IJPSR (2019), Volume 10, Issue 1 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 16 May 2018; received in revised form, 19 July 2018; accepted, 25 July 2018; published 01 January 2019

SCREENING OF *SIMAROUBA GLUACA* FOR ANTIDIABETIC AND ANTIOXIDANT ACTIVITIES

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Keywords:

Methanolic extract, *Simarouba glauca*, Streptozotocin, Antidiabetic, Insulin, Antioxidant

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ABSTRACT: The objective of the study was to evaluate the antidiabetic activity of methanolic extract of *Simarouba glauca* in STZ induced diabetes in rats for type I diabetic mellitus. The leaves of *Simarouba glauca* were dried under shade and then powdered, and extracted with 90% methanol by reflux. Preliminary phytochemical studies and acute toxicity studies were also carried out on a methanolic extract of *Simarouba glauca*. After overnight fasting, for type I diabetes was induced in rats by i.p. Injection of STZ, at a dose of 65 mg/kg/b.w. Group A served as normal control while group B was considered as diabetic control. Group C was standard receiving insulin 4 U/kg, and Group D diabetic animals were treated with *Simarouba glauca* (250 mg/kg and 500 mg/kg). During the study, body weight and fasting blood glucose level were taken at 0 and 30th day. At the end of the study, animals in all groups were sacrificed; blood sample, pancreas, and liver were collected - biochemical parameters such as lipid profiles, SGOT, SGPT, HbA_{1C} and antioxidative activity. Histopathological studies of pancreas and liver were performed. *Simarouba glauca* showed decreased blood glucose levels and improved body mass and also showed improvisation in lipid profile, HbA_{1C} of the normal control was found to be 6.2%, diabetic control 14.83% and the preventive group was 10.42% for the lower dose, and in a higher dose, we were got 8%. Similarly, SGPT and SGOT, we were found significantly reduced compared to diabetic control. The antioxidant activity showed a significant reduction. Hence, it may facilitate to prevent diabetic complication.

INTRODUCTION: Diabetes was one of the first diseases described, with an Egyptian manuscript from C.1500 BCE mentioning too great emptying of the urine. The first described cases are believed to be of type 1 diabetes. Indian physicians around the same time identified the disease and classified it as madhumeha or "honey urine noting the urine would attract ants.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.10(1).294-02

The article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.10(1).294-02

World Health Organization estimates that about 347 million people worldwide have diabetes, India accounts for the largest number of people suffering diabetes -50.8 million [1]. Type 1 diabetes mellitus is characterized by loss of the insulin-producing beta cells of the islets of langerhans in the pancreas, leading to insulin deficiency.

This type can be further classified as immune-mediated or idiopathic. The majority of type 1 diabetes is of the immune-mediated nature; in which beta cells lose is a T-cell-mediated autoimmune attack. There is no known preventive measure against type 1 diabetes, which causes approximately 10% of diabetes mellitus cases in North America and Europe.

Most affected people are otherwise healthy, and of a healthy weight when onset occurs, sensitivity and responsiveness to insulin are usually normal, especially in the early stages [2]. Pancreas transplant has been tried with limited success in type 1 DM. Experimental replacement of *β*-cells (by transplant or from a stem cell) is being investigated in several research programs islet cell transplantation is less invasive than a pancreas transplant which is currently the most commonly used approach in humans. In one variant of this procedure, islet cells are injected into the patient liver, where they take up residence and is to produce insulin. Diabetes without proper treatments can cause many complications. Acute complication included hypoglycemia, diabetic ketoacidosis, or non-ketotic hyperosmolar coma.

Serious long-term complications include cardiovascular disease, chronic renal failure, and diabetic retinopathy (retinal damage). Adequate treatment of diabetes is thus important, as well as blood pressure control and dietary therapy and exercise are critical both in preventing and managing DM, and the results of the diabetes prevention program research group indicate that changes in lifestyle (7% weight loss and 150 min of physical activity per week) reduces the incidence of diabetes by 58%. Smoking should be avoided as it not only increases the prevalence of diabetes, regardless of exercise, strict diet, and low body mass index, but it greatly increases the probability of patients developing large vessel disease in the presence of DM [3].

Plants have always been among the common sources of medicines, either processed as traditional preparations or used to extract pure active principles. Because of the large chemical diversity among natural products, many research groups screen plant extracts in their search for new promising therapeutic candidates for infectious diseases [4]. *Simarouba glauca* is a species of flowering tree that is native to Florida, South America, and the Lesser Antilles. Common names include paradise-tree, dysentery-bark, and bitter wood. *Simarouba glauca* is one of the important herbal drugs used against dysentery hence its bark is also known as dysentery bark. The bark and leaf extract of Simarouba is well known for its different types of pharmacological properties such as hemostatic, antihelminthic, antiparasitic, anti-dysenteric, antipyretic and anti-cancerous. The bark is used to cure fever, malaria, stomach and bowel disorders, hemorrhages, amoebiasis as well as leaf, fruit pulp and seeds are possessing medicinal properties such as analgesic, antimicrobial, antiviral, astringent emmenagogue, stomachic tonic, and vermifuge. The crushed seeds are used as Antigo against snake bites. The crude drug contents and active principles such as glaucarubin, quassinoids, ailanthinone, benzo-quinone, hola-canthone, melianone, simaroubidin, simarolide, simarubin, simarubolide, sistosterol. These are mainly involved in pharmacological activities of this plant [5].

