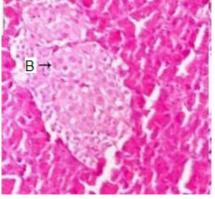
**Table 4:** Effect of *H. syriacus* Flower Extracts on the Serum lipid profiles in Alloxan-diabetic rats after 21 days of treatment

Ехр		Blood glucose concentration (mg/dl) (mean ± S.E.M.)					
Groups	Treatment	TGL mg/dl	HDL mg/dl	VLDL mg/dl	LDL mg/dl	Total Cholesterol mg/dl	
1	Normal control	74.83 ± 2.4	56.3 ± 1.8	25 ± 2.8	25 ± 1.8	58.3 ± 2.8	
2	Diabetic Control	132 ± 3.5	42.2 ± 2.1	42.3 ± 2.3	37.7 ± 1.2	92.2 ± 4.5	
3	Metformin (150mg/kg)	92 ± 2.6	48 ± 1.8	29.3 ± 2.9	28.2 ± 3.1	62.3 ± 1.4	
4	Hibiscus syriacus Ethanol extract (400mg/kg)	109 ± 3.2	51.3 ± 0.7	35.2 ± 3.6	29.2 ± 2.5	75.4 ± 2.3	
5	Hibiscus syriacus Aqueous extract (400mg/kg)	118 ± 2.6	50.5±0.9	39.8±2.9	35.2±3.7	82.6±2.8	

Significantly different from control: \* p < 0.05



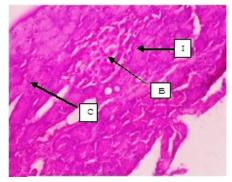




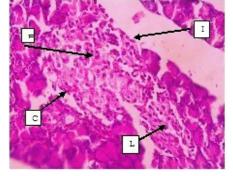
(3A) Histopathological study of Normal Control rat B= Beta cells, I= Islets of Langerhans

(3B) Histopathological study of Diabetic Control rat I= Islets of Langerhans, L= lymphocytes, C= Congestion, F=fibrosis

(3C) Histopathological study of Standard group B= Beta cells



(3D) Histopathological study of Aqueous extract treated group I= Islets of Langerhans, L= lymphocytes, B= Beta cells



(3E) Histopathological study of Ethanol extract treated group I= Islets of Langerhans, L= lymphocytes, C= Congestion, F=fibrosis

 $\textbf{Fig. 3:} \ Histopathological \ Figures \ of \ rat \ pancreases \ after \ 21 \ days \ of \ treatment \ of \ \textit{Hibiscus syriacus} \ Flowers \ Extracts$ 

of Hibiscus syriacus L. and Metformin, which were earlier under necroses by alloxan. Fig. (3A-3E) depicts the islets of the pancreas of rats in different groups. Histopathology (Fig: 3B) of the diabetic control group showed reduced cellular population and extensive damage of the islets of Langerhans and they appeared to be irregular. Treatment of diabetic rats with Metformin showed moderate expansion of cellular population and size of islet cells (Fig: 3C). However, ethanol and aqueous extracts (400 mg/kg) treated-diabetic rats showed partial restoration of normal cellular population and size of islet cells (Fig 3D & 3E).

## **Discussion**

The overall findings show that ethanol and aqueous extracts of *H. syriacus* L. flowers possess marked antihyperglycemic activity, which was proved by improving glucose tolerance test and lowering the blood glucose levels in alloxan-induced diabetic rats in multi dose (sub acute) treatment studies. The ethanol extract of *H. syriacus* L. and metformin exhibited remarkable blood glucose lowering effect in glucose tolerance test. The hypoglycemic effect of plant extract comparable to metformin, suggests that the test extracts may act by regenerating the ß cells in



alloxan- & induced diabetes. Alloxan causes diabetes through its ability to destroy the insulin-producing & cells of the pancreas.

In vitro studies have shown that alloxan is selectively toxic to the pancreatic ß cells, causing cell necrosis. The cytotoxic action of alloxan is mediated by reactive oxygen species, with a simultaneous massive increase in cytosolic calcium concentration, leading to a rapid destruction of ß cells.<sup>[22]</sup>

Our study observed pancreas damage in alloxantreated diabetic control rats (Fig. 3B). The metformintreated group showed regeneration of ß cells (Fig. 3C). The comparable regeneration of ß cells was also shown by ethanol and aqueous extracts of Hibiscus syriacus L. (Fig. 3D & 3E). The anti-diabetic activity of *H. syriacus* L. may be due to the presence of flavonoids. It is reported that flavonoids constitute the active biological principles of most medicinal plants with hypoglycemic and antidiabetic properties.<sup>[23]</sup> After *H. syriacus* L. treatment, blood glucose, TC, TG, LDL and VLDL of all tested rats were significantly decreased and at the same time, HDL was increased. This provided evidence in support of the view that H. syriacus L. could play an important role in treating diabetic patients. Our study reveals that the plant containing flavonoid phytoconstituent may produce hypoglycemic potential.

#### CONCLUSION

We concluded from the proposed study that H. syriacus L. ethanol and aqueous extracts produce significant anti-diabetic activity. However, ethanol extract (400 mg/kg) treated-diabetic rats showed better restoration of normal cellular population and size of islet cells than aqueous extract. This anti-diabetic potential of extract may be due to flavonoid constituent present therein. However, these preclinical data help us carry out clinical trials to discover promising medicine to treat diabetes and hyperlipidemic disorders in the future.

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#### ABBREVIATIONS

DM: Diabetes mellitus

OECD: Organization for Economic Cooperation and Development

EEHS: Ethanolic extract of *Hibiscus syriacus* AEHS: Aqueous extract of *Hibiscus syriacus* 

WHO: World Health Organization

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