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A concise review of the bioactivity and pharmacological properties of the genus *Codium* (Bryopsidales, Chlorophyta)

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Abstract

The genus *Codium* is one of the most important genera of marine green macroalgae. Its distribution is widespread worldwide and it has a high degree of diversity in species and characteristics. This genus plays an important ecological role in marine ecosystems as it is a primary producer. However, some species in the genus *Codium* are invasive species and may disturb the functioning of the ecosystem. Economically, *Codium* has promising potential as a source of diverse nutritional and pharmacological compounds. *Codium* is edible, has a high nutrient value, and is rich in bioactive compounds. Hence, some species of *Codium* have been consumed as food and used as herbal medicines in some Asian countries. In recent decades, studies of the bioactivity and pharmacological properties of the genus *Codium* have attracted the attention of scientists. This review aims to identify gaps in studies analyzing *Codium* that have been conducted in the past three decades by assessing published research articles on its bioactivity and pharmacological properties. Compounds obtained from *Codium* have demonstrated significant biological activities, such as immunostimulatory, anticoagulant, anticancer, anti-inflammatory, antioxidant, antiviral, antibacterial, antifungal, antitumor, anti-angiogenic, osteoprotective, and anti-obesity activities. This review provides information that can be used as a future guideline for sustainably utilizing the genus *Codium*.

Keywords Chlorophyceae · Utilization · Distribution · Bioactive compounds · Pharmaceutical · Drug

Introduction

Codium (Bryopsidales) is a diverse genus of marine green macroalgae belonging to the Codiaceae family (Verbruggen et al. 2007). *Codium* has attracted global attention because of its high biodiversity, ecological features as an invasive species, and high potential for producing bioactive compounds. The genus *Codium* comprises approximately 166 species that are distributed in marine environments throughout the world and have been cultivated in some countries (Verbruggen et al. 2007; Hwang et al. 2008; Kang et al. 2008; Guiry and Guiry 2022; Hwang and Park 2020). Recently, molecular identification of *Codium* species has been used to avoid their misidentification, owing to their high morphological plasticity (Provan et al. 2008; de Oliveira-Carvalho et al. 2012; Verbruggen 2014; Verbruggen and Costa 2015; Muha et al. 2019). Some species of *Codium* that have been identified earlier are *C. coactum* Okamura, *C. contractum* Kjellman, *C. fragile* (Suringar) Hariot, and *C. minus* (Schmidt) P.C. Silva (Woo and Sook 2015). Some new *Codium* species that have been identified in recent years include *C. bernabei* (González et al. 2012), *C. pernambucensis* (de Oliveira-Carvalho et al. 2012), *C. recurvatum* (Verbruggen et al. 2012), and *C. lucasii* (An et al. 2015). *Codium fragile*, one of the most popular and edible green algae species, is also one of the most invasive species originating from the Northwest Pacific (Japan) (Provan et al. 2008). This species then spread to the Northeast Pacific, the North Atlantic, Australia, and

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New Zealand (Dromgoole 1975; Schmidt and Scheibling 2005; Muha et al. 2019). Species of *Codium* play an important role in marine ecosystems. Some of them are invasive species that can disturb marine ecosystems but can also have a balance impact if they coexist with other *Codium* species.

Codium has become one of the main macroalgae consumed in some Asian countries, such as Japan, China, and Korea. *Codium* has high nutritional properties, including its composition of carbohydrates, proteins, lipids, vitamins, and minerals (Tabarsa et al. 2013; Jung and Park 2020; Monmai et al. 2020), as well as bioactive compounds, such as siphonaxanthin (Akimoto et al. 2007; Ganesan et al. 2010), canthaxanthin (Ahn et al. 2021), oleamide (Moon et al. 2018b), and sulfated polysaccharides (Wang et al. 2021). Recently, sulfated polysaccharides from *Codium* species such as *C. pugniforme, C. yezoense, C. latum, and C. vermilara* were identified as sulfated glucan, sulfated galactan, sulfated arabinan, and sulfated mannan (Bilan et al. 2006; Fernández et al. 2012, 2014; Li et al. 2015). Bioactive compounds and polysaccharides present in *Codium* possess interesting pharmacological effects, including immunostimulatory (Yang et al. 2019, 2021), anti-inflammatory (Yoon et al. 2011; Moon et al. 2018b), anticancer (Hye et al. 2018), anticoagulant (Choi et al. 2013), antioxidant (Wang et al. 2020), anti-obesity (Kolsi et al. 2017a, b), osteoprotective (Surget et al. 2017), and antiviral (Yim et al. 2021) activities. However, the ecology, nutrient value, bioactive compound composition, and bioactivity of *Codium* have not yet been comprehensively reviewed to determine the gap in studies analyzing *Codium*, which can be used as a direction for future studies and management of the genus *Codium*.

Distribution of genus *Codium*

The genus *Codium* is found worldwide (Fig. 1). The green alga *Codium* is believed to have certain invasive properties because of its ability to thrive in temperate waters. *Codium tomentosum* (Stackhouse, 1797) is native to the northeast Atlantic coast and inhabits in rock pools and lower seashores throughout the year (Rey et al. 2020). *Codium decorticatum* (Woodward) M.A. Howe is a species found in tropical and subtropical climates worldwide. There are 105 subspecies of *C. decorticatum* along the Atlantic coast of South America, ranging latitudinally from 3°S to 42°S (Fernández et al. 2015). This species grows on firm substrates in subtidal habitats. *Codium bursa* (Olivi) C. Agardh is typically found in temperate and subtropical climates. It can grow in diameters ranging

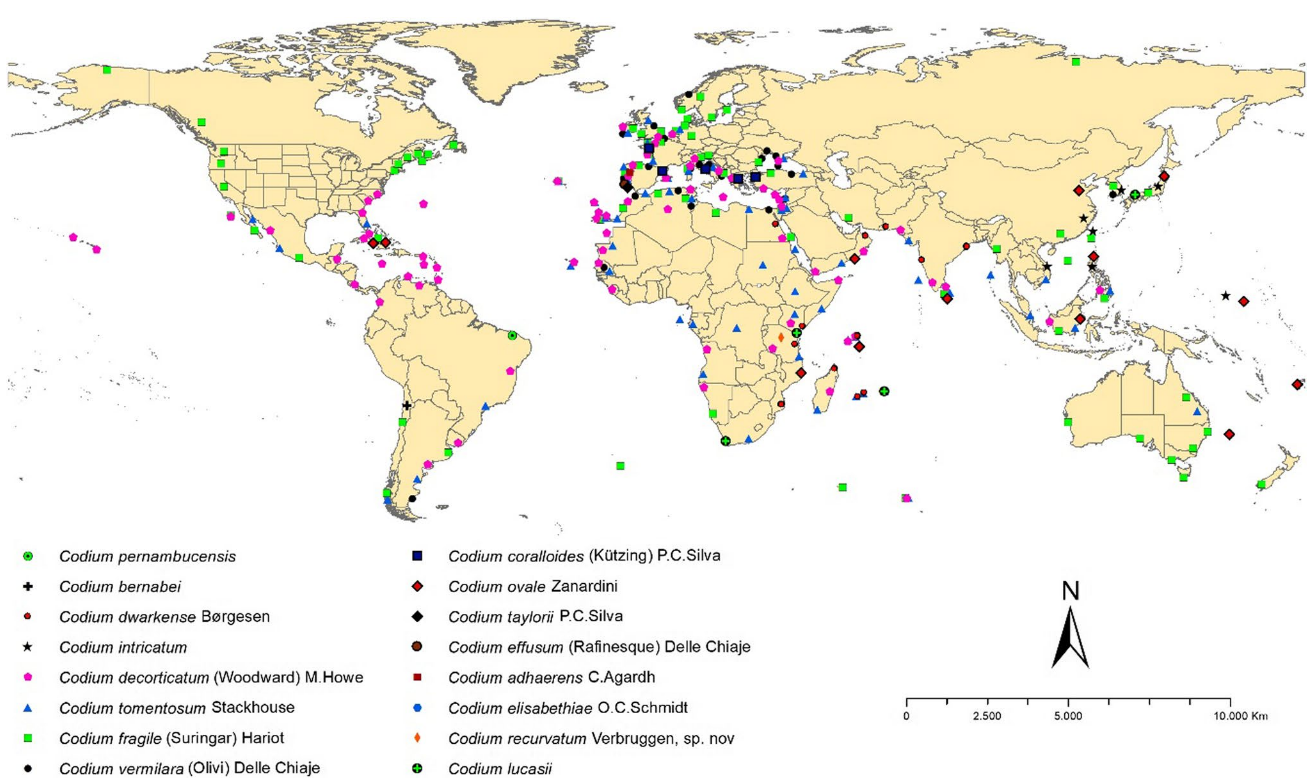

Fig. 1 Distribution of genus *Codium* in the world based on some studies (Gisone et al. 2006; Provan et al. 2008; de Oliveira-Carvalho et al. 2012; González et al. 2012; Verbruggen et al. 2012; Guiry and Guiry 2022; Muha et al. 2019; Neto et al. 2020)

from a few millimeters to 40 cm, and it grows in a hollow spherical form (Jerkovi et al. 2019). Some species of the genus *Codium* are invasive. Among the species within *Codium*, *C. fragile* is the most invasive seaweed in the world and is believed to be native to Japan, from which it accidentally spread to other parts of the world (Provan et al. 2008). Native to East Asia, it has invaded many parts of the world and now has a nearly global distribution (Hubbard and Garbary 2002; Provan et al. 2005; Schmidt and Scheibling 2005).

