MarineMedicine

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ORIGINAL RESEARCH ARTICLE

Undaria pinnatifida (Wakame) Attenuates Hyperglycemia-dysregulated Signaling and Metabolic Enzyme Activities in Isolated Rat Jejunum: An *ex vivo* and *in silico* Investigation

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Abstract

Background/Objectives: Diabetes mellitus is associated with impaired glucose metabolism and dysregulated metabolic signaling pathways. This study aimed to evaluate the potential of *Undaria pinnatifida* extracts to inhibit intestinal glucose absorption and modulate related biochemical pathways using an *ex vivo* experimental model. **Methods:** Freshly isolated rat jejunum tissues were incubated with glucose and varying concentrations of aqueous and ethanol extracts of *U. pinnatifida* for 2 hours at 37 °C. Acarbose was used as a positive control. Biochemical assays were conducted to examine glucose absorption, ATPase activity, glutathione metabolism, digestive enzyme activity, and key metabolic regulators. *In silico* molecular docking was also performed to evaluate the interactions of identified phytoconstituents with sodium glucose co-transporter 1 (*SGLT1*). **Results:** Exposure to high glucose levels significantly increased jejunal glucose absorption, reduced ATPase activity, disrupted glutathione metabolism, and elevated digestive enzyme activity and metabolic regulators, including acetylcholinesterase, Ectonucleoside Triphosphate Diphosphohydrolase (ENTPDase), glucose-6-phosphatase (G-6-Pase), fructose-1,6-bisphosphatase (F-1,6-Bpase), and glycogen phosphorylase. Treatment with *U. pinnatifida* extracts reversed most of these dysregulations. *In silico* analysis further revealed that fucoxanthinol, among other phytoconstituents, showed a higher binding affinity to *SGLT1* compared to Sotagliflozin, a clinically approved inhibitor. **Conclusion:** *U. pinnatifida* extracts demonstrated the ability to modulate glucose absorption and restore dysregulated intestinal biochemical parameters. These findings support the therapeutic potential of this seaweed in managing intestinal dysregulation in diabetic conditions.

Keywords: *Undaria pinnatifida*, Fucoxanthinol, Hyperglycemia, Glucose absorption, *SGLT1*, Jejunum

About this Article:
Received: 10 September 2025
Accepted: 26 November 2025
Published: 15 January 2026

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Cite this Article:
Magwaza, S.N., Olofinsan, K.A., Hlongwane, N.P., et al. *Undaria pinnatifida* (Wakame) Attenuates Hyperglycemia-dysregulated Signaling and Metabolic Enzyme Activities in Isolated Rat Jejunum: An *ex vivo* and *in silico* Investigation. *MarineMedicine*. 2026,2(1):56–76. https://doi.org/10.64187/mm.2026.v2.i1.004

1. Introduction

The intestine, particularly the small intestine, plays a vital role in breaking down food and absorbing nutrients like glucose.[1,2] One of its key functions is the regulation of postprandial hyperglycemia. After carbohydrate ingestion, glucose is predominantly absorbed in the jejunum, subsequently entering the bloodstream and causing an increase in blood glucose concentration.[2] In healthy individuals, insulin regulates this rise, facilitating glucose uptake into peripheral tissues for energy production or storage.[2] However, in individuals with insulin resistance or impaired glucose metabolism, frequently observed in obesity and type 2 diabetes, glucose absorption may be excessive or dysregulated, leading to postprandial hyperglycemia.[3] Elevated blood glucose levels characterize this condition due to inefficient uptake by peripheral tissues. Contributing factors include increased glucose influx from dietary carbohydrates, enhanced hepatic glucose production, impaired pancreatic insulin secretion, and diminished glucose uptake by skeletal muscle and adipose tissue after absorption from the small intestine.[4]

The intestine is increasingly recognized as an active regulator of metabolic health, extending beyond its traditional role in nutrient absorption.[5] It exerts systemic effects through the release of incretin hormones such as glucagon-like peptide-1 (*GLP-1*), modulation of gut microbial balance, and control of oxidative damage.[5,6] Among the key antioxidant defense mechanisms in the intestine, the glutathione metabolism modulated by the gut microbiota plays a vital role in preserving redox homeostasis and maintaining epithelial barrier integrity.[7] Glutathione, a major intracellular antioxidant, protects against oxidative damage and supports intestinal function.[8] Impaired glutathione activity, commonly observed in metabolic disorders, can exacerbate intestinal inflammation and compromise gut function.[8] The interplay between the gut microbiota and glutathione metabolism constitutes a crucial axis influencing intestinal and systemic metabolic health.[7,9]

On the other hand, the sodium-glucose cotransporter 1 (*SGLT1*), which serves as the main transporter for active glucose uptake at the enterocyte apical membrane, is another key regulator of intestinal glucose processing.[10] Improper regulation of *SGLT1* may result in the overabsorption of glucose and play a role in the development of postprandial hyperglycemia. Intestinal motility and secretion are also modulated by cholinergic and purinergic pathways. Signaling through acetylcholine (cholinergic) stimulates smooth muscle contraction and increases intestinal motility, thereby influencing the transit and absorption of nutrients [11]. Meanwhile, signaling through extracellular nucleotides like ATP (purinergic) controls ion transport, secretion, and local gastrointestinal blood flow.[12] Metabolic dysfunctions and compromised gut activity have been associated with changes in these neurochemical signaling pathways, which may be modulated by seaweed extracts.

Seaweed represents a promising natural source of bioactive compounds. Brown seaweeds, in particular, are rich in bioactive substances such as fucoxanthin, polyphenols, sulfated polysaccharides, and dietary fiber, which have been associated with various metabolic benefits.[13] These compounds may exert anti-obesity effects by enhancing lipid metabolism and promoting thermogenesis, as fucoxanthin has been shown to stimulate energy expenditure and inhibit adipogenesis in animal models.[13] Seaweeds also possess anti-diabetic properties, as their components can inhibit carbohydrate-digesting enzymes such as α-amylase and α-glucosidase, thereby helping to control postprandial blood glucose levels. Additionally, seaweed extracts have been reported to improve insulin sensitivity and reduce oxidative stress.[14] Beyond their systemic effects, seaweeds may support gut health through their high fiber content, which can positively influence the gut microbiota and promote metabolic regulation.[15] Moreover, these compounds may enhance intestinal antioxidant defenses, including glutathione-associated pathways.[13] Together, these properties highlight the potential of seaweeds as functional dietary components in managing hyperglycemia and metabolic dysfunction associated with diabetes, when *Undaria pinnatifida* (Harvey) Suringar (Alariaceae) is widely consumed in many countries in the world.

Undaria pinnatifida, commonly known as Wakame, is an edible brown seaweed traditionally consumed in East Asia and increasingly recognized for its rich profile of bioactive compounds, including fucoxanthin, phlorotannins, sulfated polysaccharides (e.g., fucoidan), and essential minerals.[16] These constituents have been associated with a broad-spectrum biological activity, such as antioxidant, anti-inflammatory, anti-obesity, and anti-diabetic effects.[14,17] Fucoxanthin

has been reported to reduce intestinal glucose absorption by downregulating the expression and translocation of glucose transporters, including *SGLT1* and *GLUT2*, in the intestine. Its metabolite fucoxanthinol may contribute to these effects, but given that direct comparative evidence on *SGLT1* regulation is limited, their individual roles should be interpreted with caution.[14] Additionally, while the systemic benefits of *U. pinnatifida* are increasingly documented, the direct influence on the crucial intestinal mechanism of glucose management is still unknown. This research gap includes its effect on the *SGLT1* transporter, cholinergic and purinergic pathways, and the maintenance of intestinal glutathione metabolism. This study tested the hypothesis that *U. pinnatifida* extract contributes to improving postprandial glucose regulation by modulating intestinal glucose absorption, redox balance, and gut neurochemical signaling. Therefore, using an isolated rat jejunum model, we aimed to evaluate its effects on glucose digestion and *SGLT1*-mediated transport, assess its impact on cholinergic and purinergic signaling pathways, and determine its influence on intestinal glutathione redox status. Together, these findings yield novel mechanistic insights into the gut-specific actions of *U. pinnatifida* and support its potential as a functional food ingredient for metabolic diseases.

