JURNAL ILMIAH MEDICAMENTO

V Vol.12 No.1 (March 2026)
page 102-114
https://doi.org/10.36733/medicamento.v12i1.12689
e-ISSN: 2356-4814

Original Article

Eucheuma cottonii as a Natural Source for Type-2 Diabetes Mellitus Management: A Narrative review

I Made Agus Mahardika[1], Putu Oka Samirana[2]*

[1]Master Program in Pharmacy, Faculty of Mathematics and Natural Sciences, Universitas Udayana, Indonesia.
[2]Department of Pharmacy, Faculty of Mathematics and Natural Sciences, Universitas Udayana, Indonesia.

Submitted : 07-10-2025
Revised : 16-02-2026
Accepted : 05-03-2026

Keywords: antidiabetic, anti-inflammatory, antioxidant, *Eucheuma cottonii*, prebiotic

Correspondence:
Putu Oka Samirana
oka_samirana@unud.ac.id

Abstract

Background: Type 2 diabetes mellitus is a chronic metabolic disorder with a steadily increasing prevalence worldwide, including in Indonesia. Standard therapeutic approaches for T2DM are commonly associated with adverse effects, which has led to increasing interest in the use of herbal products and nutraceuticals. *Eucheuma cottonii,* an abundant red seaweed species in Indonesian waters, holds considerable potential as a preventive and therapeutic agent for T2DM due to its bioactive compound content.
Objective: This study aimed to evaluate the potential of *E. cottonii* as a therapeutic agent through a literature review.
Methods: This study is a literature review. Relevant literature was collected from several databases using specific keywords, and a total of 30 articles that met the inclusion criteria were selected for analysis.
Results: Evidence suggested that *E. cottonii* comprises numerous bioactive substances compounds including flavonoids, phenolics, sulfated polysaccharides, and carrageenan, which demonstrate antidiabetic activity through multiple mechanisms. These compounds inhibit α-amylase and α-glucosidase enzymes, lower blood glucose levels, and enhance insulin secretion via dipeptidyl peptidase-4 inhibition. The antioxidant activity of *E. cottonii* is demonstrated by elevated levels of endogenous enzymes (SOD, GPx, GSH) and reduced ROS and MDA, while its anti-inflammatory effects were reflected in decreased expression of pro-inflammatory cytokines and inflammatory enzymes (COX-2, LOX-5). Moreover, *E. cottonii* functions as a prebiotic, modulating gut microbiota, enhancing the population of *Bifidobacterium* spp., and improving the *Firmicutes/Bacteroidetes ratio*, thereby contributing to better glucose metabolism.
Conclusion: Based on these bioactivities, *E. cottonii* demonstrates strong potential for development as a multifunctional nutraceutical for the prevention and management of T2DM through antihyperglycemic, antioxidant, anti-inflammatory, and gut microbiota–modulating mechanisms.

How to Cite: (*citation style* AMA 11th Ed.)
Mahardika IMA, Samirana PO. *Eucheuma cottonii* as a Natural Source for Type-2 Diabetes Mellitus Management: A Narrative review. *J. Ilm. Medicam.*, 2026;12(1): 102-114. https://doi.org/10.36733/medicamento.v12i1.12689

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disease with a growing prevalence, increasing from 5.7% in 2007 to 8.5% in 2018, and it is estimated to reach 16.09% by 2045.[1–4] Approximately 90–95% of diabetes cases are attributable to type 2 diabetes mellitus (T2DM), a metabolic disorder characterized by increased insulin resistance and pancreatic β-cell dysfunction, ultimately resulting in impaired insulin secretion.[5–7] The etiology of T2DM is associated with lifestyle factors, obesity, gut dysbiosis, genetic predisposition, and aging.[8–10] Furthermore, evidence indicates that oxidative stress and inflammation contribute to insulin resistance by activating stress kinases such as c-Jun N-terminal kinase (JNK) and inhibitor of κB kinase (IKK), inhibiting insulin receptor substrate-1 (IRS-1), and impairing insulin signaling. They also reduce adiponectin expression in adipose tissue, further disrupting insulin function. Hyperglycemia, in turn, generates free radicals and triggers chronic inflammation, creating a vicious cycle that exacerbates diabetes progression.[11]

Standard therapies for T2DM, including insulin and oral hypoglycemic drugs, are often associated with adverse effects and contraindications in patients with certain conditions.[12,13] Consequently, with the growing demand for safe and affordable treatment options, natural products have gained attention as alternatives. Herbal medicines are considered potential complementary therapies due to their good efficacy and minimal adverse effects. T2DM itself can be prevented through healthy lifestyle practices, particularly proper nutrition and physical activity.[14] In this context,

nutraceuticals including probiotics, prebiotics, and plant-derived bioactive compounds are gaining attention as potential strategies for both prevention and management of T2DM.[15]

Seaweed is a natural resource with any therapeutic potential and has been employed as a source of nutraceuticals. Empirical evidence shows that high seaweed consumption in countries such as Japan, Korea, and China correlates with lower rates of metabolic disorders compared with Western countries.[16] *E. cottonii* (commonly known as *Kappaphycus alvarezii*) is the most widely cultivated seaweed species globally, including in Indonesia.[17,18] This alga contains a variety of bioactive metabolites, including flavonoids, tannins, phenolic compounds, glycosides, and steroids,[19] as well as several terpenoids, such as C20-cyclo-octen and C23-cyclo-octenyl chlorinated compounds, heptalenecarbolactone, and heptalenecarboxylate derivatives. In addition, *E. cottonii* contains primary metabolites such as fatty acids, lipids, amino acids, proteins, sugars, and polysaccharides.[20] These metabolites contribute to the antidiabetic, anti-inflammatory, and antioxidant activities of the alga.[18,20–23] Its high dietary fiber content also plays a role in maintaining gut microbiota balance. Furthermore, studies have shown that carrageenan derived from *E. cottonii* has potential as a therapeutic option for metabolic syndrome, primarily through its antioxidant and antidiabetic properties.[24,25]

Currently, no comprehensive review has integrated the multiple bioactivities of *E. cottonii* that are relevant to diabetes therapy. Therefore, this literature review discusses the benefits of *E. cottonii* for the treatment and prevention of diabetes mellitus. The review focuses on several bioactivities of *E. cottonii* relevant in the prevention and therapeutic management of diabetes mellitus, including reduced intestinal glucose absorption, increased pancreatic insulin secretion, anti-inflammatory effects, antioxidant activity, and its ability to maintain gut microflora balance. The findings of this review are expected to serve as a reference for the development of *E. cottonii* as a health product, particularly for diabetes mellitus.

METHODS

A comprehensive literature search was performed across PubMed, ScienceDirect, Scopus, Google Scholar, Springer, and PMID databases to identify relevant studies published between 2016 and 2025. The search strategy employed the following keywords and Boolean operators: ("*Kappaphycus alvarezii*" OR "*Eucheuma cottonii*") AND (anti-diabetic" OR "diabetes treatment" OR "glucose lowering" OR "alpha-amylase inhibition" OR "alpha-glucosidase inhibition" OR antioxidant OR "anti-inflammatory" OR "metabolic syndrome" OR prebiotic OR probiotic).

All identified records were exported to Mendeley reference management software for duplicate removal. The remaining articles underwent a stepwise screening process, beginning with title and abstract review, followed by full-text assessment based on predefined inclusion and exclusion criteria.

Original research articles published in English within the last ten years (2016–2025), available in full text with a DOI, and reporting bioactivities of *E. cottonii* related to antidiabetic, antioxidant, anti-inflammatory, or prebiotic effects were included. Review articles, surveys, and case reports were excluded. Studies that met the eligibility criteria and were relevant to the research objective were subsequently extracted and summarized in tabular form for qualitative analysis and discussion.

