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Anti-diabetic effects of marine natural products through redox modulation via Nrf2/HO-1 cytoprotective pathways

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Diabetes mellitus (DM), a major global health concern, is a chronic metabolic disorder. Bioactive compounds sourced from numerous marine natural products recently have drawn attention as novel therapeutic approaches. Considering these chemicals and their role in cellular redox modulation by involving the nuclear factor erythroid 2-related factor 2 (Nrf2)/heme oxygenase 1 (HO-1) pathway, the current study attempts to highlight their anti-diabetic effects and the molecular mechanisms involved. Reactive oxygen species (ROS)-mediated oxidative stress, inflammation, and cellular damage are linked to most human pathologies specifically DM. The Nrf2/HO-1 pathway is a key defense mechanism developed by the cells to combat ROS burst. Marine natural compounds have strong pharmacological potential in triggering cellular antioxidant defense mechanisms by declining oxidative damage and inflammation linked to DM. How marine natural products potentially alleviate DM specifically type 2 diabetes (T2D) and its related issues is especially focused on. The literature was thoroughly analyzed to open a discussion about specific marine compounds and their well-established anti-diabetic effects to elucidate possible therapeutic applications. Furthermore, opportunities and the pros and cons of using these marine bioactive compounds as complementary treatment for DM are also discussed. The diverse characteristics of marine natural products, specifically with regard to redox control, offer promising opportunities for drug discovery and therapeutic interventions in clinical trials.

KEYWORDS

diabetes mellitus, therapeutics, ROS, marine bioactive compounds, Nrf2, HO-1

1 Introduction

The World Health Organization (WHO) declared diabetes mellitus (DM) as a major problem alongside chronic respiratory illnesses, cancer, and cardiovascular diseases (CVDs). The rising DM cases have impacted the human development, health, and economical situations of countries (Roglic, 2016). The WHO approved the global framework for non-communicable diseases (NCDs) in 2013 composed of multi-target goals for 2025. DM and its main risk factors include reduction of poor diets and physical inactivity, minimizing the rise in DM prevalence, improving treatment accessibility, and reducing early age deaths (Beaglehole et al., 2011; World Health Organization (WHO), 2018).

DM is caused by insufficient insulin secretion by pancreatic β cells or by an immune system resistant to insulin (Khan et al., 2022; Maestas et al., 2024). Type 1 diabetes (T1D) is a genetic disorder where the pancreas does not produce insulin at all (Galicia-Garcia et al., 2020; Roep et al., 2021). In type 2 diabetes (T2D), body cells develop insulin resistance that causes a progressive decrease in insulin production, and gestational diabetes during pregnancy results in complications during pregnancy and birth (Galicia-Garcia et al., 2020; Choi et al., 2024; Maestas et al., 2024). T2D risk is increased by gestational diabetes and later on by poor lifestyle (Eizirik et al., 2020; Elliott et al., 2024). Two intermediate stages between normal and diabetic blood glucose levels are impaired fasting glucose (IFG) and impaired fasting glycemia (IGT), and individuals suffering from both of these conditions have a higher risk of developing CVD than a normal person (Ahmadizar et al., 2021; Zuo et al., 2021; Poznyak et al., 2022).

Complementary and alternative medicine (CAM) improves overall health and follows global trends for better life standards. The US National Center for Complementary and Alternative Medicine (NCCAM) defines CAM as a group of medical and healthcare systems, practices, and products that are not presently considered part of conventional medicine. Alternative medicine is used in place of conventional treatment, whereas complementary medicine is used in addition to it (Tangkiatkumjai et al., 2020). Because these marine bioactive compounds have been reported to exert no or little adverse responses than already known drugs, they became an attractive option (Hassan et al., 2022). Along with herbal medicines, massage therapy, acupuncture, faith healing, hypnosis, and music therapies are also included in CAM (Kumar et al., 2006). Medicinal plants cure multiple diseases, and usage of herbal treatments has increased by multi-fold in the USA during the past decade (Vuksan et al., 2000); over three million Americans use CAM therapies against DM (Ranasinghe et al., 2012). In-depth investigation of the underlying molecular mechanisms on how these bioactives work could provide important novel insights for the proper cure of DM. However, the exploration of novel anti-diabetic drugs would be enhanced by the application of certain computational tools (Wang et al., 2020).

