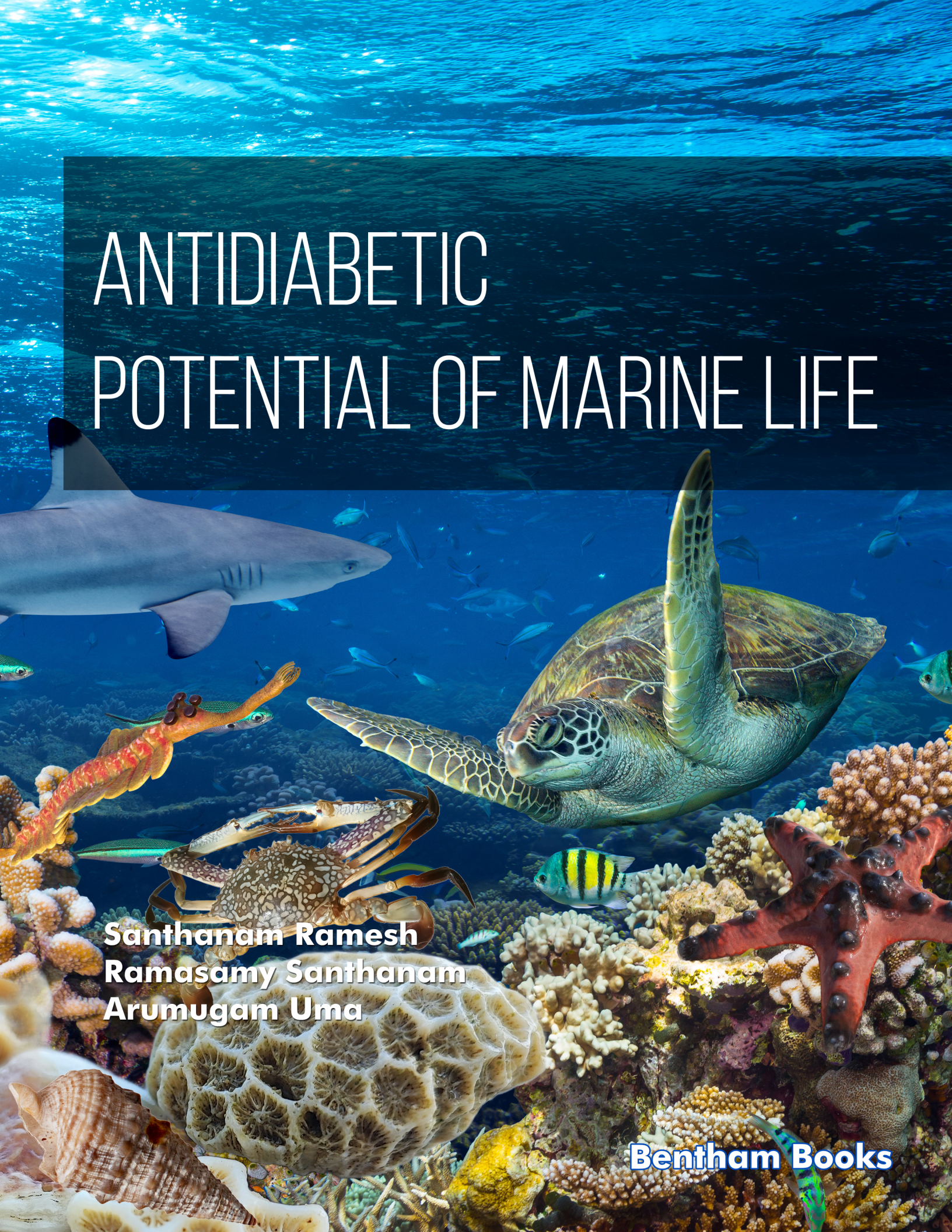
ANTIDIABETIC POTENTIAL OF MARINE LIFE



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Medicinal Chemistry and Marine Life

(*Volume 2*)

Antidiabetic Potential of Marine Life

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FOREWORD

It is my privilege to write this Foreword for my former teacher and guide, Dr. Ramasamy Santhanam (an author and former Dean of the Thoothukudi Fisheries College and Research Institute, the first fisheries college in Tamil Nadu functioning under this University), for his book titled " Medicinal Chemistry and Marine Life: Volume 2. Antidiabetic Potential of Marine Life".

Diabetes mellitus, a chronic metabolic disorder, is characterized by a rise in blood glucose levels, and it is considered to be a major health hazard. The International Diabetes Federation (IDF) has reported that the number of people suffering from diabetes may increase to 693 million by the year 2045. Because of the increasing number of diabetic patients and the limited number of antidiabetic drugs, the search for new antidiabetic compounds, especially from marine sources, has attracted much interest from the scientific community. The marine environment is considered to be a vast and relatively unexploited source of antidiabetic compounds, which offer great scope for the development of new drugs.

The present title, the first of its kind, deals with marine life possessing potential antidiabetic compounds. I strongly hope that his publication will serve as a valuable resource for the students and teachers of both fisheries and pharmaceutical sciences, besides serving as a potential guide for drug industries in the development of novel, antidiabetic drugs.

I congratulate the team of authors for their timely contribution.

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Preface

Diabetes mellitus is a metabolic disorder that is associated with several life-threatening complications, including atherosclerosis, retinopathy, and nephropathy. Diabetes is usually caused by the interaction of genetic and environmental factors and is characterized by a lack of insulin secretion and insulin resistance, which may lead to metabolism disorders of fat, protein, and carbohydrates. In 2013, it was estimated that more than 382 million people had diabetes, and this number is expected to increase to 500 million by 2030. It is expected that this disease will be the 7th leading cause of death. The current therapies available for the treatment of this disorder mainly include oral antidiabetic drugs and insulin injections. However, it is reported that the continuous use of synthetic drugs may cause many side effects. Therefore, there is an urgent need for safe and efficient antidiabetic drugs for the management of this disorder. Marine biota, such as marine microbes, marine plants, and marine animals, have been found to be promising sources with potent antidiabetic activity.

