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Pharmacological Potential of *Sargassum ilicifolium*: Mechanistic Insights into Antidiabetic and Hypolipidemic Activity through Chlorogenic Acid-mediated SGLT2 Inhibition

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Abstract

Background: Diabetes mellitus is a chronic metabolic disorder characterised by hyperglycemia and dyslipidemia, often associated with pancreatic β-cell damage and altered glucose transport mechanisms. Natural marine products have gained attention as potential sources of safer antidiabetic agents, particularly targeting Sodium Glucose Cotransporter 2 (SGLT2)-mediated glucose reabsorption. **Aim:** To evaluate the hypolipidemic and antidiabetic activities of *Sargassum ilicifolium* extract in an alloxan-induced diabetic rat model and to investigate the SGLT2 inhibitory potential of its chief constituent, chlorogenic acid, through in silico and in vitro studies. **Methods:** *Sargassum ilicifolium* extract was administered at doses of 200 mg/kg and 400 mg/kg to alloxan-induced diabetic rats. Biochemical parameters, including blood glucose, total cholesterol, Low Density Lipoprotein (LDL), Very Low Density Lipoprotein (VLDL), triglycerides, and High Density Lipoprotein (HDL), were assessed. Histopathological examination of pancreatic tissue was performed to evaluate β-cell architecture. Chlorogenic acid was isolated and characterised using spectroscopic techniques. Its SGLT2 inhibitory activity was analysed using western blot analysis and 2-NBDG uptake assay in HK-2 cells at IC_{50} (184 µg/mL) and IC_{25} (98 µg/mL). **Results:** Treatment with *S. ilicifolium* extract significantly reduced blood glucose, total cholesterol, LDL, VLDL, and triglyceride levels, and markedly increased HDL levels in diabetic rats. Histological analysis demonstrated restoration of pancreatic β-cell architecture following treatment. *In vitro* studies showed a concentration-dependent reduction in SGLT2 protein expression in Human Kidney (HK)-2 cells upon chlorogenic acid treatment. Molecular docking revealed a strong binding affinity of chlorogenic acid with SGLT2 (–8.17 kcal/mol). The 2-NBDG uptake assay showed decreased fluorescence intensity, confirming inhibition of SGLT2-mediated glucose uptake. **Conclusion:** *Sargassum ilicifolium* extract exhibits significant hypolipidemic and antidiabetic effects, while chlorogenic acid acts as a potential natural SGLT2 inhibitor. These findings suggest that *S. ilicifolium* could serve as a promising marine-derived therapeutic candidate for the management of diabetes mellitus and its associated metabolic complications.

Major Findings: Chlorogenic acid was isolated from *S. ilicifolium* extract and structurally elucidated using spectroscopic analysis. *S. ilicifolium* extract demonstrated significant hypolipidemic and antidiabetic activities in the experimental model. Western blot studies confirmed that the antidiabetic activity of *S. ilicifolium* extract is mediated through the inhibition of SGLT2 protein expression.

Keywords: Chlorogenic Acid, Hyperlipidemia, *Sargassum ilicifolium*, SGLT2

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1. Introduction

Type 2 Diabetes Mellitus (T2DM) is a progressive metabolic disorder which is caused by insulin resistance, β-cell dysfunction, and impaired glucose metabolism. It is a non-communicable disease worldwide, affecting a huge population with high morbidity and mortality. T2DM is closely associated with various metabolic abnormalities, with dyslipidemia being one of the most common and serious complications[1-2]. Diabetic dyslipidemia[3] presents with elevated plasma triglycerides, decreased HDL cholesterol and small, dense LDL particles. This atherogenic lipid profile greatly increases the risk of macrovascular complications, especially Cardiovascular Disease (CVD), the leading cause of death among diabetic patients[4].

SGLT2[5] is a transporter protein that is highly expressed in the proximal convoluted tubules of the kidney, which facilitates the reabsorption of 90% of glucose from the glomerular filtrate[6]. Inhibiting SGLT2 protein promotes glycosuria, lowering plasma glucose levels independent of insulin secretion. SGLT2 inhibitors have also shown effects on body weight, blood pressure, lipid parameters, and cardioprotective activities. These pleiotropic effects have made SGLT2 inhibition a therapeutic target in the integrated management of T2DM and its complications, especially diabetic dyslipidemia[7].

Marine algae, especially brown seaweeds like *S. ilicifolium*[8], have gained attention for their various therapeutic potentials. This brown alga contains a variety of secondary metabolites, including sulfated polysaccharides, phlorotannins, fucoidans, and phenolic compounds, which exhibit antioxidant, anti-inflammatory, antihyperglycemic, and lipid-lowering activities[9]. Preclinical and *in vitro* studies have shown that extracts of *S. ilicifolium* can modulate carbohydrate and lipid metabolism, reduce oxidative stress, and improve insulin sensitivity, which were the key factors for the pathophysiology of T2DM and diabetic dyslipidemia[10].

One of the key bioactive compounds present in *S. ilicifolium* is chlorogenic acid[11], a polyphenolic derivative seen in terrestrial plants and known for its various pharmacological effects. Chlorogenic acid has been extensively studied for its ability to attenuate postprandial hyperglycemia by inhibiting intestinal glucose absorption and modulating glucose-6-phosphatase activity in the liver. It also exerts antihyperlipidemic effects by regulating lipid metabolism, reducing hepatic lipid accumulation, and improving plasma lipid profiles[12]. Moreover, chlorogenic acid exhibits potent antioxidant and anti-inflammatory activities, which are the two key drivers of diabetic complication s[13].

Therefore, our current study deals with the investigation of antidiabetic and hypolipidemic activity of the ethanolic extract of *S. ilicifolium* in diabetic rats. In addition, *in vitro* and *in vivo* studies were carried out using chlorogenic acid to analyse its inhibitory activity against the SGLT2 protein.