The habitat of *Codium* is rocky substrate in the intertidal zone. Sheltered rocky habitats are critical for *Codium* as these habitats allow for algae to grow and reproduce (Bulleri et al. 2006; Woo and Sook 2015). In addition to the habitat, other ecological factors also affect the characteristics of *Codium*. Seasonal patterns affect the morphology and chloroplast physiology (Benson et al. 1983), growth (Hanisak 1979), reproductive characteristics (Churchill and Moeller 1972; Prince and Trowbridge 2004), and the nutritional value of *Codium* (Malea et al. 2015). Furthermore, water movement and substratum type may contribute to the vegetative recruitment ability (Scheibling and Gagnon 2006) and the formation and growth of spongy and filamentous thalli (Nanba et al. 2005). In new habitats, they can have ecological and economic impacts; for example, they may compete with native kelps or fucoids (Scheibling and Gagnon 2006; Drouin et al. 2011; Armitage and Sjøtun 2016), influence the seaweed-associated fauna composition (Schmidt and Scheibling 2006; Drouin et al. 2011; Armitage and Sjøtun 2016), negatively affect commercial bivalve beds, change the sediment from sand to pebbles and cobbles (Ben-Avraham 1971), and impact ecosystem services (Vilà et al. 2010). In addition to nutrient over-enrichment, the invasion by non-native species has been detrimental to biodiversity and ecosystem functioning in many coastal ecosystems (Thomsen et al. 2006).

Biochemical properties

Marine macroalgae are rich sources of new bioactive compounds and functional foods with potentially beneficial health effects (Kim et al. 2020). They have been reported to have nutritional value due to their vitamin, protein, and mineral content (Ortiz et al. 2009; Holdt and Kraan 2011; El-Said and El-Sikaily 2013; Lafarga et al. 2020). Marine macroalgae contain protein, carbohydrate, and low-fat, hence, they can contribute a few calories to the diet (Rupérez 2002). The variations in the nutritional composition of algae may be influenced by complex endogenous growth-related, morphological, and reproductive changes, as well as exogenous factors including temperature, light intensity, day length, and concentration of nutrients (Stirk et al. 2007; Rey et al. 2020; Marques et al. 2021).

Sulfated polysaccharides

Green macroalgae contain different typical carbohydrates, including cellulose, xylan, and sulfated polysaccharides. There is a lack study on the structures of sulfated polysaccharides from marine green macroalgae compare to those from marine red or brown macroalgae (Farias et al. 2008). The structural heterogeneity of sulfated polysaccharides within *Codium* species are different for each species (Fig. 2). The unusual complex pyruvylated and sulfated galactans in *C. yezoense* consist of linear backbone units of 3-linked β-D-galactopyranosyl components divided by oligosaccharides connected by links at C6 (Bilan et al. 2007). The sulfated

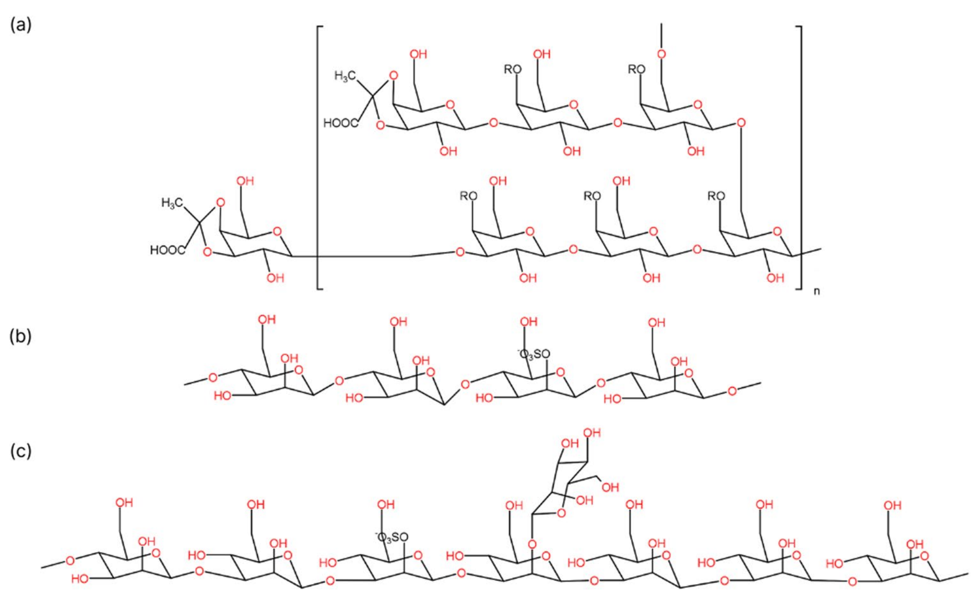

Fig. 2 Structure of sulfated polysaccharide from *Codium* species, including (a) sulfated galactan from *C. fragile*; (b) sulfated mannan from *C. vermilara*; (c) sulfated mannan from *C. fragile* (Lee et al. 2010; Wang et al. 2014)

galactan of *C. isthmocladum* primarily consists of 4-sulfated 3-linked β-D-galactopyranosyl units (Farias et al. 2008). A family of sulfated polysaccharides, including sulfated arabinans, sulfated galactans and sulfated arabinogalactans as the main components, was found in the room-temperature water extracts of *C. fragile* and *C. vermilara* (Ciancia et al. 2007; Estevez et al. 2009). Moreover, the sulfated polysaccharide in *C. latum*, *C. pugniforme* (syn. *C. spongiosum),*and *C. vermilara* were described as sulfated arabinan, sulfated glucan, and sulfated mannan, respectively (Bilan et al. 2006; Fernández et al. 2012, 2014). Sulfated galactans from *C. fragile* differs from the *C. cylindricum*. Regarding to its galactose content, *C. fragile* also contains arabinose residues or known as sulfated arabinogalactan (Love and Percival 1964), and *C. cylindricum* (syn. *C. divaricatum*) contains glucose residues, probably forming sulfated glucogalactan (Matsubara et al. 2001). The analysis of sulfated galactans from various *Codium* species has revealed that 3-linked β-D-galactopyranosyl has comparable backbones. The structures of the sulfated polysaccharides directly affect their biological activities in regards to their main structure, molecular weight, degree of sulfation, monosaccharide composition, and glycosidic linkages (Sabry et al. 2019).

Lipids

Lipid is a component in macroalgae that has attracted attention due to its fatty acid fraction. Polyunsaturated fatty acids (PUFAs) are essential lipids for human metabolism. However, human can not synthesize them and must obtain them through their daily intake. The major PUFAs detected in macroalgae were C18 and C20 PUFAs, namely linoleic, arachidonic and eicosapentaenoic acids (Pereira et al. 2012). In Chlorophyta, the PUFAs content ranges from 17–61% with α-linolenic acid as the most abundant fatty acid (Allan et al. 2010; Goecke et al. 2010; Pereira et al. 2012; Schmid et al. 2018). Meanwhile, in *Codium* lipids are mostly in the form of LFA and SFA with an unusual structure of fatty acids. Long-chain fatty acids are present in *Codium* species, with palmitic acid being the most common saturated fatty acid (SFA) and oleic acid being the most common monounsaturated fatty acid (MUFA) (Shameel 1990). The content of fatty acids in *Codium* varies depending on various factors, such as species, growth age, nutrient, season, temperature, salinity, location, and depth (Xu et al. 1998; Dembitsky and Hanus 2003). *Codium* species contain an unusual structure of several branched fatty acids (Aliya and Shameel 1993; Dembitsky and Hanus 2003). *Codium tomentosum* contains α-linolenic acid, palmitic, palmitoleic, oleic, hexadecatrienoic, eicosatrienoic and eicosapentaenoic acids (da Costa et al. 2015). Meanwhile, α-linolenic, palmitic acid, oleic, linoleic, and hexadecatrienoic acids were detected in *C. fragile*, C. *tomentosum, C. geppi* and *Codium* sp. (Khotimchenko 2003). Moreover, Ortiz et al. (2009) observed that the most abundant fatty acids in *C. fragile* was palmitic acid. Aliya and Shameel (1993) investigated 43 different fatty acids which identified as methyl esters fatty acid in *C. decorticatum*, *C. flabellatum*, and *C. iyengarii*. Dembitsky and Hanus (2003) investigated fatty acid variability of *C. dwarkense* and *C. taylorii* and identified 40 volatile compounds of monoenoic acid and polyenoic acid. Furthermore, these three *Codium* species contained eight sterols including ergosterol, ostreasterol, clerosterol, decortinone, decortinol, isodecortinol, cholesteryl acetate and cholesteryl galactoside (Aliya and Shameel 1993).

