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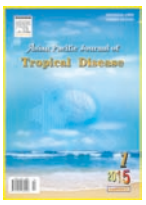

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Marine bioactive agents: a short review on new marine antidiabetic compounds

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ABSTRACT

From medicinal point of view, marine environment is a diversified source of several biologically active compounds that are relatively untapped. Exploitation of marine resources may provide valuable leads which carry economic and scientific potential. Diabetes is a metabolic disorder and a major cause of mortality and morbidity in both developed and developing countries. Several antidiabetics are available but the major limitations of these synthetic drugs are cost, effectiveness and adverse effects. The relative safety of drugs from natural source is the main reason behind exploring marine resources as a source of therapeutic, food and nutritional compounds. Marine resources provide many compounds including polyphenols, peptides, pigments, phlorotannins and sterols that could be used for the treatment of diabetes and associated complications. The present review focuses on potential marine resources that provide bioactive agents for diabetes treatment.

1. Introduction

Diabetes mellitus, a chronic metabolic disorder of abnormal sugar metabolism characterized by elevated blood sugar level is a major contributor to morbidity and mortality in many developed and developing countries, including United States and India. The defected insulin functions including defect in secretion, site of action and action are the principle factors responsible for diabetes. The severity of diabetes is connected with the consecutive destruction of microstructures mainly retina, nephron, and neuron affecting eyes, kidneys and nerves. The disease is also associated with several cardiovascular diseases and related conditions[1,2]. It is believed that oxidative stress plays a crucial role in the development of diabetes and its complications[3].

The body is made up of millions of cells that need energy to maintain physiological functioning and the energy is obtained from food in the form of sugar. The movement of sugar through a cell membrane is regulated by two mechanisms, receptor which acts as a door and insulin that unlocks the receptors. Hyperglycemia associated with defected insulin is type 1 diabetes while type 2 diabetes is characterized with increasing sugar level related to defected receptors. The occurrence of type 2 diabetes is more common than type 1 diabetes[4,5]. More than 20 million population worldwide suffers from type 1 diabetes with 2 to 5 percent rise per year in many countries[2]. Type 2 diabetes is the most common type of diabetes covering 90%-95% of all diabetes cases[6]. Worldwide prevalence of diabetes was 280 million during 2011 and it is supposed to be 500 million up to 2030[2].

The selection of proper preventive measures is necessary to reduce disease burden on health and economy. Although several synthetic drugs are available for the treatment of diabetes mellitus, none of these medications are cheap or completely effective. Furthermore, prolonged use of these drugs may produce undesirable side effects[3]. Patients with type 1 diabetes completely depend on external insulin injection for survival

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and maintaining a normal life, and a daily insulin injection is not comfortable. Type 2 diabetes can be managed by modifying lifestyle, administering oral antidiabetic drugs, and in very less cases requiring insulin[7]. Several therapies are available for type 2 diabetes that mainly include antioxidant and immune therapy, α-glucosidase inhibitors, islet therapy, and different oral antidiabetic drugs[8-10]. These antidiabetic therapies produce burden on public health and economy of the country due to its limited efficacy and wide-range side effects. To avoid such losses, a novel preventive and regenerative therapy is needed to protect beta-cell mass and prolong the diabetes onset[6].

In search of a novel source, marine source is an unexplored one with potential therapeutic agents and functional ingredients that can be used for the treatment of various disease conditions or may be employed as adjuvent therapy. A lot of marine agents have been already identified for therir biological activities including disease curing potential. The various peptides isolated from fish and algae have been found to possess several biological activities like anticancer action, lipid lowering action, and anticoagulant. Marine bacteria and fish oil are the richest source of omega-3 fatty acids whereas antioxidants such as carotenoids and phenolics are extensively distributed in crustaceans and seaweeds[11]. The present review briefly focuses on the potential uses of marine-derived compounds as a therapeutic approach to drug treatment of diabetes and associated complications.

