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REVIEW

A concise review of the potential utilization based on bioactivity and pharmacological properties of the genus *Gelidium* (Gelidiales, Rhodophyta)

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Abstract

Being an agarophyte, *Gelidium* is extensively exploited for its agar-producing capacity. However, the food value and medicinal importance of this red alga are not to be underestimated. The pharmacological properties of *Gelidium* species have potential for the pharmaceutical, nutraceutical and cosmeceutical industries. This review collects, identifies and analyzes comprehensively the studies that deal with the bioactive properties of *Gelidium* species in the last decade. The principal bioactive compounds of *Gelidium* include R-phycoerythrin, R-phycocyanin, alkaloids, terpenoids, tannins, flavonoids, saponins, coumarins, cardiac glycosides, and steroids. *Gelidium* in the form of extracts or isolated compounds have been reported to show antibacterial, antioxidant, anticancer, anti-inflammatory, anti-obesity, immunomodulatory, neuroprotective, and antidiabetic properties. Most of the evidence has been reported in various in vitro models. Therefore, further experiments using appropriate animal and human subjects are necessary to develop the preclinical findings into clinical use. The main challenge in developing bioactive compounds on a commercial scale is the sustainable supply of *Gelidium* biomass that requires integrated seaweed aquaculture through employing biotechnological approaches and effective utilization of industrial byproducts.

Keywords Seaweed · Macroalgae · Bioactive · Pharmacological · Agarophyte · *Gelidium* · Rhodophyta

Introduction

Macroalgae are one of the most potential marine resources because of their polysaccharide and bioactive compounds (Zemke-White and Ohno 1999; Bixler and Porse 2011; Ale and Meyer 2013; Andrade et al. 2013). *Gelidium* is one of the agar-producing red macroalgae and has been used as sea vegetable, human food and as traditional herb medicine in East Asian countries. *Gelidium* has been used as a food ingredient for centuries by boiling it in water to make edible agar (McHugh 1991). It contains polysaccharides in the form of agar, which consist of agarose and a small mixture of agaropectin (Qi et al. 2008; Bixler and Porse 2011). Agarose is a neutral agar that consisted of a linear polymer of the disaccharide agarobiose consisting of 1,3-linked-D-galactose and 1,4-linked 3,6-anhydrous-L-galactose, while a sulphated galactan with some anionic structure such as small anionic amounts of pyruvic, D-glucuronic acid and acid ester sulfates build up agaropectin (Qi et al. 2008; Park et al. 2011). Polysaccharides from agarophytes have been used in industry for a long time (Bixler and Porse 2011). Agar production

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increased by 7% from 2009 to 2015 with an increase in sales value of 6% (Porse and Rudolph 2017). *Gracilaria* and *Gelidium* species are the prominent agar-producing species in the world. The agar produced by *Gelidium* shows stronger gel strength compared to the agar produced by *Gracilaria*. Hence, *Gelidium* is widely used commercially and industrially as a reagent for the manufacture of bacto agar and agarose (Porse and Rudolph 2017). *Gelidium* also produces some bioactive compounds that potentially can be applied and developed in the pharmaceutical, food, and nutraceutical industries. These compounds include R-phycoerythrin, R-phycocyanin, alkaloids, terpenoids, tannins, flavonoids, saponins, coumarins, cardiac glycosides and steroids (Mohy El-Din and Alagawany 2019; Sukwong et al. 2019). The bioactivity of *Gelidium* bioactive compounds includes antibacterial, antioxidant, anticancer, antitumor, anti-inflammatory, immune-promoting, neuroprotective, and antidiabetic activities (Bouhlal et al. 2010; Rhimou et al. 2010a; Hannan et al. 2013; Oumaskour et al. 2013; Wang et al. 2013; Kang et al. 2016; Alghazeer et al. 2018; Saeed et al. 2020).

A comprehensive review of agarophyte macroalgae from the genus *Gracilaria* has been done by Torres et al. (2019). Previous reviews on the commercial utilization, cultivation, and harvest methods of the genus *Gelidium* were conducted by McHugh (1991), Santelices (1991), Melo (1998), Friedlander (2008), Porse and Rudolph (2017) and Santos and Melo (2018). However, there is no up-to-date comprehensive review on the bioactivity and pharmacological properties of *Gelidium*. The main aim of this review is to analyse the potential and challenge of the current utilization of *Gelidium* as a source of bioactive compounds. This study was done systematically by collecting, identifying, screening, and analysing scientific articles published during 2001–2021. This review gives updated information on *Gelidium* potential utilization and application in the industry. Hence, we can find the research gaps and future directions on the utilisation of *Gelidium*.

Distribution

Gelidium belongs to the division Rhodophyta, class Florideophyceae, order Gelidiales, and family Gelidiaceae. *Gelidium* can be found both in the tropics and subtropics, with the highest diversity concentrated in the tropics. The highest producers of *Gelidium* species are Morroco, Japan, Republic of Korea, and Indonesia which produced 9,500 t dry weight of *Gelidium* or 85% of world total production (Porse and Rudolph 2017). *Gelidium* species also have been reported in other countries including Madagascar (Boo et al. 2022), Brazil (Iha et al. 2015), China (Fei and Huang 1991), India (Santelices 1991), Argentina (Croce et al. 2015) Portugal (Melo 1998), Spain (Melo 1998), South Africa (Melo 1998), Australia (Kim and Boo 2012) and other locations as shown in Fig. 1.

Morphology

Morphologically *Gelidium* can be identified based on the characteristics of the thallus including thallus tips, branching pattern, cell size, cystocarp, nutritive filament, pericarp, holdfast and apical cell. The genus *Gelidium* is one of the most diverse among the Gelidiaceae having high plasticity. Furthermore, within its wide geographical range and environmental conditions, *Gelidium* shows physiological and morphological adaptations (Santelices 1991). The tropical *Gelidium* species have a higher optimum temperature for growth compared to the subtropical species. Morphologically, *Gelidum* species have a cartilaginous thallus, red to deep purple or blackish color, arising from cylindrical or compressed, branched or unbranched creeping axes with numerous short haptera extending as individual axes or forming massive disc-like holdfasts disconnected from the interior of the cortical cells, are distichously, feathery or irregularly branched, with translucent rhizoidal filaments in the cortex and medulla, horned globose cystocarps and cruciate tetrasporangia arranged in sori (Santelices 2007; Kim et al. 2011; Guiry and Guiry 2022).

Taxonomy

Currently, 144 *Gelidium* species are accepted in Algaebase, as well as 1 accepted subspecies, 16 accepted varieties, and 8 accepted formae (Guiry and Guiry 2022). *Gelidium* species show high plasticity of morphological features and characteristics, hence it is difficult to identify the species solely based on morphological features. Molecular approaches are useful tools to identify and analyse the phylogenetic relationship of the *Gelidium* species which will give information regarding taxonomy and evolutionary pattern. The use of DNA barcoding to identify *Gelidium* species is increasing. The plastid RuBisCO (*rbcL*), mitochondrial cytochrome *c* oxidase (*cox1*/COI) and the chloroplast universal plastid amplicon (UPA) are commonly used for identification and phylogenetic analysis of *Gelidium* species (Freshwater et al. 2010; Kim et al. 2012; Iha et al. 2015; López et al. 2017; Boo et al. 2022). Freshwater et al. (2010) compared COI and *rbcL* and verified the barcoding gap among six *Gelidium* species. Kim and Boo (2012) identified and analysed the phylogenetic relationship of two *Gelidium* species, namely *G. crinale* and *G. pusillum*, using mitochondrial cox1 and plastid *rbcL* markers. They found that both species were different based on the dataset of mitochondrial *cox1* and plastid *rbcL* markers. The phylogenetic relationship of *G. crinale*

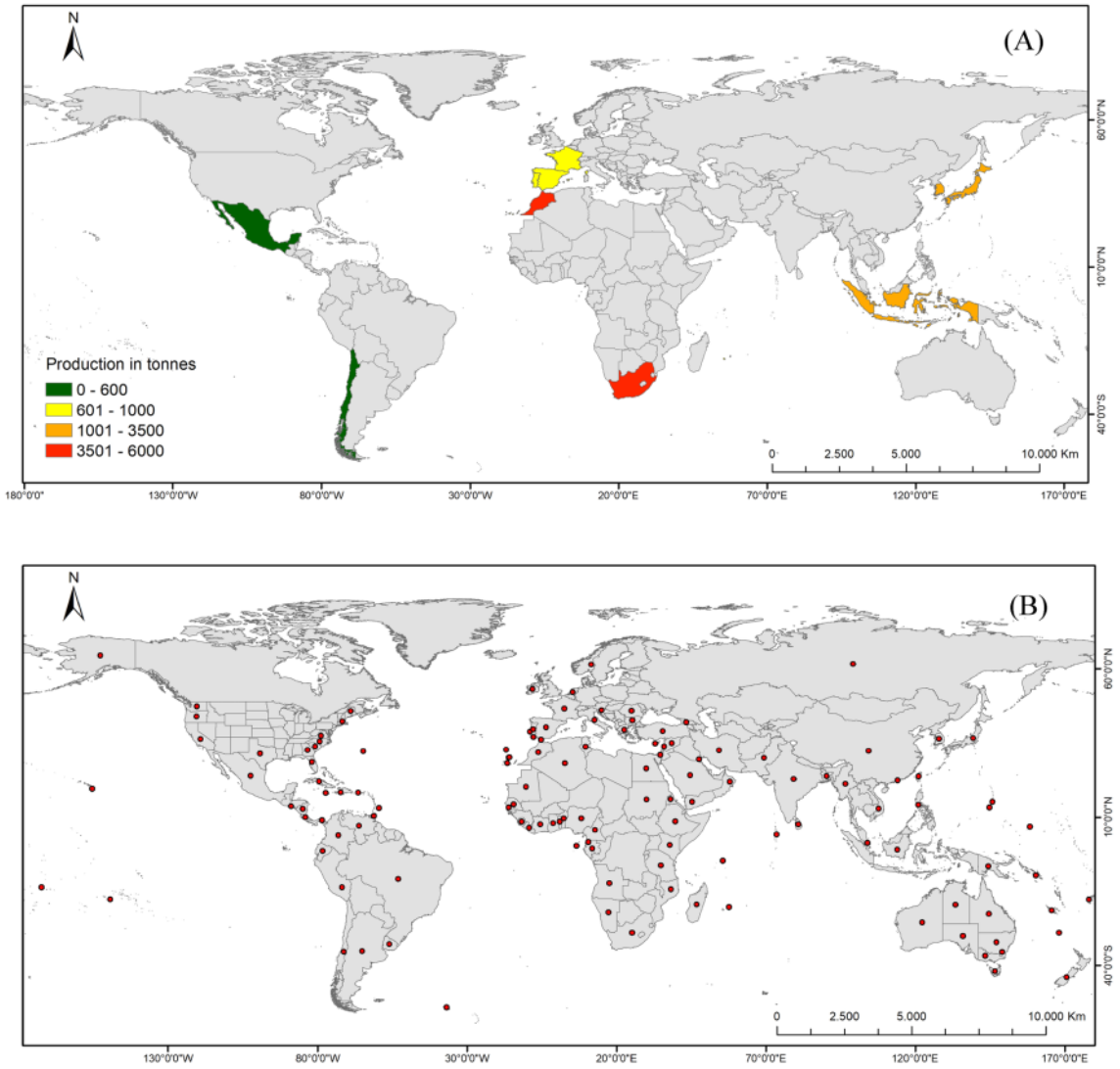

Fig. 1 Geographic distribution of *Gelidium* in the world based on (**A**) top producers of *Gelidium* and (**B**) global distribution of *Gelidium* (Porse and Rudolph 2017; Guiry & Guiry 2022)

