frontiers | Frontiers in Marine Science

REVIEW
published: 22 June 2022
doi: 10.3389/fmars.2022.912924

Remarkable Natural Biological Resource of Algae for Medical Applications

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With increasing consumer awareness of the use of natural products in pharmaceuticals and medicine, it is noted that algae can be considered an appropriate source. Algae produce many bioactive components, which have application potential in pharmaceutical industries, such as fatty acids, phycobiliprotein, polysaccharides, phenolic compounds, carotenoids, and so on. However, it is still a long way before the truly widespread application of algae in medicine, and some research and technical bottlenecks still need to be resolved for further practical use. Here, we provide an in-depth review of the current understanding of algal-based medical application, with a focus on the main pharmaceutical activity and current application stage including *in vitro*, animal, and clinical studies. Furthermore, we propose some possible solutions to the obstacles that should be overcome for achieving the practical applications of algal-based medicine. Notably, animal and clinical studies on algal drugs and treatments should continue to push forward and expand for promoting the practical applications. Moreover, the developments in interdisciplinary research of algal biology and other disciplines provide new insight for driving algae-based medical application.

Keywords: algae, pharmaceutical activity, medical application, animal models, clinical studies, interdisciplinary research

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Specialty section:
This article was submitted to Marine Biotechnology and Bioproducts, a section of the journal Frontiers in Marine Science

Received: *08 April 2022*
Accepted: *26 May 2022*
Published: *22 June 2022*

Citation:
Dai N, Wang Q, Xu B and Chen H (2022) Remarkable Natural Biological Resource of Algae for Medical Applications. Front. Mar. Sci. 9:912924. doi: 10.3389/fmars.2022.912924

INTRODUCTION

Algae are polyphyletic, broad, and diverse group of unicellular-to-multicellular prokaryotic/eukaryotic organisms (Chen and Wang, 2021). Algae grow fast, and have simple structure and strong adaptability to different environments. They produce many bioactive components, some of which have found application potential in the cosmetics, health products and pharmaceutical industries (Blunt et al., 2017; Chen et al., 2020a). In recent years, dried algal biomass and algal-derived bioactive compounds, including fatty acids, polysaccharides, carotenoids, phycobiliprotein, terpenes, etc. (Blunt et al., 2015; Chojnacka and Kim, 2015; Chen et al., 2021b), have been widely

concerned in the screening and application of natural pharmaceuticals (Barsanti et al., 2011; Olasehinde et al., 2017; Iravani and Soufi, 2021).

Algae are currently classified into 10 major phyla (Cyanobacteria, Glaucophyta, Rhodophyta, Chlorophyta, Cryptophyta, Euglenozoa, Miozoa, Ochrophyta, Bacillariophyta, Charophyta), which vary greatly in size and can be divided into macroalgae and microalgae according to significant differences in shape and size (Parsaeimehr and Lutzu, 2016; Guiry and Guiry, 2022), both of which have been found to have great potential in the field of medicine. **Figure 1** shows potential pharmaceutical metabolites and corresponding representative alga genera in the 10 major phyla/classes.

Macroalgae (also called Seaweeds), a group of multicellular algae, have been proved to be important sources of bioactive compounds with diverse structures and high value in pharmaceutical industry and biomedical treatment (Mohy El-Din and Alagawany, 2019; Li et al., 2021b). The potential source of bioactive components includes fatty acids, protein, polysaccharide, and polyphenols, possessing potent anti-cancer, anti-bacterial, anti-viral, and anti-inflammatory properties (Haq et al., 2019; Kuznetsova et al., 2021). Aiming at the pharmaceutical potential of macroalgae, the common alga species that have been studied are brown algae *Ishige okamurae* (Kim et al., 2020), *Padina australis* (Santoso et al., 2013), *Sargassum hornschuchii* (Mohy El-Din and Alagawany, 2019) and *Sargassum fusiforme* (Zhang et al., 2020a); red algae, *Grateloupia chiangii* (Hwang et al., 2020), *Gelidium crinale* (Mohy El-Din and Alagawany, 2019), *Hypnea musciformis* (Souza et al., 2018), and *Palisada perforata* (formerly *Laurencia papillosa*) (Omar et al., 2018); green algae silpau (*Dictyosphaeria versluysii*) (Srimariana and Apituley, 2019), *Ulva rigida* (Mezghani et al., 2016), *Turbinaria ornata* (Deepak et al., 2017), and *Chaetomorpha* sp. (Haq et al., 2019). *Sargassum fusiforme* (Phaeophyceae), one of the most concerned macroalgae species in the research field of pharmaceutical applications, can possibly "treat goiter, tumor and neck mass, disperse bind of Qi and borborygmi in the upper and lower abdomen, and resolve twelve kinds of swellings", according to the records of "*Shen Nong's Canon of Materia Medica*" (Zhang et al., 2020a). The main possible pharmaceutical components in *Sargassum fusiforme* are polysaccharides, proteins, and