DM is treated with continuous insulin dosage or chemical agents such as acarbose, pioglitazone, and miglitol that block digestive enzymes, or oral medication like sulfonylureas and biguanides. Preventing CVD is a major goal during diabetes treatment, and a key concept in this therapy system is to get the patient to have optimal disease control, which includes managing their blood pressure, cholesterol, and glucose levels (ElSayed et al., 2022; Li et al., 2023). Chronic high blood glucose level generates ROS burst, which develops diabetes, diabetes-induced retinal impairment, nephropathy, neuropathy, and CVD (Yuan et al., 2019; Caturano et al., 2023). Consequently, reducing carbohydrate absorption postprandial may be a good way to keep blood glucose levels within the permissible range (Olaokun et al., 2013; Nasab et al., 2020). Synthetic or chemically modified drugs to cure diabetes and associated pathologies are expensive and may have side effects (Groop and Pociot, 2014). The quest for novel and cheaper natural bioactive compounds as alternative drug molecules is a vital component of contemporary pharmaceuticals (Mayer et al., 2010; Yuan et al., 2019; Gagare et al., 2024). Natural resources in oceans are deemed for proper entry into new pharmaceuticals and nutritional supplements (Beygmoradi and Homaei, 2017; Banday et al., 2024). Herein, we highlighted that products derived from marine life could promisingly be the next authentic DM treatment options.

The possible medicinal uses of phytoplanktons and related marine life are not much known. Diseases such as diabetes, Parkinson's disease (PD), Alzheimer's disease (AD), and many others can be treated by inhibiting certain enzymes at multiple cellular events (Nowell et al., 2023). The enzymes aldose reductase (AR), protein tyrosine phosphatase, and α-glucosidase are deleterious to T2D and associated disorders. Biologically active insulin, fucoxanthin, dysidine, benzene acetamide, 2-piperidione, n-hexadecanoic acid, and hundreds of other compounds have been isolated from the red or brown algae, diatoms, ascidians, and corals (Bhattacharjee et al., 2014; Pathak et al., 2022). Marine natural products are equipped with certain specialized functional groups on BACs, indicating that the origin of certain specialized enzymes in the cells of those organisms may be of potential therapeutic applications. Moreover, the presence of plenty of reducing sites, –OH, and structural diversity make marine BACs superior to already known plant BACs. Other marine substances are notable examples of inhibitors of these enzymes and have antioxidant potential (Bhattacharjee et al., 2014). Activation of the GLUT-4 receptor improves peripheral glucose consumption and may also control diabetes. Fucoxanthin inhibits the activities of insulin resistance causing protein factors including adipokines, tumor necrosis factor-α (TNF-α), monocyte chemoattractant protein-1 (MCP-1), and

Abbreviations: ARE, Antioxidant response element; CAM, Complementary and alternative medicine; CVD, Cardiovascular disease; DCs, Dendritic cells; DM, Diabetes mellitus; DPP4, Dipeptidyl-peptidase 4; ERK, Signal-regulated kinase; FBG, Fasting blood glucose; GHb, Glycosylated hemoglobin; GLUT4, Glucose transporter protein type 4; HFD, High-fat diet; HO-1, Heme oxygenase-1; IDDM, Insulin-dependent diabetes mellitus; IGG, Impaired fasting glucose; IL-6, Interleukin-6; IκB, Inhibitor of kappa B; iNKT, Invariant natural killer T; IRS, Insulin receptor substrate; JNK, Jun N-terminal kinase; MCP-1, Monocyte chemoattractant protein-1; NCCAM, National Center for Complementary and Alternative Medicine; NCDs, Noncommunicable diseases; PKB, Protein kinase B; PTP1B, Protein tyrosine phosphatase 1B; ROS, Reactive oxygen species; T1D, Type 1 diabetes; TNF-α, Tumor necrosis factor-α; TRP, Transient receptor potential.

interleukin-6 (IL-6). Biological insulin mimicking human insulin has been isolated from spotted dogfish and hammerhead sharks (*Sphyrna lewini*), which is shown to have a potent receptor binding capability and is a promising new bio-insulin (Bhattacharjee et al., 2014).

2 Redox modulation in diabetes

Marine natural products may stabilize and modulate the production of ROS, and activate or inhibit enzymatic activities to reduce insulin resistance altogether by provoking the Nrf2/HO-1 redox responsive pathway (Figure 1). Imbalance in antioxidants and ROS levels may lead to heavy cellular oxidative stress and chronic conditions may lead to pathologies like diabetes (West, 2000). After macrophages and dendritic cells (DCs) enter the islets, T cells in T1D autoimmune destroy pancreatic β cells. In contrast, NF-κB and other redox-dependent transcription factors activate DCs and macrophages by generating intracellular ROS as a result of interactions between receptors and ligands (Figure 1), or ROS from neighboring pancreatic phagocytes. The pancreatic lymph nodes receive β-cell antigens transported by activated DCs and macrophages, which enhance ROS production, proinflammatory cytokines, and synapses with reactive T cells (Sun et al., 2023). Innate and adaptive immune responses rely solely on ROS generation for their development and are the primary culprits in islet cell autoimmunity (Delmastro and Piganelli, 2011; Waldron-Lynch and Herold, 2011). There are several uses for transient receptor potential (TRP) channels in normal and disease conditions. Redox TRPs, a subset of these channels, are recently recognized as important in identifying any changes in cellular redox homeostasis to respond quickly. Hyperglycemia is a major cause of diabetes and its associated pathologies. Variations in the oxidative state of cells can affect the activity of many redox TRP channels (TRPA1, TRPC5, TRPMs, and TRPV1). By focusing on these redox TRPs, a new therapeutic approach to treat diabetes is possible. Natural drugs that modulated redox TRP activation may serve as novel therapeutic targets for the efficient treatment of hyperglycemia-induced alterations in cellular redox states, diabetes, and associated diseases (Adhya and Sharma, 2019). When ROS activate stress-sensitive serine/threonine kinases, i.e., c-Jun N-terminal kinase (JNK) and other kinases, the insulin receptor substrate (IRS) protein is phosphorylated at serine residues. Tissues are normally sensitive to insulin, and phosphorylation impairs insulin signaling to induce insulin