showed a kinship with *G. capense* and *G. coulteri*, while *G. pusillum's* relationship and infraspecific classification were still not determined. Based on the morphological characteristic and DNA barcoding using mitochondrial *cox1* and plastid *rbcL*, Boo et al. (2022) observed the diversity of *Gelidium* species in southern Madagascar and identified some new records of *Gelidium* species, namely *G. usmanghanii*, *G. leptum* and *G. sclerophyllum*. Iha et al. (2015) used DNA barcoding of some Brazilian specimens of Gelidiales and to confirm three *Gelidium* species namely *G. crinale*, *G. floridanum*, *G. microdonticum*. Moreover, next-generation genome sequencing has been used to obtain the complete mitochondrial genomes of *Gelidium* species (Yang et al. 2014; Boo et al. 2016).

Cultivation

To date, the supply of *Gelidium* species is collected from the wild stock. Several cultivation methods of *Gelidium* have been developed to overcome the dependency on wild stock. The development of *Gelidium* cultivation for providing seedstock

using vegetative propagation and spore culture have been developed in laboratory, sea, pond, and tank culture systems (Fei and Huang 1991; Melo et al. 1991; Titlyanov and Titlyanova 2006; Titlyanov et al. 2006; Boulus et al. 2007; Friedlander 2008; Otaíza et al. 2018, 2019; Alemañ et al. 2019). Unfortunately, most of the cultivation technology of *Gelidium* is still at the experimental level and cannot fulfill the commercial demand. Plantlets of *Gelidium* can be also regenerated from callus and protoplasts through cell culture. However, there is a limited update on the cell culture of *Gelidium*. Cultivation experiments of *Gelidium* are commonly based on the fragmentation of thalli and spore. Otaíza et al. (2018) observed the fragmentation of *G. lingulatum* and investigated the optimum cultivation condition including the substrate, irradiance, and temperature. The effect of physical, chemical, and biological factors was also investigated in fragment thalli cultivation (Friedlander 2008; Otaíza et al. 2019). The cultivation from *Gelidium* fragment thalli showed a slow growth rate reaching 1.2% day^{-1} (Otaíza et al. 2019), 2% day^{-1} (Melo et al. 1991), 4.6% day^{-1} (Fei and Huang 1991), and 11–13% day^{-1} (Titlyanov and Titlyanova 2006). Besides the slow growth, the cultivation of thallus fragments is not environmentally friendly compared to spore culture. However, spore cultivation also has some limitations and drawbacks. Further studies on spore culture are needed before it can be applied. Studies on genetic engineering and efficient cultivation technology are needed to overcome the slow growth of *Gelidium*.

Nutrient content

Gelidium species contain carbohydrate (40.64–67.3% dw), protein (11.31–15.8% dw), lipid (0.0–2.16% dw) and ash (5.5–24.74% dw) (Park et al. 2011; Siddique et al. 2013; Ashoush et al. 2017). Major minerals of *Gelidium* species are Ca (0.091–0.87% dw), Mg (0.045–0.23% dw), K (0.054–0.56% dw), Na (0.128–0.53% dw) (Panayotova and Stancheva 2013; Rubio et al. 2017). The monosaccharide composition of *Gelidium* species mainly consists of galactose, glucose, xylose, galacturonic acid and the sulfated polysaccharide (Park et al. 2012; Meinita et al. 2017; Cui et al. 2019).

Agar characteristics

Gelidium has been used extensively to extract high-quality agar for biotechnological applications. Agar yield and characteristics such as gel strength, gelling temperature, and melting point vary depending on the extraction techniques, species, country of origin, and seaweed harvesting period (Table 1). In general, *Gelidium* species yield a better-quality agar in terms of gel strength compared to other agarophytes, however, the yield is relatively low. Although the quality of *Gelidium* agar extracted by hot water extraction is adequate, several techniques, including alkaline pretreatment, enzymatic hydrolysis, ultrasonication, stirring, and autoclaving have been employed to increase agar yield and extract high-quality agar. Among seaweed species used for agar extraction, *Gelidium amansii* yields the highest quantity of agar (49.10% by sonication and autoclaving). Gómez Barrio et al. (2022) have shown that ultrasound-assisted extraction can improve yield and gel strength compared to conventional extraction. Alkali pretreatment followed by enzymatic hydrolysis or ultrasonication with *Gelidium corneum* (formerly *Gelidium sesquipedale*) can result in higher yield of agar and stronger gel strength compared to alkali pretreatment alone (Li et al. 2021). Again, higher yield of agar and stronger gel strength were observed in sonicated *G. amansii* when the autoclave method was applied rather than direct heating (Din et al. 2019).

Utilization

Gelidium has been widely used, especially in East Asian countries including China, Japan and Korea. The utilization of *Gelidium* species has developed from the traditional use by the community to the modern utilization. Traditionally, macroalgae have been widely used by people in East Asian countries both for food and herbal medicine. People in South East Asian countries have long experience using *Gelidium* as food ingredient by boiling it in water to make edible agar and also by consuming *Gelidium* in the form of conventional strip and square (McHugh 1991; Armisen 1995). *Gelidium* is one of the macroalgae which has been commonly used in China as herbal medicine since two thousand years ago for stomach ailments, hemorrhoids, and anal fistulas (Chengkui et al. 1984).

In modern times, *Gelidium* is mainly used in food technology, pharmaceutical and bioenergy fields based on their primary and secondary metabolites. In bioenergy field, several studies have reported biohydrogen, bioethanol, biodiesel and platform chemical production from *Gelidium* (Wi et al. 2009; Afify et al. 2010; Jeong and Park 2010; Park et al. 2011; Meinita et al. 2013, 2021; Ra et al. 2015).

The research on bioactivity of *Gelidium* extracted compounds is also increasing during 2001–2021 as shown in Fig. 2a. We found 63 research articles focused on the bioactivities of *Gelidium* species. *Gelidium* has been widely studied for antibacterial, antioxidant, anticancer, antitumor, anti-inflammatory, immune-promoting, neuroprotective, antidiabetic activities (Fig. 2b).

Sixteen *Gelidium* species have been studied during 2001–2021 (Fig. 3). *Gelidium amansii* (formerly *Gelidium elegans*) was the most well-studied species (34.8%) in the genus *Gelidium*, followed by *Gelidium spinosum* (formerly *Gelidium latifolium*) (10.1%), *Gelidium corneum* (10.1%) and *Gelidium pristoides* (6.7%). The pharmacological

Table 1 Yield, gel strength, gelling point, and melting point of agar extracted from various species of *Gelidium*

Gelidium species	Agar extraction technique	Agar yield (%)	Gel strength (g cm^{-2})	Gelling point	Melting point	Country	Ref
Gelidium corneum	Conventional extraction and ultrasound-assisted extraction	1.50 –15.85	377 ± 136 and 438 ± 47	n.d	n.d	Ireland	(Gómez Barrio et al. 2022)
Gelidium corneum	Traditional extraction conditions (95 ℃, 3 h)	18.4	~750	n.d	n.d	Portugal	(Gomes-Dias et al. 2022)
Gelidium sp.	Not mentioned	8.21	674	31.5 ^{0}C	80 ℃	Indonesia	(Subaryono and Sinurat 2021)
Gelidium corneum	0.5% NaOH plus enzymatic hydrolysis and/or ultrasonication	3.3 – 18.2	119 –670	n.d	n.d	Ireland	(Li et al. 2021)
Gelidium corneum; Gelidium microdon	i) Alkali pretreatment using 10% NaOH solution and heated in a water bath at 90 ℃ for 2 h ii) Alkali pretreatment using 0.5% Na_2CO_3 solution at 90 ℃ for 30 min	i) 6.20 – 20.50 ii) 12.23 – 17.73	528.55 ± 11.08 and 489.00 ± 19.41	34–39 ℃	85.65–86.71℃, 86.32–87.13℃,	Morroco	(Belattmania et al. 2021)
Gelidium spinosum	Not mentioned	32.79 ± 0.78 – 39.26 ± 0.37	206.83 ± 5.36 to 591.85 ± 2.42	47.46 ± 0.20 ℃	93.86 ± 0.27 ℃	Turkey	(Öğretmen and Kaya 2019)
Gelidium amansii	i) Sonication pretreatment using autoclaving method and ii) Direct heating	Autoclaving 49.10 and Direct heating 13.26	840	26.9 to 25.2 ℃	51.4 ℃ to 68.0 ℃,	Malaysia	(Din et al. 2019)
Gelidium spinosum	Water bath plus magnetic stirrer extraction method	45.79 ± 0.85 and 37.29 ± 0.76	n.d	39.06 ± 0.26 ℃	94.8 ± 0.29 ℃	Turkey	(Öğretmen and Duyar 2018)
Gelidium amansii	Not mentioned	3.5 – 4.8	742	25.80.1 ℃	76.80.1 ℃	Malaysia	(Chew et al. 2018)
Gelidium spp.	Alkaline treatment with 6% alkali at 80 ℃ for 1.5 h	23.14	1068.15	28.1 − 43.2 ℃	96.4 − 99.6 ℃	China	(Wang et al. 2017)
Gelidium robustum	0.1 M phosphate buffer, pH 6.3, for 12 h	35% to 37	205 ± 5 – 444 ± 25	33.3 °C -35.3 °C	91.9—95.2 °C	Mexico	(Hurtado et al. 2011)
Gelidium canariense	0.5% (w/v) solution of Na_2CO_3 at 85–90 °C for 30 min	18 to 27.8	n.d	n.d	n.d	Algeria	(Freile-Pelegrín et al. 1995)
Gelidium spinosum	Hot water extraction	26% — 42.5	400—800	n.d	n.d	France	(Mouradi-Givernaud et al. 1992)

