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Bioactive Constituents and Pharmacological Activities of the Green Seaweed Genus *Codium*: A Systematic Review (2020–2026)

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ABSTRACT

Marine macroalgae represent an abundant yet underutilized source of bioactive compounds with immense potential in the pharmaceutical, nutraceutical, and biotechnological sectors. Among them, the green algae genus *Codium* (*Chlorophyta*, *Bryopsidales*) is distinguished by its structural and chemical diversity, producing sulfated polysaccharides, glycoproteins, lectins, polar lipids, carotenoids, and phenolic compounds. Despite numerous individual studies reporting its bioactivities, a comprehensive synthesis of *Codium*'s phytochemical composition, pharmacological effects, and applied potential has been lacking. This systematic review consolidates current knowledge on *Codium*'s chemical structures, bioactivities, and structure–activity relationships (SAR). The review followed the PRISMA 2020 protocol. Peer-reviewed studies were retrieved from PubMed, ScienceDirect, Wiley Online Library, and Scopus using the keywords "*Codium*," extracts, fractions, polysaccharides, and bioactivity terms. From 1,034 records identified, 729 remained after duplicate removal; 347 records named *Codium* in their title or abstract, and 113 studies published between 2020 and 2026 met the inclusion criteria and were coded from their abstracts. Thematic analysis was conducted across chemical composition, pharmacological activity, SAR, and applications. *Codium* species produced sulfated galactans, galactoarabinans and mannans, lectins, membrane polar lipids, fatty acids, siphonaxanthin, loliolide, and phenolics, and were also formulated into nanoparticles, liposomes, ointments, and nanoemulsions. Reported effects included antioxidant (48 studies), anti-inflammatory (26), antimicrobial including antifungal (25), anticancer (21), neuroprotective or organ-protective (17), metabolic (12), immunomodulatory (11), skin-related (10), and anticoagulant (4) activities, with sulfation pattern, molecular weight, and backbone type emerging as structural determinants in the best-characterized polysaccharides. *C. fragile* was the most investigated species (55 of 113 studies), South Korea contributed 38 studies, and 41 studies (36.3%) appeared in 2024–2026. Methodological variation in extraction and bioassays prevents quantitative synthesis; 78 studies were in vitro (four with in silico support), 34 used animal models, and only two included a clinical test. The genus nevertheless offers opportunities in functional food, cosmeceutical, drug-delivery, and biomaterial sectors. Standardized extraction, species-level identification, and in vivo validation will be crucial for unlocking *Codium*'s therapeutic and industrial applications.

1. Introduction

Marine algae are increasingly recognized as an untapped reservoir of bioactive compounds with high potential in the fields of nutraceuticals, pharmaceuticals, and biotechnology. Their structural diversity, rapid biomass productivity, and chemical adaptability have made them ideal candidates for natural product discovery and sustainable industrial applications [1]. Algae-derived compounds, including polysaccharides, polyphenols, fatty acids, and sterols, exhibit multiple pharmacological properties such as antioxidant, antimicrobial, antitumor, and neuroprotective activities, contributing to the development of functional foods and marine-based therapeutics [2,3]. These compounds are now regarded as promising leads for next-generation drugs with broad biomedical and biotechnological relevance.

Within this vast marine biodiversity, green macroalgae of the genus *Codium* (Bryopsidales, Chlorophyta) stand out for their ecological abundance and biochemical richness. *Codium* species are distributed across tropical and subtropical marine ecosystems, particularly in the Indo-Pacific region, and are known to contain diverse metabolites such as sulfated polysaccharides, sterols, flavonoids, and polyunsaturated fatty acids [4,5]. These compounds are associated with strong pharmacological effects, including anticoagulant, anti-inflammatory, anticancer, antioxidant, and antimicrobial activities [6]. Recent analytical studies have highlighted the presence of siphonaxanthin, clerosterol, and galactofuranose-linked sulfated polysaccharides that exhibit significant bioactivity in human cell and animal models, supporting the potential of *Codium* as a marine pharmacophore. Moreover, the edible nature of several *Codium* species enhances their suitability for nutraceutical applications and sustainable aquaculture systems.

Despite growing scientific interest, studies on *Codium* remain fragmented and lack comprehensive synthesis. Previous works have focused on isolated bioactivities or single-compound investigations without integrating chemical structure, mechanistic pathways, and industrial implications [7,8]. Furthermore, variations in extraction techniques, solvent polarity, and assay models have led to inconsistent results regarding compound yield and bioactivity profiles [9]. While some research has elucidated the anticoagulant and antiangiogenic mechanisms of *Codium* sulfated polysaccharides, others have explored its antioxidant or

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antimicrobial actions independently, leaving the structure–activity relationships (SAR) largely unexplored [3,10]. This fragmentation underscores the need for a systematic approach that unifies chemical, biological, and pharmacological evidence to elucidate the comprehensive therapeutic potential of this genus. Existing reviews have addressed the genus only in part: a concise review of its bioactivity and pharmacological properties [4] and a review restricted to its sulfated polysaccharides [11]. The present review adds a four-database PRISMA 2020 search, a study-level evidence table, and a cross-study analysis of species, test systems, activities, and structure–activity relationships.

The systematic literature review (SLR) approach provides a robust methodological framework to address these research gaps by synthesizing and analyzing data from existing studies with transparency and replicability. Through the PRISMA-guided process, this review critically examines empirical findings on the bioactive compounds of *Codium*, focusing on four major dimensions: chemical composition, pharmacological activity, structure–activity relationships, and industrial relevance [1]. By consolidating data from multiple disciplines—marine biochemistry, pharmacognosy, and bioengineering—the study aims to identify recurring molecular structures responsible for biological activity, determine the mechanisms underlying pharmacological responses, and assess the feasibility of large-scale applications. This integrative approach not only enhances the scientific understanding of *Codium* bioactivity but also contributes to future drug development and sustainable marine biotechnology.

The significance of this study extends beyond academic synthesis; it provides practical implications for the development of marine-derived health products and eco-friendly biomaterials. By systematically organizing available evidence, this review positions *Codium* as a valuable bioresource for the blue economy, aligning with global priorities for sustainable marine exploitation and green innovation [2,6]. Furthermore, it contributes to bridging the gap between marine natural product chemistry and industrial bioprocessing, offering new perspectives for nutraceutical formulation, cosmeceutical innovation, and marine-based pharmaceuticals. Thus, this systematic review serves not only as a comprehensive scientific reference but also as a foundation for translating *Codium*'s biochemical potential into tangible, sustainable solutions for health and industry in the 21st century.

The primary objective of this systematic literature review is to comprehensively analyze and synthesize existing scientific evidence on the bioactivity, chemical composition, and pharmacological potential of the genus *Codium*. Specifically, this study aims to (1) identify and classify the diverse bioactive compounds and phytochemical constituents present in various *Codium* species; (2) evaluate their reported pharmacological activities, including antioxidant, anti-inflammatory, anticoagulant, anticancer, and antimicrobial effects; (3) elucidate the structure–activity relationships (SAR) underlying these bioactivities to understand molecular mechanisms of action; and (4) assess the potential industrial applications of *Codium* compounds in pharmaceuticals, nutraceuticals, cosmeceuticals, and biotechnological innovation. Through a systematic synthesis of peer-reviewed literature, this review seeks to bridge the current research gaps, establish an integrated understanding of *Codium*'s therapeutic value, and provide a scientific foundation for future research and sustainable marine-based product development.

2. Method

2.1. Research Design

This study adopted a Systematic Literature Review (SLR) design following the PRISMA 2020 (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) framework [12]. The purpose of this approach was to synthesize, analyze, and integrate scientific findings related to the bioactivity, chemical structures, and pharmacological potential of the genus *Codium*. The PRISMA method ensured transparency, accuracy, and reproducibility in each stage of the review process, which consisted of four sequential steps: identification, screening, eligibility, and inclusion. The literature search used specific keywords such as "*Codium*," "bioactive compounds," "extract," "polysaccharide," and "bioactivity", applied to peer-reviewed articles without a lower date limit; the review was restricted to studies published from 2020 onwards (2020–2026).

2.2. Data Sources, Search Strategy, and Inclusion Criteria

A comprehensive search was conducted across four bibliographic databases—PubMed, ScienceDirect, Wiley Online Library, and Scopus—to cover biomedical, chemical, marine-science, and multidisciplinary sources. Boolean operators and keyword combinations of three concept blocks were used: (i) *Codium* names (e.g., "*Codium*," "*C. fragile*," "*C. tomentosum*," "*C. isthmocladum*"), (ii) preparation or compound terms (extract, fraction, polysaccharide, sulfated, lipid, carotenoid), and (iii) bioactivity terms (bioactivity, anticoagulant, antioxidant, anti-inflammatory, anticancer, antimicrobial). PubMed was searched in the title/abstract field; because ScienceDirect allows at most eight Boolean operators per field, its query was split into sub-strings whose results were merged; Wiley was searched with the Advanced Search title/abstract/keyword fields; and Scopus was searched in the title, abstract, and keyword fields. Records were exported in RIS or NBIB format on 2 and 8 October 2026. The first Scopus export (365 records) carried bibliographic data and citation counts but no abstracts, so Scopus was exported again with abstracts and author keywords (362 of 365 records with abstracts), and this second export was used to code the Scopus-only studies (Section 2.4). Only peer-reviewed journal articles written in English were included.

Inclusion criteria were as follows:

a. The study focused on the genus *Codium* or its derived compounds.
b. Contained empirical data on bioactivity, structural characterization, or pharmacological analysis.
c. Published in a peer-reviewed journal between 2020 and 2026.
d. Provided complete methodological details regarding extraction, isolation, or testing procedures.

Exclusion criteria included review articles (as typed in the database or evident from the title), conference papers, errata and book chapters, non-English papers, studies on unrelated algal genera, studies that only mentioned *Codium* without testing it for bioactivity (e.g., taxonomy, ecology, physiology, contaminants, bioenergy, food preservation, feed trials), and publications lacking analytical or experimental bioactivity data.

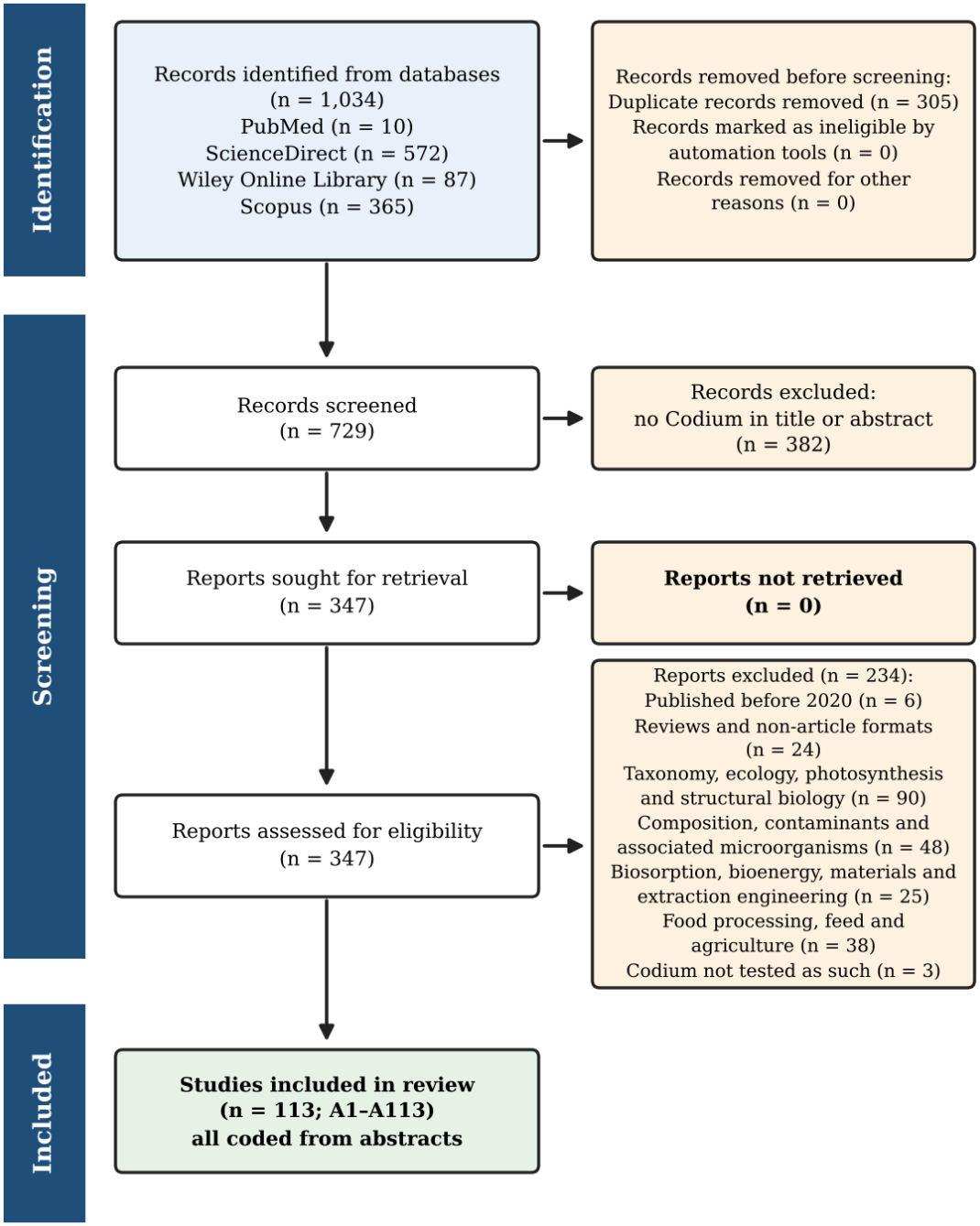


Figure 2.1. PRISMA 2020 flow diagram of the study selection process.

2.3. PRISMA Flow Diagram

This review followed the PRISMA 2020 model with four major stages to ensure systematic article selection and quality control.

a. Identification: A total of 1,034 records were retrieved from the four databases (PubMed 10, ScienceDirect 572, Wiley Online Library 87, Scopus 365) using the defined search terms. No records were marked ineligible by automation tools or removed for other reasons (n = 0). After removal of 305 duplicates (matched by DOI or normalized title), 729 unique records remained.

b. Screening: 382 records were excluded because *Codium* was not named in the title or abstract (reviews and studies on unrelated algal genera). Titles and abstracts were checked for records from PubMed, ScienceDirect, and Wiley. Scopus-only records were first screened on their titles because the first Scopus export had no abstracts; after a second export with abstracts, the 186 Scopus records that name *Codium* only in the abstract were re-screened. Seven of them had already been included and seven had already been assessed and excluded, so 172 further reports passed to eligibility assessment.

c. Eligibility: All 347 remaining reports were sought for retrieval and none was unretrievable at record level (reports not retrieved, n = 0), because assessment used the title and abstract fields of the exports. The 347 reports were assessed against the inclusion criteria, emphasizing compound isolation, chemical structure elucidation, and biological testing of *Codium* material.

Two hundred thirty-four were excluded: studies published before 2020 (n = 6), which fall outside the date window of this review; review articles (n = 14; e.g., [4]; [11]; [13]); non-journal formats (n = 10; e.g., a conference paper [14] and a book chapter [15]); taxonomy, phylogeny, genomics, and palaeontology (n = 30; e.g., [16]; [17]; [18]; [19]); ecology, invasion, reproduction, and cultivation (n = 50; e.g., [20]; [21]; [22]; [23]); photosynthesis, pigments, and structural biology (n = 10; e.g., [24]; [25]; [26]); chemical composition, lipidomics, contaminants, and metals (n = 32; e.g., [27]; [28]; [29]; [30]; [31]); associated microorganisms (n = 16; e.g., [32]; [33]; [34]); biosorption, bioenergy, materials, and extraction engineering (n = 25; e.g., [35]; [36]; [37]; [38]); food processing, preservation, feed, and agriculture (n = 38; e.g., [39]; [40]; [41]; [42]); and records in which *Codium* material was not tested or was not the stated source (n = 3). Multi-species studies were included when a *Codium* extract or compound was tested in a bioassay, even when another species was more active. Assessment was based on titles and abstracts; full-text verification is pending.

d. Inclusion: Finally, 113 articles published from 2020 onwards met all criteria and were included in the qualitative synthesis, 80 from the original screening (A1–A80) and 33 from the abstract-level re-screening of Scopus records (A81–A113). These studies encompassed diverse *Codium* species and covered anticoagulant, immunomodulatory, anticancer, anti-inflammatory, antioxidant, antimicrobial, antifungal, neuroprotective, metabolic, skin-related, antiviral, larvicidal, and antialgal effects.

The selection process is summarized in Figure 2.1, following the PRISMA 2020 structure.

2.4. Thematic Analysis Procedure

A thematic analysis approach was employed to extract and interpret key findings from the 113 selected articles. Each study was coded manually based on essential elements such as the *Codium* species investigated, sampling location and extraction method, identified chemical structures, type of bioactivity tested, and pharmacological mechanisms reported. The coding process was conducted iteratively through four main stages: data familiarization, generation of initial codes, identification and refinement of emerging themes, and synthesis into core thematic categories, including chemical composition, pharmacological activity, structure–activity relationship, and industrial potential. All 113 studies were coded from their abstracts: 25 studies that also appeared in PubMed, ScienceDirect, or Wiley from those records, and the other 88 studies from the abstracts and author keywords of the second Scopus export; for multi-species studies, only the *Codium* material was coded, and the most active species is named when the abstract gave no *Codium*-specific value; items not reported in an abstract are marked as not investigated or not chemically profiled. Activity counts were obtained by keyword coding of the activity descriptor of each study, so a study can contribute to more than one activity category. Citation counts are those reported by Scopus on 8 and 14 October 2026 and were used descriptively only. This structured approach kept data interpretation coherent and transparent, but it does not replace full-text extraction.

3. Results

3.1. Overview of the Reviewed Studies

This section provides a concise synthesis of the 113 empirical studies (A1–A113) included in this systematic review on the genus *Codium*. The selected works, published between 2020 and 2026, encompass a wide geographic distribution across 26 countries (South Korea, Portugal, Egypt, India, China, Brazil, Spain, Morocco, Pakistan, Philippines, Turkey, Greece, Saudi Arabia, Tunisia, Algeria, Australia, Chile, Croatia, France, Japan, Malaysia, Mexico, Russia, South Africa, Sri Lanka, Vietnam). The reviewed studies employed in vitro, in vivo, in silico, and, in two cases, clinical test designs to explore the phytochemical composition, biological activities, and pharmacological mechanisms of *Codium* species. Analytical techniques such as GC–MS, LC–MS and UPLC-QTOF-MS/MS, HPLC, FTIR, NMR, ion-exchange and size-exclusion chromatography, molecular docking, and molecular dynamics were used for compound isolation and structure elucidation. The bioactivities reported include antioxidant, anticancer, anti-inflammatory, immunomodulatory, neuroprotective, antimicrobial, antifungal, metabolic, skin-related, anticoagulant, antiviral, larvicidal, and antialgal effects. Chemically, *Codium* species are characterized by sulfated polysaccharides, glycoproteins, lectins, polar lipids, carotenoids, terpenoids, and phenolic compounds, each contributing to their pharmacological potential. Mechanistic insights across studies emphasize distinct structure–activity relationships (SAR), where sulfate position, molecular weight, and glycosylation patterns influence bioactivity. Design was read from the abstracts and country was inferred from author lists, journals, and abstracts; both should be verified against the full texts. Collectively, the findings affirm *Codium* as a promising marine source of bioactive compounds with potential for nutraceutical and pharmaceutical development.

