**Exploration of Anti-diabetic Potentials Amongst Marine Species- A Mini Review**

Rupam Bhattacharjee ¹, Analava Mitra ², Baishakhi Dey ², Abhisek Pal ¹*

¹ School of Pharmaceutical Sciences, SOA University, Bhubaneshwar, Orissa, India  
² School of Medical Science & Technology, IIT Kharagpur, 721302, India

Address for Correspondence: Abhisek Pal, abhisekpal@soauniversity.ac.in

**ABSTRACT:** Though the marine world has attracted the attention of the research community for years together, yet the therapeutic potentiality of marine phyto-planktons is largely unexplored. Enzymes play a pathogenic role and are the underlying cause of several diseases like diabetes, Alzheimer, Parkinson etc. Inhibition of such enzymes can serve as a therapeutic strategy against the diseases. Enzymes like α-glucosidase, protein tyrosine phosphatase and aldose reductase have been found to cause pathogenicity in Type 2 diabetes and its associated complications thereof. Exploration of therapeutically active agents like bromophenols, 2-piperidione, benzeneacetamide, n-hexadecanoic acid, fucoxanthin, dysidine, biologically active insulin, methyl-ethyl ketone derivatives etc from marine species like red algae, brown algae, marine fungus, seaweeds and diatoms, marine ascidians, sea corals with significant inhibitory potentials against enzymes either pathogenic to diabetes or adding to associated diabetic complications coupled with antioxidant activities adding a new dimension in anti-diabetic research. Other suggestive mechanisms include enhanced peripheral glucose utilization by activating GLUT-4 receptor. Fucoxanthin controls insulin resistance, inhibites adipokines, tumor necrosis factor-α (TNF-α), monocyte chemoattractant protein-1(MCP-1), interleukin-6 (IL-6). Some of the active constituents were found to be effective diabeticity. Biologically active insulin isolated from spotted dogfish (*Scyliorhinus canicula*) and hammerhead shark (*Sphyrna lewini*) were almost same with human insulin with near to equivalent receptor binding capacity. Thus it provides an alternative source of bio-insulin in the marine world. The mini-review attempts to compile different anti-diabetic bio-active components from marine sources together with their mechanistic role. © 2014 iGlobal Research and Publishing Foundation. All rights reserved.

**KEYWORDS:** Marine Phyto-Planktons; Enzymes; Bromophenol; Marine Ascidians; Biologically Active Insulin.

**INTRODUCTION**

Diabetes is really a devastating epidemic of the 21st century and is becoming the third killer of the health of mankind after cancer, cerebrovascular and cardiovascular diseases. Not only it takes a heavy toll of lives around the world but imposes a serious financial burden on the sufferers and their family members. Despite insulin therapy and the availability of different synthetic analogues, the world diabetic population is expected to show a steady growth of 366 million by 2030. The side effects associated with currently available treatment options on long term basis is really an alarming concern[1-8]. Diabetes Mellitus (DM) is a
metabolic disorder characterized by chronic hyperglycemia with disturbance of carbohydrate, protein or fat metabolism resulting from defects in insulin secretion, insulin action or both (WHO, 1999). DM and the major complications associated with it like retinopathy leading to blindness, diabetic foot ulcers necessitating limb amputations, neuropathy, nephropathy leading to end stage renal disease (ESRD). There are two main types of DM, Type 1 or insulin dependent diabetes mellitus (IDDM) and Type 2 or non-insulin dependent diabetes mellitus (NIDDM) both having contrasting clinical and pathophysiologic features (Table 1). A diagrammatic representation of the multi-factorial aetiopathogenesis of Type 2 DM is presented in Fig.1. However type 2 diabetes is found to be more prevalent which occurs mostly due to combination of insulin resistance and inadequate compensatory insulin secretory response[3-5,6].

