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## RESEARCH ARTICLE

# BIOACTIVITIES AND POTENTIAL APPLICATION OF INDIAN RED AND BROWN ALGAE IN PHARMACEUTICS

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## Abstract

A wide variety of red (Rhodophyta) and brown (Phaeophyceae) algae in Indian marine ecosystems possess an abundant and sustainable supply of bioactive compounds of considerable pharmacological importance. These macroalgae synthesise a wide variety of secondary metabolites (sulfated polysaccharides such as carrageenan and fucoidan, phlorotannins, polyphenols, sterols, flavonoids, and others). Recent studies have focused on their potential applicability in anticancer, antidiabetic, antioxidant, anti-inflammatory, antimicrobial, neuroprotective, antihypertensive, and anti-obesity activities. The therapeutic potential of Indian red and brown algae and their bioactivities and mechanisms of action are discussed and reviewed in this article. Special attention is given to algae such as *Gracilaria edulis*, *Kappaphycus alvarezii*, *Turbinaria conoides* and *Padina tetrastrum*. We also review these effects on a pharmacological level and address the limitations that exist in terms of clinical validation, standardisation, and bioavailability. The review highlights the requirement for further in vivo and translational studies, in combination with new biotechnological methods, to exploit these marine products for drug production. The sustainability of the Indian algae growing environment, as well as its bioactive richness, has potential for further use in the pharma and nutritional industries.

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## Introduction:-

Marine algae were traditionally used for food, agriculture and folk medicine along the coastlines of the world. Over the past few decades, scientific studies have shown that red (Rhodophyta) and brown (Phaeophyceae) seaweeds are prolific sources of exciting bioactive molecules with numerous uses beneficial for human life. They are, namely, the sulfated polysaccharides (carrageenan, fucoidan), phenolic compounds (phlorotannins), and other secondary metabolites including flavonoids, terpenoids, sterols, and peptides [1-4]. Taken together, these compounds have shown antioxidant, anti-inflammatory, anticancer, antidiabetic, antimicrobial, antithrombotic, neuroprotective, and antihypertensive effects in preclinical studies [2,5].

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India, with about 7500 km of coastline and diverse marine ecosystems, harbours hundreds of species of red and brown algae. Here, the most important are *Gracilaria edulis*, *Gelidiella acerosa*, *Hypnea musciformis* (red algae) and *Sargassum wightii*, *Turbinaria conoides* and *Padina tetrastrum* (brown algae) that have been reported with valuable pharmacological properties [6–8]. Owing to the growing resistance of synthetic drugs and consumer demand for green therapeutic agents, the Indian marine algae serve as potential sources of drug candidates as well as functional foods [9].

Although many in vitro and in vivo studies have proven their potential, commercial and clinical translation of algal therapeutics is premature. However, their pharmaceutical development has been restricted due to issues like metabolite content instability, standardisation of extraction methods, low bioavailability, and lack of clinical validation [10,11].

This review offers a detailed summary of the bioactivities of Indian red and brown algae, focusing on their pharmacological mechanisms and therapeutic utility. It also highlights important research gaps and outlines strategies for their future development as natural alternatives for synthetic drugs used in the management of chronic diseases.

#### **Anticancer Activity:**

Cancer is a complex disease that is defined by the unrestricted growth of malignant cells that infiltrate healthy tissues and spread to other sites. It is still responsible for a substantial proportion of deaths in the world, leading to an estimated 10 million fatalities and over 19 million new cases in 2020. Of these, the most commonly diagnosed cancers are breast, lung, colon and rectum, prostate, skin, and stomach, whereas cervical cancer continues to be a significant health problem in many developing countries [12].

Many therapeutic modalities, such as surgery, chemotherapy, radiotherapy, immunotherapy, targeted therapy, and stem cell transplantation, have markedly enhanced the treatment of cancer. But these treatments often induce toxic effects, high cost and drug resistance; therefore, it is desirable to find a safer and effective drug against both diseases [13].

Nature is still a very rich reservoir of anticancer compounds and many drugs used in chemotherapy, including paclitaxel, vincristine, doxorubicin and actinomycin D, derived from plants and micro-organisms. Marine natural products have also attracted attention for their chemical diversity, bioactivities and unique purposes. Of these, red and brown macroalgae are being considered as promising candidates, owing to the high levels of sulfated polysaccharides, phlorotannins, and sterols that have been shown to induce cytotoxic, antiproliferative, and pro-apoptotic effects in a range of cancer cell lines [14,15].

This chapter provides an insight into the anticancer activity of some selected Indian red and brown algae, discussing the molecular mechanisms that play significant roles in drug discovery.

#### **Anticancer Activities of Red Algae:**

Some Indian red algae have been reported to show excellent anticancer potential in both animal and cell models due to their potent anticancer mechanisms such as apoptotic induction, cell cycle arrest, signal regulation and ROS generation.