Proteins

The protein content of marine macroalgae is also variable and the highest content is generally found in marine green and red algae, compared to brown algae (Holdt and Kraan 2011). *Codium tomentosum* is known to contain 11.00–18.8% dw of total protein (Celikler et al. 2009; Rodrigues et al. 2015). A similar protein content was also found in *C. galeatum* (12% dw) and *C. fragile* (10.8% dw) (Ortiz et al. 2009; Skrzypczyk et al. 2018). Bioactive compounds derived from proteins such as lectins can be obtained from *Codium* species. Carneiro et al. (2020) isolated lectins from *C. isthmocladum* and found two novel lectins, CiL-1 and CiL-2, with unique sequences not found in other lectins.

Minerals and vitamins

Minerals and vitamins are present in macroalgae at high levels and have received considerable attention because the macrominerals and trace elements content in macroalgae are comparable to land-plants and can be used to fulfill human daily needs intake (Rupérez 2002). Macroalgae can selectively absorb minerals from the surrounding seawater and accumulate them in their cells (Cabrita et al. 2016). As for the major minerals, most macroalgae show abundant contents of sodium (Na), magnesium (Mg), potassium (K), and calcium (Ca). As expected, high Na content was found in *C. fragile* and *C. tomentosum* (92.3 and 11.79 mg g^{-1} dw), (Moreda-Pineiro et al. 2012; El-Said and El-Sikaily 2013), while *C. iyengarii* contains high K (231.7 mg g^{-1} dw) (Rizvi and Shameel 2004). However, the availability of minerals content in marine macroalgae is influenced by intrinsic and extrinsic factors. The intrinsic factors are including specific forms of hydroxyl, carboxyl, amino, and sulfhydryl esters functional groups from their polysaccharides, lipid, and proteins, and extrinsic factors are including pH, temperature, salinity, and other external factors in the growth medium (Circuncis et al. 2018).

Trace elements are classified into two subclasses: (a) cobalt (Co), copper (Cu), iron (Fe), manganese (Mn), and zinc (Zn), which are required for biochemical processes but may be toxic at high concentrations, and (b) arsenic (As), cadmium (Cd), chromium (Cr), lead (Pb), and mercury (Hg), which are not required for biochemical processes but are the most important contaminants in aquatic environments. Among the trace minerals, strontium (Sr), barium (Ba), and Fe were found in high concentrations in *C. fragile* (Malea et al. 2015; Seo et al. 2019). A high content of Fe is present in *C. reediae* (91.0–196.0 µg g^{-1} dw) (Mcdermid and Stuercke 2003). For heavy metals, As exhibited the highest content (4.25 µg g^{-1} dw), while Cd exhibited the lowest content (0.05 µg g^{-1} dw) in *C. fragile* (Malea et al. 2015). Heavy metal contamination is a factor that is used to assess the safety of edible macroalgae (Zheng et al. 2013).

Macroalgae contain more vitamins A, B-12, and C, β-carotene, pantothenate, folate, riboflavin, and niacin than fruits and vegetables from regular land cultivars (Garcı et al. 2007). The carotenoids and tocols in *Codium* were found to be the source of vitamins A and E. In *C. fragile*, all types of tocols were found, with 1617.6 µg g^{-1} dw for the total tocol content and β-carotene having the high amount (197.9 µg g^{-1} dw) (Ortiz et al. 2009). Chemical structure of tocols derivated compounds from *Codium* species is shown in Fig. 3. Meanwhile, *C. tomentosum* contains vitamins A, C, and E (less than 1.0 mg g^{-1}) and a total carotene content of 15.80 mg per 100 g dw (Celikler et al. 2009).

Bioactivities

From 1990–2021, increasing attention has been paid to the bioactivity and pharmacological properties of the genus *Codium* (Fig. 4). We found 70 articles that focused on the bioactivity and pharmacological properties of the genus *Codium*, including immunostimulatory (15.4%), anticoagulant (14.1%), anticancer (12.8%), anti-inflammatory (12.8%), antioxidant (11.5%), antiviral (7.7%), antibacterial (3.8%), antifungal (3.8%), antitumor (3.8%), anti-angiogenic (2.6%), osteoprotective (2.6%), anti-obesity (2.6%), anti-melanogenic (1.3%), anti-sarcopenia (1.3%), antihypertensive (1.3%), neuroprotective (1.3%), and antiprotozoal (1.3%) activities (Fig. 5).

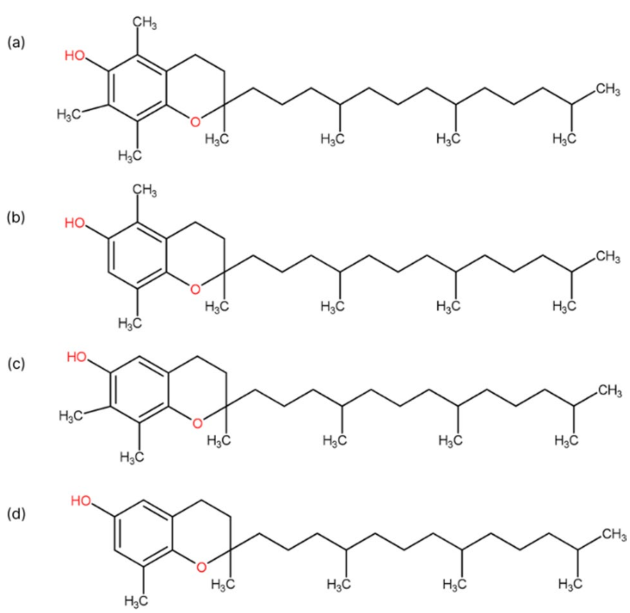

Fig. 3 Structure of tocols found in *Codium* species, including (a) α-Tocopherol; (b) β-Tocopherol; (c) γ-Tocopherol; (d) δ-Tocopherol (Ortiz et al. 2009)

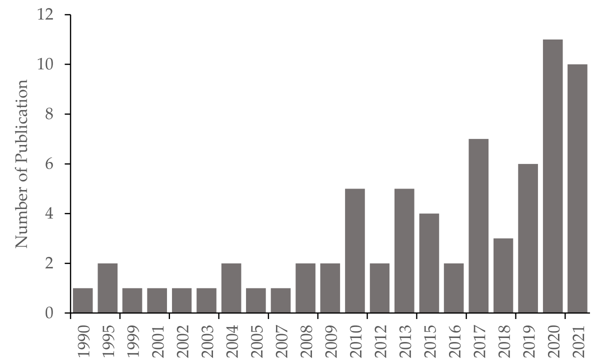

Fig. 4 Number of publication of genus *Codium* based on publication year

Marine macroalgae contain bioactive compounds such as flavonoids, coumarins, fucosterol, phlorotannin, tocopherols, and nitrogen-containing compounds, including alkaloids, chlorophyll derivatives, amino acids, and amines, which are potential molecules with various pharmacological properties (Celikler et al. 2009; Ali et al. 2015; Gaspar et al. 2020; Meinita et al. 2021, 2022; Harwanto et al. 2022). Several carotenoids, including siphonaxanthin and canthaxanthin, have been reported in *C. fragile*. Siphonaxanthin is a keto-carotenoid found in siphonaceous green macroalgae, including *Codium*, that promotes the absorption of available green and blue-green light underwater (Akimoto et al. 2007; Ganesan et al. 2010). Furthermore, siphonaxanthin is known to have beneficial effects on health and to have various other applications (Ganesan et al. 2010; Yim et al. 2021). *Codium* also contains canthaxanthin, a carotenoid suggested to regulate changes in signaling molecules in *C. fragile* extracts (Ahn et al. 2021). Two new sulfonoglycosides, codioside E (1) and codioside F (2), have also been identified from the methanol extract of *C. dwarkense* (Ali et al. 2017).

