RESEARCH PAPER

Marine Derived Metabolites as Multi-targeted agents against Diabetes and Obesity

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ABSTRACT
Diabetes mellitus and obesity are two parallel epidemics in the 21st century in which >1 billion people are affected globally and imposing a tremendous burden on the medical, social and economic domains. Although there have been considerable advances in the pharmacological interventions used to treat these metabolic disorders, the current synthetic treatment is affected by several drawbacks, such as a narrow spectrum of effectiveness, side effects and the focus on a single target, which is not sufficient to overcome the multifactorial and complex nature of these metabolic disorders. More than 70% of the earth's surface is covered by the sea, which is an enormous and largely unexplored source of structurally new and biologically active secondary metabolites. This systematic review comprehensively analyzes the current knowledge of marine metabolites as multi-targeted therapeutic approaches to diabetes and obesity including phlorotannins, sulfated polysaccharides (fucoidans, carrageenans, alginates), carotenoids (fucoxanthin, astaxanthin), omega-3 polyunsaturated fatty acids (EPA, DHA), bioactive peptides, alkaloids, terpenoids and sterols. Their mechanisms of action are critically examined on some of the major molecular targets such as α-glucosidase, α-amylase, dipeptidyl peptidase-4 (DPP-4), peroxisome proliferator-activated receptor-gamma (PPAR-γ), AMP-activated protein kinase (AMPK), pancreatic lipase, CCAAT/enhancer binding protein alpha (C/EBP-α), and sterol regulatory element-binding protein 1c (SREBP-1c). These compounds have been studied for their anti-inflammatory, antioxidant, gut microbiome-modulating and insulin-sensitizing properties, which are discussed in detail. In vitro, in vivo and available clinical evidence is thoroughly assessed. We also discuss problems of bioavailability, structural optimization, and the translational gaps and outline future research needs for the development of marine products as nutraceuticals and pharmaceuticals against metabolic diseases. The evidence presented here shows that marine metabolites are a rich pipeline of multitargeted intervention strategies for managing diabetes and obesity.

Keywords: Marine metabolites , Diabetes mellitus, Obesity, Phlorotannins, Fucoxanthin, Sulfated polysaccharides, Alpha-glucosidase inhibition, AMPK , PPAR-γ, Multitargeted therapy..
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1.INTRODUCTION

Type 2 diabetes mellitus (T2DM) and obesity is an epidemic worldwide, changing the face of non-communicable diseases (NCDs) burden all over the world. As of 2021, the International Diabetes Federation (IDF) reports that around 537 million adults had diabetes, and this is expected to rise to 783 million by 2045. At the same time, it is estimated that more than 650 million adults are obese, and that obesity is directly responsible for cardiovascular disease, non-alcoholic fatty liver disease, some cancers and for a premature progression of T2DM.^([2])

There are myriad pathophysiological mechanisms shared between obesity and T2DM such as chronic low grade inflammation, insulin resistance, dysregulated adipokine secretion, oxidative stress and gut microbial imbalance. These disorders are not just disorders of glucose or lipid metabolism alone, they are multiple interconnected biological network dysfunctions. Traditional drug-targeting strategies that target one enzyme or receptor pathway have become less effective for these diseases of this level of mechanistic complexity. Single-target drugs like metformin (AMPK activator), sitagliptin (DPP-4 inhibitor) and orlistat (pancreatic lipase inhibitor) are effective on their own, but they only treat one aspect of the disease process and are often unable to provide sustained metabolic control when used in isolation.^([4])

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In the light of this development, natural products, especially marine organisms have attracted great scientific attention as a source for multitargeted bioactive compounds. The marine environment is the largest on Earth, covering about 71% of the surface and containing an estimated 500,000 to 10 million species, all adapted to the conditions of extreme pressure, salinity, temperature and nutrient limitation. These selective pressures have led to the evolution of pharmacologically and structurally unique and diverse secondary metabolites, which do not occur in the terrestrial realm. Macroalgae, microalgae, sponges, corals, sea cucumbers, fish, shellfish, marine fungi and cyanobacteria are a remarkably diverse group of marine organisms that produce a variety of chemical scaffolds, such as polyphenols, polysaccharides, carotenoids, lipids, peptides, alkaloids, terpenoids, and polyketides, many of which possess strong biological activity towards metabolic targets. [6]

Polypharmacology – the ability of a single compound or formulation to target multiple receptors – is especially important with regard to metabolic disease. Marine metabolites are structurally complex and multifunctional compounds, and interact with multiple molecular pathways simultaneously, providing therapeutic benefits over synthetic agents with single targets. For example, phlorotannins from brown algae have been shown to demonstrate an inhibitory effect on the 5 targets like alpha-glucosidase, alpha-amylase, DPP-4, and pancreatic lipase – and to activate PPARγ signaling, a five-target profile in one compound class.^([7,8])

This review summarizes comprehensively published data (2020-2026) on marine-derived metabolites, as multitargeted agents in diabetes and obesity, focusing on elucidation of the molecular mechanisms, preclinical and clinical study of efficacy and identification of translational opportunities. The review is organised on the basis of chemical classes, each section covers detailed information on the source organisms, chemical structure, major molecular targets, in-vitro and in-vivo evidence, and therapeutic applications. A critical evaluation of bioavailability challenges, structure-activity relationships and directions for future research are also given

Background of the work

Diabetes mellitus and obesity represent two of the most pressing public health crises of the 21st century, often described as parallel, intertwined epidemics. According to the International Diabetes Federation (IDF), approximately 537 million adults were living with diabetes globally as of 2021, a figure projected to reach 783 million by 2045. Simultaneously, over 650 million adults are classified as obese worldwide, with obesity serving as a major risk factor for Type 2 Diabetes Mellitus (T2DM), cardiovascular disease, non-alcoholic fatty liver disease, and certain cancers.^([9])

The pathophysiology underlying both conditions is deeply interconnected. Shared mechanisms include chronic low-grade inflammation (meta-inflammation), insulin resistance, oxidative stress, dysregulated adipokine secretion, impaired incretin signaling, and gut microbial dysbiosis. This mechanistic complexity renders single-target pharmacological approaches such as metformin (AMPK activator), sitagliptin (DPP-4 inhibitor), and orlistat (pancreatic lipase inhibitor) insufficient for comprehensive and sustained metabolic control. Moreover, existing synthetic drugs are frequently associated with adverse effects, narrow therapeutic windows, and high treatment costs, underscoring the urgent need for safer, multi-targeted therapeutic alternatives.^([9])

Natural products, particularly those of marine origin, have emerged as a compelling and largely untapped reservoir of structurally novel bioactive compounds. The marine environment, covering over 71% of the Earth's surface and harboring an estimated 500,000 to 10 million species, subjects its organisms to extreme evolutionary pressures high salinity, pressure, temperature fluctuations, and nutrient limitation — that have driven the biosynthesis of chemically diverse and pharmacologically unique secondary metabolites. These include phlorotannins, sulfated polysaccharides (fucoidans, carrageenans, alginates), carotenoids (fucoxanthin, astaxanthin), omega-3 polyunsaturated fatty acids (EPA, DHA), bioactive peptides, alkaloids, terpenoids, and sterols.^([10])

What distinguishes marine metabolites from conventional single-target drugs is their inherent polypharmacology — the capacity of a single compound or compound class to simultaneously modulate multiple molecular targets. For instance, phlorotannins from brown algae have demonstrated inhibitory activity against α-glucosidase, α-amylase, DPP-4, and pancreatic lipase, while also activating PPAR-γ signaling - a multi-target profile rarely achievable with a single synthetic molecule.^([10])

Despite considerable preclinical evidence, significant gaps remain in the clinical translation of marine metabolites, particularly concerning bioavailability, formulation stability, dose standardization, and large-scale human trial data. This review was therefore undertaken to systematically consolidate and critically evaluate the current body of evidence on marine metabolites as multi-targeted agents for diabetes and obesity management

The Marine Metabolome: Diversity and Pharmacological

Significance

The marine metabolome is one of the most diverse natural product science repositories. Under the evolutionary pressures of marine environments, the biosynthetic machinery of marine organisms has evolved to yield secondary metabolites that have remarkable structural novelty. The classes that are unique to or mainly present in marine organisms include halogenated compounds,

polyether toxins, sulfated biomolecules, highly oxygenated terpenoids and non-ribosomal peptides.^([12])