*Gracilaria edulis* presence antiproliferation activity on human pulmonary adenocarcinoma A549 cell line in vitro and in vivo, with systemic toxicity was not observed [16]. Its extract-mediated synthesis of zinc oxide nanoparticles exhibited cytotoxic effect against SiHa cervical cancer cells via ROS-mediated apoptosis [17]. Correspondingly, sterol-enriched fraction from *Porphyra dentata* inhibits tumour growth in 4T1 breast cancer mice by inhibiting the accumulation of MDSCs as active ingredients:  $\beta$ -sitosterol and campesterol [18,19].

*Porphyra umbilicalis* dietary supplementation markedly suppressed the frequency of dysplastic skin lesions in HPV16 transgenic mice, indicating protective effects against cancer development induced by the virus [20]. Anti-adipogenic and ROS scavenging activities of *Gelidium amansii* in 3T3-L1 cells apply to cancer-related metabolic disturbances [21]. The red seaweed, *Kappaphycus alvarezii* and its sulfated polysaccharides, including

carrageenans, had an effect on breast, colon and liver cancer cell lines and in this context, are considered as promising chemopreventive agents [22] .

Extracts of *Laurencia papillosa* also induced the dose-dependent cytotoxicity of MCF-7 breast cancer cells and apoptosis signals through the apoptotic signalling cascades [23] . New ceramides (ITTs) were also extracted from the methanolic extract of *Hypnea musciformis*, displaying potent in vitro cytotoxicity on MCF-7 cells and in vivo tumour inhibitory effects in Ehrlich ascites carcinoma (EAC) models by suppression of VEGF-B and midkine growth factor expressions [24] .

*Gracilaria acerosa* extract indicated the capability to block the PI3K/Akt pathway and activate GSK3 $\beta$ , targeting to promote apoptosis. It also presented antimetastatic activity via down-regulation of matrix metalloproteinase-2 (MMP2), indicating the bidirectional involvement of this compound on both tumour suppression and metastasis inhibition [25] . The methanol extracted *Acanthophora spicifera* exhibited cytotoxicity towards Dalton's Ascitic Lymphoma (DAL) in a murine model, and the polysaccharides recovered from *Gracilariopsis lemaneiformis* have been reported to induce apoptosis in lung, liver and breast cells [26-27] .

#### **Anticancer Activities of Brown Algae:**

Indian brown algae are a potential reservoir of various bioactive compounds such as fucoidans, phlorotannins, terpenes, polyphenols, sterols and alkaloids, among which are known to exhibit significant anticancer activity in vitro and in vivo.

A fucoidan extracted from *Sargassum ilicifolium* was found to be highly cytotoxic to cancer cell lines and, thus, suggested to be a natural chemotherapeutic candidate [28] . In the same context, the extracts of *Padina tetrastrum* were observed to significantly decrease tumour cell count and survival in Ehrlich ascites carcinoma (EAC) models in a dose-dependent manner, and therefore validated its apoptotic as well as antiproliferative effect [29].

A unique association of C11-hydrocarbons, sulfur-containing compounds, quinone derivatives and terpenoids has been reported in the brown seaweed *Dictyopteris australis*; all these compounds have cytotoxic or chemopreventive roles [30] . *Turbinaria ornata*, rich in fucoxanthin, fucosterol, polyphenols, saponins and terpenes, has been demonstrated to exhibit extensive anticancer effects, which have been ascribed to the synergistic action taking place among these metabolites [31] .

The brown seaweed *Hormophysa cuneiformis* exhibited potent inhibition on HepG2, HL60, A549, and HCT116 cancer cell lines, at an IC<sub>50</sub> of 44.6 $\mu$ g/mL, with that level of cytotoxicity across all tumour types [32, 33] . The ethanolic extract of *Stoechospermum marginatum* also brought about concentration and time-dependent apoptosis in cancer cells with cytotoxicity approaching that of quercetin, a standard antioxidant compound [34] .

Extracts of *Cystoseira indica* also suppressed tumorigenic growth of MCF-7 human breast adenocarcinoma cells, while *Colpomenia sinuosa* organics induced cytotoxicity in cervical, breast and colon cancer cells, including HCT-116, in a dose- and time-dependent manner [35,36] . *Spatoglossum asperum* also exhibited anticancer activity, with 35% and 26% suppression in Huh7 (liver) and HeLa (cervical) cell lines [37] .

Taken together, these results reinforce the wide pharmacological potential of Indian brown algae in the development of new anticancer drugs.