2. Materials and Methods

2.1 Collection and Preparation of *U. pinnatifida*

In December 2023, U. pinnatifida was collected from the Yzerfontein coastline in the Western Cape, South Africa, under a permit issued by the Department of Forestry, Fisheries, and Environment (Reference: RES2021/92; BABS discovery notification: 001321N). The species was taxonomically identified at the Bews Herbarium, located at Pietermaritzburg Campus of the University of KwaZulu-Natal, and a voucher specimen was archived with an accession number NU0092415. Its classification was further validated using online databases, including the World Register of Marine Species (WoRMS) (https://www.marinespecies.org/aphia.php?p=taxdetails&id=145721) and AlgaeBase (https://www.algaebase.org/search/species/detail/?species_id=350). After collection, the seaweed was thoroughly washed with freshwater to eliminate salt and surface impurities before freeze-drying. It was subsequently ground into a fine powder and stored in sealed containers under cool conditions until further analysis.

2.2 Undaria pinnatifida Ethanol and Aqueous Extraction

The crude ethanolic extract of *U. pinnatifida* was prepared using a previously published method proposed by Mesmar et al.[18], after slight modifications. Ten grams of powdered seaweed was extracted with 100 mL of 90% ethanol at room temperature for 24 hours, with intermittent shaking at 150 rpm. To collect the supernatant, the mixture was centrifuged at 4,000 × g for 30 minutes at room temperature. The pellet was re-extracted twice under the same conditions, and all supernatants were mixed and concentrated using a rotary evaporator set at 40 ℃. The remaining pellet from ethanol extraction was vacuum-dried at 40 ℃ and used for aqueous extraction. The dried material was suspended in 1.5% (*w/v*) distilled water and stirred continuously at room temperature overnight. After filtration using Buchner funnel lined with a Whatman TG 100 Separating Gauze, the supernatant was mixed with a two-fold volume of 90% ethanol and refrigerated at 4 ℃ overnight to allow precipitation. The ethanol was added dropwise with gentle stirring at a rate of approximately 2 mL per minute. The resulting precipitation was recovered by centrifugation at 4,000 × g for 30 minutes at 4 ℃, and subsequently lyophilized to obtain the aqueous extract. The lyophilized extract was blended into powder and stored at 4 ℃ until further analysis

2.3 Animals

Five male Wistar rats weighing 180–200 g were obtained from the Biomedical Research Unit of the University of KwaZulu-Natal in Durban, South Africa. The animals were housed under controlled environmental conditions, including a 12-hour light/dark cycle, a temperature of 24 ± 1 ℃, and 40–60% relative humidity. Food (Meadows, Pietermaritzburg, South Africa) and water were provided *ad libitum*. Following an 8-hour overnight fast, the animals were sacrificed humanely with isoflurane inhalation. The small intestines (jejunum) were then removed and used immediately for *ex vivo* experiments. All animal experiments were conducted after obtaining approval from the Animal Research Ethics Committee of the University of KwaZulu-Natal, Durban, South Africa (Ethical approval number: AREC/00007168/2024.

2.4 Intestinal Glucose Absorption

The effect of *U. pinnatifida* on jejunal glucose absorption was assessed using a modified version of a previously published method.[19] Freshly excised jejunal tissue segments were cut into 5-cm lengths. Each segment was everted to expose the mucosal surface, and the luminal contents were gently flushed with Krebs buffer using a sterile syringe. Each jejunal segment was transferred to a test tube containing 8 mL of Krebs buffer (118 mM NaCl, 5 mM KCl, 1.3 mM $CaCl_2 \cdot 2H_2O$, 1.2 mM KH_2PO_4, 1.2 mM $MgSO_4$, and 25 mM $NaHCO_3$) with 11.1 mM glucose and different concentrations (30–240 µg/mL) of the *U. pinnatifida* extracts. The solution was incubated for 2 h at 37 ℃ in a 5% CO_2 incubator. The control sample was prepared without *U. pinnatifida* extract, whereas acarbose (240 µg/mL) was used as a positive control. All experiments were done in triplicate, and the solution's initial and final glucose concentrations were measured using an automated chemistry analyzer (Labmax Plenno, Labtest Inc., Lagoa Santa, Brazil). The following formula was used for calculating glucose uptake by intestinal tissue:

$$\text{Glucose absorption per cm of rat jejunum} = \frac{GC_1 - GC_2}{\text{length of jejunum in cm}} \quad (1)$$

where, GC1 and GC2 are the glucose concentrations before and after the incubation, respectively.

After 2 hours of incubation, each jejunum tissue was removed from the incubation buffer, homogenized in cold 50 mM phosphate buffer (pH 7.5) with 1% Triton X-100, and centrifuged at 15,000 rpm for 10 minutes at 4 ℃. The collected supernatants were kept at −20 ℃ for biochemical analysis.

2.5 Assessment of Digestive Enzyme Inhibitory Activity

2.5.1 Lipase Inhibitory Activity

The lipase activity in the seaweed extracts or orlistat pre-treated jejunal tissue homogenate was assessed following a slightly modified method as outlined previously.[20] Briefly, 100 µL of the jejunal tissue supernatant was combined with 169 µL of Tris buffer (containing 100 mM Tris–HCl and 5 mM $CaCl_2$, pH 7.0) and incubated at 37 ℃ for 15 minutes. Subsequently, 5 µL of 10 mM p-nitrophenyl butyrate (p-NPB) prepared in dimethylformamide was added, followed by a second incubation at 37 ℃ for an additional 15 minutes. The enzyme inhibitory activity was measured by recording absorbance at 405 nm every minute for 5 minutes. Lipase activity was calculated based on the rate of absorbance change per minute (ΔA/min).

2.5.2 α-Amylase Inhibitory Activity

Amylase activity in seaweed extracts or acarbose pre-treated jejunal tissue samples was investigated using a known protocol, with minor changes.[21] Fifty microliters of the jejunal supernatant were mixed with 50 µL of 1% starch solution prepared in phosphate buffer to measure the α-amylase activity. The reaction mixture was incubated at 37 ℃ for 30 minutes. After incubation, 200 µL of dinitrosalicylic acid (DNS) reagent (8.77 mM DNS, 10.62 mM Phenol, 5.6 mM Sodium metabisulfite, 0.2 mM NaOH, and 212.6 mM Potassium Sodium Tartrate·$4H_2O$) was added, and the solution was heated for 10 minutes at 100 ℃ to facilitate color development. The absorbance readings were then taken at 540 nm at 1-minute intervals for 5 minutes. The amount of reducing sugars formed during the reaction was employed for evaluating the amylase activity, which was expressed as the change in absorbance per minute (ΔA/min).