Though a few books are presently available on the therapeutic potential of marine biota, a comprehensive volume dealing with the antidiabetic potential of the different constituents of marine life has not been published so far. The present book, prepared by the scientists of both pharmaceutical and marine biology disciplines, will be the first of its kind to answer this long-felt need. It deals with aspects such as marine-derived molecules and lead compounds with antidiabetic activity, the antidiabetic potential of marine microorganisms, marine macroalgae, marine plants (seagrass and mangrove plants), marine invertebrates, ascidians, and marine fishes, and antidiabetic potential of marine fishery by-products such as fish oils, fish and shellfish wastes, as well as chitosan and its derivatives. It is hoped that the present publication will be of great use as a standard text-cum-reference for teachers, students, and researchers of various disciplines, such as biomedical sciences, pharmaceutical sciences, marine biology, and fisheries science. It will also be a valuable reference for libraries of colleges and universities and as a guide for the pharmaceutical industries involved in the development of new antidiabetic drugs from marine microbes, marine plants, and marine animals.

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CHAPTER 1

Introduction

Abstract: The formation of diabetes as a metabolic disorder, the causes of the formation of type 1 and type 2 diabetes, risk factors associated with type 2 diabetes mellitus, and the components of marine biota possessing antidiabetic compounds are dealt with in this chapter

Keywords: Antidiabetic compounds, Diabetes mellitus, Marine biota, Risk factors, Type 1 diabetes mellitus, Type 2 diabetes mellitus.

INTRODUCTION

Diabetes Mellitus (DM) has been reported to be one of the top 10 causes of human death globally. 4.2 million deaths were caused by it in 2019, and by 2045, the number is believed to rise to more than 700 million cases [1]. The incidence of diabetes increases most rapidly in low- and middle-income countries due to changes in lifestyle and an aging population. DM is nothing but a metabolic disorder in which the body cells are unable to use glucose effectively. This situation arises due to either low insulin (Type 1 diabetes) or insulin insensitivity (Type 2 diabetes). Among these two types of DM, the incidence of T2DM is becoming more common and accounts for about 90% of all the cases of diabetes [2]. This diabetic condition is characterized by a fasting blood glucose level higher than 126 mg/dL. DM is also known to cause complications like cardiovascular complications, ulcerations, dyslipidemia, endoplasmic reticulum stress, neuropathy, nephropathy, and retinopathy in affected persons. The management practices of diabetes include boosting of insulin sensitivity, reduction of alpha-glucosidase activity, *etc.*

TYPE 1 DIABETES AND TYPE 2 DIABETES: FACTORS, DIFFERENCES, AND CAUSES

Factors Associated with Type 1 and Type 2 DM

Several factors contribute to the formation of both type 1 and type 2 DM and are given below in Table **1**.

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Table 1. Factors associated with the type 1 and type 2 DM [3].

Factor	Type 1 DM	Type 2 DM
Family history	Less than 20%	About 60%
Genetic locus	Unknown	Chromosome 6
Age at onset	<35 yrs	>40-45 yrs
Type of onset	Abrupt	Gradual
Body weight	Normal	Obesity/Non-obesity
Frequency of occurrence	10-20%	80-90%
Pathogenesis	Autoimmune damage of β-cells	Impaired insulin secretion and insulin resistance
Blood insulin level	Reduced insulin	Normal or increased insulin
Condition of Islet cells	Insulitis and β-cell destruction	No insulitis and late fibrosis of islets
Clinical management	Insulin and diet	Insulin, diet, oral drugs, and exercise

Differences between Type 1 and Type 2 Diabetes

Several differences have been reported between type 1 diabetes and type 2 diabetes in the causes, onset of symptoms, and treatment. Type 1 diabetes is not caused by diet and lifestyle habits; it is an autoimmune condition that develops suddenly and is caused by genetics or other unknown factors. On the other hand, type 2 diabetes is often found to develop over time and is due to the lack of adequate exercise and obesity, which are the biggest risk factors. The causes of type 1 diabetes and type 2 diabetes are given below [4]:

Causes of Diabetes

Type 1 Diabetes

i. The immune system of the body is largely responsible for inhibiting foreign invaders, like harmful viruses and bacteria.
ii. Type 1 diabetes is known to be caused by an autoimmune reaction. In type 1 diabetes patients, the immune system is believed to mistake the body's own healthy cells for harmful bacteria and viruses.
iii. The immune system may destroy the insulin-producing beta cells in the pancreas. Under such conditions, the body may not be able to produce insulin. The destruction of the body's own cells by the immune system may be due to genetic and environmental factors, like exposure to viruses.

Type 2 Diabetes

i. People with type 2 diabetes have insulin resistance. Though the bodies of these people still produce insulin, they are unable to use it effectively.
ii. Several lifestyle factors, such as less activity and obesity, are largely responsible for this type of DM.
iii. Genetic and environmental factors may also play an important role in this type of DM. For example, more insulin produced by the pancreas is not effectively used by the body of people with type 2 diabetes. As a result, glucose accumulates in the bloodstream.

RISK FACTORS ASSOCIATED WITH TYPE 2 DIABETES

Several factors have been reported to be responsible for the development of diabetes mellitus (Fig. **1**). Among them, the modifiable risk factors such as physical inactivity, overweight/obesity, poor dietary habits, hypertension, smoking, and certain medications (*e.g*. glucocorticoids) and non-modifiable risk factors like genetics, family history, race/ethnicity, increasing age (>45), and history of gestational diabetes are important ones [5].

MARINE BIOTA AS A SOURCE OF BIOACTIVE COMPOUNDS

The marine ecosystems are considered to be the vast and relatively unexploited sources of bioactive compounds with high chemical diversity. Such metabolites include sulfated polysaccharides, proteins, polyphenols, sterols, fatty acids, tannins, flavonoids, pigments, *etc*. These compounds have been reported to possess remarkable pharmacological activities.

Exclusive metabolites have remarkable pharmacological activities like anticancer, antioxidant, anti-inflammatory, antihyperlipidemic, antidiabetic, antibacterial, antifungal, antiviral, antihypertensive, anticoagulant, immunomodulatory, neuroprotective, *etc.*

MARINE BIOTA AND THEIR ANTIDIABETICS

Among the different components of marine biota, sponges, corals, bacteria, fungi, mollusks, ascidians, brown algae, red algae, and green algae have been reported to possess antidiabetic agents [3].