Table 3.1. Summary of Empirical Studies on the Genus *Codium* (A1–A113)

Code	Authors & Year	Full Title	Article Type	Country	Research Type	*Codium* Source	Phytochemical Profile of *Codium*	Pharmacological Activities of *Codium* Bioactive Compounds	Mechanistic Insights / SAR	Key Research Findings
A1	Park et al. [43]	Cancer immunotherapy using a polysaccharide from *Codium fragile* in a murine model	Journal article	South Korea	Experimental in vitro + in vivo (BMDCs; B16 melanoma and CT-26 carcinoma mice)	*C. fragile*	Polysaccharide (CFP)	Immunomodulatory (dendritic-cell activation); anticancer adjuvant	DC activation in spleen and lymph nodes; OVA-specific T-cell activation and tumour infiltration of IFN-γ- and TNF-α-producing T cells	CFP with a tumour antigen inhibited B16 growth and enhanced anti-PD-L1 therapy in CT-26-bearing mice

Code	Authors & Year	Full Title	Article Type	Country	Research Type	*Codium* Source	Phytochemical Profile of *Codium*	Pharmacological Activities of *Codium* Bioactive Compounds	Mechanistic Insights / SAR	Key Research Findings
A2	J. Kim et al. [44]	*Codium fragile* ameliorates high-fat diet-induced metabolism by modulating the gut microbiota in mice	Journal article	South Korea	Experimental in vivo (high-fat-diet mice, 12 weeks)	*C. fragile*	Extract (not chemically profiled)	Anti-obesity	Modulation of gut microbiota (↑ Bacteroidetes, ↓ Verrucomicrobia) and predicted intestinal metabolic pathways	Lower body weight, adipocyte size, serum cholesterol and glucose
A3	J. E. Kim et al. [45]	Co-immunomodulatory activities of anionic macromolecules extracted from *Codium fragile* with red ginseng extract on peritoneal macrophage of immune-suppressed mice	Journal article	South Korea	Experimental in vivo (cyclophosphamide-immunosuppressed mice, oral) + ex vivo macrophages	*C. fragile*	Anionic macromolecules (CFAM) combined with red ginseng extract	Immunomodulatory	↑ macrophage viability and NO; ↑ iNOS, COX-2, TLR-4, IL-1β, IL-6, TNF-α and IFN-γ expression	CFAM enhanced the immune activity of red ginseng extract in peritoneal macrophages of immunosuppressed mice
A4	Vasquez & Lirio [46]	Content analysis, cytotoxic, and anti-metastasis potential of bioactive polysaccharides from green alga *Codium intricatum* Okamura	Journal article	Philippines	Experimental in vitro (MTT on MCF-7 and dermal fibroblasts; MMP-1 assay)	*C. intricatum* (Ilocos Norte, Philippines)	Hot-water crude polysaccharide and ion-exchange fractions: carbohydrate 2.07–16.1%, sulfate 1.81–9.9%; FT-IR and NMR consistent with sulfated galactans	Cytotoxic (MCF-7); anti-metastatic	Inhibition of MMP-1 production in UVB-exposed fibroblasts	Crude polysaccharide and fractions inhibited MCF-7 growth concentration-dependently and stimulated fibroblast proliferation
A5	Fahem et al. [47]	Cytotoxic activity assessment and GC-MS screening of two *Codium* species extracts	Journal article	Algeria	Experimental in vitro (MTT on HeLa cells; flash chromatography, GC-MS)	*C. bursa* and *C. fragile* (north Tunisian coast; spring and summer)	Solvent extracts; active petroleum-ether fraction: 6,10,14-trimethyl-2-pentadecanone, 2-dodecanone, 1-dodecanol, dodecyl acrylate and two terpenoid derivatives (GC-MS)	Cytotoxic (HeLa)	Not investigated; activity higher in spring than in summer	Petroleum-ether extract of *C. bursa* was most active (IC50 115.8 µg/mL)
A6	Arguelles [48]	Evaluation of nutritional composition and in vitro antioxidant and antibacterial activities of *Codium intricatum* Okamura from Ilocos Norte (Philippines)	Journal article	Philippines	Experimental in vitro (proximate and elemental analysis; radical scavenging; MIC/MBC)	*C. intricatum* (Ilocos Norte, Philippines)	Ash 37.16%, carbohydrate 32.16%; Na > K > Ca > Mg > Fe, with Pb and Cd detected; phenolics	Antioxidant (EC50 40.79 mg GAE/mL); antibacterial	Radical scavenging correlated with phenolic content	Methanol extract inhibited MRSA (MIC 250 µg/mL), *B. cereus* and *L. monocytogenes* but not Gram-negative bacteria
A7	Bellan et al. [49]	Green does not always mean go: A sulfated galactan from *Codium isthmocladum* green seaweed reduces melanoma metastasis through direct regulation of malignancy features	Journal article	Brazil	Experimental in vitro (B16-F10 cells) + in vivo (mice)	*C. isthmocladum*	Sulfated homogalactan 3G4S	Antitumor; antimetastatic (melanoma)	Not cytotoxic; reduced invasion, colony formation and membrane glycoconjugates of B16-F10 cells	3G4S reduced solid tumour growth and metastasis in mice without side effects
A8	Zhang et al. [50]	Human peripheral blood dendritic cell and T cell activation by *Codium fragile* polysaccharide	Journal article	South Korea	Experimental in vitro (human monocyte-derived and peripheral blood dendritic cells)	*C. fragile*	Polysaccharide (CFP)	Immunomodulatory (human DC and T-cell activation)	↑ CD80, CD83, CD86 and MHC I/II; BDCA1+ and BDCA3+ DCs activated CD4 and cytotoxic CD8 T cells	CFP directly activated human blood dendritic cells and downstream T-cell responses
A9	Monmai et al. [51]	Immune-enhancing effects of anionic macromolecules extracted from *Codium fragile* coupled with arachidonic acid in RAW264.7 cells	Journal article	South Korea	Experimental in vitro (RAW264.7 macrophages)	*C. fragile*	Anionic macromolecules (sulfated polysaccharides) combined with arachidonic acid	Immunomodulatory	↑ NO, iNOS, COX-2, IL-1β, IL-6 and TNF-α via NF-κB p65, p38 and ERK1/2	Co-treatment with arachidonic acid enhanced macrophage activation more than *Codium* alone

Code	Authors & Year	Full Title	Article Type	Country	Research Type	*Codium* Source	Phytochemical Profile of *Codium*	Pharmacological Activities of *Codium* Bioactive Compounds	Mechanistic Insights / SAR	Key Research Findings
A10	Zbakh et al. [52]	Insights on the anti-inflammatory and antitumor activities of extracts from the marine green alga *Codium decorticatum*	Journal article	Morocco	Experimental in vitro (endothelial cells; cancer cell lines; MTT and flow cytometry)	*C. decorticatum*	n-Hexane, dichloromethane and acetone/methanol extracts	Anti-inflammatory; cytotoxic (HeLa)	↓ IL-8 and E-selectin expression in LPS/TNF-α-stimulated endothelial cells; apoptosis induction	Dichloromethane extract had IC50 37.22 µg/mL against HeLa cells
A11	Silva et al. [53]	Natural approaches for neurological Disorders—The neuroprotective potential of *Codium tomentosum*	Journal article	Portugal	Experimental in vitro (6-OHDA model in SH-SY5Y cells) + GC-MS	*C. tomentosum*	Enriched fractions; terpenes, alcohols, carboxylic acids, aldehydes, esters, ketones and hydrocarbons (tentative GC-MS)	Neuroprotective (Parkinson's disease model)	↓ ROS, mitochondrial dysfunction, DNA damage and caspase-3 activity	Four fractions restored viability to levels similar to or above vitamin E (90.11%)
A12	Carneiro et al. [54]	New lectins from *Codium isthmocladum* Vickers show unique amino acid sequence and antibiofilm effect on pathogenic bacteria	Journal article	Brazil	Experimental in vitro (lectin purification, MALDI-ToF MS, sequencing, biofilm assays) + in silico 3D model	*C. isthmocladum*	Lectins CiL-1 (12 kDa, 112 residues, two repeated domains) and CiL-2 (oligomeric)	Antibiofilm (*S. aureus*, *S. epidermidis*); haemagglutinating	Galactoside- and GalNAc-specific binding; predicted β-barrel fold with two monosaccharide-binding sites	No direct antibacterial activity, but significant inhibition of staphylococcal biofilm formation
A13	Park et al. [55]	Polysaccharide from *Codium fragile* induces anti-cancer immunity by activating natural killer cells	Journal article	South Korea	Experimental in vitro + in vivo (mouse tumor models)	*C. fragile*	Polysaccharide (CFP)	Immunomodulatory; anticancer	NK-cell activation (↑ CD69, IFN-γ, perforin, granzyme B); IL-12-dependent; effect lost after NK depletion	CFP prevented lung infiltration of CT-26 carcinoma and B16 melanoma cells without significant body-weight loss
A14	Wang et al. [56]	Protective effects of sulfated polysaccharides isolated from the enzymatic digest of *Codium fragile* against hydrogen peroxide-induced oxidative stress in in vitro and in vivo models	Journal article	South Korea	Experimental in vitro (Vero cells) + in vivo (zebrafish)	*C. fragile*	Sulfated polysaccharides from enzymatic digest (CFCE-PS): 55.78% carbohydrate, 21.06% sulfate	Antioxidant	Hydroxyl, alkyl and DPPH radical scavenging (IC50 1.21, 1.42 and 6.14 mg/mL); ↓ intracellular ROS and apoptosis	Protected Vero cells and zebrafish against H2O2-induced oxidative damage
A15	Zheng et al. [57]	Siphonaxanthin, a carotenoid from green algae *Codium cylindricum*, protects Ob/Ob mice fed on a high-fat diet against lipotoxicity by ameliorating somatic stresses and restoring anti-oxidative capacity	Journal article	Japan	Experimental in vitro (HepG2) + in vivo (Ob/Ob mice on high-fat diet)	*C. cylindricum*	Siphonaxanthin (carotenoid)	Metabolic; antioxidant; liver and kidney protection	Nrf2-regulated antioxidant signalling; restored β-oxidation and ER-associated degradation genes in kidney	Lowered plasma glucose, ALT and hepatic lipid peroxidation, but did not improve steatosis or adiposity
A16	Mendes et al. [58]	A nanophytosomes formulation based on elderberry anthocyanins and *Codium* lipids to mitigate mitochondrial dysfunctions	Journal article	Portugal	Experimental in vitro (nanoformulation, SH-SY5Y cells)	*C. tomentosum*	Membrane polar lipids (26% non-phosphorus polar lipids, 74% phospholipids; high PUFA)	Mitochondrial protection (neuroprotective potential)	Targets mitochondria, improves complexes I and II, preserves membrane potential	Nanophytosomes (108.74 ± 24.74 nm) protected SH-SY5Y cells against rotenone and glutamate toxicity
A17	Yim et al. [59]	Antiviral activity of two marine carotenoids against SARS-CoV-2 virus entry in silico and in vitro	Journal article	South Korea	In silico (docking) + in vitro (pseudovirus assay)	*C. fragile*	Siphonaxanthin (carotenoid)	Antiviral (SARS-CoV-2)	Predicted binding to Spike glycoprotein; inhibition of pseudovirus entry in ACE2-HEK293 cells	IC50 87.4 µM; fucoxanthin was inactive; low predicted acute toxicity and good GI absorption

Code	Authors & Year	Full Title	Article Type	Country	Research Type	*Codium* Source	Phytochemical Profile of *Codium*	Pharmacological Activities of *Codium* Bioactive Compounds	Mechanistic Insights / SAR	Key Research Findings
A18	Yan et al. [60]	Degradation of *Codium cylindricum* polysaccharides by H2O2-Vc-ultrasonic and H2O2-Fe2+-ultrasonic treatment: Structural characterization and antioxidant activity	Journal article	China	Experimental in vitro (degradation, antioxidant assays)	*C. cylindricum*	Polysaccharides degraded by H2O2-Vc/H2O2-Fe2+-ultrasonic treatment (Man, Gal, Ara, Glc, Rib)	Antioxidant	Lower molecular weight gave better antioxidant activity; basic structure unchanged	Antioxidant activity of both degraded polysaccharides was significantly enhanced
A19	Yan et al. [61]	Degradation, structural characterization and hypoglycemic activity of polysaccharides from *Codium cylindricum*	Journal article	China	Experimental in vitro (structural analysis; α-amylase and α-glucosidase inhibition)	*C. cylindricum*	Polysaccharides degraded by ultrasound-assisted H2O2–vitamin C and H2O2–Fe2+ (LC-MS, AFM, NMR; same monosaccharides and glycosidic configuration)	Hypoglycaemic (enzyme inhibition)	Degradation improved solubility, reduced particle size and enhanced enzyme inhibition	Moderate α-amylase and α-glucosidase inhibition, increased after degradation
A20	Yang et al. [62]	Effects of sulfated polysaccharides isolated from *Codium fragile* on inflammatory cytokine gene expression and *Edwardsiella tarda* infection in rockfish, *Sebastes schlegelii*	Journal article	South Korea	Experimental in vitro + in vivo (rockfish)	*C. fragile*	Sulfated polysaccharides (SPs)	Immunostimulatory / anti-inflammatory; antibacterial (MIC 2 mg/mL)	Altered IL-1β, IL-8, IL-6, TNF-α and IL-10 expression (up in vitro, down in head kidney and spleen in vivo)	Dietary SPs (0.1%) for 4 weeks lowered cumulative mortality after *Edwardsiella tarda* challenge
A21	Jang et al. [63]	Extracellular vesicles from Korean *Codium fragile* and *Sargassum fusiforme* negatively regulate melanin synthesis	Journal article	South Korea	Experimental in vitro + 3D epidermis model + clinical test	*C. fragile* (and *Sargassum fusiforme*)	Extracellular vesicles (EV)	Anti-melanogenic (skin whitening)	Downregulation of MITF, tyrosinase and TRP1	Effective at 25 μg/mL without affecting MNT-1 viability; cream with EV (5 μg/mL) improved skin brightness by 1.31% in a clinical test
A22	T. I. Kim et al. [64]	Extract of seaweed *Codium fragile* inhibits integrin αIIbβ3-induced outside-in signaling and arterial thrombosis	Journal article	South Korea	Experimental in vitro (platelet assays) + in vivo (FeCl3 arterial thrombosis and tail bleeding in mice)	*C. fragile*	Ethanol extract; phytol as main GC-MS constituent (160.8 mg/kg, isomers)	Antiplatelet; antithrombotic	↓ c-Src, Syk, PLCγ2, PI3K/AKT and MAPK phosphorylation; inhibition of integrin αIIbβ3 outside-in signalling	Oral extract blocked arterial thrombus formation without prolonging bleeding time
A23	Ahn et al. [65]	Identifying *Codium fragile* extract components and their effects on muscle weight and exercise endurance	Journal article	South Korea	Experimental in vivo (mice) + in vitro (UPLC-QTOF-MS/MS, cell assays)	*C. fragile*	Lysophosphatidylcholine, canthaxanthin, retinoic acid, α-tocopherol, unsaturated fatty acids	Muscle function (anti-sarcopenia potential)	mTORC1-mediated protein synthesis; SIRT1/PGC-1α-related mitochondrial biogenesis; canthaxanthin acts synergistically	Extract feeding increased exercise endurance and muscle weight in mice
A24	Wang et al. [66]	Intranasal administration of *Codium fragile* polysaccharide elicits anti-cancer immunity against Lewis lung carcinoma	Journal article	South Korea	Experimental in vivo (intranasal administration in C57BL/6 mice; Lewis lung carcinoma)	*C. fragile*	Polysaccharide (CFP)	Immunomodulatory; anticancer	Activation of macrophages, conventional DCs (CCR7), NK and T cells in mediastinal lymph nodes; effect required NK and CD8 T cells	Inhibited lung infiltration of carcinoma cells and improved anti-PD-L1 therapy

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A25	Radman et al. [67]	Less polar compounds and targeted antioxidant potential (in vitro and in vivo) of *Codium adhaerens* C. Agardh 1822	Journal article	Croatia	Experimental in vitro (four antioxidant assays) + in vivo (zebrafish, including embryotoxicity)	*C. adhaerens* (Adriatic Sea, Croatia)	Volatile compounds (HS-SPME, hydrodistillation); fatty acids (ω6 > ω3); less polar fractions by UHPLC-ESI-HRMS (fucoxanthin, pheophytin a and pheophorbide a, as reported)	Antioxidant	Activity attributed to pigments with known antioxidant properties	In vivo zebrafish results agreed with in vitro assays; air drying changed the volatile profile
A26	Silva et al. [68]	Loliolide, a new therapeutic option for neurological diseases? In vitro neuroprotective and anti-inflammatory activities of a monoterpenoid lactone isolated from *Codium tomentosum*	Journal article	Portugal	Experimental in vitro (6-OHDA model in SH-SY5Y cells; RAW264.7 macrophages)	*C. tomentosum*	Loliolide isolated from the diethyl ether extract (column chromatography; NMR)	Neuroprotective; anti-inflammatory	Mitochondrial protection, ↓ oxidative stress and apoptosis, NF-κB inhibition; ↓ NO, TNF-α and IL-6	Loliolide increased the viability of 6-OHDA-exposed cells by 40%
A27	Soares et al. [69]	Multi-step subcritical water extracts of *Fucus vesiculosus* L. and *Codium tomentosum* Stackhouse: Composition, health-benefits and safety	Journal article	Portugal	Experimental in vitro (brain-enzyme inhibition; ROS/RNS scavenging; UHPLC-MS/MS and ICP-MS safety screening)	*C. tomentosum* (with *Fucus vesiculosus*)	Four-step subcritical-water fractions; phenolics highest in step 1; Maillard and caramelization products at higher temperatures	Neuroprotective-related enzyme inhibition; antioxidant	Inhibition of five enzymes linked to Alzheimer's disease, Parkinson's disease and depression	Step-4 fractions were most active; early fractions contained arsenic and high iodine
A28	Li et al. [70]	Preparation and characterization of folic acid conjugated sulfated polysaccharides on NK cell activation and cellular uptake in HeLa cells	Journal article	South Korea	Experimental in vitro (conjugate synthesis, cell assays)	*C. fragile*	Sulfated polysaccharide conjugated to folic acid (SP-FA; FT-IR, 1H NMR)	Immunomodulatory; targeted anticancer	NK-cell activation via NF-κB and MAPK; ↑ IFN-γ, TNF-α, perforin, granzyme B; folate-receptor targeting	SP and SP-FA were not directly toxic but enhanced NK-cell cytotoxicity against HeLa cells
A29	G. H. Kim et al. [71]	Protective effect of *Codium fragile* extract on fine dust (PM2.5)-induced toxicity in nasal cavity, lung, and brain cells	Journal article	South Korea	Experimental in vitro (five cell lines exposed to PM2.5)	*C. fragile*	40% ethanol extract (highest phenolics) and water extract (highest polysaccharides)	Antioxidant; cytoprotective against PM2.5	↓ intracellular ROS in nasal, lung, brain, hippocampal and microglial cells	Ethanol extract better reduced ROS, whereas the water extract gave higher cell viability
A30	Wang et al. [72]	Anti-inflammatory effect of sulfated polysaccharides isolated from *Codium fragile* in vitro in RAW 264.7 macrophages and in vivo in zebrafish	Journal article	South Korea	Experimental in vitro (LPS-stimulated RAW264.7) + in vivo (zebrafish)	*C. fragile*	Sulfated polysaccharides (CFCE-PS)	Anti-inflammatory	↓ PGE2, NO, IL-1β, TNF-α and IL-6; ↓ ROS, cell death and NO in zebrafish	Concentration-dependent anti-inflammatory activity in vitro and in vivo
A31	Bartolomeu et al. [73]	Bioprospecting antibiotic properties in photodynamic therapy of lipids from *Codium tomentosum* and *Chlorella vulgaris*	Journal article	Portugal	Experimental in vitro (antimicrobial photodynamic therapy)	*C. tomentosum* (with *Chlorella vulgaris*)	Total lipid extract; polar lipid fractions (phospholipids, glycolipids, betaine lipids; LC-MS)	Antibacterial (*S. aureus*) with photodynamic therapy	Light-activated photodynamic inactivation	About 6 log10 (CFU/mL) reduction after 15 min (total extract) and after 60 min (polar lipid fraction)
A32	Keskinkaya et al. [74]	Chemical composition, in vitro antimicrobial and antioxidant activities of marine macroalgae *Codium fragile* (Suringar) Hariot	Journal article	Turkey	Experimental in vitro (LC-ESI-MS/MS; MIC; DPPH, ABTS and CUPRAC assays)	*C. fragile*	Gallic acid, 4-hydroxybenzaldehyde, 4-hydroxybenzoic acid, p-coumaric acid, salicylic acid, biochanin A and diosgenin; TPC 10.34–64.67 µg GAE/mg	Antimicrobial (MIC 1.562–3.125 mg/mL); antioxidant	Not investigated	All extracts were antimicrobial; the water extract was the best radical scavenger