*n.d., not determined

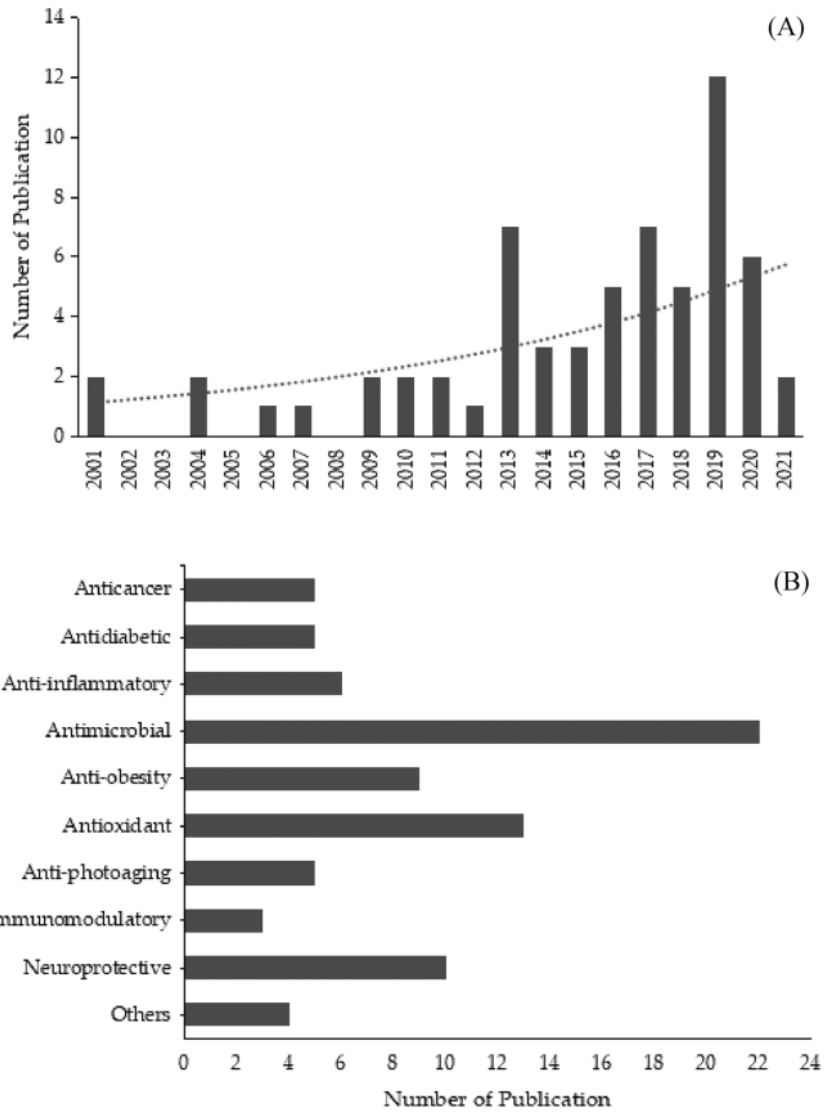

Fig. 2 The number of publications on *Gelidium* (**A**) based on the year and (**B**) based on the bioactivities

properties of *G. amansii* encompassed their bioactivity as anticancer, antimicrobial, anti-inflammatory, immunomodulatory, neuroprotective, antidiabetic, anti-photoaging, anti-obesity and other bioactivities. Most of studies focused on the antimicrobial (26.8%), antioxidant (15.9%) and neuroprotective (12.2%) activities of *Gelidium* species.

Bioactive compounds

Macroalgae produces secondary metabolites in response to environmental stress. Macroalgae as sessile organisms produce secondary metabolites to survive from environmental pressures. Macroalgae that live in different environmental conditions may also produce different types of bioactives. The types of bioactive compounds in *Gelidium* can be seen in Table 2.

The chemical structure of some bioactive compounds found in *Gelidium* can be seen in Fig. 4. Red algae contain photosynthetic pigments namely, phycoerythrin and phycocyanin (Ficner et al. 1992; Kohata et al. 2010). Phycocyanin and phycoerythrin are pigments in *Gelidium* that show bright colors (Pangestuti and Kim 2011). Phycocyanin is a blue pigment while phycoerythrin is a red pigment, and both are water-soluble compounds

(Sukwong et al. 2019). These compounds have remarkable antioxidant activity (Pan-utai and Iamtham 2019).

Mycosporine-like amino acids (MAAs) are small water soluble molecules categorised as secondary metabolites synthesized by macroalgae inculding Gelidium species that have bioactivity as photoprotectors and antioxidants (Pandey et al. 2017). MAAs such as shinorine and porphyra-334 isolated from *Gelidium* sp. have been investigated in the pharmaceutical field. Their immunomodulatory effects have been investigated in human myelomocytic cell lines and they have anti-inflammatory activity (Becker et al. 2016). Shinorine and porphyra-334 are MAAs which can be found in organism that live in the high intensity of sun exposure. Hence, they can be developed as UV protectors and cell proliferation activator in cosmetic products because they show a protective response on human fibroblast cells from UV induction (Oyamada et al. 2008; Lalegerie et al. 2019; Sen and Mallick 2021).

Cholesterol and lumichrome isolated from *G. microdon* have been shown to have antibacterial properties (Silva et al. 2013). Other compounds found in *Gelidium* are alkaloids, terpenoids, tannins, flavonoids, saponins, coumarins, cardiac glycosides, and steroids (Mohy El-Din and Alagawany 2019). Alkaloid compounds in macroalgae contain many biological amines and contain halogenated cyclic nitrogen-containing compounds (Güven et al. 2010). Bioactive compounds such as flavonoids, alkaloids, tannins, terpenoids, saponins, and steroids in macroalgae have the potential to be used as antioxidants and antibacterials (Taleb-Contini et al. 2003; Shan et al. 2007; Güven et al. 2010). Terpenoids play a role in the development of new pesticides and may become prototype agrochemical agents (Born et al. 2012). Coumarin is a natural product with pharmacological properties such as anti-inflammatory, antibacterial, antioxidant and neuroprotective properties (Kontogiorgis and Hadjipavlou-Litina 2005; Venugopala et al. 2013). Cardiac glycosides have been extensively studied for their anticancer activity (Kepp et al. 2012).

Pharmacological properties

Anticancer activity

Gelidium spp. extracts have shown anticancer properties (Table 3) and can be used as new chemotherapeutic agents or as a source of chemical leads for new agents (Rocha et al. 2018; Meinita et al. 2022). For example, an ethanol extract of *G. latifolium* showed inhibited human colorectal carcinoma (Caco-2) cell lines with a substantial inhibition (85%) at a concentration of 200 µg mL^{-1}. However, the extract also had a cytotoxic effect on normal cells, namely Human Corneal Epithelial Cells (HCEC) with inhibition not exceeding 24% at a concentration of 200 µg mL^{-1}. The IC_{50} against Caco-2 cell line was 120 µg mL^{-1} which is classified as moderate cytotoxic activity (Alghazeer et al. 2018). Futhermore, polysaccharide extract from *G. corneum* showed potential cytotoxity against a number of cancer cell lines (Abdala Díaz et al. 2019).

Chen et al. (2004) examined the effects of freeze-dried PBS and DMSO extracts from *G. amansii* agar which were tested on three cancer cell lines. The results showed that both extracts can inhibit Hepa-1 and NIH-3T3 cells, but not the growth of HL-60 cells. This study was confirmed by Xu et al. (2004) who reported that *G. amansii* extract had IC_{50} values greater than 50 µg mL^{-1} against three cancer cell lines and one normal cell line. In addition, Silva et al. (2013) stated that crude methanol extracts from *G. microdon* showed moderate inhibition against MCF-7, NCI-H460 and A375-C5 cell lines with an IC_{50} ranging from 36 to 75 µg mL^{-1}.

As shown above, extracts of several *Gelidium* species showed moderate and potential cytotoxicity against multiple cancer cell lines. However, the cytotoxicity of *Gelidium* extracts is not limited to cancer cells, but also affects normal cells. Thus further research is needed on the potential of using *Gelidium* species as a source of anticancer compounds.

