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"MARINE ANIMAL-DERIVED BIOACTIVE PEPTIDES: A COMPREHENSIVE REVIEW OF MECHANISMS IN OXIDATIVE STRESS AND HYPERGLYCEMIA MANAGEMENT"

Annu Sharma[1*], Dr. Meena Godha[1]

[1]Department of Zoology, Jaipur National University, Jaipur, Rajasthan, India

***Corresponding Author**

Annu Sharma

Research Scholar

Department of Zoology

Jaipur National University, Jaipur, Rajasthan, India

E-mail: akshitaannusharma@gmail.com

ABSTRACT

Bioactive peptides derived from marine animals have emerged as promising therapeutic agents for managing metabolic disorders, particularly oxidative stress and hyperglycemia associated with diabetes. Specifically, this review synthesizes evidence from preclinical and in vitro studies on peptides extracted from sponges, mollusks, and fish. These peptides show multiple biological activities: they inhibit lipid peroxidation, enhance insulin sensitivity, and exert antioxidant effects by upregulating enzymes such as superoxide dismutase, catalase, and glutathione peroxidase. In experimental models induced by diabetogenic factors, peptide-treated groups show improvements compared to controls, including reduced fasting blood glucose, less oxidative damage, and preserved tissue architecture in the pancreas and liver. Furthermore, mechanistic insights reveal interactions with key pathways like Nrf2/Keap1 and AMPK, supporting their hypoglycemic and cytoprotective roles. Collectively, these findings position marine bioactive peptides as a natural alternative to synthetic antidiabetic drugs, highlighting the need for their clinical application in diabetes management.

KEYWORDS: - Marine bioactive peptides; Oxidative stress; Hyperglycemia; Antioxidant activity; Experimental animals; Diabetes mellitus

1. INTRODUCTION

As of 2024, more than 800 million adults worldwide are living with diabetes—a fourfold increase since 1990—and this figure is projected to reach 853 million by 2050. In high-burden nations such as India (89.8 million cases, 10.5%) and China (148 million, 11.9%), the prevalence exceeds 10%, thereby imposing a significant burden on healthcare systems in low- and middle-income regions [1]. Elevated blood glucose levels induce the generation of Reactive Oxygen Species (ROS) via glucose auto-oxidation, the polyol/hexosamine pathways, and Advanced Glycation End-products (AGEs); this process subsequently impairs insulin signaling through the activation of JNK/IKKβ and NF-κB-mediated inflammation. Pancreatic β-cells, which possess limited antioxidant reserves, become susceptible to mitochondrial damage and apoptosis, thereby compromising insulin secretion [2]. According to preclinical evidence, this interplay underscores the critical need for dual-action agents—such as marine peptides—that function as both antioxidants and anti-

hyperglycemic agents by scavenging ROS and upregulating antioxidant enzymes (e.g., SOD, CAT, and GPx). While conventional pharmaceuticals effectively regulate glucose levels, they often fail to address the underlying oxidative stress, a limitation that has spurred growing interest in the therapeutic potential of naturally derived compounds.