RESULT AND DISCUSSION

From the article search using the specified keywords, a total of 1,670 articles were obtained from Google Scholar, 55 from ScienceDirect, 18 from MDPI, 29 from PubMed, 162 from Scopus, and 36 from Springer. All retrieved records underwent a stepwise screening process, beginning with title and abstract screening, followed by full-text assessment, as illustrated in **Figure 1.**

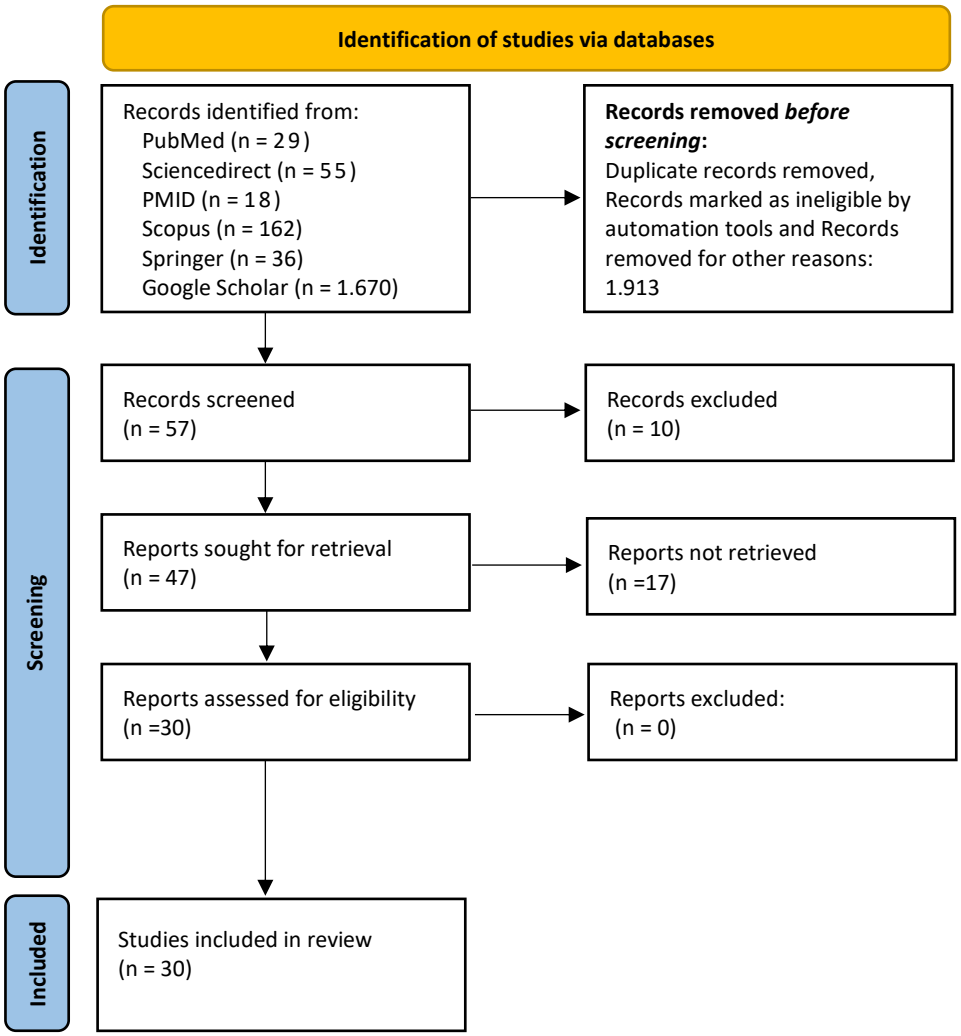

Figure 1. Flow diagram of the article screening and selection process

After applying the predefined inclusion and exclusion criteria, 30 studies were deemed eligible and subsequently included in this literature review. A summary of the characteristics and main findings of these studies is presented in **Table 1**.

Table 1. Bioactivities of *Eucheuma cottonii*

Algae	Bioactivity	Ref
	Antihyperglycemic	
Carrageenan	Inhibits α-glucosidase	25
Algal hydrolysate	inhibits α-amylase and indirectly inhibits α-glucosidase	26
Sulfated poligalactan	Inhibits α-amylase, α-glucosidase and, Dipeptidyl peptidase (DPP)-4	27
Aqueous extract	Lowers blood glucose and restores HbA1c and plasma insulin	28
	Antioxidant	
Carrageenan	Increases antioxidant enzyme levels: Glutathione Peroxidase (GPx), Superoxide Dismutase (SOD), Catalase (CAT), Glutathione S-transferase (GST), Glutathione (GSH) in diabetic rats	29
Peptides	Enhances SOD and GSH activity while reducing ROS and Malondialdehyde (MDA)	30
Active fraction	Reduces plasma glycated albumin, Nε-(carboxymethyl) lysine (CML), and expression of Receptor for Advanced Glycation End Products (RAGE), NADPH oxidase (NOX4), and H2O2 in diabetic rat kidneys	31,32
Ethanol extract	Restores endogenous antioxidant balance by increasing GSH, CAT, GST and decreasing *Lipid Peroxidation* (LPO) in hepatotoxic rats	33
	Lowers Serum Glutamic Pyruvic Transaminase (SGPT), Serum Glutamic Oxaloacetic Transaminase (SGOT), Alkaline Phosphatase (ALP), MDA and increases SOD, GPx in hepatotoxic mice	34
	Scavenges free radicals (H2O2, DPPH, FRAP)	35,36
Algal hydrolysate	Scavenges DPPH free radicals	26
Algal juice		37
Whole algae		38,39
Aqueous extract		40
Sulfated poligalactan		41
Methanol extract	Inhibits LPO and scavenges DPPH free radicals	42–44
	Scavenges DPPH free radicals	45

Algae	Bioactivity	Ref
	Anti-inflammatory	
Sulfated poligalactan	Inhibits Cyclooxygenase (COX)-1 and -2, and Lipoxygenase-1 (LOX-1)	27
Non-isoprenoid carboxylated oxosin cyclic ether	Inhibits COX-2	46
Ethanol extract	Reduces proinflammatory cytokines (Tumor Necrosis Factor (TNF)-α, Interleukin (IL)-1β, IL-6, leptin), suppresses NF-κB and ERK1/2 signaling, decreasing Matrix Metalloproteinases (MMP) -1 and 13, and Prostaglandin E2 (PGE2) levels	47,48
Whole Algae	Improves intestinal injury, increases mucin-2 secretion, and decreases TNF-α, IL-1β, IL-6, LT, and COX-2 in chemotherapy-induced intestinal mucosal damage	49,50
Lipid	Inhibits proteinase activity, comparable to salicylic acid	51
4-(2-kloroetil)-5-7-(metoksimetil) undec -3-enil) cyclooct -4- enone	Inhibits COX-2 and LOX-5 enzymes with IC50 values superior to conventional drugs such as aspirin and ibuprofen	44
2-etil-6- (4 – methoxy -2 -((2 -oxotetrahydro-2H-pyran-4-yl)methyl)butoxy)-6-oxohexyl 5-ethyloct-4-enoate	Inhibits LOX-5 enzyme in vitro with IC50 values superior to aspirin and ibuprofen	52
Methanol extract	Reduces NF-κB, TNF-α, IL-4, EGFR, and MMP-9 while increasing IFN-γ expression in ovalbumin-induced asthmatic mice	53
	Prebiotic	
Whole Algae	Modulates the balance of gut microbiota phyla, specifically Firmicutes and Bacteroidetes, and exerts prebiotic effects through the promotion of Bifidobacterium growth	16,54