Antioxidant activity

Antioxidants play a role in the potential prevention of several diseases related to oxidative stress, occurring when the balance between antioxidants and reactive oxygen species (ROS) is disturbed (Corsetto et al. 2020). Table 4 summarizes the antioxidant activity of *Gelidium*. The antioxidant activity of *Gelidium* was mostly determining by evaluating DPPH (2,2-diphenyl-1-picrylhydrazyl) degradation. Based on research carried out, the degradation rate of *Gelidium* extract against DPPH is medium but its antioxidant activity is low (Alghazeer et al. 2018; Abdala Díaz et al. 2019; Nursid et al. 2020; Saeed et al. 2020). The antioxidant parameters based on IC_{50} are very strong (50 ppm), strong (50–100 ppm), moderate (100–150 ppm), and weak (> 200 ppm) (Molyneux 2004; Juszczak et al. 2019). Mohy El-Din and Alagawany (2019) showed that *G. crinale* extract had the lowest antioxidant effect compared to the other macroalgae using total antioxidant capacity (TAC) evaluation. This is consistent with recent findings (Lekameera et al. 2008) that brown algae have stronger antioxidant activity than red or green algae. *Gelidium* sp. showed a low antioxidant effect based on DPPH assay (Ishakani et al. 2016), FRAP method (Ortiz-Viedma et al. 2021), and ORAC assay (Pacheco et al. 2020) compared to other algae tested. On the other hand, *G. foliaceum*, *G. microdon*, and *G. pristoides* demonstrated the highest free radical scavenging activity of the macroalgae tested (Rengasamy et al. 2015;

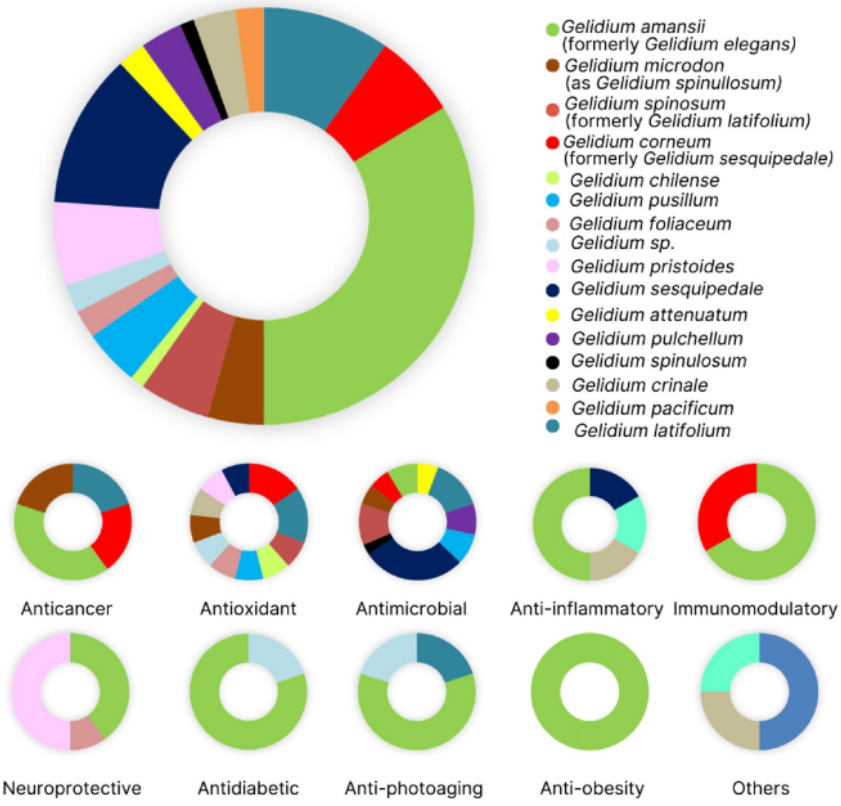

Fig. 3 The number of publications on *Gelidium* based on the species and their bioactivities

Paiva et al. 2016; Olasehinde et al. 2019b). In other studies of hydromethanolic, chloroform, diethyl ether, ethyl acetate, and n-butanol fractions of *G. corneum* possessed low antioxidant activity compared to synthetic antioxidants BHT, α-tocopherol and ascorbic acid (Metidji et al. 2015). Amongst the five extracts, the ethyl acetate fraction had the maximum activity (87.02%), followed by the diethyl ether fraction (83.52%), however, there was a substantial

Table 2 Bioactive compounds of *Gelidium*

Species	Compound	Reference
G. amansii	R-phycoerythrin (R-PE)	(Baghel et al. 2015; Sukwong et al. 2019)
G. amansii	R-phycocyanin (R- PC)	(Baghel et al. 2015; Sukwong et al. 2019)
Gelidium sp.	Shinorine	(Pandey et al. 2017)
Gelidium sp.	Porphyra-334	(Pandey et al. 2017)
G. microdon	Cholesterol	(Silva et al. 2013)
G. microdon	Lumichrome	(Silva et al. 2013)
G. crinale	Alkaloids	(Metidji et al. 2015; Mohy El-Din and Alagawany 2019)
G. crinale	Terpenoids	(Mohy El-Din and Alagawany 2019)
G. crinale	Tannins	(Mohy El-Din and Alagawany 2019)
G. crinale	Flavonoids	(Mohy El-Din and Alagawany 2019)
G. crinale and *G. corneum*	Saponins	(Metidji et al. 2015; Mohy El-Din and Alagawany 2019)
G. crinale	Coumarins	(Mohy El-Din and Alagawany 2019)
G. crinale	Cardiac Glycosides	(Mohy El-Din and Alagawany 2019)
G. crinale	Steroids	(Mohy El-Din and Alagawany 2019)
G. corneum	Anthocyane	(Metidji et al. 2015)

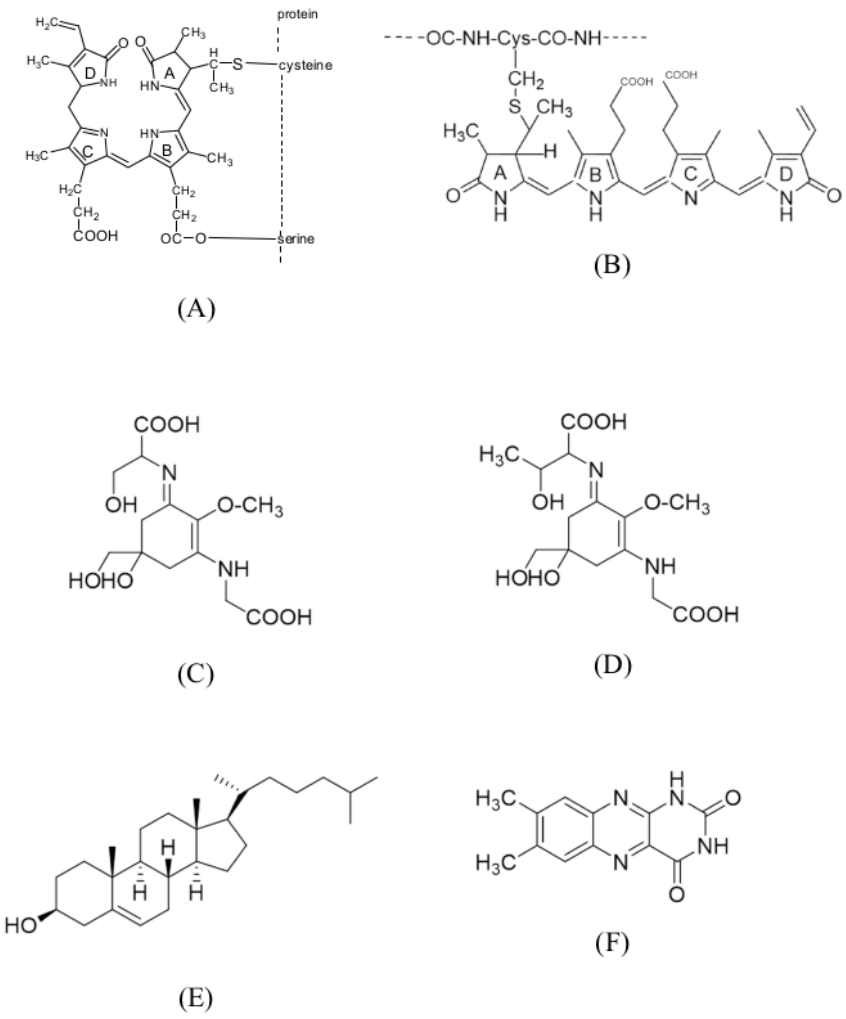

Fig. 4 Structures of R-phycoerythrin (**A**), Phycocyanobilin (**B**) Shinorine (**C**) Porphyra-334 (**D**) Cholesterol (**E**) Lumichrome (**F**) isolated from *Gelidium*

difference when compared to the positive control in the β-carotene-linoleate assay. Furthermore, MAAs extract namely asterina 330 plus palythine (AS-330 + PNE) from *G. corneum* revealed a significant activity of β-carotene oxidation inhibition referring to superoxide radical scavenging and vitamin E (de la Coba et al. 2009). Based on β-carotene-linoleate assay, *Gelidium* extracts have potential as an antioxidant agent.

Antimicrobial activity

Antimicrobial activity against bacteria, fungi, and viruses has been studied (Table 5). Antibacterial activity was tested using the disc diffusion technique (Bouhlal et al. 2010; Rhimou et al. 2010a; Oumaskour et al. 2013; Saeed et al. 2020). *Gelidium* extracts show high inhibitory activity against both Gram-positive (Rhimou et al. 2010a; Oumaskour et al. 2013) and Gram-negative bacteria (Bouhlal et al. 2010; Rhimou et al. 2010a). *Gelidium pusillum* showed antibacterial activity against all strains of bacteria tested and the highest activity was exhibited by *G. microdon* (as *G. spinulosum*) against *Staphylococcus aureus*. Among five *Gelidium* spp. tested, *G. attenuatum* possessed highest antibacterial activity, while *G. corneum* exhibited weak inhibition against all of the bacteria strains (Bouhlal et al. 2013). On the contrary, Oumaskour et al. (2013) observed that *G. corneum* showed highest inhibition and *G. spinosum* (formerly *G. latifolium*) possessed moderate inhibition. *Gelidium spinosum* showed weak and moderate inhibition against the bacteria tested but higher inhibition against *P. mirabilis* compared to positive control (Saeed et al. 2020). *Gelidium microdon* showed higher antibacterial activity after

Table 3 Anticancer activities of *Gelidium* extracts

Species	Experimental Models	Extract or Constituent	Study Type	Optimum Dose (μg mL^{-1})	IC_{50} (μg mL^{-1})	Ref
G. spinosum	Human colorectal carcinoma (Caco2) cell lines	Methanol extract	In vitro	200	120	(Alghazeer et al. 2018)
G. corneum	Human leukemia cell line (U-937), human colon cancer cell line (HTC-116), and human malignant melanoma (G-361)	Sulfated polysaccharides	In vitro	-	60.01 ± 4.84	(Abdala Díaz et al. 2019)
G. amansii	Murine hepatoma cells (Hepa-1c1c7), human leukemia cells (HL-60), and normal murine embryo fibroblast cells (NIH-3T3)	Phosphate-buffered saline (PBS) and dimethyl sulfoxide (DMSO) extract	In vitro	150	-	(Chen et al. 2004)
G. microdon	Breast adenocarcinoma (MCF-7), non-small cell lung cancer (NCI-H460) and melanoma (A375-C5)	Methanol extract	In vitro	-	36.3 ± 8.0 to ≥ 200	(Silva et al. 2013)
G. amansii	KB, hepatocellular carcinoma Bel7402 and lung cancer A549,	Methanol extract	In vitro	-	> 50	(Xu et al. 2004)

$IC_{50} < 100$ μg mL^{-1}, potential cytotoxicity; $100 < IC_{50} < 1000$ μg mL^{-1}, moderate cytotoxicity; $IC_{50} > 1000$ μg mL^{-1}, non-toxic (Prayong et al. 2008)

removal of chlorophylls against methicillin resistant *S. aureus (MRSA)* compared to remaining bacteria (Silva et al. 2013).