Herbal medicines are frequently considered to be less toxic and freer from side effects than synthetic ones. The use of traditional treatments for diabetes generally declined in occidental societies. *Simarouba glauca* leaves extract were reported to many activities. *Simarouba glauca* extracts were capable of scavenging H_2O_2 in a concentration-dependent manner. Extracts were highly effective in scavenging free radicals such as DPPH and chelating ferrous iron. The scope of this study is to explore the antidiabetic especially focus on type I diabetes and antioxidant activities of leaves of *Simarouba glauca* in animal models.

MATERIALS AND METHOD: The fresh leaves of *Simarouba glauca* were collected and authenticated by Botanist, Bangalore. For future references; (Karnataka College of Pharmacy, Department of Pharmacology, Bangalore, India).

Preparation of Extract: The leaves of *Simarouba glauca* were, chopped into small pieces and dried under shade at room temperature for seven days. The dried leaves were powdered and passed through the sieve (coarse10/40). The powder was used for the preparation of methanolic extract.

Method for Extraction: Each 100 g powder was subjected to extraction with 1000 ml methanol in a reflux condenser for 3 cycles of 7 h each till the volume reduced to half. The extract was filtered through Whatmann filter paper no.1 and evaporated to dryness to get constant weight. And methanolic extract was subjected to preliminary phytochemical screening [6, 7, 8, 9].

Phytochemical Analysis of *Simarouba glauca*: Preliminary qualitative analysis of *Simarouba glauca* was analyzed qualitatively.

Experimental Animals: Wistar rats weighing 200-250g were used for the experiment. They were acclimatized for one week before the experiment. Animals were caged in a fully ventilated room, were maintained in 12:12 h light and dark cycle and were housed at a temperature of 25 ± 2 °C. They had free access to a standard chow diet and water *ad libitum*. All the experiments conducted on the animals were by the standards set for the use of the laboratory animal use, and the experimental protocols were duly approved by the IAEC (Institutional Animal Ethical Committee) of Karnataka College of Pharmacy, Bangalore.

Reg. no. 1564/PO/Re/S/11/CPCSEA, date of registration 27/02/2017

Experimental Design:

Acute Oral Toxicity Study: The acute oral toxicity study was performed according to the OECD guidelines no. 425.

Streptozotocin-Induced Diabetes Mellitus:

Induction of Diabetes: [10] Diabetes was induced in 16 h fasted Male rats (200-250 g) by intraperitoneal injection of 65 mg/kg body weight of streptozotocin. Streptozotocin was dissolved in 0.1 M cold sodium citrate buffer (pH 4.5) immediately before use. The rats were then given 5% w/v glucose solution in feeding bottles for the next 24 h in their cages to prevent hypoglycemia. After 72 h, rats with marked hyperglycaemic fasting blood glucose> 180 mg/dL were selected and used for the study 64. All the animals were allowed free access to tap water and pellet diet and maintained at room temperature in polyethylene cages. The rats were divided into following groups consisting of six rats' each [11].

Group 1: Administered vehicle serves as Normal control.

Group 2: Administered Streptozotocin (65 mg/kg i.p.) serves as diabetic control

Group 3: Administered Reference standard, Insulin (4U/kg, i.p.)

Group 4: Diabetic rats treated with the methanolic extract of *Simarouba glauca* (250 mg/kg, p.o. once daily).

Group 5: Diabetic rats treated with the methanolic extract of *Simarouba glauca* (500 mg/kg, p.o. once daily).

Body weights of rats were taken at the end of the treatment using electronic balance. Fasting blood glucose level of rats were taken on before and after the treatment, *i.e.*, 0, and 30th day of treatment by using one-touch glucometer by vein puncture. At the end of the experimental period, all the animals were anesthetized using a high dose of Phenobarbital for tissue histology. Blood collected by Cardiac puncture was centrifuged at 2500 rpm for 15 min and analyzed for various biochemical parameters, antioxidant and glycosylated hemoglobin (HbA1c).

Histopathological Studies:

Preparation of Isolated Tissue: The animals were euthanized using a high dose of pentobarbital and sacrificed. And the pancreas and liver of each animal were isolated and was cut into small pieces, preserved and fixed with 10% formaldehyde. The samples were then dehydrated and embedded in paraffin. After sectioning (5 µm thick) with a rotary slicer (LEICA RM2135, Wetzlar, Germany), hematoxylin and eosin stain (H&E).