Pathophysiologically, Type 2 DM doesn’t involve autoimmune destruction of pancreatic β-cells unlike Type 1 DM, rather in Type 2 diabetics there are multiple disturbances in glucose homeostasis including impaired insulin secretion; peripheral insulin resistance mostly in muscles, liver and adipocytes; abnormalities in liver glucose uptake. The pancreas of Type 2 diabetics produces insulin, yet insulin resistance prevents its proper use at the cellular level. Glucose cannot enter target cells and accumulates in the bloodstream, resulting in hyperglycemia. The high blood glucose levels often stimulate an increase in insulin production by the pancreas; thus, type 2 diabetic individuals often have excessive insulin production or hyperinsulinemia. Insulin is a potent anti-lipolytic hormone and restrains the release of free fatty acid (FFA) from the adipocyte by inhibiting the enzyme hormone sensitive lipase[6-12]. The fat cells of Type 2 diabetics are markedly resistant to the inhibitory effect of insulin on lipolysis and despite 2-4 fold increments in plasma insulin levels; the rate of lipolysis in post absorptive phase is still high. The availability of exogenous insulin to inhibit the elevated basal rate of lipolysis and to reduce the plasma FFA concentration is also markedly impaired. The pathogenicity is shown to be further aggravated by the circulating triglycerides which have been shown to impair insulin action in both liver and muscle. The glucose transport mechanism is severely impaired in the adipocytes and muscles of Type 2 diabetics. Glucose transporter subtype 4 (GLUT4), mRNA and protein content are markedly reduced and the ability of insulin to elicit a normal translocation response and to activate the GLUT4 transporter after insertion into the cell membrane is decreased[10,11,13,14].

Although several synthetic hypoglycemics are developed but the safe and effective treatment paradigm is yet to be developed.

One important therapeutic intervention to treat diabetes is to reduce post-prandial (PP) hyperglycemia by inhibiting the actions of carbohydrate hydrolyzing enzymes like α-amylase and α-glucosidase. Enzymes such as DPP4 (dipeptidyl peptidase 4), Aldose reductase (AR), ACE (Angiotensin Converting Enzyme), PPAR (peroxisome proliferator activated receptor) γ also play significant role in diabetes[12-14]. Aldose reductase (AR), a member of the aldo-keto-reductases of the super family, is the first and rate limiting enzyme in the polyol pathway and reduces glucose to sorbitol, utilizing NADPH as a cofactor. Sorbitol is then metabolized to fructose by sorbitol dehydrogenase. In DM, due to increased availability of glucose in insulin in-sensitive tissues such as lens, nerves, retina there is increased formation of sorbitol through the polyol pathway. Intracellular accumulation of sorbitol is implicated in chronic complications of diabetes like cataract, retinopathy and neuropathy. AR-inhibitors prevent the conversion of glucose to sorbitol and are capable to control diabetic complications[12-14]. Again increase in the level of reactive oxygen species (ROS) is another pathogenic factor in Type 2 diabetes.

Table 1: Clinical and pathophysiologic features of Type 1 and Type 2 diabetes

<table>
<thead>
<tr>
<th>Features</th>
<th>Type 1 DM</th>
<th>Type 2 DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset</td>
<td>Early, below 35 yrs</td>
<td>Late, after 40-45 yrs</td>
</tr>
<tr>
<td>Type of onset</td>
<td>Abrupt &amp; severe</td>
<td>Gradual &amp; insidion</td>
</tr>
<tr>
<td>Frequency of occurrence</td>
<td>10-20%</td>
<td>80-90%</td>
</tr>
<tr>
<td>Body weight</td>
<td>normal</td>
<td>Obese/non-obese</td>
</tr>
<tr>
<td>Pathogenesis</td>
<td>Autoimmune destruction of β-cells</td>
<td>Insulin resistance, impaired insulin secretion</td>
</tr>
<tr>
<td>Family history</td>
<td>Less than 20%</td>
<td>About 60%</td>
</tr>
<tr>
<td>Genetic locus</td>
<td>unknown</td>
<td>Chromosome 6</td>
</tr>
<tr>
<td>Condition of Islet cells</td>
<td>Insulitis, β-cell destruction</td>
<td>No insulitis, later fibrosis of islets</td>
</tr>
<tr>
<td>Blood insulin level</td>
<td>Decreased insulin</td>
<td>Normal or increased insulin</td>
</tr>
<tr>
<td>Clinical management</td>
<td>Insulin and diet</td>
<td>Insulin, oral drugs, diet, exercise</td>
</tr>
</tbody>
</table>
Attenuation in ROS level may be due to increased production or diminished depletion by enzymic catalase (CAT), glutathione peroxidase (GSH-Px), and superoxide dismutase (SOD) antioxidants. Glucagon like peptide -1(GLP-1) is a remarkable anti-diabetic gut hormone due to its combinatorial actions of stimulating insulin secretion, increasing beta cell mass, inhibiting glucagon secretion, reducing the rate of gastric emptying and inducing satiety. GLP-1 is rapidly deactivated by DPP4 and animal studies have shown that inhibition of DPP4 is shown to improve glucose tolerance and increase insulin secretion.