2. Materials and Methods

2.1 Chemicals and Instruments

Metformin, alloxan, Dulbecco Modified Eagle's medium (DMEM), and ethanol of high grade were purchased from Sigma Aldrich (USA). The isolated yellow solid compound was subjected to spectral characterisation using Fourier Transform Infrared Spectroscopy (FTIR), Nuclear Magnetic Resonance (NMR), and mass spectrometric techniques. FTIR spectra were recorded using a PerkinElmer FTIR spectrophotometer (Model 1650) over the wavenumber range of 4000–400cm^{-1}. ^{1}H and ^{13}C NMR spectra were obtained using a Bruker Avance NMR spectrometer operating at 400MHz and 100MHz, respectively, with Tetramethylsilane (TMS) as the internal standard. Mass spectrometric analysis was carried out using a JEOL AccuTOF JMS-T100 LC mass spectrometer.

2.2 Collection of *Sargassum ilicifolium*

Fresh samples of *S. ilicifolium* were collected near Rameswaram, Tamil Nadu, India (9.2876° N, 79.3173° E) from the intertidal zone during low tide. The algae were authenticated as *S. ilicifolium* (TAGGAB D18-A/2024/SPC NO-086) and *Sargassum longiotum*(TAGGAB D18-A/2024/SPC NO-98). algae were then washed with seawater and then with distilled water to remove epiphytes, sand, and other impurities. The seaweeds were then shade-dried for 5 days to preserve the thermolabile phytoconstituents and subsequently ground into a fine powder.

2.3 Preparation of *Sargassum ilicifolium* Extract

The extraction of bioactive phytoconstituents in *S. ilicifolium* was made with ethanol, due to its capacity to dissolve a wide variety of metabolites. 250g of the *S. ilicifolium* dried powder was added to 2500mL of ethanol (1:10 w/v ratio) and soaked for 48 hours with intermittent stirring. Soxhlet extraction was carried out, and the filtrate obtained was concentrated in a rotary evaporator under reduced pressure and dried at 40°C. 12.5g of dried extract with a yield of 5% was obtained and kept at 4°C for further experiments[14].

2.4 LC–MS Analysis

Sargassum ilicifolium extract was filtered (0.2µm), and 10µL was injected into an ACQUITY UPLC BEH C18 column using formic acid and acetonitrile as the mobile phase; compounds were identified by comparing m/z values with spectral libraries.

2.5 Isolation of Chlorogenic Acid

The dried extract was adsorbed on silica gel and subjected to column chromatography using solvents of increasing polarity; fractions 84-92 with identical Rf values were pooled. The combined fractions were concentrated, treated with activated charcoal in hot ethanol, and filtered. Crystallisation of the filtrate yielded a yellow solid, which was subjected to spectral characterisation, and the research manuscript was communicated to the Asian Journal of Pharmaceutical and Clinical Research (AJPCR).

2.6 Molecular Docking

Molecular docking studies were carried out using AutoDock tools. The crystal structure of the protein SGLT2 was downloaded from the Protein Data Bank (PDB ID-8HB0)[15]. Water molecules and cocrystallised ligand were removed from the crystal structure by making use of the PyMOL software. Proteins were further prepared for docking by the addition of polar hydrogens, Gasteiger charges were added, and then the receptors were saved in Protein Data Bank Partial Charges AutoDock Atom Types (PDBQT) format in AutoDock Tools. The structure of chlorogenic acid was retrieved from PubChem, and energy minimisation was performed in Avagadro software, and rotatable bonds and charges were assigned. Grid boxes were set at the glucose-binding pocket of SGLT2, and the prepared chlorogenic acid was allowed to interact with this region. Docking was carried out using the AutoDock Vina tool, and the results were obtained, yielding binding poses and binding affinity. The interaction of the protein-ligand complex was visualised using PyMOL and Discovery Studio.

2.7 MTT Assay

Cell viability of the isolated compound was assessed using the MTT assay in HK-2 cells. The cells were seeded in a 96-well plate with a density of $\times 10^3$ cells/well and kept for 24 hours at 37°C in 5% CO_2 incubator. Varying concentrations of chlorogenic acid (50, 100, 200, 400 and 800 µg/mL) were added to these cells and incubated for 24 hours. At the end of incubation, 20µL of MTT reagent was added, kept for 4 hours, and later the reagent was discarded, and the formazan crystals formed were dissolved by adding Dimethyl Sulfoxide (DMSO). The absorbance of the 96-well plate was read at 570nm in a microplate reader. A graph is plotted with increasing concentration of chlorogenic acid along the x-axis and the percentage of viable cells along the y-axis. IC_{50} and IC_{25} values were obtained from the graph[16].

2.8 Western Blotting

Western blot analysis was performed to determine the expression of SGLT2 upon treatment with chlorogenic acid. HK-2 cells were initially exposed to 30 mM glucose and subsequently treated with chlorogenic acid at two concentrations, 119 µg/mL and 238 µg/mL (IC_{25} and IC_{50} values). Untreated cells act as the control, while cells subjected only to high glucose serve as the negative control. As a positive control, cells were exposed to 1mM metformin after high-glucose treatment.

After the incubation of 3 hours, cell lysis was carried out using Radioimmunoprecipitation (RIPA) buffer supplemented with protease and phosphatase inhibitors, by placing the sample on ice for 30 minutes to prevent protein degradation. The lysates were centrifuged at 12,000 × g for 10 minutes at 4°C, and the supernatant, which contained the proteins, was collected. Protein concentrations were quantified using

the BCA assay. For electrophoresis, 20–30µg of protein was mixed with an equal volume of Laemmli buffer and heated at 95°C for 5 minutes. Then, the proteins were resolved on a 10–12% Sodium Dodecyl Sulfate-Polyacrylamide Gel Electrophoresis (SDS-PAGE) gel and then transferred onto a Polyvinylidene Fluoride (PVDF) membrane using a wet transfer system at 100 V for 1–1.5 hours at 4°C.

The membranes were then blocked with Bovine Serum Albumin (BSA) in Tris Buffered Saline with Tween (TBST) for 1 hour and incubated overnight at 4°C with the primary anti-SGLT2 antibody. After washing, membranes were incubated with a Horseradish Peroxidase (HRP)- conjugated secondary antibody (1:5000 dilution) for 1 hour at room temperature. Protein bands were then visualised using Enhanced Chemiluminescence (ECL) reagents and imaged with a chemiluminescence detection system[17].

