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Unlocking the Therapeutic Potential of Seaweed-Derived Bioactive Compounds for Human Health

Sreeranjani K[1], Kavitha P.S[2*], Kalarani M.K[3] ,Jamuna P[4]

[1]Department of Fruit Science, Horticultural College and Research Institute, Tamil Nadu Agricultural University, Coimbatore, Tamil Nadu, India. E-mail : sreekana22@gmail.com, ORCID: 0009-0005-9231-9522
[2*]Department of Fruit Science, Horticultural College and Research Institute, Tamil Nadu Agricultural University, Coimbatore, Tamil Nadu, India. E-mail : kavitha.ps@tnau.ac.in, ORCID: 0000-0002-0946-1845
[3]Director of Crop Management ,Tamil Nadu Agricultural University, Coimbatore, Tamil Nadu, India. E-mail : directorscms@tnau.ac.in
[4]Department of Fruit Science, Horticultural College and Research Institute, Tamil Nadu Agricultural University, Coimbatore, Tamil Nadu, India. E-mail : jamunaperumal66@gmail.com, ORCID: 0000-0001-9371-3322

Abstract:
Background:
Seaweeds are a significant source of structurally varied bioactive chemicals with substantial medicinal promise. Sulfated polysaccharides, carotenoids, phlorotannins, bioactive peptides, sterols and phycobiliproteins demonstrate a wide range of pharmacological effects. Nonetheless, their conversion into clinically authorised treatments is constrained by issues pertaining to standardisation, bioavailability, structural variability and inadequate clinical data.
Objective:
This review sought to critically assess current advancements (2020-2026) in the chemistry, extraction methodologies, pharmacological mechanisms, therapeutic uses, translational research and future potential of bioactive chemicals obtained from seaweed for human health.
Methods:
A comprehensive review of recent literature was performed to consolidate evidence regarding the principal categories of bioactive chemicals obtained from seaweed encompassing fucoidan, carrageenan, alginate, ulvan, phlorotannin, fucoxanthin, bioactive peptides, sterols and phycobiliproteins. Emphasis was directed on their extraction methodologies, structure-activity relationships, molecular mechanisms, pharmacological properties, bioavailability, translational progress and novel drug-delivery techniques.
Results:
Bioactive chemicals produced from seaweed exhibit substantial antioxidant, anti-inflammatory, antibacterial, immunomodulatory and anticancer properties via modulating many molecular signalling pathways, including NF-κB, PI3K/Akt/mTOR, MAPK, Nrf2 and caspase-mediated cascades. These chemicals regulate oxidative stress, inflammation, apoptosis, angiogenesis, metastasis and immunological responses, underscoring their promise in the prevention and therapy of chronic, multifactorial disorders. Recent advancements in extraction technologies, nano-enabled delivery systems and pharmacokinetic research have enhanced the translational potential of these drugs. Nonetheless, significant obstacles persist, such as inadequate standardisation, restricted bioavailability, insufficient pharmacokinetic characterisation and a lack of large-scale clinical trials.
Keywords: Anticancer activity, Anti-inflammatory activity, Bioactive compounds, Functional nutraceuticals, Seaweed, Molecular mechanisms

1. Introduction

The marine ecosystems occupy nearly 70% of the Earth's surface and represent the largest reservoir of biological diversity, providing an immense source of structurally unique natural products with significant pharmaceutical potential. Seaweeds or marine macroalgae hold significant ecological, economic and growing pharmaceutical importance among marine species. Seaweeds, as primary producers in coastal ecosystems, are fundamental to marine food webs, significantly aid in global carbon sequestration and establish structural habitats that sustain several lineage species [59]. Their ecological footprint is remarkably low compared to their biomass yields; in contrast to terrestrial crops, freshwater or synthetic fertilizers, rendering it an appealing option for sustainable blue bioeconomy advancement [62]. Worldwide, seaweed production has shown significant growth. FAO estimations referenced by [62] indicate that cultivated seaweed production attained almost 35.8 million tonnes or 97% of total global seaweed production, with a market valuation of nearly US$11.8 billion. The global seaweed market increased more than threefold during twenty years, rising from roughly US$5 billion in 2000 to US$17 billion in 2021 [64]. Countries such as China, Indonesia Japan, South Korea and

the Philippines lead in production. The World Bank's Global Seaweed New and Emerging Markets Report 2030 forecasts ten emerging markets with a potential combined growth of an additional US$11.8 billion by 2030, highlighting the significant untapped economic potential of this sector.

The pharmacological significance of substances obtained from seaweed encompasses a remarkable array of therapeutic targets. Sulfated polysaccharides, including fucoidan and carrageenan, possess established anticoagulant, antiviral and immunomodulatory effects [73]. Phlorotannins, polyphenolic compounds unique to brown algae, demonstrate significant antioxidant and anti-inflammatory properties via specific molecular mechanisms, including the inhibition of nuclear factor kappa-B(NF-κB) signalling and the suppression of cyclooxygenase-2(COX-2) expression [10]. Fucoxanthin, a marine carotenoid, has attracted significant interest because of its anti-obesity, hepatoprotective, neuroprotective and particularly anticancer attributes, supported by both preclinical and preliminary clinical studies [2]. Bioactive peptides obtained from seaweed proteins have antihypertensive, antidiabetic, antioxidant and antibacterial properties [22]. The extensive pharmacological activity of seaweed-derived chemicals makes them interesting candidates in drug research and nutraceutical development. Besides human health, seaweed-derived compounds are significant in sustainable agriculture. Seaweed extracts are rich in polysaccharides, phytohormones, betaines, minerals and phenolics, which function as plant biostimulants that enhance seed germination, root development, vegetative growth, crop yield and tolerance to abiotic stresses like drought, salinity and temperature extremes [5,22]. The molecular basis of these biostimulant actions is increasingly recognized at the transcriptome and metabolomic levels, where seaweed extracts alter stress-sensitive gene networks, increase nutrient usage efficiency and activate innate plant defence [22]. These features indicate that seaweed-derived products could be promising alternatives to synthetic agrochemicals in the global trend for sustainable low-input farming systems. Seaweeds represent a distinctive and growing niche at the intersection of marine biology, natural product chemistry, medicine and sustainable agriculture. The worldwide drive for natural and functional health products, along with the powerful bioactivities of seaweed-derived chemicals, has fostered a climate conducive to rapid scientific and commercial advancement. This review aims to consolidate the current knowledge, pinpointing knowledge deficiencies and emphasising avenues for future research.