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A33	Seo et al. [75]	*Codium fragile* reduces adipose tissue expansion and fatty liver incidence by downregulating adipo- and lipogenesis	Journal article	South Korea	Experimental in vivo (C57BL/6 mice on a high-fat diet, 7 weeks)	*C. fragile*	Extract (not chemically profiled)	Anti-obesity; fatty-liver reduction	↓ PPARγ, aP2, SREBP-1c and FAS expression in adipose tissue and liver	100 mg/kg reduced body weight, serum cholesterol and hepatic lipids
A34	Alves et al. [76]	*Codium isthmocladum* lectin 1 (CiL-1): Interaction with N-glycans explains antinociceptive and anti-inflammatory activities in adult zebrafish (*Danio rerio*)	Journal article	Brazil	Experimental in vivo (adult zebrafish) + in silico	*C. isthmocladum*	Galactose-binding lectin CiL-1	Antinociceptive; anti-inflammatory; reduces ROS	Lectin–N-glycan binding modulating the TRPA1 channel; LacNac2 gave the most favorable binding energy	Effective at all tested doses; reduced ROS in brain and liver
A35	Hafez et al. [77]	Fillet fish fortified with algal extracts of *Codium tomentosum* and *Actinotrichia fragilis*, as a potential antibacterial and antioxidant food supplement	Journal article	Egypt	Experimental in vitro (antibacterial, antioxidant and PBMC assays; HPLC) + food fortification	*C. tomentosum* (Red Sea; with *Actinotrichia fragilis*)	Aqueous extract; polyphenols by HPLC; TPC 32.28 mg/g, TFC 4.54 mg/g	Antibacterial; antioxidant (IC50 75.32 µg/mL)	Not investigated	Low toxicity to normal PBMCs; fish fillet fortified with the extract had the highest acceptance
A36	Mallabo et al. [78]	Inhibitory effect of sulfated polysaccharide from *Codium edule* P.C. Silva against 2,4-dinitrofluorobenzene (DNFB)-induced allergic contact dermatitis on female BALB/c mice	Journal article	Philippines	Experimental in vivo (DNFB-induced allergic contact dermatitis in BALB/c mice)	*C. edule*	Sulfated heteropolysaccharide F1 with β-D-galactan and β-L-arabinan units (DEAE chromatography; LC-MS)	Anti-inflammatory; anti-allergic (contact dermatitis)	↓ serum IFN-γ and TNF-α; compared with prednisolone	Non-toxic at 2000 mg/kg; reduced ear thickness, erythema and inflammatory infiltration
A37	Rabecca et al. [79]	Phytochemical and anti-inflammatory properties of green macroalga *Codium tomentosum*	Journal article	India	Experimental in vitro (GC-MS, membrane stabilization, protease inhibition)	*C. tomentosum*	Ethanol extract: 30 compounds incl. hexadecanoic acid methyl ester, octadecanoic acid, tris(2,4-di-tert-butylphenyl) phosphate; tannins, flavonoids, phenols, alkaloids	Anti-inflammatory	Membrane stabilization and protease inhibition; phenolic phosphate suggested as active principle	Significant anti-inflammatory activity of the ethanol extract
A38	Oh et al. [80]	Potential prebiotic and anti-obesity effects of *Codium fragile* extract	Journal article	South Korea	Experimental in vitro (fermentation with gut microbes; 3T3-L1 adipocytes)	*C. fragile*	Extract (TPC and TFC after fermentation)	Prebiotic; anti-obesity; antioxidant	Promoted beneficial microbes and suppressed pathogens; inhibited adipocyte differentiation	Fermentation with the extract increased phenolics and DPPH activity relative to glucose
A39	Rodrigues-Souza et al. [81]	Protective potential of sulfated polysaccharides from tropical seaweeds against alkylating- and oxidizing-induced genotoxicity	Journal article	Brazil	Experimental in vitro (comet assay, HepG2 cells)	*C. isthmocladum* (with a brown-seaweed fucan)	Sulfated galactan 3G4S	Antigenotoxic; antioxidant	Direct antioxidant action blocking initiation of the oxidative chain reaction	Not genotoxic; 81.38% DNA-damage reduction (72 h pretreatment) and 55.41% (simultaneous H2O2); no protection against alkylating MMS
A40	Abdel Haleem et al. [82]	Screening and evaluation of different algal extracts and prospects for controlling the disease vector mosquito *Culex pipiens* L	Journal article	Egypt	Experimental in vitro (larval bioassay, enzyme markers)	*C. tomentosum* (one of eight algal extracts)	Methanolic extract (not chemically profiled)	Larvicidal (*Culex pipiens*)	↑ SOD, catalase and glutathione peroxidase activity (oxidative stress)	LC50 69.85 ppm at 72 h, second only to *Galaxaura elongata* (31.13 ppm)

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A41	Pedro et al. [83]	Season affects three insufficiently studied seaweed species (*Bifurcaria bifurcata*, *Codium* sp., *Ericaria selaginoides*): bioactivity alterations	Journal article	Portugal	Experimental in vitro (DPPH, FRAP, ABTS; COX-2 inhibition; seasonal comparison)	*Codium* sp. (with *Bifurcaria bifurcata* and *Ericaria selaginoides*)	Seasonal ethanol extracts; phenolics	Antioxidant; weak anti-inflammatory	Season affected activity	*Codium* sp. had the highest FRAP but low COX-2 inhibition (13.6–15.5%)
A42	Li et al. [84]	Structure and anticoagulant activity of a galactofuranose-containing sulfated polysaccharide from the green seaweed, *Codium isthmocladum*	Journal article	China	Experimental in vitro (structural analysis; coagulation assays)	*C. isthmocladum*	Sulfated arabinan F2-1 (100 kDa, 18% sulfate; →4)-β-L-Arap backbone; β-D-Galf side chains)	Anticoagulant	Structure by methylation, desulfation, GC-MS, IR and NMR; galactofuranose is rare in seaweeds	F2-1 showed significant anticoagulant activity in vitro
A43	Figueroa et al. [85]	Sulfated polysaccharide extracted from the green algae *Codium bernabei*: Physicochemical characterization and antioxidant, anticoagulant and antitumor activity	Journal article	Chile	Experimental in vitro (GC-MS, GPC, FTIR, TGA, SEM; ABTS, DPPH; PT and aPTT; cancer cell lines)	*C. bernabei* (Chilean coast)	Hot-water polysaccharide fractions (TPs, APs): sulfated galactan, 17.4–19.3% sulfate, < 20 kDa	Antioxidant; anticoagulant; cytotoxic (HCT-116, MCF-7, HL-60)	Not investigated	aPTT prolonged only at 1000 µg/mL; TPs were more antioxidant (35% scavenging)
A44	Miguel et al. [86]	An antibacterial and bioactive sponge incorporating *Codium* sp.-mediated biosynthesized silver nanoparticles for the management of high exudate wounds	Journal article	Portugal	Experimental in vitro (material characterization, fibroblasts)	*Codium* sp.	Polysaccharide sponges with biosynthesized silver nanoparticles (46.10 ± 0.22 nm; ζ −18.20 mV)	Antibacterial; biocompatible (wound dressing)	Silver-nanoparticle antimicrobial action; high swelling (~2000%) and biodegradability	Sponges were biocompatible with fibroblasts, prevented microbial growth and lost ~80% weight in 5 days
A45	Ma et al. [87]	A novel sulfated mannan-carboxymethyl-5-fluorouracil-folic acid conjugates for targeted anticancer drug delivery	Journal article	South Korea	Experimental in vitro + in vivo (HCT-116 xenograft mice)	*C. fragile*	Sulfated polysaccharide CFP2 conjugated to carboxymethyl-5-FU and folic acid (NMR)	Anticancer drug delivery	Folate-targeted conjugate; controlled release (49.9% at 96 h, pH 7.4); enhanced apoptosis and uptake	Conjugates were safe and effective in the xenograft model
A46	Kim et al. [88]	*Codium fragile* suppressed chronic PM2.5-exposed pulmonary dysfunction via TLR/TGF-β pathway in BALB/c mice	Journal article	South Korea	Experimental in vivo (BALB/c mice, chronic PM2.5 exposure)	*C. fragile*	Aqueous extract: palmitic and stearic acids, oleamide, hexadecanamide, 13-docosenamide (GC/MS, UPLC-Q-TOF/MS)	Lung-protective; antioxidant; anti-inflammatory; antifibrotic	TLR4/MyD88/NF-κB and TGF-β1/Smad pathways; ↑ SOD and GSH, ↓ MDA; mitochondrial protection	Improved pulmonary oxidative, inflammatory, apoptotic and fibrotic markers
A47	Kim et al. [89]	*Codium fragile* suppresses PM2.5-induced cognitive dysfunction by regulating gut–brain axis via TLR-4/MyD88 pathway	Journal article	South Korea	Experimental in vivo (mice, chronic PM2.5 exposure; behavioural tests)	*C. fragile*	Aqueous extract: hexadecanamide, oleamide, octadecanamide, stearidonic and linolenic acids (UPLC-Q-TOF/MS)	Neuroprotective (cognitive function); gut–brain axis	TLR-4/MyD88 pathway; cholinergic system; gut microbiome, SCFAs and tight-junction proteins	Improved Y-maze, passive avoidance and Morris water maze performance
A48	Arunkumar et al. [90]	Cytotoxic characterization of optically negative *Codium fragile* polysaccharide against HeLa and MCF cell lines	Journal article	India	Experimental in vitro (cytotoxicity, FTIR)	*C. fragile* (one of eight seaweeds)	Low-molecular polysaccharide (6–8 kDa), optically negative L-form sulfated arabinogalactan	Cytotoxic (HeLa, MCF); antioxidant	>14 kDa fraction showed the strongest cytotoxicity and antioxidant activity	Cell survival 24–98.6% (HeLa) and 4.7–58% (MCF) across species; *C. fragile* had the lowest IC50
A49	González-Ballesteros et al. [91]	Gold nanoparticles synthesized by an aqueous extract of *Codium tomentosum* as potential antitumoral enhancers of Gemcitabine	Journal article	Spain	Experimental in vitro (HepG2 and BxPC-3 cells)	*C. tomentosum*	Aqueous extract used to synthesize gold nanoparticles (Au@CT; UV-Vis, FTIR, XRD, HPSEC)	Antiproliferative; antioxidant	Synergy with gemcitabine in HepG2 cells	Au@CT enhanced gemcitabine activity

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A50	Gupta [92]	Anti-inflammatory activity of *Codium elongatum* on Carrageenan-induced paw edema in Wistar male rats	Journal article	India	Experimental in vivo (carrageenan-induced paw oedema in Wistar rats)	*C. elongatum*	Water extract (250 mg/kg) and isolated polysaccharide (500 mg/kg)	Anti-inflammatory	Attributed to COX-2 pathway blockade	Both preparations reduced paw oedema significantly versus phenylbutazone
A51	Gangegoda et al. [93]	Antioxidant and antimicrobial properties of *Codium fragile* (Suringar) methanol extract: Insights from molecular docking analysis	Journal article	Sri Lanka	Experimental in vitro + in silico (docking)	*C. fragile*	Crude methanol extract (CME), polyphenolic (PPP) and polysaccharide (PSP) portions; phenols 74.54 µg GE/g (PPP)	Antioxidant; anti-inflammatory; antimicrobial	Docking supported antibacterial activity	High DPPH activity in PSP and PPP; CME best anti-inflammatory; only CME and PSP active against Gram-positive bacteria
A52	Lakhrem et al. [94]	Anti-vasculogenic, antioxidant, and anti-inflammatory activities of sulfated polysaccharide derived from *Codium tomentosum*: Pharmacokinetic assay	Journal article	Tunisia	Experimental in vitro (antioxidant assays) + in vivo (rat paw oedema; chick CAM) + in silico ADME	*C. tomentosum*	Sulfated polysaccharide (PCT)	Anti-inflammatory; antioxidant; anti-angiogenic	↓ MDA, ↑ SOD, GPx and GSH; protection of lymphocyte DNA; predicted bioavailability	Reduced paw oedema, leukocyte migration and CAM neovascularization dose-dependently
A53	Negm et al. [5]	Chemical composition and bioactivity of *Codium dwarkense* collected from the earthquake crack region of Ras Muhammad National Park, Red Sea, Egypt	Journal article	Egypt	Experimental in vitro (composition and bioassays)	*C. dwarkense* (Earthquake Crack, Ras Muhammad National Park, Red Sea)	Phenolics 250.08 mg GAE/g; flavonoids 85.4 mg rutin/g; quercetin, apigenin, pyrogallol, zeaxanthin, benzoic acid; hexadecanoic and oleic acids; vitamins C and E	Antimicrobial; antioxidant; antidiabetic; anti-inflammatory; anticancer	Not investigated	Significant activities attributed to the unique crack habitat; proposed as a functional-food resource
A54	Choi et al. [95]	*Codium fragile* extract prevents atopic dermatitis in DNCB-induced mice	Journal article	South Korea	Experimental in vivo (DNCB-induced atopic dermatitis in BALB/c mice)	*C. fragile*	Extract (not chemically profiled)	Anti-atopic dermatitis	Reduced epidermal thickening, ear swelling and lymphoid-organ weights	Extract alleviated dermatitis severity scores and histological lesions
A55	Oh et al. [96]	Effects of potential prebiotics from *Codium fragile* on intestinal diseases	Journal article	South Korea	Experimental in vivo (DSS-induced colitis in mice; 10-week feeding)	*C. fragile*	Extract; acetic acid as main caecal metabolite	Prebiotic; anti-colitis	↑ *Akkermansia muciniphila*; ↓ faecal β-glucuronidase and neutrophil activity	Alleviated disease activity index, colon shortening and histological damage
A56	S. A. Lee et al. [97]	Immuno-enhancing effect of *Codium fragile* extracts in RAW264.7 macrophages	Journal article	South Korea	Experimental in vitro (RAW264.7 macrophages; splenocytes)	*C. fragile*	Aqueous extract	Immunomodulatory	↑ NO, iNOS, TNF-α, IL-6, GM-CSF, G-CSF and MCP-1; MAPK and NF-κB p65 activation	Immune-enhancing effect at 1 mg/mL without cytotoxicity
A57	Jang et al. [98]	In vitro anti-inflammatory and skin protective effects of *Codium fragile* extract on macrophages and human keratinocytes in atopic dermatitis	Journal article	South Korea	Experimental in vitro (LPS-stimulated RAW264.7; TNF-α/IFN-γ-stimulated HaCaT)	*C. fragile*	Extract	Anti-inflammatory; skin-barrier protection (atopic dermatitis)	↓ NO, IL-1β, IL-4, IL-6, iNOS, COX-2 and TNF-α; NF-κB, ERK, p38 and JNK inhibition; ↓ TSLP; ↑ FLG, IVL and LOR	Extract combined anti-inflammatory and skin-barrier effects
A58	Park et al. [99]	Optimization of desalting conditions for the green seaweed *Codium fragile* for use as a functional food with hypnotic effects	Journal article	South Korea	Experimental (desalting optimization by RSM) + in vivo (pentobarbital-induced sleep test; EEG)	*C. fragile*	Desalted biomass; ethanol extract; total phenolics inversely related to salt content	Hypnotic (sleep-promoting)	↑ non-REM sleep without change in delta activity	Optimal desalting at 42.8 °C for 1 h; 1000 mg/kg extract prolonged sleep

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A59	Ryu et al. [100]	Photoimmunotherapy using indocyanine green-loaded *Codium fragile* polysaccharide and chitosan nanoparticles suppresses tumor growth and metastasis	Journal article	South Korea	Experimental in vitro (CT-26 cells) + in vivo (tumour-bearing mice)	*C. fragile*	Polysaccharide (CFP)–chitosan nanoparticles loaded with indocyanine green	Anticancer (photo-immunotherapy); immunomodulatory	808-nm laser-induced apoptosis/necrosis; DC activation and cytotoxic T-lymphocyte stimulation	Eliminated primary CT-26 tumours and inhibited rechallenged lung metastases
A60	Y.-L. Lee et al. [101]	Protective effects of *Codium fragile* extract against acetaminophen-induced liver injury	Journal article	South Korea	Experimental in vitro (HepG2) + in vivo (acetaminophen-induced liver injury in BALB/c mice)	*C. fragile*	Extract containing loliolide	Hepatoprotective; anti-inflammatory	↓ ALT and AST; ↓ TNF-α and IL-6; inhibition of ERK and p38 phosphorylation	Extract and loliolide were non-cytotoxic and protected against liver damage
A61	Quach et al. [102]	Structural characteristics and cytotoxic activity of sulfated polysaccharide from green seaweed *Codium geppiorum*	Journal article	Vietnam	Experimental in vitro (NMR, SAXS; cytotoxicity on three cancer cell lines)	*C. geppiorum* (central coast, Vietnam)	Linear sulfated galactan: →4)-β-D-Galp3S-(1→, →3)-β-D-Galp4S-(1→ and →3)-β-D-Galp-(1→; rod-like conformation	Cytotoxic	Not investigated	IC50 51.85 (HT29), 89.30 (8505c) and 72.22 µg/mL (HeLa)
A62	Li et al. [103]	Structure and anticoagulant activity of a galactoarabinan sulfate polysaccharide and its oligosaccharide from the green algae, *Codium fragile*	Journal article	China	Experimental in vitro (structural analysis, coagulation assays)	*C. fragile*	Sulfated galactoarabinan CZS-0-1 (Ara:Gal:Glc 9:2:1; 21% sulfate; 810 kDa; (1→3)-β-L-Arap backbone)	Anticoagulant (heparin-like)	Inhibits FIIa and FXa with heparin cofactors; activity depends on molecular weight	Reducing molecular weight markedly lowered anticoagulant activity
A63	Khan et al. [104]	The antioxidant, anti-obesogenic, and anti-diabetic potential of selected South African marine algal species	Journal article	South Africa	Experimental in vitro + in silico (docking)	*C. fragile* (with two other seaweeds)	Aqueous and ethanol extracts; LC-MS compounds; phenolics and flavonoids	Antioxidant; anti-obesogenic; anti-diabetic	Inhibition of α-amylase, α-glucosidase and pancreatic lipase; docking of LC-MS compounds	Potent antioxidant capacity, enzyme inhibition and increased yeast glucose uptake (species-specific values not in abstract)
A64	Fomenko et al. [105]	The effect of a lipid extract from the marine green algae *Codium fragile* (Suringar) Hariot 1889 on metabolic reactions under acute stress	Journal article	Russia	Experimental in vivo (mice under acute stress)	*C. fragile*	Lipid extract rich in ω-3 and ω-6 polyunsaturated fatty acids	Metabolic; antioxidant	Restored lipid and carbohydrate metabolism and endogenous antioxidant defence	Not inferior to a reference omega-3 preparation, with higher antioxidant activity
A65	Martins et al. [106]	Towards a zero-waste sustainable biorefinery of *Codium* sp. seaweed: From bioactives application to soil enhancement materials	Journal article	Portugal	Experimental in vitro (five extracts; biochar production)	*Codium* sp.	Five extracts (ethyl acetate, ethanol, hydroethanolic, others); post-extraction biomass biochars (56–75% C)	Antioxidant; anti-enzymatic; photoprotective; anti-inflammatory	Elastase inhibition; reduced UVB-induced ROS; reduced TNF-α after LPS	Hydroethanolic extract inhibited elastase by 88% at 200 µg/mL and reduced ROS by 30%; biochar (AMC) improved soil water retention
A66	H. L. Lee et al. [107]	*Codium fragile* extract ameliorates respiratory function by controlling allergic inflammation in ovalbumin-induced bronchial disorders in mice	Journal article	South Korea	Experimental in vivo (ovalbumin-induced allergic airway inflammation in mice)	*C. fragile*	Water extract; oleamide as marker (HPLC-PDA)	Anti-allergic; anti-inflammatory; respiratory protection	↓ Th2 cytokines (IL-5, IL-13, IL-33), TNF-α and IL-1β; inhibition of NF-κB and TGF-β/Smad	Reduced bronchial wall thickness, mucus score and inflammatory cells
A67	Ko et al. [108]	*Codium minus* extract inhibits adipogenesis by regulating adipogenic transcription and lipid metabolism factors in 3T3-L1 adipocytes	Journal article	South Korea	Experimental in vitro (3T3-L1 adipocytes)	*C. minus*	Extract	Anti-adipogenic	↓ PPARγ, C/EBPα, SREBP-1 and FABP4	Lowered intracellular lipid and triglyceride accumulation