2.9 NBDG Glucose Uptake Assay

The NBDG glucose uptake assay was done in HK-2 cells to evaluate SGLT2-mediated glucose uptake in the presence of chlorogenic acid at concentrations of 98 and 236 mg/mL. HK-2 cells were seeded in DMEM medium containing 5.5 mM glucose in plates with black bottoms and allowed to adhere. After overnight incubation, the cells were pretreated with High Glucose (HG, 25 or 30mM), HG + Chlorogenic Acid (CA) at IC_{25} (98 µg/mL), HG + CA at IC50 (184 µg/mL), and HG + metformin (1mM, positive control) and allowed to stand for 24 hours. Untreated cells act as a control group. At the end of incubation, the cells were washed with Phosphate-Buffered Saline (PBS) and cultured in glucose-free DMEM medium to deplete the residual glucose. Then, the addition of 2-NBDG (100 µM) was done and allowed for 30–60 minutes at 37°C in the dark for its uptake by the cells. The cells were then washed with cold Phosphate Buffered Saline (PBS) to remove the excess dye. Cellular fluorescence was measured with excitation at 465-488nm and emission at 535–550nm using a Nikon ECLIPSE Ti2 Series fluorescence microscope. Fluorescence intensity was evaluated using Nikon Imaging Software (NIS)- Elements imaging software, and the data were expressed as Relative Fluorescence Units (RFU) or as a percentage of the control after normalisation to either cell count or protein content[18].

2.10 Acute Toxicity Studies

The animal studies were approved by the institutional animal ethics committee (DMIHER/ IEAC/24-25/13 dated 25/4/2024). Acute oral toxicity of *S ilicifolium* extract was evaluated following the Organisation for Economic Cooperation and Development (OECD) Test Guideline 423 (Acute Toxic Class Method). Healthy adult female rats were used for this experiment. The rats were fasted overnight with water available ad libitum before dosing. The rats were randomly classified into four different treatment groups (Groups I-IV) based on the concentration of the extract being administered. The extract was administered by single oral gavage at doses of 5, 50, 300, and 2000 mg/kg body weight along with untreated rats, which served as a control vehicle. Animals were observed individually at least once within the first 30 minutes post-dosing, periodically during the first 24 hours, and daily for 14 days for any signs of toxicity or mortality. Body weights were recorded before the administration of the extract, on days 7 and 14, and at death. At the end of the observation period, surviving animals were euthanised and subjected to gross necropsy to assess any pathological changes. No mortality or treatment-related toxicity was observed at any dose, and classification of the extract was based on mortality outcomes according to OECD criteria[19].

2.11 Anti Diabetic Studies

Adult male Wistar rats were used for the experimentation. All animals were maintained on a standard pellet diet with free access to tap water and housed under controlled conditions, including a 12-hour light/dark cycle and ambient temperature of 20–25 °C. Each cage was clearly labelled, and rats were individually identified by a unique code marked on the tail. Following a one-week acclimatisation period to laboratory conditions, animals were randomly allocated into six groups, each containing six rats, and housed in separate stainless-steel cages.

2.12 Induction of Diabetes

Thirty adult Wistar rats aged 8–12 weeks, weighing between 190 and 250g, were chosen for the experiment. Alloxan was used for the induction of diabetes. These rats were fasted overnight, and diabetes was induced by a single intraperitoneal injection of alloxan at 50 mg/kg, prepared in a cold citrate buffer (0.1M, pH 4.5). After

a period of 72 hours, the fasting blood glucose levels were measured using a glucometer. Rats having a high glucose level of greater than 250 mg/dL were selected for inclusion in the diabetic experimental studies.

2.13 Experimental Design and Animal Treatment

Group I: Normal healthy groups were categorised as the control group

Group II: Rats were administered 50 mg/kg of alloxan (i.p.) (disease control) 28 days

Group III: Positive control administered 5 mg/kg metformin and 50 mg/kg alloxan (i.p.) for 28 days

Group IV: Treated with 200 mg/kg *S. ilicifolium* extract and 50 mg/kg alloxan (i.p.) for 28 days

Group V: Treated with 400 mg/kg *S. longiotom* extract and 50 mg/kg alloxan (i.p.) for 28 days

2.14 Measurement of Blood Glucose and Lipid Profiling

The blood samples were collected from tail vein puncture, and fasting blood glucose levels of the treatment and control groups were recorded at regular intervals of 0, 8, 15, 21 and 28 days. Glucose levels were determined using the ACCU-CHECK glucometer (Roche Products Pvt. Ltd., India)[20].

The blood samples were collected by the retroorbital plexus puncture method from the treated and control groups on 0, 8, 15, 21 and 28 days. The tubes were kept aside for 30 minutes for clotting to occur, and the serum

Table 1. LC-MS analysis of compounds in the ethanolic extract of *S. illicifolium*

S. No.	Compound Name	Class	Mol. Formula	Mol. Wt. (Da)	Peak Match (%)	RT
Alkaloids						
1	Trigonelline	Alkaloid	$C_7H_7NO_2$	137.05	99.4	1.88
2	Salsolinol	Alkaloid	$C_{10}H_{13}NO_2$	179.09	99.5	2.8
3	DL-Stachydrine	Alkaloid	$C_7H_{13}NO_2$	143.09	99	2.46
4	3-Pyridylacetic acid	Alkaloid-related	$C_7H_7NO_2$	137.05	98.9	8.2
5	NP-019811	Alkaloid-like	$C_6H_7NO_2$	125.05	99.8	2.1
Glycosides						
6	D-(+)-Maltose	Glycoside	$C_{12}H_{22}O_{11}$	342.12	99.5	2.88
7	(2R,3R,4S,5S,6R)-oxane-triol derivative	Glycoside	$C_{16}H_{28}O_7$	332.18	99.8	3.18
8	NP-013538	Glycoside-like	$C_{12}H_{16}O_8$	288.08	99.1	3.5
10	Glucoside derivative (reported fragment)	Glycoside	–	–	–	3.7
Flavonoids						
11	Quercetin	Flavonoid	$C_{15}H_{10}O_7$	302.24	–	6.1
12	Kaempferol	Flavonoid	$C_{15}H_{10}O_6$	286.24	–	9.1
13	Luteolin	Flavonoid	$C_{15}H_{10}O_6$	286.24	–	5.5
14	Apigenin	Flavonoid	$C_{15}H_{10}O_5$	270.24	–	8
15	Naringenin	Flavonoid	$C_{15}H_{12}O_5$	272.25	–	5.5
Polyphenol						
16	Chlorogenic acid	Polyphenol	$C_{16}H_{18}O_9$	354.31	>99	4.5
17	Caffeic acid	Polyphenol	$C_9H_8O_4$	180.16	–	3.8
18	Ferulic acid	Polyphenol	$C_{10}H_{10}O_4$	194.18	–	4.3
19	Gallic acid	Polyphenol	$C_7H_6O_5$	170.12	–	3.2
20	p-Coumaric acid	Polyphenol	$C_9H_8O_3$	164.16	–	4.8

was separated by centrifugation at 2500rpm at 25°C for 10 minutes. The serum was then used for the analysis of triglycerides, total cholesterol, HDL, LDL and VLDL by using a clinical chemistry analyser.