2. Seaweeds as a source of bioactive compounds

2.1 Classification of seaweeds

Based on their photosynthetic pigmentation, storage carbohydrates, cell wall composition and reproductive biology, seaweeds are divided into three major taxonomic groups. These are the red algae (Rhodophyta), the green algae (Chlorophyta) and the brown algae (Phaeophyta). This tripartite classification does not adequately capture the phylogenetic complexity of algae but remains the most popular framework in pharmaceutical and practical research [18]. Brown algae (Phaeophyceae) are the most pharmacologically studied and structurally complicated. The predominance of the carotenoid fucoxanthin and chlorophyll C, which obscure the underlying chlorophyll a, is what gives them their distinctive brown-yellow colour. From minute filamentous forms to the enormous kelps (Macrocystis, Laminaria, Sargassum), there are about 2000 known species [43]. Many of the most clinically promising seaweed-derived chemicals are from brown algae species, and these compounds have been the focus of extensive pharmacological research [28].

The red algae (Rhodophyta) are the largest and oldest group, comprising 6000-7500 species. They are distinguished by the lack of flagellated stages in their life cycle and by phycobiliprotein pigments (phycoerythrin, phycocyanin) that give them their characteristic red to purple colouration. The important bioactive substances from Rhodophyta are mycosporine-like amino acids with UV-protective qualities, floridean starch, carrageenan, agar and a range of halogenated secondary metabolites with antimicrobial and antiviral properties [21]. Large-scale commercial cultivation is used for species like Porphyra, Gracilaria, Kappaphycus and Eucheuma. Phylogenetically, green algae (Chlorophyta) are the closest relatives of terrestrial plants with the same chlorophyll a/b based photosynthetic system and starch storage metabolism. About 1200-1500 marine species are identified. The bioactive compounds include the sulfated polysaccharide ulvan, a distinctive compound with immunomodulatory and plant defence-inducing activities, carotenoids, sterols and several polyphenols [18].

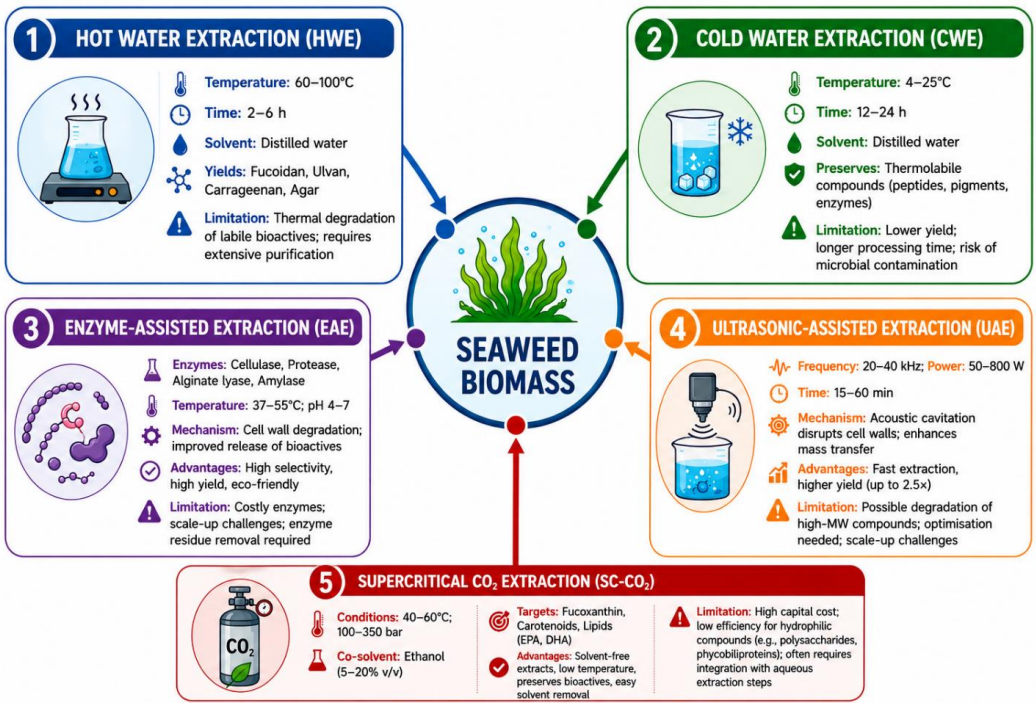
2.2 Extraction Methods of Seaweed Bioactive Compounds

The extraction method used to recover bioactive compounds from seaweed biomass greatly affects yield, structural integrity, biological activity and commercial viability. The stiff algal cell wall, made of complex polysaccharide matrices, must be broken to release intracellular and cell-wall-associated metabolites. The major extraction strategies applicable to seaweed bioactive compounds are schematically illustrated in Figure 1. The figure highlights the operating principles, advantages, limitations and major bioactive compounds recovered by each method.

Fig. 1. Comparative overview of extraction approaches used to obtain bioactive metabolites from seaweed biomass

3. Principal Bioactive Constituents in Seaweeds

Seaweeds synthesise a great diversity of primary and secondary metabolites whose diversity and relative abundance vary greatly among species, geographic origin, season, life stage and environmental conditions. Following the classification and extraction of seaweeds, it is essential to understand the major classes of bioactive compounds



responsible for their therapeutic properties. Seaweeds as food sources possess nutritional value with primary metabolites such as proteins, polysaccharides, lipids, vitamins and minerals. Secondary metabolites, including phlorotannins, terpenoids, halogenated chemicals and alkaloids, are mostly used for ecological protection but show important pharmacological actions in mammalian systems [33]. Nutritionally, seaweeds have a unique character that is different from both terrestrial crops and animal feeds. The protein content of most brown and green algae is in the range of about 5-15% dry weight, but in some red algae, such as Porphyra and Palmaria, it can reach 25-47%, with a profile of essential amino acids comparable in several species to conventional sources of protein [23,12]. The carbohydrate fraction (20-60% dry weight) is mostly formed by non-digestible polysaccharides, which constitute the dietary fibre, with important prebiotic potential. The lipid content is usually low (1-5%), although seaweeds are rather rich in polyunsaturated fatty acids (PUFAs), notably eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in some brown species[25]. Seaweeds are also good providers of minerals, including iodine, calcium, magnesium, potassium and iron and vitamins such as vitamins A, C, E, B12 and K [19]. Along with verified beneficial bioactivities, these nutritional properties strongly place seaweeds in the nutraceutical food category.