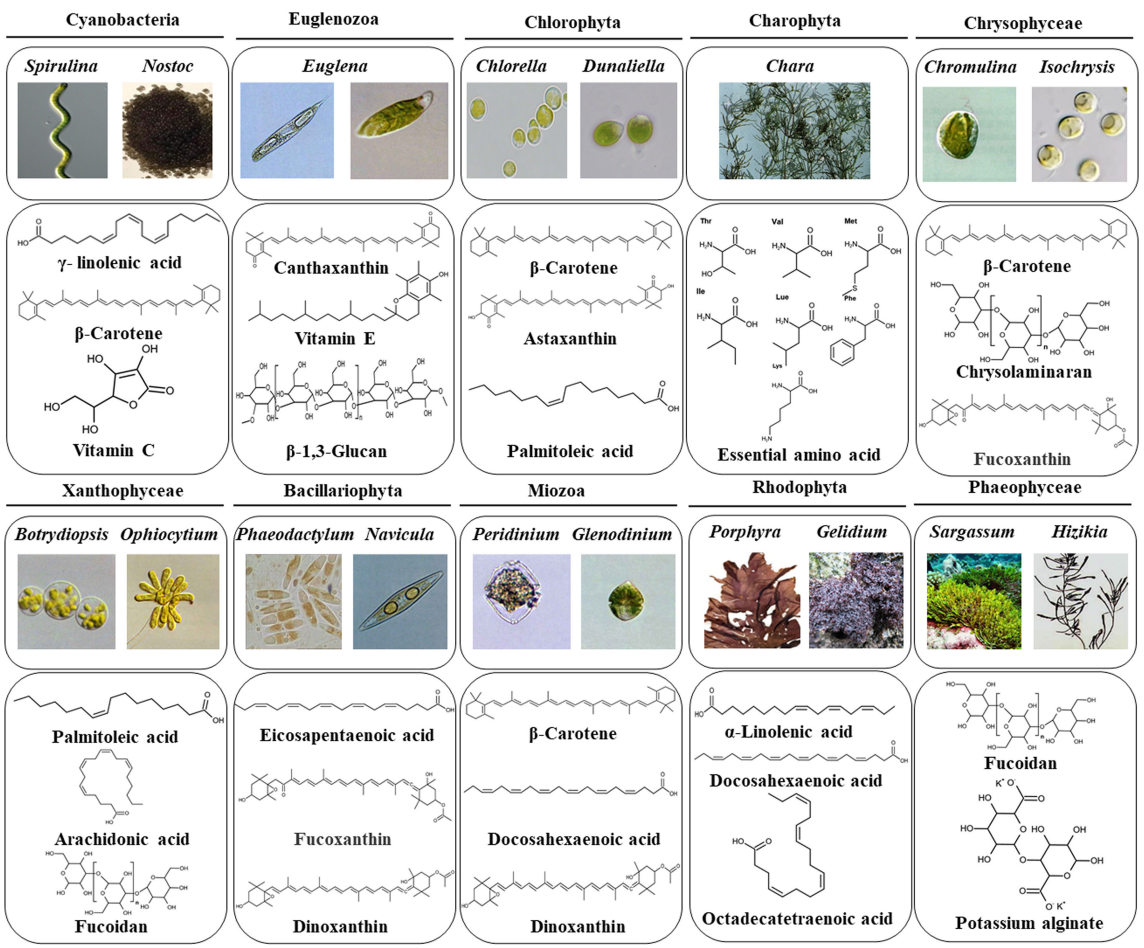

FIGURE 1 | Representative algae species and pharmaceutical components in ten major phyla/classes.

microelements, which play critical roles in anti-tumor, anti-aging, anti-virus, anti-bacteria, immunity, etc. (Jin et al., 2020; Zhang et al., 2020a).

In the research field of medical applications, microalgae have attracted more and more attention due to their diverse biological and pharmaceutical properties, such as the case with Cyanobacteria (*Nostoc*, *Aphanizomenon flos-aquae*, and *Arthrospira*/*Spirulina*, etc.) and some eukaryotic algae (*Chlorella*, *Dunaliella*, *Scenedesmus* - Chlorophyta, and *Cryptomonas* - Cryptophyta, etc.) (Martinez-Galero et al., 2016; Abidizadegan et al., 2021). Cyanobacteria are photosynthetic prokaryotes with numerous biological activities, having a wide range of applications in human health (Raja et al., 2016). *Spirulina* (also called *Arthrospira*) is a kind of microfilamentous Cyanobacteria, and is considered as a sustainable and eco-friendly microalga. The U.S. Food and Drug Administration (FDA) has classified *Spirulina* products as "generally recognized as safe" (GRAS) for human consumption, and the Dietary Supplements Information Expert Committee (DSI-EC) has concluded that the consumption of *Spirulina* would not cause serious health hazards (Marles et al., 2011).

For deep understanding of the current state of algal-based medical application, and exploring possible solutions to the current bottleneck, this review clarifies the current state of efforts to combine algae with the medical application and shows prospects for the future. It will provide a theoretical reference for researchers and decision makers in order to guide the future directions of algal and medical research, with particular regard to algae-based pharmaceuticals production and medical application.

PHARMACEUTICAL ACTIVE OF ALGAE–WHAT CAN ALGAE DO IN MEDICINE?

Abundant algae species and their metabolites show a variety of excellent pharmaceutical activities. In the early stage, microalgae biomass was applied in the form of tablets, powder and water agent, and its pharmaceutical effect was concerned. In recent years, more and more researches have turned to the identification and application of effective pharmaceutical components in algae. Algae produce a wide variety of bioactive metabolites, and some pharmaceutical components with most attention include fatty acids, phycobiliprotein, polysaccharides, phenolic compounds, and carotenoids, etc. (Maheswari et al., 2018). At present, the researches on the pharmaceutical application of algae mainly focused on anti-cancer, anti-bacterial and anti-viral, anti-hypertensive and anti-hyperglycemic, and so on (**Table 1**).

Anti-Cancer

Oxidative stress and reactive oxygen species (ROS) have been linked to a number of chronic human diseases, including some types of cancer (Galli et al., 2005). Thus, antioxidants have vital roles in carcinogenesis. Some algae produce a variety of secondary metabolites, which have significant antioxidant potential and exhibit anti-cancer activity against several types

TABLE 1 | The main algal pharmaceutical application.

Pharmaceutical application	Representative metabolites	Representative algae species	References
Anti-cancer	Polysaccharides Penichryfurans A	*Sargassum fusiforme* *Dictyota dichotoma* *Penicillium chrysogenum* inhabited *Grateloupia turuturu* (Rhodophyta)	(Dellai et al., 2013; El-Shaibany et al., 2020; Zhang et al., 2020a; Chen et al., 2021a)
Anti-bacterial	Chlorellin Fatty acids Terpenes Polysaccharides	*Chlorella vulgaris* *Sargassum fusiforme* *Chlamydomonas reinhardtii*	(Pratt et al., 1944; Manivasagan and Oh, 2016; Shannon and Abu-Ghannam, 2016; Vishwakarma and Vavilala, 2019)
Anti-viral	Sulfated polymannuroguluronate Diterpenes Polysaccharides Lectins	*Saccharina japonica* (Phaeophyceae) *Sargassum fusiforme* *Dictyota pfaffii* (formerly *Dictyota friabilis*) (Phaeophyceae) *Dictyota menstrualis* *Grateloupia chiangii*	(Barbosa et al., 2004; Pereira et al., 2004; Pereira et al., 2005; Wu et al., 2011; Hwang et al., 2020; Zhang et al., 2020a)
Anti-hypertensive	Phlorotannins	*Ecklonia cava*	(Wijesinghe et al., 2011)
Anti-hyperglycemic	Polysaccharides	*Sargassum fusiforme* *Sargassum pallidum*	(Cao et al., 2019a; Cao et al., 2019b; Jia et al., 2020a; Jia et al., 2020b)
Anti-inflammatory	Fucoxanthin	*Alsidium corallinum*	(Ben Saad et al., 2019; Liu et al., 2020)
Anti-obesity	Fucoxanthin	*Ascophyllum nodosum*	(Apostolidis and Lee, 2011)
Anti-aging	Polysaccharides Carotenoids Phenolics Fatty acids	*Sargassum fusiforme* *Scenedesmus rubescens* (Chlorophyta)	(Olasehinde et al., 2017; Campiche et al., 2018; Chen et al., 2020b)
Anti-coagulant	Sulphated fucoidan Phycocyanin	*Fucus vesiculosus* *Ascophyllum nodosum* *Arthrospira platensis* (Cyanobacteria)	(Nishino and Nagumo, 1991; 1992; Matou et al., 2002; Jensen et al., 2016)

of cancers (Dellai et al., 2013). Some studies have shown that *Sargassum fusiforme* polysaccharides could enhance the immune regulation of the body, induce tumor cell apoptosis, promote the expression of tumor suppressor genes, and inhibit tumor angiogenesis, showing a good anti-cancer activity (Zhang et al., 2020a).

The anti-cancer activity of algae is usually related to its antioxidant activity. However, a study showed that the extracts from brown algae *Dictyota dichotoma* had anti-cancer activity and a significant cytotoxic activity probably due to the presence of non-polar cytotoxic compounds, which is independent of its antioxidant capability (El-Shaibany et al., 2020). Interestingly, besides medical algae, some symbiotic bacteria of algae can also produce substances with cytotoxic activity for anti-cancer. In a study by Chen et al. (2021a), penichryfurans A (1), a new N-acetyl–glucosamine derivatives from an endophytic fungus *Penicillium chrysogenum* which inhabited *Grateloupia turuturu* (Rhodophyta), exhibited strong cytotoxicity towards the HepG2 cell line.