2.15 Tissue Collection and Processing

After the experiment, the animals were sacrificed, and the target organ was removed. The pancreatic tissues were carefully isolated, washed in an ice-cold saline, and then kept in 10% buffered neutral formalin solution for nearly 24 to 48 hours. The tissues were then dehydrated using ethanol, washed with xylene and then embedded in paraffin. The tissues fixed in the paraffin were then sliced using a rotary microtome with a 4–5µm thickness, placed on a glass slide, deparaffinised, and then hematoxylin and eosin were used for staining. The slides were then viewed under a microscope, and the architecture of the tissues of different groups was examined.

2.16 Statistical Analysis

Statistical comparisons between groups were conducted using One-Way Analysis of Variance (ANOVA), with statistical significance set at $p < 0.05$. When significant differences were detected, Tukey's post hoc test was applied to identify specific group differences. To evaluate changes in body weight within each group from day 0 to day 15, a paired t-test was utilised. Data were presented as mean ± Standard Error of the Mean (SEM) and summarised in tables and figures. A p-value less than 0.05 was considered indicative of statistical significance.

3. Results

3.1 Liquid Chromatography- Mass Spectrometry (LC-MS) Analysis

Compounds that are found to be present in the extract are given in Table 1, and notable ones were

Table 2. Molecular docking between Chlorogenic acid and human SGLT2 (PDB ID: 8HB0)

Target (PDB ID)	PubChem ID	Compound Name	Binding Energy (kcal/mol)	Predicted Inhibitory Constant
Human SGLT2 (PDB ID: 8HB0)	1794427	Chlorogenic acid	-8.17	1.03 µM

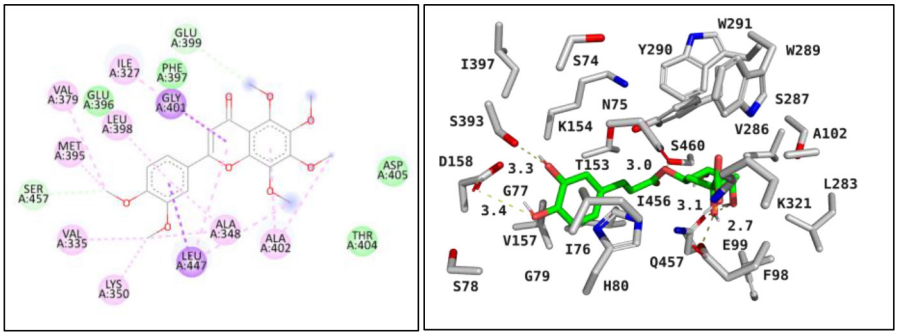


Figure 1. 2D and 3D interaction between Chlorogenic acid and the binding site residues of human SGLT2 (PDB ID: 8HB0).

Table 3. Summary of molecular interactions between Chlorogenic acid and the binding site residues of human SGLT2 (PDB ID: 8HB0)

S. No.	Interaction Type	Binding Residues
1	Hydrophobic interactions	V157, I76, I456, F98, W291, W289, Y290, V286, A102, L283
2	Hydrophilic interaction	T153, S460, E99, K154, S393, S287, Q457, K321
3	Hydrogen bond interactions	T153, S460, E99, D158, S393
4	π-π interactions	Y290, W291
5	Cation-π interactions	Possibly K154 (near aromatic ring)
6	Alkyl-π interactions	F98, I76 (π–alkyl)

caffeic acid, naringenin, coumaric acid, quercetin and luteolin. The key phytochemical is found to be chlorogenic acid with m/z of 354.31 and RT of 4.5 minutes.

3.2 Molecular Docking

Chlorogenic acid, being the most prominent phytoconstituent in *S. illicifolium* extract, undergoes molecular docking with the target protein SGLT2. The 2D and 3D molecular interactions of chlorogenic acid with human SGLT2 protein are given in Figure 1 and Tables 2 and 3. Chlorogenic binds with the SGLT2 protein with a binding energy of -8.17 kcal/mol at the glucose-binding pocket of the transporter protein. A hydrogen bond is formed between the amino acids Glu99, Thr153, Asp158, Ser393 and Gln457 with chlorogenic acid at a distance of 2.9, 3, 3.4, 3.3, and 3.1 Å. The receptor-ligand complex was stabilised by hydrophobic interactions with Ile76, Phe98, Ala102, Val157, Val286, Trp289, Tyr290, Trp291, Leu283, and Ile456. Moreover, π–π interactions with Tyr290 and Trp291, cation–π interactions with Lys154, and alkyl–π contacts with Phe98 and Ile76.

MTT Assay

Cell viability of chlorogenic acid was determined by MTT assay in HK-2 cells. The results show that there is an increase in the cytotoxic activity at higher concentrations of chlorogenic acid. 15% of cytotoxic activity was seen at 50 µg/mL and 80% of cell death at 800 µg/mL (Figures 2 and 3). It was found that the IC_{50} of chlorogenic acid in HK-2 cells was found to be 184 µg/mL

3.4 Western Blotting

The effect of chlorogenic acid on the expression of SGLT2 protein on HK-2 cells was evaluated by western blotting (Figure 4). There is a marked increase in the expression of SGLT2 protein in cells exposed to high glucose concentration. Treatment with chlorogenic acid at 98 µg/mL and 184 µg/mL markedly decreases the expression of SGLT2 protein in a dose-dependent manner. Cells treated with the standard drug, metformin, show a significant decrease in the SGLT2 protein.