3.1 Sulfated Polysaccharides

The sulfated polysaccharides are undoubtedly the most important of seaweed bioactives, combining structural innovation, chemical variety and a remarkable number of biological effects. Their pharmacological importance is mainly due to the presence of sulphate ester groups. These groups confer a polyanionic nature and are vital for interaction with protein receptors such as growth factor receptors, and viral surface proteins and for modulation of immune cell activation [73]. The classic sulfated polysaccharide of brown algae is fucoidan, which has a backbone of α-L-fucopyranose residues, with different patterns of sulfation and branching depending on the species from which it is extracted. Fucoidan was first isolated from Kylin in 1913 and has been found in dozens of brown algae species, including Fucus veiculosus, Laminaria japonica, Sargassum fusiforme and Undaria pinnatifida. Among the most often reported biological properties of any seaweed are anticoagulant, antiviral, anti-inflammatory, immunostimulatory, antitumour and anti-angiogenic activity[7]. High molecular fucoidans are prone to show higher anticoagulant activity by inhibiting the intrinsic coagulation cascade. However, lower molecular weight fractions showed increased cellular uptake and anticancer activity [39]. Fucoidan structures are species-specific and so pharmacological effects cannot be generalised, requiring species-specific and fraction-specific characterization.

Alginate is the main structural polysaccharide of the cell wall of brown algae and is a block copolymer comprising β-D-mannuronic acid (M-blocks) and α-L-guluronic acid (G-blocks). Its use as a gelling, thickening and

encapsulation agent for commercial purposes is well established in culinary, pharmaceutical and biological applications [54]. Carrageenan is a group of sulfated galactans that are isolated mostly from red algae belonging to the genera Kappaphycus, Eucheuma, and Gigartina. They are differentiated into three major types, kappa (κ), iota (ι) and lambda (λ), depending on the quantity and location of sulphate groups and the pattern of 3,6,anhydrogalactose bridges that control their gelling compounds. Carrageenan is a common ingredient in pharmaceutical products and a food additive in pharmaceutical formulations. Carrageenan oligosaccharides and low molecular-weight derivatives have antiviral action against enveloped viruses like SARS-CoV-2 through steric inhibition of viral entry and immunostimulatory effects through stimulation of macrophages and dendritic cells [34]. Ulvan is the primary sulfated polysaccharide of green algae, particularly of the genus Ulvan (sea lettuce). It is a complicated structure, it consists of rhamnose, glucuronic acid, iduronic acid and xylose. Ulvan has recently received considerable interest in agriculture as a plant immunity elicitor: foliar application of ulvan activates defence pathways dependent on both salicylate and jasmonate, enhancing resistance to fungal, bacterial and viral pathogens [22].

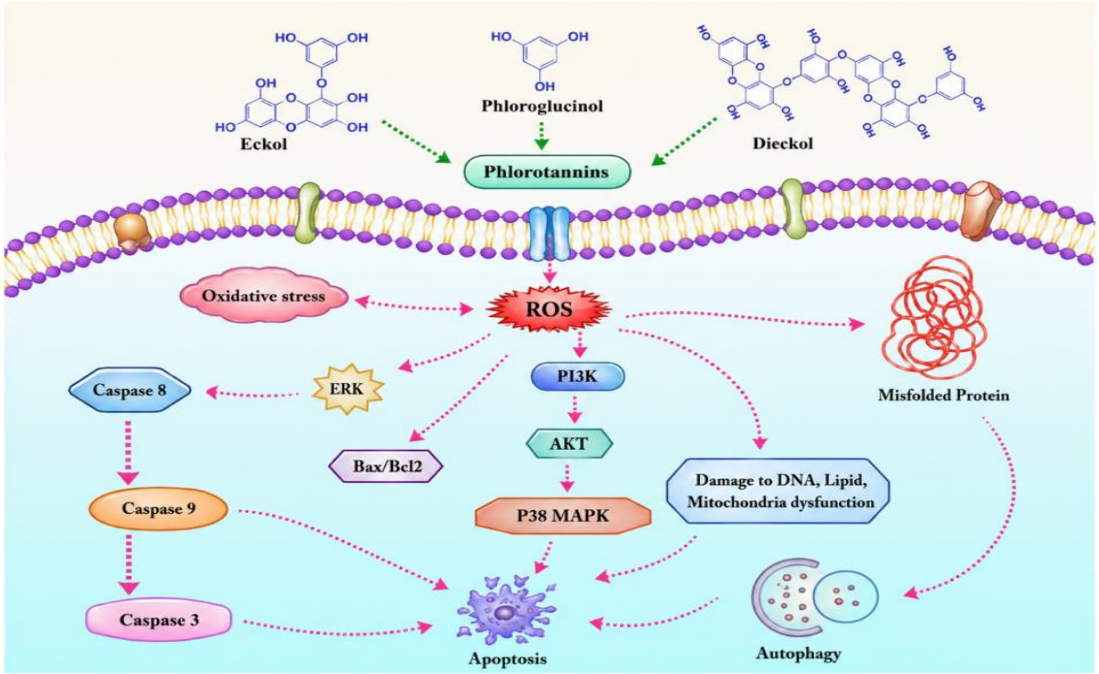
3.2 Polyphenols and Phlorotannins

Phlorotannins are a structurally unique group of polyphenols that occur only in brown seaweeds and differ from terrestrial tannins in that they are built up from phloroglucinol (1,3,5-trihydroxybenzene)units linked by aryl-aryl and aryl-ether bonds, whereas terrestrial plants have catechol groups. This biosynthetic origin and the resultant diversity of the structures comprising eckols, phlorofucofuroeckols and dieckols are unique to the marine environment [36]. Ecklonia cava, Ecklonia stolonifera and Fucus vesiculosus are species rich in phlorotannins, the quantity of which depends on the species and environmental conditions and can vary from trace levels to more than 155 dry weight [10]. Phlorotannins have broad pharmacological activity due to the abundance of hydroxyl groups that can quench radicals and chelate metals; they exhibit a very high antioxidant capacity, often surpassing that of terrestrial polyphenols such as epigallocatechin gallate (EGCG) from green tea in many tests [26,27]. Antimicrobial activities against both Gram-positive and Gram-negative bacteria, such as methicillin-resistant Staphylococcus aureus, have been reported and linked to the loss of bacterial membrane integrity and interference with quorum sensing [36]. The molecular mechanisms through which seaweed-derived compounds regulate oxidative stress, apoptosis, autophagy and intracellular signalling pathways are illustrated in Figure 2.