Anti-Bacterial and Anti-Viral

With increasing consumer awareness of the use of natural antimicrobial products, it is noted that algae could be considered as an appropriate source. The bactericidal and anti-bacterial compounds have been isolated from *Chlorella vulgaris* (Chlorophyta) for the first time, which have been shown to effectively inhibit some bacteria, such as *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Streptococcus pyogenes*, and *Bacillus subtilis* (Pratt et al., 1944). Some bioactive components in algae have been reported as bacterial inhibitors, such as fatty acids, terpenes, and polysaccharides (Shannon and Abu-Ghannam, 2016). The biocompatibility, biodegradability and nontoxicity of algal polysaccharides make them promising leads in the field of nanobiotechnological applications in drug delivery, wound dressing, and tissue engineering (Manivasagan and Oh, 2016). The anti-bacterial and anti-biofilm potential of polysaccharides extracted from *Chlamydomonas reinhardtii* (Chlorophyta) were evaluated, and showed that it could not only inhibit the formation of biofilm but also dissolve the preformed biofilms effectively, suggesting the broad application prospect as anti-biofilm agents (Vishwakarma and Vavilala, 2019).

Some algal metabolites also showed good potential in some anti-viral tests. Human immunodeficiency virus (HIV) is the retrovirus that causes acquired immune deficiency disease syndrome (AIDS). China's first anti-AIDS drug, a novel heparin-like sulfated polysaccharide (sulfated polymannuroguluronate, SPMG) extracted from brown alga *Saccharina japonica* (formerly *Laminaria japonica*) (Phaeophyceae), has entered Phase II clinical trials, demonstrating the pharmaceutical active of SPMG in inhibiting HIV replication and interfering with HIV entry into host T lymphocytes (Wu et al., 2011). Polysaccharides from *Sargassum fusiforme* also show the positive impact in inhibiting the infection and replication of HIV-1 at various stages of the viral life cycle (Zhang et al., 2020a). Two diterpenes from the brown algae *Dictyota friabilis* (formerly *Dictyota pfaffi*) and *Dictyota menstrualis*, (6R)-6-hydroxydichotoma-3,14-diene-1,17-dial and its acetate derivative, have been reported to be excellent inhibition against recombinant HIV-1 reverse transcriptase (Barbosa et al., 2004; Pereira et al., 2004; Pereira et al., 2005). In a study by Hwang et al. (2020), purification and structural characterization of a novel mannose-binding lectin in *Grateloupia chiangii* (Rhodophyta) (GCL) indicated that its mannose binding properties and tandem repeat structure might make it an anti-viral agent with anti-viral protective effect.

Anti-Hypertensive and Anti-Hyperglycemic

The phlorotannins isolated from the brown macroalga *Ecklonia cava* were reported for angiotensin-converting enzyme inhibitory effect (Wijesinghe et al., 2011). As the part of the renin angiotensin system, angiotensin I converting enzyme and angiotensin II converting enzyme could control blood pressure by regulating the volume of fluids in the body (Niu et al., 2002).

Different from monosaccharides or oligosaccharides, algal polysaccharides do not raise blood glucose level, but have hypoglycemic activity, which can regulate glucose metabolism disorders and insulin resistance by promoting insulin secretion through its hypoglycemic activity (Zhang et al., 2020a). For example, two polysaccharide fractions acquired from *Sargassum fusiforme* could significantly improve hyperglycemia, hyperlipidemia and liver and kidney function in diabetic rats (Jia et al., 2020b), and also promote glycogen synthesis in the liver and skeletal muscles (Jia et al., 2020a). In other studies, two polysaccharides isolated and purified from *Sargassum pallidum* also showed the remarkable abilities in enhancing glucose consumption, glycogen synthesis and the activities of pyruvate kinase and hexokinase in insulin-resistance HepG2 cells (Cao et al., 2019a; Cao et al., 2019b).

Other Medical Applications

Oxidative stress plays important roles in endothelial dysfunction (Schramm et al., 2012), lung disease (Paola Rosanna and Salvatore, 2012), and gastrointestinal dysfunction (Kim et al., 2012), all of which involve inflammatory reactions. A study showed that pre-treatment with red alga *Alsidium corallinum* reduced the hydrogen peroxide (H_2O_2)-induced toxicity in H9c2 cardiomyocytes, indicating the protective effect against H_2O_2-induced inflammatory responses (Ben Saad et al., 2019). Several studies have indicated that fucoxanthin, a natural product of carotenoids obtained from marine algae, has a potential protective effect on a variety of inflammation-related diseases, as its strong antioxidant capacity and gut microbiota regulation [as the review in detail by Liu et al. (2020)].

The imbalance of lipid metabolism leads to the formation of obesity. Many natural products derived from marine algae have been considered as valuable therapeutic targets for the treatment of obesity. For example, fucoxanthin are the bioactive components in brown algae that has received numerous attention, and their anti-obesity properties have been demonstrated in extensive work (Apostolidis and Lee, 2011).

A close relationship is between the prevention of oxidative damage and anti-aging. Polysaccharides derived from *Sargassum fusiforme* regulated anti-oxidant enzymes for scavenging excess free radicals, which prevented oxidative damage during the aging

process (Chen et al., 2020b). UV irradiation is a main cause of skin ageing, so protect skin from UV irradiation-induced damage is important for anti-aging. Campiche et al. (2018) found that a dry extract of the microalga *Scenedesmus rubescens* (Chlorophyta) was able to suppress cellular signs of ageing induced by UV irradiation, which may be used as a preventive or regenerative agent for anti-ageing strategies. The pathogenesis of Alzheimer's disease (AD) is also associated with oxidative stress, as well as cholinergic dysfunction, neuronal damage, protein misfolding and aggregation. Some microalgal bioactive compounds, such as carotenoids, phenolics and fatty acids, showed the anti-oxidant, anti-cholinesterase activities, and the inhibitory effects of β-amyloid aggregation and neuronal death, which could be used as pharmaceuticals with anti-oxidant and neuroprotective potentials for AD treatment (Olasehinde et al., 2017).

Fucoidan shows anti-coagulant activity, which increased with the increase of sulphation concentration when fucoidan and thrombin interact with each other directly (Nishino and Nagumo, 1991; Matou et al., 2002). Sulphated fucoidan, extracted from *Fucus vesiculosus* and *Ascophyllum nodosum*, have been granted patents related to its use as anti-coagulant substances (Nishino and Nagumo, 1992). An aqueous Cyanophyta extract from *Arthrospira platensis* (formerly *Spirulina platensis*) containing high doses of phycocyanin has showed safety in terms of markers of anti-coagulant activity and platelet activation status, and provided rapid and potent relief of chronic pain (Jensen et al., 2016).

PROGRESS AND STATUS—HOW FAR FROM PRACTICAL APPLICATION?