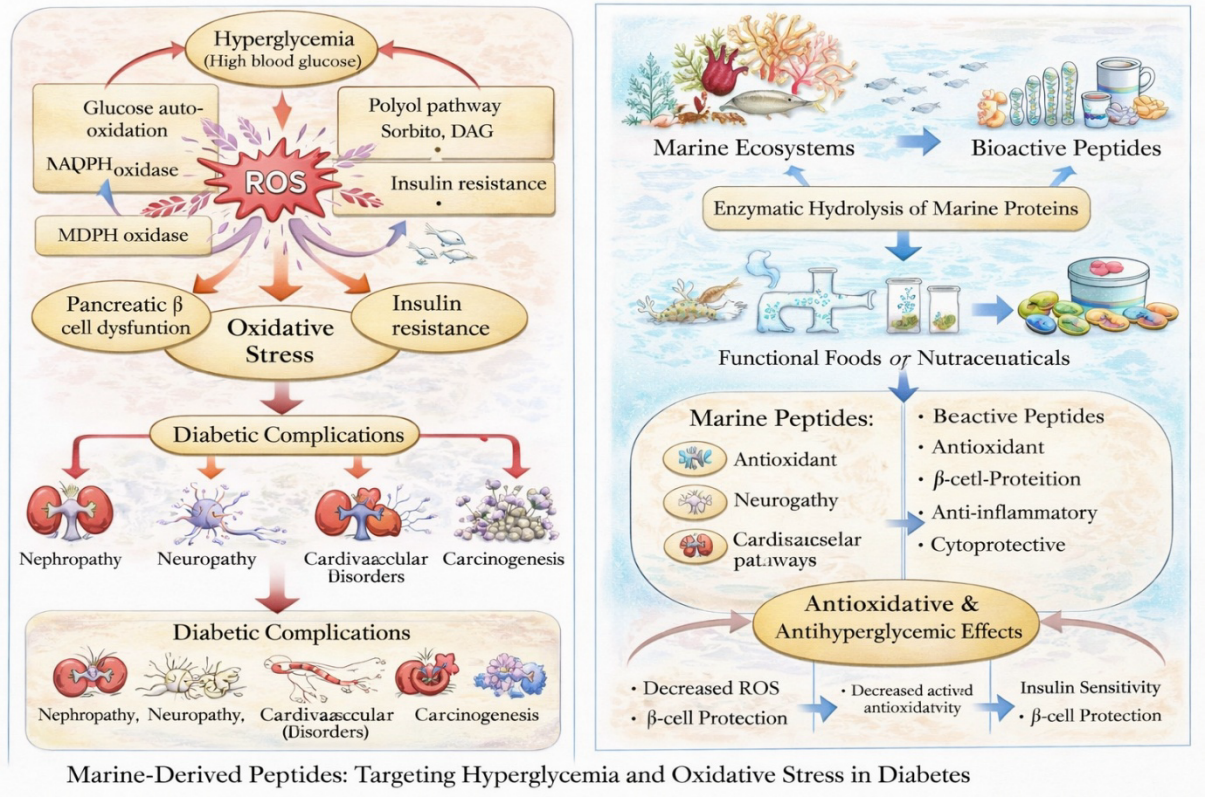

Figure 1: Marine Bioactive Peptides in Diabetes and Oxidative Stress Management

Oxidative stress and elevated blood glucose levels are two closely interrelated pathological conditions that play a pivotal role in the onset and progression of metabolic disorders, particularly diabetes. Persistently high blood glucose levels lead to the excessive generation of reactive oxygen species (ROS), which overwhelm the body's endogenous antioxidant defense system, thereby inflicting oxidative damage upon lipids, proteins, and nucleic acids. This imbalance contributes to insulin resistance, beta-cell dysfunction, and chronic complications such as nephropathy, neuropathy, and cardiovascular disorders. Conventional anti-diabetic medications are effective in controlling blood glucose levels; however, their long-term use is often associated with adverse side effects, diminished antioxidant protection, and a significant economic burden [3]. Consequently, there is growing scientific interest in identifying natural, safe, and multifunctional therapeutic agents capable of simultaneously mitigating both elevated blood glucose levels and oxidative stress.

Marine ecosystems, owing to their immense biodiversity and unique environmental pressures, serve as rich repositories of biologically active compounds. Marine organisms—including fish, mollusks, crustaceans, echinoderms, and cnidarians—produce a diverse array of biologically

active peptides that exhibit antioxidant, anti-diabetic, anti-inflammatory, and cytoprotective properties. These peptides, released through the enzymatic hydrolysis or digestion of marine proteins, have emerged as promising candidates for the development of novel functional foods and nutraceuticals [4].

1.2. Oxidative Mechanisms and Antioxidant Therapy in Diabetes

Oxidative stress occurs when the production of Reactive Oxygen Species (ROS) overwhelms the capacity of antioxidant defense mechanisms. In diabetic conditions, chronic hyperglycemia accelerates ROS generation through several pathways, including glucose auto-oxidation, protein glycation, and the activation of the polyol and hexosamine pathways. Elevated ROS levels impair insulin signaling and damage pancreatic β-cells, which are particularly vulnerable due to their relatively low content of antioxidant enzymes [5].

Animal models of diabetes have clearly demonstrated that oxidative stress acts as both a cause and an effect of hyperglycemia. Reduced activities of antioxidant enzymes—such as Superoxide Dismutase (SOD), Catalase (CAT), and Glutathione Peroxidase (GPx)—accompanied by increased lipid peroxidation, are commonly observed in diabetic animals. Therefore, therapeutic strategies that integrate blood glucose control with antioxidant defense are considered highly beneficial in preventing the progression of the disease [6].