Fig. 2. Mechanistic overview of the cellular signalling pathways regulated by phlorotannins during cancer inhibition

3.3. Pigments

Seaweeds are rich suppliers of many photosynthetic and accessory pigments, many of which have significant biological activity in addition to their light-harvesting roles. Fucoxanthin is the most prevalent marine carotenoid numerically and the most pharmacologically important seaweed pigment. Structurally, it is a xanthophyll sub-class carotenoid and is characterised by an allenic link, a 5,6-monoepoxide group and several hydroxyl and carbonyl



functional groups missing in terrestrial carotenoids [2]. This distinct structural characteristic encompasses a range of activities that are not present in β-carotene or other common carotenoids. Fucoxanthin shows strong anti-obesity activity through activation of uncoupling protein 1 in white adipose tissue [47], hepatoprotective activity by regulating fatty acid metabolism and neuroprotective effects by inhibiting neuroinflammation. Other biologically active seaweed pigments

include phycobiliproteins from red algae, primarily phycoerythrin (red) and phycocyanin (blue), which have drawn attention as natural food colourants and as pharmacological agents with antioxidants, anti-inflammatory and potentially antitumor activities [12]. Carotenoids other than fucoxanthin, such as β-carotene, zeaxanthin and astaxanthin, are primarily derived from microalgae.

3.4 Proteins, Peptides and Amino acids

Enzymes, lectins, glycoproteins, cell wall-associated proteins, and phycobiliproteins are among the structurally varied seaweed proteins. Seaweed proteins are hydrolysed by gastrointestinal proteases, food processing or guided enzymatic degradation to produce bioactive peptides with a length of 2-20 amino acids that show a variety of pharmacological effects both in vitro and in vivo [23]. Porphyra and Sargassum have been found to have antihypertensive peptides that block the angiotensin converting enzyme (ACE) [1]. These peptides share structural similarities with well-known ACE-inhibitor medications. Antidiabetic peptides may help regulate postprandial hyperglycemia by inhibiting α-glucosidase and dipeptidyl peptidase IV (DPP-IV). Numerous seaweed species have been shown to have antioxidant peptides that contain proline and aromatic amino acids like tryptophan and tyrosine.

3.5 Sterols and other secondary metabolites

A variety of phytosterols, terpenoids and halogenated chemicals are produced by seaweeds. Fucosterol (24-ethylidene cholesterol), which is the most common sterol in brown algae, has been demonstrated to limit the generation of inflammatory cytokines, inhibit lipid peroxidation and alter cholesterol metabolism. Isofucosterol and 28-isofucosterol are two of the unique sterols produced by green algae. Particularly prevalent in red algae (such as Laurencia and Callophycus), terpenoids, including sesqui and diterpenes, show cytotoxicity against cancer cell lines in addition to antibacterial and antifouling properties. With a wide antibacterial spectrum against clinical pathogens, halogenated terpenes and phenols from red algae are among the most structurally unique natural compounds found in the marine environment. The major classes of seaweed-derived bioactive compounds and their representative constituents are summarized in Figure 3.

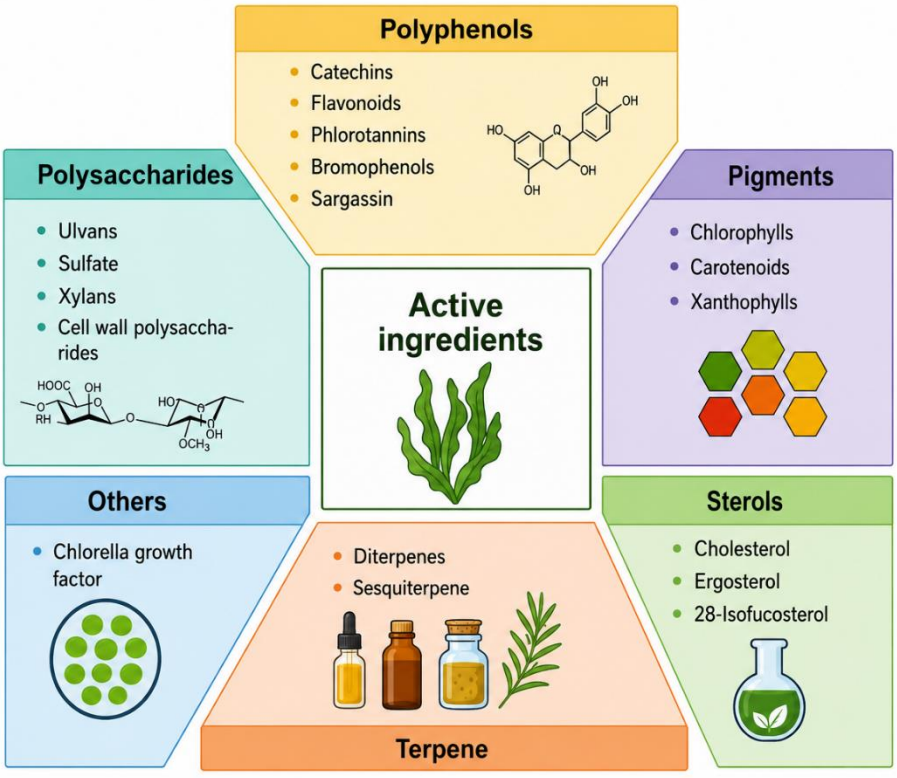


Fig.3. Major categories of seaweed-derived bioactive metabolites and their representative chemical constituents The diverse bioactive constituents described above contribute to a broad spectrum of pharmacological activities through multiple molecular pathways.

4. Therapeutic and Pharmacological Properties of Seaweed-Derived Metabolites

4.1. Antioxidant activity

A key pathological mechanism in ageing, cancer, cardiovascular disease, diabetes, neurodegeneration and chronic inflammation is oxidative stress, which is defined as an imbalance between the production of reactive oxygen species (ROS) and the ability of cellular antioxidant defence systems. Seaweed-derived chemicals have emerged as some of the most potent natural antioxidant agents discovered to date and the hunt for safe and effective natural antioxidants has subsequently become a key research priority in pharmacology and nutrition [4]. Through different

ways, several seaweed component groups contribute to antioxidant action. Phlorotannins from brown algae are consistently the most potent [27]. Resonance stabilisation of the resultant phenoxy radical within the polycyclic aromatic skeleton and the abundance of phenolic hydroxyl groups available for hydrogen atom donation are the main causes of this activity. Additionally, phenolotannins exhibit superoxide anion scavenging and iron-chelating properties, indicating multifactorial antioxidant protection [12].