With more and more attention paid to the potential algal bioactive components and their pharmaceutical activities, researchers have continued to explore and evaluate the application of algae and its active components in disease treatment, with a view to realizing commercialization and practical application as soon as possible. Among them, the evaluation of algal products *in vitro*, animal, and clinical studies are the key step before the practically medical application of algal-derived pharmaceuticals. In order to better understand the progress and status of the application of algae in medicine, as well as how far it is from real practical, we summarize the medical application of algae products *in vitro*, animal, and clinical studies (**Table 2**).

In Vitro Studies

In vitro study is an effective way to screen potential drug candidates and identify drug targets. Many algae have been shown to have good pharmaceutical activity *in vitro* studies, and cyanobacteria are getting a lot of attention. Seddek et al. (2019) studied the anti-bacterial activities of three Cyanobacteria, *Nostoc oryzae* (formerly *Anabaena oryzae*), *Oscillatoria* sp., and *Stigonema ocellatum* extracts against human pathogenic fungi and bacterial strains, as well as the anti-oxidant and anti-cancer activities, and indicated that these extracts exhibited appreciable anti-microbial, anti-oxidant and anti-cancer activities. Ghosh et al. (2016) showed that purified pigments from three cyanobacterial species, *Lyngbya*, *Microcoleus* and *Synechocystis* sp., had the potent anti-oxidant and anti-hyperglycemic activities, which could be used as potential medicines for controlling postprandial hyperglycemia. Combining iso-bolographic analysis, bioactivity analysis and *in vitro* digestion studies, Paliwal et al. (2015) also pointed that phycobiliprotein-containing water and carotenoid-containing methanolic extracts of three different cyanobacteria, *Pseudanabaena* sp., *Spirulina* sp. and *Lyngbya* sp., showed different degrees of antioxidant and anti-nephrolithe activities. A report by Koníčková et al. (2014) showed that *Spirulina* not only had anti-proliferative effects, but also showed the anti-oxidant activity, inhibiting the production of mitochondrial ROS and affecting glutathione redox status. Sagara et al. (2015) reported that *Spirulina* extracts protected PC12 cells against iron-induced toxicity, which might protect against neurodegenerative disorders caused by excessive iron accumulation in the brain.

In recent years, the medicinal value of bioactive components derived from eukaryotic algae have been verified *in vitro* studies, particularly the studies on anti-cancer activity. The mechanism of anti-cancer effects of algae-derived astaxanthin has been investigated *in vitro* study (Kim et al., 2016). Various concentrations of astaxanthin were used to treat the human gastric adenocarcinoma cell lines, and the viabilities of cancer cell lines were suppressed by astaxanthin in a dose-dependent manner. Neumann et al. (2019) showed that fucoxanthin, another kind of carotenoid from *Phaeodactylum tricornutum* (Bacillariophyta), possessed antiproliferative and antioxidant activities *in vitro*. As another carotenoids-rich alga, a vitro study indicated that *Dunaliella salina* (Chlorophyta) had anti-oxidative, anti-proliferative, anti-inflammatory, and proapoptotic effects, and thus endorsed its anti-cancer effect on human oral squamous carcinoma cells (Chiu et al., 2017). Additionally, mycosporine-like amino acids are regarded as anti-cancer factors because of their anti-proliferative activities and antioxidant activities. Antioxidant activity of mycosporine-like amino acids isolated from red macroalgae *Neopyropia elongata* (formerly *Porphyra rosengurttii*) has been analysed *in vitro*, and the anti-photoaging role of asterina-330 has been examined, which affects initiating and mediating of the aging process (Coba et al., 2008). Three brominated sesquiterpenes (aplysistatin, palisadin A and palisadin B) from the methanol extract of red macroalga *Chondrophycus intermedius* (formerly *Laurencia intermedia*) showed the anti-microbial activities against human pathogen, and anti-cancer activities against human liver cancer (Hep-G2), breast cancer (MDA-MB-231) and muscle rhabdomyosarcoma (RD) cell lines (Tran et al., 2020). Polysaccharides have immunostimulating effects that cause inhabitation of tumor cell activity *in vitro*. For example, exopolysaccharides from the red microalga *Porphyridium purpureum* (formerly *Porphyridium cruentum*) has potential as an anti-cancer agent that inhibits the growth of different cancer

TABLE 2 | *In vitro*, animal, and clinical studies of pharmaceutical application of algae.

	Medicinal component	Medicinal application	Algae species	References
In vitro studies	Organic solvent extracts	Antimicrobial, antioxidant, and cytotoxic activity against breast cancer	*Nostoc oryzae* (formerly *Anabaena oryzae*), *Oscillatoria* sp. and *Stigonema ocellatum*	(Seddek et al., 2019)
	Purified pigments	Anti-oxidant and anti-hyperglycemic activities for controlling postprandial hyperglycemia	*Lyngbya*, *Microcoleus* and *Synechocystis* sp.	(Ghosh et al., 2016)
	Phycobiliprotein Carotenoid	Antioxidant and anti-nephrolithe activities	*Pseudanabaena* sp., *Spirulina* sp. and *Lyngbya* sp.	(Paliwal et al., 2015)
	Bilirubin-like tetrapyrrolic compounds	Anti-proliferative effects and antioxidant	*Arthrospira platensis* (Cyanobacteria)	(Koníčková et al., 2014)
	Cell extracts	Protect against neurodegenerative disorders	*Spirulina*	(Sagara et al., 2015)
	Astaxanthin	Anticancer effects against gastric adenocarcinoma	/	(Kim et al., 2016)
	Fucoxanthin	Antiproliferative and antioxidant activities	*Phaeodactylum tricornutum* (Bacillariophyta)	(Neumann et al., 2019)
	Carotenoids	Antioxidative, antiproliferative, anti-inflammatory, and proapoptotic effects against oral squamous carcinoma	*Dunaliella salina*	(Chiu et al., 2017)
	Brominated sesquiterpenes (aplysistatin, palisadin A and palisadin B)	Antimicrobial activities against human pathogen, and anticancer activities against liver cancer, breast cancer and muscle rhabdomyosarcoma	*Chondrophycus intermedius* (formerly *Laurencia intermedia*)	(Tran et al., 2020)
	Mycosporine-like amino acids asterina-330	Anti-photoaging role that affects initiating and mediating of the aging process	*Neopyropia elongate* (formerly *Porphyra rosengurttii*) (Rhodophyta)	(Coba et al., 2008)
	Exopolysaccharides	Anti-cancer agent that inhibits the growth of different cancer cell lines	*Porphyridium cruentum*	(Gardeva et al., 2009)
	Laminaran and fucoidan	Significant anti-tumor activity on SK-MEL-28 human melanoma cells	*Eisenia bicyclis*	(Ermakova et al., 2013)
	Laminaran and fucoidan	Effectively inhibit the colony formation of HT-29 cells	*Alaria marginata*	(Usoltseva Menshova et al., 2016)
	Fucoidan	Produce artificial bone scaffolds	/	(Venkatesan et al., 2014)
	Carrageenan	Carrageenan-based hydrogels improve the cartilage differentiation	/	(Rocha et al., 2011)
Animal studies	Polysaccharides	Antitumor and immunomodulatory activities in nasopharyngeal carcinoma	*Sargassum fusiforme*	(Fan et al., 2018)
	Polysaccharides	Anti-enterovirus 71 (EV71) activity	*Monostroma latissimum* (Chlorophyta)	(Wang et al., 2018)
	Cell extracts	Artificial skin tissue to positively affect viability and proliferation of mouse fibroblasts without cytotoxicity	*Spirulina*	(Jung et al., 2013)
	Lectin	Hypoglycemic and hypolipidemic effects, diminish insulin resistance, and ameliorate pancreatic beta-cell function along with enzymatic activities toward oxidative stress caused by diabetes	*Alsidium seaforthii* (formerly *Bryothamnion seaforthii*) (Rhodophyta)	(Alves et al., 2020)
	Fucoidan	Relieve the symptoms of diabetes and obesity; Anti-aging therapy (Alzheimer's disease)	*Sargassum fusiforme*	(Hu et al., 2016; Cheng et al., 2019; Wei et al., 2020; Zhang et al., 2020b)
	Ethanol extracts	Ameliorate memory impairment *via* anti-inflammatory, anti-oxidant and anti-amyloidogenic mechanisms	*Nannochloropsis oceanica* (Eustigmatophyceae)	(Choi et al., 2017)
	Cell extracts	Alleviate postmenopausal symptoms	*Sargassum fusiforme* and *Pueraria lobata*	(Lee et al., 2020)
	Oligosaccharides	Anti-ageing	*Ulva lactuca* and *Ulva prolifera* (Chlorophyta)	(Liu et al., 2019)
	Biomass	Mitigate the toxic effects induced by lead	*Spirulina*	(Gargouri et al., 2016)
	Biomass	Improve spermatogenesis and steroidogenesis after Cd exposure	*Arthrospira platensis* (Cyanobacteria)	(Farag et al., 2016)
	Biomass	Protect liver tissues from CCl_4 and gamma-radiation-induced hepatotoxicity	*Arthrospira platensis* (Cyanobacteria)	(Enas et al., 2017)
	PUFAs	Hepato- and reno-protective effect against nickel-induced toxicity	*Dunaliella* sp.	(Dahmen-Ben Moussa et al., 2016)
	Biomass	Protect against anti-tuberculosis drugs-induced oxidative stress in kidney tissues	*Limnospira fusiformis* (Cyanobacteria)	(Martin and Sabina, 2016)
	Biomass	Hepato-renal and gastroprotective activity		(Peter et al., 2017)