#### **Antidiabetic Activity:**

Diabetes mellitus is a set of chronic metabolic disorders due to defects in insulin secretion, insulin action or both, leading to elevated blood sugars. Current health statistics reveal the dominant disease to be diabetes, with over 324 million predicted worldwide by 2025 [38] . Certain chemical drugs can also be used as palliative treatment, while having unacceptable long-term adverse effects (toxicity of the liver and potential carcinogenesis) [39,40] . This has stimulated an increasing attention towards natural products, particularly of marine sources, which, indeed, are harmless, cost-effective and effective.

Seaweeds, specifically red and brown macroalgae, are extremely rich in a wide range of bioactive molecules such as sulfated polysaccharides, phlorotannins, sterols, flavonoids and peptides. These compounds have demonstrated their promise in diabetes treatment both in vitro and in vivo as they can hinder the enzymes, act as an insulin sensitiser, and also have antioxidant properties [41,42] .

#### Antidiabetic Activities of Red Algae:

The potential of red seaweeds in diabetes treatment is interesting, particularly due to the inhibition of carbohydrate-hydrolysing enzymes and pancreatic function.

The hypotensive and antihyperglycemic action of *Hypnea cornuta* has been related to the presence of polysaccharides, and animal model tests showed a significant reduction of postprandial concentration of blood glucose and anti- $\beta$ -cell injury [43,44] . In addition, the high  $\alpha$ -amylase inhibition activity in the *Gracilaria corticata* was also uncovered and was presumed to be due to its polyphenolic compounds, indicating the role of its polyphenolic compounds in regulating the digestion of carbohydrate [45] .

Stigmasterol, a phytosterol that showed antioxidant and  $\alpha$ -amylase inhibitory activities, was obtained from *Gelidium spinosum*. In vivo work demonstrated that stigmasterol significantly reduced serum glucose, urea, and creatinine levels in streptozotocin-induced diabetic rats [46] . The ethyl acetate extract of *Laurencia dendroidea* also demonstrated to have high antioxidant activity (DPPH IC<sub>50</sub> = 312.09 $\mu$ g/mL) and hypoglycemic effect in diabetic models [47] . *Jania rubens* extracts improve glucose metabolism and insulin sensitivity, and can serve as a management option for type 2 DM [48] . *Portieria hornemannii* has been demonstrated to suppress key diabetic enzymes such as  $\alpha$ -amylase,  $\alpha$ -glucosidase, and DPP-IV, which eventually leads to the glucose release and uptake inhibition [49] .

S.No	Algal Species	Type	Bioactive Compounds	Reported Bioactivities	References
1	<i>Gracilaria edulis</i>	Red	Sulfated galactans, polyphenols	Anticancer, Antidiabetic, Antioxidant, Antithrombotic, Analgesic, Neuroprotective	[16,17,106]
2	<i>Gelidiella acerosa</i>	Red	Sulfated polysaccharides, phytol	Antioxidant, Anticancer, Neuroprotective, Antihypertensive, Antithrombotic	[25,98,28]
3	<i>Hypnea musciformis</i>	Red	Ceramides, carotenoids, sulfated galactans	Anticancer, Antioxidant, Antidiabetic, Anti-obesity, Antihypertensive	[24, 69,105] .
4	<i>Kappaphycus alvarezii</i>	Red	Carrageenan	Anticancer, Anti-obesity, Antihypertensive, Neurotrophic	[22,168,228]
5	<i>Laurencia papillosa</i>	Red	Diterpenes, acetogenins, sterols	Anticancer, Antioxidant, Neuroprotective	[23,161,162]
6	<i>Acanthophora spicifera</i>	Red	Apigenin, sterols	Anti-inflammatory, Antithrombotic, Antioxidant	[26,101]
7	<i>Gracilaria corticata</i>	Red	Phenolics, galactans	Antioxidant, Antibacterial, Antidiabetic	[27,97]

8	Hypnea valentiae	Red	Carrageenan	Antioxidant, Antidiabetic, Antimicrobial	【69】
9	Gelidium pusillum	Red	Agar, flavonoids	Antioxidant, Neuroprotective	【29】
10	Jania rubens	Red	Calcium carbonate, terpenoids	Antioxidant, Antithrombotic, Antihypertensive	【30,119】

Table 1 Bioactivities of Indian red algae

Acanthopora muscoides inhibited enzyme activity, lowered blood glucose, and haematological and biochemical changes of DM 【50】. The antioxidant and hypocholesterolemic effects of the sulfated galactans from Spyridia hypnoides may be relevant for the treatment of diabetes-induced sequelae 【51】. Galaxaura oblongata significantly improved the antioxidant condition and immune related gene expression of fish models, which indirectly suggested that it may also play a role in metabolism regulation 【52】.

#### Antidiabetic Activities of Brown Algae:

The antidiabetic potential of these extracts is suggested to be associated with the inhibition of carbohydrate-digesting enzymes, antioxidant properties, and the glucose-modulating properties of some Indian brown algae.