Statistical Analysis: The results are expressed as mean ± S.D from n=6 rats in each group. The significance of difference among the groups was assessed using one-way analysis of variance (ANOVA) followed by Tukey's test.

RESULTS: *Simarouba glauca* was analyzed qualitatively. It was observed that the extract might contain Alkaloids, Phenols, Tannins, Flavonoids, cardiac glycosides, carbohydrates, saponin, and triterpenoids.

TABLE 1: PRELIMINARY QUALITATIVE ANALYSIS OF LEAVES OF *SIMAROUBA GLAUCA*

S. no.	Phytochemical constituents	Observation
1	Alkaloids	+
2	Phenols	+
3	Tannins	+
4	Flavonoids	+
5	Anthraquinones	-
6	Cardiac glycosides	+
7	Carbohydrates	+
8	Saponins	+
9	Triterpenoids	+

Present (+) or absent (-)

Acute Toxicity Study: The LD_{50} of the extract of *Simarouba glauca* was found to be 5000 mg/kg after conducting the acute toxicity studies. So $1/10^{th}$ and $1/20^{th}$ of the dose were selected, and the experiment was carried out.

For Streptozotocin-Induced Type I DM Model: Effect of methanolic extract of *Simarouba glauca* (250 mg and 500 mg/kg. P.o./ 30 days) on STZ (65 mg/kg i.p./single dose) treated rats on body weight, blood glucose, lipid profiles, Biochemical parameters, antioxidant, glycosylated haemoglobin (HbA1c) and tissue histology.

TABLE 2: EFFECT OF ORAL ADMINISTRATION OF METHANOLIC EXTRACT OF *SIMAROUBA GLAUCA* (250 mg AND 500 mg/kg.po/day/30DAYs) ON STREPTO-ZOTOCIN (65 mg/kg.ip/single DOSE) TREATED RATSON BODY WEIGHT AFTER 30 DAYS OF TREATMENT

Group	B.W. (gm/kg)
Normal control	180.2 ± 0.3073
Diabetic control	153.3 ± 1.476*
STD (Insulin 4U/k.g., s.c.)	175.2 ± 1.138#
Simarouba glauca (250 mg/kg)	168.2 ± 1.014†
Simarouba glauca (500 mg/kg)	172.8 ± 1.014†

Values are expressed as mean ± SEM, n = 6 in each group. *P<0.001. when compared to the control group. #P<0.001 when compared to preventive diabetic control group. †P<0.001 when compared to diabetic control group.

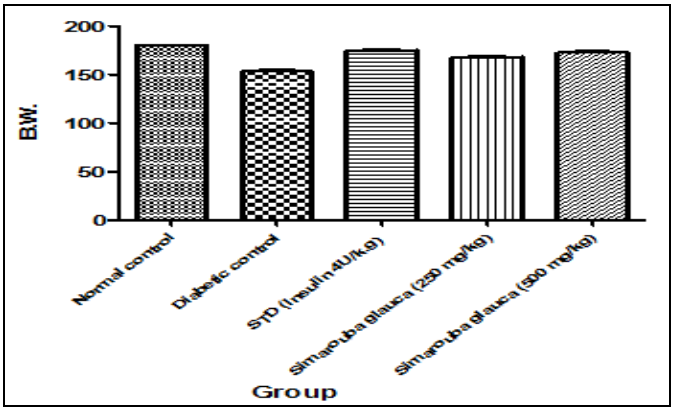


FIG. 1: EFFECT OF ORAL ADMINISTRATION OF METHANOLIC EXTRACT OF *SIMAROUBA GLAUCA* ON BODY WEIGHT. Values are expressed as mean ± SEM, n = 6

TABLE 3: EFFECT OF ORAL ADMINISTRATION OF METHANOLIC EXTRACT OF *SIMAROUBA GLAUCA* (250 mg AND 500 mg/kg. po / day / 30 DAYS) ON STREPTOZOTOCIN (65 mg/kg.ip/SINGLE DOSE) TREATED RATSON BLOOD GLUCOSE LEVEL AFTER 30 DAYS OF TREATMENT

Group	Blood glucose level (mg/dl)
Normal control	88.50 ± 0.8851
Diabetic control	512.0 ± 33.45*
STD (Insulin 4U/k.g., s.c.)	113.5 ± 6.026#
S. glauca (250 mg/kg)	126.8 ± 1.662†
S. glauca (500 mg/kg)	104.5 ± 5.271†

Values are expressed as mean ± SEM, n = 6 in each group. *P<0.001.when compared to the control group. #P<0.001 when compared to preventive diabetic control group. †P<0.001 when compared to diabetic control group.