Classification of Marine Sources Relevant to Metabolic Disease

Marine macroalgae (seaweeds) can be divided into three groups; namely, Phaeophyceae or brown algae, Rhodophyceae or red algae and Chlorophyceae or green algae; and these are the most widely studied sources of the marine metabolites with antidiabetic and anti-obesity properties. Phlorotannins, fucoidans, alginates, laminarin and fucoxanthin are all known to exhibit potent anti-diabetic properties and are produced by brown algae including Ecklonia cava, Fucus vesiculosus, Sargassum species, Undaria pinnatifida, and Laminaria japonica. .^([11,12])

Microalgae such as Haematococcus pluvialis, a rich source of astaxanthin, Spirulina platensis, Chlorella vulgaris, Nannochloropsis species and Phaeodactylum tricornutum provide carotenoids, phycobiliproteins and omega-3 PUFAs. Previously grouped with algae, cyanobacteria are a unique class of secondary metabolites, such as lipopeptides and polyketides, which are important to metabolic disease.^([13])

The Phylum Porifera, or marine sponges, are bioaccumulators of an amazing array of secondary metabolites, many of which are produced by their associated microbial symbionts, which are filter-feeders and sessile. The compounds of sponge origin of metabolic disease concerns are Manzamine alkaloids, Bromotyrosine derivatives, Terpenoids and Polyketides. Bioactive compounds with antiproliferative and antidiabetic and anti-lipase activities have also been isolated from marine invertebrates such as sea cucumbers (holothurians), tunicates (ascidians), echinoderms and molluscs, among others

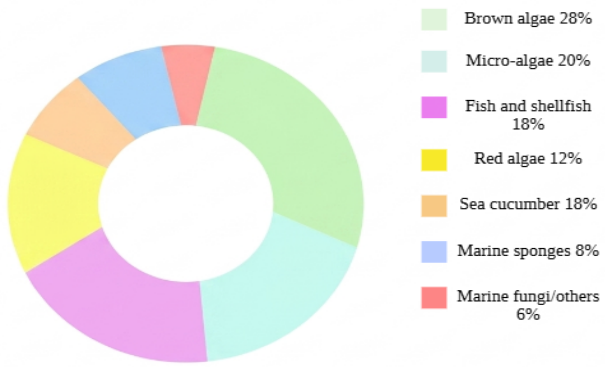


Figure 1 Representation of each marine source

The Case for Multitargeted Marine Therapies

At least the following interconnected dysfunctions are involved in the pathogenesis of T2DM and obesity: (i) peripheral insulin resistance in skeletal muscle, adipose and liver; (ii) enhanced hepatic gluconeogenesis; (iii) dysregulated incretin axis (GLP-1, GIP); (iv) elevated post-prandial glucose from accelerated carbohydrate digestion; (v) increased adipogenesis and lipogenesis; (vi) chronic low-grade neuroinflammation and adipose tissue inflammation; (vii) oxidative stress mediated beta cell apoptosis; (viii) gut dysbiosis disrupting metabolic homeostasis.^([15,16]) A multitargeted agent which would target three or more of these mechanisms would, in theory, be more effective with lower doses per mechanism and thus have less adverse effect burden due to high dose monotherapy. Marine metabolites also modulate the activation of transcription factors (PPAR-γ via fucoxanthin), activate intracellular kinases, which sense energy levels (AMPK via fucoxanthin, astaxanthin), and suppress inflammatory cascades (NF-kB via omega-3 PUFAs), all at once, making them a very attractive multitargeted pharmacological paradigm.^([17,18])

Table 1. Classification of key marine sources and their primary bioactive metabolites relevant to diabetes and obesity

Marine Source	Representative Species	Key Metabolites	Primary Targets
Brown algae	Ecklonia cava, Fucus vesiculosus, Sargassum sp.	Phlorotannins, fucoidan, fucoxanthin, alginate	α-glucosidase, DPP4, PPAR-γ, lipase
Red algae	Eucheuma cottonii, Kappaphycus alvarezii	Carrageenan, floridoside, bromophenols	α-glucosidase, α-amylase, lipase
Green algae	Caulerpa sp, Ulva lactuca	Ulvan, chlorophyll derivatives, sterols	Lipase, AMPK, antioxidant
Marine microalgae	Haematococcus, Spirulina, Phaeodactylum	Astaxanthin, fucoxanthin, EPA, phycocyanin	PPAR-γ, AMPK, NF-κB, PLIN-1
Sea cucumber	Holothuria scabra, Apostichopus japonicus	Saponins, polysaccharides, collagen peptides	DPP-4, α-glucosidase, lipase
Marine sponges	Dysidea sp., Petrosia sp.	Terpenoids, alkaloids, polyketides	Insulin signaling, AMPK, PTP1B
Fish & shellfish	Salmon, tuna, shrimp, oyster	EPA, DHA, bioactive peptides, chitosan	PPARs, GLP-1, ACE,

Phlorotannins as Multi-targeted Antidiabetic and Aniti-obesity Agents

Phlorotannins are polyphenolic compounds only synthesised in marine plants, specifically brown algae, via the acetate-malonate (polyketide) pathway, with phloroglucinol, 1,3,5-trihydroxybenzene, as the basic unit of the monomer. They differ in structure because of differences in degree of polymerization, in hydroxylation, and in the pattern of ether or phenyl linkages, resulting in compounds classified as fuhalols, phlorethols, fucols, fucophlorethols, eckols, and carmalols.^([19,20])

Alpha-Glucosidase and Alpha-Amylase Inhibition

Major intestinal and pancreatic enzymes responsible for breaking down dietary carbohydrates to absorbable carbohydrates are alpha-glucosidase and alpha-amylase. The enzymes are inhibited, slowing down the absorption of carbohydrates, and reducing postprandial hyperglycemia, which is the main action of marketed drugs, such as acarbose and voglibose. Recently a number of phlorotannins from Ecklonia cava, Eisenia bicyclis and Fucus vesiculosus have been shown to be very potent competitive inhibitors of both enzymes.^([21]) These values for dieckol are as low as 0.6–7.2 μM against alpha-glucosidase, which are significantly better than the reference drug acarbose (IC50≈ 521 μM). The molecular docking studies have been performed to confirm that dieckol interacts with active site of alpha-glucosidase via multiple hydrogen bonding with catalytic residues Asp215, Asp352, and His280 and hydrophobic interactions which helps to stabilize the enzyme:dieckol complex. The IC50 values of Phlorofucofuroeckol A were 12.3 μM and 2.8 μM for alpha-amylase and alpha-glucosidase, respectively, where enzyme kinetics showed competitive inhibition.^([22])

Kim et al. (2022) systematically studied 16 phlorotannins extracted from Ecklonia stolonifera for their inhibitory activity against alpha-glucosidase and alpha-amylase and found structure-activity relationships, with indications that the degree of polymerization and the number of furan rings increased the inhibitory strength. The trimer eckstolonol exhibited the best α-glucosidase inhibition (IC50 = 1.4 μM) and dieckol possessed the best α-amylase inhibitory activity.^([24])

DPP-4 Inhibition and Incretin Enhancement

Major enzymes in the large intestine and pancreas that hydrolyze food carbohydrates to absorbable carbohydrates are alpha-glucosidase and alpha-amylase . The enzymes are inhibited, slowing down the absorption of carbohydrates, and reducing postprandial hyperglycemia, which is the main action of marketed drugs, such as acarbose and voglibose. Recently a number of phlorotannins from

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Dipeptidyl peptidase-4 (DPP-4, CD26) is a serine protease which rapidly degrades glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) that are essential stimulators of insulin secretion from pancreatic beta cells after a meal. One of the more important classes of drugs for the treatment of T2DM is DPP-4 inhibitors—also known as gliptins. Several phlorotannins have shown in vitro DPP-4 inhibitory activity.^([25])

Lee et al. (2021) reported that eckol, phlorofucofuroeckol B and 7-phloroeckol inhibited the DPP-4 by competitively binding to the active site of DPP-4 with IC50 of 28.4 μM, 19.7 μM and 34.2 μM respectively. The hydroxyl groups of the scaffold of phlorotannins were involved in hydrogen bonding with Glu205, Glu206, Tyr547 and Arg125 residues within the DPP-4 binding pocket. Based on these findings, it was concluded that the phlorotannin mechanism of action was a dual-target effect, with insulin secretion and the digestion of carbohydrates being inhibited simultaneously, which is not possible by any individual marketed synthetic drug.^([27])