3.5 2-NBDG Uptake Assay

The uptake of glucose by the HK-2 cells was evaluated by the 2-NBDG uptake assay, which is specific for the assessment of SGLT2-mediated glucose uptake. The fluorescence intensity of the treated and untreated cells is given in Figure 5. In the control group, the cells show low fluorescence intensity, whereas cells exposed to high glucose concentration exhibited increased fluorescence intensity. The intensity of the fluorescence was decreased in a concentration-dependent manner in cells treated with chlorogenic acid at IC_{25} of 98 µg/mL and IC_{50} of 184 µg/mL. Metformin at 1mM is used as a positive control, and cells do not emit any fluorescence, which indicates the inhibition of SLGT2 protein expression and, thereby, no glucose transport occurs.

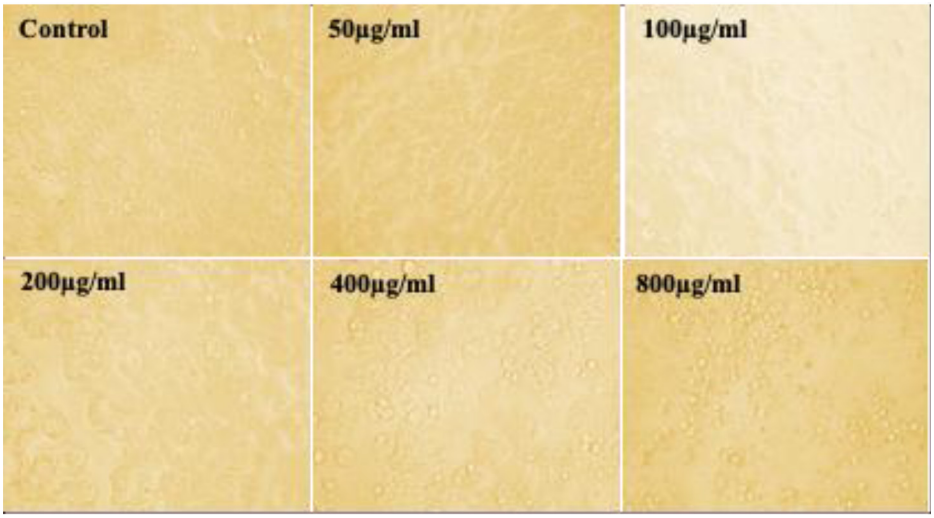


Figure 2. Cell viability of varying concentrations of Chlorogenic acid in HK-2 cells.

3.6. Acute Toxicity Studies

Acute toxicity studies show that none of the animals shows any observable signs of toxicity. All the animals were well-tolerated up to a high dose of 2000 mg/kg, which suggested that the extract is safe to be administered

3.7 Antidiabetic Activity

The effect of the ethanolic extract of *S. illicifolium* on glucose metabolism was evaluated by measuring Fasting Blood Glucose (FBG) levels at weekly intervals after 12 hours of fasting in treated and control groups. As shown in Table 4, diabetic animals (Disease Control) showed hyperglycemia compared to that of the Normal Control group, which further increased throughout the study period. Treatment with *S. illicifolium* extract resulted in a significant reduction in the blood glucose levels when compared to the diseased group, with significant decreases observed from day 8 through day 28. At the end of the experiment, the fasting blood glucose level in the *S. illicifolium* group was 203.33 ± 18.78 mg/dL, which displays the attenuation of hyperglycemia compared to the untreated diabetic animals (344.00 ± 16.42 mg/dL). The hypoglycemic effect of *S. illicifolium* was compared to that of the *S. longiotom* extract-treated group and found that *S. illicifolium* is efficient in controlling the rise in the blood glucose level. These results show that *S. illicifolium* extract possesses a hypoglycemic effect on diabetic rats.

3.8 Hypolipidemic Activity

The level of total cholesterol in the control and experimental groups was evaluated over 28 days at 5 different period of intervals and summarised in Table 5. Disease group animals show a drastic increase in the serum cholesterol, increasing from 99.67±3.27 to 183.67±6.28 mg/dL on day 28, whereas healthy animals have low cholesterol values around 98.67±1.75 throughout the study. Treatment with *S. illicifolium* produced a significant reduction in cholesterol levels compared to the diseased group, from 140.83±6.43 mg/dL on day 15 to 128.17±7.71 mg/dL on day 28. A similar effect was found in treatment with *S. longiotom*, which showed cholesterol levels reduced to 109.83±6.01 mg/dL on day 28. These results highlight that both *Sargassum* species exhibit cholesterol-lowering activity in diabetic rats.

Analysis of serum HDL concentrations (Table 6) shows a significant decrease in the untreated diseased group, whereas treatment with *S. illicifolium* restored

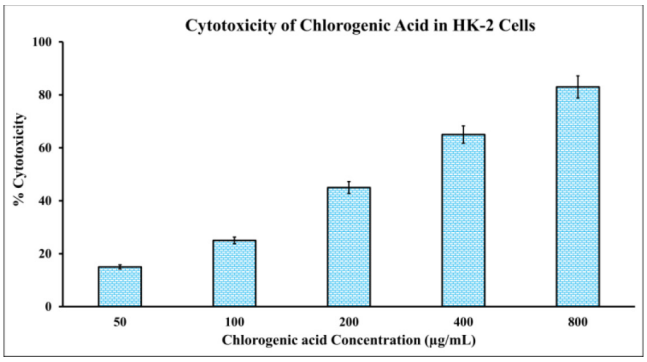


Figure 3. Cytotoxicity of different concentrations of Chlorogenic acid in HK-2 cells.

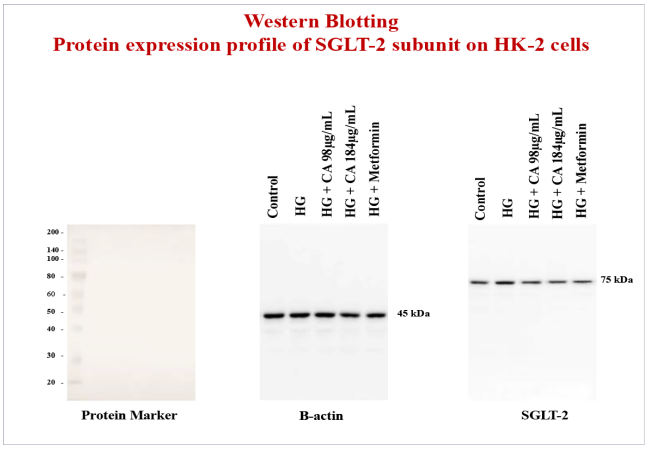


Figure 4. Western blot analysis of SGLT2 (HG - high glucose and CA - chlorogenic acid).

