IJPSR (2018), Volume 9, Issue 7 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 14 October, 2017; received in revised form, 18 December, 2017; accepted, 30 December, 2017; published 01 July, 2018

AN INVESTIGATION ON THE TYPE I ANTIDIABETIC ACTIVITY OF METHANOLIC EXTRACT OF *MARINE ALGAE*, *GRACILARIA EDULIS* AND *SARGASSUM POLYCYSTUM*

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Keywords:

Methanolic extract, *Sargassum polycystum*, *Gracilaria edulis*, Streptozotocin, Antidiabetic, Insulin

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ABSTRACT: The objective of this study was to evaluate the antidiabetic activity of methanolic extract of marine algae *Sargassum polycystum* (MSP) and *Gracilaria edulis* (MGE) in STZ induced diabetes in rats for Type I diabetic mellitus. The marine algae SP and GE were dried under shade and then powdered, and extracted with methanol. Preliminary phytochemical studies and acute toxicity studies were also carried out on methanolic extract of SP, and GE. After overnight fasting, for type I diabetes was induced in rats by I.P. injection of STZ dissolved in 0.1 M sodium citrate buffer at pH 4.5, at a dose of 65 mg/kg body weight. Group A served as normal control while group B was considered as diabetic control. Group C was standard receiving insulin 4U/kg and Group D diabetic animals were treated with MSP and MGE (250 mg/kg and 500 mg/kg) respectively. During the study, body weight and fasting blood glucose level were taken at 0 and 30th day. At the end of study, animals in all groups were sacrificed, blood sample, pancreas were collected. Biochemical parameters such as total cholesterol, HDL cholesterol, TG, LDL cholesterol, histopathological studies of pancreas were performed. Significant antidiabetic activity of MSP and MGE observed in the present investigation could be the result of decreased blood glucose levels and improved body mass. Methanolic extract of SP and GE also showed improvisation in lipid profile and may have protective effect in DM related cardiovascular complications.

INTRODUCTION: World Health Organization (WHO) estimates that about 347 million people worldwide have diabetes, particularly in developing countries. In 2012, diabetes- 371 million adults worldwide with the prevalence of 8.3%. Increase to approximately 552 million adults by 2030 with the prevalence of 9.9%.India accounts for the largest number of people suffering diabetes - 50.8 million. Earning the title "diabetes capital of the world.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.9(7).2952-59

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.9(7).2952-59

Diabetes is a group of metabolic diseases in which a person has high blood sugar, either because the pancreas does not produce enough insulin, or because cells do not respond to the insulin that is produced [1].

This high blood sugar produces the classical symptoms of polyuria, polydipsia and polyphagia. After a long duration of metabolic derangement, specific complications of diabetes (retinopathy, nephropathy, and neuropathy) may occur. Arteriosclerosis is also accelerated. Depending on the severity of the metabolic abnormality, diabetes may be asymptomatic, or may be associated with symptoms, or may progress to ketoacidosis and coma [2]. The term "type 1 diabetes "has replaced several former terms, including childhood onset

diabetes, juvenile diabetes, and insulin-dependent mellitus (IDDM). 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.

Sargassum polycystum (sargassaceae) is a marine species found in the large communities on rocks in lower intertidal zones in relatively calm water. The erect branches have numerous spines on the stem. Leaves are lanceolate to oblong with serratious, and vesicles are spherical. The plants are 1 - 2 m high [3]. Plants dark-brown, 20 - 30 cm in height with the basal portion forming a thick discoid holdfast; upper portion richly branched; axes of the plant rough due to presence of short processes; leaves about 2 cm long and 0.5 ram broad, becoming smaller upwards; margins of the leaves dentate and apex rounded; mid rib more or less conspicuous; vesicles small, spherical and 1 - 2 mm broad; receptacles somewhat spinulose and very much refined. It grows in all months of the year on rocks, stones and dead corals in the littoral and sub littoral regions. This alginophyte is available in exploitable quantities. It is used as raw material along with other species of Sargassum for the production of sodium alginate [4].