2. Marine pharmacology

The base of the most disease therapies is natural products, and majority of components including drugs of modern pharmaceuticals also depend on these natural resources[12]. Since the last few years, marine source has provided many biologically active structures such as phycocolloids, pigments, phlorotannins and fucoidans[13] which are successfully employed for the development of industries as nutritional supplements, therapeutic agents, fine chemicals, and cosmetics. Wide range of therapeutically active agents including anticancer agents and antiviral has been successfully isolated from these natural sources and now are in clinical use[14]. Nowadays, researchers focus on marine source as a potential source for bioactive compounds to obtain new alternative therapies and hypoglycemic agents for diabetes[13].

The marine source mainly includes fishes, algae, salts and microorganism[13]. The secondary metabolites obtained from marine organisms might be a potential source of bioactive compounds and offer different leads for the development of novel pharmaceutical agents[15]. Nutritional bioactives such as receptors, transcription factors and enzymes obtained from marine source are almost the same as those needed for pharmaceutical industries. These compounds also help to maintain homeostasis of cells that principally affects during the progress of disease thereby producing health promoting effect[11,16]. Mostly these bioactive agents are used as nutritional food. Some of marine bioactive agents are found to be effective against tuberculosis and herpes simplex virus infection[17,18]. Methanolic extracts of seaweeds from the west coast of India show antiplasmodial activity. Several marine bioactive agents have antitumor potential[19-21]. *Ascophyllum nodosum*, the brown seaweed from northeast coastal region of United States contains phenolic compounds that possess antioxidant activity and inhibitory effect on α-glucosidase and α-amylase[22]. Some of the reported activities of marine sources are listed in Table 1.

Table 1
Reported activities of different marine sources.

Activity	Marine sources	References
Antiviral	Bacteria	14
	Algae	14, 15
	Sponge	14
	Fungi	14
Cancer	Cytarabine, Ara-C	12
Antiviral	Vidarabine, Ara-A	12
Pain	Ziconotide, ω-conotoxin	12
Cancer	Trabectidine, ET-743	12
Cancer	Indole alkaloid	20
Breast tumor suppressor	Polyphenol rich seaweed (*Eucheuma cottonii*)	19
Antioxidant, Enzyme inhibitor	*Streptomyces* sp. VITMSS05 strain	33
Antibacterial, Cytotoxicity, Haemolytics	Sea grasses	34
Antibiotic, Immune suppressor, Anticancer	Marine cyanobacterial secondary metabolites	35

The phenomenal biodiversity of marine world is responsible for wide distribution of many bioactive compounds such as sterols, antioxidants, pigments, polyunsaturated fatty acids, and polysaccharides. Organisms of marine source reside in complex habitats and expose to extreme conditions that bolth lead to the production of diverse biologically active secondary metabolites which are not found in other organisms. Many bioactive agents are used in the treatment of cardiovascular complications, mainly including polypeptides, astaxanthines, algal-polysaccharides, n-3PUFAs from fish oil and soluble fibers. Polypeptides help to maintain blood pressure whereas astaxanthines have the ability to reduce inflammation and thereby produce protective action against hypertension and atherosclerosis. The antihypertensive activity of algal-polysaccharides can help reduce cholesterol. The compound n-3PUFAs from fish oil has the lipid lowering activity to reduce atherosclerosis and hypertensive[11]. Figure 1 focuses on some of potential marine sources showing beneficial effects on human cardiovascular system.

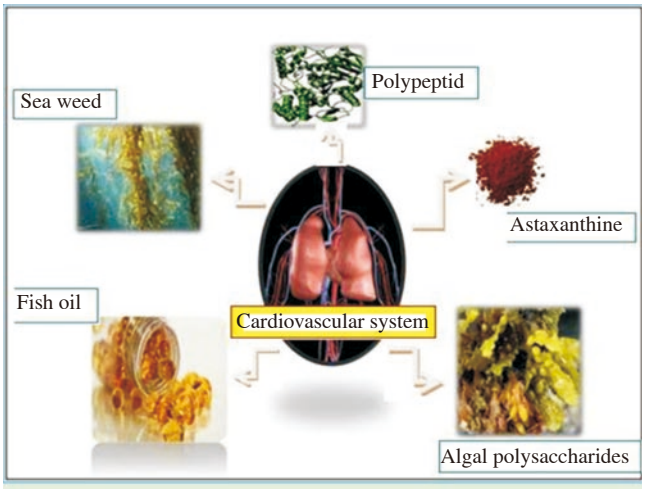

Figure 1. Examples of marine sources showing beneficial effects on the human cardiovascular system.