2.5.3 Cholesterol-esterase Inhibitory Activity

Cholesterol esterase activity in seaweed extracts or orlistat pre-treated jejunal supernatants was determined using a procedure adapted from a previously published method proposed by Pietsch and Gutschow.[22] The assay was performed by combining 100 µL of the supernatant with 100 µL of 5.16 mM taurocholic acid and 90 µL of 0.2 mM p-nitrophenylbutyrate (p-NPB), when all prepared in a 100 mM sodium phosphate buffer (pH 7.0) containing 100 mM NaCl. To initiate the enzymatic reaction, 5 µL of porcine pancreatic cholesterol esterase (1 µg/mL) was added. The reaction mixture was then incubated at 25 ℃ for 5 minutes. The reading of absorbance was recorded at 405 nm every minute for 5 minutes, and the activity of enzymes was determined based on the rate of absorbance change per minute (ΔA/min)

2.6 Determination of Cholinergic Enzyme Activity

The acetylcholinesterase activity in seaweed extracts or acarbose pre-treated jejunal tissue was assessed using Ellman's colorimetric method[23], which is commonly used to evaluate cholinergic activity in biological samples. In this assay, 200 µL of the tissue homogenate was combined with 100 µL of Ellman's reagent (3.3 mM, pH 7.0; purchased from Thermo Fisher Scientific, South Africa) and 500 µL of phosphate buffer (0.1 mM, pH 8.0). The solution was then incubated for 20 minutes at 25 ℃. Subsequently, 100 µL of 0.05 M acetylcholine iodide was introduced to initiate the enzyme reaction. As the acetylcholine was broken down, it released thiocholine, which reacted with Ellman's reagent to form a yellow-colored compound, 5-thio-2-nitrobenzoate. The absorbance of the colored solution was recorded at 412 nm at every 3 minutes for 9 minutes, before the calculation of the sample acetylcholinesterase activity from the rate of change of absorbance per minute (ΔA/min).

2.7 Determination of Purinergic Enzyme Activities

2.7.1 Assessment of ATPase Activity

The activity of adenosine triphosphatase (ATPase) was determined by measuring the amount of inorganic phosphate (Pi) released during ATP hydrolysis.[24] For the assessment of ATPase activity, 200 µL of tissue homogenate was combined with a reaction mixture consisting of 200 µL of 5 mM potassium chloride (KCl), 1,300 µL of 0.1 mM Tris-HCl buffer, and 40 µL of 50 mM ATP. The mixture was stirred continuously and incubated for 30 minutes at 37 ℃. The reaction was terminated by the addition of 1 mL of distilled water and an ammonium molybdate reagent. Subsequently, 1 mL of freshly prepared 9% ascorbic acid was introduced, and the mixture was incubated at room temperature for 30 minutes to facilitate color formation before absorbance was recorded at 660 nm using a spectrophotometer. ATPase activity was quantified based on the amount of inorganic phosphate (µmol Pi) released per minute.

2.7.2 Assessment of ENTPDase Activity

Ectonucleoside Triphosphate Diphosphohydrolase (ENTPDase) activity was evaluated by quantifying the amount of inorganic phosphate (Pi) released during ATP hydrolysis.[25] A volume of 20 µL of the intestinal tissue homogenate was mixed with 200 µL of a reaction solution composed of $CaCl_2$ (1.5 mM), KCl (5 mM), ethylenediaminetetraacetic acid (EDTA) (0.1 mM), glucose (10 mM), sucrose (225 mM), and Tris-HCl buffer (45 mM). This mixture was incubated at 37 ℃ for 10 minutes. Afterwards, 20 µL of 50 mM ATP was added, and the combined solution was gently mixed and incubated for an additional 20 minutes at the same temperature. The enzymatic process was halted by introducing 200 microliters of 10% trichloroacetic acid. For colorimetric detection, 200 microliters of 1.25% (*w/v*) ammonium molybdate and freshly prepared 9% ascorbic acid solutions were added, then the sample was chilled on ice for 10 minutes. ENTPDase activity was determined by measuring the absorbance at 600 nm, with enzyme activity reported as micromoles of inorganic phosphate released per minute.

2.8 Assessment of Glucogenic Enzyme Activities

2.8.1 Glucose-6-phosphatase

The glucose-6-phosphatase (G-6-Pase) activity was evaluated using a colorimetric approach that relied on the release of inorganic phosphate.[26] A one hundred microliters of jejunal homogenates were incubated at 37 ℃ for 30 minutes with a mixture containing 50 mM ATP, 0.25 mM glucose, 5 mM potassium chloride, and 0.1 mM Tris-HCl buffer to measure glucose-6-phosphatase activity. The reaction was terminated by adding 1 mL of distilled water along with 1.25% ammonium molybdate. Subsequently, freshly prepared 9% ascorbic acid was added, and the solution was incubated for an additional 30 minutes. Absorbance was measured at 660 nm using a spectrophotometer. Enzyme activity was determined by calculating the amount of inorganic phosphate released, referencing a standard curve, and expressed as micromoles of inorganic phosphate released per minute.

2.8.2 Fructose-1,6-bisphosphatase

Fructose-1,6-bisphosphatase (Fruc-1,6-BPase) activity was assessed using a colorimetric assay based on the breakdown of fructose-1,6-bisphosphate.[26] For the assay, 100 µL of jejunal homogenate was incubated at 37 ℃ for 15 minutes with a 100 µL reaction solution containing 0.1 M Tris-HCl buffer (pH 7.0), 0.05 M fructose-1,6-bisphosphate, 0.1 M magnesium chloride, 0.1 M potassium chloride, and 1 mM EDTA. The enzymatic reaction was terminated by adding 50 µL of 10% trichloroacetic acid. Following centrifugation at 5,000 × g for 10 minutes, the supernatant was collected. Freshly prepared 9% ascorbic acid (50 µL) was then added, and the mixture was incubated for 30 minutes. Absorbance was measured at 680 nm. Enzyme activity was quantified by relating the released inorganic phosphate to a standard curve and expressed as micromoles of phosphate liberated per minute.

2.9 Glycogen Phosphorylase

The activity of glycogen phosphorylase was determined using a colorimetric test based on the release of inorganic phosphate.[26] For the glycogen phosphorylase assay, 100 µL of jejunal homogenate was mixed with a 100 µL reaction solution containing glucose-1-phosphate (64 mM) and glycogen (4%), then incubated for 10 minutes at 30 ℃. To stop the reaction, 1 mL of 20% ammonium molybdate reagent, Elon reducer, and distilled water were introduced before the solution was incubated at 30 ℃ for 45 minutes to allow the color to develop. The absorbance was recorded at 600 nm, and enzyme activity was quantified by comparing the amount of released inorganic phosphate (Pi) against a standard curve, with results expressed as micromoles of Pi released per minute.

2.10 Glutathione and Glutathione-Linked Enzyme Assay

2.10.1 Reduced Glutathione Levels

Reduced glutathione (GSH) levels in jejunal samples were measured using a colorimetric test based on Ellman's method.[23] To remove proteins, 150 µL of jejunal supernatant was treated with an equal volume of 10% trichloroacetic acid (TCA). The solution was then spun in a centrifuge machine at 2,000 rpm for 10 minutes at 25 ℃. Following separation, 80 µL of the clear liquid was collected and placed into a 96-well plate, where it was mixed with 40 µL of a 0.5 mM 5,5'-dithiobis (2-nitrobenzoic acid) (DTNB) solution (prepared in 0.1 M phosphate buffer, pH 8.0). After that, 200 µL of 0.2 M phosphate buffer (pH 7.8) was added, and the plate was kept at room temperature (25 ℃) for 15 minutes. The level of GSH was quantified by measuring the absorbance and comparing it to a standard curve prepared from known GSH concentrations.

2.10.2 Glutathione Reductase Activity

Glutathione reductase (GR) activity in tissue samples was determined by a spectrophotometric method that measures the NADPH-dependent reduction of oxidized glutathione (GSSG).[27] In a 96-well microplate, 10 µL of jejunal supernatant was combined with 221 µL of 50 mM Tris-HCl buffer (pH 8.0) containing EDTA (1 mM) and 38 µL of GSSG (8 mM). The reaction was started by adding 10 µL of NADPH at 25 ℃. Absorbance at 340 nm was recorded every 2 minutes over an 8-minute period using a microplate reader, with the decrease in absorbance reflecting NADPH oxidation. The activity of GR was determined using the molar extinction coefficient of NADPH ($\varepsilon = 6.22\ mM^{-1}\ cm^{-1}$), and results were expressed as units of enzyme activity per milligram of protein.