CHAPTER 2

Marine Life as a Source of Antidiabetics

Abstract: The properties and chemistry of antidiabetics, the percentage contribution of bioactive compounds by the different components of marine life, and modes of action of antidiabetic compounds derived from certain marine sources are given in this chapter. Further, the role of marine life components in the inhibition of type 2 diabetes, anti-diabetes properties of marine micro and macroorganisms, and marine bioactive compounds such as fucoxanthin, astaxanthin, polyphenol, polysaccharide, krill oil, and fish collagen peptides, as well as their sources and potential applications against diabetes have also been dealt with in this chapter.

Keywords: Antidiabetic compounds, Bioactive compounds, Diabetes, Marine sources, Marine microorganisms, Polysaccharide.

INTRODUCTION

Owing to the limited number of anti-diabetic drugs and worldwide increasing number of diabetic patients, there is an urgent need for the search for new antidiabetic compounds and marine biota that have attracted much interest from the scientific community and offer vast scope in this regard. Among the marine biota, sponges, ascidians, and mollusks have already been reported to yield commercially approved anticancer drugs. For example, the Caribbean sponge *Tethya crypta* has yielded cytarabine (Cytosar-U®, Ara-C, DepoCyt®) to treat non-Hodgkin's lymphoma and acute myelocytic leukemia, vidarabine (Ara-A) derived from the same species is used in the treatment of herpes simplex infections, eribulin (Halaven®) produced by the sponge *Halichondria okadai* is used for the treatment of advanced liposarcoma and metastatic breast cancer, trabectedin (Yondelis®) derived from the tunicate *Ecteinascidia turbinata* has been approved for the treatment of ovarian cancer and tissue sarcomas, and ziconotide (Prialt®), produced by the cone snail *Conus magus* is used in the treatment of severe and chronic pain. It is also worth mentioning that the terpene (Dysidine) derived from the sponge *Dysidea villosa* has already undergone preclinical trials for the treatment of diabetes, and many such antidiabetic lead compounds are under screening. Therefore, the marine biota can offer vast scope in the production of promising antidiabetic compounds in the future [8].

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Antidiabetics: Properties, Chemistry, and Marine Life Possessing Antidiabetics

The anti-diabetic (anti-glycaemic) properties largely relate to the correction of hyperglycemic and hypoglycemic activities, as well asincreased or reduced secretion of insulin. The factors associated with these phenomena are the inhibition of α-glucosidase, Protein Tyrosine Phosphatase 1B (PTP1B), Dipeptidyl Peptidase IV (DPP-IV), and Glycogen Synthase Kinase-3 beta (GSK-3β), or the protection of beta pancreatic cells. Several bio-actives derived from marine organisms have been reported to possess the aforesaid antidiabetic properties. The chief marine biota possessing antidiabetics and the chemistry of such compounds are given in Tables **1** and **2**.

Table 1. Marine biota possessing antidiabetic properties [3].

Marine Biota	% Contribution of Antidiabetics
Sponges	31
Corals	24
Microbiota	15
Molluscs	6
Ascidians	6
Brown algae	5
Red algae	4
Green algae	1
Others	8

Table 2. Chemical class of antidiabetics derived from marine biota [6].

Marine Biota	Chemistry of Antidiabetics
Marine microorganisms	Antioxidants
Seaweeds	Peptides, amino acids, sterols
Sponges	Peptides
Cnidarians	Phenols
Bryozoans	Alkaloids
Crustaceans	Chitosan, minerals
Mollusks	Polypropionates
Echinoderms	Sterols
Tunicates	Peptides and alkaloids

Modes of Action of Antidiabetic Compounds Derived from Certain Marine Sources

The important antidiabetic compounds derived from major marine resources include phlorotannin, sodium alginate, fucosterol, phenylmethylene hydantoins, n-3 PUFAs, and collagen peptides. The modes of action of these bioactive compounds are given in Table **3**.

Table 3. Antidiabetic effects of marine bioactive compounds of certain marine sources and their modes of action [7].

Marine Source	Antidiabetic Compound	Mode of Action
Ascophyllum nodosum (Alga)	Phlorotannin	Alpha-glucosidase and alpha-amylase inhibitory activities
Laminaria angustata (Alga)	Sodium alginate	Inhibitory action of increase in bold glucose and insulin levels
Pelvetia siliquosa (Alga)	Fucosterol	Decrease in serum glucose level and inhibition of sorbitol in lenses
Ulva rigida (Alga)	Ethanolic Extracts	Reduction in blood glucose levels
Hemimycale arabica (Sponge)	Phenylmethylene hydantoins	Inhibitory action of glycogen synthase kinase-3beta
Fish Oils	n-3 PUFAs	Decrease in blood glucose oxidation; increase in fat oxidation; and maintenance of phosphatidylinositol-3' kinase activity
Wild Fish	Collagen peptides	Reduction in free fatty acids, cytochrome P450, and hs-CRP

Role of Marine Life Components in the Inhibition of Type 2 Diabetes

Among the different components of marine life, microorganisms such as fungi and diatoms (yellow-green algae) and macro-organisms like seaweeds (yellow and red seaweeds), sponges, and ascidians have been reported to possess significant antidiabetic properties as shown in Tables **4** and **5**.

Selected Marine Bioactives and their Potential Applications Against Diabetes

The potential marine bioactives with antidiabetic properties include compounds like fucoxanthin, astaxanthin, polyphenol, polysaccharide, krill oil, and fish collagen peptides [9].

CHAPTER 3

Antidiabetic Potential of Marine Microbiota

Abstract: Among the marine biota, the macro-organisms have yielded a considerable number of bioactive compounds in the last 50 years of bioprospecting research. Owing to the repeated derivation of known bioactive compounds and reduced number of novel compounds from these macroorganisms, scientists are now trying to concentrate on the less investigated drug sources like marine bacteria and fungi among the microbes, as well as microalgae other than cyanobacteria (blue-green algae) such as yellow-green algae (diatoms) and dinoflagellates, which are known to possess promising bioactive compounds including novel antidiabetics. Further, unlike macroorganisms, microorganisms are known to possess the advantage of sustainable production of considerable quantities of bioactive compounds by large-scale cultivation.