3. Antidiabetics of marine sources

3.1. Palinurin

Several bioactive compounds obtained from marine source have been revealed as antidiabetic agent. Some of marine bioactive antidiabetic agents, their sources and key mechanisms of action is mentioned in Table 2. Glycogen synthase kinase 3β (GSK-3β) enzyme is a crucial player in several disorders such as cancer, Alzheimer's disease, diabetes and mood disorders. Therefore, it is recognised as a possible therapeutic target for the management of these diseases. The study performed by Bidon-Chanal *et al.* (2013) revealed that isopropanolic extracts of *Ircinia dendroides* have the significant human recombinant GSK-3β inhibitory effect when performed *in vitro*. This inhibitory effect is the result of sesquiterpene, a palinurin. It is suggested that the inhibition of GSK-3β could be due to non-ATP/substrate competitive mechanism. The binding of palinurin to allosteric site at N-terminal lobe of enzyme is a mechanism by which it exhibits the inhibitory effect. This binding further alters the accessibility of the ATP γ-phosphate by constraining the conformation of the glycine-rich loop which indicates selectivity of palinurin towards GSK-3β. The selective binding mechanism of palinurin to GSK-3β might be used for the treatment of GSK-3b-mediated diseases[23].

3.2. 3,4-Dibromo-5-(2-bromo-3,4-dihydroxy-6-(ethoxymethyl)benzyl) benzene-1,2-diol analogues

3,4-Dibromo-5-(2-bromo-3,4-dihydroxy-6- (isopropoxymethyl) benzyl)benzene-1,2-diol (HPN), a synthetic analogue of bromophenol from marine red alga has been revealed as a potential and novel compound for the management of diabetes. A bromophenol, 3,4-dibromo-5-(2-bromo-3,4-dihydroxy-6-(ethoxymethyl)benzyl)benzene-1,2-diol (BPN) is richly distributed in red agae, *Rhodomela confervoides*, which has potent protein tyrosine phosphatase 1B (PTP1B) inhibitory action. The study performed on HPN showed PTP1B inhibitiory effect as that of BPN. HPN exhibited better inhibitory activity against PTP1B than BPN. It showed high selectivity against protein tyrosine phosphatase, mainly T-cell protein tyrosine phosphatase, leucocyte antigen-related tyrosine phosphatase and Src homology 2-containing protein tyrosine phosphatase-1. The HPN treatment showed significant dose-dependent reduction in glucose level and serum lipid, especially triglycerides and total cholesterol. At high and medium doses, HPN remarkably decreased HbA1c levels whereas reduction in insulin level was observed at high doses. The antihyperglycemic effects produced by HPN were the same as those of rosiglitazone, an antidiabetic drug. Therefore, HPN could be a novel drug for the treatment of type 2 diabetes[24,25].

3.3. Euryspongins A-C

Hiroyuki *et al.* (2013) believed that three new unique sesquiterpenes, euryspongins A–C, isolated from a marine sponge *Euryspongia* sp. which was collected at Iriomote Island, Okinawa, Japan, possess antidiabetic potential. Euryspongins A contains a bicyclic furano-sesquiterpene structure with six and eight-membered rings, whereas Euryspongins B and C has α, β-unsaturated-γ-lactone ring instead of the furan ring in A. These compounds produce inhibitory effect on protein tyrosine phosphatase 1B (PTP1B), an important target enzyme for the treatment of diabetes[26].