Metabolite Profile of *Eucheuma cottonii*

Phytochemical analysis indicated a relatively high abundance of bioactive constituents in this seaweed. Quantitative analysis revealed that *E. cottonii* contains alkaloids (1.91 ± 0.58 ATE/g), flavonoids (1.63 ± 0.73 CAE/g), tannins (2.94 ± 0.41 CAE/g), total phenolics (3.39 ± 0.45 GAE/g), glycosides (1.88 ± 0.11 mg/g), and steroids (2.51 ± 0.15 mg/g). Qualitative GC-MS analysis identified at least 94 metabolites, such as phenols, aromatic compounds (vanillin, benzophenone, benzene, diphenylamine), fatty acids (octadecanoic acid), and long-chain alkanes (decane, dodecane, hexadecane, heptadecane, dotriacontane).[19] Another study demonstrated that the bioactive fraction responsible for antidiabetic activity contains several phytochemical constituents, such as Pheophorbide A, Shogaol, Thymol, Cafestol, Cinnamic acid, and several phenolic and terpenoid derivatives including Putrescine, Kahweol, Pyrogallol, (E)-p-coumaric acid, (−)-Lupinine, (E)-Ferulic acid, p-Cymene, and Anacardic acid.[31]

In addition to its secondary metabolites, dried *E. cottonii* is also rich in macro- and micronutrients. Its composition includes 38.3% carbohydrates (approximately 90% soluble fiber), 1.34% protein, and 0.62% lipid. Major minerals include potassium (20%) and sodium (3.7%) with a Na:K ratio of 0.19, along with chloride (23%), bromine (0.12%), while iodine was undetected. Furthermore, the alga contains calcium (28.96 g/kg), magnesium (5.69 g/kg), and trace elements such as Fe, B, and Mn.[16]

Role of *Eucheuma cottonii* in Type 2 Diabetes Therapy

Inhibition of Glucose Absorption

One therapeutic approach in the DM management is through the inhibition of glucose absorption in the gastrointestinal tract. In this mechanism, two key enzymes play a central role: α-amylase and α-glucosidase. As illustrated in **Figure 2**, these enzymes act synergistically in digesting complex carbohydrates into glucose that is readily absorbed in the gastrointestinal tract. α-Amylase enzyme is responsible for breaking down polysaccharides into disaccharides such as maltose and isomaltose. These disaccharides are subsequently converted into monosaccharides through α-glucosidase activity, an enzyme bound to the brush border membrane of the small intestine, to produce free glucose.[55] Therefore, inhibition of these digestive enzymes activities can slow carbohydrate degradation into glucose, leading to reduced intestinal glucose absorption and ultimately contributing to blood glucose regulation.[56]

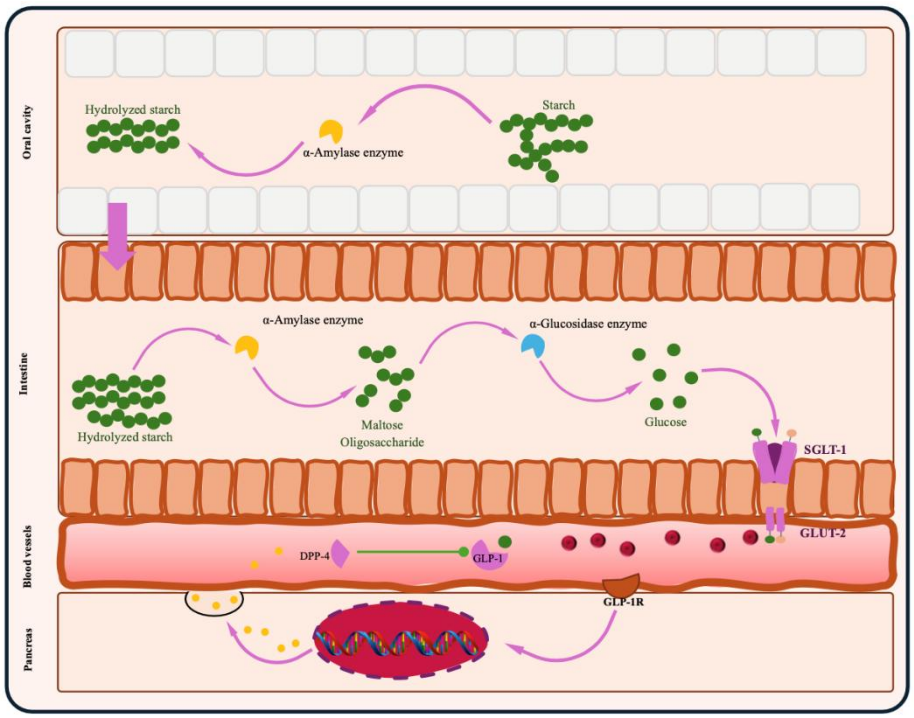

Figure 2. Carbohydrate Digestion and Insulin Secretion[57]

The process of carbohydrate digestion is initiated in the oral cavity, where salivary α-amylase breaks down starch into maltose and short-chain oligosaccharides, followed by pancreatic α-amylase activity in the duodenum. These products are subsequently hydrolyzed by α-glucosidase into free glucose for absorption. The rise in glucose levels stimulates insulin secretion and activates the incretin system, including the release of GLP-1, which enhances pancreatic β-cell insulin secretion in a glucose-dependent manner. However, active GLP-1 has a short half-life as it is rapidly hydrolyzed by the enzyme DPP-4[55,57,58]. Potential role of *E. cottonii* in modulating carbohydrate digestion and the incretin pathway through inhibition of α-amylase, α-glucosidase, and DPP-4, thereby reducing glucose absorption and prolonging active GLP-1 levels to maintain glucose-dependent insulin secretion.

E. cottonii exhibits promising antihyperglycemic potential by targeting digestive enzymes involved in carbohydrate metabolism. In Vitro studies have demonstrated that hydrolysates derived from dried *E. cottonii* powder and its carrageenan hydrolysates can inhibit α-amylase activity, showing an IC_{50} of 1.87 ± 0.104 mg/mL for the dried powder hydrolysate and 1.85 ± 0.105 mg/mL for the carrageenan hydrolysate. This effect was even stronger compared with acarbose, which exhibited an IC_{50} value of 3.67 ± 0.057 mg/mL. In the same study, rats administered dried *E. cottonii* powder hydrolysates and carrageenan hydrolysates showed significantly reduced blood glucose levels after oral sucrose loading compared with rats given aquadest. This effect was comparable to that of acarbose, an α-glucosidase inhibitor. These findings suggest that both hydrolysates can inhibit intestinal α-glucosidase, thereby preventing postprandial hyperglycemia.[26]

Consistently, in vitro studies also showed that carrageenan extracted from *E. cottonii* demonstrated inhibitory activity against α-glucosidase.[25] Furthermore, active constituents such as sulfated polygalactans obtained from *E. cottonii* showed strong inhibitory effects on both α-amylase and α-glucosidase, with IC_{50} values of 0.15 mg/mL for α-amylase and 0.09 mg/mL for α-glucosidase.[27] In vivo studies have also corroborated these findings, where administration of aqueous *E. cottonii* extract to diabetic rats induced by alloxan, significantly lowered blood glucose levels, normalized glycated hemoglobin (HbA1c), and increased plasma insulin levels.[28]

Enhancement of Insulin Secretion

Dipeptidyl peptidase-4 (DPP-4) plays a key role in inactivating incretin hormones such as glucagon-like peptide-1 (GLP-1), which are involved in insulin secretion. As illustrated in **Figure 2**, DPP-4 inhibitors suppress the activity of this enzyme, thereby reducing GLP-1 degradation. This prolongs the action of GLP-1, enhances insulin sensitivity and activity, and ultimately lowers blood glucose levels.[58] Several phytochemical compounds, such as phenolics, alkaloids, peptides, sterols, and terpenoids, have been demonstrated to exert inhibitory effects on DPP-4.[58] A study further revealed that sulfated polygalactans isolated from *E. cottonii* demonstrated potent DPP-4 inhibitory activity (IC_{50}: 0.12 mg/mL).[27] The inhibition of DPP-4 consequently promotes increased insulin secretion in the body.