Crude extracts of Turbinaria conoides exhibited a potent inhibition ( $\alpha$ -amylase >  $\alpha$ -glucosidase > DPP-IV) of the postprandial hyperglycemia by degrading the complex carbohydrate to glucose 【53】. Sargassum polycystum extract has been reported to cause a reduction in blood glucose and plasma insulin concentrations in diabetic obese mice by another research group, demonstrating a systemic hypoglycemic effect of the extract 【54】. Cystoseira trinodis showed the maximum activity as an enzyme inhibitor, with its ethyl acetate extract showing the highest activity in  $\alpha$ -amylase inhibition and methanolic extract being the most potent in  $\alpha$ -glucosidase inhibition. Furthermore, Cystoseira trinodis significantly reduced fasting blood glucose in alloxan-induced diabetic hyperglycaemic mice, reiterating their antidiabetic activity in vivo 【55,56】.

The anti- $\alpha$ -glucosidase capacity of Dictyopteris australis and Dictyopteris hoytii has also been studied. Two bromobenzene inhibitors were purified from D. hoytii, whereas zonarol, a marine hydroquinone produced from Dictyopteris polypodioides, exerted inhibitory activity on  $\alpha$ -glucosidase in competitive and mixed modes of inhibition 【57,58】. The  $\alpha$ -amylase inhibitory activity was observed in the protein hydrolysates of Padina tetrastrum by subcritical water hydrolysis. In addition, its antioxidant activity, especially as an H<sub>2</sub>O<sub>2</sub> scavenger, also supports its potential use to prevent oxidative stress-related diabetic complications 【59,60】.

Extracts of Hydroclathrus clathratus may lower biochemical markers in albino rats with alloxan-induced diabetes, likely through its antioxidant and anti-inflammatory properties 【61】. The 80% MeOH extract of the Colpomenia sinuosa showed strong  $\alpha$ -glucosidase inhibition ( $IC_{50} = 3.50 \pm 0.75 \mu\text{g/mL}$ ) with better inhibition potency than the standard drug, acarbose ( $IC_{50} = 160.15 \pm 27.52 \mu\text{g/mL}$ ). Sirophysalis trinodis extracts significantly decreased postprandial blood glucose in diabetic rats 【62】. Another brown macroalga, Padina pavonica, has also been reported to exhibit antioxidative ability, which can suppress the progression of oxidative stress, one of the factors that can promote the development of diabetic complications 【63】.

#### Antioxidant Activity:

Oxidative stress, a disturbance in the balance between reactive oxygen species (ROS) and the body's antioxidant system, is the underlying mechanism of many chronic diseases like cancer, neurodegenerative diseases, cardiovascular diseases and skin ageing. Antioxidants are bioactive constituents that neutralise free radicals that put a defensive shield around cellular molecules (DNA, protein and lipids), which would cause oxidative destruction.

Indian red and brown macroalgae are very abundant sources of natural antioxidants such as polyphenols, flavonoids, carotenoids, phlorotannins, and sulfated polysaccharides. Such agents exert their effects by scavenging ROS, chelating metal ions, enhancing the activity of endogenous antioxidant enzymes, or altering oxidative signalling pathways. In addition, several recently published studies have shown that extracts of algae can effectively decrease oxidative stress, rendering them highly appealing for drug, nutraceutical and cosmeceutical development 【64】.

**Antioxidant Activities of Red Algae:**

*Gracilaria corticata* exhibited high antioxidant activity (i.e.,  $4.00 \pm 0.35$  mg GAE/g phenolic and  $3.33 \pm 0.12$  mg CE/g flavonoid). The DPPH and ABTS scavenging activities were 20.32% and 32.65% indicating its ROS-scavenging ability [65]. Significant antioxidant activities among *Gelidium acerosa* and *Gelidium pusillum* extracts were observed, with differences in vitro assay methods, chelating metals and inhibiting oxidative enzymes. Higher total antioxidant activity was correlated with *G. pusillum* than *Hypnea musciformis* as a result of their higher phenolic content [66,67].

The higher DPPH and OH radical scavenging of the carrageenan-enriched extracts of *Hypnea valentiae* was observed with 65.74% and 65.72% scavenging, respectively. The carrageenan from this species exhibited 70.1% antioxidant activity at 250  $\mu$ g/mL [68]. The methanol extract of *Gracilaria filicina* inhibited 82% DPPH radical activity and the 65% superoxide anion (20% was the value for the reference compound BHT and  $\alpha$ -tocopherol), showing immense free radical scavenging efficiency [69].

*Halymenia porphyraeformis* was also found to activate the Nrf2 signalling pathway, which heightens the expression of endogenous antioxidant enzymes, indicating it has a potential gene regulatory MoA [70]. While showing toxicity in brine shrimp bioassay by  $LC_{50}$  (acute) and 275.72  $\mu$ g/mL  $LC_{50}$  (chronic), *Acanthopora spicifera* had the potential to moderate oxidative damage [71]. *Asparagopsis taxiformis* extracts (methanol, chloroform, petroleum ether, ethyl acetate) seemed to have radical scavenging ability; the methanol extract showed 85% superoxide inhibition and strong FRAP activity, probably due to its polyphenolic content [72].