Recent study showed that athrogenic diet caused significant elevation in plasma cholesterol, triglyceride, LDL, serum MDA, NO, leptin and TNF-alpha levels while, it produced significant decline in plasma HDL and serum adiponectin levels compared with lean control rats. However, treatment of dyslipidemia rats with species of Sargassum methanolic extract induced significant improvement of plasma lipid profile, marked decrease in serum MDA, NO, leptin, TNF-alpha level in concomitant with remarkable increase in serum adiponectin level.

These results indicated that species of Sargassum extract plays a vital role in ameliorating dyslipidaemia and its complications particularly oxidative stress and implication. This could be attributed to the hypolipidemic effect, antilipidperoxidative activity and ant inflammatory property of species of Sargassum methanolic extract [5].

Gracilaria edulis (Gracilariaceae) is a major Indian agarophyte has been successfully cultivated in an experimental scale from spores at sea off Narakkal, Kochi. They were allowed to grow to mature size of 30 cm [6]. It grows abundantly on sea grass beds in shallow lagoons formed between the shores and fringing coral reefs. It is also attached to small stones and shells on sandy and muddy areas. This agarophyte occurs throughout the year in harvestable quantities. It is used as raw material for the production of agar and also consumed in the form of porridge by coastal people. It can also be used for preparing jelly, payasam, wafer and pickle [7].

Therapeutic options for diabetes like oral hypoglycemic agents and insulin, which have limitations of their own such as they are costly and chances of side effects are high. Ayurveda and other traditional medicinal system for the treatment of diabetes play an important role as alternative medicine due to less side effects and low cost. Traditonal plant medicines has been investigated for the treatment of diabetes because of their effectiveness, less side effects and relatively low cost. Among the many plants used for management of diabetes *Sargassum polycystum* and *Gracilaria edulisis* used traditionally for treating diabetes and various diseases. Therefore the present study was undertaken to evaluate antidiabetic activity of marine algae in streptozotocin induced diabetic rats.

MATERIALS AND METHOD:

Plant Material: The marine algae *Sargassum polycystum* and *Gracilaria edulis* was collected during August, from the Mandapam coast (latitude 90 17’ Longitude 790 22, E), Gulf of manner. The sample was identified by Scientist incharge, at the Centre for Marine and Fisheries Research Institution (CMFRI), Mandapam, Tamil Nadu, India.

Extraction of the Plant Materials and Sample Preparation: The algae of *Sargassum polycystum* and *Gracilaria edulis* were, chopped into small pieces and dried under shade at room temperature for seven days. The dried algae were powdered and passed through the sieve (coarse 10/40). The powder was used for the preparation of methanolic extract. Dried and powdered algae of *Sargassum polycystum* and *Gracilaria edulis* (each 1.0 kg) were extracted with boiling 70% MeOH in a reflux condition. After filtration, the extract obtained was concentrated in a rotary shaker and evaporated to dryness to get constant weight. The Qualitative phytochemicals screening were carried out on the Methanolic extract of *Sargassum polycystum* and *Gracilaria edulis*. To detect various phyto-constituents present in them [8, 9].

Experimental Animals: Male Wister rats weighing between 200 - 250 g were procured from NIMHANS Bangalore, Karnataka. The animals were acclimatized for ten days under laboratory conditions. They were housed in polypropylene cages and maintained at 27 ºC ± 2 ºC, Relative humidity 65 ± 7.5% under 12 hours light /dark cycle. The animals were fed with rodent pellet diet (Gold Mohur Lipton India Ltd.,) and water *ad libitum*. The study protocols were duly approved by the Institutional Animal Ethics Committee (IAEC) of Karnataka College of pharmacy, Bangalore - 560064, India. Studies were performed in accordance with the CPCSEA guidelines.