4.2 Anti-inflammatory activity

Chronic low-grade inflammation is a common pathogenic hallmark of most non-communicable diseases, including type 2 diabetes, atherosclerosis, Alzheimer's disease and cancer. Increased interest in the therapeutic modulation of inflammatory pathways with natural compounds has emerged as an alternative or complement to classical non-steroidal anti-inflammatory drugs (NSAIDS) that have substantial gastrointestinal and cardiovascular side effect profiles with chronic use. Compounds produced from seaweed have been shown to exert anti-inflammatory effects via several mechanistically diverse mechanisms [8,43]. The NF-κB signalling cascade is the most well-studied anti-inflammatory mechanism among the seaweed chemicals. NF-κB is a master transcription factor that regulates expression of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6, IL-8),adhesion molecules(ICAM-1, VCAM-1)and inflammatory enzymes (COX-2, iNOS). Phlorotannins (dieckol, eckol and phlorofucofuroeckol- A from Ecklonia cava) inhibit NF-κB nuclear translocation by inhibiting IκB kinase (IKK) phosphorylation and maintaining the cytoplasmic sequestration of p65/p50 dimer, thus preventing transcriptional activation of pro-inflammatory gene networks [10]. This process has been confirmed in lipopolysaccharide (LPS) activated RAW264.7 macrophage cells and in rodent models of acute and chronic inflammation.

Fucoidan reduces complement activation, inhibits selectin-mediated leukocyte recruitment to sites of inflammation by competing with heparan sulphate for selectin binding and in certain experimental settings, modifies macrophage polarisation toward an M2 anti-inflammatory phenotype in order to suppress inflammatory responses through different but complementary mechanisms [7]. By suppressing NF-κB activation, lowering COX-2 and iNOS transcription and simultaneously activating the Nrf2 pathway to up-regulate antioxidant and cytoprotective enzymes, fucoxanthin attenuates inflammatory responses, addressing both the oxidative and inflammatory aspects of the pathological state[47].In vitro macrophage models have demonstrated that ulvan decreases pro-inflammatory cytokine release, possibly by modifying TLR-4 and MyD88-dependent signalling pathways.

4.3 Antimicrobial Activity

The hunt for new antimicrobial drugs, especially those having modes of action different from those of current antibiotics, has become more intense due to the growing global burden of antimicrobial resistance (AMR). Seaweed-derived metabolites have been demonstrated to exhibit efficacy against a wide range of bacterial, fungal and viral infections, and marine species have long been known as prolific sources of structurally unique antimicrobial compounds[13,36]. Through a variety of mechanisms, phenolotannins demonstrate antibacterial activity against both Gram-positive (Staphylococcus aureus, Bacillus cereus, Listeria monocytogenes) and Gram-negative (Escherichia coli, Pseudomonas aeruginosa, Salmonella typhimurium) bacteria. These mechanisms include disruption of bacterial cell membrane integrity and permeability, inhibition of oxidative phosphorylation and energy metabolism, interference with quorum sensing (QS) signalling in Chromobacterium violaceum and synergistic potentiation of conventional antibiotics against resistant strains, including MRSA[36]. Because there are few treatment options for MRSA infections, phlorotannin's anti-MRSA efficacy is especially important from a clinical standpoint.

A variety of enveloped RNA viruses, such as influenza, herpes simplex virus (HSV), HIV, dengue virus and most importantly SARS-CoV-2, the cause of COVID-19, are susceptible to the antiviral activity of fucoidans and other sulfated polysaccharides. To impede viral entry, the suggested mechanism is competitive suppression of viral attachment to heparan sulphate proteoglycans on host cell surfaces. It has been demonstrated that fucoidan from Undaria pinnatifida reduces the influence. While carrageenan nasal sprays have shown clinical benefit in lowering the duration of upper respiratory tract infections through antiviral barrier mechanisms [46,34]. A virus titre both in vitro and in animal models. Red and green algal terpenoids, especially halogenated sesqui and diterpenes, have strong and frequently species-specific antibacterial properties against drug-resistant bacteria and clinical fungal infections (Candida albicans ,Aspergillus fumigatus). Similar to azole antifungals, their methods include membrane disruption and suppression of ergosterol production.

4.4 Immunomodulatory Effects

The ability to alter immune function by up-regulating or down-regulating particular immunological pathways is known as immunomodulation and it is a pharmacologically valuable trait that can be used in a variety of situations, from autoimmune and cancer immunotherapy to immunodeficiency and infection. Seaweed-derived substances, especially fucoidan and carrageenan oligosaccharides, are well-known immunomodulators that can boost innate immunity, increase the cytotoxic activity of NK cells and macrophages, alter adaptive T cell responses and increase the production of antibodies [73].

Fucoidan activates macrophages and dendritic cells via TLR-4 and TLR-2 signalling pathways, leading to increased cytokine secretion (IFN-γ, IL-12, TNF-α)and up-regulation of co-stimulatory molecules (CD80,CD86,MHC-II), thus enhancing antigen presentation and adaptive immune priming[7]. Fucoidan has also been demonstrated to directly promote NK cell proliferation and cytolytic activity in vitro and in rodent models, an action of potential

importance to both anti-infective and anti-tumour immunity. In clinical aspects, modest randomized trials have demonstrated that fucoidan administration in cancer patients receiving chemotherapy is correlated with retained NK cell numbers and reduced chemotherapy-associated immunosuppression[68]. Phycobiliproteins from red algae, especially C-phycocyanin and phycoerythrin, possess immunostimulatory and anti-inflammatory properties: they stimulate lymphocyte proliferation, induce the production of interferon and inhibit the activity of myeloperoxidase, thereby contributing to the resolution of inflammatory processes without general suppression of immune competence[12].The pharmacological effects of seaweed bioactive chemicals are mechanistically varied, addressing numerous signalling pathways at the same time-a feature of particular importance in multifactorial chronic diseases where single-target treatment techniques have often proven insufficient. Among the numerous biological activities reported for seaweed-derived metabolites, their anticancer potential has attracted particular attention because of their ability to target multiple hallmarks of cancer simultaneously.

5. Anticancer Potential of Seaweed-Derived Bioactive Metabolites

Cancer continues to be one of the leading causes of mortality worldwide, accounting for approximately 19 million newly diagnosed cases and nearly 10 million deaths each year[2]. Despite remarkable progress in radiation therapy,surgery and immunotherapy, the efficacy of traditional treatments is restricted by drug resistance, systemic toxicity, tumour heterogeneity and the lack of curative alternatives for many advanced malignancies. Natural product pharmacology has a long and fruitful history of providing new anticancer leads and paclitaxel, vincristine, doxorubicin, and camptothecin derivatives are among the most clinically important drugs from natural sources. Marine organisms, including seaweeds, are increasingly recognized as promising sources of new anticancer agents. Compounds produced from seaweed target hallmarks of cancer, including uncontrolled proliferation, evasion of apoptosis, persistent angiogenesis, tissue invasion and metastasis through a variety of pathways. This multi-target engagement is pharmacologically advantageous in the cancer setting, because the genetic plasticity of tumour cells allows rapid development of resistance to drugs with a single mode of action. The following subsections critically discuss the major anticancer pathways and the main seaweed compounds involved, based on evidence from current pre-clinical and early clinical research.