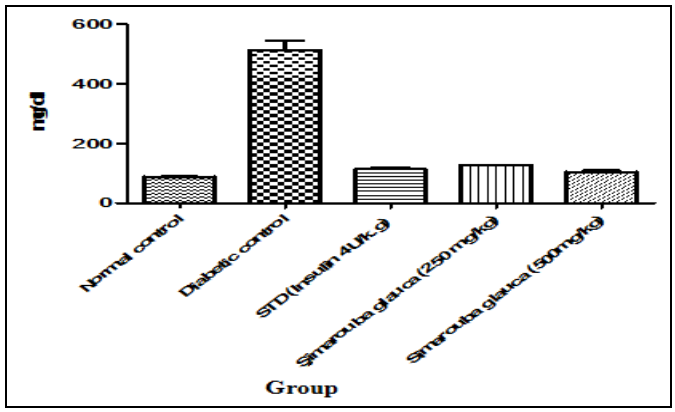


FIG. 2: BLOOD GLUCOSE LEVEL
Values are expressed as mean ± SEM, n = 6

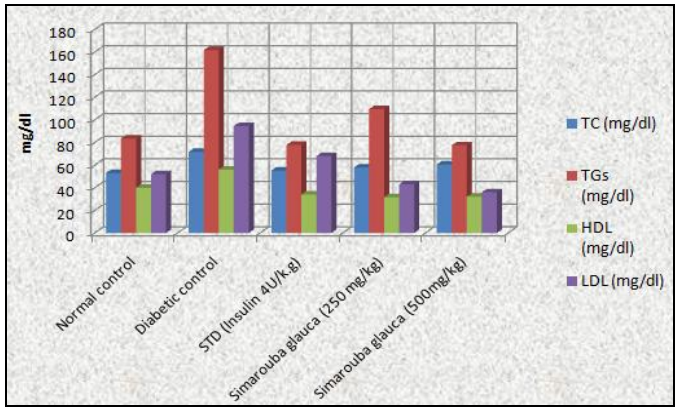


FIG. 3: LIPID PROFILE
Values are expressed as mean ± SEM, n = 6

TABLE 4: EFFECT OF ORAL ADMINISTRATION OF METHANOLIC EXTRACT OF *SIMAROUBA GLAUCA* (250 mg AND 500 mg/kg.po/DAY/30DAYS) ON STREPTOZOTOCIN (65 mg/kg.ip/SINGLE DOSE) TREATED RATSON LIPID PROFILE LEVEL AFTER 30 DAYS OF TREATMENT

Lipid profile/ Group	Normal control	Diabetic control	STD (Insulin 4U/k.g, s.c.)	*Simarouba glauca* (250 mg/kg)	*Simarouba glauca* (500 mg/kg)
TC (mg/dl)	53 ± 0.76	71.7 ± 0.60*	55.2 ± 0.42#	57.9 ± 0.76†	60.6 ± 0.48†
TGs (mg/dl)	83.5 ± 0.67	161.6 ± 16.8*	77.8 ± 1.14#	109.5 ± 0.87†	77.5 ± 0.58†
HDL (mg/dl)	40 ± 0.76	56 ± 1.49*	34 ± 0.58#	31.54 ± 0.68†	32.01 ± 0.49†
LDL (mg/dl)	52 ± 0.58	94.5 ± 0.68*	68 ± 1.30#	43 ± 0.85	36 ± 0.95†

Values are expressed as mean ± SEM, n = 6 in each group. *P<0.001.when compared to the control group. #P<0.001 when compared to preventive diabetic control group. †P<0.001 when compared to diabetic control group.

TABLE 5: EFFECT OF ORAL ADMINISTRATION OF METHANOLIC EXTRACT OF *SIMAROUBA GLAUCA* (250 mg AND 500 mg/kg.po/day/30DAYS) ON STREPTOZOTOCIN (65 mg/kg.ip/SINGLE DOSE) TREATED RATSON SERUM GLYCATED HAEMOGLOBIN AFTER 30 DAYS OF TREATMENT

Group	Serum glycated hemoglobin (%)
Normal control	6.233 ± 0.1202
Diabetic control	14.83 ± 0.3333*
STD (Insulin 4U/k.g., s.c.)	9 ± 0.2887#
Simarouba glauca (250 mg/kg)	10.42 ± 0.2007†
Simarouba glauca (500 mg/kg)	8 ± 0.2887†

Values are expressed as mean ± SEM, n = 6 in each group. *P<0.001. When compared to the control group. #P<0.001 when compared to preventive diabetic control group. †P<0.001 when compared to diabetic control group.