Research on algal lipids found that loliolide, a ubiquitous monoterpenoid lactone isolated from *C. tomentosum*, may be used as a neuroprotective agent (Silva et al. 2021). The properties of oleamide, an amide derived from the fatty acid oleic acid of *Codium*, have been reviewed (Kwon et al. 2001; Moon et al. 2018b). Chemical structure of lipid derivated compounds from *Codium* species is shown in Fig. 6.

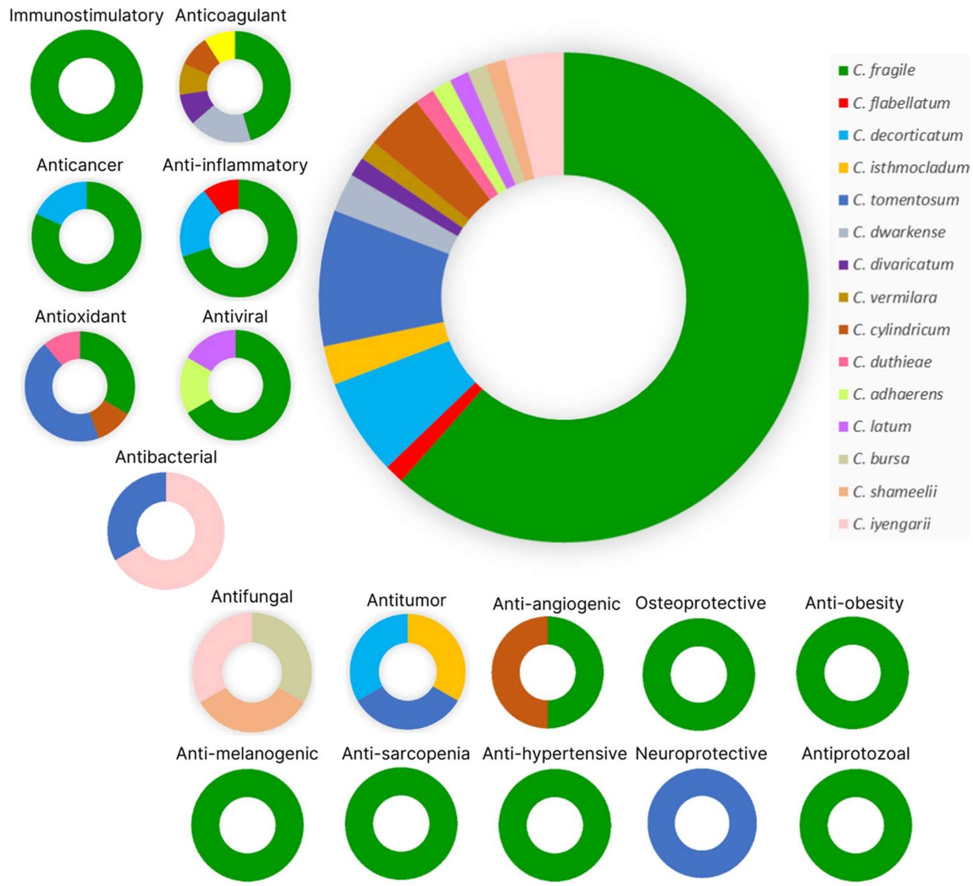

Fig. 5 Number of publications on bioactivity and pharmacological properties of the genus *Codium* based on the species

Codium has demonstrated significant biological activity both in vitro and in vivo. We review the biological activities attributed specifically to *Codium*, focusing on those with potential nutraceutical and pharmacological properties. *Codium fragile* is the most widely studied species in terms of bioactivity. Based on previous research, the polysaccharides and their bioactive compounds in the genus *Codium* exhibited the highest bioactivity (Table 1).

Immunostimulatory activity

Immunomodulation, which includes immunostimulatory and immunosuppressive effects, is a complicated mechanism that regulates the pathophysiology and etiology of different immune-related disorders. Immunomodulatory substances can be used as immune stimulators to reduce the negative effects of immunosuppressive medicines (Prendergast and Jaffee 2007).Sulfated polysaccharides from marine algae have been shown to have immunostimulatory properties. According to Tabarsa et al. (2013), *C. fragile* contained sulfated polysaccharide fractions (F_1 and F_2) in the form of D-galactan with pyruvates and sulfates. The sulfated polysaccharide triggered nitric oxide (NO) production by activating protein and mRNA expression of inducible nitric oxide synthase (iNOS). The sulfated polysaccharides of *C. fragile* may activate the expression of cytokines inflammatory, including tumor necrosis factor (TNF-α), interleukin (IL)-1, IL-6, and IL-10, as well as promote inflammatory mediators, iNOS and NO production, and protein expression in the RAW 264.7 murine macrophage cell line. As a result, the nuclear factor κB (NF-κB) and mitogen-activated protein kinase (MAPK) pathways are also activated by *C. fragile* sulfated polysaccharides, which seem to stimulate the immune system. Among these two fractions, the F_2 fraction, which has a high protein content (14.7%), possessed the most immune-stimulating activity. Furthermore, the F_2 fraction can stimulate the gene expression of inflammatory cytokines, including IL-1β, TNF-α, and interferon gamma (IFN-γ) in human cell lines and mouse models (Surayot and You 2017; Yang et al. 2019). The expression of inflammatory cytokines was upregulated in the F_2 fraction via the NF-κB and MAPK pathways. The F_2 fraction and folic acid-conjugated sulfated polysaccharides significantly increased natural killer cell proliferation and cytotoxicity against HeLa cells (Surayot and You 2017; Li et al. 2020). In addition, in vitro, the F_2 fraction was shown to stimulate the expression of the IL-1β gene in head kidney (HK) cells, while in vivo gene expressions of IL-1β and IL-8 were up-regulated in peritoneal cells, HK cells, the liver, the gill, and the spleen. TNF-α, IFN-γ, and lysozyme gene expressions

Table 1 Bioactivity of *Codium* species

Bioactivity	Species	Extract or Compound	Study Type	Effects	Ref
Immunostimulatory	*C. fragile*	Sulfated polysaccharides	In vitro and in vivo	↑ inflammatory cytokines ↑ anti-inflammatory cytokines (IL-10)	(Yang et al. 2021)
	C. fragile	Sulfated polysaccharides	In vitro and in vivo	↑ IL-1β gene expression in HK cells	(Yang et al. 2019)
	C. fragile	Sulfated polysaccharides	In vitro	↑ natural killers cell proliferation and the cytotoxicity against HeLa cells	(Surayot and You 2017)
	C. fragile	Sulfated polysaccharides	In vitro	Stimulated inflammatory biomarkers expression Stimulated NF-$_\kappa$B and MAPK pathway	(Tabarsa et al. 2013)
	C. fragile	Crude anionic macromolecules	In vitro	With arachidonic acid ↑ immune response	(Monmai et al. 2020)
	C. fragile	Crude anionic macromolecules	In vivo	With red ginseng ↓ immune biomarkers	(Kim et al. 2019)
	C. fragile	Crude anionic macromolecules	In vivo	↑ immune-associated genes expression	(Monmai et al. 2019)
	C. fragile	Sulfated galactan	In vitro and in vivo	↑ expression and production of cytokines	(Lee et al. 2010)
	C. fragile	Crude anionic macromolecules	In vivo	With red ginseng ↓ immune biomarkers in cyclophosphamide-treated mice	(Jung and Park 2020)
	C. fragile	Sulfated glycoproteins	In vitro	Activate NF-κB pathway Stimulated phosphorylation of MAPK pathway	(Tabarsa et al. 2015)
	C. fragile	Sulfated polysaccharides	In vitro	↑ the NK cells cytotoxicity against HeLa cells	(Li et al. 2020)
Anticoagulant	*C. fragile*	Codiase	In vitro	Prolongation of the APTT and PT ↓ the blood clotting pathways	(Choi et al. 2013)
	C. fragile	Proteoglycan	In silico	Prolongation of the TT	(Rogers et al. 1990)
	C. fragile	Sulphated polysaccharides and proteoglycan	In silico	Prolongation of the TT	(Jurd et al. 1995)
	C. fragile	Crude polysaccharide	In vitro	Prolongation of the APTT	(Athukorala et al. 2007)
	C. fragile	Ethanolic extract	In vitro and in vivo	↓ion of platelet αIIbβ3 integrin outside-in signal transduction	(Kim et al. 2021)
	C. dwarkense	Sulfated polysaccharides	In vivo	Prolongation of the APTT and PT ↓ the number of microthrombi	(Golakiya et al. 2017)
	C. divaricatum	Sulfated polysaccharides	In vivo	↑ Prolongation of the APTT and TT	(Li et al. 2015)
	C. vermilara	Sulfated arabinans	In silico	↑ Prolongation of the APTT and TT	(Fernández et al. 2013)
	C. cylindricum	Sulfated polysaccharides	In vitro	↑ Prolongation of the APTT and TT	(Matsubara et al. 2001)
	C. isthmocladum	Sulfated polysaccharides	In vitro	↑ Prolongation of the APTT	(Sabry et al. 2019)
	C. dwarkense	Sulfated polysaccharides	In vitro	↑ Prolongation of the APTT	(Siddhanta et al. 1999)
Anticancer	*C. fragile*	Methanolic and aqueous extracts	In vitro	↓ the growth of CT-26 cells ↓ the protein expression of the anti-apoptotic	(Kim et al. 2008)
	C. fragile	Polysaccharide	In vitro and in vivo	↓ the growth of B16 tumors ↑ anti-cancer immunity	(Park et al. 2020b)
	C. fragile	Crude polysaccharide	In vitro	↑ the sensitivity of TRAIL ↑ the protein levels of c-caspase 8 and c-caspase3 by ↓ c-FLIP expression	(Hye et al. 2018)
	C. fragile	Polysaccharides	In vitro and in vivo	↓ the Lewis lung carcinoma cells infiltration into the lungs ↑ anti-cancer immunity	(Wang et al. 2021)
	C. fragile	Polysaccharides	In vitro and in vivo	↓ the CT-26 tumor cells infiltration into the lungs ↑ anti-cancer immunity	(Park et al. 2020a)