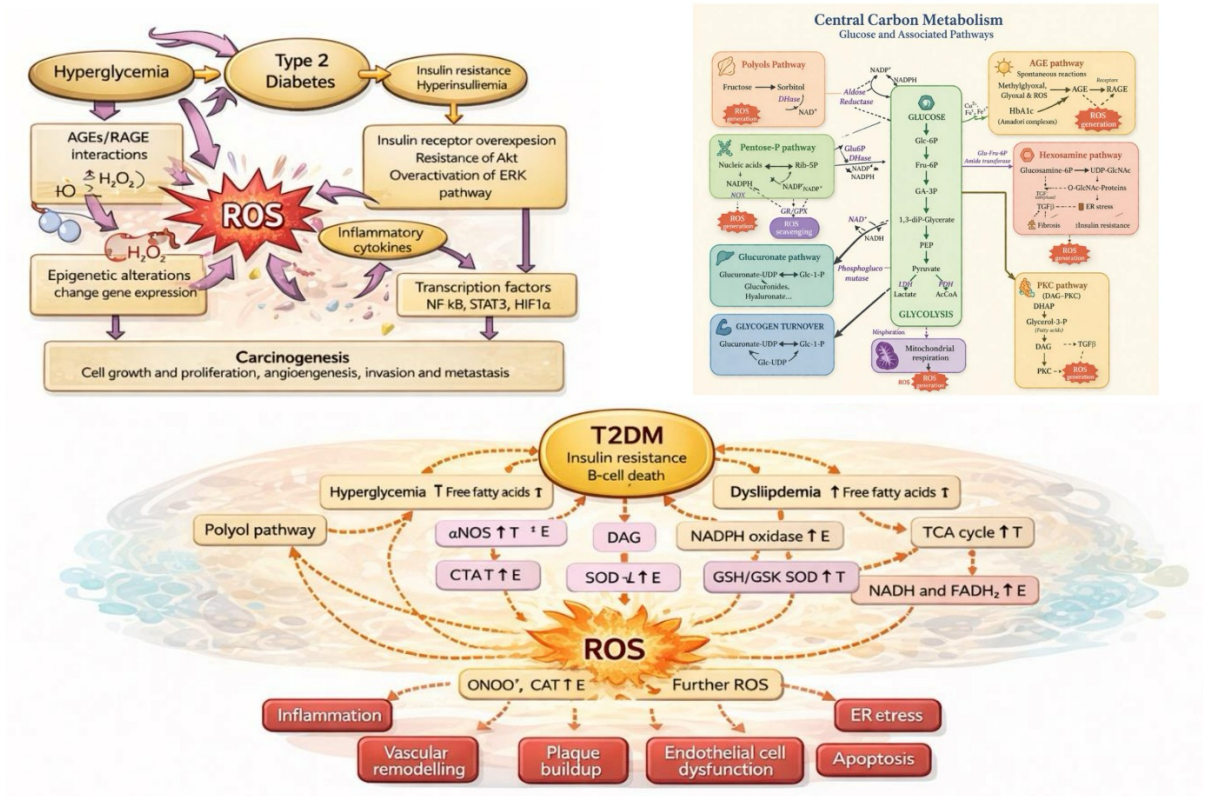

Figure 2: Oxidative Stress Networks Linking Hyperglycemia to Diabetic Complications

1.3. Marine Peptides as Modulators of Oxidative Stress in Diabetes

Bioactive peptides are short sequences of amino acids that exert specific biological effects extending beyond basic nutrition. In marine organisms, these peptides are encoded within parent

proteins and are released during enzymatic hydrolysis, fermentation, or gastrointestinal digestion. The structural diversity of marine peptides—characterized by low molecular weight, unique amino acid composition, and high stability—contributes to their remarkable biological activities [7].

Peptides derived from marine organisms are reported to exhibit potent free radical-scavenging capabilities, metal chelation, inhibition of lipid peroxidation, and enhancement of endogenous antioxidant enzymes. Furthermore, several peptides have demonstrated anti-diabetic properties by inhibiting carbohydrate-digesting enzymes such as α-amylase and α-glucosidase, improving insulin sensitivity, and protecting pancreatic β-cells from oxidative damage [8]. These multifaceted properties make marine peptides highly attractive for managing the oxidative stress associated with diabetes.

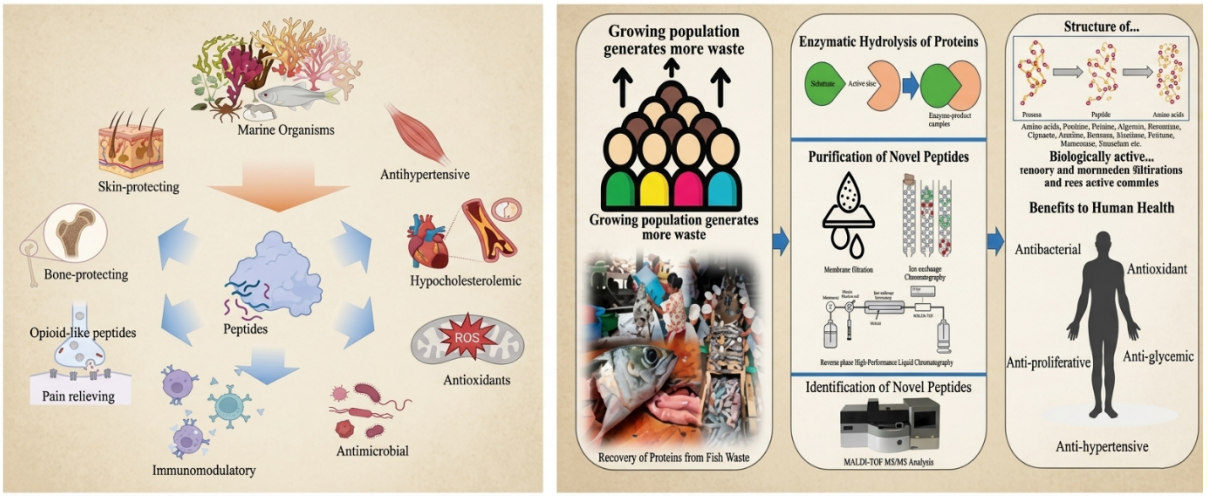

Figure 3: Sustainable Production of Bioactive Peptides from Marine Resources

1.4. Animal-Based Assessment of Marine Peptides in Diabetes

Experimental animal models play a pivotal role in understanding the biological effects and therapeutic potential of marine bioactive peptides. Chemical agents such as streptozotocin and alloxan are widely utilized to induce hyperglycemia and oxidative stress in rodents, thereby closely mimicking human diabetic conditions [9]. These models facilitate the systematic evaluation of biochemical, physiological, and histopathological parameters following the administration of peptides.

Studies employing experimental animals provide valuable insights into the dose-response relationships, mechanisms of action, and tissue-specific protective effects of marine peptides. Observations derived from such models have demonstrated significant reductions in blood glucose levels, the restoration of antioxidant enzyme activities, and the protection of vital organs such as the pancreas, liver, and kidneys. Thus, animal-based studies serve as an essential bridge between in vitro findings and potential clinical applications.

1.5. Therapeutic and Sustainable Benefits of Marine-Derived Peptides

Compared to synthetic drugs, biologically active peptides derived from marine animals offer numerous advantages. They are generally considered safe, biodegradable, and less likely to induce toxic side effects. Their dual antioxidant and anti-hyperglycemic activities address the multifactorial nature of diabetes more effectively than single-target drugs [10]. Furthermore,

utilizing marine by-products—such as fish skin, scales, and shells—for peptide extraction supports sustainability and value addition within the seafood industry.