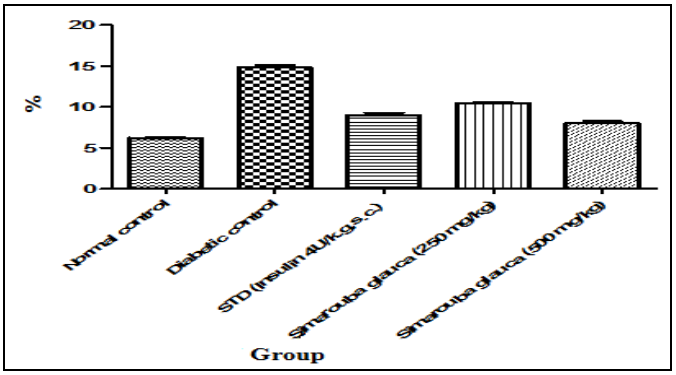


FIG. 4: SERUM GLYCATED HEMOGLOBIN
Values are expressed as mean ± SEM, n = 6

TABLE 6: EFFECT OF ORAL ADMINISTRATION OF METHANOLIC EXTRACT OF *SIMAROUBA GLAUCA* (250 mg AND 500 mg/kg.po/DAY/30DAYS) ON STREPTOZOTOCIN (65 mg/kg.ip/SINGLE DOSE) TREATED RATSON SERUM SGOT AND SGPT AFTER 30 DAYS OF TREATMENT

Parameters/ Group	Normal control	Diabetic control	STD (Insulin 4U/k.g, s.c.)	*Simarouba glauca* (250 mg/kg)	*Simarouba glauca* (500 mg/kg)
SGPT (U/L)	43.2 ± 0.70	81 ± 1.23*	81 ± 1.18#	78.1 ± 0.187†	66.8 ± 1.17†
SGOT (U/L)	129.5 ± 1.28	436 ± 1.47*	166 ± 0.149#	212.6 ± 0.578†	146.6 ± 0.157†

Values are expressed as mean ± SEM, n = 6 in each group. *P<0.001.when compared to control group. #P<0.001 when compared to preventive diabetic control group. †P<0.001 when compared to diabetic control group.

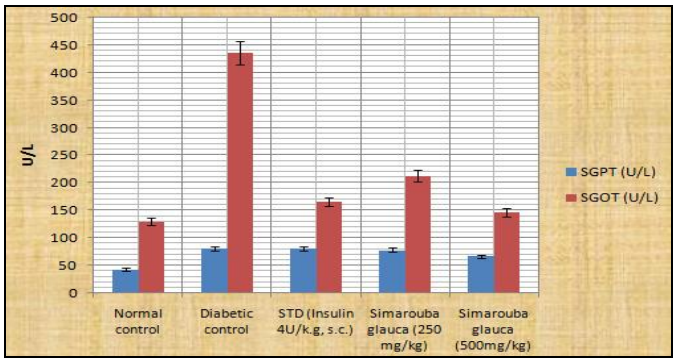


FIG. 5: SGPT & SGOT
Values are expressed as mean ± SEM, n = 6

TABLE 7: EFFECT OF ORAL ADMINISTRATION OF METHANOLIC EXTRACT OF *SIMAROUBA GLAUCA* (250 mg AND 500 mg/kg.po/DAY/30DAYS) ON STREPTOZOTOCIN (65 mg/kg.ip/SINGLE DOSE) TREATED RATSON CATALASE AND NO ACTIVITY AFTER 30 DAYS OF TREATMENT

Parameters/ Group	Normal control	Diabetic control	STD (Insulin 4U/k.g, s.c.)	*Simarouba glauca* (250 mg/kg)	*Simarouba glauca* (500 mg/kg)
Catalase (U/mg)	114.3 ± 0.4410	253.8 ± 1.447*	155.0 ± 1.414#	192.8 ± 0.7923†	186.5 ± 1.176†
NO ((µM))	128.3 ± 1.085	542.7 ± 0 .988*	156.3 ± 0.4944#	314.7 ± 1.308†	162.3 ± .7649†

Values are expressed as mean ± SEM, n = 6 in each group. *P<0.001.when compared to the control group. #P<0.001 when compared to preventive diabetic control group. †P<0.001 when compared to diabetic control group.