PPAR-γ Activation and Insulin Sensitization

The master transcriptional regulator of adipogenesis and insulin sensitivity is peroxisome proliferator-activated receptor gamma (PPAR-γ) which is the molecular target of the thiazolidinedione class of insulin sensitizers, rosiglitazone and pioglitazone. Phlorotannins induce PPAR-γ activity to enhance glucose uptake in adipocytes and also in skeletal muscle cells. Dieckol was demonstrated to up-regulate the expression of PPAR-γ in 3T3-L1 adipocytes at concentrations of 10–50 μM, which shows a 40–60% increase in GLUT4 translocation and insulin-stimulated glucose uptake over control.^([28])

Cho et al. (2023) conducted a network pharmacology study in 2023 to identify the key targets of phlorotannin in T2DM, which are identified as PPAR-γ, AMPK, IRS-1, PI3K, and Akt, and the binding energy of dieckol to PPAR-γ ligand-binding domain is −9.3 kcal/mol, which is similar to rosiglitazone (−10.1 kcal/mol) .^([29])

Anti-Adipogenic Effects

Phlorotannins have anti-adipogenic properties, which are shown to inhibit the transcriptional pathway of adipogenesis. eckol and dieckol (10-100 μM) significantly inhibited lipid accumulation measured by Oil Red O staining, mRNA expression of C/EBP-α and PPAR-γ, activation of SREBP-1c and expression of fatty acid synthase (FAS) and acetyl-CoA carboxylase (ACC) in 3T3-L1 preadipocytes. In diet-induced obese mouse models, Ecklonia cava extract (200 mg/kg/day for 12 weeks) decreased body weight gain by 18.4%, epididymal fat pad by 31.2% and hepatic lipid accumulation by 27.5% when compared with high-fat diet controls.^([31])

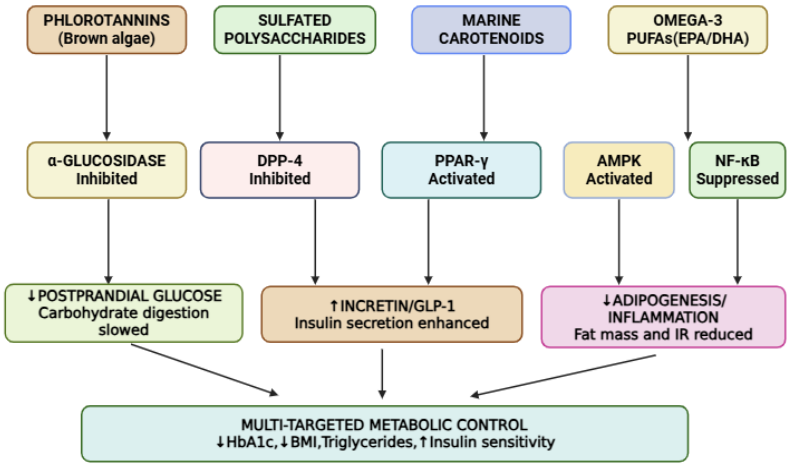


Figure 2: Multi-targeted pathway: marine compound classes → molecular targets → pathway effects → clinical outcomes.

Sulfated Polysaccharides: Fucodians, Carrageenans, and Alginates

The sulfated polysaccharides are a structurally and functionally heterogeneous class of marine biopolymers, mainly located in the cell walls and extracellular matrices of marine algae and invertebrates. All of these characters: sulfation degree, monosaccharide composition, molecular weight, and glycosidic linkage configurations have roles in their biological activities.^([32])

Active phytochemical compounds of brown algae

Fucoidans are sulfated L-fucose-rich polysaccharides which are mainly extracted from brown algae, such as Fucus vesiculosus, Undaria pinnatifida, Sargassum thunbergii, Ascophyllum nodosum, Laminaria japonica. Levoglucosan is a fucopyranose polymer, mainly composed of (1→3)- or (1→3)/(1→4)-linked L-fucopyranose residues with degrees of sulfation at C-2, C-3 or C-4, and may contain minor amounts of galactose, mannose, xylose, and uronic acids.^([33])

The antidiabetic activities of fucoidans are very complex. There are two mechanisms by which fucoidans reduce the absorption of postprandial glucose: they inhibit alpha-glucosidase and alpha-amylase activities. Secondly, they promote glucose uptake in insulin sensitive tissues without binding insulin receptors, which is of special importance for insulin-resistant condition (IRC) (34). Third, Gao et al. (2022) showed that fucoidan from Undaria pinnatifida could activate AMPK in the hepatocytes by a mechanism similar to the main effect of metformin, which is to inhibit the expression of gluconeogenic enzymes (PEPCK, G6Pase), and to inhibit hepatic glucose production.^([36])

Fourth, fucoidans are known to protect the pancreatic beta cells from the apoptosis by glucolipotoxicity to facilitate the insulin secretion.Fourth, fucoidans could enhance insulin secretion from pancreatic beta cells by preventing the apoptosis induced by glucolipotoxicity. When diabetic rats were treated with fucoidan (150 mg/kg for 30 days), their beta cell mass was restored by 42%, the ratio of Bax to Bcl-2 was lowered, and activities of antioxidant enzymes (SOD, CAT, GPx) were increased while oxidative stress (MDA, 8-OHdG) in the pancreas was decreased.^([37])

Fucoidans and Obesity

Anti-obesity effect of fucoidans involves pancreatic lipase inhibition, adipogenesis inhibition, transcription factor regulation of lipid metabolism and lipolysis stimulation.

In a 2021 study, Wang et al. showed that fucoidan from Sargassum horneri is a potent inhibitor of pancreatic lipase, with an IC50 of 0.38 mg/mL and significantly suppress the differentiation of 3T3-L1 cells into adipocytes by inhibiting the expression of C/EBP-α and PPAR-γ at both the mRNA and protein levels.^([38])

FUCOIDAN supplementation (400 mg/kg/day for 10 weeks) in the diet-induced obesity mouse model significantly lowered the total body weight gain by 21.3%, white adipose tissue mass by 34.7%, total cholesterol by 22%, triglycerides by 31%, LDL-C by 18%, and HDL-C by 15%, and normalized the serum leptin and adiponectin levels. Mechanistically the effects were suggested to be due to up-regulation of expression of two enzymes involved in the lipolysis of white adipose tissue, specifically that of hormone-sensitive lipase (HSL) and adipose triglyceride lipase (ATGL) .^([39])

Carrageenans

Carrageenans are sulfated galactans obtained from red algae (Eucheuma, Kappaphycus, Chondrus, Gigartina species), which are categorized into three types, kappa, iota and lambda, according to their sulfation pattern and ability to form gels. It is known that high molecular weight lambda-carrageenan has proinflammatory activity whereas low molecular weight kappa- and iota-carrageenans exhibit antidiabetic activity. The low-molecular-weight kappa-carrageenan (LMWKC) from Eucheuma cottonii was reported to inhibit alpha-glucosidase (IC50 = 2.8 mg/mL) and alpha-amylase (IC50 = 4.1 mg/mL) and to improve oral glucose tolerance in type 2 diabetic mice; it also reduced fasting blood glucose by 28.4% after 4 weeks of oral supplementation at 200 mg/kg.^([40])

Alginates and Laminarin

Alginates are structural polysaccharides (polyuronic acids containing mannuronic and gulururonic acid residues) extracted from brown algae, and having known viscogenic and gel-forming properties that slow gastric emptying and glucose absorption in the small intestine.^([41])

Their antidiabetic activity is mostly attributed to physical effect by decreasing glucose diffusion through the epithelial cell wall of the gut, however, there are also recent reports of direct enzyme inhibitory and microbiome-modulating activity. There was a 19.2% reduction in the postprandial blood glucose rise in healthy volunteers when laminarin was taken along with a standard carbohydrate meal, as a result of the barrier effect of glucose diffusion through its viscosity in the gastrointestinal tract.^([42])