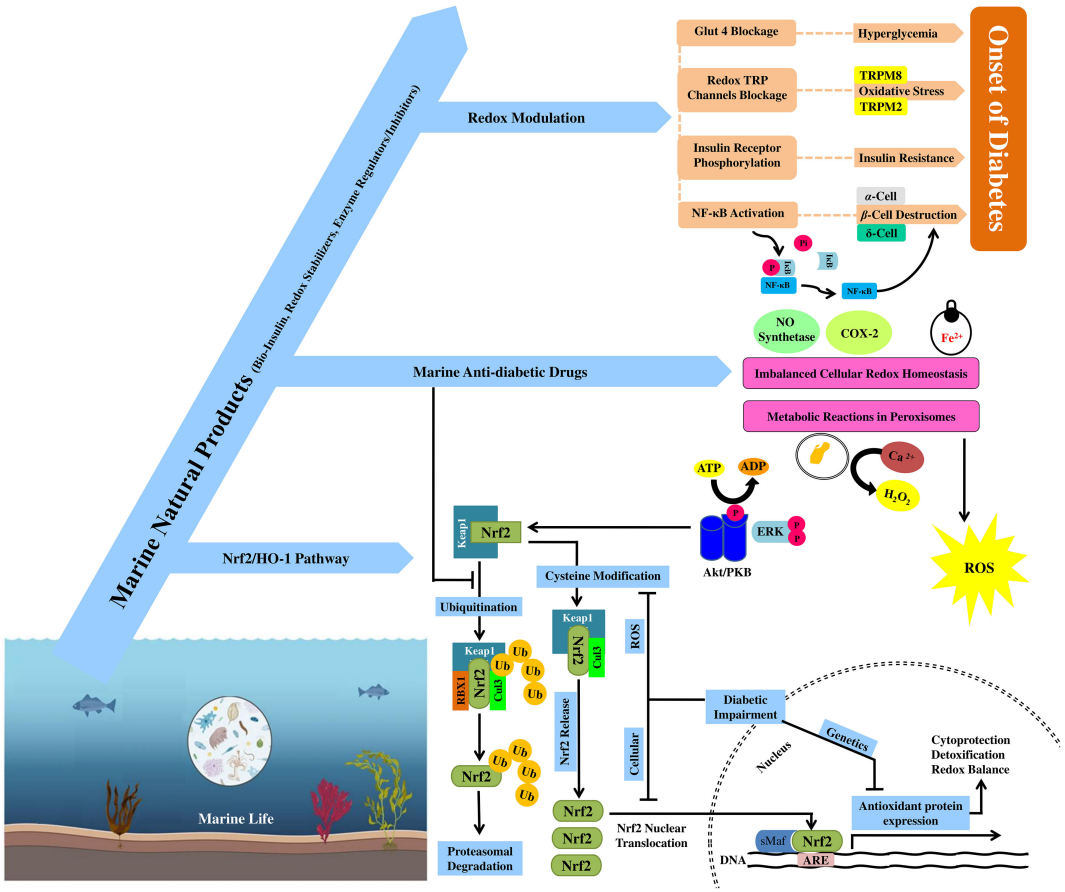


FIGURE 1
Anti-diabetic effects of marine natural products through redox modulation and activation of the Nrf2/HO-1 cytoprotective pathway. Interplay between marine natural products, redox modulation, and the Nrf2/HO-1 pathway to pose anti-diabetic effects. The mechanism of ubiquitination of Nrf2 and its nuclear movement after releasing from its inhibitor Keap1 or (INrf2) in the cytoplasm. Role of redox modulation in diabetes through multiple signaling cascades to overcome the onset of diabetes (GLUT-4 and redox TRP channel blockage, phosphorylation of IκB and insulin receptors).

resistance (Han, 2016). A high-fat diet (HFD) has also been shown to increase the formation of ROS in mitochondria, which *in vivo* causes insulin resistance. Many insulin resistance models, including those brought on by glucocorticoids and inflammation, solely rely on ROS (Geer et al., 2014).