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A68	Qadir et al. [109]	Cosmeceutical potential of *Codium iyengarii* extract loaded nanoemulsion	Journal article	Pakistan	Experimental in vitro + in vivo + clinical evaluation of a topical nanoemulsion	*C. iyengarii*	Ethanolic extract (40 compounds; TPC 7.61 mg GAE/g, TFC 19.89 mg QE/g) loaded in a nanoemulsion (183.67 nm)	Cosmeceutical (photoprotection, SPF 2.23; tyrosinase inhibition 52%; skin hydration)	Not investigated	Clinical test: transepidermal water loss −37.47% and skin hydration +29.47% after 4 h
A69	Kalavathy et al. [110]	Formulation of topical ointment using seaweed extracts of *Ulva lactuca* and *Codium tomentosum* and their physicochemical, antioxidant, anti-inflammatory, antibacterial and wound healing properties	Journal article	India	Experimental in vitro (DPPH; albumin denaturation, proteinase and haemolysis assays; antibacterial; Vero wound-healing assay)	*C. tomentosum* (with *Ulva lactuca*)	Seaweed extracts formulated as topical ointments	Antioxidant; anti-inflammatory; antibacterial; wound healing	Not investigated	*C. tomentosum* ointment closed 75% of the wound area in Vero cells
A70	S. A. Lee et al. [111]	Immune-enhancing effects of *Porphyra yezoensis* and *Codium fragile* extracts	Journal article	South Korea	Experimental in vitro (RAW264.7) + in vivo (cyclophosphamide-immunosuppressed mice)	*C. fragile* (with *Porphyra yezoensis*)	Extracts; combination CFPY	Immunomodulatory	MAPK and NF-κB activation; ↑ splenocyte proliferation and NK-cell activity	*C. fragile* alone was inactive at 0.15 mg/mL; the combination was active
A71	Costa et al. [112]	Optimization of nanoencapsulation of *Codium tomentosum* extract and its potential application in yogurt fortification	Journal article	Portugal	Experimental in vitro (phytosome optimization; antioxidant and cholinesterase assays) + yogurt prototypes	*C. tomentosum*	Subcritical-water extract in phytosomes modified with DSPE-PEG-maleimide and apolipoprotein E	Antioxidant; cholinesterase inhibition (AChE, BuChE)	Not investigated	Fortified yogurts retained antioxidant and anti-cholinesterase capacity but had poor sensory acceptance
A72	Mahmoud et al. [113]	Preparation of a new ternary deep eutectic solvent for the green extraction of sulfated polysaccharides from *Codium vermilara*: a Box–Behnken optimization study	Journal article	Egypt	Experimental in vitro (extraction optimization, cell assays)	*C. vermilara*	Sulfated polysaccharide extracted with a ternary deep eutectic solvent (yield 17.80 ± 0.1%; S 10.15%)	Antioxidant and anticancer (A375, A-431) evaluated	Not reported in abstract	Deep-eutectic-solvent extract was more porous and richer in sulfur than the hot-water extract; potency values need full-text check
A73	Sousa et al. [114]	Seasonal variation in the composition and antioxidant potential of *Codium tomentosum* and *Ulva lacinulata* produced in a land-based integrated multi-trophic aquaculture system	Journal article	Portugal	Experimental in vitro (seasonal composition; ABTS and superoxide assays)	*C. tomentosum* (IMTA, Ria de Aveiro, Portugal; with *Ulva lacinulata*)	Higher lipid and PUFA content than Ulva; minerals; Pb, Cd, Hg and inorganic As below regulatory limits	Antioxidant (lower than Ulva)	Season affected composition	Both species judged safe and suitable as sea vegetables
A74	Ak et al. [115]	Targeted delivery of seaweed bioactives: liposomal encapsulation of *Ulva lactuca* and *Codium fragile* for antibacterial enhancement	Journal article	Turkey	Experimental in vitro (liposome characterization; MIC; DPPH)	*C. fragile subsp. fragile* (Aegean and Marmara Seas; with *Ulva lactuca*)	Extracts in liposomes (encapsulation efficiency 67.56–76.92%)	Antibacterial (E. coli, *S. aureus*); antioxidant	Liposomal encapsulation enhanced antibacterial activity	Liposomal *C. fragile* MIC 0.0025 µg/µL versus 0.0050 µg/µL for the free extract
A75	Sun et al. [116]	Antialgal compounds from *Codium fragile*: Isolation, identification and inhibitory effects on red tide microalgae	Journal article	China	Experimental in vitro (bioactivity-guided isolation)	*C. fragile*	Myristic acid, oleic acid, 7-hydroxyheptanoic acid, 15-nor-amorph-11-en-4β-ol, 3,7-dimethyloctane-1,7-diol, loliolide	Antialgal (red-tide microalgae)	Distinct cell damage (shrinkage, swelling, rupture, collapse) compared with potassium dichromate	EC50-96h 14.2 to >500 µg/mL; oleic acid EC50 12.4 µg/mL (*H. akashiwo*) and 15.8 µg/mL (*P. globosa*)

Code	Authors & Year	Full Title	Article Type	Country	Research Type	*Codium* Source	Phytochemical Profile of *Codium*	Pharmacological Activities of *Codium* Bioactive Compounds	Mechanistic Insights / SAR	Key Research Findings
A76	G. Lee et al. [117]	Anti-neuroinflammatory effects of a representative low-molecular-weight component isolated from *Codium fragile* through inhibition of the NF-κB pathway in microglia and macrophage cells	Journal article	South Korea	Experimental in vitro (LPS-stimulated BV2 microglia and RAW264.7)	*C. fragile*	Aqueous extract; uracil isolated as main low-molecular-weight marker (HPLC)	Anti-neuroinflammatory	Inhibition of the NF-κB pathway; ↓ pro-inflammatory cytokines	Both the extract and uracil were active
A77	G. H. Lee et al. [118]	Antioxidants and anti-diabetic effect of *Codium fragile* ethanol extract	Journal article	South Korea	Experimental in vitro (RIN-m5F β-cells) + in vivo (streptozotocin-diabetic rats)	*C. fragile*	Ethanol extract	Antioxidant; antidiabetic	↓ ROS; ↑ SOD2 and catalase; ↓ cleaved caspase-3 and PARP1	Oral extract increased body weight and lowered blood glucose in diabetic rats
A78	Kolanchinathan et al. [119]	Assessment of GC-MS and antioxidant properties of seaweed extracts as a new larvicidal agent targeting *Culex quinquefasciatus*	Journal article	India	Experimental in vitro (GC-MS, larvicidal and antioxidant assays)	*C. fragile* (with *Turbinaria conoides*)	Ethanolic extract: 20 compounds by GC-MS (hexadecanoic acid 27.79%, octadecanoic acid 5.9%)	Larvicidal (*Culex quinquefasciatus*); antioxidant	Not investigated	Chloroform extracts of *C. fragile* and *T. conoides* showed significant larvicidal effects
A79	Benhniya et al. [120]	Bioactive sulfated polysaccharides from green algae *Codium tomentosum* Stackhouse, 1797: Structural characterization and therapeutic potential	Journal article	Morocco	Experimental in vitro (FTIR, XRD, UV–Vis, SEM–EDS; antiviral, antimicrobial and antioxidant assays)	*C. tomentosum* (Morocco)	Sulfated polysaccharide PSCT: yield 22.01%; neutral sugars 66.84%, sulfate 8.73%, uronic acids 4.13%; mainly galactose and arabinose	Antiviral (HSV-1, EC50 12.22 µg/mL); antimicrobial (MIC 0.05–0.78 mg/mL); antioxidant	Not investigated	No cytotoxicity (CC50 > 200 µg/mL); moderate antioxidant activity (IC50 1.25 mg/mL)
A80	Matias et al. [121]	Circular approach for the sustainable valorization of IMTA *Codium* sp. for multitarget skin care applications	Journal article	Portugal	Experimental in vitro (RAW264.7 macrophages, HaCaT keratinocytes; antimicrobial assays) + biochar production	*Codium* sp. (IMTA)	Five polarity-gradient fractions; biochars from residual biomass	Antioxidant; anti-inflammatory; photoprotective; wound healing; antimicrobial (*C. acnes*)	Possible membrane-potential disturbance in bacteria	Fraction F1 reduced UV-induced ROS by 33%; F5 increased cell migration by 44%; F3 IC50 51.23 µg/mL against *C. acnes*
A81	Alsaggaf et al. [122]	Synergistic antimicrobial action of phyco-synthesized silver nanoparticles and nano-fungal chitosan composites against drug resistant bacterial pathogens	Journal article	Saudi Arabia	Experimental in vitro (green synthesis; FTIR, particle sizing; antibacterial assays, SEM)	*C. capitatum*	Aqueous extract used to synthesize silver nanoparticles (Ag-NPs, 37.2 nm); nanoconjugates with fungal chitosan nanoparticles	Antibacterial (drug-resistant *Salmonella Typhimurium* and *S. aureus*)	Cell-surface alteration and lethal damage to bacterial structure (SEM)	All nanoparticles were inhibitory; chitosan/Ag-NP nanoconjugates were the most active
A82	El Zawawy et al. [123]	A novel study on the inhibitory effect of marine macroalgal extracts on hyphal growth and biofilm formation of candidemia isolates	Journal article	Egypt	Experimental in vitro (anticandidal, biofilm and hyphal assays; GC-MS)	*C. arabicum* (with *Cladostephus spongiosus* and *Laurencia papillosa*)	Acetone and ethanol extracts	Anticandidal; antibiofilm (*Candida spp.*)	Not investigated for the *Codium* extract	The acetone extract of *C. spongiosus* was the most active; results for *C. arabicum* were not given separately in the abstract
A83	Lopes et al. [124]	Valuing bioactive lipids from green, red and brown macroalgae from aquaculture, to foster functionality and biotechnological applications	Journal article	Portugal	Experimental in vitro (fatty acid profiling; radical scavenging; COX-2 inhibition; MDA-MB-231 cytotoxicity)	*C. tomentosum* (IMTA; with five other macroalgae)	Lipid extracts; fatty acid profiles and lipid quality indices	Antioxidant; anti-inflammatory (COX-2 inhibition); antiproliferative	COX-2 inhibition	*C. tomentosum* lipid extract inhibited COX-2 activity by up to 80%; the strongest antioxidant and cytotoxic extracts came from other species

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A84	Silva et al. [125]	Seaweeds' neuroprotective potential set in vitro on a human cellular stress model	Journal article	Portugal	Experimental in vitro (dopamine-induced toxicity in SH-SY5Y cells)	*C. tomentosum* (with other seaweeds)	Extracts	Neuroprotective	Mitochondrial membrane potential, caspase-3 and H2O2 assessed for the most active extract	*C. tomentosum* extract (1000 µg/mL) reduced dopamine toxicity by 10–15%; *Saccorhiza polyschides* was the most active
A85	Vega et al. [126]	Antioxidant activity of extracts from marine macroalgae, wild-collected and cultivated, in an integrated multi-trophic aquaculture system	Journal article	Spain	Experimental in vitro (DPPH, reducing power; pigments and phenolics)	*C. intertextum* (Canary Islands; wild and IMTA-cultivated; with nine other macroalgae)	Methanolic and hydroethanolic extracts; chlorophyll a and carotenoids among the highest in *C. intertextum*	Antioxidant	Reducing power correlated with polyphenols and phycoerythrin	IMTA cultivation raised pigment content of *C. intertextum* without lowering antioxidant activity in several species
A86	Zhong et al. [127]	LC-ESI-QTOF-MS/MS characterization of seaweed phenolics and their antioxidant potential	Journal article	Australia	Experimental in vitro (LC-ESI-QTOF-MS/MS, HPLC-PDA; DPPH, ABTS, FRAP)	*Codium* sp. (with seven other seaweeds)	Phenolic compounds (54 tentatively identified across the eight seaweeds); TPC, TFC, TTC	Antioxidant	Antioxidant capacity correlated with polyphenol content	Brown seaweeds had the highest phenolic content and antioxidant potential, above the green *Codium* sp.
A87	Elkhateeb et al. [128]	Evaluation of bioactive phytochemical characterization, antioxidant, antimicrobial, and antihemolytic properties of some seaweeds collected from Red Sea coast, Egypt	Journal article	Egypt	Experimental in vitro (DPPH, NO and H2O2 scavenging; antihemolytic and antimicrobial assays; HPLC)	*C. tomentosum* (Red Sea; with nine other seaweeds)	Ethanolic extract with the highest TPC (18.83 mg/g) and TFC (3.77 mg/g); phenolic acids and flavonoids by HPLC	Antioxidant; antihemolytic; antimicrobial	Activity linked to phenolic and flavonoid content	*C. tomentosum* extract gave DPPH IC50 5.41 mg/mL and H2O2 IC50 0.425 mg/mL, low hemolysis and strong antimicrobial activity
A88	Gómez-Hernández et al. [129]	In vitro antifungal activity screening of beach-cast seaweeds collected in Yucatan, Mexico	Journal article	Mexico	Experimental in vitro (dilution assays against fungal phytopathogens)	*C. isthmocladum* (beach-cast, Yucatan; with four other seaweeds)	Aqueous extract	Antifungal (*Fusarium oxysporum*, *Colletotrichum gloeosporioides*, *Pseudocercospora fijiensis*)	Not investigated	Only the *Halymenia floresii* extract was active; the *C. isthmocladum* extract showed no antifungal activity
A89	Kim et al. [130]	Potential antidiabetic effects of seaweed extracts by upregulating glucose utilization and alleviating inflammation in C2C12 myotubes	Journal article	South Korea	Experimental in vitro (α-glucosidase inhibition; glucose uptake in C2C12 myotubes)	*C. fragile* (with six other seaweeds)	Water extract	Antidiabetic; anti-inflammatory	AMPK phosphorylation (blocked by compound C); ↓ LPS-induced TNF-α	*C. fragile* extract inhibited α-glucosidase and enhanced glucose utilization in myotubes partly via AMPK
A90	Mahyoub [131]	Bioactivity of two marine algae extracts and their synthesized silver nanoparticles as safe controls against *Musca domestica* housefly	Journal article	Saudi Arabia	Experimental in vitro (larval bioassay; SEM, FTIR, XRD of nanoparticles)	*C. edule* (with *Avrainvillea amadelpha*)	Extract and extract-synthesized silver nanoparticles	Larvicidal (*Musca domestica*)	Not investigated	*C. edule* extract LC50 300.37 ppm; with silver nanoparticles LC50 21.34 ppm
A91	Nazarudin et al. [132]	Preliminary evaluation of the biochemical and antioxidant properties of seaweed species predominantly distributed in Peninsular Malaysia	Journal article	Malaysia	Experimental in vitro (lipids, pigments, GC-MS; DPPH)	*Codium* sp. (Peninsular Malaysia; with four other seaweeds)	High total carotenoids (159.18 µg/g) and the highest chlorophyll b (305.29 µg/g); hexadecanoic acid, stigmast-5-en-3-ol, neophytadiene	Antioxidant	Not investigated	*Ulva intestinalis* gave the highest DPPH inhibition; differences between species were small
A92	Sun et al. [133]	Screening and isolation of glyceroglycolipids with antialgal activity from several marine macroalgae	Journal article	China	Experimental in vitro (antialgal bioassay-guided fractionation)	*C. fragile* (with five other macroalgae)	Glyceroglycolipid-containing extract; no active glyceroglycolipid isolated from *C. fragile*	Antialgal (*Karenia mikimotoi*, *Phaeocystis globosa*)	Not investigated	The *C. fragile* extract was antialgal, but the active glyceroglycolipids were isolated only from other species

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A93	Trikka et al. [134]	Biochemical characterization of eight Greek algae as candidate species for local seaweed cultivation	Journal article	Greece	Experimental in vitro (polyphenols, antioxidant activity, fatty acids, elements)	*C. fragile* (with seven other seaweeds)	Phenolics; oleic acid (highest in *C. fragile*); α-linolenic acid	Antioxidant	Not investigated	*C. fragile* was among the species with the highest phenolic content and strongest antioxidant activity
A94	Yalçın et al. [135]	HPLC detection and antioxidant capacity determination of brown, red and green algal pigments in seaweed extracts	Journal article	Turkey	Experimental in vitro (RP-HPLC pigment analysis; CUPRAC and ABTS/TEAC)	*C. fragile* (with other seaweeds)	Pigments: chlorophyll a and b, β-carotene, violaxanthin and siphonaxanthin	Antioxidant	HPLC-quantified pigments explained 3–100% of the antioxidant capacity of green algal extracts	Siphonaxanthin and β-carotene were notably high in *C. fragile*
A95	Yasmeen et al. [136]	Phycochemical analyses and pharmacological activities of seven macroalgae of Arabian Sea (northern coast line)	Journal article	Pakistan	Experimental in vivo (analgesic and anti-inflammatory models) + phycochemical analysis	*C. flabellatum* (Karachi coast; with six other seaweeds)	Methanol extract; saponins 3.47% (highest), phenols, flavonoids, tannins	Analgesic; anti-inflammatory	Not investigated	*C. flabellatum* extract had a highly significant anti-inflammatory effect from the 1st to the 5th hour
A96	Yim et al. [137]	Inhibition of SARS-CoV-2 virus entry by the crude polysaccharides of seaweeds and abalone viscera in vitro	Journal article	South Korea	Experimental in vitro (SARS-CoV-2 pseudovirus entry in HEK293/ACE2 cells)	*C. fragile* (with five other seaweeds and abalone viscera)	Crude polysaccharide	Antiviral (SARS-CoV-2 entry)	Activity associated with high molecular weight, high carbohydrate and fucose content and branching	Most crude polysaccharides inhibited entry (IC50 12–289 μg/mL); *Sargassum horneri* was the most active
A97	Fayzi et al. [138]	Antioxidant and antifungal activity of some Moroccan seaweeds against three postharvest fungal pathogens	Journal article	Morocco	Experimental in vitro (DPPH; mycelial growth inhibition)	*C. tomentosum* (Agadir; with three other seaweeds)	Aqueous extract; total phenolics and flavonoids	Antioxidant; antifungal (postharvest *Penicillium spp.*)	Not investigated	*Bifurcaria bifurcata* and *Ulva fasciata* were the most antioxidant and antifungal extracts, above *C. tomentosum*
A98	Mendes et al. [139]	Brain effects of SC-Nanophytosomes on a rotenone-induced rat model of Parkinson's disease—A proof of concept for a mitochondria-targeted therapy	Journal article	Portugal	Experimental in vivo (rotenone-induced Parkinson's disease rat model; ex vivo brain mitochondria)	*C. tomentosum*	Membrane polar lipids formulated with elderberry anthocyanins as SC-Nanophytosomes	Neuroprotective (Parkinson's disease model); antioxidant	Restored respiratory chain function, complex I activity, α-synuclein levels and SOD and catalase activities	Oral SC-Nanophytosomes improved motor symptoms and mitigated brain mitochondrial dysfunction
A99	Salem et al. [140]	UV-induced antibacterial activity of green-synthesized TiO2 nanoparticles for the potential reuse of raw surface and underground water	Journal article	Egypt	Experimental in vitro (green synthesis of TiO2 nanoparticles; UV-activated antibacterial and antibiofilm assays; RPE1 cytotoxicity)	*C. fragile* (Red Sea, Hurghada; with *Caulerpa racemosa* and *Cystoseira myrica*)	Ethyl acetate extract used to synthesize TiO2 nanoparticles (125–131 nm, anatase)	Antibacterial; antibiofilm	UV activation required for bactericidal activity	TiO2-NPs were non-toxic to RPE1 cells; the *C. racemosa*-based particles performed best in water treatment
A100	Goutzourelas et al. [141]	Antioxidant activity and inhibition of liver cancer cells' growth of extracts from 14 marine macroalgae species of the Mediterranean Sea	Journal article	Greece	Experimental in vitro (DPPH, ABTS, •OH, O2•− scavenging; DNA plasmid protection; HepG2 growth by XTT)	*C. fragile* (Aegean Sea; with 13 other macroalgae)	Extract; total polyphenol content	Antioxidant; anticancer (HepG2)	Antioxidant activity correlated with TPC	*Gigartina teedei* was the strongest antioxidant and *Padina pavonica* the strongest HepG2 inhibitor
A101	Mendes et al. [142]	Mitochondrial dysfunction in skeletal muscle of rotenone-induced rat model of Parkinson's disease: SC-Nanophytosomes as therapeutic approach	Journal article	Portugal	Experimental in vivo (rotenone-induced Parkinson's disease rat model; skeletal muscle)	*C. tomentosum*	Membrane polar lipids formulated with elderberry anthocyanins as SC-Nanophytosomes	Neuroprotective; muscle mitochondrial protection; antioxidant	Restored complex I and II activity and muscle lipidome; more reduced redox environment	SC-Nanophytosomes mitigated skeletal-muscle mitochondrial dysfunction linked to motor disability