The ethyl acetate extract of *Eucheuma denticulatum* (EDEE) showed potential towards antioxidant activity and free radical scavenging activity with a total phenolic content of  $81.34 \pm 0.99$  mg GAE/g, whereas the total flavonoid content of  $5.64 \pm 0.12$  mg QE/g and DPPH  $IC_{50}$  of 1031.5 ppm, respectively, it could be a good candidate for modulation of oxidative stress [73].

**Antioxidant Activities of Brown Algae:**

At 200  $\mu$ g/mL, the *Sargassum wightii* crude extract has its DPPH scavenging activity equivalent to that of gallic acid and rutin [74]. The major potential of DPPH (64.14%) and ABTS inhibition (15.02%) for *Turbinaria ornata* also supports its role in attenuating the oxidative stress [75,76]. The methanolic extracts from *Padina tetrastratica* demonstrated most prominently the phenolic (85.61 mg GAE/g) and the flavonoid (41.77 mg QE/g) content, which were the highest in brown algae. It exhibited a percentage scavenging activity of 77.07% and 77.65% (DPPH and ABTS), and a powerful scavenging activity of  $H_2O_2$  (67.89%) and nitric oxide (70.64%). The  $IC_{50}$  of DPPH scavenging activity was 0.96  $\mu$ g/mL, indicating the strong antioxidant potential [77,78].

The diterpenoids from *Dictyota dichotoma* exhibited strong antioxidant activity in the ABTS assay. Its main constituent, fucoxanthin, demonstrated about 13.5 times more powerful hydroxyl radical scavenging ability in comparison with vitamin E [79]. The ethanol extract of *Turbinaria conoides* demonstrated powerful DPPH-radical scavenging activity owing to high phenolic concentration (105.97 mg GAE/g) [80].

The dichloromethane: methanol extract of *Colpomenia sinuosa* demonstrated significant antioxidant potential while it was cytotoxic against colon cells with two different antitumoral activities because of the phenolic compounds, diterpenes and carotenoids that it contains [81]. Sulfated polysaccharide (fucan) fraction of *Lobophora variegata* was highly active in both the phosphomolybdate and radical scavenging assays (EC for hydroxyl radicals = 0.12 mg/mL) [82]. The ethyl acetate extract of *Gracilaria edulis* exhibited potent antioxidant activities by a series of assays (FRAP, DPPH, ABTS, and metal chelation), thus confirming the potential secondary metabolites [83].

**Anti-inflammatory Activity:**

Inflammation is a complex and multifaceted biologic response driven by the response of immune cells, e.g. macrophages and neutrophils, to pathogens, tissue injury or irritants. This cascade results in the release of pro-inflammatory mediators such as TNF- $\alpha$ , interleukins and prostaglandins, as well as activation of signalling molecules like COX-2, iNOS and NF- $\kappa$ B, and while the acute inflammation aids in tissue repair, chronic inflammation leads to pathogenesis of several diseases, including arthritis, cardiovascular diseases and cancer [84-86].

Marine macroalgae, especially red and brown algae, are rich in bioactive secondary metabolites, including halogenated diterpenes, acetogenins, sulfated polysaccharides, and phlorotannins. They have been reported to exert anti-inflammatory activity by inhibiting the major signalling pathways, including NF- $\kappa$ B and MAPK, blocking the production of pro-inflammatory cytokines, and expression of anti-inflammatory mediators [87-90] .

#### **Anti-inflammatory Activities of Red Algae:**

New drimane-type quinols were synthesised from *Gracilaria salicornia*, and selectively showed 5-lipoxygenase and COX-2 inhibitory activity, as proved by in silico molecular modeling [91-93] . *Laurencia majuscula* supplied the acetogenins and sesquiterpenes maneonene, which significantly reduce the release of nitric oxide from activated macrophages, where the compounds 5 and 18 also showed stronger inhibitory activity [94] . Anti-inflammatory and immunomodulatory activity of *Gelidiella acerosa* on papillomavirus-induced skin cancer via NF- $\kappa$ B and immunosuppression was demonstrated through IL-10. Its effects were similar to those of dexamethasone, an anti-inflammatory medication, and could possibly be used to treat lung inflammation [95] . It has shown an outstanding anti-inflammatory activity on carrageenan-induced paw oedema models, in particular at a 50mg/kg dose level, which might be due to its phenolic components [96] .