Keywords: Antidiabetic potential, Antarctic lichen, Bacteria, Blue-green algae (cyanobacteria), Fungi, Green algae, Haptophyte alga, Marine microbiota, Ochrophyte algae, Red algae, Yellow-green algae (diatoms).

INTRODUCTION

The marine microbiota constitutes microalgae, including prokaryotic cyanobacteria, eukaryotic microalgae, and endophytic bacterial and fungal diversity. Among these components, certain species of marine microalgae have been reported to serve as functional foods. The bioactive compounds of these microalgae, such as amino acids, peptides, Polyunsaturated Fatty Acids (PUFAs), pigments, scytonemins, pterins, and phenolic compounds, have demonstrated a wide range of therapeutic effects, including anti-inflammatory, antioxidant, and immune-modulatory properties, which help improve insulin sensitivity, thereby potentially alleviating diabetes mellitus. However, the FDA has not approved any microalgae-based antidiabetic products. More research and clinical studies are therefore needed to confirm the antidiabetic potential of these marine microalgae. Apart from these marine microalgae, marine microbes such as the endophytic bacterial and fungal diversity have been extensively studied for their antioxidant, antibacterial, cytotoxic, antidiabetic, and anti-immunosuppressive properties [6 - 8].

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Antidiabetic Potential of Marine Microalgae

Marine microalgae such as cyanobacteria, yellow-green algae, haptophyte alga, ochrophyte algae, green algae, and red algae have been reported to possess antidiabetic properties.

Antidiabetic Blue-Green Algae (Cyanobacteria)

Aphanothece sp. (Fig. **1**)

Global distribution: This picocyanobacterial species has a global distribution, which includes most of the world's oceans.

Ecology: It is known to occur in tropical to subtropical swamps and in brackish-water environments.

Antidiabetics and their mechanisms of action: The extracellular polysaccharide of this species has been reported to possess antidiabetic activity by inhibiting alpha-glucosidase at 8.1% [20].

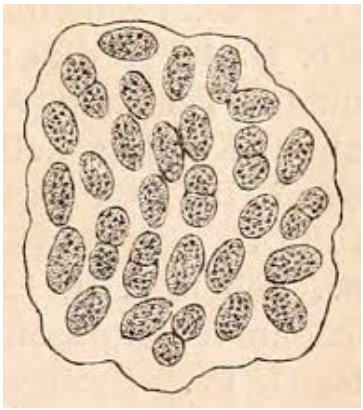

Fig. (1). *Aphanothece* sp Engler, Adolf *et al.* Creative Commons Attribution-Share Alike 4.0 International license.
https://commons.wikimedia.org/wiki/File:Die_Nat%C3%BCrlichen_Pflanzenfamilien_nebst_ihren_Gattungen_und_wichtigeren_Arten_in%E2%80%A6Fig_49M.jpg.

Arthrospira platensis (= Spirulina platensis)

Global distribution: It is most widely distributed in Asia and Africa.

Ecology: This planktonic filamentous cyanobacterium grows in alkaline, brackish, and saline waters.

Antidiabetics and their mechanisms of action: The crude methanol extracts of this species have shown α-amylase and α-glucosidase inhibitory activities with IC50

values of 13.3 and 9.6 mg/mL, respectively, and percentage values of 96.5 and 97.4, respectively [18]. The oral administration of 80% ethanol extracts of this species at 2.5mg/kg bw to alloxan-induced diabetic rats for 30 days showed a highly hypoglycemic effect [19] (Fig. **2**).

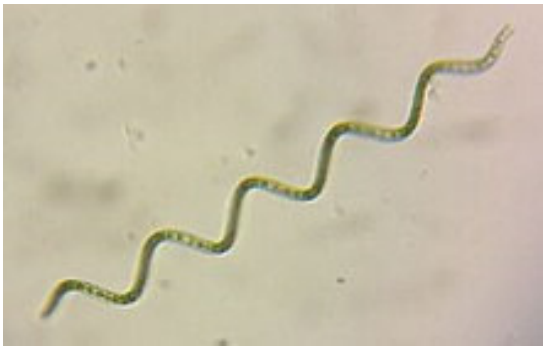

Fig. (2). *Arthrospira platensis*: FarmerOnMars ; Creative Commons Attribution-Share Alike 3.0 Unported license.; https://commons.wikimedia.org/wiki/File:SingleSpirulinaInMicroscope4WEB.jpg.

Chroococcus **sp.** (Fig. **3**)

Global distribution: It is widely distributed across North America.

Ecology: It is commonly seen in eutrophic lakes and ponds. It may also be seen in estuarine environments.

Antidiabetics and their mechanisms of action: The extract of this species has shown alpha-glucosidase inhibition with a percentage value of 13 [20].

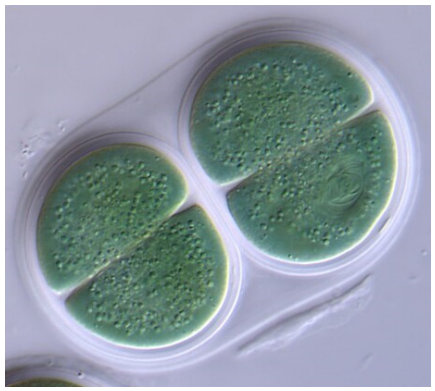

Fig. (3). *Chroococcus* sp.(M. Lorenz, Creative Commons Attribution 4.0 International license. https://commons.wikimedia.org/wiki/File:SAG_36.85_Chroococcus_turgidus_SWES6wk_ML_160818_010_ovl_prime.jpg.