5.1 Apoptosis Induction

Apoptosis is a tightly regulated form of programmed cell death that plays a fundamental role in maintaining tissue homeostasis by eliminating damaged or abnormal cells. In many cancers, this regulatory mechanism is disrupted through the overexpression of anti-apoptotic proteins such as Bcl-2, Bcl-xl and surviving or through the suppression of pro-apoptotic mediators including Bax, Bak and caspases. Consequently, restoring apoptotic signalling has become an important therapeutic strategy in contemporary cancer treatment. Among seaweed-derived metabolites, fucoidan has demonstrated a remarkable ability to tigger apoptosis in a variety of human cancer cell lines through activation of the intrinsic mitochondrial pathway. Treatment with fucoidan increases the Bax/Bcl-2 ratio, promotes mitochondrial release of cytochrome c and subsequently activates the caspase-9/caspase-3 signalling cascade, ultimately leading to DNA fragmentation and apoptotic cell death. These effects have been documented in breast, colon, gastric, lung prostrate, bladder and hepatocellular carcinoma models [7].In addition to mitochondrial-mediated apoptosis, fucoidan has also been reported to stimulate the extrinsic apoptotic pathway by enhancing the expression of FAS ligand (FasL) and tumour necrosis factor-related apoptosis-inducing ligand (TRAIL) receptors, thereby increasing the susceptibility of malignant cells to receptor-mediated cell death [7].Notably ,several experimental studies have indicated that fucoidan preferentially induces apoptosis in cytotoxic effects on normal healthy cells, highlighting its potential as a selective anticancer agent.

Fucoxanthin also exhibits potent pro-apoptotic activity through both intrinsic and extrinsic signalling pathways.It promotes mitochondrial oxidative stress,disrupts mitochondrial membrane potential,facilitates cytochrome c release and activates downstream caspase cascades,resulting in apoptotic cell death [2].In triple-negative breast cancer cell lines (MDA-MB-231 and MDA-MB-468),fucoxanthin significantly reduced cell viability in a concentration and time-dependent manner while increasing Annexin V-positive cells and PARP cleavage, confirming apoptosis induction.Furthermore,several mechanistic studies have demonstrated that fucoxanthin suppresses the PI3K/Akt/mTOR signalling pathway,thereby inhibiting tumour cell survival and proliferation while enhancing apoptotic responses [2].

5.2 Cell Cycle Arrest

Cancer cells are defined by their capacity to escape the regulatory checkpoints of the cell cycle. This leads to uncontrolled cell proliferation even with genetic instability. Pharmacological induction of cell cycle arrest during the G1/S or G2/M transition is a commonly used anticancer approach that allows DNA repair mechanisms to function, or in the case of irreversible damage, triggers apoptosis. Bioactive chemicals included in seaweeds, namely fucoidan and fucoxanthin, have shown the ability to inhibit cancer cell proliferation at different phases of the cell cycle. Fucoidan from Fucus vesiculosus was shown to induce G1 phase arrest of human bladder cancer T24 cells by increasing the expression of cyclin-dependent kinase (CDK) inhibitor p21WAF1/CIP1, dephosphorylation of retinoblastoma protein, disruption of assembly of CDK4/6-Cyclin D1 complex and inhibition of release of E2f transcription factor required for S phase entry [49]. Similar G1 arrest mechanisms have been reported in colon cancer, hepatocellular carcinoma and breast cancer cell lines. Fucoidan induced G2/M phase arrest in CL-6 cholangiocarcinoma cells and increased the expression of p21 and p27 but decreased the expression of cyclin B1 and CDK1. Moreover, fucoidan promoted caspase-

dependent death, indicating the involvement of numerous antiproliferative mechanisms [14]. Fucoxanthin treatment of cancer cells from diverse tumour lineages consistently results in decreased S-phase entrance and proliferative index, with G1 arrest coupled with decreased cyclin D1 and CDK4 expression [2].

5.3 Anti-Angiogenic and Anti-Metastasis activities

Angiogenesis, the formation of new blood vessels from the existing vascular network, is a critical event that supports tumour growth beyond 1-2 mm in diameter by supplying oxygen and essential nutrients. Among the numerous pro-angiogenic mediators, vascular endothelial growth factor(VEGF) is considered the principal regulator of tumour neovascularization and therefore represents an important therapeutic target in cancer management. Seaweed-derived bioactive compounds, particularly fucoidan, have demonstrated significant anti-angiogenic potential in several experimental studies. Fucoidan inhibits VEGF-stimulated proliferation, migration and tube formation of human umbilical vein endothelial cells while suppressing VEGFR-2 phosphorylation and its downstream ERK/Akt signalling pathways. These molecular events ultimately reduce tumour-associated vascularization in xenograft models, highlighting the therapeutic potential of fucoidan as an anti-angiogenic agent[7].Metastasis remains the primary cause of cancer-related mortality and involves a complex sequence of biological events, including epithelial-to-mesenchymal transition, degradation of the extracellular matrix,intravasation, survival within the circulation, extravasation and colonization of distant organs. Seaweed-derived metabolites have been reported to interfere with multiple stages of this metastatic cascade. Phlorotannins and phloroglucinol suppress cancer cell migration and invasion by inhibiting the expression and activity of matrix metalloproteinases (MMP-2 and MMP-9), enzymes responsible for extracellular matrix degradation. In addition, these compounds reduce CAV1-mediated cellular motility and inhibit Warburg-type metabolic reprogramming, thereby limiting the energy supply required for metastatic progression in melanoma (B16-F10) and breast cancer (MDA-MB-231)cells[58]. Fucoidan further suppresses metastatic progression by reversing epithelial-to-mesenchymal transition through the downregulation of mesenchymal markers, including vimetin, N-cadherin and fibronectin, while simultaneously restoring the expression of the epithelial marker E-cadherin. Moreover, it attenuates hypoxia-inducible factor-1α (HIF-1α)-dependent signalling, thereby reducing the transcriptional programmes that promote tumour invasion and metastasis under hypoxic conditions[7]. Similarly, fucoxanthin inhibits TNF-α- and VEGF-mediated invasion signalling and decreases matrix metalloproteinase expression, resulting in reduced invasiveness of gastric, prostate and breast cancer cells [2]. The major seaweed-derived bioactive compounds, their source species, molecular mechanisms of action and therapeutic applications are summarized in Table 1.