Table 1 (continued)

Bioactivity	Species	Extract or Compound	Study Type	Effects	Ref
	C. fragile	Polysaccharide	In vitro	Stimulated PBDCs subset Activated Th1 and CTLs cells	(Zhang et al. 2020)
	C. fragile	Clerosterol	In vitro	Moderate toxicity Regulated Bax, Bcl-2 and caspases 3 and 9	(Kim et al. 2013)
	C. fragile	Methanol extracts	In vitro	↑ the expression of TNF-a- induced MMP-9 ↓ NF-kB activity in the human breast cancer MDA-MB-231 cells	(Dilshara et al. 2016)
	C. decorticatum	Dichloromethane extract	In vitro	↓the HeLa cell growth in a dose and time-dependent manner ↑ apoptosis in a concentration-dependent manner	(Zbakh et al. 2020)
	C. decorticatum	Glycoprotein (GLP)	In vitro	↓ cell growth in breast, cervical and lung cancer cells	(Senthilkumar and Jayanthi 2016)
Anti-inflammatory	*C. fragile*	Aqueous extract	In vitro and in vivo	↓ pro-inflammatory cytokine and mediator ↓ NF-$_{K}$B activation and MAPKs pathways ↓ carrageenan-induced rat paw edema thickness	(Ah et al. 2017)
	C. fragile	Ethanolic extracts	In vitro	↓ pro-inflammatory cytokine and mediator ↓ NF-$_{K}$B activation and MAPKs pathways	(Yoon et al. 2011)
	C. fragile	Oleamide	In vitro and in vivo	↓ inflammatory responses in LPS-induced RAW 264.7 murine macrophages ↓ carrageenan-induced rat paw edema inflammatory	(Moon et al. 2018b)
	C. fragile	Ethanolic extracts	In vitro	↓ inflammatory responses in PGN-induced RAW 264.7 cells ↓ ERK 1/2, JNK 1/2 and p38 MAPK phosphorylation	(Han et al. 2010)
	C. fragile	Methanol extract	In vitro	↓ inflammatory responses in LPS-induced RAW 264.7 cells ↓ NF-$_{K}$B activation pathways	(Kang et al. 2012)
	C. fragile	Buthanol, ethylacetate, and clerosterol	In vitro and in vivo	↓ UVB-induced inflammatory ↓ protein carbonyls in BALB/c mice	(Lee et al. 2013)
	C. decorticatum	*n*-hexane, dichloromethane and acetone/methanol extracts	In vitro	no significant cytotoxicity	(Zbakh et al. 2020)
	C. fragile	Methanol extracts	In vivo	↓ rates of edema and erythema	(Khan et al. 2008)
	C. decorticatum	Dichloromethane extract Methanol extract	In vitro	↓ the pro-inflammatory cytokines Interleukin-8 (IL-8) in LPS- and TNF-α- stimulated endothelial cells ↓ the LPS-induced mRNA expression of E-selectin and IL-8	(Zbakh et al. 2020)
	C. flabellatum	Methanol extract	In vivo	↑ analgesic effect ↓ acute and chronic inflammation	(Yasmeen et al. 2021)
Antioxidant	*C. fragile*	Sulfated polysaccharides	In vitro and in vivo	↓ the intracellular ROS levels ↑ the survival rate and normalized the heartbeat	(Wang et al. 2020)
	C. fragile	Hexane, ethyl acetate and methanol extracts	In vitro	Flavonoids with low levels of condensed tannins have a fascinating antioxidant profile	(Kolsi et al. 2017a, b)
	C. fragile	Aqueous extract	In vitro	High scavenging activities against $O_2^{\cdot-}$, HO$^{\cdot}$, H_2O_2, DPPH free radicals, and ROS	(Heo et al. 2005)

Table 1 (continued)

Bioactivity	Species	Extract or Compound	Study Type	Effects	Ref
	C. cylindricum	Polysaccaharide	In vitro	Significant improvement on DPPH radical, superoxide anion radical and reducing power	(Yan et al. 2021)
	C. tomentosum	Crude ethanolic extracts	In vitro	No genotoxic effect	(Celikler et al. 2009)
	C. tomentosum	Lipid extract	In vitro	Promoted a 50% inhibition (IC50) in the ABTS•+assay, while in DPPH• assay only a 20% inhibition (IC20) ↓COX-2 activity	(Lopes et al. 2020)
	C. tomentosum	Lipid extract	In vitro	Scavenging activity of C. tomentosum lipid extracts was more efficient against ABTS•+ than DPPH• radicals	(Rey et al. 2020)
	C. tomentosum	Water extract	In vitro	Revealed antioxidant activity against both reactive oxygen (superoxide radical) and reactive nitrogen (nitric oxide) species	(Valentão et al. 2010)
	C. duthieae	Methanol extract	In vitro	High radical scavenging ability and oxygen radical absorbance capacity (ORAC)	(Rengasamy et al. 2015)
Antiviral	*C. fragile*	Siphonaxanthin	In vitro and in silico	High toxicity with IC_{50} of 87.4 μM	(Yim et al. 2021)
	C. fragile	Polysaccharides	In vitro	↓ HSV-1 infection without cytotoxity	(Kulshreshtha et al. 2015)
	C. fragile	Sulfated galactan	In vitro and in vivo	↓ the replication of HSV-2 ↓ virus infection rates in mice	(Ohta et al. 2009)
	C. adhaerens	Sulfated polysaccharides	In vitro	have potent anti-HSV-1 activities marked inhibitory effects against virus replication	(Lee et al. 2004)
	C. fragile	Sulfated polysaccharides	In vitro	have potent anti-HSV-1 activities marked inhibitory effects against virus replication	(Lee et al. 2004)
	C. latum	Sulfated polysaccharides	In vitro	have potent anti-HSV-1 activities marked inhibitory effects against virus replication	(Lee et al. 2004)
Antibacterial	*C. iyengarii*	Steroidal glycosides and clerosterol galactoside	In vitro	Moderate bactericidal activity	(Ali et al. 2010)
	C. tomentosum	Methanol extract	In vitro	Significant inhibitory activity against GES-22	(Houchi et al. 2019)
	C. iyengarii	Methanol extract	In vitro	No antibacterial activity	(Rizvi and Shameel 2004)
Antifungal	*C. bursa*	Headspace solid-phase microextraction (HS-SPME), hydrodistillation (HD), and supercritical CO_2 extraction (SC-CO2)	In vivo	exhibited antifungal effects against Fusarium spp, Penicillium expansum, Aspergillus flavus, and Rhizophus spp	(Jerkovi et al. 2019)
	C. shameelii	Methanol extract	In vitro	Weak antifungal activity	(Rizvi and Shameel 2004)
	C. iyengarii	Methanol extract	In vitro	Significant antifungal activity on human and animal pathogen	(Rizvi and Shameel 2004)
Antitumor	*C. isthmocladum*	Sulfated homogalactan	In vivo and in vitro	↓ solid tumor growth and metastasis	(Bellan et al. 2020)
	C. tomentosum	Ethanol extract	In vivo	↓ tumor initiation	(El-Masry et al. 1995)
	C. decorticatum	*n*-hexane, dichloromethane and acetone/methanol extracts	In vitro	Exerted weak cytotoxic effects on cell viability of SKBR-3, HT-29, PC3 and MIA PaCa-2 cells, with IC50 ranged from 74 to 120 μg/mL	(Zbakh et al. 2020)
Anti-angiogenic	*C. fragile*	Siphonaxanthin	In vitro and ex vivo	↓ HUVECs proliferation and tube formation ↓ microvessel outgrowth	(Ganesan et al. 2010)
	C. cylindricum	Sulfated galactan	Ex vivo	↓ HUVEC tube formation ↓ microvessel formation	(Matsubara et al. 2003)