3 Nrf2/HO-1 redox responsive cytoprotective pathways in diabetes

An important transcription factor controlling the expression of antioxidant proteins and phase II detoxifying enzymes is Nrf2 (Figure 1) (He et al., 2020). Normally, Nrf2 is inhibited by the cytosolic repressor protein Kelch-like ECH-associated protein 1 (Keap1) and causes its ubiquitination and proteasomal destruction (Cuadrado et al., 2019). Nrf2 is activated and released from the Keap1–Nrf2 complex upon oxidative stress-mediated damage to Keap1 cysteine residues (Cuadrado et al., 2019). After translocation into the nucleus and being firmly attached onto antioxidant response elements (AREs), Nrf2 activates target gene transcription (Baird and Yamamoto, 2020). Additionally, upon transgenic Nrf2 deletion, mice showed reduced levels of antioxidant-encoding genes at both basal and inducible levels, making them very susceptible to develop oxidative stress, diabetes, inflammation, and nephropathy. Activation of Nrf2 is a promising target that could reduce the severity of diabetic kidney injury caused by chronic oxidative stress (Tanase et al., 2022).

Cellular ROS burst dissociates Nrf2 from its inhibitor Keap1 (INrf2)/Cul3–Rbx1 complex and translocates into the nucleus (Kaspar and Jaiswal, 2010; Iso et al., 2016; Baird and Yamamoto, 2020), where it attaches to ARE and activates the expression of downstream antioxidant hemeoxygenase-1 (HO-1) (Figure 1) (Loboda et al., 2016; Hammad et al., 2023). HO-1 is essential in the early stages of homeostatic adaptive responses because it removes excess heme by decomposing into biliverdin, which quickly reduced to bilirubin, iron ions, and carbon monoxide (CO) that reduces oxidative stress-induced tissue damage, inflammation, and apoptosis (Figure 1) (Loboda et al., 2016; Mancuso, 2023). Nrf2 and HO-1 both provide essential cytoprotective responses against any slight change in cellular redox homeostasis (Figure 1). The development of diabetes is predominantly linked to the downregulation of the Nrf2/HO-1 pathway, and their absence contributes to increased oxidative stress, inflammation, and immunological dysregulation (Loboda et al., 2016; Mancuso, 2023).

4 Marine natural products with anti-diabetic effects

Two primary treatments for diabetes are insulin injection and oral anti-diabetic medications, but long-term medication with synthetic drugs leads to slower recovery and a plethora of side effects. Marine natural drugs seem a potential source of anti-diabetic medication due to their strong antioxidant nature and bioactivity (Figure 1) (Unnikrishnan and Jayasri, 2018). The medicinal and pharmacological potential of biologically active compounds from marine plants or non-plant sources has not been focused on until early this century (De la Calle, 2009; Karthikeyan et al., 2022). Pathogenicity in T2D and its associated disorders can be caused by dysregulation in enzyme activities such as α-glucosidase, protein tyrosine phosphatase (PTP), and AR, which can be regulated by marine natural products (Hansen, 2002; Magwaza and Islam, 2023; Banday et al., 2024).

The biologically active insulin, methyl-ethyl ketone derivatives, fucoxanthin, dysidine, 2-piperidione, benzene acetamide, n-hexadecenoic acid, and many other related compounds from brown or red algae, diatoms, ascidians, and corals from the ocean could be novel anti-diabetic drugs that may target enzyme modulation and higher antioxidant activity (Debbab et al., 2010; Bhattacharjee et al., 2014). Activation of the GLUT-4 receptor, which improves peripheral glucose utilization, is another possible anti-diabetic mechanism (Dugani et al., 2008). Fucoxanthin mediates insulin resistance by lowering the expression of adipokines, TNF-α, IL-6, and MCP-1 (Maeda et al., 2007; Maeda et al., 2008). Human insulin and biologically active insulin derived from hammerhead sharks and spotted dogfish are comparable and showed equivalent receptor binding capabilities (Anderson et al., 2002).

A range of bioactive substances such as dietary fibers, omega-3 fatty acids, pigments, sulfated polysaccharides, phlorotannins, polyphenols, and essential amino acids are found in brown algae, all of which pose strong anti-diabetic effects. PTP, α-glucosidase, and α-amylase are among the enzymes that are specifically inhibited by phenols, while GLUT-4 and AMPK signaling cascades are activated to enhance peripheral glucose absorption. Phlorotannin-rich extracts of seaweeds are a strong inhibitor of α-glucosidase and α-amylase (Lee et al., 2009; Lee and Jeon, 2013). Marine algal compounds control blood glucose levels by blocking enzymes that hydrolyze proteins and carbohydrates, enhancing insulin sensitivity, increasing glucose absorption, and averting problems associated with diabetes (Unnikrishnan and Jayasri, 2018).