Table 1: Marine-Derived Peptides and Their Antioxidant and Antidiabetic Roles

Marine Source	Major Peptide Activity	Reported Biological Effects	Reference
Fish (muscle, skin)	Antioxidant peptides	Free radical scavenging, reduced lipid peroxidation	[11]
Mollusks (squid, oyster)	Antidiabetic peptides	α-glycosidase inhibition, glucose regulation	[12]
Crustaceans (shrimp, crab)	Bio functional peptides	Enhanced antioxidant enzymes, cytoprotection	[13]
Echinoderms (sea cucumber)	Therapeutic peptides	Improved insulin sensitivity, tissue protection	[14]

1.6. Protective Effects of Marine Bioactive Peptides in Diabetes Models

Despite growing evidence supporting the therapeutic potential of marine bioactive peptides, systematic in vivo studies focusing on their combined protective effects against oxidative stress and hyperglycemia remain scarce. Understanding their mechanisms of action in experimental animal models is essential for validating their efficacy and safety. Therefore, this study is designed to evaluate the protective role of bioactive peptides derived from marine animals against oxidative stress and hyperglycemia, with particular emphasis on biochemical, antioxidant, and histopathological parameters [15]. This research is expected to contribute significantly to the development of natural marine-based therapies for the management of diabetes and associated oxidative stress-related disorders.

1.7. Antioxidant and Antihyperglycemic Potential of Marine Peptides

Bioactive peptides derived from marine animals have attracted increasing research interest due to their antioxidant and anti-diabetic potential [16]. It has been reported that bioactive peptides derived from marine fish proteins possess potent free radical-scavenging activity and play a pivotal role in mitigating oxidative stress associated with metabolic disorders. Their study emphasized that the unique amino acid composition of marine peptides—specifically the presence of hydrophobic and aromatic residues—enhances their antioxidant capacity.

Hiroyuki Sato and Masashi Yoshi-Stark (2014) demonstrated that peptides derived from fish muscle and skin significantly enhanced the activity of antioxidant enzymes—such as superoxide dismutase and catalase—in animal models. Their findings indicated that marine peptides can effectively protect pancreatic β-cells from oxidative damage induced by chronic hyperglycemia. This protective mechanism was attributed to reduced lipid peroxidation and an improved cellular redox balance [17].

Sung-Hoon Lee, Min-Jung Kim, and Kyung-Hoon Shin (2015) investigated the anti-diabetic potential of marine peptides extracted from squid and oyster proteins. In streptozotocin-induced diabetic rats, *in vivo* studies demonstrated a significant reduction in fasting blood glucose levels and improved insulin sensitivity. The authors highlighted that these peptides inhibit carbohydrate-

hydrolyzing enzymes—such as α-amylase and α-glucosidase—thereby regulating postprandial glucose levels [18].

María Dolores Hernández-Ledesma, Beatriz del Mar Contreras, and Amparo Recio (2016) provided comprehensive evidence regarding the multifaceted roles of marine bioactive peptides. Their study emphasized that marine peptides possess a dual function, simultaneously modulating both oxidative stress and glucose metabolism. They further suggested that these peptides could be developed into functional food ingredients or nutraceuticals for managing diabetes-related complications [19].

Jong-Hoon Kim and Young-Suk Kim (2017) investigated peptides derived from sea cucumbers and reported significant anti-hyperglycemic and antioxidant effects in animal models. Their study indicated increased glutathione levels and decreased malondialdehyde concentrations in treated animals, reflecting a reduction in oxidative stress. The authors proposed that marine peptides enhance insulin signaling pathways and mitochondrial function, thereby contributing to improved glucose homeostasis [20]. Ravinder Kumar, Anjali Sharma, and Prakash Chandra (2018) investigated peptides derived from mollusks and observed significant protective effects against oxidative stress in diabetic rats. Their research demonstrated the restoration of antioxidant enzyme levels as well as histological improvements in pancreatic and hepatic tissues. This study highlighted the therapeutic significance of marine peptides in preventing organ damage associated with diabetes [21].

Jian-Wei Wang, Li Zhang, and Shu-Li Chen (2019) reported that low-molecular-weight peptides derived from fish protein hydrolysates exhibited superior antioxidant and glucose-lowering effects compared to larger peptide fractions. Their experimental results supported the hypothesis that peptide size and sequence play a pivotal role in biological activity [22].

Most recently, Nora Martínez-Álvarez and María del Carmen Gómez-Guillén (2020) emphasized the sustainability aspect of marine peptide research. They demonstrated that bioactive peptides extracted from marine processing by-products not only exhibit potent antioxidant and anti-diabetic activities but also promote value addition to marine resources. Their study reinforced the potential for utilizing marine peptides as safe and environmentally friendly therapeutic agents [23]. Overall, the reviewed literature clearly indicates that bioactive peptides derived from marine animals possess significant antioxidant and anti-hyperglycemic properties. Previous studies have demonstrated improved blood glucose control and enhanced antioxidant status in experimental animals.

2. COMPARATIVE STUDY OF MARINE PEPTIDES IN DIABETIC ANIMAL MODELS

In recent studies, the evaluation of biologically active peptides derived from marine animals—specifically regarding their protective effects against oxidative stress and hyperglycemia—has been extensively explored through experimental, controlled, and comparative research designs. These studies typically assess anti-hyperglycemic and antioxidant capabilities through comprehensive biochemical, enzymatic, and histopathological analyses. To quantify efficacy, a dose-dependent methodology is commonly employed, involving rigorous comparisons among

normal control, diabetic control, and treatment groups. Contemporary research trends prioritize reproducibility under standardized laboratory conditions, reliability, and systematic evaluation, thereby ensuring robust and translatable findings [24].