Experimental Design:

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

Induced Streptozotocin Diabetes Mellitus: [10] Diabetes was induced in 16 hr fasted Male rats (200 - 250g) by I.P. 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 hr in their cages to prevent hypoglycemia. After 72 h, rats with marked hyperglycemic fasting blood glucose >180 mg/dl were selected and used for the study. 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.

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 (4 U/kg, i.p.).
Group 4: Diabetic rats treated with methanolic extract of *Sargassum polycystum*, dose obtained from acute toxicity.
Group 5: Diabetic rats treated with methanolic extract of *Gracilaria edulis*, dose obtained from acute toxicity.

Body weights of rats were taken at 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. Later withdrawal the blood for analyzed various biochemical parameters. At the end of experimental period sacrifice the animals with high dose of pentobarbital for tissue histology.

Biochemical Parameters: The biochemical parameters like Glucose, Triglyceride, Total Cholesterol, HDL, LDL, were estimated as per the standard procedure prescribed by the manufacturer's instruction manual provided in the kit. (DELTA LABS kit, Bangalore, India) using Semi Auto analyzer.

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

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: *Sargassum polycystum* and *Gracilaria edulis* was analyzed qualitatively. It was observed that the mixture contains carbohydrates, phytosterols, flavonoids, and glycosides but does not contain alkaloids, tannins, saponin fixed oil, amino acids and proteins.

TABLE 1: PRELIMINARY QUALITATIVE ANALYSIS OF *SARGASSUM POLYCYSTUM* AND *GRACILARIA EDULIS*

S. no.	Phytochemical Constituent	Observation	
		G. edulis	*S. polycystum*
1	Alkaloids	-	-
2	Carbohydrates	+	+
3	Glycosides	+	+
4	Proteins and amino acids	+	_
5	Saponin	-	-
6	Tannins	-	-
7	Phytosterol	+	+
8	Flavonoids	-	+
9	Fixed oils & fats	-	--

Acute Toxicity Study: The LD_{50} of the extract of *Gracilaria edulis* (GE) and, *Sargassum polycystum* (SP) was found to be 5000 mg/kg, after conducting the acute oral toxicity studies. So $1/10^{th}$ and $1/20^{th}$ of doses (250 and 500 mg/kg) were selected and the experiment was carried out.

For Streptozotocin Induced Type I DM Model: Effect of methanolic extract of *Sargassum polycystum* and *Gracilaria edulis* (250 mg and 500 mg / kg. p.o / day / 30days) on Streptozotocin (65 mg / kg. i.p / single dose) treated rats on body weight, cholesterol, triglyceride, HDL, LDL, after 30 days of treatment.

TABLE 2: EFFECT ON BODY WEIGHT

S. no.	Name of Group	Weight (Gm/Kg)
1	Normal Control	254 ± 1.23
2	Diabetic Control	187 ± 1.14
3	SLD (250 mg/kg)	203 ± 1.18
4	SHD (500 mg/kg)	235 ± 1.28
5	ELD (250 mg/kg)	206 ± 1.28
6	EHD (500 mg/kg)	229 ± 0.70
7	STD (INSULIN) 4 U/kg	240 ± 0.33

Values are expressed as Mean ± S.E.M (n = 6). Diabetic control group showed significant decrease (p <0.001) in the body weight on 30^{th} day of treatment when compared with normal control and significantly increase in test group. *Sargassum polycystum* low dose (SLD), *Sargassum polycystum* high dose (SHD), *Gracilaria edulis* low dose (ELD), *Gracilaria edulis* high dose (EHD), Standard (STD)