(Continued)

TABLE 2 | Continued

	Medicinal component	Medicinal application	Algae species	References
			Limnospira fusiformis (Cyanobacteria)	
	Biomass	Protective effects on vancomycin-induced renal cortical oxidative stress	*Spirulina*	(Bayomy et al., 2016)
Clinical	Biomass	Improve antioxidant status of COPD patients	*Spirulina*	(Ismail et al., 2015)
studies	Calcium spirulan (Ca-SP)	Promising efficacy in the treatment of oral diseases	*Spirulina platensis*	(Mader et al., 2016)
	Biomass	Putative beneficial cardiovascular effects on well treated, obesity-related hypertension	*Limnospira maxima* (formerly *Spirulina maxima*) (Cyanobacteria)	(Szulinska et al., 2017)
	Biomass	Increase people's ability to resist mental and physical fatigue	*Spirulina*	(Johnson et al., 2016)
	Alginate	β-cell islet encapsulation for the treatment of type I diabetes, choroid plexus cell encapsulation for Parkinson's disease, and glucagon peptide-1 transfected mesenchymal cell encapsulation for the treatment of space occupying intracerebral hemorrhage	/	(Andersen et al., 2011)
	Griffithsin	Anti-HIV pre-exposure prophylactic	/	(Lee, 2019)
	Cell extract	Improve physical and cognitive symptoms of depression as well as anxiety symptoms in patients who were receiving standard antidepressant therapy	*Chlorella vulgaris*	(Panahi et al., 2015)
	Aqueous cyanophyta extract	Anticoagulant activity and platelet activation	*Arthrospira platensis* (Cyanobacteria)	(Jensen et al., 2016)
	(poly)phenols	Modest decrease in DNA damage in a subset of the total population who were obese	*Ascophyllum nodosum*	(Baldrick et al., 2018)

cell lines (Gardeva et al., 2009). In other studies, the polysaccharide did not show direct cytotoxicity, but exhibited significant anti-tumor activity on SK-MEL-28 human melanoma cells and could effectively inhibit the colony formation of HT-29 cells (Ermakova et al., 2013; Usoltseva Menshova et al., 2016).

Algae-derived bioactive substances are also used in regenerative medicine. For example, chitosan-alginate with fucoidan has been constructed by using freeze-drying technique to produce artificial bone scaffolds, and revealed profound cytocompatibility, enhanced cell proliferation, and increased alkaline phosphatase secretion compared to the chitosan-alginate scaffolds *in vitro* analyses using the MG-63 cell line (Venkatesan et al., 2014). Carrageenan-based hydrogels were utilized for encapsulation of both cells and transforming growth factor-β1 (TGFβ1), and human adipose-derived stem cells (hASCs) encapsulated with TGF-β1 improved the cartilage differentiation of hASCs (Rocha et al., 2011).

Animal Studies

Animal study is important step before a drug can enter clinical or practical application. After drug candidates are identified *in vitro*, one of the key stages of preclinical research is to understand drug absorption, distribution, metabolism, and excretion using animal models, which can guide clinical research on the form of administration (oral, inhaled, injection), administration frequency and dose. Animal study can also assess the possible side effects and toxicity of drugs beyond the target disease.

Several animal-based studies have examined the pharmaceutical activity of algae in anti-cancer. The anti-cancer effects of *Sargassum fusiforme* polysaccharides on nasopharyngeal carcinoma were investigated in mice, and it was showed that polysaccharides had anti-tumor and immunomodulatory activities in nasopharyngeal carcinoma (Fan et al., 2018). *Monostroma latissimum* (Chlorophyta) polysaccharides showed the anti-enterovirus 71 (EV71) activity, which markedly improved survival and decreased viral titers in EV71-infected mice (Wang et al., 2018). A study evaluating *Spirulina* extract-imbedded nanofiber as a scaffold for an artificial skin tissue demonstrated a positive effect on the viability and proliferation of mouse fibroblasts without cytotoxicity (Jung et al., 2013).

Algae and their bioactive components provided a novel perspective into the treatment strategy on metabolic disease. The lectin isolated from the red alga *Alsidium seaforthii* (formerly *Bryothamnion seaforthii*) might exert hypoglycemic and hypolipidemic effects in rats with streptozotocin-induced diabetes, reducing insulin resistance and improving pancreatic beta-cell function along with enzymatic activities in response to oxidative stress caused by type 2 diabetes (Alves et al., 2020). In another study, *Sargassum fusiforme* fucoidan could significantly relieve the symptoms of diabetes by decreasing the relative abundances of the diabetes-related intestinal bacteria in streptozotocin-induced diabetic mice (Cheng et al., 2019). Zhang et al. (2020b) investigated the effects of *Sargassum fusiforme* fucoidan on obesity-associated insulin resistance, oxidative stress, serum biochemical parameters, and pathological changes in liver and intestine of high-fat diet (HFD)-fed mice, which was suggested that fucoidan could improve HFD-induced insulin resistance by activating the Nrf2 pathway, remodeling gut microbiota, and reducing intestinal inflammation. In addition, five polysaccharides prepared from *Sargassum fusiforme* could significantly prevent early fasting hypoglycemia without inducing hyperglycemia, and prevent HFD-induced weight gain in C57BL/6J male mice fed an HFD for 4 weeks (Wei et al., 2020).