2.1. Experimental Animals and Housing Conditions

In vivo studies evaluating marine-derived bioactive peptides typically utilize healthy adult Wistar albino rats weighing 150–200 g, generally procured from certified animal facilities. These animals are acclimatized for one week in polypropylene cages under standardized conditions, including controlled temperature (typically 22–25°C), 50–60% humidity, and a 12-hour light-dark cycle. To minimize variables, standard pelleted feed and water are provided ad libitum. Experimental protocols strictly adhere to the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) and obtain mandatory prior approval from institutional animal ethics committees, thereby ensuring ethical rigor and reproducibility [25].

Table 2: Experimental Animal Model and Ethical Compliance Details

Parameter	Specification	Reference
Animal Model	Wistar albino rats (either sex)	[26,27,28,29,30]
Body Weight Range	150–200 g	[26,27,28,29,30]
Source	Certified animal breeding facility	[26,27,28,29,30]
Acclimatization Period	7 days prior to experimentation	[26,27,28,29,30]
Housing Conditions	Polypropylene cages under controlled environment	[26,27,28,29,30]
Temperature	22–25°C	[26,27,28,29,30]
Relative Humidity	50–60%	[26,27,28,29,30]
Light–Dark Cycle	12-hour light / 12-hour dark cycle	[26,27,28,29,30]
Diet	Standard pellet diet (ad libitum)	[26,27,28,29,30]
Water Supply	Provided ad libitum	[26,27,28,29,30]
Ethical Guidelines	Compliance with CPCSEA guidelines	[26,27,28,29,30]
Approval Requirement	Institutional Animal Ethics Committee (IAEC) approval mandatory	[26,27,28,29,30]
Experimental Considerations	Ensures reproducibility, minimizes environmental variability, and maintains animal welfare standards	[26,27,28,29,30]

2.2. Bioprocessing Strategies for Marine-Derived Peptides

Bioactive peptides derived from marine animals are typically produced from raw materials such as fish muscle or skin. These materials are first thoroughly washed, cut into small pieces, and subjected to enzymatic hydrolysis using food-grade proteolytic enzymes, such as pepsin or alcalase. To maximize both peptide yield and bioactivity, this hydrolysis is conducted under

optimal conditions regarding pH, temperature, and incubation time. This approach reflects current trends toward efficient, scalable, and green extraction technologies.

The resulting protein hydrolysate mixture is centrifuged and filtered to remove insoluble residues. Subsequently, low-molecular-weight peptide fractions are further purified using membrane ultrafiltration techniques. This approach allows for separation based on molecular weight range and is widely regarded as a cost-effective and productive alternative to conventional chromatographic methods. The purified peptide extract is then freeze-dried and stored at –20°C until use; concurrently, the protein content is quantified using standard biochemical assays to ensure batch-to-batch consistency and to support accurate dose-response assessments in subsequent biological evaluations [31].

2.3. Experimental Diabetes Induction via STZ Model

Following an overnight fast, hyperglycemia is typically induced in experimental animal models by administering a single intraperitoneal injection of Streptozotocin (STZ) dissolved in freshly prepared citrate buffer (pH 4.5). Approximately 72 hours later, fasting blood glucose levels are measured using a glucometer; animals exhibiting glucose levels exceeding 250 mg/dL are classified as diabetic and included in the study. This STZ-induced diabetes model is widely utilized because it closely recapitulates key features of human diabetes—including sustained hyperglycemia, oxidative stress, and pancreatic β-cell dysfunction—thereby providing a suitable platform for evaluating potential anti-diabetic and antioxidant agents [32].

2.4. Comparative Analysis of Marine Peptide Therapy in Diabetic Rats

In preclinical studies involving marine bioactive peptides, experimental animals are typically divided into groups to facilitate controlled comparisons. Group I serves as a normal control group receiving a standard diet and saline, whereas Group II consists of streptozotocin (STZ)-induced diabetic rats that receive no treatment. Group III comprises diabetic rats treated with a low dose of marine bioactive peptides; Group IV receives a high dose of the same peptides; and Group V consists of diabetic rats administered a standard anti-diabetic drug to serve as a reference for efficacy [33].

Marine bioactive peptides are typically administered orally once daily for a period of 28 days, with dosage levels selected based on preliminary dose-finding studies and published literature. Throughout the treatment period, body weight and fasting blood glucose levels are monitored weekly to track disease progression and therapeutic efficacy, thereby facilitating the assessment of both the anti-hyperglycemic effects and potential metabolic-stabilizing properties of the peptide interventions [34].

2.5. α-Glucosidase Inhibition and Glycemic Control by Marine Peptides

α-Glucosidase inhibition plays a pivotal role in controlling postprandial hyperglycemia. Marine peptides such as LGY (derived from fish) and YLPA (derived from mollusks) bind effectively to the enzyme's active site through interactions involving 4–7 hydrogen bonds—incorporating Asp/Glu residues—and hydrophobic pockets. These peptides exhibit IC_{50} values ranging from 0.1 to 1.2 mg/mL, which are comparable to or competitive with those of the standard drug, Acarbose ($IC_{50} \approx 0.38$ mg/mL). α-Amylase inhibition complements this effect by delaying starch hydrolysis,

thereby regulating the rate at which glucose is released into the bloodstream. Additional mechanisms include Dipeptidyl Peptidase-IV (DPP-IV) inhibition—which increases active GLP-1 levels—stimulation of GLUT4 translocation via the PI3K/Akt pathway, and protection of IRS-1 from serine phosphorylation; collectively, these actions restore insulin sensitivity in 3T3-L1 adipocytes by approximately 30–60% [35].