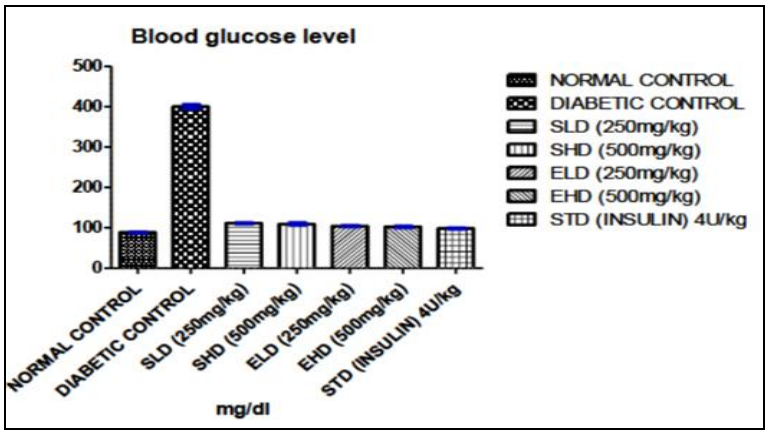


FIG. 1: EFFECT OF METHANOLIC EXTRACT OF *SARGASSUM POLYCYSTUM* AND *GRACILARIA EDULIS* (250 mg AND 500 mg/kg. po/ DAY / 30 DAYS) ON STREPTOZOTOCIN (65 mg/kg.ip/ SINGLE DOSE) TREATED RATS ON BLOOD GLUCOSE LEVEL (mg/dl) AFTER 30 DAYS OF TREATMENT. Values are expressed as Mean ± S.E.M (n=6). Showed significant decrease (p<0.01) in the blood glucose on 30^{th} day of treatment when compared with diabetic control.

TABLE 3: EFFECT OF METHANOLIC EXTRACTS OF *SARGASSUM POLYCYSTUM* AND *GRACILARIA EDULIS* (250 mg AND 500 mg / kg.po / DAY /30 DAYS) ON STREPTOZOTOCIN (65 mg/kg.ip/ SINGLE DOSE) TREATED RAT ON LDL, TGs, TC, AND HDL AFTER 30 DAYS OF TREATMENT

Normal Control	Diabetic Control	SHD 500mg/kg	SLD 250mg/kg	EHD 500mg/kg	ELD 250mg/kg	STD (Insulin, 4U/kg)
LDL >130mg/dl						
99 ± 0.76	136 ± 0.60$^{###}$	98 ± 0.42***	99 ± 0.76***	97 ± 0.48***	100 ± 0.76***	101 ± 0.76***
Triglycerides 150-199mg/dl						
176 ± 0.67	212 ± 16.84$^{###}$	161 ± 1.14***	181 ± 0.87***	186 ± 0.58***	169 ± 0.84***	199 ± 0.76***
Total Cholesterol 200-239 mg/dl						
197 ± 0.76	232 ± 1.49$^{###}$	184 ± 0.58***	200 ± 0.68***	195 ± 0.49***	201 ± 0.58***	203 ± 0.68***
HDL 50-60mg/dl						
61 ± 0.58	46 ± 0.68$^{###}$	64 ± 1.30***	55 ± 0.85***	64 ± 0.95***	58 ± 0.95***	64 ± 1.26***

Values are expressed as Mean + S.E.M (n = 6). *** $p<0.05$; when compared to diabetic control $^{###}$ $p<0.001$; when compared to normal controls. Treated Wister rats showed significant improved in the serum LDL, TGs, TC and HDL on 30th day of treatment when compared with diabetic control.