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A102	Miguel et al. [143]	Chemical composition of macroalgae polysaccharides from Galician and Portugal coasts: Seasonal variations and biological properties	Journal article	Portugal	Experimental in vitro (seasonal polysaccharide characterization; radical scavenging; biocompatibility and wound scratch assays)	*Codium* sp. (Galician and north Portuguese coasts; winter, spring, summer; with *Osmundea sp.*)	Crude sulfated polysaccharides; galactose as major monosaccharide; glucose increased seasonally	Antioxidant; wound healing (fibroblast migration)	Sulfate content tracked antioxidant activity	*Codium* sp. polysaccharides gained glucose seasonally; summer *Osmundea sp.* polysaccharide was the most antioxidant and pro-migratory
A103	Toledo et al. [144]	Seaweed extracts to control postharvest phytopathogenic fungi in Rocha pear	Journal article	Portugal	Experimental in vitro (mycelial growth and spore germination) + in vivo fruit assay (Rocha pear)	*Codium* sp. (with three other seaweeds)	n-Hexane, ethyl acetate, aqueous, ethanolic and hydroethanolic extracts	Antifungal (postharvest phytopathogens)	Not investigated	*Asparagopsis armata* extracts were the most active in vitro and a *Sargassum muticum* extract in pears; *Codium* sp. was not among the most active
A104	Ahn et al. [145]	Neuropilin-2 acts a critical determinant for epithelial-to-mesenchymal transition and aggressive behaviors of human head and neck cancer	Journal article	South Korea	Experimental in vitro (HNC cell proliferation, migration, invasion, sphere formation) + patient tissue analysis	*C. fragile*	Methanol extract (MECF)	Anticancer; antimetastatic (head and neck cancer)	Repressed neuropilin-2 and the RSK1/Sox2/Zeb1 axis; reduced EMT and cancer-stem-cell properties	MECF reduced aggressive behaviors of HNC cells and is proposed as an NRP2 inhibitor
A105	Buscaglia et al. [146]	Development of an eco-friendly procedure to generate valuable active polyphenolic purified fractions from marine macrophytes	Journal article	France	Experimental in vitro (Diaion HP-20 purification; radical scavenging; EUCAST antibacterial assays)	*C. fragile* (with *Bifurcaria bifurcata* and three halophytes)	Aqueous ethanol extract and phenolic-enriched fractions (1H NMR)	Antioxidant; antibacterial	Purification increased phenolic content and radical-scavenging capacity	Fractions of all species gained antioxidant capacity; antibacterial activity came mainly from *B. bifurcata*
A106	Rizwan et al. [147]	Biomedical properties, characterization of seaweeds species and antimicrobial activity	Journal article	Pakistan	Experimental in vitro (phytochemical screening; DPPH; disc diffusion)	*C. decorticatum* (Buleji; with four other seaweeds)	Ethanol and methanol extracts; flavonoids, tannins and proteins	Antioxidant; antibacterial; antifungal	Not investigated	The ethanolic *C. decorticatum* extract gave the largest inhibition of *Aspergillus niger*
A107	Sunwoo et al. [148]	Evaluation of antioxidant activity of residue from bioethanol production using seaweed biomass	Journal article	South Korea	Experimental in vitro (DPPH, FRAP; ROS in H2O2-treated RAW 264.7 cells)	*C. fragile* (with eight other seaweeds)	Bioethanol residue extracts (water, ethanol, methanol)	Antioxidant	Not investigated	*Ascophyllum nodosum* residue extract was the most antioxidant; green algae gave the lowest ethanol yields
A108	Kavalappa et al. [149]	Siphonaxanthin inhibits the growth of breast cancer cell subtypes by modulating the expression of cellular proteins associated with antioxidant defence, cell survival and apoptosis signaling	Journal article	India	Experimental in vitro (WST-1; western blot; DAPI staining in MCF-7 and MDA-MB-231 cells)	*Codium* sp.	Purified siphonaxanthin	Anticancer (breast cancer)	↓ SOD-2 and Nrf2; ↓ pAkt, pERK1/2 and NF-κB; ↓ Bcl-2, p-Bad and PARP	Siphonaxanthin inhibited both breast cancer subtypes at 5 μM and induced apoptosis
A109	Lee et al. [150]	Phlorofucofuroeckol-A: A natural compound with potential to attenuate inflammatory diseases caused by airborne fine dust	Journal article	South Korea	Experimental in vitro (fine-dust-induced inflammation in RAW 264.7 cells; NMR, LC-MS/MS)	*C. fragile* (with *Ecklonia cava* and *E. stolonifera*)	Siphonaxanthin purified from *C. fragile*; fucoxanthin, dieckol and phlorofucofuroeckol-A from *Ecklonia spp.*	Anti-inflammatory	NF-κB/MAPK modulation shown for phlorofucofuroeckol-A	All purified compounds were protective without cytotoxicity; phlorofucofuroeckol-A was the most active

Code	Authors & Year	Full Title	Article Type	Country	Research Type	*Codium* Source	Phytochemical Profile of *Codium*	Pharmacological Activities of *Codium* Bioactive Compounds	Mechanistic Insights / SAR	Key Research Findings
A110	Sneha et al. [6]	Potential benefits of bioactive compounds from seaweed extracts: Their prospects and pharmacological promises	Journal article	India	Experimental in vitro (MTT on PC12 cells; cell cycle; agar diffusion and microdilution; GC-MS, FT-IR)	*C. decorticatum* (with *Dictyota dichotoma* and *Amphiroa fragilissima*)	Solvent extracts; saponins, flavonoids, alkaloids, steroids, phenolics, tannins and terpenes (qualitative)	Antiproliferative; antibacterial; antifungal	Not investigated	The methanolic *A. fragilissima* extract was superior to the other extracts, including those of *C. decorticatum*
A111	Castillo et al. [151]	Unveiling the metabolomic, phytochemical and bioactive profile of twelve macroalgae from the Adriatic Sea: A comprehensive analysis using MSPD-UHPLC-QTOF	Journal article	Spain	Experimental in vitro (MSPD extraction; TPC; antioxidant assay; HPLC-MS/MS and UHPLC-QToF metabolomics)	*C. adhaerens* and *C. vermilara* (Adriatic Sea; with ten other macroalgae)	Phenolics; *Chlorophyta* enriched in coumarins, benzaldehydes and flavanones; fatty acid esters of hydroxy fatty acids (FAHFAs)	Antioxidant	Taxon-specific phenolic profiles may explain antioxidant differences	*Ulva lactuca* had the highest phenolic content and antioxidant activity among the green algae
A112	Cherif et al. [152]	Fatty acid profile, nutritional potential and biological activity of green macroalgae from the northern Tunisian coast	Journal article	Tunisia	Experimental in vitro (fatty acid GC profiling; antibacterial and anti-microalgal assays)	*C. fragile* and *C. tomentosum* (north Tunisian coast; with eight other green algae)	Fatty acids: saturated fatty acids dominant, palmitic acid highest in *C. tomentosum*	Antibacterial; algicidal	Not investigated	*Ulva linza* and *Bryopsis muscosa* had the broadest antibacterial spectrum
A113	Valverde-Urrea et al. [153]	Screening antifungal and antioxidant activity of macroalgae from SE Spain highlights the invader *Rugulopteryx okamurae*	Journal article	Spain	Experimental in vitro (DPPH; fungistatic assay; LC-MS/MS)	*C. fragile* (south-eastern Spain; non-native; with four other macroalgae)	Methanol and ethyl acetate extracts	Antioxidant; antifungal (*Fusarium oxysporum* f. sp. cubense TR4)	Not investigated	All extracts were antioxidant; *Rugulopteryx okamurae* was the most active and *C. fragile* had low antifungal activity

3.1.1. Characteristics by Year of Publication

The distribution of the reviewed studies by year shows sustained interest in the *Codium* genus since 2020, the lower date limit of this review. The annual count was 21 in 2020, 24 in 2021 (the peak year), 17 in 2022, 10 in 2023, 20 in 2024, 12 in 2025, and 9 in 2026 (a partial year at the time of the searches). Early studies in the window focused on immune-activating polysaccharides and sulfated galactans, whereas recent studies expanded toward disease models in mice, formulation, drug delivery, and applied biorefinery concepts, indicating an increasing emphasis on translational research linking chemical structures to therapeutic functions.

Table 3.2. Distribution of Reviewed Studies by Publication Year

No	Year Category	Number of Studies	Percentage (%)	Article Codes	Description
1	2020–2021	45	39.8	A1–A29, A81–A96	Immune-activating polysaccharides, sulfated galactans with anticoagulant and antimetastatic effects, anti-obesity and PM2.5-protective extracts, neuroprotective loliolide, lectin pharmacology, skin-whitening vesicles and lipid nanocarriers; multi-species antioxidant, antimicrobial and antifungal screens, and inhibition of SARS-CoV-2 entry by crude polysaccharides.
2	2022–2023	27	23.9	A30–A49, A97–A103	Disease models in mice (obesity, allergy, dermatitis, respiratory and cognitive injury), polysaccharide–drug and nanoparticle systems, anti-inflammatory and antibacterial formulations, and seasonal and cultivation effects on bioactivity; polar-lipid nanophytosomes in a rat model of Parkinson's disease and postharvest antifungal screens.
3	2024–2026	41	36.3	A50–A80, A104–A113	Peak output: hepatic, respiratory and skin-barrier models, anti-neuroinflammatory components, topical and nano-formulations, green extraction, biorefinery concepts and docking-supported studies; purified siphonaxanthin against breast cancer, an NRP2-inhibiting extract in head and neck cancer, and Mediterranean antioxidant and antifungal screens.

As shown in Table 3.2, 45 studies (39.8%) were published in 2020–2021, 27 (23.9%) in 2022–2023, and 41 (36.3%) in 2024–2026, so output recovered after a dip in 2022–2023. Part of this volume reflects the addition of Scopus, which indexes many Korean, Portuguese, and Indian journals that the other three databases cover less well. Scopus citation counts of the included studies (as of 8 and 14 October 2026) were highest for Zhong et al. [127] (170), Yan et al. [60] (96), Figueroa et al. [85] (90), Vega et al. [126] (81), and Silva et al. [68] (79).

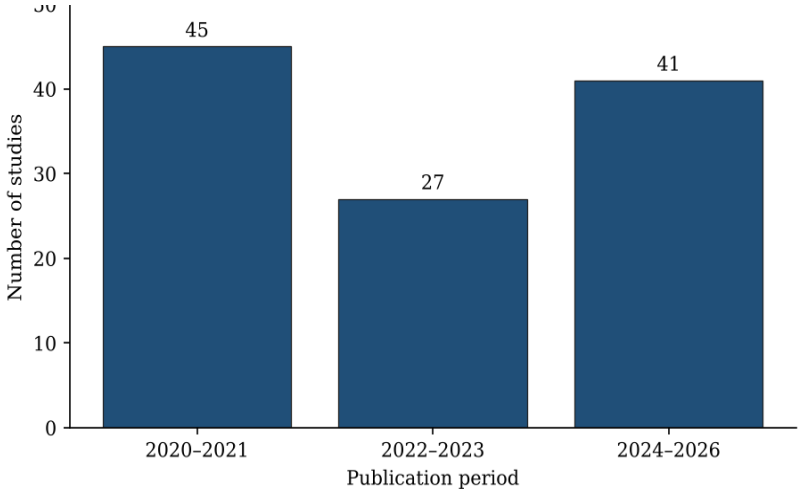


Figure 3.1. Distribution of Reviewed Studies on the Genus *Codium* by Publication Year

3.1.2. Characteristics by Country of Study

The reviewed studies were conducted across a wide geographical range, reflecting the global distribution and scientific interest in *Codium* species. Research activity is notably concentrated in Asia, where South Korea dominates immunomodulatory, anticancer, anti-obesity, and disease-model studies, followed by India and China. Portugal contributes lipid-based, neuroprotective, formulation, and biorefinery work, Brazil provides studies of sulfated galactans and lectins, and Egypt, Spain, Greece, Morocco, Pakistan, the Philippines, and other countries add regional screening of local *Codium* species, often within multi-species surveys. Country was inferred from the first or corresponding author, the journal, the abstract, or the title; all assignments should be verified against the full texts.

Table 3.3. Distribution of Reviewed Studies by Country of Origin

No	Country	Number of Studies	Percentage (%)	Article Codes	Description
1	South Korea	38	33.6	38 studies (see Table 3.1)	Immunomodulatory and anticancer polysaccharides; anti-obesity, anti-melanogenic and anti-inflammatory extracts; PM2.5, respiratory, hepatic and skin models in mice; antiviral carotenoid work. Anti-diabetic, anti-inflammatory and anti-metastatic extracts, siphonaxanthin against fine-dust inflammation, and seaweed polysaccharides against SARS-CoV-2 entry were added.
2	Portugal	17	15.0	17 studies (see Table 3.1)	Lipid-based nanomedicine and photodynamic antibacterial work, neuroprotective loliolide, polysaccharide wound-dressing sponges, nanoencapsulation, IMTA-grown material and biorefinery. Nanophytosomes in a rat Parkinson's model, lipid COX-2 inhibition, neuroprotective and postharvest antifungal screens, and seasonal polysaccharides were added.
3	Egypt	7	6.2	A35, A40, A53, A72, A82, A87, A99	Habitat-linked bioactivity of *C. dwarkense*, larvicidal screening, green extraction of sulfated polysaccharides and fish-fillet fortification. Antioxidant, antimicrobial and anticandidal screens and TiO2 nanoparticles for water disinfection were added.
4	India	7	6.2	A37, A48, A50, A69, A78, A108, A110	Glycoprotein-induced apoptosis, polysaccharide cytotoxicity, GC–MS profiling with anti-inflammatory and larvicidal assays, paw-edema and ointment studies. Purified siphonaxanthin against breast cancer and antiproliferative and antimicrobial screening of *C. decorticatum* were added.
5	China	6	5.3	A18, A19, A42, A62, A75, A92	Sulfated galactoarabinan and galactofuranose-containing polysaccharides with anticoagulant activity, polysaccharide degradation and hypoglycemic activity, and antialgal compounds. Antialgal glyceroglycolipid screening was added.
6	Brazil	4	3.5	A7, A12, A34, A39	Sulfated galactans with anticoagulant, antigenotoxic and antimetastatic effects, and lectin pharmacology and antibiofilm activity.
7	Spain	4	3.5	A49, A85, A111, A113	Gold nanoparticles synthesized with an aqueous extract as an antitumoral enhancer. Antioxidant screening of Canary Islands, Adriatic and south-eastern Spanish macroalgae was added.
8	Morocco	3	2.7	A10, A79, A97	Algicidal screening against toxic cyanobacteria, anti-inflammatory and antitumor extracts, and sulfated polysaccharide characterization. Antioxidant and antifungal screening of Agadir seaweeds was added.
9	Pakistan	3	2.7	A68, A95, A106	Cosmeceutical nanoemulsion with a clinical skin-hydration test. Antioxidant, antimicrobial, analgesic and anti-inflammatory screening of local seaweeds was added.
10	Philippines	3	2.7	A4, A6, A36	Antioxidant, antibacterial, cytotoxic and anti-metastatic assays on *C. intricatum* and an anti-allergic polysaccharide in mice.
11	Turkey	3	2.7	A32, A74, A94	Antimicrobial and antioxidant screening and liposomal encapsulation for antibacterial enhancement. HPLC pigment profiling with antioxidant capacity was added.

No	Country	Number of Studies	Percentage (%)	Article Codes	Description
12	Greece	2	1.8	A93, A100	Antioxidant and liver-cancer screening of Aegean macroalgae and biochemical characterization of candidate species for cultivation.
13	Saudi Arabia	2	1.8	A81, A90	Silver nanoparticles synthesized with *C. capitatum* and *C. edule* extracts for antibacterial and larvicidal use.
14	Tunisia	2	1.8	A52, A112	Anti-angiogenic, antioxidant and anti-inflammatory sulfated polysaccharide. Fatty acid profiling with antibacterial and anti-microalgal assays was added.
15	Algeria	1	0.9	A5	Cytotoxic activity and GC–MS screening of *C. bursa* and *C. fragile* extracts from the north Tunisian coast.
16	Australia	1	0.9	A86	LC-ESI-QTOF-MS/MS phenolic profiling and antioxidant potential of eight seaweeds.
17	Chile	1	0.9	A43	Physicochemical characterization of a sulfated galactan from *C. bernabei* with antioxidant, anticoagulant and antitumor activity.
18	Croatia	1	0.9	A25	Volatile and less polar compounds with in vitro and in vivo (zebrafish) antioxidant potential.
19	France	1	0.9	A105	Eco-friendly purification of phenolic fractions with antioxidant and antibacterial testing.
20	Japan	1	0.9	A15	Siphonaxanthin protection against lipotoxicity in obese mice.
21	Malaysia	1	0.9	A91	Biochemical and antioxidant screening of five seaweeds from Peninsular Malaysia.
22	Mexico	1	0.9	A88	Antifungal screening of beach-cast seaweeds from Yucatan.
23	Russia	1	0.9	A64	Lipid extract and metabolic responses under acute stress.
24	South Africa	1	0.9	A63	Antioxidant, anti-obesogenic and anti-diabetic screening.
25	Sri Lanka	1	0.9	A51	Extract fractions with antioxidant and antimicrobial activity supported by docking.
26	Vietnam	1	0.9	A61	Structure and cytotoxicity of a linear sulfated galactan.

As shown in Table 3.3, *Codium* research exhibits a strong geographical concentration in Asia (66 of 113 studies, 58.4%), followed by Europe (26, 23.0%), Africa (14, 12.4%), South America (5, 4.4%), and North America and Oceania (1 study each, 0.9%). South Korea alone contributed 38 studies (33.6%), mostly on *C. fragile* polysaccharides and extracts, followed by Portugal (17), Egypt (7), and India (7). This distribution mirrors regional access to edible and abundant *Codium* species and the presence of marine biotechnology programs, while North America and Oceania are represented only by single multi-species screens and the tropical Indo-Pacific mainly by single reports.

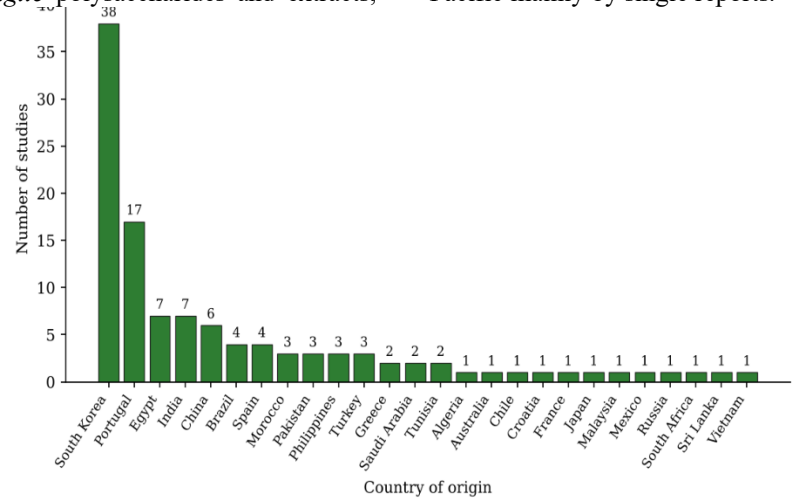


Figure 3.2. Distribution of Reviewed Studies on the Genus *Codium* by Country of Origin

3.1.3. Characteristics by Type of Article

The reviewed *Codium* studies are all peer-reviewed journal articles, indicating that research on the genus has consolidated into mainstream scientific discourse. Review articles [11], book chapters, conference papers, and errata were excluded by design, so this table reflects the inclusion criteria as much as the literature. The journals span pharmacology, glycobiology, food science, nutrition, marine biotechnology, nanotechnology, and environmental science, which underscores the multidisciplinary nature of marine natural product research; Marine Drugs (13 studies), the International Journal of Molecular Sciences (7), and the International Journal of Biological Macromolecules (4) were the most frequent outlets.

Table 3.4. Distribution of Reviewed Studies by Article Type

No	Article Type	Number of Studies	Percentage (%)	Article Codes	Description
1	Journal Article	113	100.0	A1–A113	Empirical experimental studies published in peer-reviewed journals, covering chemical characterization, bioassays, and mechanistic work.