Numerous aquatic creatures including bacteria, micro- and macroalgae, sea grasses, sponges, corals, sea anemones, fish, salmon skin, a shark fusion single-domain protein, and by-products from fish and shellfish have been investigated for their possible anti-diabetic properties. The anti-hyperglycemic and anti-diabetic characteristics of marine creatures have been studied using both *in vitro* and *in vivo* studies (Lauritano and Ianora, 2016; Rayapu et al., 2021). Out of 500 cyanobacteria from freshwater and marine environments, only 38 species showed putative α-glucosidase and α-amylase modulating activity (Cannell et al., 1987). Investigation of drug molecules that block β-glucosidase in bacteria is ongoing due to the enzyme function in the breakdown of polysaccharides and the digestion of glycoproteins and glycolipids, which make it a viable target for the treatment of diabetes and obesity. Many glucosidase inhibitors have been discovered from microbes connected to marine sponges (*Aka coralliphaga*) (Pandey et al., 2013). Actinomycete *Streptomyces* sp. produces bioactive pyrostatins A and B that inhibit and regulate the expression levels of N-acetyl-glycosaminidase. At 100 m ocean depth, another strain

of *Streptomyces corchorusii* subsp. *Rhodomarinus* isolated from Otsuchi Bay showed notable α-amylase inhibition (Imada, 2005).

Different marine fungi have also been reported for their anti-diabetic, anti-inflammatory, and anti-cancer effects (Debbab et al., 2010; Shams Ul Hassan et al., 2021). Aquastatin A showed a strong inhibitory impact on the PTP1B enzyme in a study on the culture broth of the marine fungus *Cosmospora* sp. SF-5060, which was isolated from intertidal silt at Gejae Island (Korea) (Debbab et al., 2010).

5 Interplay between marine natural products, redox modulation, and the Nrf2/HO-1 pathway in diabetes

Oxidative stress prevents Nrf2 from being ubiquitinated and degraded under basal levels, which phosphorylates and translocates it into the nucleus to attach to ARE at promoter regions of target genes (HO-1) for their transcriptional activation (Bryan et al., 2013; Dinkova-Kostova and Abramov, 2015). Upon its expression, HO-1 catabolizes heme into bilirubin, Fe^{2+}, and CO. Bilirubin exceptionally scavenges intracellular ROS burst to lower down oxidative stress (Aayadi et al., 2017). Various marine natural products provide protection by activating protein kinase B (PKB, Akt) and extracellular signal-regulated kinase (ERK). Under oxidative stress, ERK and the PKB/Akt pathway also facilitate Nrf2 nuclear translocation and hence improve the transcriptional control of the HO-1 gene to protect cells against oxidative damage (Kim and Jang, 2014; Han et al., 2017). Marine drug molecules also protect cells from ultraviolet B (UVB) and H_2O_2-induced oxidative damage, but they also raise the levels of HO-1 and Nrf2 by phosphorylation of ERK and activation of Akt. The prevention and treatment of oxidative damage and related disorders are involved with the proper modulation and activation of the Nrf2-Keap1 signaling pathway to mitigate the cell/tissue damage (Kang et al., 2004).

The natural pigment echinochrome A from sea urchins has therapeutic properties due to its capacity to efficiently scavenge water-soluble radical ions especially $O_2^{\bullet-}$. Echinochrome A exhibits exceptional ability to scavenge peroxy radicals and bind Fe^{2+} ions. Free radical chelating activity of hydroxyl groups on echinochrome A neutralize ROS in order to maintain cellular redox homeostasis (Lebedev et al., 2008; Popov and Krivoshapko, 2013). H_2O_2 is produced when this polyhydroxynaphthoquinone is exposed to ROS in the presence of Ca^{2+} ions. One hypothesis states that physiological H_2O_2 levels could function as a second messenger in intracellular and intercellular signal transduction. The optimum quantity of echinochrome A neutralized $O_2^{\bullet-}$ to less toxic H_2O_2, in order to control gene expression and production of stress- and antioxidant-related enzymes (Lebedev et al., 2005; Popov and Krivoshapko, 2013).

Marine substances are also known to impede the enzymes producing eicosanoids, which lowers the production of pro-inflammatory molecules such as prostaglandins and leukotrienes. These substances might prevent the activation of transcription factors controlling the expression of genes linked to inflammation and oxidation such as cyclooxygenase-2 (COX-2), inducible NO synthase, TNF-α, IL-1β, and IL-6 (Kim et al., 2004; Popov and Krivoshapko, 2013).

