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International Digital Organization for Scientific Research IDOSRJES11200000
IDOSR JOURNAL OF EXPERIMENTAL SCIENCES 11(2): 137-144, 2025.
https://doi.org/10.59298/IDOSR/JES/112.137144

Role of Marine-Derived Bioactive Compounds in Combating Obesity-Linked Diabetes (Diabesity): Emerging Evidence and Future Perspectives

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ABSTRACT

The global rise of obesity and type 2 diabetes mellitus (T2DM), collectively referred to as diabesity, represents one of the most pressing health challenges of the twenty-first century. These intertwined metabolic disorders share common pathophysiological features, including insulin resistance, chronic low-grade inflammation, oxidative stress, and dysregulation of lipid metabolism. While lifestyle modification and pharmacotherapy remain central to management, their limitations underscore the need for alternative and complementary therapeutic strategies. Marine ecosystems, encompassing algae, sponges, fish, mollusks, and microorganisms, have emerged as a vast reservoir of structurally diverse bioactive compounds with promising anti-obesity and antidiabetic properties. Polysaccharides, peptides, polyunsaturated fatty acids, polyphenols, alkaloids, and carotenoids derived from marine organisms exhibit multifaceted mechanisms, including modulation of glucose uptake, enhancement of insulin sensitivity, regulation of adipogenesis, and attenuation of oxidative and inflammatory pathways. This review synthesizes current evidence on marine-derived compounds in the prevention and management of diabesity, highlighting mechanistic insights, preclinical and clinical findings, as well as challenges in translation to clinical practice. Furthermore, future perspectives on bioprospecting, biotechnology-driven synthesis, and personalized nutrition approaches are discussed. Harnessing the therapeutic potential of marine bioresources could open new frontiers in combating diabesity and reducing its global burden.

Keywords: Marine bioactive compounds, diabesity, insulin resistance, obesity, type 2 diabetes mellitus

INTRODUCTION

Obesity and type 2 diabetes mellitus (T2DM) are two interconnected health crises that have reached epidemic proportions globally, posing severe threats to public health and straining healthcare systems[1, 2]. Together, these conditions are often described under the umbrella term "diabesity," emphasizing their intimate pathophysiological and epidemiological link. Diabesity is not merely the coexistence of obesity and diabetes but rather a synergistic interaction in which excess adiposity drives insulin resistance, pancreatic β-cell dysfunction, systemic inflammation, and metabolic dysregulation that culminate in diabetes onset and progression[3–6]. This dual burden is associated with significant morbidity and mortality due to cardiovascular disease, renal impairment, neuropathy, and other metabolic complications. According to the International Diabetes Federation and the World Health Organization, the prevalence of both obesity and diabetes has tripled over the past three decades, with projections suggesting an even steeper rise in low- and middle-income countries undergoing nutritional and lifestyle transitions[7, 8].

The pathophysiology of diabesity is multifaceted, involving a complex interplay between genetic susceptibility, environmental influences, sedentary behavior, and dietary patterns dominated by energy-dense foods. Central to this condition is insulin resistance, in which the responsiveness of peripheral tissues such as muscle, liver, and adipose tissue to insulin action becomes impaired[3, 9, 10]. Adipose tissue in obesity is no longer considered a passive energy storage site but an active endocrine organ that secretes adipokines, cytokines, and chemokines. These bioactive molecules mediate chronic low-grade inflammation, oxidative stress, and metabolic dysfunction, thereby fostering the development of T2DM. Furthermore, obesity promotes lipotoxicity, ectopic fat deposition in the liver and muscle, and mitochondrial dysfunction, all of which exacerbate insulin resistance and β-cell exhaustion[11–13].

Current strategies for the prevention and management of diabesity emphasize lifestyle interventions, including dietary modification, physical activity, and weight reduction. Pharmacological therapies such as metformin, GLP-1 receptor agonists, and SGLT2 inhibitors have demonstrated efficacy, and bariatric surgery offers dramatic metabolic improvement in severe cases[14, 15]. However, these interventions face several limitations, including limited long-term adherence, side effects, high cost, and variable efficacy across individuals. Consequently, there is an urgent need for novel, sustainable, and accessible therapeutic approaches that can complement existing strategies and target multiple pathways involved in diabesity pathogenesis[16].