Table 1 (continued)

Bioactivity	Species	Extract or Compound	Study Type	Effects	Ref
Osteoprotective	*C. fragile*	Phenolic compounds	In vivo	↑ mineralogenic activity more than 1.5-fold	(Surget et al. 2017)
	C. fragile	Aqueous extract	In vitro and in vivo	Regulated the immune system Exhibited less proteoglycan loss and lower OARSI scores	(Moon et al. 2018a)
Anti-obesity	*C. fragile*	Sulfated polysaccharides	In vivo	↓ the body weights Protected hepatic functioning	(Kolsi et al. 2017c)
	C. fragile	Crude extract	In vivo	↓ the body weights Modulating gut microbiota	(Kim et al. 2020)
Anti-melanogenic	*C. fragile*	Extracellular vesicles	In vitro and in vivo	↓ protein synthesis ↑ skin brightness	(Jang et al. 2021)
Anti-sarcopenia	*C. fragile*	Ethanolic extract	In vivo	Regulated protein synthesis ↑ skeletal muscle mass and function	(Ahn et al. 2021)
Anti-hypertensive	*C. fragile*	Methanolic extract	In vitro	↓ ACE activity	(Heo et al. 2005)
Neuroprotective	*C. tomentosum*	Loliolide	In vitro	↑ cell viability ↓ oxidative stress	(Silva et al. 2021)
Antiprotozoal	*C. fragile*	Crude extract	In vitro	Exhibited high toxicity in all parasite organism, except *Mycobacterium tuberculosi*	(Spavieri et al. 2010)

were mainly upregulated, but they differed depending on the tissue type or time point in olive flounder (*Paralychthys olivaceus*) (Yang et al. 2019). Similar results were obtained in rockfish, *Sebastes schlegelii*, induced by *Edwardsiella tarda*, a pathogenic bacterium in fish. This result indicates that IL-1β and IL-6 gene expression was upregulated in the HK of the 0.5% group on day 1, whereas IL-1β gene expression was downregulated in the liver on day 3 (Yang et al. 2021). In addition, sulfated glycoproteins (NF_2) and sulfated galactan of *C. fragile* have immunostimulatory effect in RAW 264.7 cells by activating the NF-κB pathway, thus stimulating the MAPK pathway, including ERK1/2, p38, and JNK1/2, as well as the nuclear translocation of c-JUN and c-FOS (Lee et al. 2010; Tabarsa et al. 2015).

According to Monmai et al. (2020), the expression and production of pro-inflammatory genes and the expression of immune-associated genes were increased by the combination of *C. fragile* and arachidonic acid via the activation of NF-κB, p-65, and MAPK signaling, including ERK1/2 and p38, which led to the immune-enhancement in RAW 264.7 cells. Another study demonstrated the immune-enhancing effects of anionic macromolecules of *C. fragile* mixed with red ginseng extract orally administered to cyclophosphamide-treated mice (Kim et al. 2019; Jung and Park 2020). These extracts upregulated the expression of immune-associated genes, thereby inhibiting immune biomarkers by activating the NF-κB and MAPK pathways. These results indicate that polysaccharides and anionic macromolecules extracted from *C. fragile* are potential sources of immunostimulatory agents.

Anticoagulant activity

In the pharmaceutical industry, there is growing interest in isolating anticoagulant compounds from marine macroalgae. Heparin is a commonly used anticoagulant, but it has some side effects, including thrombocytopenia and spontaneous bleeding (Tardy-poncet et al. 1994). Therefore, it is important to investigate alternatives to anticoagulant agents with fewer heparin-like side effects. Algal polysaccharides have been reported to exhibit heparin-like activity (Faggio et al. 2016). Extracts of *C. fragile* ssp. *atlanticum* through low-molecular weight sulfated polysaccharides and high-molecular weight (sulfated) proteoglycans have exhibited anticoagulant properties (Rogers et al. 1990; Jurd et al. 1995). These molecules prolong the thrombin time (TT) and act as antithrombin agents due to potentiation of the activity of the cofactors heparin II and antithrombin III. Furthermore, Athukorala et al. (2007) reported that the crude polysaccharide fraction (CpoF) of *C. fragile* and *Sargassum horneri* showed potent anticoagulant properties, with activated partial thromboplastin time (APTT) values of > 300 s. The most potent activity was recorded in the > 30 kDa fraction. The highest molecular weight fraction significantly prolonged clotting times in the APTT and TT assays but had an insignificant effect on the prothrombin time (PT). In addition to prolonging the APTT and PT, *C. dwarkense* sulfated polysaccharides may reduce the number of microthrombi in the histopathology of the lung, liver, and mesentery with less structural damage in vivo (Golakiya et al. 2017).

In contrast, codiase, a new bifunctional fibrinolytic serine protease isolated from *C. fragile*, exhibits anticoagulant properties with the prolongation of the APTT and PT, which leads to the inhibition of coagulation factors (Choi et al. 2013). Furthermore, codiase has the potential to block blood-clotting pathways by increasing the anticoagulant action of naturally existing blood factors. An insignificant reduction in fibrinogen levels by codiase may otherwise favor anticoagulation. *Codium fragile* significantly inhibited platelet activation by downregulating αIIbβ3 signaling and prevented $FeCl_3$-induced arterial thrombus formation without prolonging the bleeding time in vivo (Kim et al. 2021). Finally, the high molecular weight molecules (i.e., polysaccharides and proteoglycans) and codiase of *C. fragile* could be used as anticoagulant agents.

Anticancer activity

Failure of apoptosis is known to trigger the development of cancer in cells (Shinkai et al. 1996). Apoptosis is a physiological process involving selective cell deletion that regulates the balance between cell proliferation and cell death. Numerous studies have reported the anticancer properties of marine macroalgae. For example, an aqueous extract of *C. fragile* may inhibit the growth of CT-26 cells and decrease the protein expression of anti-apoptotic Bcl-xL, leading to caspase-3 and caspase-7 activation (Kim et al. 2008). Treatment with *C. fragile* increases the sensitivity of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) and the protein levels of c-caspase-8 and c-caspase-3 by inhibiting cellular FLICE-inhibitory protein (c-FLIP) expression (Hye et al. 2018).

In addition, *C. fragile* polysaccharides increase the NK cell activation in mice by promoting the activation of bone marrow-derived dendritic cells (BMDCs) in vitro and dendritic cells (DCs) in tumor-bearing mice in vivo (Park et al. 2020b). In an animal model, *C. fragile* polysaccharides significantly suppressed B16 tumor growth. Moreover, *C. fragile* polysaccharide treatment inhibited CT-26 cell growth by enhancing anti-cancer immunity mediated by anti-PD-L1 antibodies. According to Wang et al. (2021), *C. fragile* polysaccharides also reduced Lewis lung carcinoma cell infiltration into the lungs and their anti-tumor growth activity required NK and CD8 T cells. Another study reported that *C. fragile* polysaccharides inhibited CT-26 and B16 cell infiltration in the lungs (Park et al. 2020a). This study also demonstrated that *C. fragile* stimulates NK cells. Moreover, *C. fragile* polysaccharides promote the stimulation of the human peripheral blood DC (PBDC) subset, resulting in T-helper 1 (Th1) cell activation and cytotoxic T lymphocyte (CTL) cell activation, which, in turn, elicits anti-cancer effects (Zhang et al. 2020). Dilshara et al. (2016) evaluated the activity of a methanol extract of *C. fragile* as a stimulator in human breast cancer MDA-MB-231 cells. They found that that treatment with the methanol extract of *C. fragile* increased the expression of TNF-α by inhibiting matrix metalloproteinase-9 (MMP-9), further inhibiting NF-κB activity. Cytotoxic effects (IC_{50} of 150 μM) were also demonstrated in A2058 human melanoma cells treated with *C. fragile* clerosterol via the upregulation of Bax, downregulation of Bcl-2, and activation of caspases 3 and 9 (Kim et al. 2013). Taken together, *C. fragile* produces compounds with therapeutic effects against cancer cells by suppressing protein expression and could be used to promote anticancer immunity (Monmai et al. 2019).