The redox regulation potential of marine natural compounds via the Nrf2/HO-1 cytoprotective pathways is highlighted by their anti-diabetic actions primarily due to their antioxidant potential to diminish oxidative damage to β cells. Through the specialized targeting of protective pathways and maintenance of cellular redox balance, these mechanisms highlight the therapeutic potential of compounds originating from marine environments in the treatment of diabetes (Dong et al., 2021).

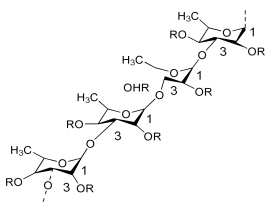
6 Preclinical and clinical studies

The anti-diabetic effects of the various compounds reported in preclinical and clinical studies have extensively been reviewed herein (Table 1).

7 Comparative analysis

Various differentiating factors exist between T1D and T2D. T1D, also known as insulin-dependent diabetes mellitus (IDDM), is characterized by insufficient pancreatic insulin production. In order

TABLE 1 Screening of bioactive chemicals in microorganisms and investigating their mechanism of action concerning their potential anti-diabetic effects.

Sr. no.	Species or source	Compounds	Structure of reported molecules	Mechanism of action	Reference
1.	Seaweeds (*Fucus vesiculosus*)	Fucoidans	 Fucoidans-I	↑α-Glucosidase inhibition ↑α-Amylase inhibition	(Shan et al., 2016)

(Continued)

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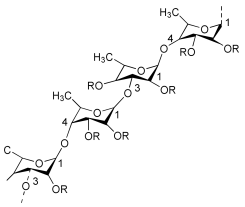
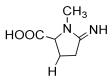
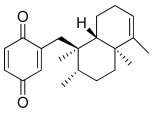
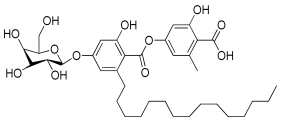
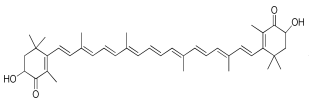
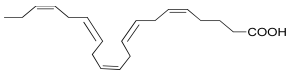
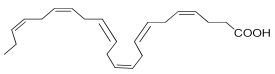
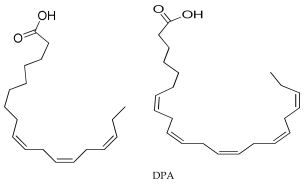
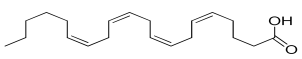
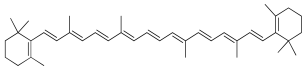
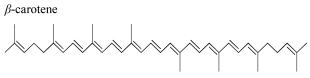
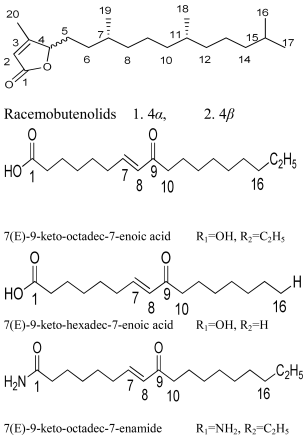
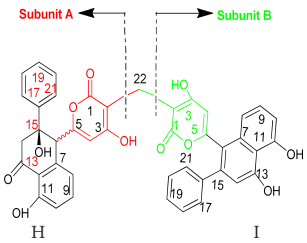
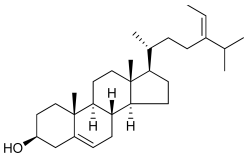
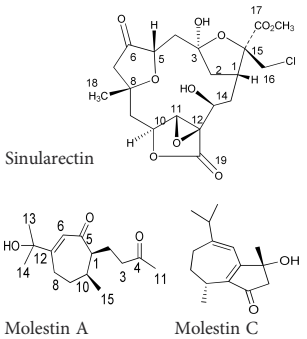
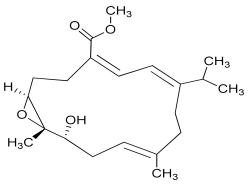
TABLE 1 Continued