In this context, marine ecosystems have garnered increasing attention as a largely untapped source of structurally diverse and functionally potent bioactive compounds. The oceans cover more than 70% of the Earth's surface and host a remarkable biodiversity, with organisms that have evolved unique metabolic pathways to adapt to extreme environmental conditions such as high pressure, salinity, and low light[17]. These adaptations often yield secondary metabolites with novel chemical scaffolds and bioactivities not found in terrestrial sources. Marine organisms such as algae, sponges, fish, mollusks, crustaceans, and marine bacteria and fungi produce polysaccharides, peptides, alkaloids, terpenes, phenolics, polyunsaturated fatty acids, and carotenoids with demonstrated potential in modulating key metabolic processes implicated in diabesity[18].

Evidence from preclinical studies indicates that these marine-derived compounds exert antidiabetic and anti-obesity effects through multiple mechanisms. Fucoidan and laminarin from brown algae, for instance, have been shown to regulate glucose metabolism, enhance insulin sensitivity, and suppress adipogenesis. Marine peptides derived from fish protein hydrolysates exhibit inhibitory activity against dipeptidyl peptidase-4 (DPP-4), a therapeutic target in T2DM, while omega-3 polyunsaturated fatty acids from fish oils improve lipid metabolism and reduce inflammation[19]. Carotenoids such as fucoxanthin from brown seaweeds and astaxanthin from microalgae display strong antioxidant and anti-inflammatory activities that contribute to improved metabolic profiles. Additionally, marine polyphenols, though less studied compared to their terrestrial counterparts, have shown promise in modulating oxidative stress and glucose homeostasis[19].

Beyond their bioactivity, marine-derived compounds offer advantages in terms of sustainability and diversity, as advances in biotechnology, aquaculture, and synthetic biology provide avenues for large-scale production. Nonetheless, significant challenges remain in translating these findings into clinical application, including issues of bioavailability, standardization, toxicity evaluation, and regulatory approval[20]. Moreover, while in vitro and animal studies provide compelling mechanistic insights, well-designed clinical trials are relatively scarce, underscoring the need for more rigorous translational research[20].

This review aims to provide a comprehensive overview of the role of marine-derived bioactive compounds in combating diabesity. It discusses the mechanistic insights, preclinical and clinical evidence, and therapeutic potential of key compounds, while also addressing the challenges and future directions in this emerging field. By bridging marine natural product research with metabolic disease management, this review underscores the untapped potential of ocean biodiversity in offering innovative solutions to one of the most pressing health challenges of our time.

2. Marine-Derived Polysaccharides in Diabesity Management

Marine-derived polysaccharides represent one of the most studied classes of bioactive compounds in the context of diabesity due to their abundance, structural complexity, and diverse biological activities[21]. Polysaccharides such as fucoidan, laminarin, alginate, and chitosan are primarily derived from brown algae, seaweed, and crustacean shells, and they have demonstrated multifaceted roles in the modulation of metabolic pathways relevant to both obesity and type 2 diabetes mellitus. Fucoidan, a sulfated polysaccharide predominantly found in brown seaweeds like *Fucus vesiculosus* and *Undaria pinnatifida*, has been reported to improve glucose homeostasis by inhibiting intestinal α-glucosidase and α-amylase activity, thereby reducing postprandial hyperglycemia[21, 22]. Beyond glycemic control, fucoidan exerts anti-inflammatory effects through suppression of pro-inflammatory cytokines such as TNF-α and IL-6, which are elevated in obesity-related insulin resistance.

Laminarin, another β-glucan-rich polysaccharide from brown algae, plays a significant role in modulating gut microbiota composition. Emerging evidence highlights the gut microbiome as a critical mediator of diabesity, and laminarin supplementation has been shown to promote the growth of beneficial short-chain fatty acid-producing bacteria, thereby enhancing insulin sensitivity and reducing systemic inflammation. Similarly, alginates derived from brown algae act as dietary fibers that delay gastric emptying, increase satiety, and lower energy intake, contributing to weight management[23, 24]. Additionally, alginates can form viscous gels in the gastrointestinal tract, reducing glucose absorption and lipid bioavailability.