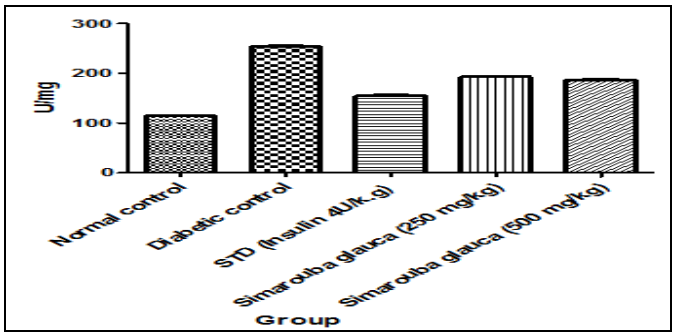


FIG. 6: CATALASE

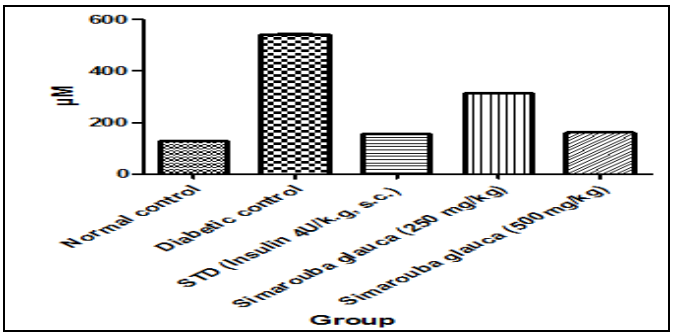
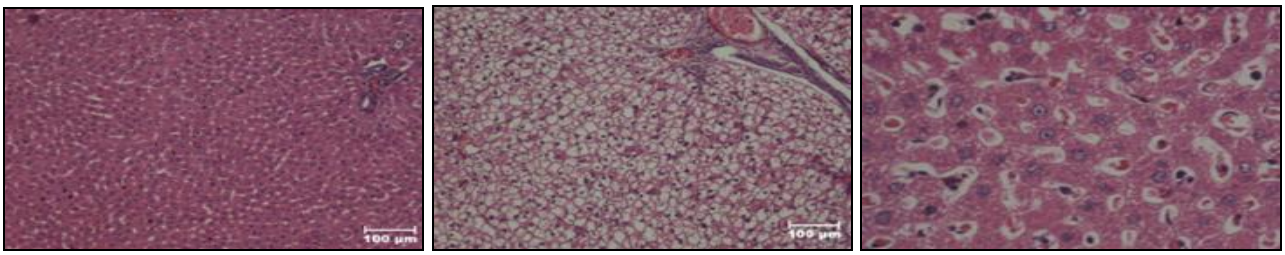


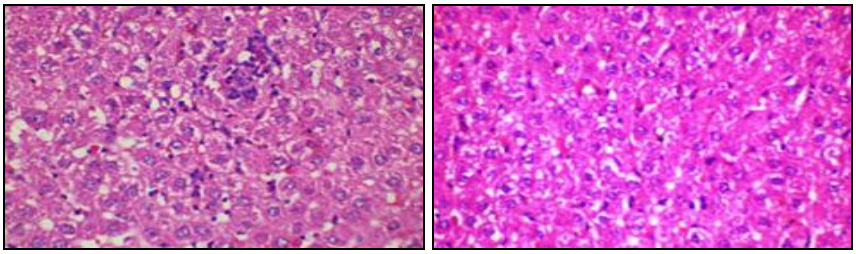
FIG. 7: NO

Values are expressed as mean ± SEM, n = 6

Histological Examination of Haematoxylin and Eosin (H&E) Stained on Tissue: Effect of oral administration of a methanolic extract of *Simarouba glauca* (250 mg and 500 mg/kg.po/day/30days) on Streptozotocin (65 mg/kg.ip/single dose) treated rats on the liver and pancreatic tissue after 30 days of treatment.



NC-LIVER **DC-LIVER** **STD (INSULIN) - LIVER**

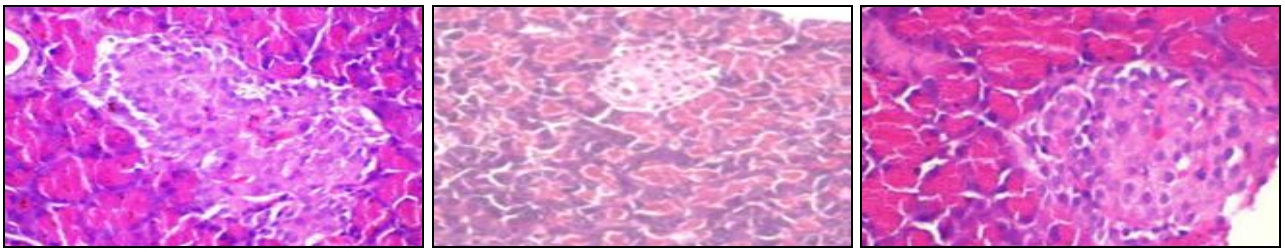


***SIMAROUBA GLAUCA* 250 mg H&E 40X-LIVER** ***SIMAROUBA GLAUCA* 500 mg H&E 40X-LIVER**

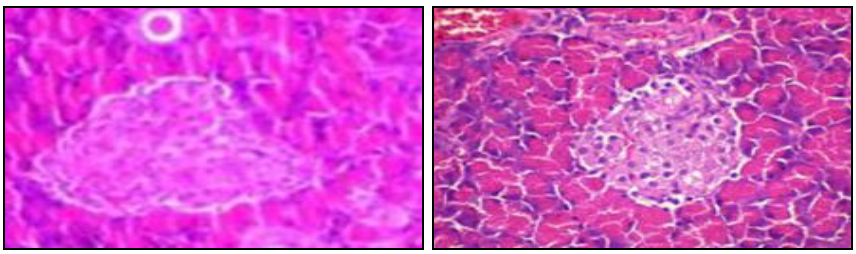
FIG. 8: LIVER HISTOLOGY; H&E

Normal Control: Liver showing normal hepatocytes with pink staining cytoplasm and blue staining vesicular nucleus and hepatocytes arranged in the cord like fashion surrounding the central vein. Hematoxylin and Eosin stain, scale bar = 100 µm.