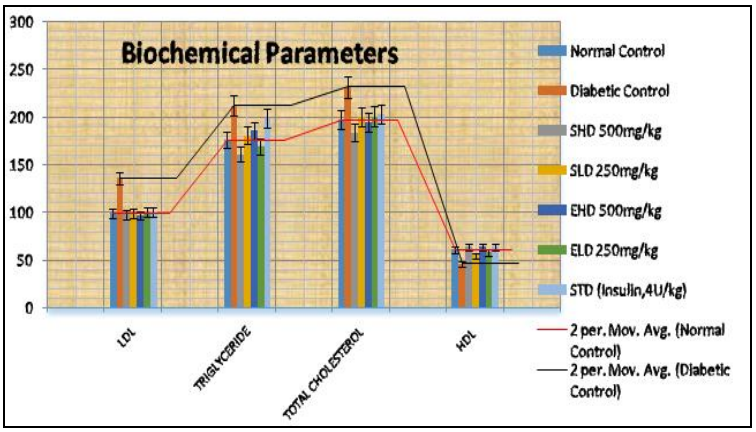


FIG. 2: EFFECT OF METHANOLIC EXTRACTS OF *SARGASSUM POLYCYSTUM* AND *GRACILARIA EDULIS* (250 mg AND 500 mg/kg.po / DAY / 30 DAYS) ON STREPTOZOTOCIN (65 mg /kg.ip/ SINGLE DOSE) TREATED RAT ON LDL, TGS, TC, AND HDL AFTER 30 DAYS OF TREATMENT

Values are expressed as Mean + S.E.M (n=6)

Pathological Changes on Pancreas:

Normal Control: Pancreatic lobules separated by connective tissue septa refer pancreatic lobules which consist largely of the exocrine acini. Most of the lobules show small, round, light - staining islets of Langerhans. The center of islet cells consists of aggregates of small β-cells (75%) having basophilic granules, while the periphery comprised of large α-cells (25%) were having eosinophilic granules. Thin walled capillaries are seen in between these cells.

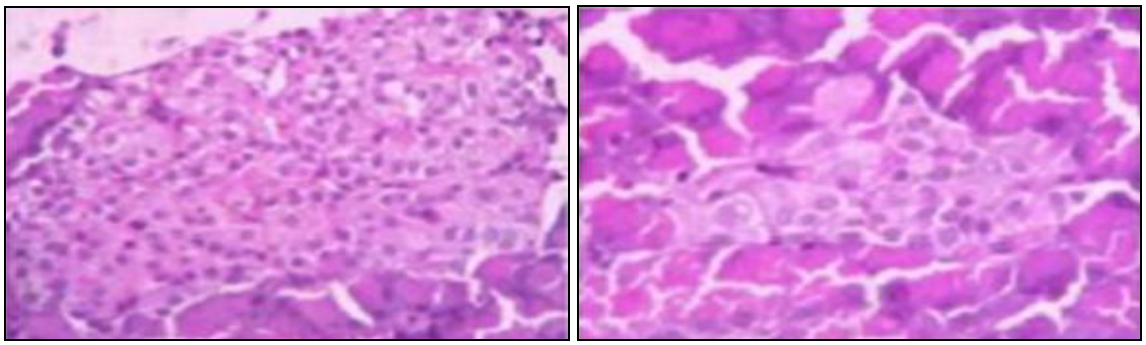
Diabetic Control: Atrophied and deranged islets are visible. Space between acini represents disorganization of pancreatic tissue. Ducts appear normal but acini appear distended.

STZ+ Insulin 4u/kg Treated: Section studied showed pancreatic lobules separated by thin fibro vascular septa. The center of islet cells consist, of mild quantitative decrease in *β*-cells (50%) having basophilic granules, while the periphery comprises of α-cells (55%) having eosinophilic granules. Also seen were few degenerated beta cells.