Apigenin from the red seaweed *Acanthophora spicifera* was reported to relieve the pain and inflammation in animal models by inhibiting the expression of TNF- $\alpha$ , IL-1 $\beta$ , IL-6 and PGE2 [97,98] . In vivo antinociceptive, anti-inflammatory and antioxidant properties of *Pterocladia capillacea* through the inhibition of xanthine oxidase and bacteria agglutination, revealing a potential wide range therapeutic application of this alga [99–101] . Extracts of *Hypnea musciformis* were found to inhibit inflammation up to 78.64% in vitro anti-inflammatory activity at a concentration of 200 $\mu$ g/mL [102] . Suppressive action of *Gracilaria edulis* extracts on COX-2 expression, PGE2 production and NF- $\kappa$ B translocation in HCV-infected human liver cancer cells having high lipophilic content, polyphenols and hydrophilic ascorbic acid [103,104] .

The extracts from the *Laurencia papillosa* showed a moderate cytotoxicity against the leukaemia cells, and the bioactivity of the extracts was influenced by the season of collection and the solvents used to extract them. Cytotoxicity happens, but its mechanism needs to be elucidated [105] .

#### **Anti-inflammatory Activities of Brown Algae:**

Ascophyllan, an antiadipogenic agent, from the brown alga, *Padina tetrastomatica*, which could decrease inflammation in adipocytes and rats, showing its antiobesity and anti-inflammatory impact [106,107] . Lipids from *Sargassum ilicifolium* extracts potently scavenged radicals and reduced ferric iron, and also suppressed the generation of NO. It is an abundant source of sterols, omega-3 PUFAs, and fucoxanthin, and has proven to be an essential anti-inflammatory component [108–110] . Furthermore, substituted 2H-pyrano [3, 2-c] pyranoids were prepared and had selective action on small inflammatory mediators, showing their therapeutic potentials [111] .

Fucoidan of *Dictyota bartayresiana* suppressed ROS, NF- $\kappa$ B and apoptosis as well in the LPS-stimulated macrophage, and it could be a promising drug [112] . Fucoidan from *Sargassum swartzii*, with anti-inflammatory activity, inhibited TLR-induced MAPK and NF- $\kappa$ B signals. Another non-polar lipophilic substance from the same alga showed the anti-inflammatory effect [113] . The alginate fraction of *Sargassum wightii* reduced the anti-inflammatory markers in the collagen-induced arthritic model, as well as the flavonoids and sulfated polysaccharides contributed to the anti-inflammatory property driven by *S. wightii* [114] . Anti-inflammatory and wound-healing effects of *Padina gymnospora* could be ascribed to the fact that it stimulates the migration of fibroblasts and decreases NO production. Areas with this may narrow the signalling and have potent healing activity and leafy pattern in fatty acid profile [115] .

Fucoidan from *Dictyota bartayresiana* suppressed ROS generation, NF- $\kappa$ B activation, and apoptosis in LPS-stimulated macrophages and was identified as a candidate drug [112] . *Sargassum swartzii* fucoidan-mediated anti-inflammatory activity was suggested to suppress TLR-induced MAPK and NF- $\kappa$ B responses. Similarly, there was anti-inflammatory activity of the nonpolar lipophilic substances from the same alga [113] . Alginic acid from *Sargassum wightii* reduced the expression of inflammatory markers in the collagen-induced arthritic model, mediated through its flavonoids and sulfated polysaccharides [114] . *Padina gymnospora* has been expressed with

anti-inflammatory and wound-healing activity as it was able to stimulate fibroblast migration, NO production (responsible for its potent healing activity) and had a band-like appearance in the foliage-like pattern from the fatty acid profile [115] .

*Cystoseira indica* showed significant phenolic contents and in vivo anti-inflammatory activities at 50mg/kg. A comparative work on fucoidans derived from several of the *Cystoseira* species also confirmed the antioxidant and anti-inflammatory activity [116]. The key enzyme in allergic inflammation, hyaluronidase, was significantly blocked by the *Sargassum tenerrimum* phlorotannins, which indicates that this might be a potential natural composite for allergy and inflammation treatment [117] . *Sargassum vulgare* and *S. macrocarpum* polysaccharides, including fucans, have been shown to be anticoagulant, antioxidant and anti-inflammatory. Their water extracts were also largely responsible for the anti-inflammatory effect [118,119] .

#### **Antimicrobial Activities:**

The rising challenge of AMR has necessitated new classes of therapeutic agents that surpass customary drug safety and efficacy. The red and brown marine macroalgae are reported as rich sources of antimicrobial compounds, which include flavonoids, alkaloids, terpenoids, phenols, fatty acids, sulfated polysaccharides, and steroids [120] . These bioactive metabolites display remarkable antiviral, antifungal, and antibacterial activities. They act to disrupt the integrity of the membrane, alter permeability of the cell, inhibit the synthesis of macromolecules, and interfere with replication and protein synthesis mechanisms [121, 122] .