Antifungal activity has been found in extracts of *G. microdon, G. spinosum* and *G. amansii*. *Gelidium microdon* showed higher antifungal activity after removal of chlorophylls against *Trichophyton rubrum* and *Microsporum canis* with minimal inhibitory concentration (MIC) and minimal lethal concentration (MLC) values ranging from 64.0 to 128.0 μg mL^{-1} (Silva et al. 2013). Saeed et al. (2020) reported that *G. spinosum* extract showed weak inhibition against *Aspergillus fumigatus* and *Aspergillus niger* compared to ketoconazole. In addition, among four fungi tested, *G. amansii* exhibited highest inhibition against *Fusarium oxysporum* (Yi et al. 2001). Besides being able to show antibacterial and antifungal activitles, *Gelidium* extracts also show antiviral. The methanol extract from *G. attenuatum* showed high antiviral activity against Herpes simplex virus type 1 withan EC_{50} value of 9.3 μg mL^{-1} (Rhimou et al. 2010b) and the *G. spinosum* n-butanol extract inhibited avian and human influenza virus replication (Kamenarska et al. 2009).

Anti-inflammatory activity

The anti-inflammatory properties of *Gelidium* potentially can play a role in treating inflammation. Inflammation is natural defense mechanism of vascular tissue to antagonism agents which attack and weaken the immune system (de Cássia da Silveira e Sá et al. 2013).

Anti-inflammatory activity of *Gelidium* has been studied in vitro and in vivo (Table 6). In vitro studies by Cui et al. (2019) showed that a *G. pacificum* sulfated polysaccharide with a molecular weight of 28,807 Da protected human monocytic (THP-1) cells from LPS-stimulated cytotoxicity. A concentration of 5 μg mL^{-1} suppressed mRNA and protein expression of the mRNA and protein expression of toll-like receptor-4 (TLR-4), myeloid differentiation factor (MyD88) and tumor necrosis factor receptor-associated factor-6 (TRAF-6). In another in vitro study, the dichloromethane/methanol (50:50) extract of *G. sesquipedale* inhibited phospholipase A2 by 100% and elastase by 95 (Oumaskour et al. 2013).

In vivo assay of sulfated galactan of *G. crinale* showed that in rat paw edema, there was an involvement of arachidonic acid metabolism (de Sousa et al. 2013). Agar free-*G. amansii* extracts also increased the production of anti-inflammatory cytokines (IL-10 antibodies) in diet-induced obese C57BL/6 J mice (Lee et al. 2018).

Immunomodulatory effect

Immune response regulation is closely related to various physiological and pathological conditions (Wang et al. 2013). Immunomodulation has complex mechanisms that

Table 4 Antioxidant activities of *Gelidium* extracts

Species	Extract or Constituent	Antioxidant Assay	DPPH	Effect	Ref
G. corneum	Sulfated polysaccharides	DPPH assay	40.21 ± 0.44%	Low antioxidant effect	(Abdala Díaz et al. 2019)
G. spinosum	Ethanol extract	DPPH assay	46.68%	Low antioxidant effect (IC_{50} = 300 µg mL^{-1})	(Nursid et al. 2020)
G. spinosum	Methanol extract	DPPH assay	nd	Low antioxidant effect (IC_{50} = 300 µg mL^{-1})	(Alghazeer et al. 2018)
G. spinosum	Ethanol, methanol, ethyl acetate, hexane, chloroform and acetone extract	DPPH assay	56.55 ± 1.20%	Low antioxidant effect (IC_{50} = 8.78 mg mL^{-1})	(Saeed et al. 2020)
G. chilense	Phenolic extract	DPPH assay and FRAP method	51.2 ± 9.1%	Low antioxidant effect	(Ortiz-Viedma et al. 2021)
G. pusillum	Methanol extract	DPPH assay	11.50 + 0.43 mM eq ascorbic acid g^{-1} DW	Low antioxidant effect	(Ishakani et al. 2016)
G. foliaceum	Methanol extract	DPPH assay	52.24 ± 0.86 mg mL^{-1}	High free radical scavenging activity	(Rengasamy et al. 2015)
G. corneum	Asterina-330 plus palythine (AS-330 + PNE)	β-carotene/ linoleate bleaching and pyrogallol autooxidation method	80.0 to 85.0%	High activity β-carotene oxidation inhibition ((IC_{50} = 10 µM)	(de la Coba et al. 2009)
Gelidium sp.	Phenolic and acetone extracts	DPPH assay and ORAC assay	4.8 ± 0.4% and 4.7 ± 0.2%	Low antioxidant effect	(Pacheco et al. 2020)
G. microdon	Phenolic extract	DPPH assay	47.73%	High free radical scavenging activity	(Paiva et al. 2016)
G. crinale	Methanol extract	TAC evaluation	0.923 mgAAE g^{-1}	Low antioxidant effect	(Mohy El-Din and Alagawany 2019)
G. pristoides	Phenolic extract	DPPH assay	153.22 µg mL^{-1}	The scavenging activity higher than remaining seaweed tested	(Olasehinde et al. 2019b)
G. corneum	Hydromethanolic crude extract and four fractions (chloroform, diethyl ether, ethyl acetate, n-butanol)	DPPH assay and β-carotene/ linoleate bleaching	61.25%	Low antioxidant effect	(Metidji et al. 2015)

nd, not determined

regulate the pathophysiology and pathogenesis of various diseases that affect the immune system (Yoo et al. 2019). The bioactive compounds in *Gelidium* have been investigated to play a role in immune promoting. Table 7 summarises the immunomodulatory activity of *Gelidium*.

A number of inflammatory mediators such as tumor necrosis factor-a (TNF-a), prostaglandin and E2 (PGE2), interleukin (IL)-1b, and IL-6 and nitric oxide (NO), are produced from macrophages (Yun et al. 2008). *Gelidium* as an immune-promoter showed that *Gelidium* gel phosphate buffered saline (PBS) extract can activate RAW 264.7 macrophages by increasing the production of immune mediators and these inflammatory mediators (Wang et al. 2013). Furthermore, hot-water extract of *G. amansii* increased immune ability in white shrimp *Litopenaeus vannamei*. In contrast, sulfated polysaccharides of *G. corneum* showed low immunomodulatory activity compared to other species (Abdala Díaz et al. 2019).

Neuroprotective activity

Neuroprotective activity is closely related to antioxidant activity, which plays a role in the defence system in the brain (Takahashi et al. 2003). Antioxidants play a role in defence while neuroprotective capacity plays a role in repairing neuronal damage in the brain (Hannan et al. 2020b). Marine algae, including *Gelidium* have been reported to have neuroprotective potential in various preclinical studies (Hannan et al. 2020a). Table 8 summarises the neuroprotective activity of *Gelidium*. A series of studies by Hannan and his team from 2012 to 2020 showed that *Gelidium* has neurotrophic and neuroprotective activities. Preliminary research suggested that *Gelidium* had highest neurotropic potential (Hannan et al. 2013). In subsequent studies, *Gelidium* has been shown to promote the morphological and functional maturation of neurons with the potential for prevention

Table 5 Antimicrobial activities of *Gelidium* extracts

Species	Extract or Constituent	Microorganism		Effect	Ref
Antibacterial					
• *G. attenuatum* • *G. spinosum* • *G. pulchellum* • *G. pusillum* • *G. corneum* • *G. microdon*	Methanol extract	Gram positive: • *Staphylococcus aureus* • *Enterococcus faecalis* ATCC 29,212 • *Enterococcus faecalis* ATCC 29,213	Gram negative: • *Escherichia coli* • *Klebseila pneumoniae*	Highest antibacterial activity with DIZ ranging from 15.0 to 35.0 mm	(Rhimou et al. 2010a)
G. spinosum	Methanol extract	• *Staphylococcus aureus* • *Staphylococcus epidermidis* • *Bacillus* sp. • *Bacillus subtilis*	• *Escherichia coli* • *Salmonella typhi Klebsiella* sp. • *Pseudomonas aeruginosa*	Highest antibacterial activity with DIZ ranging from 15.0 to 34.0 mm	(Alghazeer et al. 2013)
• *G. attenuatum* • *G. spinosum* • *G. pulchellum* • *G. pusillum* • *G. corneum*	Methanol extract	• *Staphylococcus epidermidis* • *Staphylococcus haemolyticus* • *Staphylococcus hominis* • *Staphylococcus simulans* • *Bacillus sp.* • *Cytophaga* sp. • *Micrococcus 5J6*	• *Klebseila pneumoniae* • *Paracoccus* sp.	DIZ ranging from 7.0 to 19.5 mm	(Bouhlal et al. 2013)
G. spinosum	Methanol extract		• *Klebseila pneumoniae* • *Proteus mirabilis*	DIZ ranging from 9.0 to 12.0 mm	(Saeed et al. 2020)
• *G. latifolium* • *G. corneum*	Dichloromethane-Methanol	• *Streptococcus faecalis* • *Bacillus cereus* • *Staphylococcus aureus* • *Staphylococcus aureus ssp aureus* • *Bacillus subtillus1*		*G. latifolium* showed moderate inhibition while *G. sesquipedale* showed highest inhibition	(Oumaskour et al. 2013)
G. microdon	Methanol extract	• *Staphylococcus aureus ATCC 25,923* • *Methicillin Resistant Staphylococcus aureus (MRSA)*	• *Escherichia coli ATCC 25,922* • *Pseudomonas aeruginosa ATCC 27,853*	Higher antibacterial activity after removal of chlorophylls	(Silva et al. 2013)
G. spinosum	Butanol extract, water extract, and volatile compound	• *Staphylococcus aureus*		Volatile compound showed highest antibacterial activity	(Kamenarska et al. 2009)
Antifungal					
G. microdon	Methanol extract	*Epidermophyton floccosum* FF9, *Microsporum canis* FF1, *Microsporum gypseum* FF3, *Trichophyton mentagrophytes* FF7, and *Trichophyton rubrum* FF5		Higher antifungal activity after removal of chlorophylls	(Silva et al. 2013)
G. spinosum	Methanol extract	*Aspergillus fumigatus* and *Aspergillus niger*		Lower than positive control	(Saeed et al. 2020)
G. amansii	Ethanol extract	*Penicilium citrinum, Aspergillus niger, Fusarium oxyssporam, and Alternaria dianth*		Highest inhibition against *Fusarium oxyssporam*	(Yi et al. 2001)
Antiviral					