Antioxidant Activity

Oxidative stress is a key factor in T2DM pathogenesis, oxidative stress disrupting regulatory pathways involved in insulin resistance and β-cell dysfunction.[59] In addition, oxidative stress accelerates the onset of vascular complications such as retinopathy, nephropathy, and cardiovascular disease.[60] The combination of Chronic elevation of glucose and lipid levels (glucolipotoxicity) is highly detrimental to cells, including pancreatic β-cells. Glucolipotoxicity interferes with critical stages of insulin biosynthesis and secretion, as well as other cellular processes vital for normal function.[61] Chronic hyperglycemia and mitochondrial dysfunction contribute to increased generation of ROS, thereby exacerbating condition of oxidative stress. In a hyperglycemic state, AGEs are produced through nonenzymatic reactions between ketone or aldehyde groups and protein amino groups. Oxidized AGEs activate their receptor, RAGE, stimulating *nicotinamide adenine dinucleotide phosphate oxidase* (NOX), thereby promoting additional ROS generation in diabetes mellitus.[62] Moreover, patients with diabetes exhibit impaired antioxidant defenses, characterized by decreased levels of enzymatic antioxidants involved in neutralizing reactive ROS, such as CAT, SOD, and GSH-Px, as well as reduced production of non-enzymatic antioxidants, including GSH and NADPH[63] As presented in the following figure (**Figure 3**).

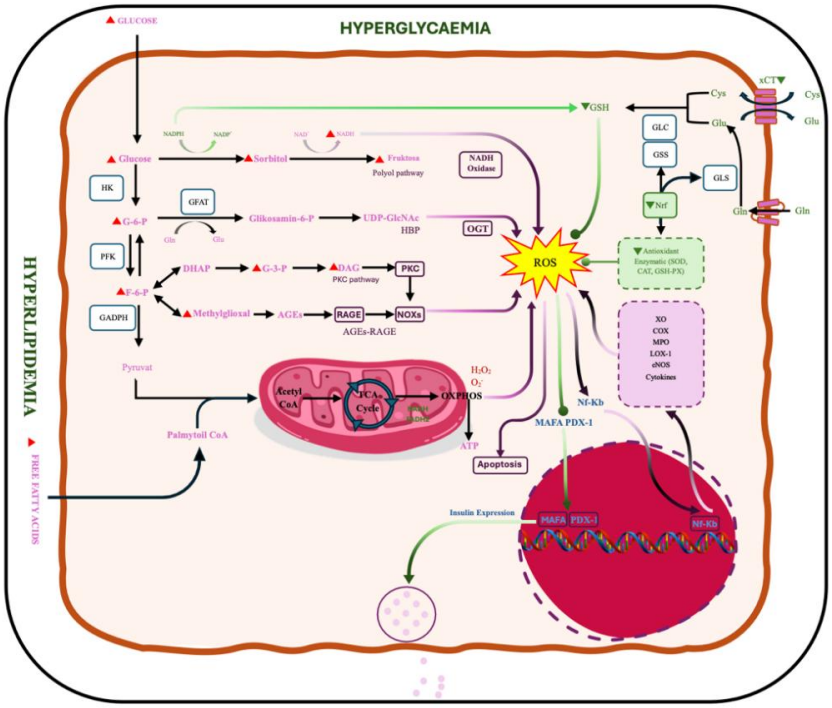

Figure 3. The Role of Oxidative Stress and Inflammation in Diabetes Mellitus.[63]

During hyperglycemia conditions, increased mitochondrial glucose oxidation generates excess ROS, especially superoxide, thereby initiating oxidative stress. Elevated glucose also activates pro-oxidative pathways such as advanced glycation end products (AGEs) formation, protein kinase-C activation, polyol pathway, and the hexosamine pathway, all of these enhance ROS production while reducing antioxidant availability, such as GSH. Hyperlipidemia and increased xanthine oxidase activity further exacerbate this condition. At the same time, antioxidant defense systems (SOD, CAT, GSH-Px) are weakened, leading to an imbalance between ROS and antioxidants. Consequently, chronic oxidative stress arises, damaging pancreatic β-cells and endothelial cells, and promoting diabetic complications. Oxidative stress also activates apoptotic pathways (PUMA), upregulates NF-κB, and suppresses insulin gene expression, thereby aggravating cellular damage through a vicious ROS–proinflammatory cycle.[63]

Evidence indicates that antioxidant-rich diets contribute to lowering the risk of T2DM.[64] In this context, *E. cottonii* has been extensively investigated for its antioxidant potential. Several studies have reported that bioactive peptides isolated from *E. cottonii* exhibit strong antioxidant activity. These compounds are not only effective in neutralizing free radicals but also provide cytoprotective effects on *human umbilical vein endothelial cells* (HUVECs) exposed to H_2O_2. Such effects are mediated through the enhancement of enzymatic antioxidants such as GSH-Px and SOD, along with the reduction of MDA and ROS levels.[30]

Other studies demonstrated that carrageenan derived from *E. cottonii* enhances the activity of several intrinsic antioxidant enzymes in alloxan induced diabetic rats, such as CAT, SOD, GSH-Px, and GST, in addition to non-enzymatic antioxidants like GSH.[29] Moreover, ethanol extracts of this alga were found to restore endogenous antioxidant balance in CCl_4-induced hepatotoxic rats by elevating GSH, CAT, and GST levels while decreasing LPO.[33] Similarly, in a lead-

induced hepatotoxicity mice model, administration of E. cottonii extracts decreased SGPT, SGOT, ALP, and MDA levels, while enhancing the activities of SOD and GSH-Px.[34]

The antioxidant activity of *E. cottonii* has also been assessed *in vitro* using various assays. For instance, its extract exhibited stronger hydrogen peroxide radical scavenging activity (27.9 ± 0.1%) compared with *C. serrulata* (22.1 ± 0.1%).[35] Furthermore, hydrolysates of *E. cottonii* demonstrated significant DPPH radical scavenging activity (IC_{50}: 2.58 ± 0.095 mg/mL).[26] These findings are consistent with numerous other reports showing that extracts or fractions of *E. cottonii* effectively scavenge free radicals using DPPH, ABTS, and FRAP methods, thereby reinforcing its potential as a natural antioxidant agent.[37–40,42–44]

Antioxidants play an essential role in diabetes therapy, particularly in preventing complications in vital organs. Active fractions of *E. cottonii* have been shown to exert antiglycation activity by reducing plasma glycated albumin and CML levels, as well as suppressing renal RAGE gene expression.[31] Consequently, the interaction of AGE with its receptor RAGE is diminished, thereby decreasing ROS production. Administration of *E. cottonii* fractions in diabetic rats also decreased H_2O_2 levels and NOX4 gene expression.[32] These effects demonstrate the potential of *E. cottonii* in preventing vascular complications in diabetes mellitus. Moreover, reduced NOX4 expression in adipocytes has been associated with lower adipose tissue inflammation and delayed onset of insulin resistance in obesity.[65]

Anti-Inflammatory Activity

Inflammation has been shown to impair insulin production and secretion from pancreatic β-cells, while simultaneously promoting insulin resistance. Chronic inflammation plays a crucial role in the pathogenesis of diabetes and the development of its complications. Persistent adipose tissue inflammation contributes to systemic inflammation and insulin resistance, leading to β-cell apoptosis and dysfunction, thereby disrupting insulin secretion. Several pro-inflammatory cytokines and gene-regulatory proteins, including IL-1β, TNF-α, and NF-κB, have been associated with disrupted insulin release and the progression of T2DM.[66] Experimental evidence in animal models indicates that exogenous TNF-α administration triggers insulin resistance, while its neutralization restores insulin responsiveness. Similarly, IL-1β, a pivotal inflammatory cytokine, impairs insulin signaling pathways, thereby contributing to insulin resistance.[67] Through NF-κB signaling, inflammation serves as a critical mediator in the development of insulin resistance in T2DM. In obesity-induced T2DM, adipocytes produce various cytokines and bioactive molecules that activate the IKKβ/NF-κB and JNK pathways. Activation of the IKKβ pathway induces nuclear translocation of NF-κB and upregulates inflammatory markers, which can lead to insulin resistance. Similarly, JNK activation promotes serine phosphorylation of IRS-1 at Ser-302 and Ser-307, negatively regulating insulin signaling. Thus, inhibition of the JNK or IKKβ/NF-κB pathways may improve or prevent the development of insulin resistance.[68]