Chitosan, derived from the deacetylation of chitin found in crustacean shells, has garnered interest for its fat-binding capacity and hypolipidemic effects[25]. Studies suggest that chitosan can reduce body weight gain by limiting intestinal fat absorption and modulating lipid metabolism. It also influences adipogenesis by downregulating key transcription factors such as PPARγ and C/EBPα, thereby inhibiting the differentiation of preadipocytes into mature adipocytes. Moreover, chitosan oligosaccharides, which are more readily absorbed

due to their lower molecular weight, have demonstrated antioxidant and anti-inflammatory effects that further contribute to improved metabolic health[26, 27].

Collectively, these polysaccharides exert synergistic effects by targeting multiple aspects of diabesity, including glucose absorption, lipid metabolism, inflammation, and gut microbiota modulation. However, challenges remain regarding the standardization of extraction processes, structural characterization, and clinical validation of these compounds. Future research should focus on optimizing formulation strategies to enhance their bioavailability and evaluating their long-term efficacy in human trials[28]. Nonetheless, marine polysaccharides represent a promising class of natural therapeutics for the integrated management of obesity-linked diabetes.

3. Marine Peptides and Proteins: Modulators of Insulin Sensitivity and Satiety

Marine-derived peptides and proteins, particularly those obtained from fish, mollusks, and algae, have emerged as potent modulators of insulin sensitivity and appetite regulation. Unlike polysaccharides, these bioactive compounds often act directly on hormonal and enzymatic pathways central to glucose metabolism and energy balance[29]. Fish protein hydrolysates, obtained through enzymatic digestion of fish muscle or by-products, yield bioactive peptides that exhibit antihyperglycemic, antihypertensive, and anti-inflammatory effects. One of their key mechanisms is the inhibition of dipeptidyl peptidase-4 (DPP-4), an enzyme responsible for the degradation of incretin hormones such as glucagon-like peptide-1 (GLP-1)[30]. By inhibiting DPP-4 activity, marine peptides prolong the half-life of GLP-1, enhancing insulin secretion, reducing glucagon release, and ultimately improving postprandial glucose control.

GLP-1 modulation is particularly relevant in the management of diabesity because it integrates satiety signaling with glucose regulation. Several studies have demonstrated that peptides derived from marine sources stimulate endogenous GLP-1 secretion from enteroendocrine L-cells, thereby promoting satiety and reducing food intake[31]. This dual action of supporting both insulin sensitivity and appetite regulation provides a unique advantage over many conventional therapies, which often target a single metabolic pathway. Furthermore, peptides such as those from salmon and sardine protein hydrolysates have been shown to activate the AMP-activated protein kinase (AMPK) pathway in skeletal muscle, leading to increased glucose uptake and improved insulin sensitivity[32].

Marine peptides also exhibit anti-inflammatory effects, which are vital in counteracting the chronic low-grade inflammation that underpins obesity and insulin resistance. By suppressing NF-κB activation and reducing levels of inflammatory mediators such as TNF-α and IL-1β, these peptides help restore metabolic balance. Additionally, some peptides act as antioxidants, scavenging free radicals and protecting pancreatic β-cells from oxidative damage, thus preserving insulin secretion capacity[33]. Beyond fish, algae-derived proteins and peptides are being increasingly explored for their hypoglycemic and satiety-promoting effects, with spirulina and chlorella proteins showing promising results in preclinical models.

Despite these encouraging findings, the translation of marine peptides into therapeutic or nutraceutical applications faces challenges[34]. Issues such as peptide stability during digestion, bioavailability, and large-scale production need to be addressed. Advances in encapsulation technologies and peptide engineering hold potential to overcome these barriers. Overall, marine peptides and proteins offer a multifaceted approach to diabesity management by targeting insulin sensitivity, appetite regulation, and inflammation, making them attractive candidates for further development[35].

4. Marine Polyunsaturated Fatty Acids: Beyond Lipid Lowering

Polyunsaturated fatty acids (PUFAs), particularly omega-3 fatty acids such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are among the most extensively studied marine-derived compounds due to their well-documented cardiovascular and metabolic benefits. These fatty acids are abundant in oily fish, krill, and certain types of algae, and they have been shown to exert profound effects beyond simple lipid lowering, influencing multiple pathways implicated in diabesity[36]. EPA and DHA improve lipid profiles by reducing plasma triglycerides, modulating cholesterol distribution, and enhancing high-density lipoprotein functionality. However, their influence extends far deeper, affecting adipokine secretion, inflammation, and insulin signaling[36–38].