2.10.3 Glutathione Peroxidase (GPx) Activity

The activity of glutathione peroxidase (GPx) in tissue samples was assessed using an Ellman colorimetric method.[23] In a 96-well microplate, 5 µL of jejunal supernatant was mixed with 210 µL of phosphate buffer (pH 6.9), 2.5 µL of GSH (100 mM), and 5 µL of distilled water, and incubated at 37 ℃ for 10 minutes. Next, 2.5 µL of 15 mM NADPH was added, followed by 1 mM DTNB (10 µL). Absorbance was recorded at 412 nm using a microplate spectrophotometer. Then, the activity of GPx was calculated by comparing absorbance to a standard curve of known GSH concentrations.

2.11 Molecular Docking of *U. pinnatifida*-derived Compounds

A search through the literature was conducted to find chemical compounds previously reported in *U. pinnatifida* seaweed. The four compounds, fucoidan, fucosterol, fucoxanthin, and fucoxanthinol, were previously reported in the plant[17], were downloaded from the PubChem database. These compounds and sotagliflozin, with respective database CID codes: 92023653, 5281328, 5281239, 11273547, and 24831714, were retrieved in SDF format. Energy minimization of the ligands was conducted using the automatic algorithm of the Chem3D Pro, version 12 (Software for Molecular Modeling and Analysis; CambridgeSoft Corporation, Cambridge, MA, USA) before the output files were imported one after the other into the working directory of the Autodock Vina, version 1.1.2 (Software for Molecular Docking and Virtual Screening: The Scripps Research Institute, La Jolla, CA, USA). After polar hydrogen molecules and Kollman charges were added to the ligand structures, the resulting structures were saved in a pdbqt file format. The 3D structure sodium-glucose co-transporter 1 (*SGLT1*) protein co-crystallized with a cholesterol molecule at 3.40 Å resolution (PDB ID: 7SL8) was also recovered from the protein data bank online. The non-standard atoms and the co-crystallized water molecules attached to the protein structure were removed with Discovery Studio software version 24.1.0.23298 (Software for Molecular Modeling and Visualization, Dassault Systèmes, Waltham, MA, USA). The PDB file output of the programme was subjected to a similar procedure as employed for the seaweed compounds. Molecular docking of the protein standard inhibitor and the *U. pinnatifida*-derived compounds was conducted with the Autodock Vina algorithm within a grid box size of X, Y, Z center coordinate of 115:122:90 and size of 37:27:37 using the default grid spacing (1 Å) and exhaustiveness. The molecular interaction of the best binding pose of each compound with the *SGLT1* protein was visualized in 2D with the aforementioned Discovery Studio software.

2.12 Statistical Analysis

All analyses were done in triplicate and presented as mean ± standard deviation. The data were analyzed using IBM SPSS Statistical software (Version 27, Chicago, USA). A one-way analysis of variance (ANOVA) was applied to compare the differences at p values < 0.05 using Tukey's HSD *post hoc* test.

3. Results

3.1 Intestinal Glucose Absorption

Figure 1 illustrates that exposure to the seaweed extract led to a reduction in glucose absorption by the intestinal tissue. *U. pinnatifida* extracts demonstrated a significant, concentration-dependent decrease in glucose uptake ($p < 0.05$), with the aqueous extract showing greater effectiveness than the ethanolic extract. At the highest tested concentration (240 µg/mL), the glucose-lowering effect of the aqueous extract was similar to that observed with the standard drug, acarbose.

3.2 Inhibition of Digestive Enzymes

As demonstrated in **Figure 2**, incubating the jejunum in glucose solution significantly increased the activities of (a) lipase, (b) cholesterol esterase, and (c) amylase activity in the untreated tissue compared to the normal tissue. The aqueous extracts displayed a better overall activity-lowering effect on the enzymes compared to the ethanolic extract for all enzymes.

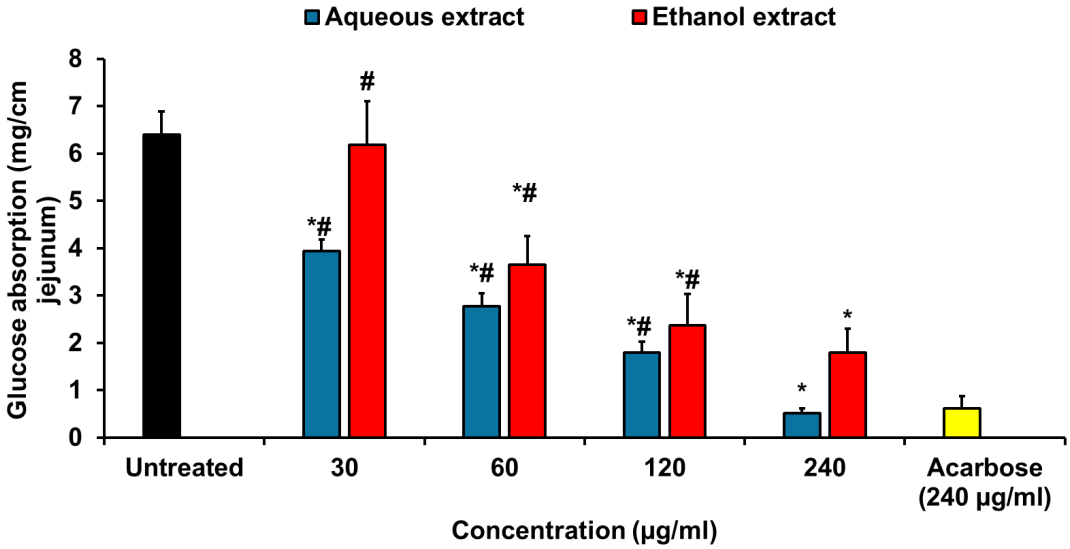

Figure 1. Effect of *U. pinnatifida* on glucose absorption of the jejunum. Data are presented as mean ± standard deviation (n = 3), where n represents independent samples. An asterisk (*) denotes a significant difference compared to the untreated control (intestine exposed to glucose alone), while a hash symbol (#) marks a significant difference compared to the acarbose treatment ($p < 0.05$; Tukey's HSD *post hoc* test, performed using IBM SPSS software for Windows).

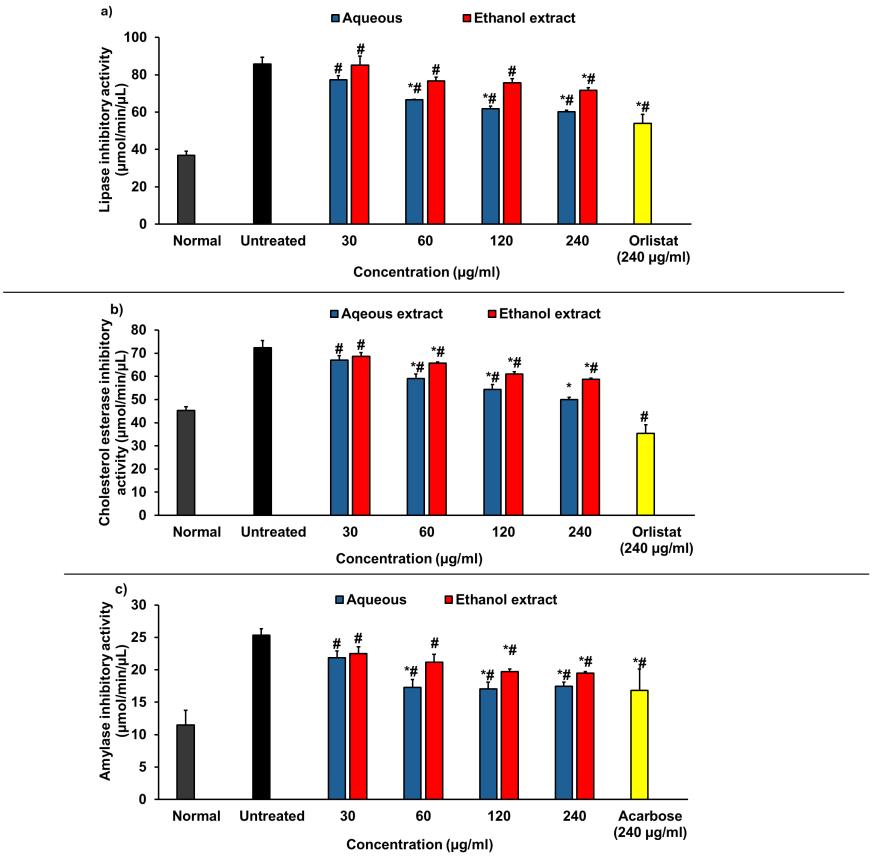

Figure 2. Effect of *U. pinnatifida* extracts on jejunal. a) lipase and b) cholesterol esterase, and c) α-amylase inhibitory activities. Results are shown as mean ± standard deviation (n = 3), where n represents independent samples. Asterisk (*) denotes a significant difference relative to the untreated group, while hash (#) indicates a significant difference compared to the normal group ($p < 0.05$, Tukey's HSD *post hoc* test, IBM SPSS for Windows). "Normal" refers to jejunal tissues without incubation.