Bioactive compounds in *E. cottonii* have demonstrated promising anti-inflammatory activity through multiple molecular pathways. One such compound, sulfated poligalactan, has been shown to inhibit pro-inflammatory enzymes including COX-1 and-2, and LOX-1, which are critical in the biosynthesis of inflammatory mediators.[27] Additionally, cyclic ether oxosin carboxylate non-isoprenoid compounds isolated from *E. cottonii* extracts exhibit radical scavenging potential in DPPH assays and inhibit COX-2 activity.[46]

These bioactivities are supported by in vivo studies across various inflammatory disease models. In IBD (inflammatory bowel disease) rat models, oral administration of *E. cottonii* ethanol extract reduced serum levels of TNF-α, IL-1β, and IL-6, while decreasing IL-1β expression in colonic tissue. Conversely, IL-10, an anti-inflammatory cytokine, showed elevated levels. Histological analyses demonstrated restoration of intestinal mucosal structure, including preserved crypt integrity in high-dose groups.[48] Similar effects were observed in obese rats with osteoarthritis, where polysaccharides from *E. cottonii* extracts suppressed the expression of IL-1β, TNF-α, and leptin, and inhibited NF-κB and activation of extracellular signal–regulated kinase 1/2 (ERK1/2). These effects were accompanied by reduced levels of tissue-degrading mediators such as MMP-1, MMP-13, and PGE2, collectively preventing cartilage degradation. These findings suggest that *E. cottonii* extracts hold promise as therapeutic agents for osteoarthritis, particularly in obesity-related conditions.[47]

Moreover, consumption of whole *E. cottonii* has been shown to protect against intestinal mucosal injury induced by chemotherapy, by enhancing mucin-2 secretion and decreasing the expression levels of TNF-α, IL-6, and IL-1β, as well as COX-2 and leukotrienes (LT).[49,50] In ovalbumin-induced allergic asthma models, methanol extracts of *E. cottonii* lowered cytokine pro-inflammatory such as TNF-α and IL-4, NF-κB, EGFR, and MMP-9 expression, while increasing IFN-γ, thereby modulating the anti-inflammatory immune response.[53] Chemically, two specific compounds isolated from *E. cottonii* 4-(2-chloroethyl)-5,7-(methoxymethyl)undec-3-enyl cyclooct-4-enone and 2-ethyl-6-(4-

methoxy-2-((2-oxotetrahydro-2H-pyran-4-yl)methyl)butoxy)-6-oxohexyl 5-ethyloct-4-enoate demonstrated high in vitro inhibitory potential against COX-2 and LOX-5, with lower IC_{50} values compared to conventional anti-inflammatory drugs such as aspirin and ibuprofen.[44,52] Lipids from this alga were also reported to effectively inhibit proteinases involved in tissue degradation, with activity comparable to salicylic acid.[51]

Despite multiple studies indicating anti-inflammatory effects, the presence of carrageenan in *E. cottonii* raises concerns regarding its use as an anti-inflammatory agent. Carrageenan is known to induce inflammation and may cause gastrointestinal disorders, such as IBD. It can alter gut microbiota, particularly *Akkermansia muciniphila*, reduce mucosal barriers, and trigger inflammatory responses by activating NF-κB through TLR4 signaling, altering macrophage activity, inducing pro-inflammatory cytokine production, and activating innate immune pathways.[69,70] Therefore, the presence of carrageenan should be carefully considered when developing *E. cottonii*-based products for anti-inflammatory purposes.

Modulation of Gut Microbiota

Intestinal microbiota contributes significantly to regulating systemic immunity and metabolic homeostasis [71,72]. It is also involved in modulating lipopolysaccharide levels, that contributes to the pathogenesis of diabetes. In patients with T2DM, both the proportion of butyrate-producing bacteria and the Firmicutes/Bacteroidetes ratio have been reported to be lower compared to non-diabetic individuals.[73]

As previously discussed, diabetes is closely linked to oxidative stress. Evidence from both animal models and clinical studies indicates that probiotic or symbiotic supplementation can alleviate oxidative stress and significantly reduce fasting glucose and insulin levels.[74]

Alterations in gut microbiota composition have been demonstrated to contribute significantly to the pathogenesis of metabolic diseases, including T2DM.[75] Prebiotic intake can help restore gut microbial balance by favoring the growth of beneficial microbes.[76] Dietary prebiotic fibers serve as selective substrates for beneficial bacteria, including *Bifidobacterium* and *Lactobacillus*, thereby enhancing host health.[77] Evidence from a meta-analysis showed that prebiotic intake markedly decreased HbA1c levels in individuals with T2DM.[78]

E. cottonii has been demonstrated to improve metabolic syndrome by suppressing obesity-associated gut microbiota and promoting beneficial gut microbes. It modulates the balance of major gut bacterial phyla, namely *Firmicutes* and *Bacteroidetes*.[16] Additionally, *E. cottonii* increases the abundance of *Bifidobacterium* spp., suggesting its potential as a prebiotic product for T2DM management.[54]

Critical Implications and Study Limitations

This review indicates that *Eucheuma cottonii* has promising potential as a natural therapeutic agent in the management of type 2 diabetes mellitus (T2DM) through a multitarget mechanism of action. Based on the literature analyzed, the reported biological activities include inhibition of carbohydrate-digesting enzymes (α-amylase and α-glucosidase), DPP-4 inhibition, as well as antioxidant and anti-inflammatory effects, and the ability to modulate gut microbiota. This multitarget approach is considered relevant given that the pathogenesis of T2DM involves multiple complex metabolic pathways.

Nevertheless, this review has several limitations. The mechanisms of action of *Eucheuma cottonii* toward these targets have not yet been comprehensively elucidated, primarily due to the limited data available in the reviewed literature. Therefore, further studies are needed to confirm and explore these mechanisms in greater depth in the future.

CONCLUSION

Based on the discussion above, *E. cottonii* emerges as a highly promising seaweed species for the development of products aimed at the prevention or management of diabetes mellitus. The ability to suppress glucose digestion, promote insulin release, exert antioxidant and anti-inflammatory actions, and sustain gut microbiota balance highlights its potential role in preventing and managing diabetes.

FUNDING

This research received no external funding.

ACKNOWLEDGMENTS

The authors acknowledge with gratitude the valuable support provided by colleagues and institutions during this study. This investigation was carried out without specific funding.

GENERATIVE AI DISCLOSURE STATEMENT

The authors employed ChatGPT (GPT-5.3, OpenAI) to support the language translation process, with all translations subsequently reviewed and validated by a language expert. The authors have confirmed the accuracy and originality of all content.