As shown in Table 3.4, journal articles constitute 100% of the 113 reviewed publications. The absence of conference proceedings reflects the exclusion of non-journal formats and the databases searched, and suggests that the evidence base is

in the form of full experimental papers rather than preliminary reports.

3.1.4. Characteristics by Research Method

The methodological approaches employed across the reviewed *Codium* studies demonstrate a strong dominance of experimental designs, reflecting the field's emphasis on empirical validation of chemical and pharmacological properties. Most studies employed in vitro assays supported by chemical and spectroscopic analyses (e.g., GC–MS, LC–MS, FTIR, NMR) for compound identification. A substantial group used in vivo models—mice, rats, zebrafish, or rockfish—to assess immune, tumor, metabolic, respiratory, cognitive, neurodegenerative, nociceptive, hepatic, intestinal, thrombotic, and skin outcomes, while a few works adopted in silico molecular docking, molecular dynamics, or 3D structural modelling to explore potential mechanisms of action. Two studies extended to human testing: one used a human epidermis model and a clinical brightness test, and the other measured transepidermal water loss and skin hydration after applying a nanoemulsion.

Table 3.5. Distribution of Reviewed Studies by Research Method

No	Research Method	Number of Studies	Percentage (%)	Article Codes	Description
1	In vitro only	74	65.5	74 studies (see Table 3.1)	Cell-based, enzymatic, antimicrobial, antifungal, anticandidal, antiviral, larvicidal and antialgal assays, often with chemical or spectroscopic characterization.
2	In vitro + in silico	4	3.5	A12, A17, A51, A63	Laboratory assays complemented by molecular docking, molecular dynamics or 3D structural modelling.
3	In vivo (with in vitro or in silico assays)	33	29.2	33 studies (see Table 3.1)	Mouse, rat, zebrafish, rockfish and chick chorioallantoic-membrane models, including tumor xenografts and metastasis, immunosuppression, high-fat-diet obesity, PM2.5 exposure, colitis, arterial thrombosis, acute stress, paw oedema and analgesic tests, a rotenone-induced Parkinson's rat model, allergic and dermatitis models and bacterial challenge.
4	Clinical test (with in vitro, 3D skin or in vivo work)	2	1.8	A21, A68	A skin-whitening vesicle study with a human epidermis model and a clinical brightness test, and a nanoemulsion study with photoprotection assays, animal testing and a clinical skin-hydration test.

As summarized in Table 3.5, in vitro experimental studies are the largest group (74 of 113, 65.5%), and 4 more (3.5%) combine in vitro assays with docking, molecular dynamics, or 3D structural modelling. Thirty-three studies (29.2%) used animal models together with in vitro or in silico work, and two studies (1.8%) included a clinical test, one of which also used animals, so 34 of the 113 studies involved animals. Evidence on safety, pharmacokinetics, and efficacy in humans is still almost absent, and translation to in vivo and clinical settings remains an important research gap.

3.2. *Codium* Sources (Species, Sampling Locations, and Extraction Methods)

The reviewed studies reveal considerable diversity in *Codium* species, geographic origins, and extraction methodologies. *C. fragile* was the most investigated species (55 of 113 studies, 48.7%), followed by *C. tomentosum* (21), *C. isthmocladum* (6), and *C. cylindricum* and *C. decorticatum* (3 each); *C. intricatum*, *C. edule*, *C. adhaerens* and *C. vermilara* were examined twice each. Eleven further species—*C. arabicum*, *C. bernabei*, *C. bursa*, *C. capitatum*, *C. dwarkense*, *C. elongatum*, *C. flabellatum*, *C. geppiorum*, *C. intertextum*, *C. iyengarii* and *C. minus*—were each examined once, and 9 studies identified the material only as *Codium* sp. Sampling locations were stated in only some abstracts (for example the north Tunisian, Chilean, Adriatic, central Vietnamese, Moroccan, Yucatan, Canary Islands, Aegean and Marmara, and Red Sea coasts), so Table 3.6 reports them only where available. Extraction approaches ranged from hot-water and deep-eutectic-solvent extraction followed by chromatography (polysaccharides) to ethanol, methanol, ethyl acetate and chloroform extraction (lipids, phenolics, carotenoids), enzymatic digestion, subcritical-water extraction, headspace solid-phase microextraction and hydrodistillation of volatiles, and vesicle isolation.

Table 3.6. Summary of *Codium* Sources, Sampling Locations, and Extraction Methods

No	*Codium* Species	Sampling Location	Extraction / Isolation Method	Article Codes	Description
1	*C. fragile*	Mostly not stated; most studies come from South Korean groups; Aegean and Marmara Seas, Turkey; Aegean Sea, Greece; Red Sea, Egypt; south-eastern Spain; La Marsa and the north Tunisian coast	Hot-water/ion-exchange and size-exclusion chromatography (polysaccharides); enzymatic digestion; ethanol, methanol and chloroform extracts; extracellular vesicle isolation; isolation of a low-molecular-weight component, fatty acids and loliolide; polysaccharide–drug, nanoparticle and liposome preparation; desalting optimization; crude polysaccharide for antiviral screening; methanol extract; siphonaxanthin purification; extract-synthesized TiO2 nanoparticles	55 studies (see Table 3.1)	Most studied species; polysaccharides with immune, anticoagulant, anticancer and anti-inflammatory activity; extracts in obesity, muscle, PM2.5, allergy, dermatitis and liver models; vesicles, siphonaxanthin, fatty acids and nanoparticle systems; multi-species antioxidant, antidiabetic, antiviral and antifungal screens; anti-metastatic extract in head and neck cancer.

No	*Codium* Species	Sampling Location	Extraction / Isolation Method	Article Codes	Description
2	*C. tomentosum*	IMTA (Ria de Aveiro, Portugal) in three studies; Red Sea, Egypt (two studies); Agadir and another Moroccan site; north Tunisian coast; otherwise not stated	Ethanol, methanol, ethyl acetate, aqueous and subcritical-water extracts; total lipid and polar lipid fractionation (LC-MS); loliolide isolation; sulfated polysaccharide extraction; gold-nanoparticle synthesis; nanoencapsulation; ointment formulation	21 studies (see Table 3.1)	Lipid-based nanocarriers, photodynamic antibacterial lipids, loliolide, sulfated polysaccharides, anti-inflammatory and larvicidal extracts, and nano- and topical formulations; nanophytosomes in a rat Parkinson's model, lipid COX-2 inhibition and multi-species antioxidant and antimicrobial screens.
3	*C. isthmocladum*	Beach-cast material from Yucatan, Mexico (one study); otherwise not stated in abstracts	Purification of a sulfated homogalactan (3G4S) and a sulfated arabinan with galactofuranose side chains (F2-1); lectin purification (CiL-1, CiL-2 and new lectins); aqueous extract for antifungal screening	A7, A12, A34, A39, A42, A88	Galactofuranose-containing and other sulfated galactans and lectins with anticoagulant, antimetastatic, antigenotoxic, anti-inflammatory and antibiofilm activity.
4	*C. vermilara*	Adriatic Sea (one study); otherwise not stated in abstracts	Ternary deep eutectic solvent extraction of sulfated polysaccharides (Box–Behnken optimization) vs hot water; matrix solid-phase dispersion with GRAS solvents for metabolomics	A72, A111	Green extraction of sulfated polysaccharides.
5	*C. decorticatum*	Buleji, Pakistan (one study); otherwise not stated in abstracts	Solvent extracts screened for anti-inflammatory, antitumor, antiproliferative, antioxidant and antimicrobial activity	A10, A106, A110	Anti-inflammatory, antitumor, antiproliferative, antioxidant and antimicrobial extracts.
6	*C. cylindricum*	Not stated in abstracts	Polysaccharide extraction, H2O2-Vc / H2O2-Fe2+ ultrasonic degradation and hypoglycemic testing; siphonaxanthin isolation	A15, A18, A19	Degraded polysaccharides with improved antioxidant activity and hypoglycemic effect; siphonaxanthin protecting obese mice.
7	*C. dwarkense*	Earthquake Crack, Ras Muhammad National Park, Red Sea, Egypt	Extract for HPLC and GC-MS profiling and bioassays	A53	Habitat-linked chemical profile with antioxidant and antimicrobial screening.
8	*C. elongatum*	Not stated in the abstract	Extract tested in carrageenan-induced paw edema	A50	Anti-inflammatory activity in rats.
9	*C. intricatum*	Ilocos Norte, Philippines (one study)	Nutritional analysis with antioxidant and antibacterial assays; polysaccharide content analysis with cytotoxic and anti-metastasis assays	A4, A6	Antioxidant, antibacterial, cytotoxic and anti-metastatic activity of extracts and polysaccharides.
10	Other species (single studies unless stated)	Chilean coast (*C. bernabei*); Adriatic Sea (*C. adhaerens*, two studies); central coast of Vietnam (*C. geppiorum*); north Tunisian coast (*C. bursa*); Karachi coast (*C. flabellatum*); Canary Islands (*C. intertextum*); otherwise not stated	Sulfated polysaccharide characterization (*C. bernabei*, *C. geppiorum*, *C. edule*); volatile, less polar and phenolic compounds (*C. adhaerens*); solvent extracts with flash chromatography and GC–MS (*C. bursa*); extract-loaded nanoemulsion (*C. iyengarii*); adipogenesis assays (*C. minus*); extract-synthesized silver nanoparticles (*C. capitatum*, *C. edule*); anticandidal extracts (*C. arabicum*); methanol extract in analgesic and anti-inflammatory models (*C. flabellatum*); antioxidant extracts from wild and IMTA material (*C. intertextum*)	A5, A25, A36, A43, A61, A67, A68, A81, A82, A85, A90, A95, A111	Single reports on anticoagulant, antitumor and cytotoxic polysaccharides and extracts, anti-allergic polysaccharide, antioxidant compounds, cosmeceutical nanoemulsion, anti-adipogenic extract, antibacterial and larvicidal nanoparticles, anticandidal and anti-inflammatory extracts.
11	*Codium* sp.	Not stated in most abstracts; IMTA-grown material in one study; Galician and north Portuguese coasts; Peninsular Malaysia	Five solvent extracts (ethyl acetate, ethanol, hydroethanolic) and biochar from residue; polysaccharide sponge with biosynthesized silver nanoparticles; seasonal extracts; circular valorization for skin care; seasonal crude polysaccharides; siphonaxanthin purification; phenolic profiling; postharvest antifungal extracts	A41, A44, A65, A80, A86, A91, A102, A103, A108	Extracts and polysaccharides used in biorefinery, wound-dressing, seasonal-bioactivity and skin-care studies; purified siphonaxanthin against breast cancer and multi-species antioxidant and antifungal screens.

Table 3.6 illustrates that *Codium* species are widely used as bioactivity sources, with *C. fragile* acting as a model species because of its edibility, wide distribution, and relatively abundant biomass. The extraction route strongly determines the compound class obtained: aqueous and chromatographic routes give sulfated polysaccharides and glycoproteins, whereas organic solvents give lipids, fatty acids, carotenoids, and phenolics. Green solvents such as deep eutectic solvents gave a higher polysaccharide yield (17.80%) with more sulfur than hot water [113], indicating that extraction is a controllable variable in bioactivity. Material from integrated multi-trophic aquaculture [114,121] and seasonal comparisons [83,114] show that cultivation and season are additional sources of variation. Because sampling site, season, and voucher information were rarely reported in the abstracts and titles, species-level molecular identification (e.g., *rbcL* and *tufA* markers) is recommended, particularly as taxonomic work continues to describe new species [16,19].

3.3. Phytochemical Profile of the Genus *Codium*

The phytochemical composition of the *Codium* genus demonstrates considerable chemical diversity, producing sulfated polysaccharides, lectins, membrane polar lipids and

fatty acids, carotenoids, terpenoids, and phenolic compounds. Sulfated polysaccharides include sulfated β-D-galactans, galactofuranose-containing sulfated polysaccharides, a sulfated mannan, and sulfated galactoarabinans of high molecular weight, while lipid studies identified phospholipids, glycolipids, betaine lipids, and polyunsaturated fatty acids. Carotenoids such as siphonaxanthin, canthaxanthin, and zeaxanthin and phenolics such as quercetin and apigenin add further chemical variety, and loliolide represents the small terpenoid fraction. Several studies also embedded *Codium* material in nanoparticles, liposomes, ointments, and nanoemulsions. Abstract-level coding of the Scopus-only studies added a sulfated arabinan with β-D-galactofuranose side chains, a linear 3- and 4-sulfated galactan, phytol, fatty acid amides such as oleamide and hexadecanamide, uracil, volatile ketones and alcohols, coumarins, benzaldehydes and flavanones, and fatty acid esters of hydroxy fatty acids to this list, whereas several recent disease-model studies did not profile their extracts chemically.

Table 3.7. Major Phytochemical Constituents Identified in *Codium* Species

No	Chemical Class	Representative Compounds	Main *Codium* Species	Analytical Methods	Biological Relevance
1	Sulfated polysaccharides (galactans, galactoarabinans, mannans)	Sulfated galactan 3G4S; galactoarabinan CZS-0-1 (810 kDa, 21% sulfate; Ara:Gal:Glc 9:2:1); galactofuranose-containing sulfated polysaccharide; sulfated mannan used in a 5-FU conjugate; arabinogalactan (6–8 kDa); sulfated polysaccharides characterized from *C. bernabei*, *C. geppiorum*, *C. edule* and *C. tomentosum*	*C. vermilara*, *C. isthmocladum*, *C. fragile*, *C. cylindricum*, *C. bernabei*, *C. geppiorum*, *C. edule*, *C. tomentosum*	NMR, methylation/desulfation, FTIR, ion-exchange and size-exclusion chromatography, LC-MS	Anticoagulant, immunomodulatory, anticancer, antimetastatic, antioxidant, anti-inflammatory, anti-allergic, hypoglycemic, antibacterial
2	Lectins	Galactose-binding lectin CiL-1; new lectins with unique sequences	*C. isthmocladum*	Protein purification, amino acid sequencing, in vitro assays, molecular docking	Antinociceptive and anti-inflammatory; antibiofilm
3	Membrane polar lipids and fatty acids	Phospholipids (74%) and non-phosphorus polar lipids (26%), glycolipids, betaine lipids; hexadecanoic, octadecanoic, myristic and oleic acids; lipid extract; less polar compounds; fatty acid esters of hydroxy fatty acids (FAHFAs); lipid extracts inhibiting COX-2; saturated-fatty-acid-rich profiles	*C. tomentosum*, *C. fragile*, *C. dwarkense*, *C. adhaerens*	LC-MS, GC-MS, bioactivity-guided isolation	Mitochondrial protection, photodynamic antibacterial, antialgal, antioxidant, metabolic response to stress
4	Carotenoids and vitamins	Siphonaxanthin, canthaxanthin, zeaxanthin; vitamin C and E; retinoic acid, α-tocopherol; siphonaxanthin purified for anticancer and anti-inflammatory testing; β-carotene and violaxanthin	*C. fragile*, *C. cylindricum*, *C. dwarkense*, *Codium* sp.	UPLC-QTOF-MS/MS, HPLC, molecular docking	Antiviral (SARS-CoV-2 pseudovirus), muscle health, protection against lipotoxicity, antioxidant, anticancer (breast cancer), anti-inflammatory
5	Phenolics and flavonoids	Quercetin, apigenin, pyrogallol, benzoic acid; tris(2,4-di-tert-butylphenyl) phosphate; tannins and alkaloids (qualitative); coumarins (7-hydroxycoumarin), benzaldehydes and flavanones; phenolic-enriched resin fractions	*C. dwarkense*, *C. tomentosum*, *C. fragile*, *C. adhaerens*, *C. vermilara*, *Codium* sp.	HPLC, GC-MS, colorimetric assays	Antioxidant, anti-inflammatory, antidiabetic, antimicrobial
6	Terpenoids and other small molecules	Loliolide; a representative low-molecular-weight component; 15-nor-amorph-11-en-4β-ol; 3,7-dimethyloctane-1,7-diol; 7-hydroxyheptanoic acid	*C. tomentosum*, *C. fragile*	Bioactivity-guided isolation, spectroscopy	Neuroprotective and anti-inflammatory; anti-neuroinflammatory (NF-κB); selective inhibition of red-tide microalgae
7	Extracellular vesicles	Nanosized vesicles from *C. fragile* tissue	*C. fragile*	Vesicle isolation and cell assays	Anti-melanogenic (MITF, tyrosinase, TRP1 downregulation)

No	Chemical Class	Representative Compounds	Main *Codium* Species	Analytical Methods	Biological Relevance
8	Formulated and nano-delivered materials	Silver-nanoparticle polysaccharide sponge; mitochondria-targeted nanophytosomes; gold nanoparticles made with an aqueous extract; indocyanine green-loaded polysaccharide–chitosan nanoparticles; liposomes; nanoencapsulated extract; extract-loaded nanoemulsion; topical ointment; silver and TiO2 nanoparticles synthesized with extracts; nanophytosomes tested in rat models	*Codium* sp., *C. tomentosum*, *C. fragile*, *C. iyengarii*, *C. capitatum*, *C. edule*	Particle characterization, encapsulation optimization, formulation tests	Antibacterial, wound healing, antitumoral enhancement, photoimmunotherapy, cosmeceutical, mitochondrial protection, larvicidal, water disinfection, neuroprotection in vivo

The results summarized in Table 3.7 indicate that the *Codium* genus supports a rich and diverse phytochemical composition that links directly to its pharmacological properties. Sulfated polysaccharides form the largest group and the best characterized class, and their structural features—arabinose- or galactose-based backbones, sulfate position, galactofuranose units, and branching—define their activities. Lectins show receptor-mediated anti-inflammatory activity and antibiofilm effects. Lipid-derived compounds offer carriers and antimicrobial agents, whereas carotenoids, phenolics, and small terpenoid molecules supply antioxidant, antiviral, neuroprotective, and metabolic effects. The growing group of formulated materials shows that *Codium* constituents are being moved from crude extracts toward delivery systems. Few studies cover sterols, which are documented in other work, so the sterol fraction is under-represented here.

Representative chemical structures of the best-defined small-molecule constituents named in the reviewed studies are shown in Figures 3.3 and 3.4: the carotenoids zeaxanthin and canthaxanthin and the terpenoid loliolide (Figure 3.3), the flavonoids apigenin and quercetin, and a sulfated galactose residue typical of the sulfated galactans that make up the best-characterized polysaccharide fraction (Figure 3.4). These drawings were prepared by the authors for illustration; they were not extracted from the included studies, and stereochemistry is shown only where it defines the sugar residue.

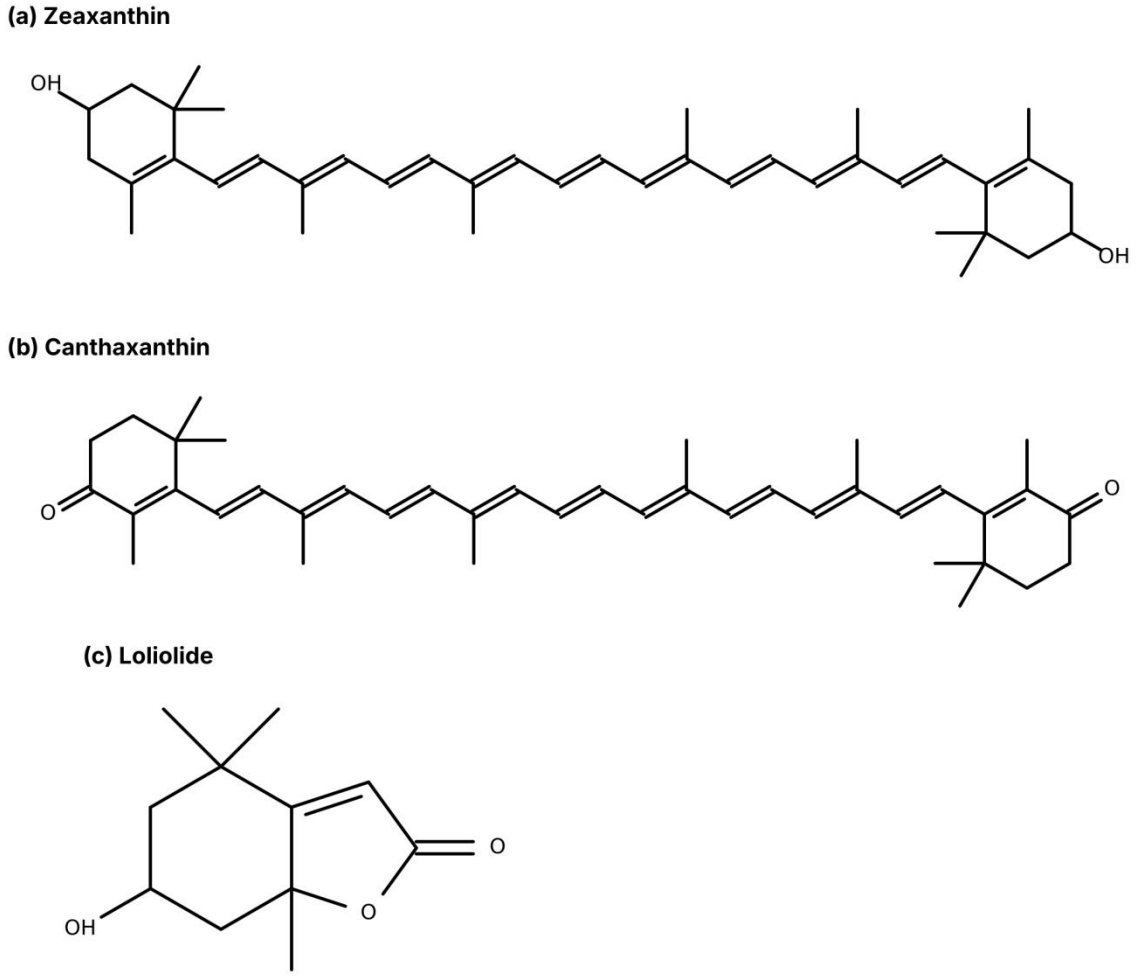


Figure 3.3. Representative structures of carotenoid and terpenoid constituents reported from *Codium*: (a) zeaxanthin, (b) canthaxanthin, and (c) loliolide. Stereochemistry is not shown.