Aging leads to a gradual decline in cell protection and physiological function. The application of algae in anti-aging therapy has been concerned and studied. A polysaccharide fucoidan isolated from *Sargassum fusiforme* exhibited a positive contribution to AD treatment in the pharmacological experiments to combat memory deficits by increasing the cognitive abilities in mice treated with scopolamine, ethanol, and sodium nitrite (Hu et al., 2016). Through the study of the suppressive possibility of *Nannochloropsis oceanica* extracts on memory deficiency in lipopolysaccharide treated mice model, it was suggested that the extracts could ameliorate memory deficit in mice by anti-inflammatory, anti-oxidant and anti-amyloidogenic mechanisms (Choi et al., 2017). Estrogen deficiency due to menopause can lead to overweight, dyslipidemia, and osteoporosis. Addition of extracts of *Sargassum fusiforme* (Phaeophyceae) and *Pueraria lobata* (Plantae, Magnoliophyta) at ratios of 3:1 showed the potential for alleviating postmenopausal symptoms in ovariectomized rats, including overweight, dyslipidemia, and osteoporosis (Lee et al., 2020). The anti-ageing effects of oligosaccharides from green algae *Ulva lactuca* and *Ulva prolifera* (formerly *Enteromorpha prolifera*) were also investigated in mice, and it was demonstrated that these oligosaccharides were ideal candidate compounds used in pharmaceuticals for preventing ageing (Liu et al., 2019).

Algae have been shown to be effective in alleviating the damage due to environmental exposure to toxic substances, for example, heavy metals. The potent protective effects of *Spirulina* on the liver tissue of neonatal rats from prenatal exposure to lead was evaluated, and it was showed that the toxic effects induced by lead were mitigated by supplemental *Spirulina* in the mother rats (Gargouri et al., 2016). Another study evaluated the effects of *Arthrospira platensis* (formerly *Spirulina platensis*) on the improvement of reproductive dysfunctions induced by cadmium chloride ($CdCl_2$) in male rats, suggesting that it significantly reduced the harmful effects of Cd and promoted beneficial effects in spermatogenesis and steroidogenesis after Cd exposure (Farag et al., 2016). In addition, *Arthrospira platensis* interference with radical mediated cell death and inflammation would protect liver tissues from CCl_4 and gamma-radiation-induced hepatotoxicity in male albino rats (Enas et al., 2017). The lipid extract of *Dunaliella* sp. rich in PUFAs showed a significant hepato- and reno-protective effect against nickel-induced toxicity in experimental rats (Dahmen-Ben Moussa et al., 2016).

In addition to the beneficial action, several clinical drugs also resulted in some harmful side effects when they were used for long periods undergo biotransformation in the liver or kidney. *Limnospira fusiformis* (formerly *Spirulina fusiformis*) has been reported to be render protection against anti-tuberculosis drugs-induced oxidative stress and nephrotoxicity in kidney tissues of rats (Martin and Sabina, 2016), and the hepato-renal and gastroprotective activity in diclofenac-treated rats (Peter et al., 2017). *Spirulina* and pycnogenol alone or in combination showed the protective effects on vancomycin-induced oxidative stress in the renal cortex of rats, and the combination therapy showed better protective effects than that of single use (Bayomy et al., 2016).

Clinical Studies

After a drug has passed preclinical trials in animal studies, it can be tried for human trials through a clinical application to the drug regulatory agency. The potential clinical uses of algae have been studied. However, in contrast to animal studies, there are a relative low number of clinical studies to evaluate the pharmaceutical activities in humans.

In clinical studies, *Spirulina* has shown promising efficacy with good anti-oxidant and anti-inflammatory effects on treatment of patients with chronic obstructive pulmonary disease (COPD) (Ismail et al., 2015) and oral disease (Mader et al., 2016). *Spirulina* supplementation has demonstrated beneficial cardiovascular effects on obesity-related hypertension in a double-blind placebo-controlled trial, offering a new treatment option for obese patients with hypertension (Szulinska et al., 2017). In addition, in another randomized, double-blind, placebo-controlled study of men, *Spirulina* increased people's ability to resist mental and physical fatigue (Johnson et al., 2016).

Algae-derived alginate has been investigated clinically for several applications, such as β-cell islet encapsulation for the treatment of type I diabetes, choroid plexus cell encapsulation for Parkinson's disease, and glucagon peptide-1 transfected mesenchymal cell encapsulation for the treatment of space occupying intracerebral hemorrhage, and several others (https://clinicaltrials.gov.) (Andersen et al., 2011). Also, clinical investigation confirmed the promising potential of alginate-based approaches for myocardial repair and regeneration (Ruvinov and Cohen, 2016).

A red algae-derived griffithsin (GRFT) protein showed great promise as the first topical protein-based anti-HIV pre-exposure prophylactic (Lee, 2019). Two phase I clinical studies have begun investigating the potential toxicity of GRFT in healthy people. According to Population Council website, GRFT could be safely used in the vagina for up to 14 days with potent anti-HIV activity, and cervical explants could be performed up to 8 hours after receiving the dose (https://www.popcouncil.org/research/developing-and-testing-a-griffithsin-non-arv-microbicide). Another phase I clinical study of GRFT was launched during 2014-2021 (https://clinicaltrials.gov/ct2/show/NCT04032717?term=griffithsin&rank=2). It was intended as an integrated preclinical/clinical program to provide a comprehensive set of data to facilitate informed decisions on whether GRFT should progress in the 5 topical microbicides pipeline.

In addition, the clinical efficacy of algae in other diseases or biomedical application are constantly being evaluated. A 6-week randomized controlled trial has provided the clinical evidence of the efficacy and safety of *Chlorella vulgaris* supplementation in adjunctive therapy of patients with major depressive disorder, and it improved the physical and cognitive symptoms of depression and anxiety symptoms in patients receiving standard antidepressant therapy (Panahi et al., 2015). In a study evaluating the safety of anti-coagulant activity and platelet activation in the daily consumption of an aqueous cyanophyta extract with high dose of phycocyanin, consumption of aqueous cyanophyta extract showed safety as

well as rapid and robust relief of chronic pain (Jensen et al., 2016). In a randomized, double-blind, placebo-controlled crossover trial, consumption of the *Ascophyllum nodosum* (poly)phenols reduced DNA damage moderately, but only in some obese people (Baldrick et al., 2018).

Algae Pharmaceutical Industrialization

According to Credence Research, the global market for algae products was valued at $33.9 billion in 2018 and is expected to reach $56.5 billion by 2027, at a compound annual growth rate of 6.0% from 2019 (Available: https://www.credenceresearch.com/report/algae-products-market). In addition, according to Meticulous Research, the microalgae market projected to reach $1.8 billion by 2028, at a compound annual growth rate of 10.3% from 2021 (Available: https://www.meticulousresearch.com/download-sample-report/cp_id=5197). The growth of algae market is mainly attributed to the inclination towards health and wellness trends and growing dietary supplements industry, growing demand for natural food colors, growing vegetarianism, growing nutraceutical industry, and increasing preference for algae-sourced products. However, low awareness about the benefits of algae, the complex production process of algae products, and excessively high production costs of microalgal bio-products, are expected to hinder the growth of the overall algae market to some extent.