#### **Antibacterial Activities of Red and Brown Algae:**

The dual antibacterial and antifungal potential of the methanolic extract of *Gracilaria corticata* is also inferred, which has been found to show antibacterial action against *Bacillus subtilis* and a range of fungal pathogens, viz. *Trichophyton mentagrophytes*, *Microsporum canis* and *M. gypseum* [123] . The cholesterol derivatives from *Laurencia papillosa* showed wide-spectrum antibacterial activities against Gram-positive and Gram-negative bacteria, showing promise for their possible medicinal use [124,125] . *Gelidiella acerosa* possesses antibacterial, antioxidant, and anticancer activities, and the extracted alga-derived nanoparticles silver and gold demonstrated greater activity against infecting or pathogenic bacteria [126-128] .

In *Padina tetrastomatica* extracts, there was a significant antibacterial effect, and among them, the most effective were the ethyl acetate extract with significantly high inhibitory effect against *Staphylococcus aureus* and less effect against *E.coli* [129] . The methanol and ethyl acetate extracts of *Turbinaria conoides* inhibited *B. subtilis*, *E. coli* and other pathogens, *E. faecalis* and *P. aeruginosa*. Its ethyl acetate extract has shown effectiveness with activity similar to streptomycin [130,131] . Hexane extract obtained from *Sargassum ilicifolium* inhibits the growth of Gram-positive bacteria, and the active compounds were identified as sterols and polyphenols, and such products are found to be less toxic and non-toxic. Therefore, these extracts can be employed for the development of anti-bacterial drugs [132,133] . Sulfated polysaccharides obtained from *Sargassum swartzii* exhibit potent anti-bacterial activity, particularly against *E. coli* strains. Hence, the derivatives are a promising antimicrobial compound [134] .

#### **Antifungal Activities of Red and Brown Algae:**

Certain red algae have high antifungal potential. *Gracilaria corticata* has also shown an activity against pathogenic yeasts and other fungi through inhibiting the fungal growth and mycelial form in a human and plant pathogenicity model [135] . C12 Acetogenins, halogenated metabolites and antifungal sesquiterpenes have been determined from *Laurencia obtusa*. These derivatives, such as palmitic acid methyl ester and trichloromethyloxirane, are effective against many fungi [136] . *Halymenia floresii* yielded the non-toxic halymeniaol, a hydroxysterol which has been reported to have antifungal as well as antimalarial effect, displaying promising antiplasmodial activity against *Plasmodium falciparum* [137] .

Of the brown algae, *Padina pavonica* has shown cytotoxic and antifungal activity against tumours and fungal cells [138] . *Sargassum polycystum* was also found to be active against the fungus *Candida albicans* and has been reported in literature to possess hepatoprotective and antiviral activity. Silver nanoparticles biosynthesised by it exhibited enhanced antifungal activity against certain fungi strains [139,140] .



**Antiviral Activities of Red and Brown Algae:**

Red algal sulfated polysaccharides have been well studied for their antiviral property. ZnO Nanoparticles derived from *Halymenia pannosa* showed good antiviral activity against Cocksackie B4 and HSV-1 [141]. Algal and Sulfated polysaccharides seem to be a good leading compound in finding new drugs, as the crude extract of *Laurencia obtusa* had high inhibition potential on HCV, which was 82.36% inhibition [142]. Sulfated galactans extracted from the red algae, *Gracilaria corticata*, have previously shown antiviral properties against diverse viruses, which include HSV, HIV, Influenza, and SARS-CoV-2 as well, demonstrating the versatility of the therapeutic potential of red algal polysaccharides [143].

Docking studies on the brown alga *Sargassum polycystum* revealed that it may also act as an antiviral against COVID through inhibitory activity against the SARS-CoV-2 PLpro enzyme [144,145]. While not all compounds isolated from *Turbinaria conoides* were found to possess significant antiviral activity, the presence of bioactive scaffolds may warrant further studies [146]. Aqueous extracts of *Lobophora variegata* were also potent inhibitors of HIV-1 replication, assessed by in vitro methods and nontoxic, underscoring its utility as an ingredient in anti-HIV therapies, even though it was derived from local algae [147].

**Neuroprotective Activities:**

Neurodegenerative diseases (NDs), such as Alzheimer's Disease (AD), Parkinson's disease (PD), Huntington's Disease (HD), amyotrophic lateral sclerosis (ALS), and multiple sclerosis, are traditionally characterised as diseases where both the structure and function of neurons and other cellular components of the central nervous system (CNS) are lost progressively. These diseases largely represent a common cause of permanent motor and cognitive disability, which are dominated by oxidative stress, neuroinflammation, protein misfolding, and mitochondrial dysfunction [148,149].