As summarized in Table 1, seaweed-derived bioactive compounds exert therapeutic effects through multiple molecular pathways, including apoptosis induction, NF- κB inhibition, PI3K/Akt/mTOR modulation, antioxidant defence and immune regulation. The current translational status, bioavailability limitations and advanced delivery strategies of major seaweed-derived bioactive compounds are summarized in Table 2.

Despite remarkable progress in understanding the pharmacological activities of seaweed-derived bioactive compounds, several scientific and translational challenges impede their clinical application. These critical knowledge gaps are discussed below.

5.4 Knowledge Gaps

Strong preclinical evidence supports the pharmacological potential of seaweed-derived bioactive chemicals but substantial information gaps restrict mechanistic understanding and traditional development. Such shortcomings should be recognized and addressed to take the seaweed pharmacology beyond empirical observation to evidence-based therapy. The key research priorities emerging from this review are the following unresolved questions

5.4.1 Structure Activity Relationships Remain Poorly Defined

The pharmacological effect of bioactive compounds obtained from seaweed and their chemical structure is not well understood, which hinders the rational development of the medication. A classic example is fucoidan, where the biological activity-anticoagulant, antiviral, anticancer, immunomodulatory-is critically dependent on the sulfation pattern, degree of sulfation, molecular weight and the geometry of the glycosidic linkage, but due to the lack of chemical characterization of the published studies, it is not possible to compare findings from one laboratory to another [9]. Most research reports only total phlorotannin concentration without molecular-level structural identification, even though the identity and amount of phloroglucinol units in the oligomeric structure dictate the antioxidant activity and anti-inflammatory selectivity. To interrogate SAR, well-characterised structural changes across a large number of bioassay endpoints are required, and this requires systematic fractionation, NMR, and mass spectrometric characterisation.

5.4.2 Limited In Vivo Pharmacokinetic and Bioavailability Data

For most seaweed-derived bioactives, comprehensive pharmacokinetic (ADME) data are still lacking. Fucoxanthin is rapidly metabolized to fucoxanthinol and amarouciaxanthin A, but the respective biological actions of these metabolites are not well recognized [2]. Moreover, the oral absorption and tissue distribution of high-molecular-weight fucoidan remain unclear and its bioavailability may be affected by gut microbiota-mediated breakdown. Advanced pharmacokinetic investigations with isotope-labelled substances and sensitive analytical systems are necessary to identify bioavailable metabolites and establish physiologically relevant tissue concentrations [11].

5.4.3 Lack of Standardisation of Bioactive Composition

Significant interspecific, seasonal and regional fluctuations in the bioactive composition of seaweeds hamper repeatability and standardization of products. Differences in fucoxanthin content and fucoidan structure across different seaweed species [9,25] are responsible for the variability of pharmacological effects. The development of harmonized reference standards and metabolomic-based chemotyping techniques is vital for the selection of high-quality raw materials and consistent treatment efficacy [61].

5.4.4 Insufficient Clinical Evidence

Extensive in vitro and animal research have shown potential pharmacological actions, but substantial clinical data are still sparse. Fucoidan has demonstrated promising results as an adjuvant to chemotherapy, but dose optimization, long-term safety and therapeutic efficacy need additional validation [68]. There is a paucity of clinical evidence for additional substances such as phlorotannins, fucosterol and bioactive peptides. To allow for clinical translation and regulatory approval [50], well-designed Phase I and II clinical trials with validated biomarkers are required.

5.4.5 Long-Term Safety and Regulatory Evaluation Remain Inadequate

Adequate long-term safety, genotoxicity and regulatory assessment of purified seaweed bioactives are still lacking. Safety concerns regarding degraded carrageenan, excessive iodine exposure and nanoparticle-based delivery systems need systematic investigation [34].In addition, the lack of harmonized international regulatory frameworks for seaweed-derived pharmaceuticals continues to hinder commercialization and clinical adoption, stressing the need for globally accepted safety and quality guidelines [56].

6.Future Perspectives

An encouraging approach to improve therapeutic efficacy is to enhance bioavailability of seaweed-derived chemicals via improved drug delivery methods, including lipid nanoparticles, polymeric carriers and nanoemulsions. Moreover, merging multi-omics techniques with AI-assisted drug discovery could speed up the discovery of new bioactive molecules, identify molecular targets and optimize lead compounds for pharmaceutical development. In parallel, harmonized quality standards and regulatory requirements will be crucial to facilitate industrial translation and market acceptance. Adequately planned multicentric clinical trials are required to establish the long-term safety, pharmacokinetics, optimal dosage and therapeutic efficacy of potential seaweed-derived bioactive chemicals. Prioritising these areas would allow the development of seaweed-derived metabolites from potential experimental candidates into evidence-based medicines and functional nutraceuticals for the prevention and management of chronic diseases.

7. Conclusion

Seaweeds are scientifically interesting and financially important in the frontier of natural product pharmacology. The diverse bioactive compounds they contain, such as sulphated polysaccharides, phlorotannins, carotenoids, bioactive peptides, sterols and pigment proteins, collectively target multiple disease-relevant pathways, including oxidative stress, chronic inflammation, antimicrobial resistance, immune dysregulation, and oncogenesis. Importantly, many of these activities function via mechanistically unique, multi-target modes of action that may provide advantages over traditional single-target therapies, especially for complicated or multifactorial diseases. Although fucoidan and carrageenan have advanced furthest to clinical use, the whole seaweed pharmacopoeia is relatively unexplored in light of its preclinical promise. Closing this gap requires concentrated advances on three fronts: rigorous standardisation of seaweed-derived extracts across harvesting and processing conditions; rational deployment of advanced drug delivery platforms to overcome the bioavailability barriers, and investments in trials to generate the clinical evidence base that requires market access. This success will move seaweed-derived bioactives from being nutraceutical adjuncts to bona fide pharmaceutical candidates that can really impact the management of major non-communicable illnesses and infectious disorders globally. Overall, integrating advanced extraction technologies, comprehensive pharmacokinetic evaluation, standardised bioactive characterization, innovative delivery systems and well-designed clinical trials will be critical for translating seaweed-derived bioactive compounds from promising experimental agents into clinically approved therapeutics and functional nutraceuticals.