3.4. Ecklonia cava

The antidiabetic potential of a brown alga, *Ecklonia cava* was studied by Kang *et al.* (2010) using streptozotocin-induced type 1 diabetes mellitus rats and C2C12 myoblasts. Methanolic extracts of *Ecklonia cava* significantly reduced plasma glucose level and increased insulin concentration in type 1 diabetes mellitus rats. *Ecklonia cava* contains a large number of polyphenolic compounds that might be responsible for antidiabetic effects. This effect of polyphenols is due to insulin-like actions through several mechanisms such as AMPK (AMP-activated protein kinase). In most of the cells, AMPK has regulatory action on intracellular fatty acid oxidation and lipid synthesis. The methanolic extract of *Ecklonia cava* increased phosphorylation of AMPK in C2C12 cells in dose-dependent manner. The extract also showed a potent radical scavenging activity which might be responsible for the improvement of diabetic complications[27].

Table 2
Examples of marine bioactive antidiabetic agents, their sources, and mechanism of action.

Bioactive agents	Marine sources	Mode of action	References
Sesquiterpene Palinurin (Axel 2013)	Sponge *Ircinia dendroides*	Inhibition of glycogen synthase kinase 3β (GSK-3β)	23
HPN analogues	Red agae *Rhodomela confervoides*	Inhibition of protein tyrosine phosphatase 1B (PTP1B)	24,25
Euryspongins A-C	Marine sponge *Euryspongia* sp.	Inhibition of protein tyrosine phosphatase 1B (PTP1B)	26
Methanolic extract	Brown alga *Ecklonia cava*	Increases phosphorylation AMP-activated protein kinase, Radical scavenging property	26
α-galactosylceramide (α-GalCer)	Marine sponge *Agelas mauritianus*	Activation of natural killer cells (NKT)	27
Docosahexaenoic acid (DHA), Eicosapentaenoic acid (EPA)	Microalgae *Isochrysis galbana*, *Nannochloropsis oculata*	Regulates glucose and lipid metabolism	29
Phenol rich extract	Macroalgae *Palmaria, Ascophyllum, Alaria*	Inhibitory of α-amylase and α-glucosidase	30
Oligopeptides	Salmon skin Chum Salmon (*Oncorhynchus kern*)	Reduction in oxidative stress	31
Bacteria	Marine sponge *Aka coralliphaga*	Inhibition of β-glucosidase	32
Polyphenols/Phlorotannins	Brown algae	Inhibition of α-glucosidase and α-amylase, Increases skeletal muscle glucose uptake, Inhibition of protein tyrosine phosphatase 1B (PTP 1B) enzyme, Increases insulin sensitivity.	13

3.5. α-galactosylceramide (α-GalCer)

A glycolipid, α-GalCer, was found to be effective in the treatment of type 1 diabetes. When studied in nude mice, it produced dose-dependent antidiabetic activity. The marine sponge *Agelas mauritianus* produces this glycoprotein which was initially studied for antimetastatic activities. The mechanism responsible for antidiabetic activity of α-GalCer is mediated through immune system. α-GalCer stimulates natural killer cells, a group of immune cells that cause selective supression of pathogenic T cells which are responsible for the destruction of pancreatic β cells, an insulin producing cells. Also α-GalCer has the ability to modulate immune response by promoting cell responses which are predominently involved in the supression of autoimmune responces. No any adverse effects had been observed in clinical trials of α-GalCer, suggesting as a promising choice for prevention of diabetes[28].

3.6. Docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA)

The marine microalgae *Isochrysis galbana* and *Nannochloropsis oculata* are rich in soluble and insoluble polysaccharide, protein and polyunsaturated fatty acids. *Isochrysis galbana* has high percentage of DHA whereas *Nannochloropsis oculata* contains a large amount of EPA. The study by Nuno *et al.* (2013) showed that in diabetic rats, these compounds regulated glucose and lipid metabolism, produced beneficial effects on intestinal mucosa and epithelium, and regulated lipoproteins and nitrogen compounds. The biological active compounds in microalgae have potential applications in functional foods and nutraceuticals. The *Isochrysis galbana* treatment reduces blood glucose, triacylglycerol and cholesterol level, and also affects lactic acid bacteria counts. The effect on lipid metabolism is dominant as both microalgae causes increase in low-density lipoproteins and reduction in high-density lipoproteins in both healthy and diabetic rats[29].