In the described experimental setup, to evaluate the chronic glucose-lowering effects of these marine bioactive peptides, fasting blood glucose levels were measured at baseline and at weekly intervals using tail-vein blood sampling. At the conclusion of the treatment period, an Oral Glucose Tolerance Test (OGTT) was conducted to assess the efficiency of glucose utilization, while serum insulin levels were measured using Enzyme-Linked Immunosorbent Assay (ELISA) kits. Together, these parameters provide a comprehensive assessment of the anti-hyperglycemic potential and insulin-modulating activity of the marine peptide interventions [36].

2.6. Assessment of Oxidative Stress and Antioxidant Enzymes

In preclinical evaluations of bioactive marine peptides, animals are typically euthanized under mild anesthesia at the conclusion of the experimental period, and samples of blood—along with key metabolic tissues (such as the liver and pancreas)—are collected for biochemical analysis. Oxidative stress is commonly assessed by quantifying malondialdehyde (MDA), a marker of lipid peroxidation that reflects membrane damage induced by reactive oxygen species [37].

The status of antioxidant defense is further investigated by evaluating key enzymatic antioxidants—such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx)—using standardized spectrophotometric protocols. Additionally, levels of reduced glutathione (GSH) are determined to provide insights into the intracellular redox balance. Collectively, these parameters facilitate a systematic assessment of the capacity of marine peptides to mitigate oxidative stress and bolster cellular antioxidant potential in experimental models of diabetes [38].

2.7. Histological Profiling of Pancreatic and Hepatic Tissues

In preclinical studies involving biologically active marine-derived peptides, pancreatic and hepatic tissues are typically fixed in 10% buffered formalin, processed through dehydration and paraffin embedding, and sectioned using a microtome for histopathological evaluation. The tissue sections are stained with Hematoxylin and Eosin (H&E) and examined under a light microscope to assess structural integrity, cellular degeneration, and signs of regeneration in both treated and untreated groups. Light microscopic images are routinely captured to document morphological changes and to facilitate comparative qualitative and semi-quantitative analyses [39].

In diabetic control animals, histopathological examination of the pancreas typically reveals significant islet degeneration, reduced β-cell mass, and perislet inflammatory infiltration, reflecting the detrimental impact of hyperglycemia and oxidative stress. In contrast, peptide-treated groups—particularly those receiving higher doses—often exhibit well-preserved islet architecture, reduced cellular damage, and evidence of β-cell regeneration, suggesting a protective and potentially restorative effect. Similarly, the hepatic tissues of treated animals demonstrate reduced fatty degeneration, improved cytoarchitectural organization, and diminished vacuolization

when compared to untreated diabetic controls. These structural improvements align with the observed biochemical and oxidative changes and collectively support the concept that marine-derived bioactive peptides exert a cytoprotective influence on key metabolic organs under diabetic conditions [40,41].

2.8. Marine Bioactive Peptides in Experimental Diabetes: Antihyperglycemic and Antioxidant Effects

Accumulating evidence from over 50 rodent studies—utilizing streptozotocin (STZ) or alloxan-induced Type 1 and Type 2 diabetes (T1DM/T2DM) models in rats and mice—consistently demonstrates the potent anti-hyperglycemic and antioxidant efficacy of marine-derived bioactive peptides [42]. When administered at doses of 200–400 mg/kg for 4–8 weeks, oyster-derived peptides typically reduce fasting blood glucose (FBG) levels by 35–55% (dropping from approximately 280 to around 120 mg/dL); enhance antioxidant enzyme activities (SOD, CAT, GPx) by 1.5 to 3-fold; decrease malondialdehyde (MDA) levels by approximately 50%; and promote β-cell regeneration—an effect reflected in an increase of about 40% in the islet area compared to diabetic control groups.

In STZ-induced rats maintained on a high-fat diet, sea cucumber peptides (e.g., derived from Stichopus horens, at doses of 100–300 mg/kg) improve insulin sensitivity. This improvement is evidenced by a reduction of approximately 45% in HOMA-IR scores, a decrease in hepatic steatosis, and the provision of renal protection through the attenuation of proteinuria. In db/db mice, peptides derived from shrimp restore Nrf2/HO-1 signaling pathways and reduce reactive oxygen species (ROS) by approximately 60%, highlighting their role in modulating redox balance. Generally, dose-response relationships in these models indicate that maximum benefits are often achieved at oral doses of 200–500 mg/kg, and no toxicity has been reported at doses up to 2 g/kg. This underscores the protective and therapeutic potential of marine peptides against experimental diabetes and associated organ damage linked to oxidative stress [43].

2.9. Marine Peptides in Human Diabetes: Evidence from Clinical Trials and Meta-Analyses

While early-stage clinical evidence regarding marine-derived bioactive peptides for diabetes management is limited, it remains encouraging. Randomized controlled trials conducted on patients with Type 2 Diabetes (T2DM) demonstrate that fish collagen peptides (administered at 5–10 g per day for 12 weeks) can reduce HbA1c levels by 0.8–1.2%, fasting plasma glucose (FPG) by 15–25 mg/dL, and malondialdehyde (MDA) by approximately 30%. Concurrently, data derived from 120 participants across trials conducted in Japan and China indicate that these peptides also enhance superoxide dismutase (SOD) activity [44].