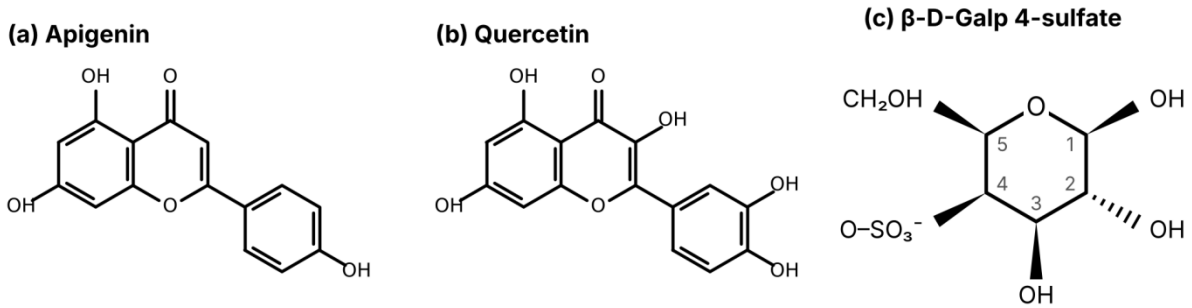


Figure 3.4. Representative phenolic and polysaccharide structural units: (a) apigenin, (b) quercetin, and (c) β-D-galactopyranose 4-sulfate, an illustrative monomer of the sulfated galactans. Sulfation positions vary among reported polysaccharides.

3.4. Pharmacological Activities of *Codium* Bioactive Compounds

The reviewed studies reveal that *Codium* species exhibit a diverse range of pharmacological activities, driven by their content of sulfated polysaccharides, lipids, glycoproteins, carotenoids, terpenoids, and phenolics. Keyword coding of the activity descriptors shows that antioxidant (48 studies), anti-inflammatory (26), antimicrobial including antifungal (25), anticancer (21), neuroprotective or organ-protective (17), metabolic (12), immunomodulatory (11), and skin-related (10) activities are the most frequent, followed by larvicidal or algicidal (6), anticoagulant or antithrombotic (4), and antiviral (3) activity. Many antioxidant and antimicrobial entries come from multi-species screens in which *Codium* was tested alongside other seaweeds and was usually not the most active species. Anticoagulant and immunomodulatory activities are the best documented at the level of purified compounds, anticancer effects were reported for polysaccharides, nanoparticles, and polysaccharide–drug conjugates, and antioxidant and anti-inflammatory activities were reported for both crude extracts and polysaccharide fractions.

Table 3.8. Pharmacological Activities of *Codium* Bioactive Compounds

No	Pharmacological Activity	Major Active Compounds	*Codium* Species	Experimental Model	Key Findings
1	Antioxidant and antigenotoxic (n = 48)	Sulfated galactan 3G4S; degraded polysaccharides; polysaccharide hydrolysates; polyphenolic fractions; extracts; less polar compounds	*C. isthmocladum*, *C. cylindricum*, *C. fragile*, *C. dwarkense*, *C. tomentosum*, *C. adhaerens*, *C. bernabei*, *C. intricatum*, *Codium* sp, *C. intertextum*, *C. decorticatum*, *C. vermilara*	In vitro (DPPH, ABTS, ORAC, comet assay); in vitro + in vivo (H2O2-induced stress, *C. adhaerens*)	3G4S reduced H2O2-induced DNA damage by 81.38%; degradation enhanced antioxidant activity; enzymatic-digest polysaccharides protected against H2O2-induced oxidative stress in vitro and in vivo; in multi-species screens *Codium* extracts were usually less antioxidant than brown or red seaweeds
2	Anticancer / cytotoxic (n = 21)	Polysaccharides; polysaccharide conjugates and nanoparticles; galactans; gold nanoparticles with extract; purified siphonaxanthin; methanol extract	*C. decorticatum*, *C. fragile*, *C. isthmocladum*, *C. tomentosum*, *C. geppiorum*, *C. intricatum*, *C. bernabei*	In vitro (MDA-MB-231, HeLa, MCF, PANC-1, A375, A-431); in vivo (xenograft, lung carcinoma, metastasis models); MCF-7, MDA-MB-231, HepG2 and head and neck cancer cells	*C. fragile* polysaccharide had the lowest IC50 among eight seaweeds; polysaccharide blocked CT-26 and B16 lung infiltration and activated NK cells; a sulfated galactan reduced melanoma metastasis; a folate-targeted conjugate and indocyanine green nanoparticles were effective in tumor models; siphonaxanthin inhibited both breast cancer subtypes at 5 μM; a methanol extract repressed the NRP2/RSK1/Sox2/Zeb1 axis
3	Anti-inflammatory, antinociceptive and anti-allergic (n = 26)	Lectin CiL-1; ethanol and hydroethanolic extracts; sulfated polysaccharides; low-molecular-weight component; siphonaxanthin; lipid extract (COX-2 inhibition)	*C. isthmocladum*, *C. tomentosum*, *C. fragile*, *C. edule*, *C. elongatum*, *C. decorticatum*, *Codium* sp, *C. flabellatum*	In vivo (zebrafish, BALB/c mice, Wistar rats); in vitro (RAW 264.7, keratinocytes, microglia, protease inhibition)	CiL-1 effective at all doses; sulfated polysaccharides were anti-inflammatory in macrophages and zebrafish; extracts reduced dermatitis and allergic bronchial inflammation in mice and carrageenan paw edema in rats; a low-molecular-weight component inhibited NF-κB in microglia and macrophages; *C. tomentosum* lipids inhibited COX-2 by up to 80%; *C. flabellatum* extract was anti-inflammatory and analgesic in vivo
4	Immunomodulatory (n = 11)	Anionic macromolecules, CFP, SP and SP-FA, sulfated polysaccharides, extracts	*C. fragile*	In vivo (mice, rockfish); in vitro (splenocytes, NK cells, macrophages, human dendritic and T cells)	Improved lymphocyte proliferation, NK activity and spleen index; NK activation through IL-12, MAPK and NF-κB; dendritic and T-cell activation; macrophage activation by extracts; rockfish mortality reduced with 0.1% dietary SPs

No	Pharmacological Activity	Major Active Compounds	*Codium* Species	Experimental Model	Key Findings
5	Neuroprotective and organ-protective (n = 17)	Loliolide; membrane polar lipids; extracts; polar-lipid nanophytosomes	*C. tomentosum*, *C. fragile*, *Codium* sp.	In vitro (SH-SY5Y, nasal, lung and brain cells); in vivo (PM2.5, acetaminophen and ovalbumin models in mice); rotenone-induced Parkinson's rat model	Protection against rotenone and glutamate toxicity; protection against PM2.5-induced toxicity, pulmonary dysfunction and cognitive dysfunction; protection against acetaminophen-induced liver injury; hypnotic effects of a desalted functional food; nanophytosomes restored brain and muscle mitochondrial function in rats
6	Antimicrobial, antifungal and antibiofilm (n = 25)	Total lipids and polar lipids; CME and PSP; sulfated polysaccharides; lectins; silver-nanoparticle sponges; liposomes; extracts; extract-synthesized silver and TiO2 nanoparticles; antifungal and anticandidal extracts	*C. tomentosum*, *C. fragile*, *C. isthmocladum*, *C. intricatum*, *Codium* sp, *C. capitatum*, *C. arabicum*, *C. decorticatum*	In vitro (CFU, MIC, biofilm assays); in silico docking	~6 log10 reduction of *S. aureus* with photodynamic therapy; SPs MIC 2 mg/mL against fish pathogens; lectins reduced biofilm; liposomal encapsulation enhanced antibacterial effect; *Codium* extracts were weak or inactive against fungal phytopathogens in most screens
7	Metabolic: anti-obesity, anti-diabetic and muscle function (n = 12)	Extracts (aqueous, ethanol); siphonaxanthin; degraded polysaccharides	*C. fragile*, *C. minus*, *C. cylindricum*	In vivo (high-fat-diet, Ob/Ob and exercise mice); in vitro (3T3-L1 adipocytes, enzyme inhibition, yeast glucose uptake)	Lower body weight, adipocyte size, cholesterol and glucose; reduced adipose expansion and fatty liver; inhibition of adipogenesis; higher endurance and muscle weight; inhibition of α-amylase, α-glucosidase and lipase; hypoglycemic polysaccharides; prebiotic effects
8	Skin, wound and cosmeceutical (n = 10)	Extracts; vesicles; nanoemulsion; ointment; IMTA-derived extracts	*C. fragile*, *C. tomentosum*, *C. iyengarii*, *Codium* sp.	In vitro (MNT-1, keratinocytes); 3D epidermis; clinical test; formulation tests	Reduced melanin synthesis (25 μg/mL), 1.31% brightness gain; elastase inhibition 88% at 200 μg/mL; skin-protective effects in atopic-dermatitis models; ointment with antioxidant, anti-inflammatory, antibacterial and wound-healing properties
9	Anticoagulant and antithrombotic (n = 4)	Galactoarabinan CZS-0-1; galactofuranose-containing polysaccharide; *C. bernabei* polysaccharide; extract	*C. isthmocladum*, *C. fragile*, *C. bernabei*	In vitro (coagulation assays); in vivo arterial thrombosis (extract)	FIIa and FXa inhibition; activity of CZS-0-1 fell with lower molecular weight; extract inhibited integrin αIIbβ3 signaling and arterial thrombosis
10	Antiviral (n = 3)	Siphonaxanthin; sulfated polysaccharide PSCT; crude polysaccharide	*C. fragile*, *C. tomentosum*	In silico docking; in vitro (SARS-CoV-2 pseudovirus, ACE2-HEK293; HSV-1 assay)	Siphonaxanthin IC50 87.4 μM for pseudovirus entry (fucoxanthin inactive); PSCT EC50 12.22 μg/mL against HSV-1 without cytotoxicity (CC50 > 200 μg/mL); *C. fragile* crude polysaccharide inhibited SARS-CoV-2 pseudovirus entry within the IC50 range of 12–289 μg/mL reported for the screened seaweeds

No	Pharmacological Activity	Major Active Compounds	*Codium* Species	Experimental Model	Key Findings
11	Larvicidal and algicidal (n = 6)	Methanolic and chloroform extracts; myristic acid, oleic acid, loliolide; extract with silver nanoparticles	*C. tomentosum*, *C. fragile*, *C. edule*	In vitro (larval, cyanobacterial and microalgal bioassays)	*C. tomentosum* LC50 69.85 ppm vs *Culex pipiens*; EC50-96h 14.2 to >500 µg/mL against red-tide microalgae; *C. edule* extract with silver nanoparticles gave LC50 21.34 ppm against *Musca domestica* larvae

The results in Table 3.8 confirm that *Codium* bioactive compounds exhibit broad-spectrum pharmacological effects that bridge marine chemistry and biomedical research. Quantitative potency data were reported inconsistently: some studies gave IC50 or EC50 values (glycoprotein, siphonaxanthin, fatty acids), others percentage reductions or log reductions, and many gave only qualitative statements. Positive controls were rarely identical across studies, so activities cannot be ranked, and the counts in parentheses are keyword-based and overlap. Anticoagulant, immunomodulatory, and anticancer effects are supported by structural and mechanistic work, whereas larvicidal, algicidal, and several metabolic and organ-protection findings rest on a few screening assays or single mouse models. Only a minority of studies used a purified, structurally defined compound; crude extracts predominate, especially in the 2023–2026 disease-model studies.

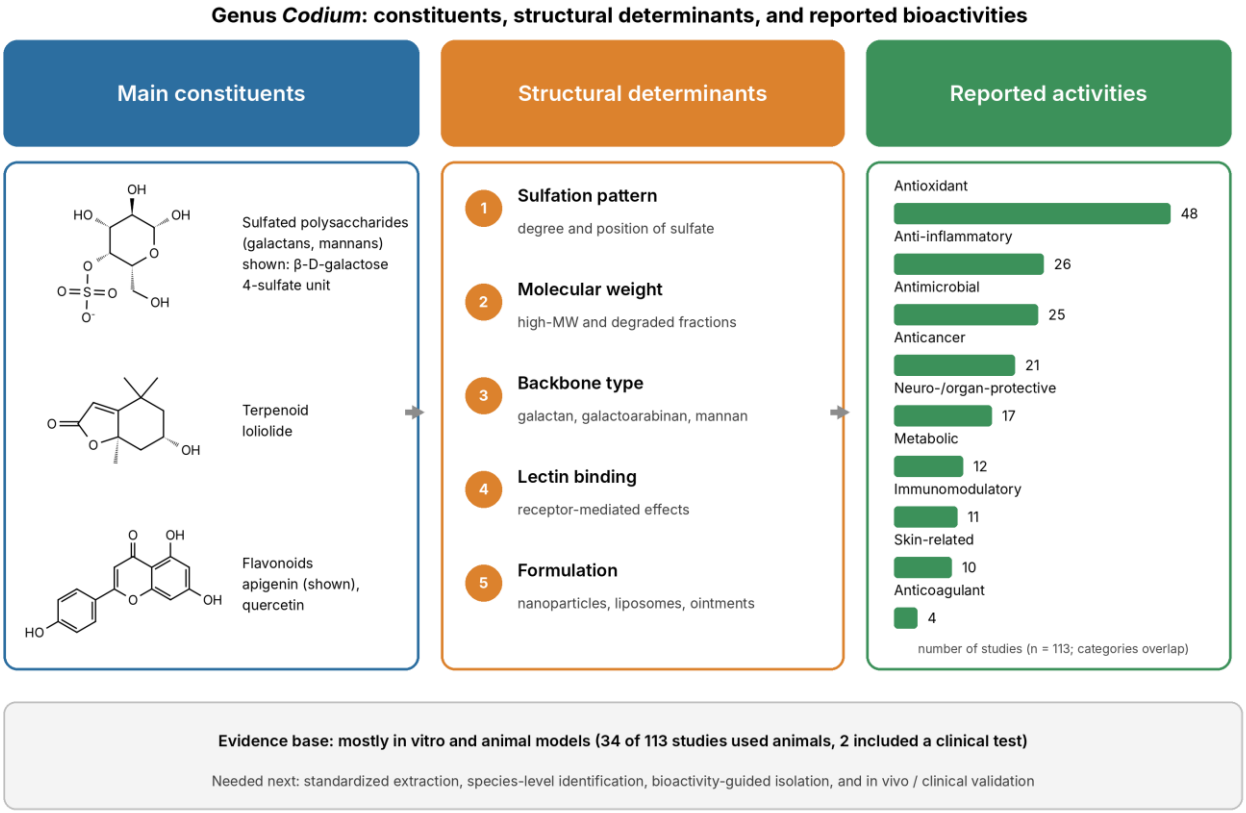


Figure 3.5. Graphical summary of the main constituents, structural determinants, and reported pharmacological activities of *Codium* across the 113 included studies. Bars show the number of studies per activity category (categories overlap). Structures were drawn by the authors for illustration.

3.5. Mechanistic Insights and Structure–Activity Relationship (SAR)

The pharmacological effects of *Codium* compounds are strongly determined by their molecular structures, particularly the arrangement and degree of sulfation, backbone type, and molecular weight of polysaccharides. Reducing the molecular weight of a galactoarabinan sulfate lowered its anticoagulant activity [103], whereas H2O2-based ultrasonic degradation of another polysaccharide improved its antioxidant activity [60], so molecular weight mattered in opposite directions depending on the activity. A sulfated galactan reduced melanoma metastasis through direct regulation of malignancy features [49]. Beyond polysaccharides, mechanisms reported in newer studies include inhibition of integrin αIIbβ3 signaling [64], NF-κB inhibition in microglia and macrophages [117], and TLR-dependent signaling in PM2.5 models [88,89]. Mechanistic information was available at abstract level for only part of the evidence base, so the structural determinants below should be read as hypotheses rather than established rules.

Table 3.9. Mechanistic and Structural Determinants of Bioactivity in *Codium* Compounds

No	Compound Class	Key Structural Features	Mechanistic Target / Pathway	Biological Effect	Related Species
1	Pyruvylated Sulfated Galactan (3G4S)	(1→3)-β-D-galactan with C6 branching, 3,4-O-pyruvyl ketal, sulfate at C-4/C-6	Direct radical scavenging; blocking of oxidative chain initiation	Antigenotoxic	*C. isthmocladum*

No	Compound Class	Key Structural Features	Mechanistic Target / Pathway	Biological Effect	Related Species
2	Sulfated Homogalactan (3G4S) and Melanoma Malignancy	Sulfated homogalactan 3G4S; not cytotoxic to melanoma cells	Reduced invasion, colony formation and membrane glycoconjugates of B16-F10 cells	Reduced solid tumour growth and metastasis in mice	*C. isthmocladum*
3	Galactofuranose-containing Sulfated Arabinan (F2-1)	100 kDa; →4)-β-L-Arap backbone with β-D-Galf side chains; 18% sulfate	Coagulation (target not reported in the abstract)	Anticoagulant	*C. isthmocladum*
4	Galactoarabinan Sulfate (CZS-0-1)	810 kDa; (1→3)-β-L-Arap backbone; sulfate at O-2/O-4; 10% β-D-Galp branches at O-4	FIIa and FXa inhibition with heparin cofactors	Heparin-like anticoagulant; activity decreases with lower molecular weight	*C. fragile*
5	Degraded Polysaccharides	Lower molecular weight after H2O2-based ultrasonic treatment; same monosaccharide units	Radical scavenging	Enhanced antioxidant activity	*C. cylindricum*
6	Optically Negative L-form Arabinogalactan	6–8 kDa; >14 kDa fraction most active; sulfated arabinogalactan	Cytotoxicity in HeLa and MCF cells	Cytotoxic, antioxidant	*C. fragile*
7	Immunostimulatory Polysaccharides and Macromolecules	CFP, CFAMs, SPs; SP-FA (folic-acid esterified)	NK-cell activation (CD69, IFN-γ, perforin, granzyme B, IL-12-dependent); MAPK and NF-κB; dendritic and T-cell activation; cytokine regulation	Immune enhancement, anti-tumor immunity, reduced fish mortality	*C. fragile*
8	Lectin CiL-1	Galactose-binding lectin; binds tetra-antennary N-glycan models (LacNac2 best)	Modulation of TRPA1 through lectin–glycan binding	Antinociceptive, anti-inflammatory, ROS reduction	*C. isthmocladum*
9	Polar Lipids	Phospholipids, glycolipids, betaine lipids, PUFA	Mitochondrial complexes I/II and membrane potential; light-activated photodynamic inactivation	Neuroprotective model, antibacterial	*C. tomentosum*
10	Siphonaxanthin and Canthaxanthin	Keto-carotenoids	Predicted Spike-glycoprotein binding; mTORC1 and SIRT1/PGC-1α signaling; somatic stress and anti-oxidative capacity (obese mice); suppression of Nrf2/SOD-2, Akt/ERK and NF-κB leading to apoptosis (breast cancer)	Antiviral; muscle mass and endurance; protection against lipotoxicity; anticancer	*C. fragile*, *C. cylindricum*, *Codium* sp.
11	Extract Inhibiting Integrin αIIbβ3	Ethanol extract; phytol as main GC–MS constituent	Integrin αIIbβ3 outside-in signaling (c-Src, Syk, PLCγ2, PI3K/AKT and MAPK)	Antiplatelet; inhibition of arterial thrombosis without prolonged bleeding	*C. fragile*
12	Uracil (Low-molecular-weight Marker)	Uracil, the main low-molecular-weight marker of an aqueous extract	NF-κB pathway in microglia and macrophage cells	Anti-neuroinflammatory	*C. fragile*
13	Extracts in PM2.5 Models	Aqueous extracts containing fatty acid amides (oleamide, hexadecanamide) and fatty acids	TLR/TGF-β pathway (lung); gut–brain axis via TLR-4/MyD88 (cognition)	Protection against PM2.5-induced pulmonary and cognitive dysfunction in mice	*C. fragile*
14	Anti-adipogenic Extracts	Extracts (not chemically profiled in the abstracts)	Adipogenic transcription and lipid-metabolism factors (3T3-L1 cells); adipo- and lipogenesis downregulation in vivo	Anti-adipogenic; reduced adipose expansion and fatty liver	*C. minus*, *C. fragile*
15	NRP2-inhibiting Methanol Extract	Methanol extract (not chemically profiled)	Neuropilin-2 and the RSK1/Sox2/Zeb1 axis	Reduced EMT, invasion and cancer-stem-cell properties of head and neck cancer cells	*C. fragile*

The findings summarized in Table 3.9 reveal that the biological efficacy of *Codium* compounds is tightly linked to specific molecular features. For sulfated polysaccharides, the position of sulfate, backbone type, and molecular weight appear more informative than total sulfate content, and the optimum molecular weight differs between anticoagulant and antioxidant activities. For immunomodulatory polysaccharides, receptor-level and signaling mechanisms were identified, and derivatization with folic acid allowed folate-receptor-targeted delivery. Newer extract-based studies name signaling pathways (integrin αIIbβ3, NF-κB, TLR/TGF-β, TLR-4/MyD88, adipogenic transcription factors) but rarely

identify the active constituent, so activity cannot yet be assigned to a defined structure. In silico approaches supported lectin, antimicrobial, antiviral, and enzyme-inhibition findings, but they remain predictive and require experimental validation.