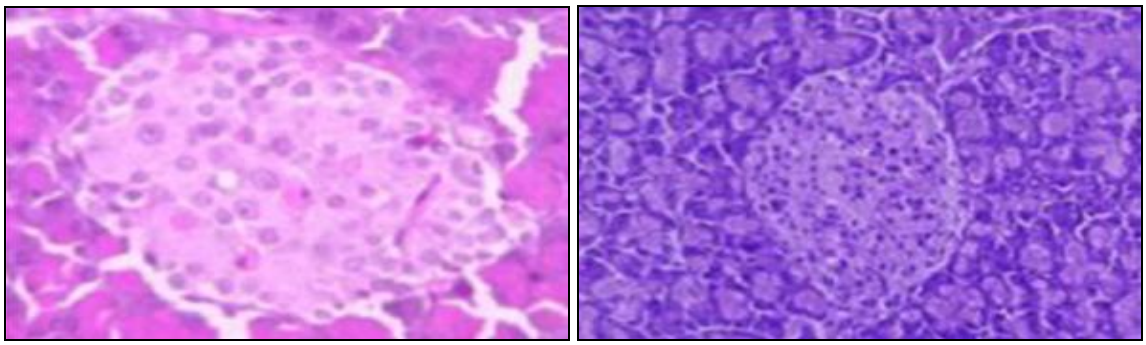
Methanolic Extract of GE 500 mg/kg Treated: Section studied showed pancreatic lobules separated by connective tissue septa. Most of the lobules showed larger areas of light-staining islets of langerhans. The center of islet cells consist of quantitative increase in β-cells (65%) having basophilic granules, while the periphery shows slight decrease in α-cells (20%) have eosinophilic granules.

Methanolic Extract of GE 250 mg/kg Treated: Section studied shows pancreatic lobules separated by fibro vascular septa. The pancreatic lobules consist of intact acinar cells and their intralobular ducts. Most of the lobules show light-staining islets of langerhans. The center of islet cells consist of quantitative decrease in Beta-cells compare to high

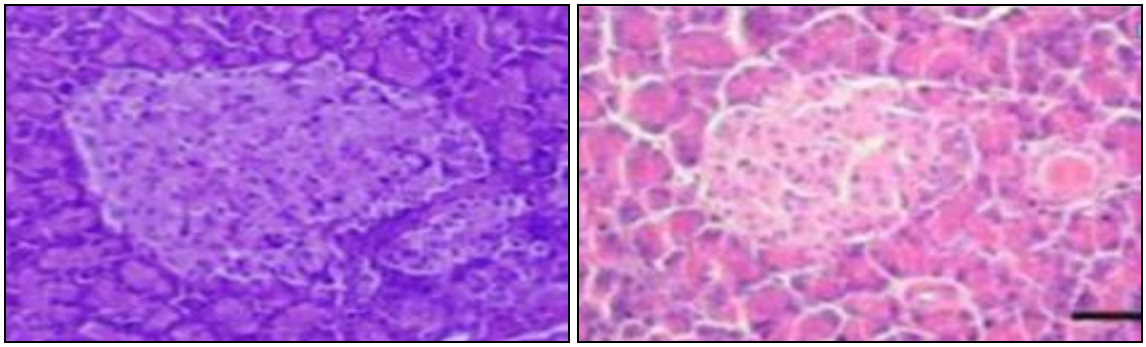
dose (55%) having basophilic granules, while the periphery comprises of increase in compare to high dose Alpha-cells (25%) having eosinophilic granules.



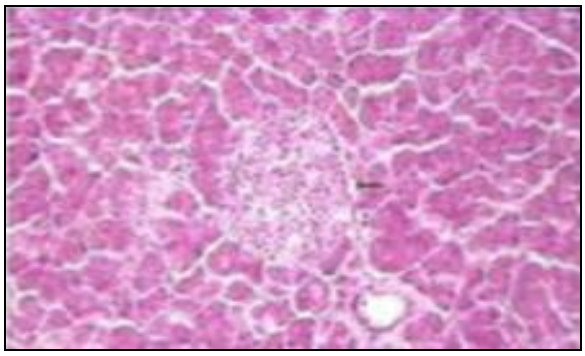
NORMAL CONTROL DIABETIC CONTROL (TYPE 1)



SECTION OF PANCREAS OF INSULIN SECTION OF PANCREAS OF GE (250 mg/kg)



SECTION OF PANCREAS OF GE (500 mg/kg) SECTION OF PANCREAS SP (250 mg/kg)



SECTION OF PANCREAS SP (500 mg/kg)

FIG. 3: HISTOLOGICAL EXAMINATION OF HEMATOXYLIN AND EOSIN (H & E) ON PANCREAS

Methanolic Extract of SP 500 mg/kg Treated: Section studied showed pancreatic lobules separated by connective tissue septa. Most of the lobules showed larger areas of light-staining islets of Langerhans. The center of islet cells consist of quantitative increase in β-cells (69%) having basophilic granules, while the periphery shows slight decrease in α-cells (34%) have eosinophilic granules.