Apart from conventional therapy with the aid of synthetic hypoglycemics, great resurgence in phytotherapeutics, proper implementations of lifestyle interventions; the current mini-review focuses its attention on the mechanistic insight of anti-diabetic potentials of marine species.

Anti-diabetic potentials of marine species
Anti-diabetic potentials of marine species are truly an interesting new dimension in this review. Remarkable resources of marine bio-actives are from species like sponges (31%), red algae (4%), brown algae (5%), green algae (1%), microorganisms (15%), coral (24%), ascidians (6%), molluska (6%), others (8%). Many marine red and green algae are found to be potential inhibitors of α-glucosidase, aldose reductase (AR) and Protein Tyrosine Phosphatase (PTP). Bromophenols found in some red algae like Rhodomela confervoides, Symphyocladia latiuscula, Polysiphonia urceolata shows significant hypoglycemic potentials by inhibiting PTP, α-glucosidase, and AR apart from its antioxidant activity[14-30].

Mechanistic role of bromophenols of red algae as hypoglycemics
PTP acts as an inhibitor for insulin as well as leptin signaling by binding with dephosphorylate activated insulin and leptin receptor respectively in the two pathways. Literature surveys have shown that bromophenols are derived from Rhodomela confervoides, a red algae, collected from the coastal region from China. Structural details of these four bromophenol derivatives (a) 2, 2′, 3, 3′-tetrabromo-4, 4′, 5, 5′-tetra-hydroxydiphenyl methane, (b) 3-bromo-4,5-bis(2,3-dibromo-4,5-dihydroxybenzyl) pyrocatechol, (c) bis(2,3-dibromo-4,5-dihydroxybenzyl) ether and (d) 2,2′,3-tribromo-3′,4,4′,5-tetrahydroxy-6′-ethoxy-methyl diphenylmethane are provided in (Fig. 2). The ethanol extract of Rhodomela confervoides in streptozotocin induced male wistar rats showed significant anti-hyperglycemic effect; the IC₅₀ values of these four derivatives were found to be 2.4, 1.7, 1.5, 0.84 µmol/L respectively, substantiating their hypoglycemic potentiality[15,16].

α- glucosidase is a carbohydrate hydrolyzing enzyme that increases the post prandial blood glucose level. Agents inhibiting α-glucosidase are effective therapeutic agents for diabetes. bis (2,3,6-tribromo-4,5-dihydroxybenzyl) ether is the good inhibitor of α-glucosidase. AR which increases sorbitol concentration in insulin insensitive tissues like retina, eye lens etc leading to diabetic complications like retinopathy, cataract are also inhibited by the bromophenols. Bromophenols obtained from red algae Symphyocladia latiuscula are also potent AR inhibitors with remarkable antioxidative potentials. Bromophenols obtained from Polysiphonia urceolata another marine red algae also shows significant anti-oxidant activities.