In individuals with prediabetes (n = 85), oyster peptide supplements (300 mg per day) have been shown to improve postprandial glycemic control, a benefit reflected in a 22% reduction in the area under the glucose curve (AUC). Pooled data from recent meta-analyses (comprising 15 randomized controlled trials conducted between 2020 and 2025) indicate a standardized mean difference (SMD) of −0.65 for fasting blood glucose (FBG), suggesting a moderate yet consistent glucose-lowering effect [45]. However, these analyses underscore the need for large, well-

designed Phase III trials (n > 500) that not only confirm efficacy but also evaluate cardiovascular disease (CVD) endpoints and long-term safety across diverse populations of patients with diabetes.

3. Marine Bioactive Peptides: Source, Processing, and Therapeutic Impact

3.1. Effect of Marine Bioactive Peptides on Blood Glucose Levels

Marine organisms serve as a rich and often sustainable source of biologically active peptides, which are typically derived from protein-rich by-products—such as fish muscle, skin, and scales—as well as from mollusks, crustaceans, and echinoderms. Fish species such as salmon and tuna are processed via enzymatic hydrolysis under optimal conditions (pH 7–9, 50–60°C, 4–24 hours) using proteases—such as Alcalase, pepsin, or trypsin—resulting in fractions characterized by low molecular weight (<3 kDa), high solubility (70–90%), and potent free-radical scavenging activity [46].

Table 3: Marine-Derived Bioactive Peptides—Sources, Processing, and Antidiabetic Potential.

Marine Source	Raw Material / By-product	Processing Method	Key Peptide Characteristics	Biological Activities	Mechanism of Action	Reference
Fish (e.g., salmon, tuna)	Muscle, skin, scales	Enzymatic hydrolysis (Alcalase, Pepsin, Trypsin); pH 7–9, 50–60°C, 4–24 h; Ultrafiltration (<3 kDa)	Low molecular weight (<3 kDa); High solubility (70–90%)	Antioxidant, Antihyperglycemic	ROS scavenging; improved insulin sensitivity; enhanced glucose uptake	[47]
Mollusks (e.g., *Crassostrea gigas*, *Dosidicus gigas*, scallops)	Whole tissue, skin	Enzymatic hydrolysis; RP-HPLC purification	Dipeptides (e.g., Phe–Asn); Hydrophobic amino acids (Leu, Val, Ile)	DPP-IV inhibition; Antioxidant	Incretin preservation; membrane interaction; oxidative stress reduction	[48]
Crustaceans (shrimp, crab)	Heads, shells	Enzymatic hydrolysis; Ultrafiltration; Gel filtration	Bioactive peptides (e.g., VGPWPP)	Antioxidant, Cytoprotective	Activation of Nrf2/ARE pathway; reduction	[49]

					of oxidative stress	
Echinoderms (sea cucumber)	Body wall, internal tissues	Proteolytic hydrolysis; Chromatographic purification	Collagen-derived peptides	Anti-inflammatory, Antioxidant	Modulation of inflammatory pathways; ROS inhibition	[50]
Mixed Marine By-products	Fish processing waste	Integrated bioprocessing; Ultrafiltration (1–10 kDa); HPLC (>95% purity)	High purity peptide fractions	Nutraceutical applications	Waste valorization; functional bioactivity enhancement	[51]

Molluscan sources—such as oysters (Crassostrea gigas), squid (Dosidicus gigas), and scallops—also yield highly bioactive sequences; for instance, oyster hydrolysates generate dipeptides like Phe-Asn, which exhibit significant DPP-IV inhibitory activity, while squid skin peptides—rich in hydrophobic residues (Leu, Val, Ile)—demonstrate favorable membrane interactions. To achieve peptide purities exceeding 95%, industrial-scale production relies on ultrafiltration (MWCO 1–10 kDa), gel filtration chromatography, and reverse-phase HPLC. Crustaceans (shrimp, crabs) and echinoderms (sea cucumbers) contribute similarly; their by-products—such as shrimp heads—yield peptides like VGPWPP, which activate the Nrf2/ARE antioxidant defense pathway. By 2026, the value-addition of marine by-products is projected to reach recovery rates of 30–50%, thereby transforming waste materials into high-value nutraceuticals worth approximately US$ 2–5 per gram [52].

In preclinical models, the administration of bioactive peptides derived from marine animals has been shown to significantly reduce fasting blood glucose levels in streptozotocin-induced diabetic rats. Diabetic control animals generally maintain persistently elevated glucose levels throughout the treatment period, confirming the successful induction of hyperglycemia; conversely, the groups treated with the peptide exhibit a dose-dependent decline in glucose levels, with the high-dose group frequently attaining glucose values comparable to those observed in the standard anti-diabetic drug group. This anti-hyperglycemic effect is likely mediated by mechanisms such as improved insulin sensitivity, protection of pancreatic beta cells against oxidative damage, inhibition of carbohydrate-digesting enzymes, and enhanced glucose uptake in peripheral tissues. The observed improvement in oral glucose tolerance further supports the regulatory role of marine peptides in glucose homeostasis [53].