Diabetic Control: Liver showing severe degeneration of hepatocytes with condensed nucleus and distortion in the architecture in the hepatocytes was observed. Hematoxylin and Eosin stain, scale bar = 100µm. STD (Insulin): Liver showing moderate degeneration of hepatocytes with a condensed nucleus and with distortion in the architecture in the hepatocytes was observed. Hematoxylin and Eosin stain, scale bar = 100 µm. *Simarouba glauca* (250 mg/kg): Individual Cell necrosis-Mild, Vacuolar Changes-Mild *Simarouba glauca* (500 mg/kg): Individual Cell necrosis-Minimal, Vacuolar Changes-Minimal.



NC-PANCREAS **DC-LIVER PANCREAS** **STD (INSULIN) - PANCREAS**



***SIMAROUBA GLAUCA* 250 mg H&E 40X-PANCREAS** ***SIMAROUBA GLAUCA* 500 mg H&E 40X PANCREAS**

FIG. 9: PANCREAS HISTOLOGY; H&E

Normal Control: Normal-Pancreas showing exocrine portion with columnar epithelial cells with a basal nucleus and apical acidophilic cytoplasm staining pink color. The acinar cells are arranged in lobules with tightly packed and surrounded interlobular septal was observed. The endocrine portion is evident by lightly staining cells than the surrounding acinar cells. Hematoxylin and Eosin stain, scale bar = 100μm Diabetic control: Pancreas showing exocrine portion with columnar epithelial cells with a basal nucleus and apical acidophilic cytoplasm staining pink color. The acinar cells are arranged in lobules with tightly packed and surrounded interlobular septal with mild vacuolar degeneration was Observed. The endocrine portion is evident by lightly staining cells than the surrounding acinar cells with loss of beta cells. Hematoxylin and Eosin stain, scale bar = 100 μm.

STD (Insulin): Pancreas showing exocrine portion with columnar epithelial cells with a basal nucleus and apical acidophilic cytoplasm staining pink color. The acinar cells are arranged in lobules with tightly packed and surrounded interlobular septal was observed. The endocrine portion is evident by lightly staining cells than the surrounding acinar cells. Hematoxylin and Eosin stain, scale bar = 100μm. *Simarouba glauca* (250 mg/kg): Pancreas showing exocrine portion with columnar epithelial cells with a basal nucleus and apical acidophilic cytoplasm staining pink color. Islet: Degenerative Changes-mild, Cytoplasmic degenerative changes in most islet cells in minimal, especially in the center of the islet, *Simarouba glauca* (500 mg/kg): Pancreas showing exocrine portion with columnar epithelial cells with a basal nucleus and apical acidophilic cytoplasm staining pink color. Islet: Degenerative Changes-minimal, Cytoplasmic degenerative changes in most islet cells, especially in the center of the islet.

DISCUSSION: Plants are considered to be medicinal if they possess pharmacological activities of possible therapeutic use. Indian Materia Medica includes about 2000 drugs of natural origin almost all of which are derived from different traditional systems. These activities are often recognized as a result of millennia of trial and error, but they have to be carefully investigated if new drugs are to be developed for use in modern treatment.

The rich biodiversity of Indian subcontinent contributes to the wealth of medicinal plants, which are very much used in traditional medical treatments (Chopra *et al.*, 1956). India is one of the 12 mega biodiversity centers with over 18,000 plant species. Over 2,500 species are formally recognized as having true medicinal value. About 7500 plants have been used in local health traditions in rural and tribal villages of India. Out of these, the medicinal efficacy of 4000 plants is either little known or unknown to the mainstream population (Pushpangadan, 1996).