Table 1. Major bioactive metabolites isolated from seaweeds, their molecular mechanisms and reported biological activities

Bioactive Compound	Source Species	Mechanism of Action	Therapeutic /Biological Target	Key Quantitative Finding	References

Fucoidan	Fucus vesiculosus, Laminaria japonica	↑ Bax/Bcl-2 ratio; cytochrome c release;caspase-9/3 cascade activation;G1 arrest via p21WAF1/CIP1 upregulation;CDK4/6-Cyclin D1 disruption	Apoptosis induction; cell cycle arrest; anti-angiogenesis; anti-metastasis	Preferential apoptosis in transformed cells sparing normal counterparts; VEGFR-2 phosphorylation suppression;VEGF-mediated tube formation blocked	[7,68]
Fucoxanthin	Undaria pinnatifida, Phaeodactylum tricornutum,Laminaria spp	PI3K/Akt/mTOR inhibition;UCP-1 activation in white adipose tissue; NF-κB and COX-2 suppression;Nrf2 pathway activation;MMP downregulation	Anti-obesity;anti-cancer;neuroprotection;hepatoprotection;anti-inflammation	Dose and time dependent reduction in TNBC cel viability; significant UCP-1-mediated thermgenesis in murine visceral fat;COX-2 transcription suppresses	[2,47]
Phlorotannins	Ecklonia cava,Ecklonia stolonifera,Fucus vesiculosus	IκB kinase (IKK) phosphorylation inhibition →cytoplasmic NF-κB sequestration;COX-2/iNOS transcription suppression; ROS scavenging	Anti-inflammation;antioxidant;antimicrobial(MRSA); anti-metastasis	Antioxidant capacity exceeds epigallocatechin gallate 9EGCG) in multiple assays;MMP-2/MMP-9 production inhibited;Warburg metabolic reprogramming suppressed in melanoma	[10,27,36]
Carrageenan(κ, ι, λ types)	Kappaphycus alvarezii. Eucheuma spp.,Gigartina spp(Rhodophyta)	Steric blockade of viral binding to heparan sulphate proteoglycans on host cell surfaces;macrophage and dendritic cell stimulation;TLR-mediated immune activation	Antiviral (SARS-CoV-2,HSV,influenza); immunostimulation; mucosal barrier protection	Carrageenan nasal sprays significantly reduced duration of upper respiratory tract infections in placebo-controlled trials	[13]

Ulvan	Ulva Lactuca,Ulva rigida (Chlorophya)	Salicylate and jasmonate dependent plant defence pathway activation;TLR-4/MyD88 signalling modulation in macrophages;rhamnose-rich structural elicitor activity	Plant immunity elicitation; anti-inflammation; immunomodulation	Foliar ulvan application significantly enhanced resistance to fungal, bacterial and viral plant pathogens; pro-inflammatory cytokine release reduced in macrophage cultures	[22]
Bioactive Peptides (ACE-inhibitory antidiabetic)	Porphyra spp.,Sargassum spp.,Palmaria palmata	Competitive inhibition of angiotensin-converting enzyme (ACE);DPP-IV inhibition ; α-glucosidase	Antihypertensive; antidiabetic(type 2); antioxidant; antibacterial	ACE-inhibitory peptides from Porphyra structurally similar to captopril; DPP-IV inhibitory IC_{50} values in µM	[14,15]
Fucosterol	Sargassum fusiforme,Laminaria spp., Ecklonia cava (Phaeophyta)	Inhibition of inflammatory cytokine generation(TNF-α, IL-6);lipid peroxidation suppression;cholesterol metabolism alteration; HMG-CoA reductase modulation	Anti-inflammation; lipid-lowering ;antidiabetic; antioxidant	Significant reduction in serum triglycerides and LDL in murine hyperlipidaemia models; cytokine suppression comparable to reference NSAID controls	[23,12]
Phycobiliproteins	Porphra spp.,Gracilaria spp;Spirulina platensis	Lymphocyte proliferation stimulation; interferon production induction; myeloperoxidase activity inhibition ;antioxidant electron-scavenging selective cytotoxicity in cancer cell lines	Immunostimulation; anti-inflammation; antioxidant; potential antitumour	C-phycocyanin IC_{50} against MCF-7 cells reported in µM range; interferon-γ induction confirmed; myeloperoxidase inhibition upto 80%at tested concentrations	[21]

Halogenated Terpenoids	Laurencia obtuse,Laurencia spp.,Callophycus serratus	Bacterial membrane disruption; ergosterol synthesis	Antibacterial ;Antifungal	Minimum inhibitory concentrations (MICs) comparable to clinical antifungal reference drugs for select compounds;strong and species-specific cytotoxicity against carcinoma cell lines	[73]
Alginate	Macrocystis pyrifera, Laminaria hyperborea,Ascophyllum nodosum (Phaeophyta)Controlled	Controlled-release encapsulation of drugs, probiotics and cells; ionic crosslinking with divalent cations (Ca^{2+}, Ba^{2+}) forming hydrogel matrices; wound-site moisture retention; prebiotic fermentation in colon	Drug delivery scaffold; wound healing;tissue engineering; gut microbiome modulation; heavy metal removal	Calcium alginate wound dressings significantly reduced healing time vs standard gauze in chronic wound RCTs; >95% encapsulation efficiency reported for various bioactives	[54]

Table 2. Translational and Clinical Development Status of Key Seaweed-Derived Bioactive Compounds

Bioactive Compound	Development Stage	Key Bioavailability	Proposed Delivery Stage	References
Fucoidan	Phase II RCT (adjunct in colorectal cancer)	Low GI absorption of intact polymer; species to species structural variability complicates standardisation	Low-MW fractionation; polymeric micelle encapsulation	[68,11]
Fucoxanthin	Preclinical/early Phase I (obesity,TNBC)	Extensive first-pass metabolism converts parent compound to fucoxanthinol;poor aqueous solubility	Lipid nanoparticle or alginate microencapsulation; co-administration with fish oil to enhance uptake	[2,42]

Phlorotannins	Preclinical (in vitro) limited human nutraceutical trials	Poor water solubility at high MW; oxidative instability during processing and storage	Nanoparticle encapsulation; cyclodextrin complexation to enhance solubility	[36,41,10]
Carrageenan	Approved food additive; nasal spray RCTs completed (antiviral)	Regulatory debate over intestinal safety of degraded forms (poligeenan);type-specific toxicity profile needs clarification	Tropical/mucosal formulations (nasal spray,gel); controlled MW fractionation	[34,46]
Bioactive Peptides	Preclinical functional food ingredient stage	Susceptibility GI proteolysis before absorption; variable yield by hydrolysis method	Microencapsulation in alginate or whey matrix; peptidomimetic analogues resistant to proteolysis	[23,1]
Alginate	Approved excipient/wound dressing; ongoing tissue engineering trials	Batch-to batch M/G ratio variability affects gel strength and degradation rate; immunogenicity of impurities	Ultrapurification protocols; hybrid hydrogels with collagen or hyaluronate for tissue engineering	[54,63,41]

Author contributions:
All authors equally contributed to the study design and conceptualisation
Funding: Not applicable.
Data availability: Not Applicable
Conflict of interest: Authors do not have any conflict of interest to declare.

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