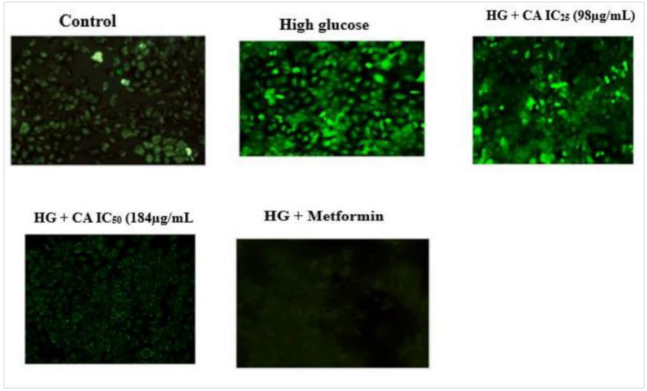


Figure 5. Fluorescence intensity of HK-2 cells in the 2-NBDG assay.

the HDL levels to the normal range of 43.50±3.01 till the end of the treatment. These values are almost similar to those of *S. longiotom*. This suggests the protective effects of *S. illicifolium* against diabetes-induced dyslipidemia.

Table 4. Effect of *S. illicifolium* extract on the blood glucose level in Alloxan-induced diabetic rats

Groups	Day 0 mg/dL	Day 8 mg/dL	Day 15 mg/dL	Day 21 mg/dL	Day 28 mg/dL
Normal Control	96.83±2.86	96.00±3.41***	95.67 ± 1.51***	94.67 ± 4.18***	97.83 ± 2.93***
Disease Control	97.50±2.88	311.33 ± 25.11	319.50 ± 21.33	334.17 ± 15.47	344.00 ± 16.42
Metformin	90.31±3.02	261.00±32.28**	230.33±26.39***	183.33±33.24***	128.00±12.02***
S. illicifolium	97.17±4.75	286.17 ±5.88**	260.83 ±3.06***	224.67±19.19***	203.33±18.78***
S. longiotom	96.50±3.94	283.83 ±9.50**	239.67±13.63***	176.17±11.32***	148.00±14.31***

Values are expressed as Mean ± SD (n = 6). Statistical analysis was carried out using one-way ANOVA followed by Dunnett's multiple comparison test. $p < 0.01$ (**), $p < 0.001$ (***) compared with Disease Control

Table 5. Effect of *S. illicifolium* extract on total cholesterol level in Alloxan-induced diabetic rats

Groups	Day 0 mg/dL	Day 8 mg/dL	Day 15 mg/dL	Day 21 mg/dL	Day 28 mg/dL
Normal Control	97.83 ± 1.72	102.17±1.47***	101.17±2.64***	100.67±1.97***	98.67 ± 1.75***
Disease Control	99.67 ± 3.27	155.00 ± 7.67	172.00 ± 4.73	178.33 ± 4.63	183.67 ± 6.28
Standard	98.50 ± 4.09	133.50 ± 4.14**	126.67±3.67***	119.67±4.32***	112.67±6.02***
S. illicifolium	98.50 ± 2.88	146.17 ± 3.43**	140.83±6.43***	133.83±7.73***	128.17±7.11***
S. longiotom	99.33 ± 2.50	134.00 ± 3.74**	123.83±4.45***	117.50±6.60***	109.83±6.01***

Values are expressed as Mean ± SD (n = 6). Statistical analysis was carried out using one-way ANOVA followed by Dunnett's multiple comparison test. $p < 0.01$ (**), $p < 0.001$ (***) compared with Disease Control.

Table 6. Effect of *S. illicifolium* extract on high-density lipoprotein (HDL) level in Alloxan-induced diabetic rats

Groups	Day 0 mg/dL	Day 8 mg/dL	Day 15 mg/dL	Day 21 mg/dL	Day 28 mg/dL
Normal Control	46.67 ±1.75	46.50±1.87***	48.00 ±0.89***	49.17 ±1.17***	49.67 ±0.82***
Disease Control	45.67 ± 3.08	34.50 ± 2.74	32.17 ± 2.48	27.50 ± 1.98	23.67 ± 1.03
Standard	47.17 ± 2.23	40.00 ± 2.10**	43.17 ±1.60***	45.00 ±1.41***	46.17 ±1.47***
S. illicifolium	43.83 ± 1.47	41.83 ± 2.93**	41.00 ±2.76***	39.67 ±3.27***	43.50 ±3.02***
S. longiotom	44.00 ± 0.89	40.00 ± 1.41**	41.67 ±1.21***	44.00 ±1.10***	45.00 ±1.41***

Values are expressed as Mean ± SD (n = 6). Statistical analysis was carried out using one-way ANOVA followed by Dunnett's multiple comparison test. $p < 0.01$ (**), $p < 0.001$ (***) compared with Disease Control

Table 7. Effect of *S. illicifolium* extract on low-density lipoprotein (LDL) level in Alloxan-induced diabetic rats

Groups	Day 0 mg/dL	Day 8 mg/dL	Day 15 mg/dL	Day 21 mg/dL	Day 28 mg/dL
Normal Control	30.33 ± 1.75	30.00 ±1.10***	30.33 ±1.63***	30.17 ±0.75***	29.83 ±1.47***
Disease Control	31.67 ± 1.21	72.67 ± 3.67	85.83 ± 3.97	93.50 ± 4.76	100.17 ± 2.14
Standard	32.17 ± 1.47	66.67 ±4.55**	56.67 ±4.76***	50.17 ±4.83***	43.33 ±4.32***
S. illicifolium	31.83 ± 1.47	75.50 ± 5.24ns	68.33 ± 4.50**	62.17 ±4.62***	57.00 ±4.56***
S. longiotom	32.17 ± 1.33	72.50 ±3.27**	61.17 ±2.40***	53.33 ±2.42***	46.50 ±1.38***

Values are expressed as Mean ± SD (n = 6). Statistical analysis was carried out using one-way ANOVA followed by Dunnett's multiple comparison test. $p < 0.01$ (**), $p < 0.001$ (***) compared with Disease Control; ns = not significant.