Anti-inflammatory activity

Inflammation is a protective response induced by a variety of stimuli, such as physical damage, precursor chemicals, microbial invasion, and immunological responses, in the body (Medzhitov 2008). The infiltration of leukocytes and macrophages is a typical inflammatory reaction. Lipopolysaccharide (LPS) rapidly triggers macrophages and stimulates the secretion of pro-inflammatory cytokines and inflammatory mediators, such as NO and PGE2 via iNOS and COX-2, respectively (Moon et al. 2018b), by upregulating the NF-κB pathway and MAPKs, including the extracellular signal-regulated kinase (ERK)1/2, c-Jun NH_2-terminal kinase (JNK), and p38 subfamilies (Sudirman et al. 2019). Currently, alternative anti-inflammatory agents are being identified from marine macroalgae.

It has been found that the extracts of *C. fragile,* including the aqueous, ethanolic, and methanol extracts, may have anti-inflammatory properties in vitro by inhibiting NO and PGE_2 production and reducing inflammatory cytokine levels in LPS-stimulated RAW 264.7 cells, or by inhibiting peptidoglycan (PGN) by blocking NF-κB and MAPK phosphorylation (Han et al. 2010; Yoon et al. 2011; Kang et al. 2012; Ah et al. 2017). Furthermore, an aqueous extract of *C. fragile* inhibited carrageenan-induced rat paw edema thickness by up to 50% in vivo (Ah et al. 2017). Moon et al (2018b) have also reported that the oleamide from *C. fragile* may inhibit the inflammatory response in LPS-induced RAW264.7 murine macrophages and reduce carrageenan-induced inflammatory edema in the rat paw

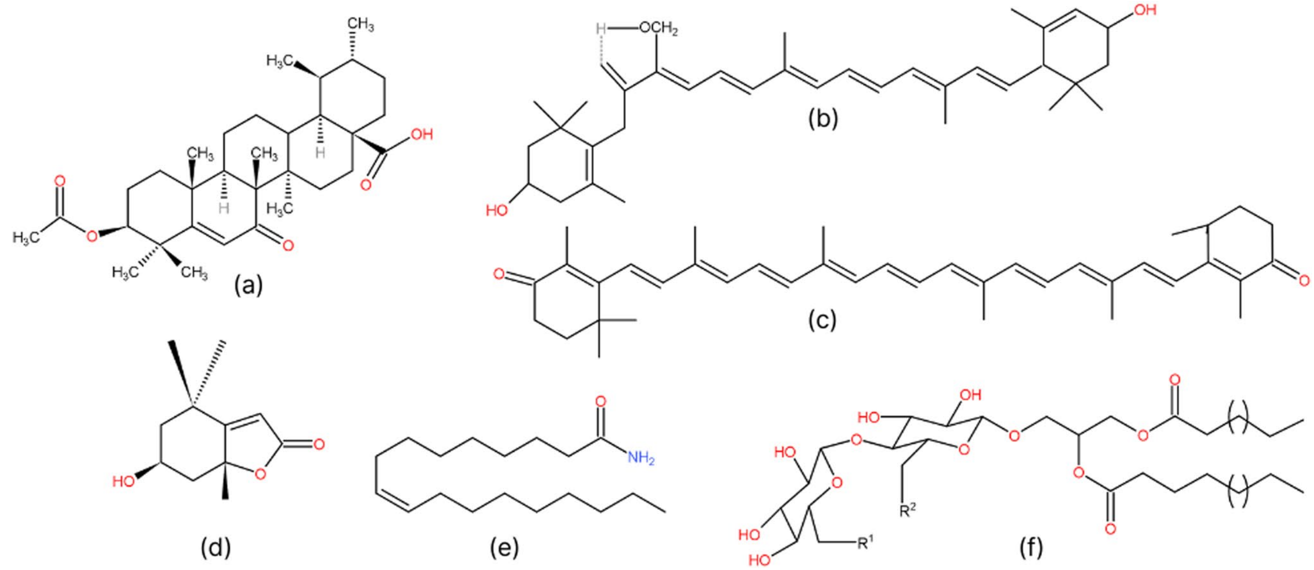

Fig. 6 Structure of bioactive compounds from *Codium* species, including (a) dwarkenoic acid (Ali et al. 2015); (b) siphonaxanthin (Ricketts 1971); (c) canthaxanthin (Rebelo et al. 2020); (d) loliolide (Silva et al. 2021); (e) oleamide (Moon et al. 2018b); (f) sulfonoglycosides: Codioside E and Codioside F (Ali et al. 2017)

model. In addition, the activation of pro-inflammatory proteins, including COX-2, iNOS, and TNF-α, along with pro-inflammatory mediators, including PGE2 and NO, due to the stimulation by ultraviolet B (UVB) irradiation in HaCaT cells decreased after treatment with *C. fragile* extract. This result also demonstrated that the *C. fragile* extract reduced oxidative damage, such as lipid peroxidation and/or protein carbonylation, possibly mediated by an increase in antioxidant defense enzymes (Lee et al. 2013).

Antioxidant activity

Antioxidants are important inhibitors of lipid peroxidation; hence, they are used to delay or prevent lipid peroxidation in foods and the oxidation of cellular substrates. All aerobic organisms produce and degrade reactive oxygen species (ROS), including hydroxyl radicals, superoxide anions, hydrogen peroxide (H_2O_2), and singlet oxygen, resulting in physiological concentrations required for normal cell function or excessive ROS production and subsequently oxidative stress (Nordberg and Arnér 2001). The overproduction of ROS causes damage to cellular macromolecules, such as proteins, DNA, and lipids. Wang et al. (2020) demonstrated that sulfated polysaccharides from *C. fragile* possessed high toxicity against hydrogen peroxide (H_2O_2)-induced oxidative stress by reducing intracellular ROS levels, increasing cell viability, and inhibiting apoptosis both in Vero cells and zebrafish in a dose-dependent manner. Furthermore, the aqueous extracts of *C. fragile* have high scavenging activity against O_2^-, $HO^\cdot$, H_2O_2, DPPH free radicals, and ROS (Heo et al. 2005). Another study reported that *C. fragile* flavonoids with low levels of condensed tannins have fascinating antioxidant profiles (Kolsi et al. 2017a, b). In addition, Celikler et al. (2009) studied the effect of the ethanolic extract of *C. tomentosum* on chromosomes induced by oxidative stress, and found that it exhibited no genotoxic effects on human lymphocytes in vitro. Finally, the development of antioxidants from marine macroalgae, especially those from *C. fragile*, is desired for use in the pharmacological industry as a substitute for synthetic antioxidants.

Antiviral activity

Viral treatments address several stages of viral replication, which are broadly defined as entry, replication, shedding, and latency (Kidgell et al. 2019). Enzymatic hydrolysates of *C. fragile* exhibited significant antiviral activity against the Herpes simplex virus (HSV-1), with an EC_{50} of 36.5–41.3 μg mL^{-1} and a multiplicity of infection (MOI) of 0.001 ID_{50}/cells without cytotoxity (1–200 μg mL^{-1}) (Kulshreshtha et al. 2015). Likewise, the extracts from proteases (P1) and carbohydrases (C3) were efficient at a higher MOI, of 0.01 ID_{50}/cells, without cytotoxicity. Selain HSV-1 *C. fragile* may also inhibit the replication of HSV-2 and the promoted mortality rate in HSV-2-infected mice i*n vivo* (Ohta et al. 2009). Another study demonstrated that siphonaxanthin derived from *C. fragile* exhibited antiviral activity against the SARS-CoV-2 pseudovirus in HEK293 cells (IC_{50} = 87.4 μM) (Yim et al. 2021). These results indicate that *C. fragile* has the potential as a source of novel antiviral agents.