In the present study, Methanolic extract of *Simarouba glauca* was evaluated for its anti-diabetic activity in Streptozotocin-induced diabetic rats. The Ethanolic extract of *Strobilanthes* asperrimus (Pradeep Kumar Samal, 2013), MeOH-H2O extract of *Grateloupia elliptica* (K.Y. Kim *et al.)*, aqueous extract of *Ulva fasciata* (abirami *et al.)*, ethanolic extract of *Sargassum Duplicatum* and *Turbinaria Decurens* (Hardoko *et al.)*, reported that these algae having anti-diabetic activity. Administration of Streptozotocin (65 mg/kg. ip/single dose) to Wister rats showed a significant increase ($p<0.001$) in the blood glucose on the 30th day of treatment when compared with normal control. Administration of methanolic extract of *Simarouba glauca* (250 mg/kg.po/day/30days) to the Streptozotocin (65 mg/kg. ip/single dose) treated Wister rats showed a significant decrease ($p<0.01$) in the blood glucose on the 30th day of treatment when compared with diabetic control. Administration of methanolic extract of *Simarouba glauca* (500 mg/ kg.po/day/30days) to the Streptozotocin (65 mg/kg. ip/single dose) treated Wister rats showed a significant decrease ($p<0.001$) in the blood glucose on the 30th day of treatment when compared with diabetic control. Administration of methanolic extract of *Simarouba glauca* (both 250 & 500 mg /kg.po/day/30days) to the Streptozotocin (65 mg/kg. ip/single dose) treated Wister rats showed Similar decrease Glucose on the 30th day of treatment when compared with standard control (Insulin 4U/kg.ip/30 days).

In the present study, we have observed that methanolic extract of leaves of *Simarouba glauca* having anti-diabetic activity. STZ is reported to produce free radicals in the body, which

specifically cut DNA chains in the pancreatic beta cells, resulting in the disorder of the function of the pancreatic beta cells and at a later phase, destruction of the beta cells by necrosis leading to type I diabetes. Uncontrolled diabetes mellitus is associated with an increase in total cholesterol, triglycerides and LDL cholesterol associated with the decrease in HDL cholesterol. Type I diabetes is associated with lower rates of cholesterol synthesis and increased absorption of dietary cholesterol.

These individuals are at high risk for the development of cardiovascular disease and have higher total serum cholesterol levels. In the present study, in the diabetic control group, there was a marked an increase in total cholesterol, LDL cholesterol and TG, while a significant decrease in HDL cholesterol level, was found. Hyperlipidemia is a known complication of diabetes mellitus and coexists with hyperglycemia and is characterized by increased level of cholesterol, TG and LDL cholesterol, and all the lipid abnormalities associated with diabetes was significantly normalized by treatment with the methanolic extract of *Simarouba glauca.* and HbA_{1C} of the normal control was found to be 6.2%, diabetic control 14.83% and the preventive group was 10.42% for the lower dose, and in a higher dose, we got 8%; meant plants have a protective effect in type I DM. Similarly SGPT and SGOT, we were found significantly reduced compared to diabetic control. The generation of oxygen-derived free radicals in diabetes is the leading cause of the development of diabetic neurological complications such as neuropathic pain and depression.

The free radicals so produced may react with polyunsaturated fatty acids in cell membranes leading to lipid peroxidation, which in turn again results in the production of free radicals. Lipid peroxidation–mediated tissue damage has been observed in the development of both types I and type II diabetes. Lipid peroxidation effects are greater in nerve root because the blood-nerve and perineurial barriers are lower at these sites.

In this study, diabetic control rats showed a significant increase in catalase and NO in STZ induced model. Catalase and NO was significantly reduced in both groups (250 mg/kg, 500 mg/kg) upon treatment with insulin and SMC.

In the present study histological picture of STZ treated pancreas of rats showed a significant decrease in beta cell density, whereas methanolic extract *Simarouba glauca* and insulin-treated diabetic rats' shows significant increase in beta cell density indicating insulin secretagogue activity. This property may be due to regenerating activity on the beta cells. Liver showing normal hepatocytes with pink staining cytoplasm and blue staining vesicular nucleus and hepatocytes arranged in the cord like fashion surrounding the central vein compared to the control group. Our data support the notion that *Simarouba glauca*, may prove to be useful for the treatment of type I DM patients.

CONCLUSION: In conclusion, our data suggest methanolic extract of *Simarouba glauca* possess potential antidiabetic activity as it lowers blood glucose level significantly. Methanolic extract of *Simarouba glauca* also possesses significant antihyperlipidemic activity as it lowers serum cholesterol and triglycerides levels, LDL cholesterol and increases HDL cholesterol level.

The antioxidant activity may facilitate to prevent diabetic complication. Further studies are needed to characterize the antidiabetic activity of the selected extract to find out the exact mechanism involved so that they can be formulated and may try clinically in the future.

ACKNOWLEDGEMENT: It is a matter of great pleasure for us that we got an opportunity to complete our project work under the supervision of Dr. Raju Koneri, Deepak Kumar Jha and the management of Karnataka Education Trust.

CONFLICT OF INTEREST: Certify that we have no conflict of interest in the subject matter.

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How to cite this article:
Abdullah NT and Koneri R: Screening of *Simarouba gluaca* for antidiabetic and antioxidant activities. Int J Pharm Sci & Res 2019; 10(1): 294-02. doi: 10.13040/IJPSR.0975-8232.10(1).294-02.