CHAPTER 4

Antidiabetic Potential of Marine Plants

Abstract: The antidiabetic potentials of the different classes of marine plants, such as macroalgae *viz*. green algae, brown algae, and red algae, as well as seagrasses and mangrove plants are dealt with in this chapter. The different chemical classes of secondary metabolites derived from these marine plants and their mechanisms of action in antidiabetic activities are also given.

Keywords: Antidiabetic potentials, α-amylase inhibitory activity, α-glucosidase inhibitory activity, Brown algae, DPP-IV inhibitory activity, Green algae, Macroalgae, Mangrove plants, PTP 1B inhibitory activity, Red algae, Sea grasses.

INTRODUCTION

Marine macroalgae or seaweeds are large visible plants that generally grow by attaching to rocks along the seashore. These algae possess nutritional applications, such as human food and animal feeds. Based on morphological characteristics, anatomical features, pigment content, nutrients, and chemical composition, these seaweeds are classified as Chlorophyta (green algae), Phaeophyceae (brown algae), and Rhodophyta (red algae). The bioactive compounds or secondary metabolites isolated from the different types of these seaweeds belong to chemical classes such as alkaloids, terpenoids, flavonoids, steroids, and phenolsand have received greater attention in recent years due to their unique and diverse therapeutic properties, including antidiabetic and antioxidant. Among these compounds, the alkaloids are known to possess cytotoxic activity, terpenoids exhibit a wide spectrum of anti-tumor activities, phenolics exert significant antioxidant activities, steroids possess antimicrobial and cardiotonic properties, tannins serve as antioxidant, antiviral, antibacterial, antiulcer, and cytotoxic agents, and flavonoids possess antioxidant, antimicrobial, and spasmolytic activities. The other miscellaneous compounds of these seaweeds, like saponins, are found to be useful in hyperglycemia and hypercholesterolemia and as anti-inflammatory, anticancer, and weight-loss drugs [18] The presently available treatment regimens for type 2 DM have been found to possess adverse side effects, and there is a great need to search for effective and side effect-free drugs that can help maintain the blood glucose level and complications in type 2 DM

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patients. Even though herbal medicines have been focused on by most of the researchers, none of these medicines have yielded a fully beneficial effect on treating patients with type 2 diabetes mellitus. The seaweeds, with their promising antidiabetic compounds, offer vast scope in the development of new and safe diabetic drugs. The antidiabetic potentials of the different classes of seaweeds are given below.

MARINE MACROALGAE (SEAWEEDS)

Green Algae

Auxenochlorella pyrenoidosa (= Chlorella pyrenoidosa)

Global distribution: It occurs worldwide.

Ecology: It is a freshwater species and is occasionally seen in marine environments.

Antidiabetics and their mechanisms of action: The extracts of this species have been reported to suppress hyperglycaemic conditions by inhibiting α-glucosidase and α-amylase enzymes in type 2 diabetes mellitus patients [33].

Capsosiphon fulvescens

Global distribution: Southwest coast of South Korea.

Ecology: It is known to reside in the upper portions of the intertidal coastal sediments and rocky shores.

Antidiabetics and their mechanisms of action: A total of three glycolipids *viz*. capsofulvesin A ((2S)-1-O-(6Z,9Z,12Z,15Z-octadecatetraenoyl)-2- O-(4Z,7Z,10Z,13Z-hexadecatetraenoyl)-3-O-β-D-galactopyranosyl glycerol), capsofulvesin B ((2S)-l-O- (9Z,12Z,15Z-octadecatrienoyl)-2-O-(10Z-13Z-hexadecadienoyl)-3-O-β-D-galactopyranosyl glycerol), and capsofulvesin C ((2S)-1-O-(6Z,9Z,12Z,15Z-octadecatetraenoyl)-3-O-β-D-galacatopyranosyl glycerol), as well as chalinasterol (Figs. **1**-**4**), have been isolated from this algal species. Of them, capsofulvesin A, B, and sterol chalinasterol exhibit antidiabetic activities by inhibiting aldose reductase with IC50 values of 52.5, 101.9, and 345.3 μM, respectively [23 - 33].

Caulerpa racemosa

Global distribution: Temperate and tropical seas; Eastern Mediterranean Sea.

Ecology: It dwells in shallow seas.

Antidiabetics and their mechanisms of action: Its acetone crude extract showed α-amylase inhibitory activity with an ED50 value of 0.09 mg/ml [23]. At 100 and 200 mg/kg concentrations, the ethanolic extract of this alga showed antidiabetic activity by significantly reducing the blood glucose levels in diabetic rats besides restoring the glucose uptake by hemidiaphragm and glucose transport by hepatic cells. Further, at 200 mg/kg, the ethanolic extract was found to restore the histoarchitecture of the pancreas (Fig. **5**) [34].

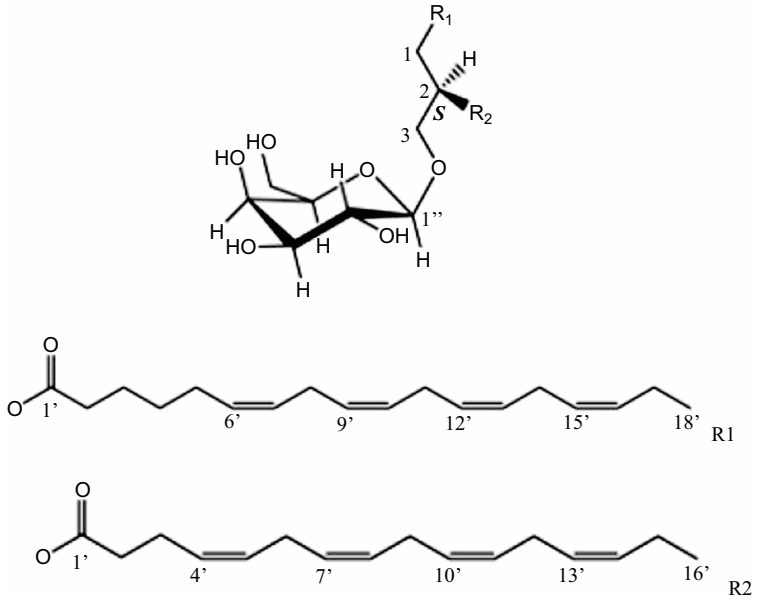

Fig. (1). Capsofulvesin A.