Table 5 (continued)

Species	Extract or Constituent	Microorganism	Effect	Ref
• *G. attenuatum* • *G. spinosum* • *G. pulchellum* • *G. pusillum* • *G. corneum* • *G. microdon*	Methanol extract	*Herpes simplex virus type 1 (HSV-1)*	Methanol extract showed highest antiviral activity	(Rhimou et al. 2010b)
G. spinosum	Butanol extract and water extract	*Avian influenza virus* A/Germany/27, strain Weybridge (A/Wey- bridge) and *Human influenza virus* A/PR8/34 (H1N1) (A/ PR8)	n-butanol extract inhibited influenza virus replication	(Kamenarska et al. 2009)

and treatment of neurodegenerative diseases (Hannan et al. 2014). Then, a proteomic study of the chloroform ($CHCl_3$) subfraction and the ethyl acetate (EtOAc) fractions of *G. amansii* ethanol extract found that neurite development was enhanced by up-regulation of several proteins such as profilin 2a, septin 7, cdc42, protein phosphatase 2A, DA11, eukaryotic translation initiation factor 5A-1, and enolasen (Hannan et al. 2017). In a hypoxia/reoxygenation-induced oxidative injury model of primary hippocampal neurons, *G. amansii* protected against oxidative damage through suppressing GluN2B expression (Hannan et al. 2020c).

Inhibition of acetylcholinesterase (AChE) activity is one of the commonly available treatment strategies against Alzheimer's disease (AD) and *G. pristoides* possessed moderate acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) inhibitory activity with IC_{50} values of 52.70 ± 1.85 and 58.28 ± 1.79 mg mL^{-1} respectively (Olasehinde et al. 2019b). Rengasamy et al. (2015) showed that *G. foliaceum* had the lowest AChE inhibitory activity with IC_{50} value of 0.16 ± 0.02 mg mL^{-1} among the macroalgae tested. *Gelidium* and its bioactives can protect against Zn–induced neuronal damage in HT-22 cells through inhibiting apoptosis and oxidative damage, and regulating redox imbalance (Olasehinde et al. 2019c, 2020). Extracts of *G. pristoides* also inhibit β-amyloid aggregation and β-secretase and cholinesterase activities (Olasehinde et al. 2019a; d). Based on these data, *Gelidium* can be a potential source of bioactive metabolites with therapeutic significance against oxidative stress-related neurodegeneration, including ischemic stroke and neurodegenerative diseases (Hannan et al. 2020c).

Antidiabetic activity

Natural antidiabetics are needed for the treatment of diabetes mellitus. Diabetes treatment uses insulin level regulation, such as diet modification and oral hypoglycemic drugs (Marles and Farnsworth 1995; Jung et al. 2006). Macroalgae have bioactive peptides that can play a role in antidiabetic activity (Admassu et al. 2018). Research on the potential antidiabetic activity of *Gelidium* is summarized in Table 9. Several in vitro and in vivo studies conducted on *Gelidium* as antidiabetic agent have been reported. The development of type II diabetes and the complications associated with the disease, including macro-vascular and micro-vascular diseases is strongly influenced by postprandial hyperglycemia (Ko et al. 2011). Inhibition of carbohydrate hydrolyzing enzymes in the digestive organs, such as α-glucosidase and α-amylase, is one therapeutic method for reducing postprandial hyperglycemia (Clissold and Edward 1988). Acetone extracts of *Gelidium* sp. decreased the α-amylase activity to $77.9 \pm 2.1\%$ and did not show significant α-glucosidase inhibition at concentrations of

Table 6 Anti-inflammatory activities of *Gelidium* extracts

Species	Extract or Constituent	Experimental Models	Study Type	Optimum Dose	Effects		Ref
					Molecular	Cellular	
G. sesquipedele	Methanol, acetone, chloroform, hexane, dichloromethane/methanol extracts	PLA inhibition and elastase assay	In vitro	nd	↓ phospholipase enzyme A2 (100%) and elastase enzyme (95%)		(Oumaskour et al. 2013)
G. pacificam	Sulfated polysaccharide	Human monocytic (THP-1) cells	In vitro	5 µg mL^{-1}	↓ LPS-stimulated cytoxicity		(Cui et al. 2019)
G. crinale	Sulfated galactan	Rat paw endema	In vivo	1 µg mL^{-1}		↓ histamine (49%) and phospholipase A2 (44%)	(de Sousa et al. 2013)
G. amansii	Cellulose nanocrystal	Human keratinocytes and mice skin	In vitro and in vivo	100 µg mL^{-1}	↓ c-Jun-induced UVB phosphorylation	↓ COX-2 induced UVB expression	(So et al. 2021)
G. amansi	Ethanol extract	Diet-induced obese (DIO) C57BL/6 J mice	In vivo	500 µg mL^{-1}		↑ production of anti-inflammatory cytokines (IL-10 antibodies)	(Lee et al. 2018)
G. amansii	Phosphate-buffered saline (PBS) or ethanol extract	RAW 264.7 macrophages	In vitro	nd	↓ cytokine production in LPS-stimulated RAW 264.7 macrophages		(Wang et al. 2013)

(1, 10, 100, 1000 µg dry extract mL^{-1}) (Pacheco et al. 2020). Furthermore, *G. amansii* exhibited greater inhibition against α-amylase and α-glucosidase compared to acarbose, an oral hypoglycemic agent. *Gelidium amansii* extract administered to STZ-induced diabetic mice can lower the level of postprandial blood glucose (Park et al. 2017a). Ko et al. (2011) also found that *G. amansii* extract exhibited high α-glucosidase inhibitory effects (96.47%) using high throughput screening. *Gelidium elegans extract also* regulated glucose homeostasis and significantly lowered blood glucose level in ICR mice administered (Choi et al. 2017a, 2018). Furthermore, the *G. elegans* extract activated insulin receptor substrate-1 (IRS-1) and phosphoinositide 3-kinase (PI3K), thus enhancing the expression of glucose transporter type 4 (GLUT4). The extract also lowered mitogen-activated protein kinase (MAPK) activity. These findings demonstrated that upregulating insulin pathway and downregulating MAPK pathway by *Gelidium* extract potentially can be used for blood metabolism.

Anti-photoaging effect

UV radiation is one of the most damaging environmental factors, causing a kind of skin damage known as photoaging. Photoaging produced by persistent UV exposure results in premature aging of the skin, which is indicated by dryness, coarse and fine wrinkle formation, laxity, and pigmentation (Xiang et al. 2011). Studies conducted on the anti-photoaging effect of *Gelidium* spp. have been reported (Table 10).

Tyrosinase inhibitors are important in cosmetics for depigmentation and may be clinically effective for the treatment of various dermatological conditions linked to melanin hyperpigmentation (Cabanes et al. 1994; Shiino et al. 2001). Previous studies have reported that *Gelidium* extracts have potential as a tyrosinase inhibitor. Nursid et al. (2020) found that *G. spinosum* extract showed low inhibition of tyrosinase (< 20%) similar to Khatulistiani et al. (2020) who observed 38.54% tyrosinase inhibition. However, Cha et al. (2011) observed higher tyrosinase inhibition (73.87%) at 20 °C. The differences may be due to different environmental conditions the algae grew in, resulting in variation in biochemical and physiological traits of *Gelidium* species (Véliz et al. 2019).

Kim et al. (014) conducted research on a fermented *G. amansii* and *Cirsium japonicum* (Angiosperm) extract mixture (FGCM) on UVB-induced skin photoaging on hairless mice. FGCM showed anti-photoaging activity by inhibiting UVB-induced matrix metalloproteinase-1 (MMP-1) expression and increased type I procollagen in vitro. Meanwhile, hairless mice administered orally with FGCM showed strong activity in decreasing the number and total depth of wrinkles on dorsal skin.

Table 7 Immunomodulatory activity of *Gelidium* extracts

Species	Extract or Constituent	Experimental Models	Study Type	Optimum Dose	Effects		Ref
					Molecular	Cellular	
G. amansii	Phosphate-buffered saline (PBS) or ethanol extract	RAW 264.7 macrophages	In vitro	150 μg mL^{-1}		↑production of immune mediators	(Wang et al. 2013)
G. corneum	Sulfated polysaccharides	human colon cancer cell line (HCT-116), human malignant melanoma (G-361), breast adenocarcinoma human (MCF-7), human leukemia cell line (U-937), and murine macrophage cell line (RAW 264.7)	In vitro	-	Low immunomodulatory activity		(Abdala Díaz et al. 2019)
G. amansii	Hot-water extract	White shrimp *Litopenaeus vannamei*	In vivo	1.0 - 2.0 g kg^{-1} in the diet		↑ immune ability	(Fu et al. 2007)

According to So et al. (2021) *G. amansii* extract inhibited UVB-induced AP-1 and COX-2 gene and protein expression in HaCaT cells. UVB irradiation activated *G. amansii* extract to suppress c-Jun translocation from cytosol to nucleus. In HaCaT cells, *G. amansii* inhibited UVB-induced phosphorylation of extracellular signal-regulated kinases (ERKs1)/2/MEK/2/B-Raf, c-Jun N-terminal kinase (JNK1)/2/MKK4/7, Akt, and epidermal growth factor receptor (EGFR).