3.3 Activity of Acetylcholinesterase

As depicted in **Figure 3**, incubating the jejunum in glucose significantly elevated ($p < 0.05$) the acetylcholinesterase activity in the untreated tissue. However, the activity of this enzyme decreased significantly and dose-dependently after the treatment with *U. pinnatifida* extracts. The effect of the aqueous extract was comparable to that of acarbose at the highest (240 µg/mL) concentration.

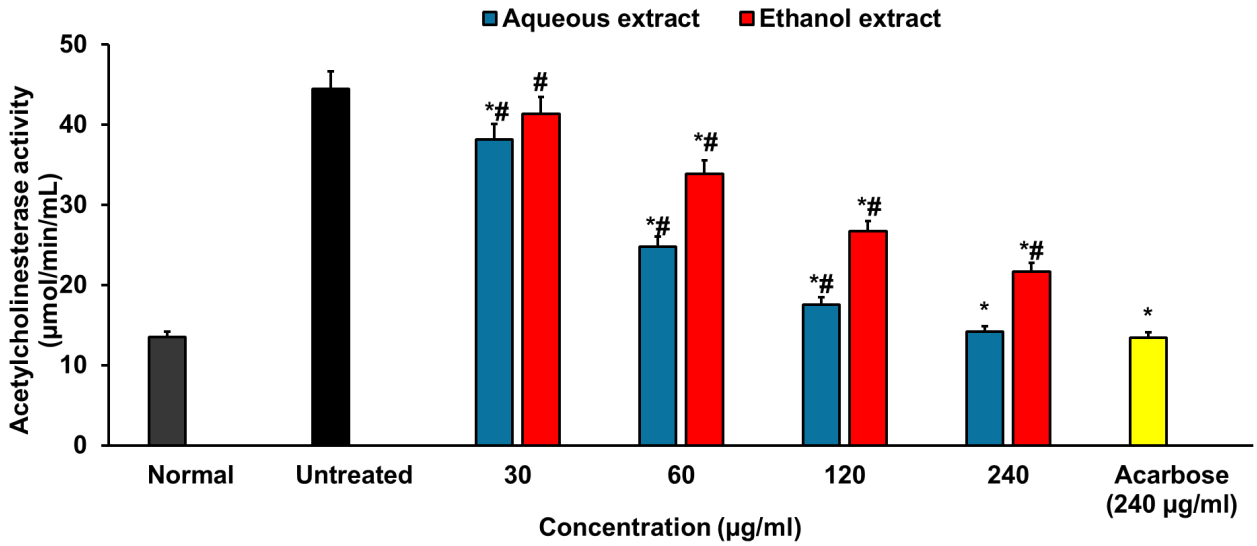

Figure 3. Effect of *U. pinnatifida* extracts on acetylcholinesterase activity in jejunal tissue. Results are shown as the mean ± standard deviation ($n = 3$), where n represents independent samples. An asterisk (*) mark denotes the significant difference from the untreated group, while a hash (#) mark denotes the significant difference from the normal group ($p < 0.05$, determined by Tukey's HSD *post hoc* test using IBM SPSS for Windows). "Normal" refers to jejunal samples without incubation.

3.4 Activities of Purinergic Enzyme

Figure 4 illustrates that incubating jejunal tissue in a high glucose solution significantly reduced ATPase activity while increasing ENTPDase activity. Treatment with *U. pinnatifida* extracts was able to counteract this effect on ATPase, but only at higher concentrations. Notably, a difference in potency was observed between the two extract types. The ethanol extract significantly increased ATPase activity at both 120 µg/mL and 240 µg/mL, whereas the aqueous extract was only effective at the higher concentration of 240 µg/mL. This differential effect suggests that the active components responsible for enhancing ATPase activity are more efficiently extracted by ethanol. We hypothesize that ethanol, being a less polar solvent, may have extracted a higher concentration of hydrophobic bioactive compounds (such as specific polyphenols or terpenoids) that are capable of activating ATPase. In contrast, both extracts significantly lowered ($p < 0.05$) ENTPDase activity. However, the aqueous extract showed a significantly better ENTPDase activity reduction compared to the ethanol extract, which was comparable to the acarbose, particularly at higher concentrations.

3.5 Activities of Glucogenic Enzymes

Data in **Figure 5** showed that G-6-Pase and Fruc-1,6-Pase activities increased significantly in the untreated intestinal sample homogenate**.** Both *U. pinnatifida* extracts produced a significant ($p < 0.05$) reduction of these activities. The inhibition of glucose-6-phosphatase was observed to be significant at 60–240 µg/mL for the aqueous extract and at 240 µg/mL for the ethanol extract. A more potent inhibition of Fruc-1,6-Pase was evident, occurring at 30–240 µg/mL for the aqueous extract and 120–240 µg/mL for the ethanol extract.

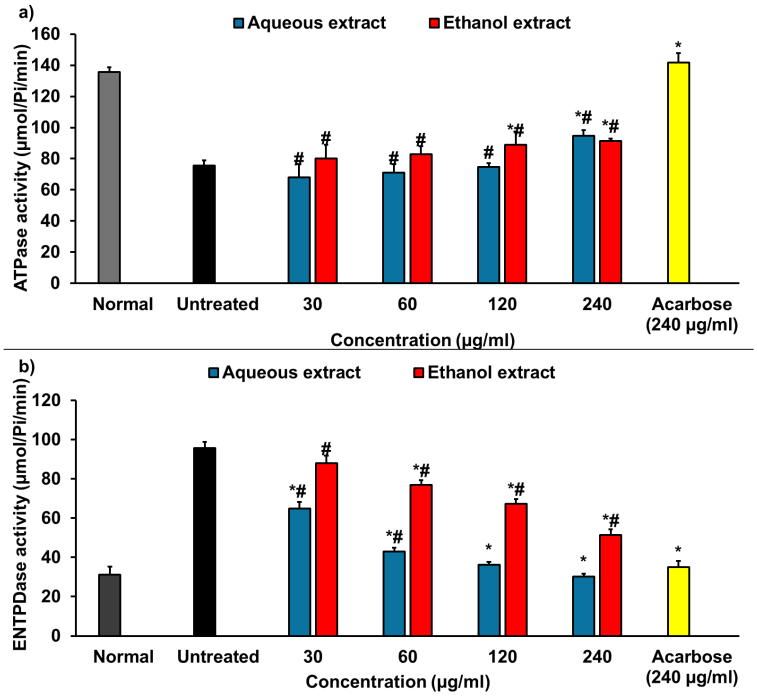

Figure 4. Effect of *U. pinnatifida* extracts on a) ATPase and b) ENTPDase activity in jejunal tissue. Results are shown as mean ± standard deviation (n = 3), where n represents independent samples. An asterisk (*) marks a significant difference from the untreated group, while a hash ($^{\#}$) marks a significant difference from the normal group ($p < 0.05$, determined by Tukey's HSD *post hoc* test using IBM SPSS for Windows). "Normal" refers to jejunal samples without incubation.