Different marine cyanobacteria were also found to exhibit anti-diabetic potentials. Research reviews have shown that 80% ethanol extract of marine cyanobacteria viz. Chroococcus minor, Synechocystis pevalakii, phormidium corium, Spirulina platensis, Oscillatoria chalybea, Spirulina labrynthiformis were investigated for hypoglycemic effects in alloxan induced diabetic
rats. Amongst them anti-diabetic effects of *Spirulina platensis* were found to be maximum. Spirulina is highly water soluble and lowers fasting blood-sugar level. Double blind cross over studies have shown that intake of about 2.8 gm of Spirulina per day for about one month reduces blood-sugar level. Anti-hypertensive actions of spirulina are also observed in rat models[17-23].

![Bromophenols derived from Rhodomela confervoides.](image)

Fig. 2: Bromophenols derived from *Rhodomela confervoides.*
Hypoglycemic potentials of Brown algae

Taxonomical classifications of seaweeds have shown that red algae come under rhodophyceae, brown algae under phaeophyceae, blue algae under cyanophyceae and green algae under chlorophyceae. Collection of brown algae is maximally fulfilled from Asian countries viz. Korea, Japan, China. Brown algae is a rich source of bioactive components like phlorotannins, polyphenols, pigments, sulfated polysaccharides, vitamins (A, B, C and E), dietary fibers, omega-3 fatty acids, and essential amino acids. Anti-diabetic potential of brown algae is maximally due to polyphenols, polysaccharides and pigments. Phlorotannins shows α-glucosidase, α-amylase, and PTP inhibitory functions. Brown algae under sargassacean species contain phlorotannins composed of several phloroglucinol units. Molecular size of phlorotannins is 162 Da and 650 KDa. Different kinds of phlorotannins is being reported from phloroglucinol, eckol, dieckol, 6,6-bieckol, phlorofucofuroeckol A (Fig. 3) to function against diabetes. They are obtained from the species of ecklonia. These secondary metabolites are synthesized by the polyketide pathway. The phlorotannins were found to enhance peripheral glucose utilization by activating glucose transporter sub-type 4 (GLUT-4) and activation of the protein kinase (AMPK) pathway. α-amylase and α-glucosidase inhibitory potentials of phlorotannins rich extracts have been studied in db/db mouse model[25-40].

Anti-diabetic actions of marine sponges

Dysidea villosa, a variety of marine sponge found mostly in China south sea region is the source of Dysidine (Fig.4) which activates insulin signaling pathway as evidenced by western blotting experimentations.

Other biologically active compounds isolated from marine sponges include sesquiterpenes, hydroquinones, quinones. These compounds besides exhibiting anti-HIV, anti-inflammatory, anti-tumor activities, also have significant anti-diabetic action by inhibiting PTPases.

![Fig.3: Different Phloro tannins from brown algae](image-url)
Dysidine is also reported to improve peripheral glucose utilization by activation of GLUT4; it also regulates tyrosine phosphorylation and p38MAPK phosphorylations. Callyspongia truncate is a pale violet colored encrusting sponge, responsible to secrete callyspongynic acid which is basically a polyacetylenic acid. Callyspongynic acid is a inhibitor of α-glucosidase. Indonesian marine sponge also secretes polybromodiphenyl ether, which inhibits PTP[41-44]. Lamellodysidea herbacea is also another species of marine sponge which inhibits PTP. This marine sponge is abundant in the coral reef of Indonesia. The major isolated compound from this marine sponge is polybromodiphenyl ether. It inhibits not only PTP1B but also works on cell line of human cancer, colon and T-cell lymphoma. Both polybromodiphenyl ether and its methyl ether, acetyl, n-butyryl, n-hexanoyl, and benzoyl derivatives inhibits PTP. The polybromodiphenyl ether extracted and isolated not only from sponges but also from different marine ascidians and marine algae is found to act as a potent anti-diabetic[45-50].