Sr. no.	Species or source	Compounds	Structure of reported molecules	Mechanism of action	Reference
			 Fucoidans-II		
2.	*Streptomyces* sp. Actinomycetes	Pyrostatin A and B	 Pyrostatin A  Pyrostatin B	↓N-acetyl-glucosaminidase	(Aoyama et al., 1995)
3.	Sponge (*Dysidea avara*)	Sesquiterpene quinone (Avarone)	 Avarone	↑PTP1B ↓AR ↑Insulin sensitivity	(Casertano et al., 2023)
4.	Fungus (*Cosmospora* sp.)	Aquastatin A	 Aquastatin A	↑PTP1B inhibition	(Debbab et al., 2010)
5.	Microalgae (*Chlorella zofingiensis*)	Astaxanthin	 Astaxanthin	Prevents advanced glycation end-products (AGE) formation	(Sun Z. et al., 2011)
6.	Microalgae (*Isochrysis galbana*)	Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)	 EPA	Reduction in glucose, triacylglycerol and cholesterol level Weight loss	(Nuño et al., 2013)
7.	Fish species	Ω-3-Polyunsaturated fatty acids (PUFA)	 DHA	↓Inflammations ↓Triglycerides Human trials for T2D management ↑Insulin sensitivity ↓Insulin resistance	(Storlien et al., 1987; Itsiopoulos et al., 2018)
8.	Microalgae (*Chlorella vulgaris*, *C. pyrenoidosa*, *C. protothecoides*) Diatoms (*Nitzschia laevis*)	Arachidonic acid, α-linoleic acid (ALA), carotenoids, EPA (structure given above in no. 6), docosapentaenoic acid (DPA)	 DPA ALA  Arachidonic acid  β-carotene  Lycopene	↓AGEs formation ↓α-Amylase, α-glucosidase Possible antioxidant	(Sun et al., 2010; Sun and Chen, 2012)

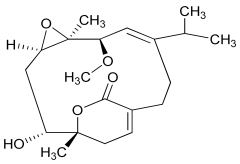
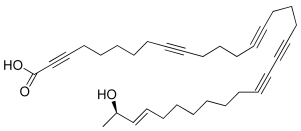
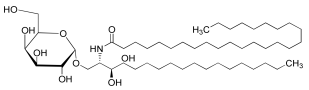
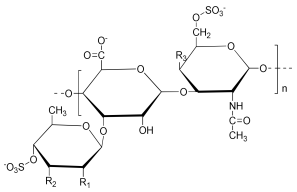
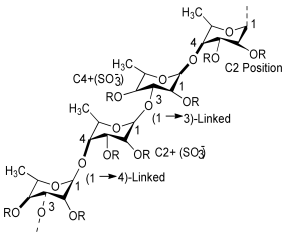
(Continued)

TABLE 1 Continued

Sr. no.	Species or source	Compounds	Structure of reported molecules	Mechanism of action	Reference
9.	Chlorophyceae (*Caulerpa racemosa*, *Ulva lectuca*)	Variable, racemobutenolids A and B, unique peptides, vitamins, pigments, carotenoids, EFAs, polyphenols		↓Human PTP1B ↑ARE pathway activator	(Wang et al., 2013; Yang et al., 2015; Shah et al., 2020)
10.	Multiple bacterial taxa (*Actinobacteria*, *proteobacteria*, *bacteroidetes*)	Multiple Wailupemycins H and I		↓α-Amylase, α,β-glucosidase	(Pandey et al., 2013; Chen et al., 2016; Hassan and Shaikh, 2017; Hassan et al., 2017)
11.	Pheophyceae (*Pelvetia siliquosa*)	Fucosterol	 Fucosterol	↑Insulin concentration ↓Serum glucose ↓Glycogen degradation	(Lee et al., 2004)
12	Soft coral (*Sinularia firma, S. erecta*) *S.* cf. *molesta*	Methanol extracts Sinularectin Molestin A Molestin C	 Sinularectin Molestin A Molestin C	↓Serum glucose ↑PTP1B inhibition	(Tamrakar et al., 2008; Chu et al., 2018)
13.	Chinese soft coral (*Sarcophyton trocheliophorum*)	Cembranoids	 Sarcophytonolide S	↑PTP1B inhibition	(Liang et al., 2018)

(Continued)

TABLE 1 Continued

Sr. no.	Species or source	Compounds	Structure of reported molecules	Mechanism of action	Reference
			 Sartrolide H		
14.	Fish and shellfish Waste (*Scyliorhinus canicula* heads) Shark (*Sphyrna lewini*)	Oils and wastes, shark liver fusion protein peptide and cholera toxin B subunit (CTB-APSL)	Multiple short bioactive peptides with anti-diabetic properties	↓Triacylglycerol ↓Blood pressure reduction ↓GHb, FBG ↑Insulin release ↓Insulin resistance ↑Pancreatic tissue injury recovery ↑Lipid metabolism regulation	(Anderson et al., 2002; Harnedy and FitzGerald, 2012; Liu et al., 2014)
15.	*Callyspongia truncate* sponge	Callyspongynic acid	 Callyspongynic acid	↓α-Glucosidase inhibition	(Nakao et al., 2002)
16.	Sponge (*Agelas mauritianus*)	α-Galactosylceramide (α-GalCer)	 α-GalCer	↑NKT cell activation	(Van Kaer, 2001)
17.	Sea cucumber (*Cucumaria frondosa*)	Fucosylated chondroitin sulfate	 Fucosylated chondroitin sulfate R1, R3=H or SO_3- R2=H, SO_3-, or Fuc	↑Metabolic enzymes ↑PKB/PI3K/GSK-3β signaling cascade	(Hu S-W. et al., 2014)
18.	Sea cucumber (*Acaudina molpadioides*)	Fucoidan		↓Blood glucose ↓Insulin resistance ↑Regulation of glucose metabolism-linked enzymes ↑PKB/GLUT4 pathway	(Hu S. et al., 2014)
19.	*Bunodosoma ranulifera*	Multiple small peptides	No particular compound reported yet	↓Dipeptidyl peptidase IV (DPPIV)	(Pascual et al., 2007)
20.	*Musculus senhousei*	Multiple small peptides	No particular compound reported yet	↓DPPIV inhibition	(Zhou et al., 2024)