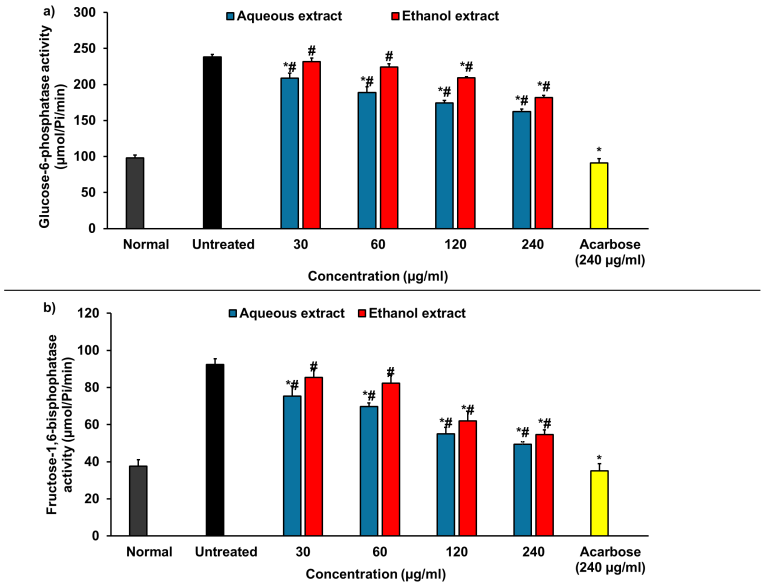

Figure 5. Effects of *U. pinnatifida* extracts on jejunal. a) glucose-6-phosphatase and b) fructose-1,6-bisphosphate activities. Results are shown as mean ± standard deviation (n = 3), where n represents independent samples. Asterisk (*) denotes a significant difference relative to the untreated group, while hash ($^{\#}$) indicates a significant difference compared to the normal group ($p < 0.05$, Tukey's HSD *post hoc* test, IBM SPSS for Windows). "Normal" refers to jejunal tissues without incubation.

3.6 Activity of Glycogen Phosphorylase

As shown in **Figure 6**, the glycogen phosphorylase activity increased considerably in the glucose-only-treated jejunal tissue homogenate. While there are reductions in the activities of the enzyme after the treatment with the *U. pinnatifida* extracts, the aqueous extract of the seaweed displayed better potency than the ethanol extract.

3.7 Glutathione Metabolism

As shown in **Figure 7**, hyperglycemic conditions significantly depleted the antioxidant defense system, marked by reductions in reduced glutathione (GSH) levels and the activities of glutathione peroxidase (GPx) and glutathione reductase (GR). Treatment with *U. pinnatifida* extracts significantly restored these parameters. The aqueous extract demonstrated a superior ability to restore antioxidant enzyme activity, increasing GPx activity from 10.12 to 21.82 µmol/min/mg and GR activity from 15.46 to 36.82 µmol/min/mg at 240 µg/mL. In contrast, the ethanol extract was more effective at replenishing GSH levels, elevating them to 268.02 µmol/mL compared to 244.83 µmol/mL with the aqueous extract (from an untreated level of 104.97 µmol/mL). At this highest concentration, the restorative effects of both extracts, particularly the aqueous extract on GPx and GR, were comparable to those of the normal and acarbose-treated control groups.

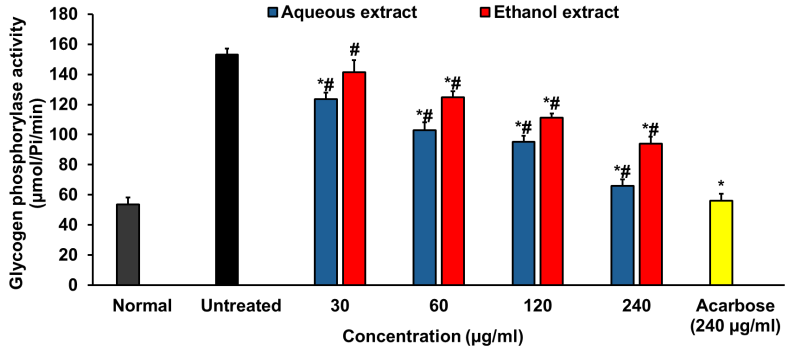

Figure 6. Effect of *U. pinnatifida* extracts on jejunal glycogen phosphorylase activity. Data are presented as mean ± standard deviation (n = 3), where n represents independent samples. An asterisk (*) indicates a statistically significant difference compared to the untreated group, while a hash ($^{\#}$) marks a significant difference relative to the normal group ($p < 0.05$, Tukey's HSD *post hoc* test, IBM SPSS for Windows). "Normal" refers to jejunum samples without incubation.

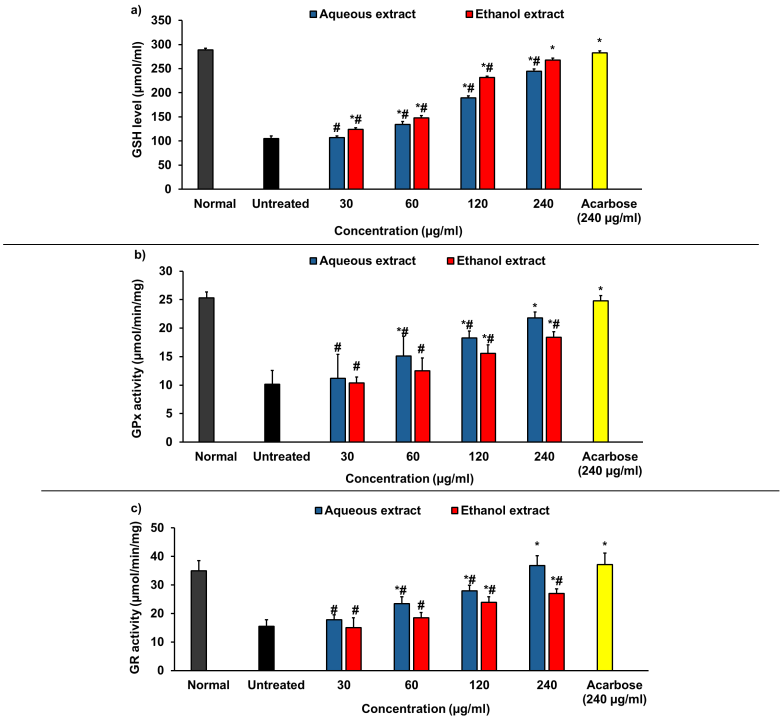

Figure 7. Effect of *U. pinnatifida* extracts on jejunal. a) reduced glutathione levels, b) glutathione peroxidase, and c) glutathione reductase enzyme activities. Results are shown as mean ± standard deviation (n = 3), where n represents independent samples. An asterisk (*) denotes a statistically significant difference from the untreated group, while a hash ($^{\#}$) signifies a significant difference compared to the normal group ($p < 0.05$, determined by Tukey's HSD *post hoc* test using IBM SPSS for Windows). "Normal" refers to jejunum samples without incubation, and "Untreated" indicates jejunum samples incubated only with glucose.

3.8 Molecular Docking

The result of molecular docking of compounds in the studied seaweed with an *SGLT1* protein is presented in **Table 1** and **Figure 8.** The cholesterol co-crystallized molecule attached to the protein molecule was re-docked with the protein to confirm the accuracy of the chosen docking active site region. As seen in **Figure 8a**, the root mean square deviation (RMSD) of the co-crystallized cholesterol structure at the selected site was 1.401 Å. This RMSD value of < 2 Å indicates good reliability of the binding energy scores obtained using the same search volume or grid for other ligands. Subsequently, **Table 1** revealed the score calculation obtained after docking the *U. pinnatifida* phytochemicals with the crystallographic *SGLT1* macromolecule. Aside from fucoidan with −4.2 kcal/mol docking score, all the other compounds from the plant had higher affinities for the co-transported protein when compared with sotagliflozin, a standard inhibitor (−7.0 kcal/mol). *Fucoxanthinol* had the lowest binding energy of −8.3 kcal/mol among the other compounds. The 2D images in **Figure 8e** further revealed that *fucoxanthinol* had a hydrogen bond with *TRP36*, three pi-sigma bonds with *TRP35*, two pi-alkyl bonds with *LEU284*, and a carbon-hydrogen bond with *SER276*. The standard compound also interacted with the active site amino acid residues of *SGLT1* via pi-sulfur and pi-pi stacked in addition to those previously described for the plant chemical constituents (**Figure 8**).