Antibacterial activity

Steroidal glycosides and clerosterol galactoside extracted from *C. iyengarii* showed moderate in vitro bactericidal activity against *Corynebacterium diptheriae, Escherichia coli*, *Klebsiella pneumoniae*, *Snigella dysentri*, *and Staphylococcus aureus* (Ali et al. 2010). A significant inhibitory activity against GES-type β-lactamase (GES-22) was observed by the methanol extract of *C. tomentosum*. Another study on the methanol extract of *C. iyengarii* exhibited no antibacterial activity against Gram-positive and Gram-negative bacteria. However, it did exhibit good antiviral activity (Rizvi and Shameel, 2004). The variability in activities between species was also demonstrated by Reichelt and Borowitzka (1984) who found that extracts of *C. adahaerens, C. muelleri* and *C. spongiosum* showed antibacterial activity against Gram-positive bacteria but not against Gram-negative bacteria, whereas extracts of *C. fragile* showed no antibacterial activity.

Antifungal activity

Similar to the antibacterial mechanisms, antifungal agents may kill or inhibit fungal pathogens. A previous study on *Codium* extracts demonstrated that they have antifungal activity. *Codium bursa* exhibits inhibitory activity against *Fusarium* spp., *Penicillium expansum*, *Aspergillus flavus*, and *Rhizophus* spp. (Jerkovi et al. 2019). *Codium iyengarii* exhibited significant antifungal activity against various pathogens, whereas *C. shameelii* showed weak antifungal activity (Rizvi and Shameel 2004).

Antitumoral activity

Marine macroalgae have been shown to be potential sources of drugs for cancer chemotherapy (Murphy et al. 2014). A sulfated homogalactan from *C. isthmocladum* showed antitumoral activity by reducing the growth and metastasis of solid tumors without any negative drawbacks. (Bellan et al. 2020). El-Masry et al. (1995) also found that *C. sinensis* showed antitumoral activity. Zbakh et al. (2020) found that the dichloromethane extract of *C. decorticatum* effectively reduced tumor cell viability and targeted human cervical cancer cell lines through the apoptotic pathway. Moreover, the dichloromethane extract of *C. decorticatum* has an antiproliferative effect by reducing cell viability human of cervical carcinoma HeLa cells through apoptosis in 25.6% of the cells.

Anti-angiogenic activity

Angiogenesis is the physiological process of forming new blood vessels. This process prevents cancer and other related diseases.. The effects of the siphonaxanthin extract from *C. fragile* and the sulfated galactan extract from *C. cylindricum* were tested in human umbilical vein endothelial cells (HUVECs) in vitro and in rat aortic rings ex vivo (Matsubara et al. 2003; Ganesan et al. 2010).

Osteoprotective activity

Previous studies have reported the osteoprotective effects of marine macroalgae, including those on osteoporosis and osteoarthritis, both in vitro and in vivo. Osteoporosis is characterized by a decrease in bone mass caused by an imbalance between bone resorption and bone creation, whereas bone homeostasis requires balanced interactions between osteoblasts and osteoclasts (Baek et al. 2016). Meanwhile, the balance in cartilage is disrupted in osteoarthritis, resulting in a substantial increase in inflammatory mediators, ROS, and degradative enzymes, resulting in cartilage degradation and the eventual loss of joint function (Shin et al. 2006). Surget et al. (2017) reported that phenolic compounds from *C. fragile* may stimulate mineralogenic activity in fish bone-derived cell lines, thereby increasing osteogenic activity by more than 1.5-fold. Moreover, osteoarthritis treatment with an aqueous extract of *C. fragile* can be relieved by regulating the immune system. The aqueous extract of *C. fragile* significantly increased the production of nitrite and inflammatory biomarkers (iNOS, MMP-13, ADAMTS-4, and ADAMTS-5) in IL-1β-induced rat primary chondrocytes via interleukin-1β-induced NF-κB signaling activation. Cartilage lesions in the aqueous extract of *C. fragile*-treated rats with osteoarthritis exhibited less proteoglycan loss and lower OARSI scores in vivo.

Anti-obesity activity

Obesity has become a global public health issue because it reduces the quality of life of individuals and increases healthcare costs (Maeda 2013). Obesity is defined as the accumulation of body fat. In particular, fat accumulation around internal organs is a major risk factor for various diseases, including type II diabetes, hypertension, dyslipidemia, and cancer (Calle and Thun 2004; Maeda 2015). In recent years, bioactive compounds from marine macroalgae, such as fucoxanthin, alginates, fucoidans, and phlorotannins, have been reported as being potential anti-obesity agents (Wan-Loy and Siew-Moi 2016). Kim et al. (2020) evaluated the anti-obesity effects of *C. fragile* extracts in mice administered a high-fat diet. They observed that *C. fragile* extract significantly decreased the body weight and modulated the gut microbiota of the animals by increasing the abundance of beneficial bacteria. It also has been demonstrated that the sulfated polysaccharides of *C. fragile* effectively decreased the body weight of rats fed a high-fat diet while also protecting hepatic function by increasing the levels of antioxidant enzymes (Kolsi et al. 2017a, b).

Other bioactivities

In addition to the biological effects mentioned above, *C. fragile* possesses antiprotozoal, antihypertensive, anti-sarcopenia, anti-angiogenic, anti-melanogenic, and neuroprotective activities. Spavieri et al. (2010) isolated a crude extract of *C. fragile* and demonstrated that it has a high toxicity in protozoan organisms, especially *Trypanosoma brucei rhodesiense* (IC_{50} = 8.9 μg mL^{-1}), but it was ineffective against *Mycobacterium tuberculosis*. The methanol extract from *C. fragile* exhibits a strong inhibition of the enzyme activity of angiotensin-converting enzyme (ACE) (IC_{50} = 0.59 mg mL^{-1}), resulting in potent antihypertensive activity (Kolsi et al. 2017a, b). Ahn et al. (2021) showed the potential of a *C. fragile* extract as a therapeutic agent for sarcopenia management. Sarcopenia is characterized by a loss of skeletal muscle mass and function (Santilli et al. 2014). Ahn et al. (2021) suggested that *C. fragile* extracts, including LPC, retinoic acid, α-tocopherol, linoleic acid, linolenic acid, and canthaxanthin, enhanced skeletal muscle mass and function by regulating protein synthesis by increasing the phosphorylation of S6K1 and improving the ERRγ-PGC-1α-SIRT1 pathway in myotubes.

Furthermore, siphonaxanthin inhibited HUVEC proliferation and tube formation, while ex vivo treatment effectively suppressed microvessel outgrowth in a dose-dependent manner. In addition, *C. fragile* extract, at a concentration of 25 μg mL^{-1}, exhibited anti-melanogenic activity through the downregulation of α-melanocyte-stimulating hormone-mediated melanin synthesis in MNT-1 human melanoma cells, as well as through the downregulation of microphthalmia-associated transcription factor, tyrosinase, and tyrosinase-related protein 1. This result, which was produced from a clinical trial, also suggested that the extracellular vesicles of *C. fragile* may enhance skin brightness. In addition, the neuroprotective activity of loliolide isolated from *C. tomentosum* can enhance cell viability and reduce oxidative stress, thereby preventing Parkinson's Disease (Silva et al. 2021).

Conclusion and future directions

In the last three decades studies on the bioactivity and pharmacological properties of the genus *Codium* have steadily increased. This indicates that the species of *Codium* have promising potential as sources of various bioactive compounds, such as sulfated polysaccharides, sulfated glycoproteins, dwarkenoic acid, siphonaxanthin, canthaxanthin oleamide, siphonaxanthin, loliode, codioside E, codioside F, α-tocopherol, β-tocopherol, γ-tocopherol, and δ-tocopherol. However, despite the increased research efforts conducted by scientists, to date, only a few products have been developed from *Codium* species in the pharmaceutical and nutraceutical industries. The present review demonstrates the gap that must be filled in the study of *Codium*. Two approaches can be applied to develop *Codium* spp. into products with a high economic value. First, ecological studies should be conducted. Ecological studies include the taxonomy, reproduction, growth, and environmental factors that influence *Codium* species and their composition (e.g. Marques et al. 2021). This genus is found worldwide as native or invasive species. The occurrence of the *Codium* species as an invasive species must be considered. A comprehensive study of the reproduction and characteristics of the genus *Codium*, as well as the dispersal mechanism, needs to be conducted to gain a full understanding of this genus. Furthermore, an aquaculture system for *Codium* species must be developed and optimized to produce high algal biomass (e.g. Hwang et al. 2008). To date, *Codium* is little cultivated globally. Second, the identification and isolation of bioactive compounds from species of *Codium* are needed. Most previously published papers did not go further to isolate and identify the bioactive compounds of *Codium*. Most studies using crude extracts of *Codium* species are still in the preliminary stage and the purported active compounds need to be tested in clinical settings. These approaches can be used to develop *Codium* species into high-value products and maintain their ecological function in marine ecosystems.

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