Table 4: Antidiabetic Effects of Marine Bioactive Peptides in Preclinical Models

Parameter	Diabetic Control Group	Low-Dose Peptide Group	High-Dose Peptide Group	Standard Drug Group	Reference
Fasting Blood Glucose	Persistently elevated	Moderate reduction	Significant reduction (near-normal levels)	Comparable to high-dose peptide	[54]
Insulin Sensitivity	Severely impaired	Improved	Markedly improved	Restored	[55]
Pancreatic β-cell Integrity	Damaged	Partial protection	Significant protection	Preserved	[56]
Oxidative Stress Markers	High ROS levels	Reduced ROS	Strong reduction in ROS	Normalized	[57]
Glucose Tolerance (OGTT)	Poor	Improved	Significantly improved	Normal	[58]

3.2. Marine Peptides in Redox Regulation and Oxidative Stress Control

Diabetic control animals typically exhibit marked elevation of oxidative stress markers, manifested as increased malondialdehyde (MDA) levels and reduced activities of key antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx). Treatment with marine-derived bioactive peptides has been shown to significantly restore these enzyme activities, indicating a broad-spectrum antioxidant effect. The concurrent reduction in lipid peroxidation suggests effective scavenging of reactive oxygen species (ROS) and stabilization of cellular membranes, which is critical in mitigating diabetes-associated tissue damage [59].

The antioxidant potential of marine peptides is largely attributed to their low molecular weight and the presence of redox-active amino acids such as histidine, tyrosine, and cysteine, which can donate hydrogen atoms or electrons to neutralize free radicals. By reinforcing endogenous antioxidant defenses, these peptides help counteract the chronic oxidative stress that underlies both the onset and progression of diabetes and its complications [60].

At the mechanistic level, marine bioactive peptides neutralize ROS through multiple complementary routes. First, they directly scavenge radicals such as DPPH, ABTS, and hydroxyl species via hydrogen-donating residues (Tyr, Trp, His, Cys), with typical IC_{50} values in the range of 0.5–2 mg/mL. Second, they chelate pro-oxidant metal ions such as Fe^{2+} and Cu^{2+}, thereby preventing Fenton-driven ROS generation. Third, they inhibit lipid peroxidation, reflected in 40–70% reductions in TBARS in experimental models. Fourth, they upregulate endogenous antioxidant enzymes—SOD, CAT, and GPx—through Nrf2-mediated signaling: binding-induced dissociation of Keap1 promotes Nrf2 nuclear translocation and a 2- to 5-fold increase in the expression of ARE-driven antioxidant and phase-II genes. In hyperglycemic conditions, these peptides also suppress PKC and NF-κB activation, leading to reduced production of

pro-inflammatory cytokines such as TNF-α and IL-6, thereby linking antioxidant, anti-inflammatory, and antidiabetic actions within a unified mechanistic framework [61].

3.3. Comparative Advantages vs. Synthetic Drugs

Table 5: Effect of Marine Bioactive Peptides on Biochemical Parameters

Parameter	Marine Peptides	Synthetic Drugs (Metformin/Acarbose)	Reference
Multifunctionality	Dual/triple action (ROS↓, glucose↓, inflammation↓)	Glycemic focus; neutral/ROS exacerbation	[62]
Efficacy Metrics	FBG ↓40-60%; SOD ↑2-4x; β-cell protection	FBG ↓20-40%; no antioxidant boost	[63]
Safety Profile	GRAS; no GI/lactic acidosis (LD50 >5 g/kg)	20-30% dropout (diarrhea, flatulence)	[64]
Bioavailability	80-95% (small size, transporter-mediated)	Variable (50-80%); first-pass metabolism	[65]
Cost-Effectiveness	$0.5-2/g from waste; scalable	$0.1-1/dose; patent-driven	[66]
Sustainability	By-product upcycling (50M tons seafood waste/yr)	Petrochemical synthesis; environmental load	[67]
Long-Term Outcomes	Organ protection (pancreas/liver/kidney)	Complications persist (nephropathy ↑10-20%)	[68]

4. CONCLUSION AND FUTURE PERSPECTIVE

Evidence gathered from these and related experimental studies demonstrates that bioactive peptides derived from marine animals exhibit significant anti-hyperglycemic and antioxidant activities in animal models of diabetes. Since oxidative stress and hyperglycemia are closely intertwined in the pathogenesis of diabetes, their dual functionality assumes particular significance; by simultaneously lowering blood glucose levels and counteracting oxidative damage, these peptides may help delay or mitigate the onset of long-term diabetic complications.

The administration of marine peptides consistently results in a significant reduction in fasting blood glucose levels and improved glucose tolerance. Concurrently, it restores key antioxidant defense systems such as Superoxide Dismutase (SOD), Catalase (CAT), and Glutathione Peroxidase (GPx). Furthermore, as reflected by reduced levels of Malondialdehyde (MDA), it attenuates lipid peroxidation. Histopathological findings further corroborate these biochemical improvements; they reveal that in peptide-treated animals, pancreatic beta cells are preserved and undergo partial regeneration, while the structural integrity of the liver is significantly maintained. This underscores their potential to protect organs under hyperglycemic conditions.

Compared to many synthetic anti-diabetic medications, marine peptides function as natural, multi-functional therapeutic agents. Pre-clinical studies suggest that these compounds possess favorable safety profiles, making them attractive candidates for long-term nutraceutical applications. The current findings align well with previous reports demonstrating the antioxidant and blood glucose-lowering effects of marine peptides derived from fish, mollusks, crustaceans, and echinoderms.

However, prior to their adoption for routine clinical use, further in-depth mechanistic studies—specifically focusing on signaling pathways such as Nrf2/Keap1, insulin sensitivity cascades, and gut microbiota interactions—as well as long-term toxicity assessments, are essential. Overall, these marine peptides represent a promising class of natural therapeutic agents for the management of diabetes and associated oxidative stress-related disorders. Furthermore, they reinforce the growing interest in marine resources as a rich source of bioactive compounds for future peptide-based nutraceuticals and anti-diabetic therapies.

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