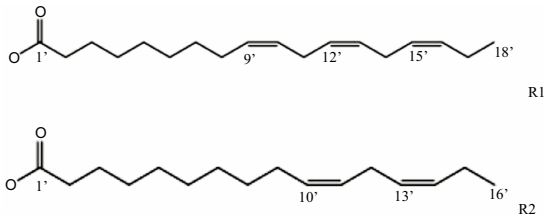

Fig. (2). Capsofulvesin B.

CHAPTER 5

Antidiabetic Properties of Marine Invertebrates

Abstract: The chemical diversity (terpenes, alkaloids, steroids, peptides, *etc*.) of marine invertebrates such as sponges, cnidarians, annelid worms, crustaceans, mollusks, and echinoderms and their mechanisms of action has been dealt with in this chapter. The mechanisms of action of these natural products, along with their potential in the discovery of novel drugs, are also given in detail.

Keywords: Chemical diversity, Marine invertebrates, Mechanisms of action, Therapeutic potential.

INTRODUCTION

The marine invertebrates such as sponges, cnidarians, annelid worms, crustaceans, mollusks, and echinoderms have yielded a substantial diversity of natural products, including terpenes, alkaloids, steroids, aliphatic hydrocarbons, carbohydrates, amino acids, peptides, *etc*., which offer immense scope in the industrial applications as agricultural products, pharmaceutics, antibiotics, nutraceutics, cosmetics, biomaterials, *etc*.

Sponges

The sponges with about 8000 described species are found to be widely distributed in marine and freshwater environments. These sessile organisms are considered to be a potential source of an enormous diversity of therapeutic compounds. The pharmaceutical interest among sponges started in the 1950s with the investigation of the therapeutically important nucleosides *viz*. spongothymidine and spongouridine from the species *Cryptotethya crypta*. These nucleosides were largely responsible for the synthesis of ara-A, an antiviral drug, and ara-C, the first marine-derived anticancer agent. Further, marine sponges have been reported to be the most important producer of novel bioactive compounds, and about 5000 compounds are believed to be extracted every year from these organisms. It is worth mentioning here that some of these secondary metabolites are in the process of a clinical and pre-clinical trial (*e.g*., as anticancer or anti-inflammatory agents) [89]. However intensive research on the antidiabetics of these organisms is

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lacking, although a wide chemical diversity of antidiabetic compounds, such as sesquiterpenes, quinones, and hydroquinones, have been derived from the marine sponge species, such as *Dysidea villosa*, *Callyspongia truncata,* and *Lamellodysidea herbacea* [90].

Agelas mauritiana

Global distribution: Tropical seas of Indo-West Pacific (Fig. **1**). Ecology: This sessile species lives at a depth range of 0 - 100 m.

Fig. (1). *Agelas* sp. Image credit: Esculapio ; Creative Commons Attribution 3.0 Unported license. https://commons.wikimedia.org/wiki/File:Agelas_oroides_Capo_Gallo_025.JPG

Antidiabetics and their mechanisms of action: α-galactosylceramide (αGalCer, KRN7000) (Fig. **2**) derived from this species is believed to protect beta-pancreatic cells and activate natural killer cells [25]. Natural Killer (NK) cells are cytotoxic lymphocytes that engage in innate immunity to remove pathogens and cancer cells in patients with type 2 diabetes mellitus.

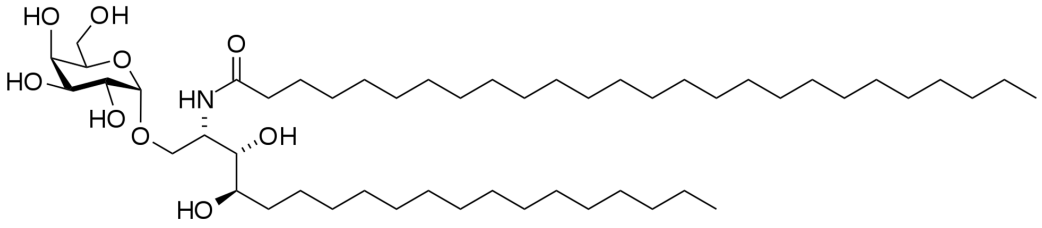

Fig. (2). α-galactosylceramide.

Agelas nakamurai

Global distribution: Tropical and subtropical West Indies, Mediterranean Sea, Red Sea, and Indian Ocean.

Ecology: It normally resides in the shallow seas up to a depth of about 30 m.

Antidiabetics and their mechanisms of action: An N-methyladenine-derived sesquiterpene *viz*. agelasine G (Fig. **3**) isolated from this species has shown Protein Tyrosine Phosphatase 1B (PTP1B) inhibiting activity with an IC_{50} value of 15 µM [2]. PTP1B is mostly involved in the negative regulation of signaling mediated by the insulin and leptin receptors. This enzyme is, therefore, known to play an important role in the development of diseases associated with insulin resistance, such as obesity and diabetes.

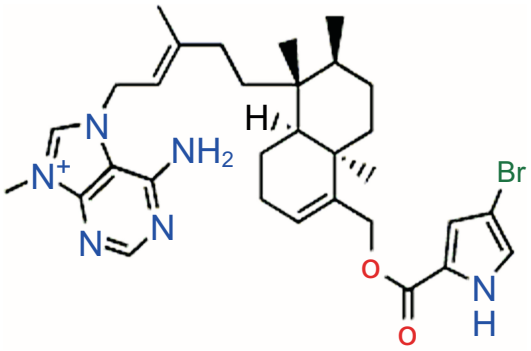

Fig. (3). Agelasine G.

Amphimedon viridis (= Haliclona viridis)

Global distribution: Caribbean, Bermuda, North Carolina, West central Pacific, and Indian Ocean.

Ecology: It commonly inhabits shallow reefs and seagrass beds. Antidiabetics and their mechanisms of action:

An ethanol extract of this species has shown a significant hypoglycemic effect, lasting for more than 8 h after the administration of single oral doses of 200 - 500 mg/kg to experimental mice [91] (Fig. **4**).