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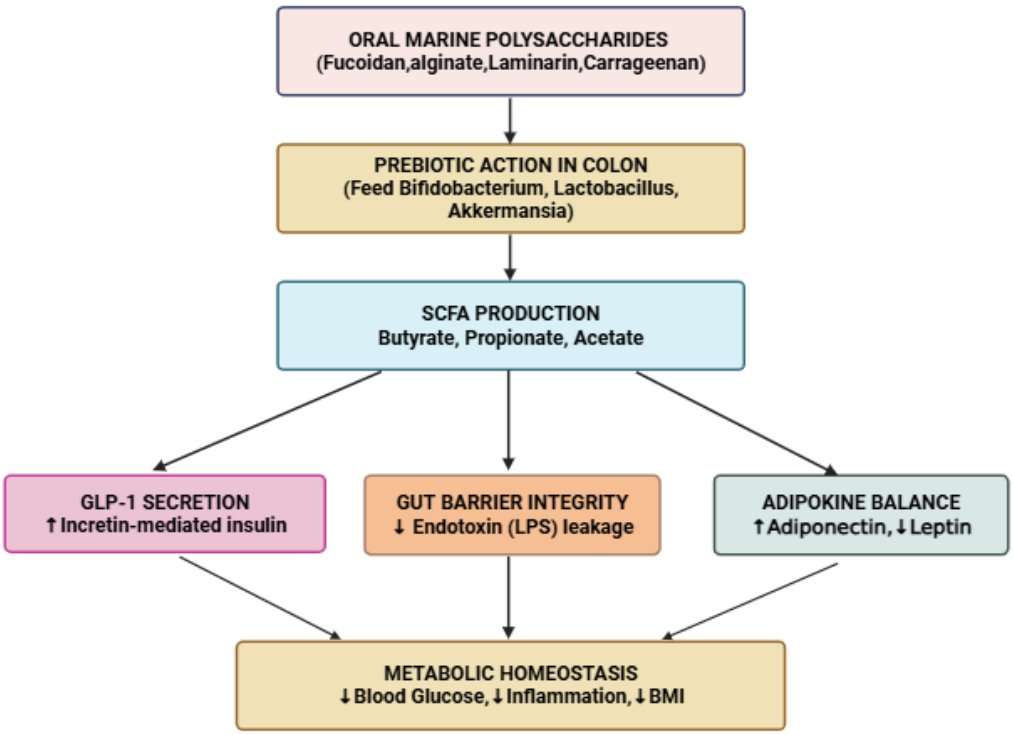


Figure 3:Marine Polysaccharide-Mediated Gut Microbiome Modulation and Metabolic Homeostasis

MARINE CAROTENOIDSFUCOXANTHINASTAXANTHIN

The marine carotenoids are the most studied class of anti-obesity compounds derived from marine origin, which have unique functional groups (allenic bonds, hydroxyl and keto groups in unusual positions). These include largely fucoxanthin and astaxanthin.^([43])

Fucoxanthin: Anti-Obesity Mechanisms

Fucoxanthin is a xanthophyll carotenoid that is mainly found in brown macroalgae (Undaria pinnatifida, Hijikia fusiformis, Ecklonia sp.) and some marine diatoms. It is characterized by its allenic bond (C=C=C), 5,6-monoepoxide, plus multiple hydroxyl and carbonyl groups, and is known to have a high level of antioxidant activity as well as special interactions with nuclear receptors.^([44])

The main mechanism of action of fucoxanthin in the treatment of obesity is its ability to activate uncoupling protein.The physiological role of 1 (UCP-1) is confined to brown adipose tissue (BAT), but in white adipose tissue (WAT) it is found. UCP-1 uncouples mitochondrial proton gradient from ATP production, producing heat and dissipating of stored energy. The browning effect of WAT mediated by UCP-1 upregulation brought about by fucoxanthin is a thermogenic pathway for fat mass reduction that is different from any drug approved to date.^([45]) In a 2021 controlled feeding study, Nishikawa et al. showed that fucoxanthin (0.05% in diet for 4 weeks) decreased white adipose tissue weight, up-regulated UCP-1 mRNA expression in white adipose tissue (WAT) by 3.8-fold, and increased the rectal temperature (which is a proxy for thermogenesis) in obese mice compared to controls. These effects were dose dependent and were associated with decreased expression of PLIN-1 (perilipin-1, a protein which stabilizes lipid droplets) which promotes lipolysis.^([46])

In addition to WAT thermogenesis, fucoxanthin has been shown to have antidiabetic activities through PPAR-γ modulation, AMPK activation in skeletal muscle (increased glucose uptake in muscle), alpha-glucosidase inhibition (IC50 of 15.3–42.8 μM, depending on the source organism and the assay conditions), and suppression of hepatic lipogenesis by downregulating SREBP-1c and FAS.^([47,48])

Fucoxanthin in Human Clinical Studies

A randomized double-blind placebo-controlled clinical study by Abidov et al. showed that the effects of Xanthigen (a combination supplement of Undaria pinnatifida fucoxanthin and pomegranate seed oil) were assessed in 151 non-diabetic obese women for 16 weeks. The fucoxanthin group showed substantial losses in body weight (mean loss was 4.9 kg vs a gain of 0.3 kg for the placebo group), waist circumference, body fat percentage, liver fat content (measured by ultrasound), serum triglycerides and C-reactive protein, while fasting blood glucose and insulin levels improved. The results were the first human clinical evidence of fucoxanthin's multiple metabolic effects.^([49])

In 2022, Mikami et al. conducted a further pilot study involving 24 patients with T2DM who received fucoxanthin-enriched Wakame extract (500 mg/day for 8 weeks), which showed a marked decrease in fasting blood glucose (−12.4%), HbA1c (−0.6 percentage points), and HOMA-IR (−18.3%) compared to baseline.^([50])

Astaxanthin

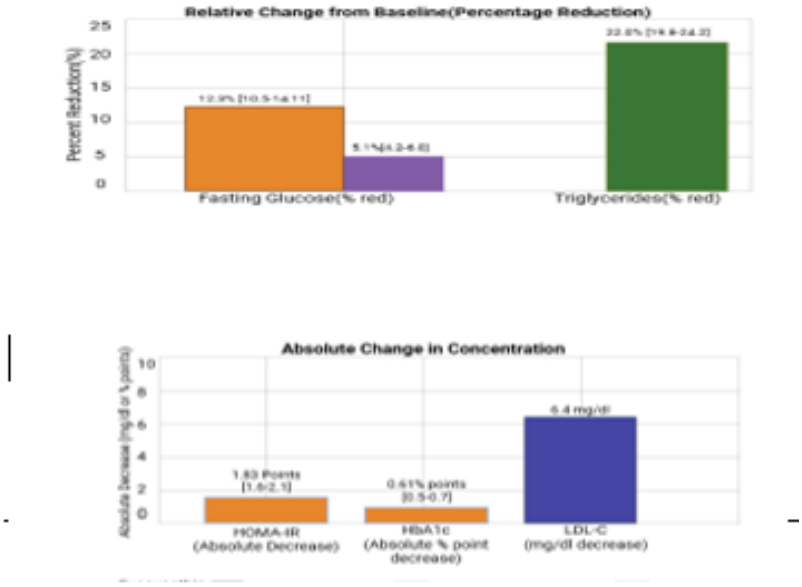
Haematococcus pluvialis is a microalga that more than any other produces the potent natural antioxidant astaxanthin

(3,3′-dihydroxy-β,β-carotene-4,4′-dione), which has a singlet oxygen quenching activity estimated to be 6,000 times that of vitamin C and 550 times that of vitamin E. The antidiabetic and anti-obesity mechanisms are mainly associated with its exceptional antioxidant properties as well as direct interactions with metabolic signaling pathways.^([51])

Astaxanthin prevents ROS production under glucolipotoxic conditions, helps preserve mitochondrial membrane potential and inhibits the intrinsic pathway of apoptosis (Bax, cytochrome c, caspase-3) in pancreatic beta cells.^([52])

Astaxanthin stimulates AMPK activity in skeletal muscle cells by an AMPK-activating mechanism that is mediated by an increase in the ratio of AMP/ATP resulting from mitochondrial uncoupling, leading to increased GLUT4 translocation and insulin-independent glucose uptake. It inhibits the NF-κB dependent inflammatory pathways decreasing secretion of TNF-α, IL-6 and MCP-1 by hypertrophied adipocytes, which helps to reduce the infiltration of adipose tissue macrophages and subsequent insulin resistance in the systemic circulation.^([53])

Huang et al. conducted a meta-analysis in 2023 of 14 randomized controlled trials to study the effects of astaxanthin on metabolic diseases, finding that astaxanthin supplementation significantly lowered fasting blood glucose. The weighted mean difference for the included studies showed a decrease in insulin, insulin resistance, total cholesterol, LDL-C and CRP (−4.2 mg/dL, −0.34, −8.1 mg/dL, −6.4 mg/dL and −0.48 mg/L respectively), which further confirmed the multitargeted clinical efficacy of astaxanthin in the studies included.^([54])



Summary of Clinical Improvements Reported in Randomized Controlled Trials of Marine Metabolites

Poly Unsaturated Fatty Acids: EPA AND DHA

Long-chain omega-3 polyunsaturated fatty acids (PUFAs) from marine sources such as fish, fish oils, microalgae (Nannochloropsis, Schizochytrium, Thraustochytrid species) and marine invertebrates are the most well-studied and clinically proven marine bioactive compounds. The mechanisms of their multitargeted actions in metabolic diseases encompass lipid metabolism, inflammatory signaling, insulin sensitivity and modulation of gut microbiota.^([55])

Lipid Metabolism and Anti-Obesity Effects.