However, although algae have been commercially developed for several decades, at present, the commercial application of algae products is only distributed in a few industries, including food, food and nutritional additives, aquatic and animal feeds, water control agents, bio-fertilizers, skin care products and bio-plastics (**Table 3**, according to https://www.sohu.com/a/454992617_99988077), and there are no commercial pharmaceutical products. By comparison, the market potential and economic benefit prospect of algae pharmaceutical market are huge. The global pharmaceutical markets are growing every year, which could reach the worth of $1170 billion in 2021 (Mishra et al., 2021). Market demand for algal products with pharmaceutical potential is also growing rapidly, which have been extensively explored in the nutraceutical market and is expected to expand into medicine market. For example, the global market values of polyunsaturated fatty acids, beta-carotene, astaxanthin, lutein and phycobilin will exceed $700 million, $261 million, $240 million, $233 million and $60 million per year, respectively (Markou and Nerantzis, 2013). Thus, the pharmaceutical activity and clinical evaluation of algal products need to be further promoted to promote the commercialization of algal products.

The biggest challenge to the commercialization of algal products is high cost, of which culture accounts for 70% of the total production cost. How to optimize the cultivation strategy to get as much biomass and target products in unit area at a low cost is an urgent problem to be solved. In particular, algal cultivation is limited by the cost of production balanced against the value of the end-product, and the high cost of the resources required for algal cultivation, including water, inorganic nutrients (mainly nitrogen and phosphate), and CO_2, hinders the commercialization of algal production (Chen et al., 2020a). The culture medium can be recycled to reduce the cost of large volume of water consumption in algal cultivation, and the components in some wastes, such as flue gas (mainly NOx and CO_2), wastewater (mainly C, N and P) and waste residue (mainly Mg, K, Ca, P, Fe, etc.), have been confirmed to be used by algae as nutrient elements for algal culture (Chen et al., 2016; Chen et al., 2018; Wang et al., 2019; Tan et al., 2020). For example, the input of industrial waste as nutrient element in the mixotrophic cultivation mode can reduce production cost, which can obtain higher biomass than the autotrophic or even heterotrophic culture mode (Chen et al., 2016; Zhan et al., 2017; Chen and Wang, 2020). Also, it should be paid to improve the design of bioreactors for improving photosynthetic efficiency and reducing culture consumption. For example, thin-film flat plate photo-bioreactors and biofilm photo-bioreactors offered many advantages over conventional cultures, such as lower water use, higher light penetration efficiency, easier harvesting, less contamination, and easier scale-up (Sun et al., 2019; Wu et al., 2019).

Furthermore, in order to optimize the cultivation strategy to improve the yield of biomass and bio-products, the deep understanding of metabolic flow and its regulation is the basis, and it is important to understand the molecular mechanisms of carbon fixation and partitioning to control and regulate biomass and bio-products production. Kareya et al. (2021) investigated the metabolic and physiological responses of a freshwater microalga, *Chlorella saccharophila*, supplemented with very low CO_2 (VLC) and high CO_2 (HC), which demonstrated that HC enhanced cell growth and total pigment productivity, but VLC increased the accumulation of sugars and antioxidants such as trehalose and α-tocopherol. The study provided valuable reference for improving the production of algal high-value bio-renewable resources by regulating CO_2.

In addition, in the production process of algal culture to produce bio-products, specific chemicals are used to dynamically divert carbon flux towards the biosynthesis of target metabolites, providing an effective non-gene interference strategy for sustainable and cost-effective algal biorefinery. For instance, Paliwal and Jutur (2021) proved that chemical molecules Brefeldin, Jasmonic acid and acetylcholine enhanced the biosynthesis of total tocopherols and β-carotene in microalgae *Scenedesmus dimorphus* UTEX1237, and propyl gallate, forskolin, Brefeldin and Jasmonic acid were involved in increasing the total carotenoid productivity. In other studies, Franz et al. (2013) demonstrated that several bioactive molecules, such as forskolin, quinacrine, epigallocatechin gallate and butylated hydroxyanisole, could increase lipid levels while maintaining or increasing the specific cell growth rate of four strains of oleaginous microalgae (*Nannochloropsis salina*, *Nannochloropsis oculata*, *Nannochloris* sp., and *Phaeodactylum tricornutum*), and Burch and Franz (2016) pointed out combined nitrogen limitation and hydrogen peroxide treatment enhanced neutral lipid accumulation in the marine diatom *Phaeodactylum tricornutum*.

TABLE 3 | The stage of microalgae application in various industries.

	Development stage				
	Research	**Pilot**	**Demonstration**	**Application and promotion**	**Commercialization**
Food industry					
Food and food additives					√
Edible oil				√	
Health industry					
Nutritional supplements					√
Fishery industry					
Aquatic bait				√	√
Water control agents				√	√
Aquatic feed				√	√
Aquatic vaccine	√	√			
Agricultural industry					
Animal feed				√	√
Bio-fertilizers				√	√
Skin care and cosmeceuticals industry					
Skin care product				√	√
Material industry					
Bio-plastics				√	√
Environmental protection industry					
Biological carbon sequestration		√	√		
Waste water treatment			√	√	
Energy industry					
Bio-energy		√	√		
Architecture and art industry					
Microalgal architecture			√	√	
Aerospace industry					
Controlled ecological life support system	√	√			

Symbol √ indicates that the microalgae industry (row) is at the development stage indicated in this column.

THE CROSS-DISCIPLINE WITH MATERIAL SCIENCE HAS PROMOTED THE DEVELOPMENT OF ALGAE-BASED MEDICAL APPLICATION

Nowadays, the trend to apply biological materials and their synthetic derivatives in medical materials and treatments is growing, which could also boost algae-based medical application. For example, the potential therapeutic effects of fucoxanthin on tumor intervention have been well documented, but its utilization is limited by low water solubility, poor stability, and limited bio-accessibility. Nano/micro-encapsulation, a technology developing based on natural edible materials (such as whey protein, casein, zein, gelatin, and starch) and advanced processing techniques, have proven to be effective in stabilizing and enhancing the bio-accessibility of fucoxanthin (as the review in detail by Wang et al. (2020)).

Algal-based materials, which can be further processed into scaffolds, hydrogels, nanofibers, and films (Hernández-González et al., 2020), have shown various applications in tissue engineering and regenerative medicine. As an example, a fucoidan-chitosan structure was designed as burn injuries healing accelerator on rabbits, due to its hydrogel-forming features and suitability for wound dressing in addition to the anticoagulant effect of fucoidan (Sezer et al., 2008). Micro- and nanofibrous scaffolds were successfully prepared by applying fucoidan and polycaprolactone *via* an electrospinning technique for bone regenerative applications (Lee et al., 2012). And what makes sense is, algae-sulfated polysaccharides with anti-inflammatory characteristics can be employed for designing immunomodulatory biomaterials, which provides an important solution in tissue engineering for controlling the immune responses (Amin et al., 2020). Overall, algal-based materials with their unique structures, physical and chemical features, and therapeutic activities can reduce the consumption of expensive and hazardous materials, decrease the toxicity, and improve the biocompatibility for fabricating scaffolds (Iravani and Soufi, 2021), which have shown promising potentials in regenerative medicine and tissue engineering purposes, but there are very limited in animal and clinical studies and future studies should be conducted.