AUTHOR CONTRIBUTION STATEMENT

I Made Agus Mahardika: Conceptualization, Data curation, Writing Original draft preparation, Visualization and Software; **Putu Oka Samirana**: Methodology, Investigation, Supervision, Validation, Writing- Reviewing and Editing.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. Wahidin M, Achadi A, Besral B, Kosen S, Nadjib M, Nurwahyuni A, Ronoatmodjo S, Rahajeng E, Pane M, Kusuma D. Projection of diabetes morbidity and mortality till 2045 in Indonesia based on risk factors and NCD prevention and control programs. *Sci Rep*. 2024;14(1):5424. doi:10.1038/s41598-024-54563-2
2. Banday MZ, Sameer AS, Nissar S. Pathophysiology of diabetes: An overview. *Avicenna J Med*. 2020;10(04):174-188. doi:10.4103/ajm.ajm_53_20
3. Kementerian Kesehatan Republik Indonesia. *Laporan Hasil Riset Kesehatan Dasar Nasional (Riskesdas) 2018*. Badan Peneliti dan Pengembangan Kesehatan; 2019.
4. Kementerian Kesehatan Republik Indonesia. *Laporan Hasil Riset Kesehatan Dasar Nasional (Riskesdas) 2007*. Badan Penelitian dan Pengembangan Kesehatan; 2008.
5. DeFronzo RA. Pathogenesis of type 2 diabetes mellitus. *Medical Clinics of North America*. 2004;88(4):787-835. doi:10.1016/j.mcna.2004.04.013
6. Muoio DM, Newgard CB. Molecular and metabolic mechanisms of insulin resistance and β-cell failure in type 2 diabetes. *Nat Rev Mol Cell Biol*. 2008;9(3):193-205. doi:10.1038/nrm2327
7. Leahy JL. Pathogenesis of Type 2 Diabetes Mellitus. *Arch Med Res*. 2005;36(3):197-209. doi:10.1016/j.arcmed.2005.01.003
8. Zheng Y, Ley SH, Hu FB. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. *Nat Rev Endocrinol*. 2018;14(2):88-98. doi:10.1038/nrendo.2017.151
9. Reed J, Bain S, Kanamarlapudi V. A Review of Current Trends with Type 2 Diabetes Epidemiology, Aetiology, Pathogenesis, Treatments and Future Perspectives. *Diabetes Metab Syndr Obes*. 2021;Volume 14:3567-3602. doi:10.2147/DMSO.S319895
10. Galicia-Garcia U, Benito-Vicente A, Jebari S, Larrea-Sebal A, Siddiqi H, Uribe KB, Ostolaza H, Martín C. Pathophysiology of Type 2 Diabetes Mellitus. *Int J Mol Sci*. 2020;21(17):6275. doi:10.3390/ijms21176275
11. Weinberg Sibony R, Segev O, Dor S, Raz I. Overview of oxidative stress and inflammation in diabetes. *J Diabetes*. 2024;16(10):e70014. doi:10.1111/1753-0407.70014
12. Derosa G, Maffioli P. Mini-Special Issue paper Management of diabetic patients with hypoglycemic agents α-Glucosidase inhibitors and their use in clinical practice. *Archives of Medical Science*. 2012;5:899-906. doi:10.5114/aoms.2012.31621
13. Lankatillake C, Huynh T, Dias DA. Understanding glycaemic control and current approaches for screening antidiabetic natural products from evidence-based medicinal plants. *Plant Methods*. 2019;15(1):105. doi:10.1186/s13007-019-0487-8
14. Appuhamy JADRN, Kebreab E, Simon M, Yada R, Milligan LP, France J. Effects of diet and exercise interventions on diabetes risk factors in adults without diabetes: meta-analyses of controlled trials. *Diabetol Metab Syndr*. 2014;6(1):127. doi:10.1186/1758-5996-6-127
15. Le Y, Wang B, Xue M. Nutraceuticals use and type 2 diabetes mellitus. *Curr Opin Pharmacol*. 2022;62:168-176. doi:10.1016/j.coph.2021.12.004

16. Wanyonyi S, Du Preez R, Brown L, Paul N, Panchal S. Kappaphycus alvarezii as a Food Supplement Prevents Diet-Induced Metabolic Syndrome in Rats. *Nutrients*. 2017;9(11):1261. doi:10.3390/nu9111261
17. Basyuni M, Puspita M, Rahmania R, Albasri H, Pratama I, Purbani D, Aznawi AA, Mubaraq A, Al Mustaniroh SS, Menne F, Rahmila YI, Salmo III SG, Susilowati A, Larekeng SH, Ardli E, Kajita T. Current biodiversity status, distribution, and prospects of seaweed in Indonesia: A systematic review. *Heliyon*. 2024;10(10):e31073. doi:10.1016/j.heliyon.2024.e31073
18. Nunes A, Azevedo GZ, de Souza Dutra F, dos Santos BR, Schneider AR, Oliveira ER, Moura S, Vianello F, Maraschin M, Lima GPP. Uses and applications of the red seaweed Kappaphycus alvarezii: a systematic review. *J Appl Phycol*. 2024;36(6):3409-3450. doi:10.1007/s10811-024-03270-6
19. Das D, Arulkumar A, Paramasivam S, Lopez-Santamarina A, Del Carmen Mondragon A, Miranda Lopez JM. Phytochemical Constituents, Antimicrobial Properties and Bioactivity of Marine Red Seaweed (Kappaphycus alvarezii) and Seagrass (Cymodocea serrulata). *Foods*. 2023;12(14). doi:10.3390/foods12142811
20. Bahrun B, Melanie H, Artanti N, Anita Y, Marraskuranto E, Tuwo A, Miyamae Y. A review of chemical diversity of Kappaphycus alvarezii: biological properties, health benefits, and food applications. *Phytochemistry Reviews*. Published online November 13, 2025. doi:10.1007/s11101-025-10197-4
21. Shihab S, Jacob A, Mathew J, Ann Mathew A, Shanamitha A. A Review on the Potential Anti-inflammatory Properties of <i>Kappaphycus alvarezii</i> *Journal of Natural Remedies*. Published online June 13, 2023:361-371. doi:10.18311/jnr/2023/32082
22. Sarian MN, Ahmed QU, Mat So'ad SZ, Alhassan AM, Murugesu S, Perumal V, Syed Mohamad SNA, Khatib A, Latip J. Antioxidant and Antidiabetic Effects of Flavonoids: A Structure-Activity Relationship Based Study. *Biomed Res Int*. 2017;2017:1-14. doi:10.1155/2017/8386065
23. Shamsudin NF, Ahmed QU, Mahmood S, Shah SAA, Sarian MN, Khattak MMAK, Khatib A, Sabere ASM, Yusoff YM, Latip J. Flavonoids as Antidiabetic and Anti-Inflammatory Agents: A Review on Structural Activity Relationship-Based Studies and Meta-Analysis. *Int J Mol Sci*. 2022;23(20):12605. doi:10.3390/ijms232012605
24. Brown L, Poudyal H, Panchal SK. Functional foods as potential therapeutic options for metabolic syndrome. *Obesity Reviews*. 2015;16(11):914-941. doi:10.1111/obr.12313
25. Suganya AM, Sanjivkumar M, Chandran MN, Palavesam A, Immanuel G. Pharmacological importance of sulphated polysaccharide carrageenan from red seaweed Kappaphycus alvarezii in comparison with commercial carrageenan. *Biomedicine & Pharmacotherapy*. 2016;84:1300-1312. doi:10.1016/j.biopha.2016.10.067
26. Yustisia I, Hardjo M, Hasri, Sari WON, Kasmiati. Optimization and characterization of Kappaphycus alvarezii and κ-carrageenan hydrolysates with potential biomedical applications. *Food Hydrocolloids for Health*. 2025;7:100205. doi:10.1016/j.fhfh.2025.100205
27. Makkar F, Chakraborty K. Antidiabetic and anti-inflammatory potential of sulphated polygalactans from red seaweeds *Kappaphycus alvarezii* and *Gracilaria opuntia*. *Int J Food Prop*. 2017;20(6):1326-1337. doi:10.1080/10942912.2016.1209216
28. Cyriac B, Eswaran K. Anti- hyperglycemic effect of aqueous extract of Kappaphycus alvarezii (Doty) Doty ex. P. Silva in alloxan-induced diabetic rats. *J Appl Phycol*. 2016;28(4):2507-2513. doi:10.1007/s10811-015-0762-7
29. Sanjivkumar M, Chandran MN, Suganya AM, Immanuel G. Investigation on bio-properties and in-vivo antioxidant potential of carrageenans against alloxan induced oxidative stress in Wistar albino rats. *Int J Biol Macromol*. 2020;151:650-662. doi:10.1016/j.ijbiomac.2020.02.227
30. Sun KL, Gao M, Wang YZ, Li XR, Wang P, Wang B. Antioxidant Peptides From Protein Hydrolysate of Marine Red Algae Eucheuma cottonii: Preparation, Identification, and Cytoprotective Mechanisms on H2O2 Oxidative Damaged HUVECs. *Front Microbiol*. 2022;13. doi:10.3389/fmicb.2022.791248
31. Yulianti E, Sunarti, Wahyuningsih MSH. The effect of Kappaphycus alvarezii fraction on plasma glucose, Advanced Glycation End-products formation, and renal RAGE gene expression. *Heliyon*. 2021;7(1):e05978. doi:10.1016/j.heliyon.2021.e05978
32. Yulianti E, Sunarti, Wahyuningsih MSH. The effect of Kappaphycus alvarezii active fraction on oxidative stress and inflammation in streptozotocin and nicotinamide-induced diabetic rats. *BMC Complement Med Ther*. 2022;22(1):15. doi:10.1186/s12906-021-03496-8
33. Vun-Sang S, Sivapragasam G, Yong WTL, Benjamin MAZ, Iqbal M. Assessment of Antioxidant and Hepatoprotective Effects of Kappaphycus alvarezii (Doty) Doty ex Silva Against Carbon Tetrachloride-Induced Liver Injury in Rats. *Journal of Tropical Biology & Conservation (JTBC)*. 2024;21:73-87. doi:10.51200/jtbc.v21i.5420