EPA and DHA are strong PPAR-α endogenous ligands which increases genes expression of mitochondrial and peroxisomal fatty acid beta-oxidation and decreases lipid accumulation in the liver. Omega-3 PUFAs also activate PPAR-α, which boosts the production of lipoprotein lipase (LPL) and apolipoprotein A-I (ApoA-I), proteins that play a key role in removing triglyceride-rich particles, or VLDL, and raise HDL-C levels. Concurrent PPAR-γ partial agonist activity leads to an improvement in the insulin sensitivity of adipocytes without thiazolidinedione-like adipogenic effects, providing insulin-sensitizing effects with a lower weight gain risk.^([57])

In metabolic syndrome patients, omega-3 PUFA supplementation has been shown to be clinically multitargeted, according to a systematic review and meta-analysis by Rios-Hoyo et al. in 2020, which included 47 randomized trials (n=6438) .^([58])

Anti-Inflammatory Mechanisms: Resolvins and Protectins are activated during resolution.

It has been recently shown that EPA & DHA are metabolic precursors of specialized pro-resolving mediators (SPMs), such as resolvins (E-series from EPA, D-series from DHA), protectins (neuroprotectins from DHA), and maresins, which have revolutionized the way their anti-inflammatory

action is viewed. These lipid mediators play an active role in terminating inflammatory processes by inhibiting infiltration of neutrophils, promoting efferocytosis by macrophages, and inhibiting production of cytokines mediated by NF-κB.^([59])

The association with obesity, chronic adipose tissue inflammation due to M1 macrophage polarization is a key aspect of insulin resistance. Resolvin D1 and resolvin E1, which are produced locally from DHA and EPA, respectively and reduce the polarization of adipose tissue macrophages towards the pro-inflammatory M1 and the anti-inflammatory M2 phenotypes, decreasing the production of TNF-α, IL-1β, and IL-6, and increasing adiponectin production by adipocytes.^([60])

GPR120 and Insulin Signaling

DHA's insulin sensitizing effects are mediated by an important receptor, GPR120, or FFAR4, which is a G protein-coupled receptor found on intestinal L-cells, macrophages and adipocytes. Intestinal L-cells express the binding protein GPR120 which improves intestinal GLP-1 secretion by binding to DHA; this increases postprandial insulin release. In macrophages, GPR120 activation by DHA inhibits inflammatory signaling mediated by both the TLR4 and TNF-α receptor by inhibiting both the TAK1 and the IKKβ kinase pathways.^([61])

GPR120 mutations were found in obese human patients (loss-of-function mutation R270H), demonstrating the physiological relevance of this pathway in human metabolic regulation.^([62])

BIOACTIVE PEPTIDES FROM MARINE SOURCES

In recent years, interest in the bioactive peptides that can be obtained from marine protein via enzymatic hydrolysis or fermentation has increased due to their antidiabetic, anti-obesity, antihypertensive, and antioxidant properties, which are short amino acid sequences (2–20 residues) released from the protein during hydrolysis or fermentation. Bioactive peptides can be isolated from the marine sources such as fish muscle protein, fish skin collagen, shellfish (shrimp, oyster, mussel, crab), squid, sea cucumber, sea urchin and microalgal proteins.^([63])

DPP-4 Inhibitory Peptides

Marine peptides with DPP-4 inhibitory activity is one of the most actively researched class in marine peptide pharmacology. These peptides are competitive inhibitors of DPP-4, thereby blocking degradation of endogenous GLP-1, and so extending incretin-mediated insulin secretion. Structure-activity relationships suggest that proline or alanine at the penultimate N-terminal position (P1 position) greatly improves the DPP-4 inhibitory activity.^([64])

Harnedy et al. (2022) isolated 5 DPP-4 inhibitory peptides from Atlantic salmon (Salmo salar) skin collagen hydrolysate having IC50 values between 28.7 μM and 96.4 μM. After simulated gastrointestinal hydrolysis the peptide GPAGPAGER was found to be resistant to gastrointestinal digestion and kept its DPP-4 inhibitory activity indicating potential for oral bioavailability. Crustacean shell chitosan is also found to possess DPP-4 inhibitory activity (IC50 = 43-112 μg/mL) with pancreatic lipase inhibitory activity (IC50 = 67-198 μg/mL) forming a dual-target peptide scaffold.^([66])

Alpha-Glucosidase and Lipase Inhibitory Peptides

The alpha-glucosidase inhibitory activity of bioactive peptides isolated from hydrolysate of the squid (Todarodes pacificus), oyster (Crassostrea gigas) and mussel (Mytilus edulis) have been reported, and the IC50 values were 1.4–8.7 mg/mL, respectively. In 2023, Li et al. found that a tripeptide (AEK) derived from muscle protein hydrolysate (MPH) of Scomber japonicus is a strong pancreatic lipase inhibitor (IC50 = 0.34 mM), it has been found that the peptide binds to the active site serine residue (Ser152) and oxyanion hole through molecular docking.^([68])

The cardiovascular comorbidities of diabetes will also be explored, along with the role of ACE Inhibitory Peptides

Around ¾ of patients with T2DM have hypertension and it greatly enhances cardiovascular risk. Marine derived ACE inhibitory peptides tackle this comorbidity aspect of the multitargeted therapeutic strategy. IC50 of Fish Collagen derived Peptides (GPRGF, GLLG and GLPG) from tuna (Thunnus sp.) skin hydrolysate against ACE in vitro ranged from 12.4–47.8 μM and significant reduction in systolic blood pressure (S.B.P) (−18 mmHg at 100 mg/kg oral dose) was observed after 6 h in spontaneously hypertensive rat (SHR) models.^([69])

Marine Alkaloids, Terpenoids and Sterols

In addition to the well characterized classes of polysaccharides, polyphenols and lipids, marine organisms are known to synthesize a variety of alkaloids, terpenoids and sterols that have been shown to possess antidiabetic and anti-obesity properties. Typically, these lower molecular weight compounds have higher bioavailability than the higher molecular weight polysaccharides.^([70])

Marine Alkaloids

The pancreatic beta cell protective effects of manzamine alkaloids isolated from marine sponges (Acanthostrongylophora species, Ircinia species) was shown by the inhibition of protein tyrosine phosphatase 1B (PTP1B), a negative regulator of insulin receptor signaling. Inhibition of PTP1B increases the activity of insulin receptor tyrosine kinase, which in turn activates downstream signaling by PI3K/Akt, increasing glucose uptake.^([71])

In a cell-based screen in 2021, Liang et al reported that lamellarin alkaloids from marine polychaetes and molluscs exhibited AMPK activating properties with lamellarin-K exhibiting glucose uptake enhancing actions in L6 myotubes (1.8-fold vs. control) similar to that of the reference compound AICAR, and an increase in GLUT4 protein expression.^([72])

Marine Terpenoids

Sargachromanol G and its related meroterpenoids, chromenes, inhibited adipocyte differentiation and lipid accumulation in 3T3-L1 cells, reducing the expression of the PPAR-γ and C/EBP-α proteins at 10-40 μM concentrations in the cells of Sargassum siliquastrum. Dollabeline diterpenes from Dictyota dichotoma were shown to exhibit α-glucosidase inhibitory activity (IC50 =

18.3–64.7 μM) and antioxidant activity, both of which are important in the pathogenesis of T2DM, which is associated with oxidative stress.^([74])

Marine Sterols

The most well studied antidiabetic and anti-obesity marine sterol is fucosterol (24-ethylidenecholesterol) which is produced by brown algae. It inhibits 4 enzymes: alpha glucosidase (IC50 = 174 μM), alpha amylase (IC50 = 203 μM), DPP-4 (IC50 = 89 μM) and pancreatic lipase (IC50 = 127 μM) in a single molecule.^([75])