Anti-obesity activity

Obesity is a global health care issue that is associated with metabolic diseases such as type II diabetes and hyperlipidemia (Aubin et al. 2008; Crawford et al. 2010). Obesity is caused by body fat accumulation in adipose tissue due to abnormalities in energy metabolism (Choi et al. 2017b). Fat accumulation is caused by two different types of white adipocyte development processes, hyperplasia (adipocyte number increase) and hypertrophy (adipocyte size increase) in white adipocyte tissue (Guilherme et al. 2008). Recent studies reported that *Gelidium* can be used as anti-obesity by reducing lipid accumulation and adipogenesis (Table 11). *Gelidium amansii* extract showed inhibited adipogenesis in 3T3-L1 preadipocytes (Lee et al. 2011), and prevent weight gain through modulation of the AMPK, PRDM16, and UCP-1 pathways in a mice model (Choi et al. 2017b). Moreover, *G. amansii* extract decreased blood glucose and serum insulin levels when administered on mice induced by obesity diet (Kang et al. 2016). This finding is in line with other reported research that *G. amansii* ethanol extracts can reduce fat accumulation in a 3T3-L1 cell model (Seo et al. 2012), and reduce body and epididymal fat weights, as well as serum total cholesterol (TC) and triglyceride (TG) levels in an obese mice model (Kang et al. 2017; Park et al. 2017b). On the other hand, hot-water extracts of *G. amansii* (GHE), can lower plasma and liver lipids in an animal model by decreasing cholesterol absorption and enhancing bile acid and fecal fat excretion (Yang et al. 2019). The water soluble fibres in *G. amansii* (GHE) may help to reduce lipid accumulation in the liver and adipose tissues. Furthermore, *G. elegans* extract at concentration of 100 μg mL^{-1} inhibited mRNA expression of PPARγ (50%) and C/EBPα (90%), thus enhancing SOD1, SOD2, Gpx, and GR levels significantly in 3T3-L1 preadipocytes and RAW 264.7 cells (Jeon et al. 2014). The extract also inhibited the expression of C/EBPβ and increased C/EBP homologous protein 10 (Choi et al. 2016). These results suggested that *G. amansii* extract has the ability to inhibit adipogenesis and fat accumulation in 3T3-L1 preadipocytes and RAW 264.7 cells. The extract reduced weight gain of high-fat diet-induced obese mice and hamster through upregulating AMPK phosphorylation, PPARα, PRDM16, UCP-1, and UCP-2 pathways. However, further clinical studies are urgently needed to determine the effect of *Gelidium* treatment on obese patients in the future.

Miscellaneous effects

Besides the above bioactivities, *Gelidium* also shows other biological activities (Table 12). Kim et al. (2016) evaluated the genotoxic effect of *G. elegans* in vitro and in vivo using five different strains of bacteria, CHL/IU cell lines, and ICR mice. In

Table 8 Neuroprotective activities of *Gelidium* extract

Species	Extract or Constituent	Experimental Models	Study Type	Optimum Dose	Effects		Ref
					Molecular	Cellular	
G. amansii	Ethanol extract	Rat hippocampal neurons	In vitro	15 µg mL^{-1}	-	↑ early neuronal differentiation ↑ the axonal and dendritic development and maturation index of neurons	(Hannan et al. 2013)
G. amansii	Ethanol extract	Rat hippocampal neurons	In vitro	15 µg mL^{-1}	-	↑ number of filopodia and dendritic spines ↑ synaptogenesis, modulate NMDA receptor recruitment	(Hannan et al. 2014)
G. amansii	Ethanol extract	Rat hippocampal neurons	In vitro	7.5 µg mL^{-1}	-	↑ neurite development by up- or down-regulating several key proteins	(Hannan et al. 2017)
G. amansii	Ethanol extract	Rat hippocampal neurons	In vitro	15 µg mL^{-1}	-	potential source of oxidative stress-related neurodegeneration	(Hannan et al. 2020c)
G. foliaceum	Methanol extract	-	In vitro	1.0 mg mL^{-1}	Low inhibition of AChE	-	(Rengasamy et al. 2015)
G. pristoides	Water extract	-	In vitro	21 to 84 µg mL^{-1}	AChE and BChE inhibitory		(Olasehinde et al. 2019b)
G. pristoides	Sulfated polysaccharide	Hippocampal neuron cell line cells (HT-22)	In vitro		↓ apoptosis, oxidative damage and AChE		(Olasehinde et al. 2020)
G. pristoides	Aquaeosus-ethanol extract	-	In vitro		↑ antioxidant enzyme activities and GSH levels ↑ in malondialdehyde and nitric oxide levels		(Olasehinde et al. 2019c)
G. pristoides	Aquaeosus-ethanol extract	-	In vitro		↓ β-amyloid aggregation, β-secretase, and cholinesterases		(Olasehinde et al. 2019d)
G. pristoides	Sulfated polysaccharide	-	In vitro		↓ β-amyloid aggregation, β-secretase, and cholinesterases		(Olasehinde et al. 2019a)

the in vitro experiment, there was no increase of mutation and chromosome aberration of bacteria at a concentration of 5000 µg per plate. Furthermore, in vivo study showed that *G. elegans* did not affect the frequency of micronucleated bone marrow polychromatic erythrocytes (MNPCE). These results suggest that *G. elegans* extract could be considered a safe dietary ingredient.

The coagulation of blood as a result of haemostasis failure causes clogging of the vascular system and is occasionally

Table 9 Antidiabetic activities of *Gelidium* extract

Species	Extract or Constituent	Experimental Models	Study Type	Optimum Dose	Effects		Ref
					Molecular	Cellular	
Gelidium sp.	Ethanol/ water hot pressurized liquid extraction (HPLE) and Acetone extract	Human colon carcinoma (HT-29) cell line	In vitro	1–1000 µg dry extract mL^{-1}	↓ α-amylase activity No effect in α-glucosidase activity		(Pacheco et al. 2020)
G. amansii	Ethanol extract	ICR mice	In vivo			↓ α-amylase and α-glucosidase activities ↓ postprandial blood glucose levels	(Park et al. 2017a)
G. elegans	Industrial extract (Newtree co., Ltd)	ICR mice	In vivo	200 mg kg^{-1}		↓ blood glucose levels ↑ glucose homeostasis	(Choi et al. 2017a)
G. amansii	Methanol extract	-	In vitro	-	↓ α-glucosidase activity		(Ko et al. 2011)
G. elegans	Industrial extract (Newtree co., Ltd)	C57BL/KsJ-db/db mice and C57BL/KsJ m+/+db mice	In vivo	50 mg kg^{-1} day^{-1}		↓ blood glucose ↑ activated IRS-1 ↓ activation of MAPK pathways	(Choi et al. 2018)

fatal. Activated partial thromboplastin time (APTT) and prothrombin time (PT) experiments revealed that *G. crinale* extracts had anticoagulant properties (Mohy El-Din and Alagawany 2019). This study suggested that the presence of phenols or their derivatives promote the anticoagulant effect. Angiotensin I-converting enzyme (ACE) is an enzyme that regulates blood pressure through the rennin-angiotensin system, which is found in the vascular endothelium lining of the lungs (Cha et al. 2006). In humans ACE inhibitors have been widely utilized to treat essential hypertension and heart failure. Both the aqueous extract and the methanol extract of *G. amansii* was shown to have low ACE inhibitory activity (9.0–18.0%) compared to other macroalgae tested.

Table 10 Anti-photoaging effects of *Gelidium* extract

Species	Extract or Constituent	Experimental Models	Study Type	Optimum Dose	Effects		Ref
					Molecular	Cellular	
G. spinosum	Ethanol extract	Tyrosinase enzyme	In vitro	1000 ppm	Low inhibition of tyrosinase	-	(Nursid et al. 2020)
G. amansii	Aqueous extract	Murine B16F10 melanocyte	In vitro	-	High inhibition of tyrosinase	-	(Cha et al. 2011)
G. amansii	Ethanol extract	SKH-1 hairless mice and Hs68 human dermal fibroblasts	In vitro *and* in vivo	200 µL of PBS + 500 mg FGCM per kg body weight	↑ type I procollagen levels ↓ UVB-induced MMP-1 expression	↓ number and total depth of wrinkles	(Kim et al. 2014)
Gelidium sp.	Water extract	Tyrosinase enzyme	In vitro	-	Low inhibition of tyrosinase	-	(Khatulistiani et al. 2020)
G. amansii	Water extract	Human keratinocyte HaCaT, Beas-2B, and Raw 264.7 cells	In vitro	100 µg mL^{-1}	↓ COX-2 expression and UVB-induced AP-1	-	(So et al. 2021)

PBS phosphate-buffered saline

Table 11 Anti-obesity effects of *Gelidium* extract

Species	Extract or Constituent	Experimental Models	Study Type	Optimum Dose	Effects		Ref
					Molecular	Cellular	
G. elegans	Ethanol extract	3T3-L1 preadipocytes and RAW264.7 cells	In vitro	100 μg mL^{-1}	↓ lipid accumulation ↓ mRNA expression of PPARγ and C/EBPα ↓ ROS production and NO level ↑ SOD1, SOD2, Gpx, and GR levels	-	(Jeon et al. 2014)
G. amansii	Ethanol extract	3T3-L1 preadipocytes and C57BL/6 mice	In vitro and in vivo	100 μg mL^{-1}	↓ differentiation of 3T3-L1	↓ blood glucose and serum insulin levels	(Kang et al. 2016)
G. amansii	Water extract	Syrian hamsters	In vivo	200 mg kg^{-1} diet		↓ triglyceride and total cholesterol ↑ AMPK phosphorylation, PPARα and UCP-2	(Yang et al. 2019)
G. amansii	Ethanol extract	3T3-L1 adipocytes	In vitro	100 μg mL^{-1}	↓ fat accumulation ↓ differentiation of 3T3-L1		(Lee et al. 2011)
G. amansii	Industrial extract (Newtree co., Ltd)	ICR mice	In vivo	50, 200 mg kg^{-1} day^{-1}		↑ AMPK, PRDM16, and UCP-1	(Choi et al. 2017b)
G. amansii	Ethanol extract	Epididymal adipose tissue and liver; C57BL/6 J mice	In vitro and in vivo	0.75 to 2.00 g per 100 g diet	↓ FAS, SREBP-1c, PPARγ, and C/EBPα ↑ HSL and phospho-AMPKα (p-AMPK)	↓ body and epididymal fat weights, TC and TG levels	(Kang et al. 2017)
G. amansii	Ethanol extract	C57BL/6 J lean mice and C57BL/6 J-ob/ob mice	In vivo	0.5%		↓ body weight, epididymal adipose tissue weight, plasma triglycerides, and hepatic lipid accumulation	(Park et al. 2017b)
G. amansii	Industrial extract (Newtree co., Ltd)	3T3-L1 pre-adipocytes	In vitro	100 μg mL^{-1}	↑ C/EBP homologous protein 10 ↓ the expression of C/EBPβ		(Choi et al. 2016)
G. amansii	Ethanol extract	3T3-L1 pre-adipocytes	In vitro	40 μg mL^{-1}	↓ PPARγ and aP2 ↓ mRNA levels of a ROS-generator, NOX4 ↑ levels of antioxidant enzymes including SOD1/2, Gpx, and GR		(Seo et al. 2012)