Methanolic Extract of SP 250 mg/kg Treated: Section studied shows pancreatic lobules separated by fibro vascular septa. The pancreatic lobules consist of intact acinar cells and their intralobular ducts. Most of the lobules show light-staining islets of Langerhans. The center of islet cells consist of quantitative decrease in Beta-cells compare to high dose (50%)having basophilic granules, while the periphery comprises of decrease in compare to high dose Alpha-cells (23%) having eosinophilic granules.

DISCUSSION: Diabetes mellitus is becoming the third killer of mankind after cancer and cardiovascular disease due to its high prevalence, morbidity and mortality. Among the currently available therapeutics, sulfonylureas are exclusively used for stimulation of the β-cells to release more insulin. Chronic hyperglycemia is associated with prolonged damage, malfunctioning and eventually failure of organs, especially the kidney, nerves, heart, eyes and blood vessels. There is a need for antidiabetic drug with multiple target and potency.

The need of herbal remedies has gone up owing to their fewer side effects, efficacy and relatively less treatment costs. Drugs of natural origin or their extracts are prescribed widely, even when their biologically active components are not known. The World Health Organization (WHO) even approves the use of natural drugs of plant origin for the treatment of different diseases, including diabetes mellitus.

Management of optimum blood glucose level through the regulation of insulin is of extreme importance in hyperglycemic disorders like Type I and II diabetes mellitus. Any agent that increases insulin secretion (in case of Type I DM) or aids in the peripheral utilization of glucose by sensitizing the cells to insulin (in case of Type II DM) is a claimant to be a drug candidate belonging to the anti-diabetic category. The ethanolic extract of *Strobilanthes asperrimus* (Pradeep KS, 2013),[11] MeOH-H_2O extract of *Grateloupia elliptica* (Kim KY *et al*.,)[12] aqueous extract of *Ulva fasciata* (Abirami *et al*.,),[13] ethanolic extract of *Sargassum duplicatum* and *Turbinaria decurens* (Hardoko *et al*.,) [14] reported that these algae having anti diabetic activity.

In present study we have observed that these algae *Sargassum polycystum* and *Gracilaria edulis* 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 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 increase in total cholesterol, triglycerides and LDL cholesterol associated with 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 present study, in diabetic control group, there was marked increase in total cholesterol, LDL cholesterol and TG, while 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 methanolic extract of algae of *Sargassum polycystum* and *Gracilaria edulis*. In the present study histological picture of STZ treated pancreas of rats showed significant decrease in beta cell density, whereas methanolic extract of marine algae *Sargassum polycystum* and *Gracilaria edulis* and insulin treated diabetic rats' shows significant increase in beta cell density indicating insulin secretogoge activity. This property may be due to regenerating activity on the beta cells.

CONCLUSION: The finding of this study indicates that methanolic extract of *Sargassum polycystum* and *Gracilaria edulis* possess potential antidiabetic activity as it lowers blood glucose level significantly. Methanolic extract of *Sargassum polycystum* and *Gracilaria edulis* also possess significant antihyperlipidemic activity as it lowers serum cholesterol and triglycerides levels, LDL cholesterol and increase HDL cholesterol level. It can be promising in the management of complications and severity of the metabolic abnormality of diabetes.

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 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:
Koneri R, Jha DK and Mubasheera MG: An investigation on the type I antidiabetic activity of methanolic extract of *Marine algae*, *Gracilaria edulis* and *Sargassum polycystum*. Int J Pharm Sci & Res 2018; 9(7): 2952-59. doi: 10.13040/IJPSR.0975-8232.9(7).2952-59.