The study by Park et al. (2022) examined the anti-obesity effects of fucosterol over 10-weeks in high-fat diet-fed mice, showing a 19.3% body weight gain decrease, lowered adipose tissue mass, enhanced glucose tolerance (AUC-OGTT ↓23%), normalization of serum insulin, leptin and adiponectin, and reduced hepatic lipid accumulation. A gene expression analysis revealed a downregulation of SREBP-1c, FAS and SCD-1 (stearoyl-CoA desaturase-1) and an upregulation of CPT-1a (carnitine palmitoyltransferase 1a), suggesting a simultaneous prevention of lipogenesis and stimulation of fatty acid oxidation.^([76])

Modulation of Gut Microbiota using marine metabolites

The gut microbiome is now a key player in understanding metabolic health, with consistent links between dysbiosis, defined as decreased diversity of microorganisms, an imbalance in the Firmicutes:Bacteroidetes ratio and the absence of short-chain fatty acid (SCFA)-producing bacteria, and obesity and T2DM. Among the most important marine metabolites that modulate the gut microbiome are marine polysaccharides which are fermentable prebiotics.^([77]) The relative abundance of Bifidobacterium, Lactobacillus, Akkermansia muciniphila, and Faecalibacterium prausnitzii was significantly increased, and the Firmicutes/Bacteroidetes ratio was significantly decreased, along with a reduction in the relative abundance of Desulfovibrio and Helicobacter, in the gut microbial community structure of mice fed the high-fat diet upon supplementation with fucoidan from Sargassum species for 8 weeks. Higher abundance of Akkermansia muciniphila was associated with an improvement in intestinal barrier integrity (increased expression of tight junction proteins: claudin-3, occludin, ZO-1), decreased endotoxemia (lower LPS levels in serum) and decreased systemic and hepatic inflammation.^([79]) Fiber substrates such as alginates and laminarin induced an increase in the production of cecal and fecal SCFA (acetate, propionate, butyrate) in rodent models when fed as fermentable fiber substrates.Fermentable fiber substrates, such as alginates and laminarin, stimulated cecal and fecal SCFA (acetate, propionate and butyrate) production in rodent models. Propionate is a gluconeogenic substrate for colonocytes and is a signal through FFAR3 (GPR41) in the portal vein that inhibits hepatic gluconeogenesis and lowers postprandial glucose excursions. Butyrate is the main energy source for colonocytes and can activate GPR43 (FFAR2) on enteroendocrine L-cells which increases the secretion of PYY and GLP-1, decreases appetite, and improves the insulin response after a meal.^([80,81]) Dahl et al. (2023, n=80 overweight subjects, 12 weeks) found that the supplementation with brown seaweed extract (6g/day) significantly increased the abundances of Bifidobacterium and Akkermansia in fecal microbiota in comparison to placebo group, which achieved antidiabetic effect by gut microbiome, providing direct clinical evidence of the gut microbiome mediated antidiabetic effect of marine polysaccharides.^([82])

Anti-inflammatory and Antioxidant Mechanisms

The anti-inflammatory and antioxidant mechanisms are as follows: Chronic low grade inflammation and oxidative stress are well-known factors – not just outcomes – of T2DM and obesity. This process is termed ‘meta-inflammation’ or ‘metabolic inflammation' and involves chronic activation of innate immune pathways in metabolically active tissues (adipose tissue, liver, pancreatic islets, hypothalamus) due to nutrient excess, lipotoxicity and LPS derived from the gut. The anti-inflammatory and antioxidant properties are unique for marine metabolites as they have the ability of being present in one molecule or in one metabolite class.^([83])

NF-κB Pathway Suppressio

The master transcription factor of inflammatory response is nuclear factor-kappa B (NF-κB) which regulates the expression of TNF-α, IL-1β, IL-6, IL-8, MCP-1, iNOS and COX-2. TLR4 and IKKβ signaling pathways lead to the activation of NF-κB by hyperglycemia, free fatty acids, and LPS. Phlorotannins (dieckol, eckol), fucoxanthin, astaxanthin and the SPMs derived from EPA and DHA (resolvin D1, protectin D1) have all been shown to inhibit NF-κB activation by blocking the phosphorylation of IKKβ, degradation of IκB-α, and NF-κB nuclear translocation in adipocytes, macrophages and pancreatic beta cells.^([85])

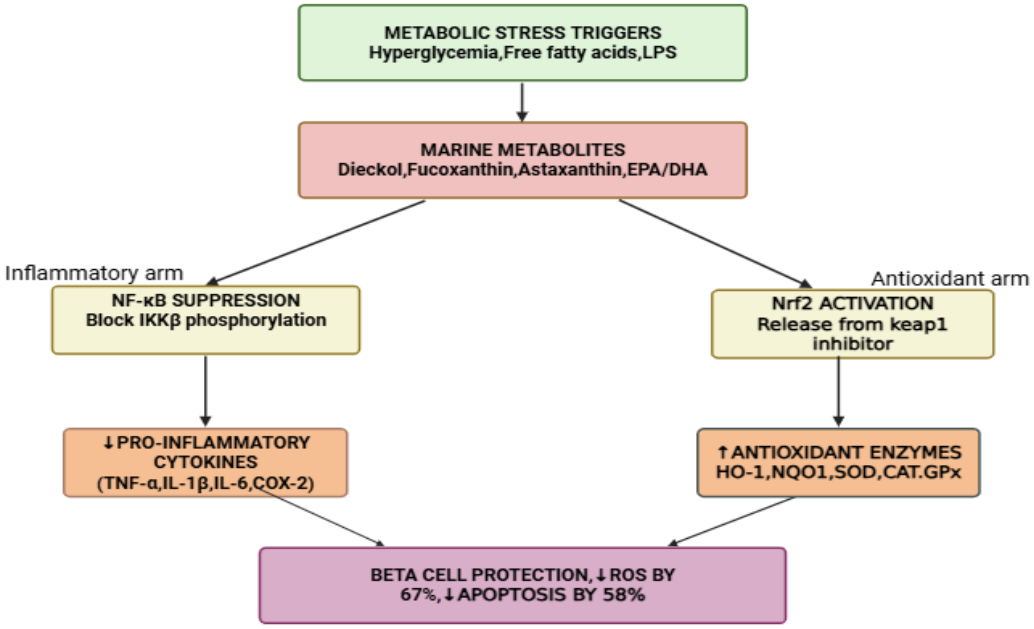


Figure 5 Dual Anti-Inflammatory (NF-κB) and Antioxidant (Nrf2) Pathways Modulated by Marine Metabolites

Nrf2 Activation and Antioxidant Defense

Nuclear factor erythroid 2-related factor 2 (Nrf2) is the master transcriptional activator of the endogenous antioxidant defense system, which regulates the expression of HO-1, NQO1, GCLC, GCLM, SOD, CAT and GPx. Multiple marine metabolites such as fucoxanthin, astaxanthin, phlorotannins and EPA activate the Nrf2 by causing the release of Nrf2 from its inhibitor, Keap1, by electrophilic modification or by inactivating Keap1 upon oxidant exposure.^([86])

A 2022 study by Zou et al. found that dieckol from Ecklonia cava could indeed activate Nrf2/HO-1/NQO1 signaling pathway in high glucose condition, reducing the intracellular accumulation of ROS by 67%, preserving mitochondrial membrane potential and decreasing beta cell apoptosis by 58% compared with high glucose controls. Phlorotannins are dual-acting anti-infla mmatory (NF-κB inhibition) and antioxidant (Nrf2 activation) agents in pancreatic beta cells, indicating the convergent multitarget nature of mechanisms of action of marine metabolites.^([87])

Table 2: Summary of key molecular targets and marine metabolite inhibitors/activators

Molecular Target	Role in Diabetes/Obesity	Marine Metabolite(s)	Effect	Key Reference
α-Glucosidase	Carbohydrate digestion	Dieckol, fucosterol, phlorofucofuroeckol	Competitive inhibition	[22,75]
α-Amylase	Starch hydrolysis	Phlorotannins, fucosterol	Competitive inhibition	[23]
DPP-4	GLP-1 degradation	Eckol, fucosterol, marine peptides	Inhibition	[26,65]
PPAR-γ	Insulin sensitivity, adipogenesis	Fucoxanthin, dieckol, DHA	Activation/modulation	[47,28]
AMPK	Energy sensing, glucose uptake	Fucoxanthin, astaxanthin, DHA	Activation	[48,53]
Pancreatic lipase	Fat absorption	Fucoidan, fucosterol, phlorotannins	Inhibition	[38,75]
NF-κB	Inflammation cascade	Dieckol, EPA, DHA, astaxanthin	Suppression	[85]