3.7. Phenolic contents of Palmaria, Ascophyllum and Alaria

Phenolic extract from marine macroalgae commonly found in UK were tested by Nwosu *et al.* (2011) for its antidiabetic potential. The phenolic extracts of *Palmaria*, *Alaria* and *Ascophyllum* exhibited inhibitory effect on α-amylase activity. The extract of *Ascophyllum* also showed inhibitory effect on α-glucosidase. Both the enzymes have regulatory role in starch digestion and blood glucose regulation[30].

3.8. Salmon skin oligopeptides

Researcher Zhu *et al.* (2010) has studied the antidiabetic effect of oligopeptides obtained from salmon skin. Oligopeptides of wild Chum Salmon (*Oncorhynchus kern*) skin from East China Sea were tested for antidiabetic potential on rats. The diabetic rats treated with oligopeptides showed decreased level of fasting glucose level and pancreatic apoptosis of islet cells. The reduction in the level of serum tumor necrosis factor-α, interferon-gamma and malondialdehyde was also observed. The level of serum superoxide dismutase and glutathione significantly increased in diabetic rats treated with oligopeptides. This indicated reversal of streptozotocin-induced reactive oxidative stress and oxidative reactions such as lipid peroxidation. This downregulation of diabetes-induced oxidative stress might be responsible for protection of pancreatic β-cells from apoptosis[31].

3.9. Marine bacteria

The enzyme glucosidase produces catalytic action on glycosidic bonds in sugars. Particularly, β-glucosidase plays a key role in degradation of polysaccharides and polysaccharides, and processing of glycoprotein and glycolipid. Thereby, β-glucosidases plays a crucial physiological role in several conditions such as diabetes, obesity and cancer. Many marine bacteria produce compounds which have the β-glucosidase inhibitor potential according to the study by Pandey *et al* (2013). The bacteria associated with marine sponge, *Aka coralliphaga,* produces a large number of glucosidase inhibitors. It exhibits significant inhibitory activity when tested with β-glucosidase inhibition assay. The phylogenetical analysis of these bacteria showed that the bacteria belonging to phylum Firmicutes, Actinobacteria, Proteobacteria and Bacteroidetes produce glucosidase inhibitors. The β-glucosidase inhibition obtained from marine sources might be useful for the management of diabetes and associated complications[32].

3.10. Polyphenols/phlorotannins from brown algae

Brown algae largely produce polyphenols which are formed by polymerization of phloroglucinol units. These marine polyphenols are formed by polyketide pathway and are called as phlorotannins. Polyphloroglucinols exhibit a broad range of activities such as antioxidant, anticancer and anti-inflammatory. The phlorotannins produce antidiabetic effect by several mechanisms such as inhibition of α-glucosidase and α-amylase, increasing skeletal muscle glucose uptake, inhibiting protein tyrosine phosphatase 1B (PTP 1B) enzyme, and increasing sensitivity of insulin[13].

4. Conclusion

Although various strategies based on plants and synthetic source have been successfully implemented for the treatment of diabetes, still it lacks an ideal drug choice to combact diabetes and associated complications. The main challenge associated with diabetes treatment is its diverse nature. Marine envirnoment is the best option to overcome these challenges as it is a unutilized source which is richly supplied with potential alternative bioactive compounds. The present study is an attempt to highlight these different marine bioactive antidiabetic compounds and their sources. Thus, the bioactive agents obtained from marine sources such as fish, algae, sponge, fungi, bacteria and sea grasses, might be an alternative source to develop novel drugs against diabetes.

Conflict of interest statement

We declare that we have no conflict of interest.

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