Nanotechnology is an interdisciplinary field with great potential, and using a biosystem to synthesize nanomaterials has emerged as a new branch of nanotechnology (Khan et al., 2019). Algae with abundant bioactive molecules have been recently acknowledged as the perfect bio-based platform for the extracellular synthesis of nanoparticles (Li et al., 2021a), which is a good substitute for hazardous and costly chemical and physical methods. Biosynthesis silver nanoparticles (AgNPs) have received a lot of attention as a cytotoxic and antimicrobial activity against pathogenic bacteria, and it also the common biogenic synthesis of metal nanoparticles based on algae. In a study by Yugay et al. (2020), polysaccharides isolated

from marine algae *Saccharina cichorioides* and *Fucus distichus* subsp. *evanescens* (formerly *Fucus evanescens*) (Phaeophyceae) were used as a reducing and stabilizing agent in the biogenic synthesis of silver nanoparticles, which possessed considerable antibacterial properties. A red algae *Gelidium corneum* extract was used as reducing agent for green synthesis of silver nanoparticles with 20-50 nm, which showed a high antimicrobial activity (Yılmaz Öztürk et al., 2020). Furthermore, some algae, such as *Ulva intestinalis* (formerly *Enteromorpha intestinalis*) (Chlorophyta) (Haglan et al., 2020), *Ellisolandia elongate* (formerly *Corallina elongate*), *Gelidium amansii* (Rhodophyta) (Hamouda et al., 2019), *Dunaliella salina* (Chlorophyta) (Singh et al., 2017), *Dictyota mertensii* (Phaeophyceae) (Fernandes-Negreiros et al., 2017), *Chloroidium ellipsoideum* (formerly *Chlorella ellipsoidea*) (Chlorophyta) (Borah et al., 2020), *Oscillatoria* sp. and *Arthrospira platensis* (Cyanobacteria) (El-Sheekh et al., 2020), have also been reported to be used for biosynthesis of silver nanoparticles and exhibited antimicrobial, antibacterial, anticancer, antiproliferative, immunomodulatory activity. Similarly, biosynthesis of some other metals nanoparticles based on the extracts of algae have been proven their medical benefits. A study reported the biosynthesis of CuO NPs *via* ultrasound method using the *Sirophysalis trinodis* (formerly *Cystoseira trinodis*) (Phaeophyceae) extracts as an eco-friendly and time saving process, which showed the significant antioxidant and antibacterial activity (Gu et al., 2018). The extract of green microalga *Botryococcus braunii* was used for the synthesis of copper and silver nanoparticles, which were found to be highly toxic against two Gram-negative bacterial strains, two Gram-positive bacterial strains, and a fungal strain (Arya et al., 2018). In another study, two samples of iron oxide nanoparticles (Fe_3O_4-NPs) have been synthesized using brown (*Colpomenia sinuosa*) and red (*Pterocladia capillacea*) macroalgae aqueous extracts, exhibiting wide spectrum of antibacterial potency (Salem et al., 2019). In addition, Phycocyanin-functionalized selenium nanoparticles (PC-SeNPs) were synthesized and showed the *in vitro* protective effects on INS-1E rat insulinoma beta cells against PA-induced cell death (Liu et al., 2017). However, as a new interdisciplinary research field and technology application, there are very limited *in vivo* and clinical studies, and future studies should be conducted toward the animal and clinical analysis of these materials for medical applications.

PROSPECT

Algae may be a rich resource of new compounds that have not yet been fully exploited and have considerable potential as drugs and nutritional supplements. However, some research and technical bottlenecks still need to be resolved for further practical use.

Since the differences of biomolecular properties among different algal taxa, it is necessary to conduct extensive research to find biomolecules with high bioactivity. How do and at what extent these biomolecules work against diseases remains elusive. Still, there is considerable scope in the study of algal pharmaceutical activity, including elucidating the exact mode of action, measuring pharmacological parameters, and developing novel formulation from the algal biomolecules. Furthermore, the composition of the metabolites in algae is complicated, different sources of algal biomass material, extraction and purification technologies, and bioactive components with various molecular weight are factors that affect the pharmaceutical activities and production costs. The development of some new technologies, such synthetic biology, genetic engineering, metabolic engineering, and total chemical synthesis, offers the solution of the supplement source of pharmacologically activity natural compounds, which is also beneficial to further study the chemical structure-activity relationship to optimize the drug activity.

Current reports of animal and clinical studies are insufficient to validate and confirm established *in vitro* reports. For example, the effects of specific bioactive compounds isolated from algae on different pathological stages and involved targets of different disease development need to be further validated in animal and clinical studies. In addition, possible heavy metal contamination and possible side effects of pharmaceutical ingredients and other metabolites in algae on humans are also issues that need to be assessed to systemically establish the safety profile of algae in various target people. It is therefore important that the more experimental researches should continue to focus on animal and clinical researches in the future.

The high production cost of algal biological products is another challenge hindering their commercialization and popularity. In order to truly realize the industrialization and meet the needs of the vast number of consumers for medical applications of biological products, the availability of biomass and yield should match with industrial production at manageable costs. Promoting algae basic biology research, especially improving the photosynthesis efficiency and optimizing metabolic pathways to significantly increase algae biomass and target metabolites to meet the needs of industrial production, is the fundamental problem to be solved in the future. In particular, increase algal biomass and bio-products yields while reducing cost per unit area and optimize culture process and equipment in terms of cost and energy consumption for large-scale algal culture are urgent problems and research directions in the future. To reduce costs, waste products should be recycled, including wastewater and waste gas, thus the development of technology processes to efficiently utilize nutrients in wastes for the algal culture is also a future direction that needs attention.

Specifically, future efforts should aim to (1) promote algae basic biology research to obtain high biomass economically and develop new technologies and equipment to solve problems in algal culture, harvest, extraction and purification of active compounds, and screening and preparation of new compounds; (2) continue to push forward and expand animal and clinical studies to validate and confirm the established *in vitro* reports; and

(3) the technological developments in interdisciplinary research of algal biology and other disciplines (e.g. material science) will be a possible direction to promote the medical application of algal pharmaceutical components. Although challenges remain in implementing algae-based pharmaceutical and medical application and commercialization, it has a promising future.

AUTHOR CONTRIBUTIONS

HC designed the review; ND, QW, BX, and HC collected, analyzed, summarized, and discussed the references and data; ND wrote the manuscript and HC edited it. All authors contributed to the article and approved the submitted version.

FUNDING

This work was supported jointly by the National Key R&D Program of China (2021YFA0909600), the National Natural Science Foundation of China (31870041 and 32170138), the Natural Science Foundation of Henan Province (212300410024), the Program for Innovative Research Team (in Science and Technology) in University of Henan Province (22IRTSTHN024), and the 111 Project (#D16014).

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