Table 1. Binding energies of *U. pinnatifida*-derived compounds with *SGLT1* in comparison with the sotagliflozin chemical drug.

***U. pinnatifida* compounds**	**Binding energy (kcal.mol^{-1})**
Fucoidan	−4.7
Fucosterol	−8.2
Fucoxanthin	−8.2
Fucoxanthinol	−8.3
Sotagliflozin	−7.0

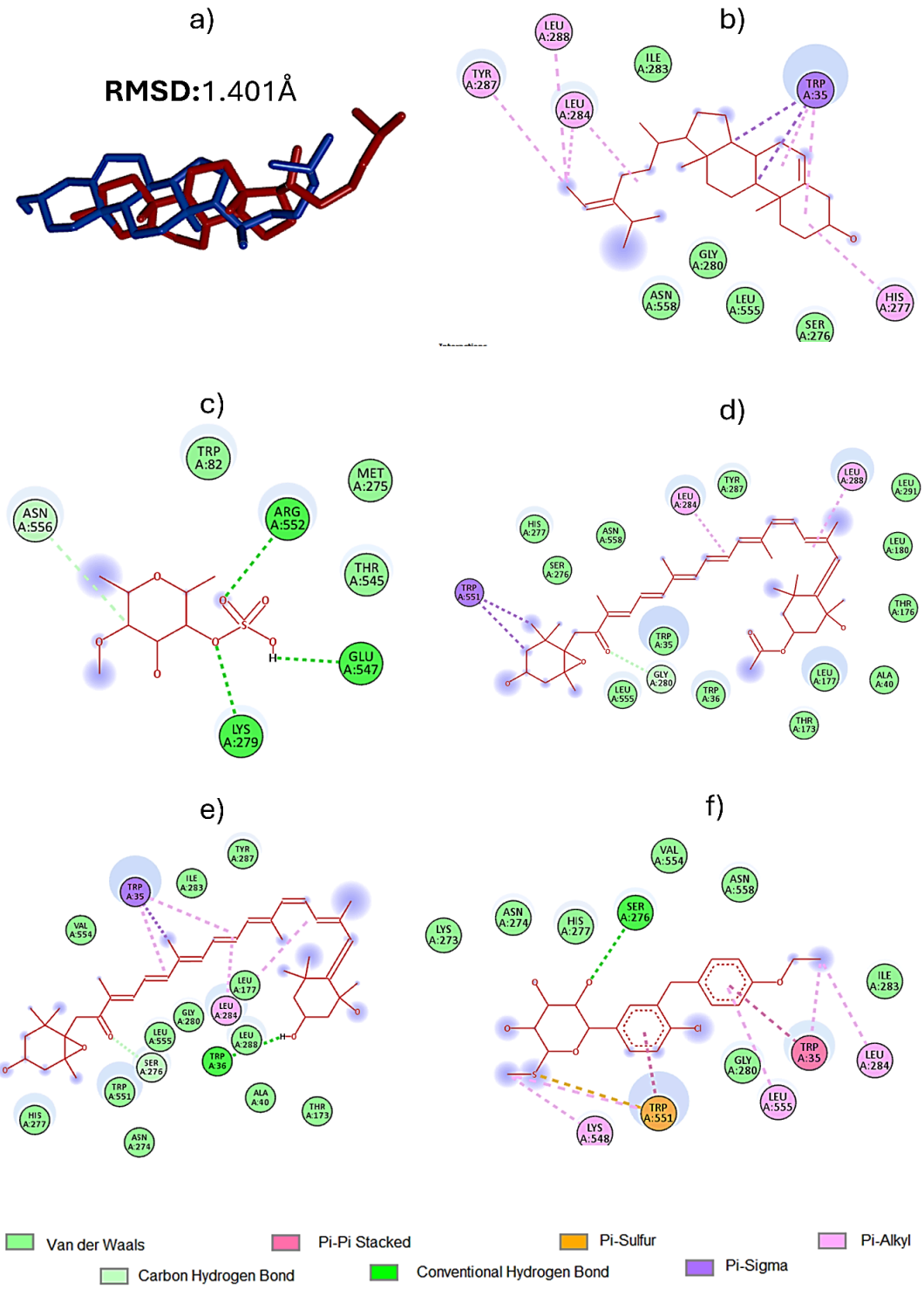

Figure 8. The superimposed images of cholesterol co-crystallized and docked with *SGLT1*. a) and 2D protein-ligand complex images of *fucosterol* b), *fucoidan* c), *fucoxanthin* d), *fucoxanthinol* e), *sotagliflozin* f) with the same co-transporter protein.

4. Discussion

The intestine plays a crucial role in facilitating the digestion, absorption, and transport of glucose and lipid molecules as well as other nutrients from ingested food materials.[28,29] Despite these functions, some studies have linked hyperglycemia-mediated redox imbalance to impair gut barrier physiology, increase inflammation, and disrupt gut microbiota in the small intestine.[30,31] These changes have been reported to influence normal nutrient absorption, transporter activity, and cell signaling pathways that could promote insulin resistance, aberrant fat storage, inflammation, and ultimately exacerbate obesity and diabetes.[31] Natural marine products such as seaweeds have been reported as a source of therapeutic agents for treating obesity and diabetes.[14] This study showed that *U. pinnatifida* seaweed extracts treatment improves jejunal dysfunctional enzyme activities and ultimately the intestinal tissue glucose absorption properties in an *ex vivo* model of diabetic hyperglycemia. To the best of our knowledge, this is the first report showing that *U. pinnatifida* modulates glucogenic, purinergic, cholinergic, and lipid-metabolizing enzyme activities in the small intestine.

Under physiological conditions, glucose absorption in the small intestine is primarily mediated by the sodium-glucose co-transporter 1 (*SGLT1*), present in the apical side of enterocytes, which transports glucose along with sodium ions. Subsequently, this glucose molecule is transported into the bloodstream by the glucose transporter 2 (*GLUT2*) located at the basolateral membrane end of the intestine.[10] However, some reports suggest upregulated expressions of *SGLT1* and *GLUT2* in the intestinal tissue of diabetic patients.[32] This process could be linked to the increased glucose absorption observed in the untreated group (**Figure 1**). The capacity of the *U. pinnatifida* extracts to decrease glucose absorption to near normal levels suggests a regulatory effect on glucose transport. This observation could be associated with the impact of the seaweed constituents on the *SGLT1* protein found on the apical side of the small intestine. The greater efficacy of the aqueous extract in reducing glucose absorption, as observed in our *ex vivo* model, may indicate a higher concentration of *SGLT1*-inhibiting compounds like *fucoxanthinol* and *fucosterol* in this extract compared to the ethanol extract. The higher affinity of compounds such as *fucosterol*, *fucoxanthin*, and, more importantly, *fucoxanthinol* (**Figure 8**) in the seaweed on this protein could reflect their abilities to strongly inhibit its absorption capacity and consequently limit the amount of glucose taken up by the co-transported for subsequent transport into the bloodstream. Furthermore, the potential contribution of *GLUT2* inhibition to the observed reduction in overall glucose absorption cannot be ruled out, although it warrants further investigation. These findings are consistent with a previously published study by Lee et al.[33], which demonstrated hypoglycemic effects of this seaweed through downregulation of *SGLT1* expression level in the Caco-2 monolayer cell model. Moreover, *U. pinnatifida* has been shown to have anti-hyperglycemic effects by inhibiting carbohydrate and lipid digestive enzymes.[16] While the seaweed extracts slightly lowered the activities of lipase, amylase, and cholesterol esterase (**Figure 2**), these findings could further indicate this seaweed as a possible source of lead compounds for diabetes and obesity management. Interestingly, sulphated polysaccharides and carotenoids in seaweeds have been shown to have inhibitory activity on the digestive enzymes[16,34] along with the involvement of other enzymes, such as acetylcholinesterase.