34. Wardani G, Farida N, Andayani R, Kuntoro M, Sudjarwo S. The potency of red seaweed (Eucheuma cottonii) extracts as hepatoprotector on lead acetate-induced hepatotoxicity in mice. *Pharmacognosy Res*. 2017;9(3):282. doi:10.4103/pr.pr_69_16
35. Das D, Arulkumar A, Paramasivam S, Lopez-Santamarina A, del Carmen Mondragon A, Miranda Lopez JM. Phytochemical Constituents, Antimicrobial Properties and Bioactivity of Marine Red Seaweed (Kappaphycus alvarezii) and Seagrass (Cymodocea serrulata). *Foods*. 2023;12(14):2811. doi:10.3390/foods12142811
36. Rudke AR, da Silva M, Andrade CJ de, Vitali L, Ferreira SRS. Green extraction of phenolic compounds and carrageenan from the red alga Kappaphycus alvarezii. *Algal Res*. 2022;67:102866. doi:10.1016/j.algal.2022.102866
37. Vaghela P, Das AK, Trivedi K, Anand KGV, Shinde P, Ghosh A. Characterization and metabolomics profiling of Kappaphycus alvarezii seaweed extract. *Algal Res*. 2022;66:102774. doi:10.1016/j.algal.2022.102774
38. Regina LZL, Sharon KTF, Lim LH, Su SF, Teo S Sen. Determination of antioxidant activity, chlorophyll and carotenoids content of Kappaphycus alvarezii: Comparison of seaweed with traditional Chinese Medicines. *Res J Biotechnol*. 2024;19(4):24-31. doi:10.25303/1904rjbt024031
39. Araújo PG, Nardelli AE, Duran R, Pereira MS, Gelli VC, Mandalka A, Eisner P, Fujii MT, Chow F. Seasonal variation of nutritional and antioxidant properties of different Kappaphycus alvarezii strains (Rhodophyta) farmed in Brazil. *J Appl Phycol*. 2022;34(3):1677-1691. doi:10.1007/s10811-022-02739-6
40. Teo BSX, Gan RY, Abdul Aziz S, Sirirak T, Mohd Asmani MF, Yusuf E. In vitro evaluation of antioxidant and antibacterial activities of Eucheuma cottonii extract and its in vivo evaluation of the wound-healing activity in mice. *J Cosmet Dermatol*. 2021;20(3):993-1001. doi:10.1111/jocd.13624
41. Makkar F, Chakraborty K. Antioxidative sulphated polygalactans from marine macroalgae as angiotensin-I converting enzyme inhibitors. *Nat Prod Res*. 2018;32(17):2100-2106. doi:10.1080/14786419.2017.1363756
42. Araújo PG, Nardelli AE, Fujii MT, Chow F. Antioxidant properties of different strains of Kappaphycus alvarezii (Rhodophyta) farmed on the Brazilian coast. *Phycologia*. 2020;59(3):272-279. doi:10.1080/00318884.2020.1736878
43. Papitha R, Selvaraj CI, Palanichamy V, Arunachalam P, Roopan SM. In vitro Antioxidant and Cytotoxic Capacity of Kappaphycus alvarezii Successive Extracts. *Curr Sci*. 2020;119(5):790. doi:10.18520/cs/v119/i5/790-798
44. Makkar F, Chakraborty K. First report of dual cyclooxygenase-2 and 5-lipoxygenase inhibitory halogen derivatives from the thallus of intertidal seaweed Kappaphycus alvarezii. *Medicinal Chemistry Research*. 2018;27(10):2331-2340. doi:10.1007/s00044-018-2239-0
45. Rajaram R, Muralisankar T, Paray BA, Al-Sadoon MK. Phytochemical profiling and antioxidant capacity of Kappaphycus alvarezii (Doty) Doty collected from seaweed farming sites of tropical coastal environment. *Aquac Res*. 2021;52(7):3438-3448. doi:10.1111/are.15188
46. Makkar F, Chakraborty K. Unprecedented antioxidative cyclic ether from the red seaweed *Kappaphycus alvarezii* with anti-cyclooxygenase and lipoxidase activities. *Nat Prod Res*. 2017;31(10):1131-1141. doi:10.1080/14786419.2016.1230113
47. Sudirman S, Chang HW, Chen CK, Kong ZL. A dietary polysaccharide from Eucheuma cottonii downregulates proinflammatory cytokines and ameliorates osteoarthritis-associated cartilage degradation in obese rats. *Food Funct*. 2019;10(9):5697-5706. doi:10.1039/C9FO01342C
48. Sudirman S, Hsu YH, He JL, Kong ZL. Dietary polysaccharide-rich extract from Eucheuma cottonii modulates the inflammatory response and suppresses colonic injury on dextran sulfate sodium-induced colitis in mice. *PLoS One*. 2018;13(10):e0205252. doi:10.1371/journal.pone.0205252
49. Zhang Q, Zhou S, Lim PE, Wei B, Xue C, Xue Y, Tang Q. *Kappaphycus Alvarezii* Compound Powder Prevents Chemotherapy-Induced Intestinal Mucositis in BALB/c Mice. *Nutr Cancer*. 2022;74(10):3735-3746. doi:10.1080/01635581.2022.2089699
50. Zhang Q, Yang R, Lim PE, Chin Y, Zhou S, Gao Y, Tang Q. Sun-Dried and Air-Dried Kappaphycus alvarezii Attenuates 5-Fluorouracil-Induced Intestinal Mucositis in Mice. *Nutr Cancer*. 2022;74(6):2113-2121. doi:10.1080/01635581.2021.1981403
51. James J, Sharma N, Joshi HC, Kumar S, Kumar AP, Hussain A. Extraction and bioactivity assessment of bio-oil from Kappaphycus alvarezii biomass using the Bligh, Dyer and Soxhlet method. *J Am Oil Chem Soc*. 2025;102(4):811-822. doi:10.1002/aocs.12931
52. Makkar F, Chakraborty K. Antioxidant and anti-inflammatory oxygenated meroterpenoids from the thalli of red seaweed Kappaphycus alvarezii. *Medicinal Chemistry Research*. 2018;27(8):2016-2026. doi:10.1007/s00044-018-2210-0