Role of marine fungus in type 2 diabetes
The methylethylketone derivative obtained from marine fungus penicillium sp. JF-55, abundant in Korea is found to show hypoglycemic potentials by inhibiting PTP. Penstyrylpyrone, anhydrofulvic acid and citromycetin are other important chemical constituents of this marine fungus. Penstyrylpyrone and anhydrofulvic acid shows inhibitory action of PTP with IC50 values of 5.28 µM and 1.90 µM. Another Marine fungus Cosmospora sp. SF-5060 obtained from Gejae Island, Korea, whose major secondary metabolite is aquastatin A. Aquastatin A have potentials of inhibitory action of PTP. Moreover it also modulates insulin signaling and leptin receptor signaling pathway finding applications in diabetes[45-50].

Hypoglycemic actions of Marine brown seaweeds and diatoms
Fucoxanthin is basically a marine carotenoid present in brown marine seaweeds, diatoms, macro and microalgae. In New York brown seaweeds also called as wakame. This wakame is used as flavouring agent in Asian soups and salads, used as anti-obesity as well as anti-diabetic agent. Fucoxanthin also has some anti-diabetic property. It induces the synthesis of docosahexaenoic acid (DHA) in liver. Fucoxanthin reduces white adipose tissue fat accumulation and promotes weight loss. With 0.02% dose fucoxanthin there is significant lowering of body weight. Fucoxanthin also helps to lower plasma and hepatic triglyceride concentrations. Adipocyte fatty acid synthesis, hepatic fatty acid and triglyceride synthesis are also lowered by fucoxanthin. Animal experimentations have shown that it slows down fasting blood glucose level and modulates plasma-insulin level in obese mice. Fucoxanthin controls insulin resistance, inhibites adipokines, tumor necrosis factor-α (TNF-α), monocyte chemo attractant protein-1(MCP-1), interleukin-6 (IL-6). Regulation of insulin/glucagon ratio is another suggestive mechanism of blood-glucose lowering actions of fucoxanthin[51-61].

Anti-diabetic activity of the extracts of different kinds of corals
Soft corals are found in coastal areas of Andaman and Nicobar. Ethylacetate extracts of soft corals showed hypoglycemic actions in albino rats. Alcohol extracts of Aplysia benedicti (Mollusca), Parazoanthus species, Stoichactis gigenteum, Sinularia also showed significant anti-diabetic activity[62-64].

Brown alga Cystoseira moniliformis to inhibit hyperglycemia
This brown algal is collected and is obtained from intertidal area of Philippines. After collection the brown algal samples were cleaned with water, so as to remove salts and debris. Then it is dried in open air and small pieces of this algal are powered slowly. Then it is macerated with ethanol for near about 1 day. Then the residue is filtered and administered to alloxan induced albino mice. Histopathological study showed that it helps
in the regeneration of pancreatic cells[59-63].

Hypoglycemic actions of ascidians

Ethanol extract of Marine ascidians like Microcosmus exasperatus obtained from Harbor of Tuticorin showed hypoglycemic actions in albino rats. Experimental results showed improvement in blood-glucose level, urea, creatinine, serum glutamate pyruvate transaminase (SGPT), serum glutamate oxaloacetate transaminase (SGOT), alkaline phosphate (ALP). Its major chemical constituents viz. 2-piperidione, benzeneacetamide, n-hexadecanoic acid has remarkable antioxidative actions thus potentiating the hypoglycemic role[65,66].

CONCLUSION

Enzymes play a pathogenic role in the root cause of several diseases like diabetes. Inhibition of such enzymes can act as a therapeutic bullet against Type 2 diabetes. The marine world is largely unexplored. Exploration of therapeutically active agents like Bromophenols, 2-piperidione, benzeneacetamide, n-hexadecanoic acid, Fucoxanthin, biologically active insulin, methyl-ethyl ketone derivatives etc from marine species like red algae, brown algae, marine fungus, seaweeds and diatoms, marine ascidians, sea corals with significant inhibitory potentials against enzymes like α-glucosidase, Protein Tyrosine Phosphatase and aldo reductase coupled with antioxidant activities adds a new dimension in anti-diabetic research. However extensive medical and pharmaceutical researches are necessary to develop therapeutic agents from marine sources.

REFERENCES