3.6. Potential Applications and Industrial Relevance

The diverse biochemical composition and pharmacological properties of *Codium* compounds offer broad potential for industrial utilization. In the pharmaceutical sector, sulfated polysaccharides are candidates for heparin-like anticoagulants, NK-cell stimulants, antimetastatic agents, and drug carriers. In biomedical materials, polysaccharide sponges loaded with biosynthesized silver nanoparticles were developed for wound dressings, and polar lipids were used to build mitochondria-targeted nanophytosomes. Nanoparticle systems based on extracts or polysaccharides were proposed for chemotherapy enhancement and photoimmunotherapy, and liposomal and nanoemulsion formulations for antibacterial and cosmeceutical use. Cosmeceutical applications include anti-melanogenic vesicles tested in a clinical brightness assay, elastase-inhibiting and photoprotective extracts, and topical ointments. Nutraceutical uses build on the edibility of *C. fragile* and *C. tomentosum*: anti-obesity, anti-diabetic, prebiotic, hypnotic, and muscle-function extracts and fortified foods. Aquaculture, agrochemical (including postharvest antifungal screening), water-disinfection, and circular-biorefinery uses are also reported.

Table 3.10. Potential Applications and Industrial Relevance of *Codium* Bioactive Compounds

No	Compound / Extract Type	Major Bioactivity	Industrial Sector	Example Applications	Related Species
1	Sulfated Polysaccharides (anticoagulant, antimetastatic)	Anticoagulant, antimetastatic	Pharmaceutical	Heparin-like anticoagulant candidates; antimetastatic leads	*C. vermilara*, *C. isthmocladum*, *C. fragile*, *C. bernabei*
2	Polysaccharide–Drug Conjugates and Nanoparticles	Targeted anticancer, NK-cell activation, photoimmunotherapy	Pharmaceutical / Drug delivery	Folate-targeted 5-FU carriers; indocyanine green photoimmunotherapy carriers; NK-cell stimulants	*C. fragile*
3	Nanoparticles and Liposomes from Extracts	Antitumoral enhancement, antibacterial enhancement	Nanomedicine	Gold-nanoparticle enhancer of gemcitabine; liposomal antibacterial formulations	*C. tomentosum*, *C. fragile*
4	Polysaccharide Sponges with Silver Nanoparticles	Antibacterial, biocompatible	Biomedical materials	Wound dressings for high-exudate wounds	*Codium* sp.
5	Membrane Polar Lipids	Mitochondrial protection, photodynamic antibacterial	Nanomedicine	Mitochondria-targeted nanophytosomes; antimicrobial photodynamic therapy	*C. tomentosum*
6	Extracts and Vesicles (skin)	Anti-melanogenic, elastase inhibition, photoprotection, anti-dermatitis	Cosmeceutical	Skin-whitening creams, anti-aging and photoprotective products, atopic-dermatitis care	*C. fragile*, *Codium* sp.
7	Topical Formulations	Wound healing, antioxidant, cosmeceutical	Cosmeceutical / Dermatology	Ointment and nanoemulsion; skin-care valorization of IMTA biomass	*C. tomentosum*, *C. iyengarii*, *Codium* sp.
8	Extracts (metabolic and muscle)	Anti-obesity, anti-diabetic, muscle function, prebiotic	Nutraceutical / Functional foods	Sports nutrition, anti-obesity supplements, anti-sarcopenia and gut-health foods	*C. fragile*, *C. minus*
9	Extracts in respiratory, hepatic and cognitive models	Protection against PM2.5, allergy and liver injury	Nutraceutical / Functional foods	Supplements for respiratory and liver health (mouse evidence only)	*C. fragile*
10	Fortified Foods	Antioxidant, antibacterial, hypnotic	Functional foods	Yogurt and fish-fillet fortification; desalted functional food with hypnotic effect	*C. tomentosum*, *C. fragile*
11	Sulfated Polysaccharides (feed)	Immunostimulatory, antibacterial	Aquaculture	Feed additive improving survival after bacterial challenge	*C. fragile*
12	Fatty Acids, Terpenoids, Extracts	Algicidal, larvicidal	Environmental / Agrochemical	Eco-friendly algicides for red tide and biological mosquito-larvae control	*C. fragile*, *C. tomentosum*
13	Post-extraction Biomass	Biochar for soil water retention	Circular bioeconomy	Zero-waste biorefinery producing extracts and soil-improving biochars	*Codium* sp.
14	Extracts (antifungal)	Antifungal against postharvest and plant pathogens	Agrochemical	Candidate biofungicides for fruit decay (weak for *Codium* in most screens)	*C. tomentosum*, *C. fragile*, *Codium* sp.
15	Extract-synthesized Metal Nanoparticles	Antibacterial, larvicidal	Environmental / Biomedical	Silver nanoparticles against drug-resistant bacteria and housefly larvae; UV-activated TiO2 nanoparticles for water disinfection	*C. capitatum*, *C. edule*, *C. fragile*

The findings in Table 3.10 confirm that *Codium* represents a multifaceted marine bioresource with applications in pharmaceuticals, biomedical materials, cosmeceuticals, nutraceuticals, aquaculture, and environmental management. The most mature evidence for translation is currently for cosmeceutical use (one clinical brightness test), aquaculture feed (in vivo challenge), and a large set of mouse disease models, whereas pharmaceutical candidates remain at the in vitro or animal stage. Circular-biorefinery designs that use both extracts and residual biomass fit blue-economy goals and may improve the economics of *Codium* utilization. Scale-up will

depend on reproducible cultivation, standardized extraction, and safety and regulatory studies.

4. Discussion

4.1. Overview of *Codium* Sources, Sampling, and Extraction Methods

The reviewed studies collectively demonstrate that *Codium* species are used as bioactivity sources across temperate, subtropical, and tropical coasts. *C. fragile* accounts for 55 of the 113 studies (48.7%), which is consistent with its edibility and wide distribution, followed by *C. tomentosum* (21) and *C. isthmocladum* (6). Sampling locations were stated in only some abstracts, for example the Earthquake Crack of Ras Muhammad National Park, Egypt [5], Ilocos Norte, Philippines [48], the north Tunisian coast [47], the Adriatic Sea [67], the central coast of Vietnam [102], the Chilean coast [85], Yucatan, Mexico [129], and the Canary Islands [126], so geographic comparison is limited. Material from integrated multi-trophic aquaculture [114,121] shows that cultivated biomass is entering bioactivity work, which may reduce the dependence on wild harvest.

Extraction route and solvent strongly shape which compounds are obtained. Polysaccharides were typically recovered by aqueous, enzymatic, or deep-eutectic-solvent extraction followed by ion-exchange and size-exclusion chromatography [56,103,113], whereas ethanol, methanol, ethyl acetate, chloroform, and hydroethanolic extracts gave lipids, phenolics, and carotenoids [93,106,119]; subcritical-water extraction was used to obtain extracts characterized for composition, health benefits, and safety [69]. Mahmoud et al. [113] reported a 17.80% yield and higher sulfur content with a ternary deep eutectic solvent compared with hot water, and Martins et al. [106] reused the residual biomass for biochar. Season and cultivation also changed bioactivity [83,114], and a study of lipid extracts showed lower seasonal shifts in domesticated than in wild-derived *C. tomentosum* [27]. Such differences prevent direct ranking of potency between studies and argue for reporting season, site, and extraction conditions.

4.2. Phytochemical Profile of the Genus *Codium*

The phytochemical characterization of *Codium* highlights its role as a reservoir of structurally diverse compounds, including sulfated polysaccharides, lipids, carotenoids, lectins, and phenolics. Li et al. [84] described a galactofuranose-containing sulfated polysaccharide from *C. isthmocladum*, Li et al. [103] described an 810 kDa galactoarabinan sulfate with 21% sulfate from *C. fragile*, and a sulfated mannan was used to build a folate-targeted drug conjugate [87]. Sulfated polysaccharides were also characterized from *C. bernabei* [85], *C. geppiorum* [102], and *C. tomentosum* [120]. These data show that the genus produces polysaccharide families with unusual linkages and substituents.

Complementing these, lipid and small-molecule studies identified phospholipids, glycolipids, and betaine lipids [58,73], loliolide from *C. tomentosum* [68], and myristic acid, oleic acid, and loliolide from *C. fragile* [116], while HPLC profiling of *C. dwarkense* revealed quercetin, apigenin, pyrogallol, zeaxanthin, and benzoic acid [5]. Siphonaxanthin [57,59] and canthaxanthin [65] represent the carotenoid fraction, and lectins [54,76] represent the protein fraction. Sterols, documented in other work, were not captured by this database set, and this should be addressed in a later update.

4.3. Pharmacological Activities of *Codium* Bioactive Compounds

The pharmacological diversity of *Codium* extracts reflects the interplay between their molecular structures and biological targets. Anticoagulant activity was shown for the galactoarabinan CZS-0-1 and for polysaccharides of *C. isthmocladum* and *C. bernabei* [84,85,103], and an extract inhibited arterial thrombosis [64]. Immunomodulatory activity was the best supported in vivo: *C. fragile* polysaccharides improved NK activity and anti-tumor immunity in mice [43,45,55], activated human dendritic and T cells [50], and enhanced macrophage responses [51,97,111]; in rockfish, dietary polysaccharides reduced mortality after bacterial challenge [62].

Beyond these, *Codium* showed anticancer, antimicrobial, metabolic, organ-protective, antiviral, and pest-control activities. A polysaccharide-folate conjugate worked in a colorectal xenograft [87], a sulfated galactan reduced melanoma metastasis [49], intranasal polysaccharide elicited immunity against lung carcinoma [66], and nanoparticle systems suppressed tumor growth or enhanced gemcitabine [91,100]. Lipids with photodynamic therapy reduced *S. aureus* by about 6 log10 [73], lectins reduced biofilm [54], and extracts reduced weight gain, adipose expansion, and fatty liver in obese mice [44,75]. Mouse models also showed protection against PM2.5-induced lung and cognitive dysfunction [88,89], allergic bronchial inflammation [107], atopic dermatitis [95], and acetaminophen liver injury [101]. Siphonaxanthin inhibited SARS-CoV-2 pseudovirus entry (IC50 87.4 μM) [59] and protected obese mice against lipotoxicity [57], and fatty acids inhibited red-tide microalgae [116]. Studies added by re-screening extend this picture: siphonaxanthin purified from *Codium* sp. inhibited breast cancer cells at 5 μM [149], a methanol extract of *C. fragile* repressed the NRP2/RSK1/Sox2/Zeb1 axis in head and neck cancer cells [145], crude *C. fragile* polysaccharide inhibited SARS-CoV-2 pseudovirus entry [137], *C. tomentosum* lipids inhibited COX-2 by up to 80% [124], and nanophytosomes made with *C. tomentosum* polar lipids reversed brain and muscle mitochondrial dysfunction in a rotenone rat model [139,142]. Several of these effects were tested in mixed-algae screens or with different positive controls, and most rely on crude extracts, so potency and specificity for *Codium* should be interpreted with caution.

4.4. Mechanistic Insights and Structure–Activity Relationship (SAR)

Mechanistic and SAR analyses reveal that the biological activity of *Codium* compounds is primarily dictated by structural configuration. Lowering the molecular weight of CZS-0-1 reduced anticoagulant activity [103], whereas degraded low-molecular-weight polysaccharides were better antioxidant scavengers [60], and the >14 kDa fraction of an L-form arabinogalactan was the most cytotoxic [90]. Immune effects were mediated by NK-cell activation through IL-12, MAPK, and NF-κB [55], and folic-acid derivatization targeted polysaccharides to folate-receptor-expressing cells [70,87]. Pathway-level mechanisms were reported for integrin αIIbβ3 [64], NF-κB in microglia [117], and TLR signaling [88,89], but the active constituents behind these extract effects remain unidentified.

Computational models expanded the mechanistic understanding. Docking supported lectin binding to TRPA1 N-

glycans [76], the antibacterial activity of *C. fragile* methanol extract components [93], enzyme inhibition by algal compounds [104], and siphonaxanthin binding to the viral Spike protein [59]. These predictions remain hypothesis-generating. Experimental validation, such as site-directed or competitive binding assays and gene-knockdown models, is needed, especially for the lipid and carotenoid findings.

4.5. Potential Applications and Industrial Relevance

The integration of *Codium* research into applied fields is advancing. Folate-targeted polysaccharide conjugates [70,87], silver-nanoparticle polysaccharide sponges [86], polar-lipid nanophytosomes [58], indocyanine green nanoparticles [100], liposomes [115], nanoencapsulated extracts [112], and extract-loaded nanoemulsions and ointments [109,110] point to drug-delivery, biomedical, and topical uses. In cosmeceutical applications, vesicles from *C. fragile* improved skin brightness by 1.31% in a clinical test [63] and hydroethanolic extracts inhibited elastase by 88% and reduced UVB-induced ROS by 30% [106]. Nutraceutical and food studies showed benefits in endurance, muscle weight, high-fat-diet metabolism, sleep, and gut health [44,65,80,96,99], and algal extracts were used to fortify yogurt and fish fillet [77,112].

From an industrial perspective, *Codium* fits circular and blue-economy models. Martins et al. [106] converted post-extraction biomass into biochars that improved soil water retention, and Yang et al. [62] showed that polysaccharides can function as aquaculture feed additives. Antialgal and larvicidal activities [82,116,119] suggest agrochemical and environmental uses. Scale-up will require reproducible cultivation or harvesting, standardized extraction, toxicity and regulatory studies, and clear compound identification.

The remaining *Codium* literature lies outside pharmacology but bears on how bioactivity research should be done. Taxonomic and genomic work continues to describe new species and to revise species concepts [16,17,18,19], which matters because many bioactivity studies name only a species epithet or *Codium* sp. Photosynthesis and pigment studies have characterized siphonaxanthin-containing antenna proteins and a biosynthetic precursor [24,25,26], complementing pharmacological work on siphonaxanthin. Surveys of composition and contaminants report nutritional value and metal accumulation in macroalgae including *Codium* [29,30], which is relevant to the safety of extracts and food products. Biosorption, bioenergy, and process-engineering studies [35,36,37,38], food preservation and agricultural uses [39,40,41], feed trials [42], and work on epibiotic and endophytic microorganisms [32,33,34] show that the biomass is valued beyond medicine, which supports the integrated biorefinery concepts above.

4.6. Critical Appraisal and Research Gaps

Despite the expanding evidence, several methodological and conceptual limitations remain. First, species-level data are mixed with data from several seaweeds in some studies [77,82,83,90,104,110,111,114,115], so *Codium*-specific results are not always visible in the title or abstract; this applies to most of the studies added by re-screening, in which *Codium* was one of several species tested [123,126,127,141,151]. Second, extraction methods, solvents, units, and positive controls vary widely, which prevents pooled analysis. Third, only 34 of 113 studies used animal models, two included a clinical test, and safety and pharmacokinetic data are almost absent. Fourth, many studies, particularly the recent disease-model studies, used crude extracts without identifying the active constituent. Fifth, 9 studies identified the material only as *Codium* sp. and voucher or molecular identification was rarely reported.

This review also has its own limitations. Scopus-only records were first screened on their titles because the first Scopus export contained no abstracts; the 186 Scopus records that name *Codium* only in the abstract were re-screened after a second export, which added 33 studies, but studies that name *Codium* only in the full text could still have been missed; one Scopus record typed as a review but with an experimental-sounding title was excluded and should be rechecked. ScienceDirect exports were limited to 100 records per file and may be incomplete, only English-language articles were included, screening and data extraction were performed by one screener, no formal risk-of-bias score was applied, and no protocol was registered in advance. Country was inferred from author lists, journals, and abstracts rather than extracted from affiliations, and page ranges and volume data taken from database exports should be verified before submission. Future studies should integrate multi-omics approaches, bioactivity-guided isolation with defined fractions, species-level molecular identification (e.g., rbcL and tufA markers), comparison with accepted positive controls, and in vivo safety and pharmacokinetic work. Updating this review with Web of Science and full-text verification is the next step.

5. Conclusion

This systematic literature review concludes that the genus *Codium* represents a promising and still underexplored marine bioresource with diverse chemical constituents and pharmacological activities. From 1,034 records identified in PubMed, ScienceDirect, Wiley Online Library, and Scopus, 113 studies published between 2020 and 2026 were synthesized. *C. fragile* was the most studied species (55 studies), South Korea the most productive country (38 studies), and 41 studies (36.3%) appeared in 2024–2026. Sulfated polysaccharides—galactans, galactoarabinans, and mannans—had the strongest mechanistic support for anticoagulant, immunomodulatory, and anticancer activity, with sulfation pattern, backbone, and molecular weight as key structural determinants. Lipids, carotenoids, glycoproteins, lectins, terpenoids, and extracts add antioxidant, anti-inflammatory, neuroprotective, antimicrobial, antifungal, metabolic, skin, antiviral, and pest-control effects, and a growing number of studies embed *Codium* material in nanoparticles, liposomes, and topical formulations. The evidence remains mostly in vitro (78 of 113 studies) or in animal models (34 studies), only two studies included a clinical test, and extracts are rarely standardized. Standardized extraction, species-level identification, bioactivity-guided isolation, and in vivo and clinical validation will be crucial for turning *Codium* into pharmaceutical, nutraceutical, cosmeceutical, and biomaterial products.

Author contributions

Marsandah: Conceptualization, Methodology, Investigation, Data curation, Formal analysis, Visualization, Writing – original draft. **Rugaiyah Andi Arfah:** Conceptualization, Supervision, Validation, Writing – review & editing. **Herlina Rasyid:** Supervision, Validation, Writing – review & editing.

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Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The search strategies, the exported bibliographic records, the screening decisions and the data-extraction sheet are available from the corresponding author on reasonable request.

Declaration of generative AI use

During the preparation of this work the authors used Claude (Anthropic) to help check references, redraw chemical structures and edit the language. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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