53. Abu Bakar N, Anyanji VU, Mustapha NM, Lim SL, Mohamed S. Seaweed (Eucheuma cottonii) reduced inflammation, mucin synthesis, eosinophil infiltration and MMP-9 expressions in asthma-induced rats compared to Loratadine. *J Funct Foods*. 2015;19:710-722. doi:10.1016/j.jff.2015.10.011
54. Bajury DM, Rawi MH, Sazali IH, Abdullah A, Sarbini SR. Prebiotic evaluation of red seaweed (*Kappaphycus alvarezii*) using *in vitro* colon model. *Int J Food Sci Nutr*. 2017;68(7):821-828. doi:10.1080/09637486.2017.1309522
55. Sharifuddin Y, Chin YX, Lim PE, Phang SM. Potential Bioactive Compounds from Seaweed for Diabetes Management. *Mar Drugs*. 2015;13(8):5447-5491. doi:10.3390/md13085447
56. Gong L, Feng D, Wang T, Ren Y, Liu Y, Wang J. Inhibitors of α-amylase and α-glucosidase: Potential linkage for whole cereal foods on prevention of hyperglycemia. *Food Sci Nutr*. 2020;8(12):6320-6337. doi:10.1002/fsn3.1987
57. Lam TP, Tran NVN, Pham LHD, Lai NVT, Dang BTN, Truong NLN, Nguyen-Vo SK, Hoang TL, Mai TT, Tran TD. Flavonoids as dual-target inhibitors against α-glucosidase and α-amylase: a systematic review of in vitro studies. *Nat Prod Bioprospect*. 2024;14(1):4. doi:10.1007/s13659-023-00424-w
58. Lin SR, Chang CH, Tsai MJ, Cheng H, Chen JC, Leong MK, Weng CF. The perceptions of natural compounds against dipeptidyl peptidase 4 in diabetes: from *in silico* to *in vivo*. *Ther Adv Chronic Dis*. 2019;10. doi:10.1177/2040622319875305
59. Fatima MT, Bhat AA, Nisar S, Fakhro KA, Al-Shabeeb Akil AS. The role of dietary antioxidants in type 2 diabetes and neurodegenerative disorders: An assessment of the benefit profile. *Heliyon*. 2023;9(1):e12698. doi:10.1016/j.heliyon.2022.e12698
60. Caturano A, D'Angelo M, Mormone A, Russo V, Mollica MP, Salvatore T, Galiero R, Rinaldi L, Vetrano E, Marfella R, Monda M, Giordano A, Sasso FC. Oxidative Stress in Type 2 Diabetes: Impacts from Pathogenesis to Lifestyle Modifications. *Curr Issues Mol Biol*. 2023;45(8):6651-6666. doi:10.3390/cimb45080420
61. Dilworth L, Stennett D, Facey A, Omoruyi F, Mohansingh S, Omoruyi FO. Diabetes and the associated complications: The role of antioxidants in diabetes therapy and care. *Biomedicine & Pharmacotherapy*. 2024;181:117641. doi:10.1016/j.biopha.2024.117641
62. Yuan T, Yang T, Chen H, Fu D, Hu Y, Wang J, Yuan Q, Yu H, Xu W, Xie X. New insights into oxidative stress and inflammation during diabetes mellitus-accelerated atherosclerosis. *Redox Biol*. 2019;20:247-260. doi:10.1016/j.redox.2018.09.025
63. Chen X, Xie N, Feng L, Huang Y, Wu Y, Zhu H, Tang J, Zhang Y. Oxidative stress in diabetes mellitus and its complications: From pathophysiology to therapeutic strategies. *Chin Med J (Engl)*. 2025;138(1):15-27. doi:10.1097/CM9.0000000000003230
64. Li X, Xue Y, Zhang Y, Wang Q, Qiu J, Zhang J, Yang C, Zhao Y, Zhang Y. Association between dietary antioxidant capacity and type 2 diabetes mellitus in Chinese adults: a population-based cross-sectional study. *Nutr Metab (Lond)*. 2024;21(1):16. doi:10.1186/s12986-024-00786-z
65. He J yi, Hong Q, Chen B xia, Cui S yuan, Liu R, Cai G yan, Guo J, Chen X mei. Ginsenoside Rb1 alleviates diabetic kidney podocyte injury by inhibiting aldose reductase activity. *Acta Pharmacol Sin*. 2022;43(2):342-353. doi:10.1038/s41401-021-00788-0
66. Li D, Zhong J, Zhang Q, Zhang J. Effects of anti-inflammatory therapies on glycemic control in type 2 diabetes mellitus. *Front Immunol*. 2023;14. doi:10.3389/fimmu.2023.1125116
67. Sun Q, Li J, Gao F. New insights into insulin: The anti-inflammatory effect and its clinical relevance. *World J Diabetes*. 2014;5(2):89-96. doi:10.4239/wjd.v5.i2.89
68. Rai U, Senapati D, Arora MK. Insights on the role of anti-inflammatory and immunosuppressive agents in the amelioration of diabetes. *Diabetol Int*. 2023;14(2):134-144. doi:10.1007/s13340-022-00607-9
69. Borsani B, De Santis R, Perico V, Penagini F, Pendezza E, Dilillo D, Bosetti A, Zuccotti GV, D'Auria E. The Role of Carrageenan in Inflammatory Bowel Diseases and Allergic Reactions: Where Do We Stand? *Nutrients*. 2021;13(10). doi:10.3390/nu13103402
70. Komisarska P, Pinyosinwat A, Saleem M, Szczuko M. Carrageenan as a Potential Factor of Inflammatory Bowel Diseases. *Nutrients*. 2024;16(9). doi:10.3390/nu16091367
71. Al-Jameel SS. Association of diabetes and microbiota: An update. *Saudi J Biol Sci*. 2021;28(8):4446-4454. doi:10.1016/j.sjbs.2021.04.041
72. Sadagopan A, Mahmoud A, Begg M, Tarhuni M, Fotso M, Gonzalez NA, Sanivarapu RR, Osman U, Latha Kumar A, Mohammed L. Understanding the Role of the Gut Microbiome in Diabetes and Therapeutics Targeting Leaky Gut: A Systematic Review. *Cureus*. Published online July 8, 2023. doi:10.7759/cureus.41559

73. Li WZ, Stirling K, Yang JJ, Zhang L. Gut microbiota and diabetes: From correlation to causality and mechanism. *World J Diabetes*. 2020;11(7):293-308. doi:10.4239/wjd.v11.i7.293

74. Xi Y, Xu PF. Diabetes and gut microbiota. *World J Diabetes*. 2021;12(10):1693-1703. doi:10.4239/wjd.v12.i10.1693

75. Almugadam BS, Liu Y, Chen S min, Wang C hao, Shao C yi, Ren B wei, Tang L, Hatziagelaki E. Alterations of Gut Microbiota in Type 2 Diabetes Individuals and the Confounding Effect of Antidiabetic Agents. *J Diabetes Res*. 2020;2020:1-14. doi:10.1155/2020/7253978

76. Holscher HD. Dietary fiber and prebiotics and the gastrointestinal microbiota. *Gut Microbes*. 2017;8(2):172-184. doi:10.1080/19490976.2017.1290756

77. Rezende ESV, Lima GC, Naves MMV. Dietary fibers as beneficial microbiota modulators: A proposed classification by prebiotic categories. *Nutrition*. 2021;89:111217. doi:10.1016/j.nut.2021.111217

78. Ojo O, Wang X, Ojo OO, Brooke J, Jiang Y, Dong Q, Thompson T. The Effect of Prebiotics and Oral Anti-Diabetic Agents on Gut Microbiome in Patients with Type 2 Diabetes: A Systematic Review and Network Meta-Analysis of Randomised Controlled Trials. *Nutrients*. 2022;14(23):5139. doi:10.3390/nu14235139