Axinyssa **sp.**

Global distribution: It is a common species of French Polynesia: Tuamotu Islands.
Ecology: It is often collected from the lagoon on pinnacles.

CHAPTER 6

Antidiabetic Properties of Marine Chordates

Abstract: The antidiabetic properties of the natural products derived from tunicates, marine elasmobranchs, teleost fishes, and soft-shelled turtles are dealt with in this chapter. The global distribution and ecology of the antidiabetic species and the modes of action of their bioactive compounds are also depicted.

Keywords: Antidiabetic properties, Antidiabetic molecules, Distribution, Ecology, Marine fishes, Soft-shelled turtle, Tunicates.

INTRODUCTION

The marine chordates are the least studied group as far as chemical diversity in general and antidiabetic properties in particular are considered. Among the different components of marine chordates, chemical diversity has been fairly well studied in tunicates. While marine fish are the least studied group. No bioprospecting investigations are available on marine reptiles and mammals. Among the tunicates, several species are known to possess natural products with a wide range of bioactive properties like anticancer and antimicrobial. Very few species of this group showed antidiabetic properties. For example, the lipids extracted from the sea pineapple Halocynthia roretzi demonstrated antidiabetic properties in mice models. Marine fish are known to be important nutrient-rich foods possessing positive properties in the reduction of type 2 diabetes mellitus. The antidiabetic compounds of marine fish, such as proteins, peptides, and ω-3 Polyunsaturated Fatty Acids (PUFAs), have been reported to be potential sources in the prevention and management of T2DM.

Tunicates

Aplidium elegans (= Sidnyum elegans)

Global distribution: Atlantic Ocean, Mediterranean Sea, and English Channel.

Ecology: It dwells on coral reefs, hiding at the bases of corals at depths of 3-30 m.

Antidiabetics and their mechanisms of action: A monophosphorylated polyketide *viz*. phosphoeleganin (Fig. **1**) derived from this species showed PTP1B inhibitory effects with an IC50 value of 1.3M. Further, this compound was also found to inhibit the aldose reductase enzyme [2].

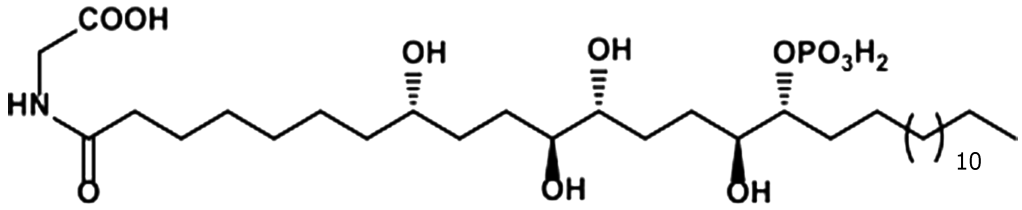

Fig. (1). Phosphoeleganin.

Ascidia ahodori

Global distribution: It is found widely distributed in polar, tropical, and temperate environments.

Ecology: This benthic species is seen on shores and littoral or intertidal areas.

Antidiabetics and their mechanisms of action: The methanol and ethyl acetate extracts of this species have shown antidiabetic activity by inhibiting the enzyme α-amylase. At the concentrations of 100, 200, and 300 µg/ml, the methanol extracts showed the percentage values of inhibition as 44, 63, and 71, respectively, and the corresponding values for the ethyl acetate extracts were nil, 29, and 45, respectively [121] (Fig. **2**).

Fig. (2). *Ascidia* sp. Gronk; Creative Commons Attribution-Share Alike 3.0 Unported, 2.5 Generic, 2.0 Generic and 1.0 Generic license.; https://commons.wikimedia.org/wiki/File:Ascidia.JPG.

Ascidia sp.

Antidiabetics and their mechanisms of action: The ethyl acetate extracts of this species have shown antidiabetic activity by inhibiting the enzyme α-amylase. At the concentrations of 100, 200, and 300 µg/ml, these extracts showed percentage values of inhibition as 44, 52, and 58, respectively [121].

Didemnum vexillum

Global distribution: North America, Europe, and New Zealand.

Ecology: It grows on seagrass and rock surfaces, and it also grows as a fouling organism on cultivated bivalves, net cages, and other man-made structures.

Antidiabetics and their mechanisms of action: The methanol and ethyl acetate extracts of this species have shown antidiabetic activity by inhibiting the enzyme α-amylase. At the methanol concentrations of 100, 200, and 300 µg/ml, the inhibition percentage values were 48, 62, and 74, respectively, and the corresponding values for the ethyl acetate extracts were 48, 54, and 61, respectively [121] (Fig. **3**).

Fig. (3). *Didemnum vexillum* U.S. Geological Survey/photo by Dann Blackwood (USGS); public domain; https://commons.wikimedia.org/wiki/File:Tunicate_colony_of_Didemnum_vexillum.JPG.

CHAPTER 7

Antidiabetics Properties of Marine Fishery By-Products

Abstract: The antidiabetic properties of marine fishery byproducts, such as peptide hydrolysates, collagen peptides, and marine fish oils (ω-3 PUFA) derived from marine fish wastes, are dealt with in this chapter. Further, the possible mechanisms involved in the antidiabetic effects of chitosan and its derivatives from marine crustaceans are also depicted.

Keywords: Antidiabetic effects, Bioactive compounds, Chitosan, Fish oils, Fasting blood glucose, Marine fishery byproducts.

INTRODUCTION

Marine fishery byproducts such as proteins, peptides, and fish oils derived from fish wastes are known to possess antidiabetic, antioxidant, anti-inflammatory, anti-hypertensive, anti-cancer, and immunomodulatory properties. Recent research investigations state that these bioactive compounds could be of great use in the treatment and management of type 2 diabetes mellitus [125].