As presented in Table 7, there is a marked increase in LDL over the study period in the diabetes group. Treatment with *S. illicifolium* reduced the increased level of LDL in diabetic rats to 57.00±4.56 mg/dL at day 28. This provides evidence of the hypolipidemic activity of *S. illicifolium* in diabetic hyperlipidemia.

The VLDL levels in the treated and control groups are provided in Table 8. *S. illicifolium* treatment maintained the VLDL concentrations near the normal range levels at 21.27±1.35, which is almost similar to the *S. longiotom* 18.93±1.96 mg/dL) groups. These results suggest that both Sargassum species are effective in reducing VLDL in diabetic hyperlipidemia.

Table 8. Effect of *S. illicifolium* extract on very low-density lipoprotein (VLDL) level in alloxan-induced diabetic rats

Groups	Day 0 mg/dL	Day 8 mg/dL	Day 15 mg/dL	Day 21 mg/dL	Day 28 mg/dL
Normal Control	19.12 ± 1.75	19.22 ± 1.20***	19.42 ± 0.69***	18.74 ± 0.65***	19.23 ± 0.79***
Disease Control	20.07 ± 1.55	29.60 ± 3.67	32.58 ± 3.77	34.30 ± 3.60	36.87 ± 3.77
Standard	19.23 ± 0.92	26.05 ± 1.34**	22.57 ± 1.47***	20.15 ± 1.93***	18.50 ± 1.48***
S. illicifolium	18.12 ± 0.63	25.87 ± 1.47**	23.53 ± 1.09***	21.92 ± 1.35***	21.27 ± 1.36***
S. longiotom	19.32 ± 1.05	24.15 ± 2.65**	21.97 ± 2.00***	20.12 ± 1.81***	18.93 ± 1.97***

Values are expressed as Mean ± SD (n = 6). Statistical analysis was carried out using one-way ANOVA followed by Dunnett's multiple comparison test. $p < 0.01$ (**), $p < 0.001$ (***) compared with Disease Control; ns = not significant.

Table 9. Effect of *S. illicifolium* extract on triglycerides (TG) level in Alloxan-induced diabetic rats

Groups	Day 0 mg/dL	Day 8 mg/dL	Day 15 mg/dL	Day 21 mg/dL	Day 28 mg/dL
Normal Control	86.17 ±4.17	84.33 ± 3.45***	82.67 ± 3.39***	82.83 ±1.94***	85.33 ±2.94***
Disease Control	87.00 ±5.14	131.50 ± 4.85	137.50 ± 5.68	142.67 ± 4.18	150.17 ± 5.00
Standard	90.33 ±2.16	125.33 ± 3.88**	117.17 ± 4.07***	103.50 ± 4.14***	92.17 ±2.79***
S. illicifolium	84.67 ±3.62	132.00 ± 5.18 ns	127.50 ± 4.23**	123.67 ± 3.78***	117.67±4.72***
S. longiotom	85.00 ± 3.69	119.50 ± 5.54**	112.00 ±8.65***	103.50 ± 5.05***	94.50 ±3.73***

Values are expressed as Mean ± SD (n = 6). Statistical analysis was carried out using one-way ANOVA followed by Dunnett's multiple comparison test. $p < 0.01$ (**), $p < 0.001$ (***) compared with Disease Control; ns = not significant.

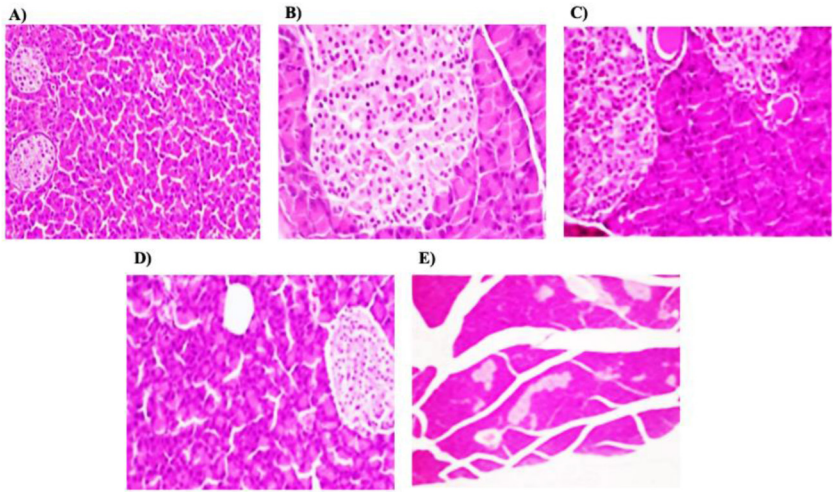


Figure 6. **(A).** Normal control pancreas; **(B).** diabetic control pancreas; **(C).** metformin-treated group; **(D).** *S. illicifolium*-treated group; **(E).** *S. longiotom*-treated group showing comparative histopathological changes.

The concentration of triglycerides in the control and treatment groups is given in Table 9. The disease group showed a marked increase in triglyceride levels, rising to 150.17±4.99 mg/dL, which indicates the onset of dyslipidemia. Diabetic rats treated with *S. illicifolium* show a decrease in triglyceride levels of 117.67±4.71 mg/dL at the end of 28 days. These findings indicate that *S. illicifolium* extract exerts a significant protective effect against diabetes-induced hypertriglyceridemia.

3.9 Histology

Histopathological examination of pancreatic tissue revealed normal architecture with well-defined islets of Langerhans and intact acinar cells in the normal control group, as given in Figure 6. In contrast, the diabetic control group showed marked distortion of pancreatic architecture characterised by severe degeneration and shrinkage of islets with reduced cellularity. Treatment with metformin resulted in partial restoration of pancreatic

structure, with improvement in islet size and cellular organisation. Administration of *S. illicifolium* produced moderate regeneration of pancreatic islets with improved cellular density compared to the diabetic control. Notably, *S. longiotom* treatment showed near-normal restoration of pancreatic architecture, with well-preserved islets and acinar cells comparable to the normal control group.