Acetylcholinesterase degrades acetylcholine, a neurotransmitter essential for the brain-gut axis, which regulates intestinal motility. Elevated acetylcholinesterase activity, often observed in diabetes, is linked to inflammation and reduced bowel movement in gastrointestinal disorders.[35] The elevated acetylcholinesterase levels in intestinal tissue exposed to high glucose (**Figure 3**) may indicate reduced acetylcholine availability that may negatively impact intestinal motility under physiological conditions. Increased activity of the enzyme with concomitant reduction of acetylcholine level observed in diabetes is associated with inflammation and decreased bowel movement in certain gastrointestinal diseases.[36] The elevated acetylcholinesterase levels in intestinal tissue exposed to high glucose (**Figure 3**) may indicate the reduced acetylcholine availability that may negatively impact intestinal movement under physiologic conditions. The decrease in enzyme activity after the treatment with the seaweed extracts suggests a potential improvement in neurotransmitter levels as well as activity, which could enhance gut movement and overall intestinal function.[37] This enhancement in intestinal motility could contribute to the observed reduction in glucose absorption by shortening the intestinal transit time, thereby limiting the duration for glucose to be absorbed via transporters like *SGLT1* and *GLUT2*.[29]

Endogenous signaling nucleotides, adenosine triphosphatase (ATPase), and ectonucleoside triphosphate diphosphohydrolase (ENTPDase) play essential roles in the modulation of purinoceptors.[12] These ecto-enzymes, which are highly expressed in the gastrointestinal tract, hydrolyze extracellular nucleotides such as adenosine triphosphate (ATP) and other purines, thereby regulating purinergic signaling by modulating the availability of nucleotides that bind to purinergic receptors. Previously, some findings have described their involvement with gastrointestinal disorders in diabetes.[12] As previously reported, hyperglycemia increases reactive oxygen species production and inflammation, a

chronic condition of the latter process has been reported to reduce ATP levels in the intestinal mucosal tissue.[38] The lower activity of ATPase in the untreated intestinal tissue suggests reduced ATP synthesis (**Figure 4a**), due to the possibility of local inflammation. Though treatment with the *U. pinnatifida* extracts had a considerable effect on ATPase activities at higher concentrations (120–240 µg/mL), the inhibition of its purinergic protein counterpart decreased with increasing concentration of the seaweed extracts. At the highest test concentration, this inhibition approached normal levels (**Figure 4b**), suggesting a potential improvement in the availability of generated ATP for optimal cellular function.

During fasting periods, gluconeogenic enzymes, including glucose-6-phosphatase (G-6-Pase) and fructose-1,6-bisphosphatase (Fruc-1,6-Pase), assist the intestines in producing glucose from non-carbohydrate molecules, including glycerol, lactate, and glutamine.[29] The elevated activities of these enzymes (**Figure 5**) and those of glycogen phosphorylase (**Figure 6**) indicate enhanced activation of gluconeogenesis and glycogenolysis in the untreated tissue sample. The breakdown of glycogen raises intracellular glucose levels, which are subsequently transported into the bloodstream, contributing to hyperglycemia. Thus, the reduced activity of G-6-Pase, Fruc-1,6-Pase, and glycogen phosphorylase in intestinal tissues treated with *U. pinnatifida* extracts likely decreases intestinal endogenous glucose production, which in turn reduces glucose availability for absorption (**Figure 1**), supporting its potential efficacy in alleviating postprandial hyperglycemia *ex vivo.* The ability of *U. pinnatifida* to inhibit these key gluconeogenic enzymes aligns with findings for other brown algae, such as *Sargassum pallidum,* which have also demonstrated antihyperglycemic effects.[39,40] However, the specific potency and unique phytochemical profile of *U. pinnatifida*, particularly its high content of fucoxanthin, may underpin its distinct efficacy in the intestinal context observed here. Furthermore, while our study demonstrates a clear inhibitory effect in jejunal tissue, it remains to be determined whether this effect is specific to the jejunum or if *U. pinnatifida* extracts similarly influence gluconeogenesis in other intestinal segments like the ileum or in the liver, the primary site of whole-body glucose production. Future studies investigating tissue-specific responses will be crucial to fully elucidate the systemic antidiabetic mechanism of this seaweed.

Glutathione (GSH) is a key antioxidant protein that promotes intestinal health through maintaining gut barrier function by protecting the tissue from reactive oxygen species (ROS) related oxidative stress and inflammation-mediated diseases in the intestine.[7] While glutathione peroxidase utilizes GSH to reduce hydrogen peroxide (H_2O_2) to water, GR regenerates GSH from its oxidized form (oxidized glutathione (GSSG)) in a reaction involving nicotinamide adenine dinucleotide phosphate (NADPH) as a reducing agent. The suppressed activities of these antioxidant enzymes after incubation with glucose only may reflect increased ROS generation on the protein, which was enhanced after treatment with the varied concentration of the seaweed extracts. Compounds including carotenoids, phenolic compounds and sulfated polysaccharides identified in *U. pinnatifida* have been described to have free radical scavenging antioxidant properties.[16,41] Therefore, the role of these phytoconstituents in the plant may have accounted for the improved protein levels and activities in the plant extract-treated experimental groups.

5. Conclusion

This study highlights the therapeutic potential of *U. pinnatifida* in alleviating postprandial hyperglycemia and potential inhibitory trends on lipid digestion, requiring further validation, primarily through inhibiting carbohydrate and lipid-digesting enzymes and suppressing intestinal glucose absorption. Notably, this is the first study to demonstrate the modulatory effects of seaweeds on cholinergic and purinergic enzyme dysregulation in intestinal tissue. Additionally, the seaweed showed potential antioxidant activity by improving the activities of enzymes involved in maintaining cellular reduced glutathione homeostasis in the intestinal tissue. It is important to note, however, that this study has limitations. The *ex vivo* experimental model, while valuable, lacks the systemic physiological context, including blood circulation and neural regulation, which may not fully simulate the in vivo intestinal microenvironment. Furthermore, the use of crude extracts means that potential synergistic effects between active components, such as fucoxanthin and fucoidan, remain uncharacterized. Though these are preliminary findings, they may lay a good foundation for future work that could assess the impact of this seaweed on intestinal biochemical and microbial health in diabetes via an *in vivo* animal model. While validating the outcomes of this study, such investigations could further reveal unexplored pharmacological uses of this seaweed in metabolic disease management.

Acknowledgements

The authors gratefully acknowledge the support of the Biomedical Research Unit, University of KwaZulu-Natal, Westville Campus, Durban for their assistance in this study.

Author Contributions

S'thandiwe N. Magwaza: Methodology, Data Curation, Writing-original draft, Editing. Kolawole O. Olofinsan: Writing-review editing, Formal analysis. Nothando P. Hlongwane: Methodology, Data Curation. **Md. Shahidul Islam:** Supervision, Funding resource, Validation. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Not applicable.

Ethics Approval

All experimental protocols were conducted in accordance with the guidelines approved by the University of KwaZulu-Natal's Animal Research Ethics Committee (Ethical Clearance Number: AREC/00007168/2024).

Funding

This work was supported by the India–South Africa Bilateral Research Grant from the National Research Foundation (NRF), Pretoria, South Africa (Grant No. 133137), and by an NRF Doctoral Scholarship (Reference: PMDS22060719747).

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