to cure T1D, insulin must be imported and administered intravenously to those with T1D in order to control blood sugar levels (Forouhi and Wareham, 2019). On the other hand, high blood glucose levels are a hallmark of T2D, commonly referred to as non-insulin-dependent diabetes mellitus (NIDDM), with insufficient insulin secretion. Oral anti-diabetic drugs that lower blood glucose levels such as biguanides and sulfonylureas are treatment options for T2D. Chemical medications that work by blocking digestive enzymes and are available to treat T2D include acarbose, pioglitazone, and miglitol. Diabetes is a major public health concern that can lead to retinopathy, nephropathy, and neuropathy (Jain and Saraf, 2010). Furthermore, most of the synthetic or modified drugs might have negative side effects that get worse if a patient used them for a long time (Groop and Pociot, 2014).

Diabetes treatments are costly, and scientists continue to look for better, less expensive alternatives with no side effects.

Alternative natural medicines are being considered by the majority of people in developing nations (Hassan et al., 2010). Natural resources provide the basis of many clinical treatments; furthermore, the majority of contemporary pharmaceutics are produced from compounds derived from marine natural resources (Mayer et al., 2010). These marine natural resources have yielded a wide variety of potent drug molecules, several of which are in clinical trials. Recently, certain novel biologically active molecules have been isolated for pharmaceuticals and nutritional supplements (Mayer et al., 2010; Sun H-H. et al., 2011; Beygmoradi and Homaei, 2017).

Diabetes has a complex array of symptoms that make management and treatment more difficult (Borse et al., 2021). The abundance of bioactive molecules from marine resources offers a viable way to tackle this complexity (Lauritano and Ianora, 2016; Cotas et al., 2024). Fish, invertebrates, marine grasses, algae, sponges, mushrooms, bacteria, and microalgae can be further explored as novel diabetic medicines (Anjum et al., 2016). Dietary fiber and complex polysaccharides in seaweed help lower blood sugar and enhance insulin sensitivity (Cotas et al., 2024). The high fatty acid content in seaweeds minimizes inflammation linked to obesity and high blood sugar (Popov and Krivoshapko, 2013). In order to treat hyperglycemia and hyperlipidemia, seaweed-derived phenolic compounds have the capacity to inhibit PPD-4 and subsequently suppress α-glucosidase and α-amylase activity, initiate signaling via AMPK and Akt, stop AGE production, and improve insulin sensitivity (Unnikrishnan and Jayasri, 2018). Moreover, marine bioactive chemicals can also manage obesity; protect pancreatic β cells; inhibit AR, PTP1B, and PPD-4; and enhance glucose uptake. There is encouraging prospect for the management of diabetes and its aftereffects through the oral and pharmaceutical supplementation of biological components derived from marine resources (Cotas et al., 2024).

8 Conclusion

A unique strategy for the treatment of diabetes has been revealed by the investigation of the anti-diabetic effects of marine natural products. Aquatic species that have been studied for their possible anti-diabetic properties include bacteria, microalgae, macroalgae, seagrass, sponges, corals, sea anemones, fish, salmon skin, a shark fusion protein, shellfish, and fish wastes. The study focused on the redox regulation potential of marine natural products via the Nrf2/HO-1 cytoprotective pathways. The relationship between oxidative stress, inflammation, and cellular damage in diabetes emphasized focusing on the Nrf2/HO-1 pathway as a novel methodology by these marine bioactives. Marine bioactive compounds have significant antioxidant, anti-inflammatory, and cytoprotective capabilities due to their complex physical structures and functional groups. This review demonstrated that micro- and macroorganisms found in the ocean contain biologically active drug molecules as potential anti-diabetic agents.

Author contributions

MN: Conceptualization, Writing – original draft, Writing – review & editing. ML: Visualization, Writing – review & editing. JX: Writing – original draft, Writing – review & editing. CW: Conceptualization, Visualization, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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