One critical mechanism of action involves the modulation of adipose tissue function. In obesity, adipose tissue often exhibits hypertrophy, hypoxia, and increased secretion of pro-inflammatory adipokines such as leptin and resistin. Omega-3 PUFAs counteract these effects by upregulating adiponectin, an insulin-sensitizing adipokine, while simultaneously reducing the secretion of inflammatory mediators[36]. This shift in adipokine balance contributes to improved insulin sensitivity and reduced systemic inflammation. Additionally, omega-3 fatty acids activate AMPK and peroxisome proliferator-activated receptors (PPARs), thereby promoting fatty acid oxidation, reducing hepatic lipogenesis, and enhancing glucose utilization[36].

The anti-inflammatory effects of EPA and DHA are particularly relevant in diabesity. These fatty acids serve as precursors for specialized pro-resolving mediators (SPMs), including resolvins, protectins, and maresins, which actively resolve inflammation rather than merely suppressing it. By limiting chronic low-grade inflammation, they help alleviate insulin resistance and protect pancreatic β-cell function. Furthermore, EPA and DHA

improve endothelial function, reduce oxidative stress, and modulate gut microbiota composition, all of which contribute to better metabolic outcomes[39].

Beyond their direct metabolic effects, omega-3 PUFAs have been associated with appetite regulation and reduced ectopic fat deposition. Studies suggest that supplementation reduces hepatic steatosis, a common feature of diabesity, by limiting triglyceride accumulation in the liver. Moreover, by altering membrane fluidity in insulin-sensitive tissues, omega-3 fatty acids enhance insulin receptor signaling efficiency[40]. Clinical trials have demonstrated variable outcomes, with some showing significant improvements in glycemic control and body weight, while others report modest effects, highlighting the need for personalized approaches and dose optimization[40].

Overall, marine-derived omega-3 fatty acids represent a cornerstone in the nutritional and therapeutic management of diabesity. Their pleiotropic effects, spanning lipid metabolism, inflammation, adipokine regulation, and glucose homeostasis, underscore their value beyond traditional lipid lowering. Continued research into optimal formulations, synergistic combinations with other bioactive compounds, and personalized supplementation strategies will be critical in harnessing their full potential.

5. Carotenoids and Polyphenols from Marine Sources

Carotenoids and polyphenols derived from marine organisms constitute a diverse group of bioactive compounds with potent antioxidant, anti-inflammatory, and anti-obesity properties, making them particularly relevant in the context of diabesity[41]. Among the most notable carotenoids are fucoxanthin, a brown seaweed pigment, and astaxanthin, commonly found in microalgae, krill, and crustaceans. Both compounds have demonstrated promising effects in preclinical and clinical studies by targeting multiple metabolic pathways. Fucoxanthin, for instance, enhances energy expenditure by upregulating uncoupling protein 1 (UCP1) expression in white adipose tissue, thereby promoting the browning of fat and increasing thermogenesis[42]. This mechanism is crucial for reducing adiposity in obese individuals. Additionally, fucoxanthin has been shown to reduce plasma glucose and insulin levels, improve lipid profiles, and decrease hepatic fat accumulation, collectively supporting its role as an anti-obesity and antidiabetic agent[43].

Astaxanthin, on the other hand, is renowned for its powerful antioxidant capacity, surpassing many terrestrial carotenoids in scavenging reactive oxygen species. By reducing oxidative stress, astaxanthin protects pancreatic β-cells, improves insulin secretion, and alleviates inflammation in adipose tissue. Its effects extend to cardiovascular protection, with studies demonstrating improved endothelial function and lipid metabolism in individuals with metabolic syndrome[43]. Astaxanthin's unique structure allows it to embed within cellular membranes, providing stability against oxidative damage and contributing to its efficacy in metabolic regulation[43].