Nrf2	Antioxidant defense	Fucoxanthin, astaxanthin, dieckol	Activation	[86,87]
UCP-1	Thermogenesis in WAT	Fucoxanthin	Upregulation	[45]
C/EBP-α/SREBP-1c	Adipogenesis, lipogenesis	Fucoidan, fucosterol, dieckol	Downregulation	[38,76]
PTP1B	Negative insulin signaling	Manzamine alkaloids	Inhibition	[71]

CLINICAL EVIDENCE AND HUMAN STUDIES

Crucial next steps are the translation of the vast preclinical data on marine metabolites to clinical validation. Although there is a wealth of in vitro and animal studies, there are relatively few and less well-designed randomized controlled trials (RCTs) in human subjects (but increasing significantly between 2020 and 2026) .^([88]) Yoshida et al. (2021) conducted a double-blind randomized controlled trial (RCT) for a phase 2 study (n=96 obese subjects with prediabetes, 24 weeks) comparing combined fucoxanthin-enriched seaweed supplement (3 mg/day fucoxanthin) with placebo. The intervention group showed significant improvements with regard to fasting plasma glucose (−9.2 mg/dL, p=0.003), 2-hour post-load glucose (−16.4 mg/dL, p<0.001), HbA1c (−0.32%, p=0.012), HOMA-IR (−0.48), body weight (−2.3 kg, p<0.001), and waist circumference (−2.7 cm, p=0.003) .^([89]) The OMACOR-DM trial was a large Norwegian randomized controlled trial (n=412) that compared high dose omega-3 PUFA supplementation (4 g of EPA+DHA per day) with placebo for 12 months in the glycemic control and cardiovascular risk markers in statin-treated T2DM patients (Dalen et al., 2022). Primary outcomes demonstrated marked decreases in serum triglycerides (−31%), non-HDL cholesterol, high-sensitivity CRP, and urinary albumin-to-creatinine ratio (urinary albumin excretion divided by urinary creatinine) after 12 months, whereas secondary outcomes showed improved insulin sensitivity after 12 months.^([90]) Pan et al. (2023) conducted a systematic review and meta-analysis of 22 RCTs examining the effects of marine polysaccharide supplementation (fucoidan/alginate/carrageenan/laminarin) in T2DM or metabolic syndrome patients (n=1,842, duration 4-52 weeks) and found a clinically meaningful class effect for the marine polysaccharides in terms of a significant reduction in fasting blood glucose (WMD −6.8 mg/dL, 95%CI: −9.2 to −4.4), HbA1c (WMD −0.41%, 95%CI: −0.58 to −0.24), serum triglycerides (WMD −17.3 mg/dL), and BMI (WMD −0.72 kg/m²).^([91]) In metabolic disorders, clinical evidence of astaxanthin's metabolic efficiency is supported by an important meta-analysis of the results of the 2024 RCTs (n=1,127, 17 trials) conducted by Zhu et al., which confirmed significant effects on fasting blood glucose (WMD −3.8 mg/dL), insulin (WMD −1.4 μIU/mL), HOMA-IR (WMD −0.29), total cholesterol (WMD −6.7 mg/dL), LDL-C (WMD −4.9 mg/dL) and CRP (WMD −0.42 mg/L) .^([92])

BIOAVAILABILITY, STABILITY, AND DELIVERY CHALLENGES

Although there is strong preclinical and emerging clinical proof of efficacy, the biotranslation of marine metabolites into oral therapeutics is hindered by a number of bioavailability and gastrointestinal stability and site-specific delivery issues. These are the most important barriers to clinical development.^([93])

PHLOROTANNINS

Despite their strong in vitro activities, phlorotannins are largely hydroxylated an

d therefore highly hydrophilic, can easily be oxidized during extraction and are rapidly phase II conjugated (methylated, sulfated, glucuronidated) after intestinal absorption which results in low oral bioavailability. The plasma levels after oral intake of phlorotannin-rich extracts in rodents indicate that less than 5 % of the ingested dose is bioavailable in its bioactive form.^([94]) To overcome limitations on bioavailability of phlorotannins, nanoencapsulation strategies have developed to be the most common solution. In the rat pharmacokinetic studies, the plasma Cmax and AUC of chitosan nanoparticles containing dieckol (78% encapsulation efficiency, 147–223 nm) were 2.8- and 3.4-fold higher than the plasma levels of the free drug. The intestinal absorption and plasma half-life were further enhanced in the PLGA nanoparticle-encapsulated phlorotannin-rich Ecklonia cava extract from 1.2 to 4.7 hours.^([95])

Sulfated Polysaccharides

The high molecular weight fucoidans (MW > 100 kDa) have low intact oral absorption because they are large and negatively charged at the intestinal pH. Fucoidans depolymerised via chemical, enzymatic or radiation methods produce low-molecular-weight fucoidans (LMWFs, 3–10 kDa) with vastly improved bioavailability and biological activity. The plasma level of LMWF

prepared by the radical depolymerization of a high-MW fucoidan from Saccharina japonica was 4.1 times as high as that of the native high-MW fucoidan after oral gavage in rats and measurable fecal excretion indicated that the plasma level of LMWF was partly due to the presence of intact molecules.^([96])

Carotenoids

Lipophilic carotenoids such as fucoxanthin and astaxanthin should be co-administered with dietary fat to facilitate their micellar solubilisation and intestinal absorption. The fucoxanthin quickly de-acetylated in the intestinal lumen to fucoxanthinol, followed by de-acetylation to produce amarouciaxanthin A in the adipose tissue, both metabolites showing biological activity. In preclinical trials, lipid-based delivery systems (self-emulsifying drug delivery systems, nano-emulsions), cyclodextrin inclusion complexes, and phospholipid complexes have shown 2-5-fold enhancement in the oral bioavailability of fucoxanthin

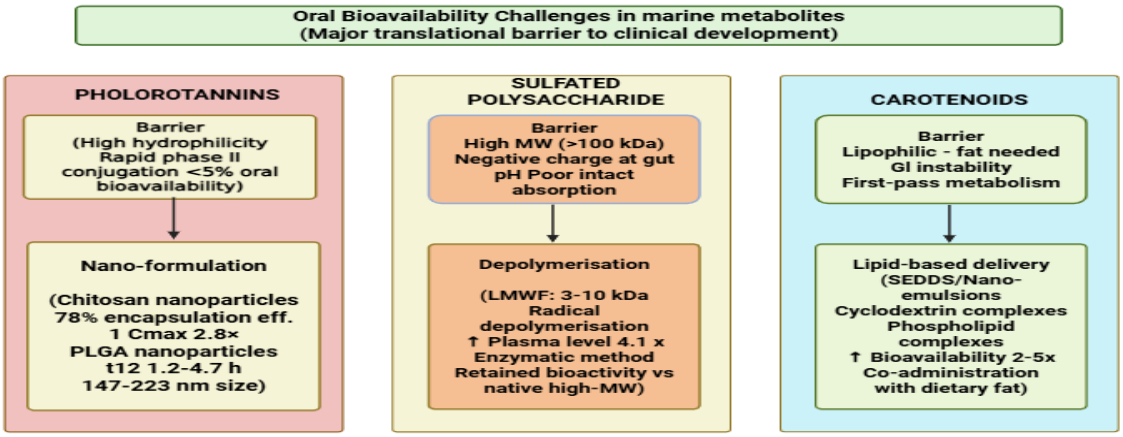


Figure 6: Bioavailability Barriers and Nanoencapsulation Solutions for Key Marine Metabolite Classes

Structure Activity Relationship

To design and optimize drugs rationally, it is crucial to have a detailed knowledge of structure-activity relationships (SARs) of metabolites found in marine sources. Systematic SAR analysis within different compound classes has led to the identification of some general rules that can be applied to the understanding of antidiabetic and anti-obesity potency.^([99]) Phlorotannins (ii): The degree of polymerization of phlorotannin and enzyme inhibitory activity tend to increase with increasing molecular weight up to an optimum of ~1,000-3,500 Da, whereafter a steric effect may be responsible for reduced inhibitory activity. (iii) The DPP-4 inhibitory activity is improved by furanyl ring incorporation (as in the case of eckol-type structures). Enzyme potency is dependent on (iii) free hydroxyl group density (methylation/acetylation decreases potency). (iv) Lower oligomers (dimers, trimers) are good for membrane permeability due to their lipophilicity.^([100]) For sulfated polysaccharides: (i) The alpha-glucosidase and lipase inhibitory activity are positively correlated with the degree of sulfation (DS) up to DS ≈ 0.8–1.2; oversulfation leads to loss of activity and greater procoagulant side effects. (ii) Low molecular weight has the disadvantage of decreasing viscosity-dependent physical mechanisms and the advantage of increased bioavailability. It can be concluded that, in comparison, fucoidan backbones are more effective in antidiabetic activity than galactan backbones in the study conducted in (iii) α-L-fucose backbone.^([101]) For carotenoids: (i) Fucoxanthin's allenic bond is an essential ingredient for UCP-1 inducing activity; synthetic analogues that do not contain this moiety are not thermogenic. (iii) C-4 and C-4' keto groups of astaxanthin give it greater electron accepting capacity and antioxidant activity than beta-carotene or zeaxanthin.