4. Discussion

LC-MS analysis shows the existence of various bioactive phytocompounds in the extract. The presence of chlorogenic acid in the seaweed was reported in previous studies[21-24]. The spectral characterisation of chlorogenic acid was done by FTIR, Proton[1]- Nuclear Magnetic Resonance (H-NMR), Carbon[13] Nuclear Magnetic Resonance (C-NMR), and mass spectrometry and communicated in our previous studies.

Molecular docking interactions between chlorogenic acid and SGLT2 proteins reveal its inhibitory activity against this protein. Inhibition of this protein diminishes the renal tubular glucose reabsorption, thereby lowering the blood glucose without stimulating insulin release. The key amino acid residues that were involved in this interaction align with the previous literature[25].

SGLT2-mediated glucose influx in HK-2 cells was assessed by the 2-NBDG uptake assay. The transport of glucose by SGLT2 is coupled with the transport of sodium ions in the ratio of 1:1. 2-NBDG enters the cells in the presence of Na+, where it is phosphorylated by the hexokinase and is responsible for intracellular fluorescence, which is detected by a fluorescence microscope. The intensity of the fluorescence is directly proportional to the amount of 2-NDBG uptake (glucose transport). Cells exposed to high glucose show a higher degree of fluorescence, which is due to the increased transport of 2-NDBG mediated by SGLT2. Treatment with IC_{25} and IC_{50} concentrations of chlorogenic acid significantly inhibited the SGLT2 protein, thereby decreasing the transport of 2-NDBG and low fluorescence intensity[26]. These results revealed that *S. illicifolium* extract exhibited antidiabetic activities. Moreover, the key phytoconstituent, chlorogenic acid, lowers the glucose reabsorption by inhibiting the SGLT2 protein in renal cells.

The antidiabetic activity of *S. illicifolium* evaluated in this study aligns with previous studies reporting the efficacy and various biological activities such as hypoglycemic, antioxidant, and alpha-amylase inhibition. The primary bioactive constituents, such as phlorotannins and other polyphenols, play a pivotal role in the inhibition of α-amylase and α-glucosidase, which decreases carbohydrate hydrolysis and glucose absorption. Studies on *Sargassum* species demonstrated a significant decrease in fasting blood glucose and improved pancreatic histopathology[27,28].

The cholesterol-lowering effect of *S. illicifolium* provides evidence in modulating lipid metabolism exhibited by marine brown algae. Bioactive constituents in *Sargassum* species revealed that the total cholesterol level is decreased by intestinal cholesterol absorption inhibition and enhances hepatic cholesterol catabolism. These mechanisms contribute to improved serum lipid profiles and decrease the risk of atherosclerosis[29].

The ethanolic extract of *S. illicifolium* modulates the lipid levels in diabetic-induced dyslipidemia rats, which aligns with previous findings that demonstrate its hypolipidemic activity. The bioactive phytoconstituents were found to lower the levels of total cholesterol, LDL, and VLDL by decreasing intestinal cholesterol absorption, increasing the secretion of bile acid, and hepatic lipid metabolism and clearance. Fucoidan, one of the prominent phytoconstituents in *Sargassum*, exhibits anti-inflammatory and antioxidant effects that protect against lipid peroxidation and dyslipidemia[30]. The level of triglycerides is reduced by inhibition of pancreatic lipase, which is required for the absorption and digestion of triglycerides in the gastrointestinal tract. Moreover, the polysaccharides in the extract increase the hydrolysis of triglycerides in the blood[31].

Alloxan-induced diabetes in rats creates various alterations in the body, such as an increase in glucose level, polyphagia, decreased insulin secretion, etc. These changes were due to the damage to the β-cells of the islets of Langerhans in the pancreas that diminishes insulin secretion. Administration of *S. illicifolium* shows improvement in the islet morphology by inhibiting the pathways involved in the apoptosis of β-cells through the bioactive constituents present in it[32].

SGLT1 and SGLT2 are the key glucose-cotransporters, with SGLT1 found in the intestine, whereas SGLT2 is found in renal cells, responsible for nearly 90% of glucose reuptake from the glomerulus filtrate. Selective inhibition of SGLT2 protein increases

the excretion of glucose in the urine, thereby decreasing its concentration in the blood[33]. Treatment of HK-2 cells exposed to high glucose with chlorogenic acid inhibits the expression of SGLT2 proteins, thereby acting as a potent therapeutic agent for T2DM.

The histological analysis of the pancreatic tissues provides the structural features in the diseased and treated groups. A normal pancreas shows well-defined islets of Langerhans and acinar cells. In the untreated diabetic rats, pancreatic tissue shows severe shrinkage of islets, β-cell depletion, acinar cell vacuolation, lymphocytic infiltration, and focal necrosis, which suggests pancreatic damage. Treatment with *S. illicifolium* extract results in the moderate restoration of tissue architecture of the pancreas, evident by the improvement in islet morphology, decreased acinar degeneration, fibrosis, and necrosis. The *S. longiotom*-treated group shows partial restoration of pancreatic histoarchitecture with a decrease in fibrosis and necrosis. The metformin-treated group shows complete preservation of pancreatic tissue.

5. Conclusion

This study demonstrates the antidiabetic and lipid-lowering (antilipidemic) effect of *S. ilicifolium* extract in diabetic rats. The extract markedly decreases the level of total cholesterol, triglycerides, LDL and VLDL and increases HDL level. The blood glucose level is also being drastically reduced by preserving the architecture of the beta-cells of the pancreas. Among the various phytochemicals present in it, chlorogenic acid is found to be the chief constituent, and it is found to decrease the blood glucose level by inhibiting the SGLT2 protein, which is confirmed by the *in vitro* studies. This revealed the hypoglycaemic, hypolipidemic activities and conservation of histologic changes of *S. ilicifolium* extract that occurs in T2DM. Taken together, these results provided evidence that *S. ilicifolium* extract, due to the presence of chlorogenic acid and other phytochemicals, has the ability to be developed as a promising therapeutic agent for the treatment of T2DM and its associated hyperlipidemia.

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Authors Contribution

Rahul Ingle contributed to the conceptualisation and literature collection. Manuscript design, experimental work, analysis and final draft preparation were done by Ch Ramya. Gurusamy Mariappan and Reena Sowmya were involved in drafting the manuscript. All authors have read and agreed to the published version of the manuscript.