Marine polyphenols, particularly phlorotannins derived from brown algae, also exhibit significant anti-diabetic and anti-obesity activities[44]. These compounds inhibit carbohydrate-digesting enzymes such as α-amylase and α-glucosidase, reducing postprandial hyperglycemia. Moreover, phlorotannins possess strong antioxidant and anti-inflammatory properties, which help mitigate the oxidative and inflammatory stress central to diabesity. They also modulate signaling pathways involved in adipogenesis, including PPARγ and C/EBPα, thereby inhibiting fat cell differentiation and lipid accumulation[45]. Emerging evidence suggests that phlorotannins may positively influence gut microbiota composition, further enhancing metabolic health.

Collectively, carotenoids and polyphenols from marine sources offer a complementary approach to diabesity management by simultaneously addressing oxidative stress, inflammation, glucose metabolism, and adiposity. However, challenges such as low bioavailability, instability during processing, and variability in compound content depending on marine species and environmental conditions remain significant barriers to clinical translation[46]. Innovative delivery systems such as nanoencapsulation and co-supplementation with synergistic compounds are being explored to overcome these limitations. As research progresses, marine carotenoids and polyphenols are poised to become key players in the nutraceutical and pharmaceutical arsenal against diabesity[47].

6. Translational Challenges and Future Directions

While preclinical and early clinical studies provide compelling evidence for the anti-obesity and antidiabetic potential of marine-derived bioactive compounds, translating these findings into practical therapeutic or nutraceutical solutions faces several hurdles. One of the foremost challenges is bioavailability[48]. Many marine polysaccharides, peptides, carotenoids, and polyphenols exhibit poor absorption, rapid metabolism, or degradation in the gastrointestinal tract, limiting their systemic efficacy. Innovative formulation strategies, including microencapsulation, liposomal delivery, and nanoemulsions, are being developed to enhance stability, absorption, and targeted delivery[48, 49].

Another challenge lies in the variability of natural sources. The chemical composition of marine bioactives can fluctuate depending on species, habitat, season, and extraction methods, complicating standardization and reproducibility. Advances in biotechnology, particularly synthetic biology and metabolic engineering, offer promising avenues to overcome these limitations by enabling the controlled production of bioactive compounds

in microbial or algal platforms[50]. Such approaches not only ensure consistency but also reduce reliance on harvesting natural marine resources, thereby promoting sustainability[50].

Toxicity and safety evaluation represent additional considerations. While many marine compounds are generally regarded as safe, some may exert dose-dependent toxic effects or interact with medications commonly used in diabesity management, such as metformin or statins. Comprehensive toxicological assessments and pharmacokinetic studies are therefore essential prior to clinical adoption[51]. Furthermore, regulatory pathways for approval of marine-derived nutraceuticals and pharmaceuticals remain complex and fragmented across jurisdictions, delaying translation to clinical use.

Future research should also prioritize personalized nutrition and medicine approaches. Diabesity is a heterogeneous condition influenced by genetics, lifestyle, gut microbiota, and environmental factors, meaning that therapeutic efficacy may vary widely among individuals. Integrating omics technologies such as genomics, metabolomics, and microbiome profiling with marine bioactive interventions could pave the way for precision strategies tailored to individual metabolic profiles.

Finally, there is a critical need for well-designed, large-scale clinical trials to validate the efficacy and safety of marine-derived compounds in diabesity management. While preclinical data are robust, human evidence remains limited and inconsistent. Collaborative efforts between academia, industry, and regulatory agencies will be vital in accelerating clinical translation. In the future, the convergence of marine biotechnology, personalized nutrition, and functional food innovation could transform the management of diabesity, turning the oceans into a sustainable reservoir of therapeutic solutions.

CONCLUSION

Marine-derived bioactive compounds represent a promising frontier in the fight against diabesity. Their structural diversity and multifunctional mechanisms of action provide a unique advantage over conventional therapies that often target singular pathways. While substantial progress has been made in elucidating their biological effects, much remains to be done in terms of clinical validation, standardization, and large-scale production. Integrating marine biotechnology with advances in nutraceutical development and personalized medicine may pave the way for novel interventions to reduce the global burden of diabesity.

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CITE AS: Masika Anna Mahinda (2025). Role of Marine-Derived Bioactive Compounds in Combating Obesity-Linked Diabetes (Diabesity): Emerging Evidence and Future Perspectives. IDOSR JOURNAL OF EXPERIMENTAL SCIENCES 11(2): 137-144. https://doi.org/10.59298/IDOSR/JES/112.137144