Bioactive Compounds of Marine Fish and their Antidiabetic Activities

The bioactive proteins, peptides, or liquids derived from the marine fishery byproducts have shown antidiabetic activities through different mechanisms in human and animal models *in vitro* (microorganisms, cell culture, *etc.*). In humans, these compounds reduce fasting blood glucose and enhance the density of beta-cells. In animal models, these compounds are known to inhibit the plasma DPP-IV enzyme activity and enhance plasma insulin level, blood glucose level, *etc.*, and in microorganisms, these bioactive compounds mainly increase insulin release from beta-cells and inhibit DPP-IV activity [125].

Antidiabetic Properties of Marine Fishery by-products

The antidiabetic properties of marine fishery by-products, *viz*. peptide hydrolysates and fish oils, have been reported to show antidiabetic properties in humans [125 - 128].

Santhanam Ramesh, Ramasamy Santhanam & Arumugam Uma

Antidiabetic Properties of Marine Fish Peptide Hydrolysates

Marine fishery byproduct-derived peptides have been reported to display anti-diabetic activities through several mechanisms, *viz*. stimulating the secretion of Glucagon-Like Peptide 1 (GLP-1), enhancing insulin release, inhibiting DPP-IV activity, increasing glucose uptake, reducing blood glucose levels, and Upregulating Glucose Transporter Type 4 (GLUT4) and peroxisome proliferator-activated receptor alpha (PPAR- α), both of which have been reported to play a crucial role in glucose metabolism and absorption. The administration of marine peptides has shown increased glucose digestion and insulin sensitivity in experimental rats with type 2 diabetes mellitus. These activities are due to the capacity of peptides to reduce the effects of oxidative stress and inflammation, as well as the enhanced expression of GLUT4 and PPAR-α. The peptides derived from the hydrolysate of the muscle of the raw sardine (*Sardine pilchardus*) have been reported to show DPP-IV inhibitory activity with an IC50 value of 1.83 mg/ml. Similarly, insulin and glucagon-like peptide 1 (GLP-1) secreted from the BRIN-BD11 and GLUTag cells of the muscle of the blue whiting fish (*Micromesistius poutassou*) showed inhibition of DPP-IV activity. The peptides from the trimmings of salmon (*Salmo salar*) displayed DPP-IV inhibitory activity with an IC50 value of 0.08 mg/ml. The peptides of the muscle of the boarfish, *Capros aper*, increase insulin secretion, GLP-1 secretion, and glucose tolerance besides inhibiting DPP-IV with an IC50 value of 1.18 mg/ml [128]. The bioactive properties of fish waste-derived peptides are shown in Fig. (**1**).

Antidiabetic Properties of Marine Fish Peptides in Humans with T2DM

The marine fish collagen peptides have been reported to show several antidiabetic effects in humans with T2DM. Such effects include reduced levels of fasting blood glucose, increased levels of insulin sensitivity and secretion index, and an increase in adiponectin [125], as shown in Table **1**.

Antidiabetic properties of marine fish collagen peptides in humans with T2DM [125].

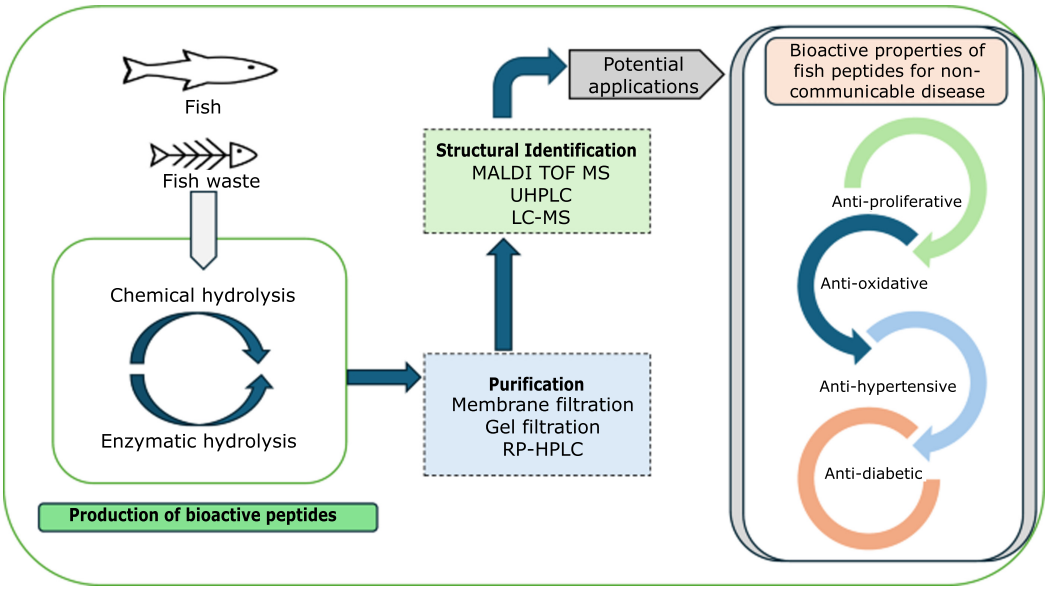

Fig. (1). Bioactive properties of fish waste-derived peptides.

Image credit: Ravi Baraiya, R. Anandan, K. Elavarasan, Patekar Prakash, Sanjaykumar Karsanbhai Rathod, S. R. Radhika Rajasree and V. Renuka (Reproduced with permission)

Table 1. Antidiabetic properties of marine fish collagen peptides in humans with T2DM [125].

Fish Peptide	Human Parameters	Administration (Dose/Duration)	Antidiabetic Effects
Marine fish collagen peptides	T2DM; Healthy	6.5 g twice/day; 3 months	Reduced levels of fasting blood glucose; increased insulin sensitivity index
--do--	T2DM; age: 21-50	2.5 or 5 g once/day; 3 months	Reduction in fasting blood glucose
--do--	T2DM; age: 21-50	10 g/day, 3 months	Reduction in fasting blood glucose
--do---	T2DM with/without hypertension	6.5 g/day; 3 months	Reduction in free fatty acids; increase in adiponectin *
--do--	T2DM and primary hypertension	6.5 g twice/day; 3 months	Reduced levels of fasting blood glucose; increased levels of insulin secretion index and insulin sensitivity index

*Adiponectin, a hormone for insulin sensitivity

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