Synergistics Effects and Combination Strategies

Considering the different but complementary mechanisms of action, marine metabolites are promising targets for combination strategies that yield synergistic multitargeted action. The term ‘marine polypharmacology' refers to utilising the wide range of bioactive properties found in marine extracts or combinations of extracts to tackle multiple disease pathways at once.^([103])

Jung et al. (2022) reported synergistic effects (combination index < 1.0 by Chou-Talalay method) in 2022 in vitro study, when fucoxanthin (UCP-1/PPAR-γ mechanism) was combined with dieckol (alpha-glucosidase/DPP-4 mechanism) in a 1:1 molar ratio in adipocyte models with high glucose and high fat. This synergic effect was proposed to be due to complementary mechanistic coverage: the thermogenesis and mitochondrial function effects of fucoxanthin and the enzyme inhibition and NF-κB suppression effects of dieckol.^([104])

The clinical supplement Xanthigen (fucoxantin + pomegranate seed oil) represents a successful combination approach, whereby the PPAR-γ activation effect of the conjugated linolenic acid in Pomegranate seed oil further enhances the UCP-1 and PPAR-γ effects of fucoxantin, resulting in more weight loss than fucoxantin does on its own. Two other omega-3 PUFA mixtures containing

marine polysaccharides have been studied: DHA + alginate was more effective than either agent alone in reducing the postprandial TG excursion, presumably due to the synergistic effect of the activation of PPAR-α by DHA and the delay in lipid absorption caused by alginate's viscosity.^([106])

The development of standardized marine metabolite combinations, with a strong support of robust pharmacokinetic and pharmacodynamic interaction studies, is an attractive approach to powerful multitargeted metabolic intervention with well characterised safety profiles. Multiple classes of bio-active molecules are found naturally together in whole seaweed extracts, such as phlorotannins, fucoidans, fucoxanthin, alginates, omega-3 lipids, and sterols – and so may be particularly effective combinations when whole extracts are optimized for efficacy.^([107])

Future Perspectives

Research Priorities and Future Directions

The points outlined above clearly demonstrate the case for marine metabolites as a valuable and complex chemical toolbox for multi-target diabetes and obesity intervention. But there are a number of research priorities that need to be addressed to realize their clinical potential.^([108]) First, there is the pressing need to conduct large-scale, well-designed randomized controlled trials involving meaningful clinical endpoints (HbA1c, HOMA-IR, cardiovascular risk markers) and standard interventions with adequate sample sizes for all major classes of compounds, but especially for phlorotannins and fucoidans, where human clinical data are sparse. Second, validated biomarkers of marine metabolite exposure (plasma fucoxanthinol, urinary phlorotannin metabolites, serum fucoidan fragments) will allow for dose-exposure-response characterization that is fundamental to the design of clinical trials and to the optimization of dose, for individual patients.^([109]) Third, sustainable marine bioprospecting and responsible aquaculture-based production of biospecies for bioactive products need to be developed to guarantee product security with the increasing clinical use. Commercial scale cultivation of high-phlorotannin Ecklonia species, high-fucoxanthin Undaria and high-astaxanthin Haematococcus species is technically possible and is commercially advanced, with their bioactive content standardized to quality standards.^([110])

Fourth, multi-omics approaches (metabolomics, transcriptomics, gut metagenomics) will be introduced in clinical trials to allow a mechanistic validation of proposed pathways in clinical subjects and discovery of response biomarkers that can predict therapeutic efficacy in individual patients.^([111])

Fifth, advanced delivery systems such as nanoparticle formulations, lipid-based systems, biopolymer matrices and mucoadhesive delivery platforms are further at the clinical-stage of development to translate the remarkable in vitro and animal achieved bioavailability improvements into human pharmacokinetic and pharmacodynamic improvements.^([112])

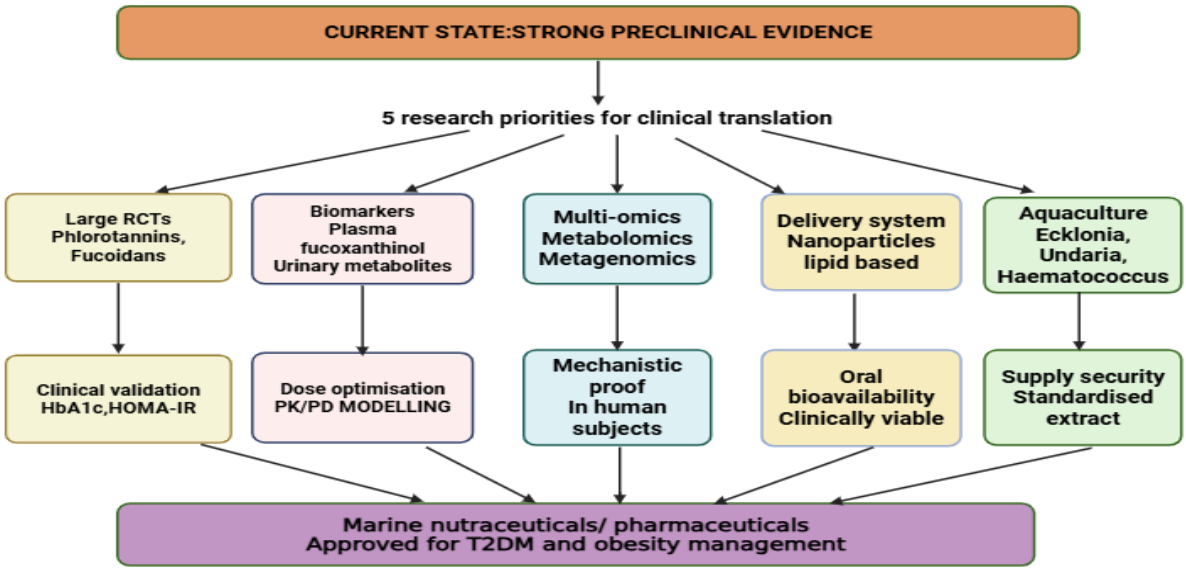


Figure 7 Proposed Research Roadmap for Clinical Translation of Marine Metabolites

CONCLUSION

Marine metabolites are an exceptional pharmaceutical resource to combat the multifactorial and complex etiology of type 2 diabetes mellitus and obesity. The diverse Three classes of compounds were reviewed: compounds herein—phlorotannins, sulfated polysaccharides, carotenoids, omega- All of these 3 PUFAs, bioactive peptides, alkaloids, terpenoids and sterols span the entire landscape of molecular targets known to play a role in metabolic disease: from carbohydrate and fat digestion enzymes to nuclear transcription factors that regulate insulin sensitivity, adipogenesis, inflammation, and oxidative stress, to modulation of the gut microbial ecosystem.^([113,114]) The multi-targeted approach of marine metabolites, in

which a single compound or naturally-occurring compound mixture targets multiple mechanistically different disease pathways, is an attractive model for metabolic disease management, which cannot be matched by traditional single-target pharmacotherapy. There is increasing clinical evidence for the translation of compounds (such as fucoxanthin, astaxanthin, omega-3 PUFAs and marine polysaccharides) from clinical trials into human metabolic disease, although further trials are needed.^([115]) However, issues of oral bioavailability, structural stability of marine extracts, standardization of marine extracts, sustainability in the supply chain and larger clinical trials have yet to be addressed in a systematic fashion. Yet, the advances in extraction and formulation techniques, multi-omics mechanistic validation and the increasing clinical evidence basis makes marine metabolites a prime candidate for natural product innovation in metabolic disease therapeutics. As the largest of all the biomes, the ocean provides even more amazing pharmaceutical opportunities and its promise to help fight the twin epidemics of diabetes and obesity is just in its initial stages.

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