Table 12 Miscellaneous effects of *Gelidium* extract

Bioactivity	Species	Extract or Constituent	Experimental Models	Study Type	Optimum Dose	Effects		Ref
						Molecular	Cellular	
Genotoxic effect	*G. elegans*	Industrial extract (Newtree co., Ltd)	*S. typhimurium* TA98, TA100, TA1535, and TA1537, *E. coli* WP2uvrA, and hamster lung cell line (CHL/IU); ICR mice	In vitro and in vivo	5000 µg plate^{-1}	No increased in reverse mutation and chromosome aberration	No effect on MNPCE	(Kim et al. 2016)
Anticoagulant	*G. crinale*	Sulphated polysaccharide extract	Normal plasma	In vitro	50 µL	Second highest anticoagulant effect after *S. hornschuchii*		(Mohy El-Din and Alagawany 2019)
Hypertension effect	*G. amansii*	Methanol extract	-	In vitro	200 µg mL^{-1}	Low ACE inhibitory activity (9.0–18.0%)		(Cha et al. 2006)
Antibiotic	*G. pacificum*	Water and ethanol extract	C57BL/6 mice	In vivo	-		Promomted antibiotic effect on mice with antibiotic-associated diarrhea (AAD)	(Cui et al. 2020)

In clinical treatment, antibiotics are used to treat various bacterial infections and infectious diseases. According to Cui et al. (2020) the sulfated polysaccharide of *G. pacificum* had beneficial effects on mice with antibiotic-associated diarrhea (AAD). This study showed that there was an increase in the richness and diversity of the gut microbiome and mucosal barrier function. *Gelidium pacificum* also can reverse metabolic disorders, inhibited the levels of cytokines inflammation and upregulated the content of SCFAs.

Prospects and Challenges

The various species of *Gelidium* are a substantial source of biomaterials, including hydrocolloids and bioactives with profound industrial and medicinal uses (Fig. 5). However, several factors need to be considered when developing *Gelidium* as a source of biomaterials at a larger scale. In the hydrocolloid industry, *Gelidium* species together with *Gracilaria* are two main agarophyte species that are used as raw materials in the agar industry. In 2015, the production of *Gelidium* species was 11,100 dry t and total production of *Gracilaria* was 114,100 dry t. These two agarophytes contribute 246 million US$ in total sales values of agar (Porse and Rudolph 2017). Agar extracted from *Gelidium* has higher gel strength and lower gelling temperature compared to *Gracilaria* (McHugh 1991; Bixler and Porse 2011). Hence, *Gelidium* is mostly chosen as agar source for bacteriological and pharmaceutical purposes. Although *Gelidium* produces high-quality agar, there are some obstacles to the large-scale production of *Gelidium*. Moreover, the agar production from *Gelidium* is steadily declining as it relies on natural stock; hence the supply of *Gelidium* biomass remains the main issue.

The first challenge is to adopt cultivation technology for *Gelidium* species. To develop an efficient cultivation method, we need to investigate the life history of *Gelidium* species. Most of the life history, reproductive features and complexity of *Gelidium* are still unknown. Rico and Guiry (1997) observed the characteristics and structure of tetrasporophytes and gametophytes of *Gelidium* and also observed the cystocarp structure and the bisexual nature of the gametophyte. The complexity and uniqueness of *Gelidium* 's life history as well as sexual gametophytes and meiotic sporophyte is challenging to be studied. Environmental parameters, including photoperiod, irradiance levels, temperature, and nutrients of *Gelidium* are also important factors in developing the optimum cultivation method (McHugh 1991).

The second challenge is to identify the potential candidate species of *Gelidium* to produce the desired bioactive compound. Out of 144 *Gelidium* species, which have been submitted to AlgaeBase (https://www.algaebase.org/), only a few species have been confirmed taxonomically (Guiry and

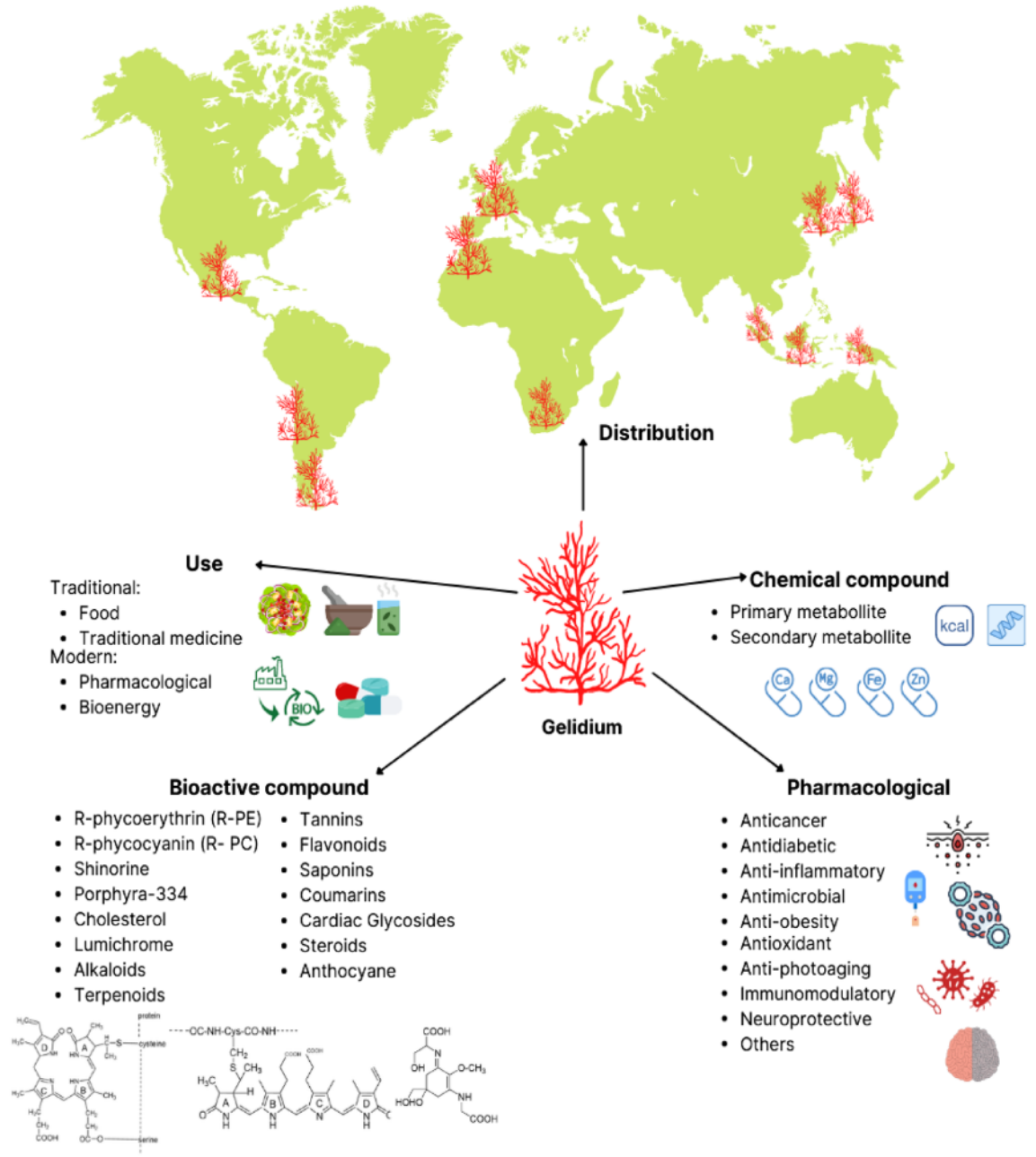

Fig. 5 The potential use, bioactive compounds and pharmacological properties of *Gelidium*

Guiry 2022). In addition, genetic studies should be done to identify the species and also to investigate the genome diversity of *Gelidium* species. Study of genome sequencing, strain development, and genome editing technologies are needed to resolve the limitation of *Gelidium* species in producing bioactive compounds and other valuable products. Advanced tools for genetic engineering potentially can be used to enhance the capability of *Gelidium* in producing desired bioactive compounds.

The third challenge is to develop efficient and sustainable extraction and isolation techniques for bioactive compounds to fulfill industrial needs. Pharmaceutical, nutraceutical and cosmeceutical industries require efficient, affordable, high yields and sustainable extraction techniques. Advanced extraction techniques such as solvent, ultrasound-assisted (UAE), microwave-assisted (MAE), enzyme-assisted (EAE) and pressurized liquid (PLE) extractions (Nigam et al. 2021) need to be used. These advanced extraction techniques can enhance and improve the yield and productivity of bioactive compounds from *Gelidium* compared to conventional extraction techniques. Once these challenges are overcome, sustainable and productive bioactive production from *Gelidium* can be feasible.

Conclusion

Gelidium spp. contain a wide variety of bioactive compounds including R-phycoerythrin, phycocyanobilin, shinorine, porphyra-334, cholesterol and lumichrome which have potential applications in pharmaceutical and nutraceutical industries. Evidence shows that *Gelidium* spp. and their bioactive compounds have pharmacological properties, including anticancer, antioxidant, antimicrobial, anti-inflammatory, immunomodulatory, neuroprotective, antidiabetic, anti-photoaging, anti-obesity and many other bioactivities, which suggest that these marine natural products can be utilized in the development of therapeutic agents against chronic human diseases and can be incorporated as functional food ingredients to sustain healthy living. As highlighted in the Prospects and Challenges, the biotechnological approaches need to be exploited towards a sustainable supply of *Gelidium* biomass to ensure efficient industrial application of *Gelidium*.

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Data Availability Data supporting reported results are available upon request.

Declarations

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