Nowadays, approximately 50 million patients suffer from neurodegenerative diseases in the world, and the estimated number is about 115 million cases by 2050 as a result of the growing ageing population of the world population [150,151]. As there is no definitive treatment, increasing attention has focused on neuron-level protective strategies. Red and brown sea algae have been more recently reported as promising natural resources of neuroprotective molecules exhibiting antioxidant, anti-inflammatory, anti-amyloidogenic and cholinesterase-inhibitory effects [152,153].

**Neuroprotective Activities of Red Algae:**

The red alga *Laurencia papillosa* has been reported to have neuroprotective effects, mostly by its antioxidant and anti-inflammatory bioactives (diterpenes, bromophenols, polyphenols) against both oxidative and inflammatory injury in neuron [154,155]. The reduced AChE inhibitory and antioxidant effect of *Gracilaria edulis* might result in cognitive benefits in AD and related neurodegenerative disorders [156]. *Hypnea valentiae* has been demonstrated earlier to possess AChE and BuChE inhibitory activities along with antioxidant activity. Mixed-type behaviour of the CO inhibitory mechanism is further evidence of a cholinergic therapeutic advantage in AD [157].

*Gelidiella acerosa* offers neuroprotection with free radical scavenging, anti-apoptotic, cholinesterase inhibition and other types of activities. Such agents, like phytol, serve to enhance the activity of neuroprotection against amyloid A toxicity, and neuronal degenerative effects [158,159]. Neuroprotection is also related to inhibition of oxidative damage, inflammation, and AChE activity involved in the pathologies of Alzheimer's and Parkinson's diseases by polyphenols and brominated metabolites isolated from *Asparagopsis taxiformis* [160]. The carrageenophyte *Kappaphycus alvarezii* also demonstrates neurotrophic activity by induction of neurite outgrowth, which is crucial for neuron development and regeneration. In surface-colonised samples incubated for 45 days, even higher activity and neurotrophic potential were observed compared to *K. striatum* and *Eucheuma denticulatum* [161].

**Neuroprotective Activities of Brown Algae:**

There is plenty of evidence that has confirmed the neuroprotective role of *Sargassum wightii* in Parkinson's disease and that the seaweed can improve dopamine levels, protect mitochondrial dysfunction, and reduce oxidative stress in the rats treated with rotenone [162]. Both its myricetin and fucoidan can relieve oxidative stress and destruction of dopaminergic neurons and cell death, therefore, making it a potential candidate for the treatment of PD [163].

The neuro-protective role of *Padina tetrastomatica* is due to its composition of fucoxanthin, sulfated polysaccharides and phenolic compounds. They afford antioxidant and enzyme inhibitory activities that are relevant for suppression of neuroinflammatory and neurodegenerative mechanisms. Indeed, diterpenes, phlorotannins, and sulfated polysaccharides present in *Dictyota dichotoma* are able to support different mechanisms of antioxidant, anti-inflammatory, and cholinesterase inhibitory activities that would be crucial for neuroprotection and attenuation of neurodegeneration progression. [164] .

#### Anti-Obesity Activities:

Obesity is an excessive accumulation of fat that endangers health, which is generally defined as a BMI > 30 kg/m<sup>2</sup>, and it is becoming a pandemic that threatens global health. It is closely related to the risk of type 2 diabetes, cardiovascular diseases, dyslipidemia, non-alcoholic fatty liver disease (NAFLD), high blood pressure, and some types of cancer. Genetic predisposition, hypothalamic defects, psychological stress and overfeeding in childhood are some of them. According to data from more than 200 countries, the proportion of the global population with obesity is estimated to reach 6% in men and 9% in women by the year 2025 [165-167] .

Anti-obesity drugs are available, but use is limited by their side effects, including stroke and cardiovascular issues [168] . This evidence raised more interest in using natural compounds from marine sources as a safer and more natural treatment of obesity. [169] Seaweed-derived molecules, which include alginates, fucoxanthin, fucoidan, and phlorotannins, have well demonstrated potential as inhibitors of fat gain, such as the inhibition of enzymes for fat adsorption, regulation of lipid, lipid metabolism, and control of appetite and satiety.

**Table 2 Bioactivities of Indian Brown Algae**

S.No	Algal Species	Type	Bioactive Compounds	Reported Bioactivities	Reference
1	<i>Turbinaria conoides</i>	Brown	Fucoxanthin, terpenes, fucoidans	Anticancer, Antioxidant, Anti-inflammatory, Anti-obesity, Antipyretic	[31,76,115]
2	<i>Sargassum wightii</i>	Brown	Fucoidan, polyphenols, alginates	Antioxidant, Antidiabetic, Antihypertensive, Anti-obesity, Antimicrobial	[112,118]
3	<i>Padina tetrastomatica</i>	Brown	Phlorotannins, sterols, sulfated polysaccharides	Antioxidant, Anti-inflammatory, Neuroprotective, Anti-obesity, Antipyretic	[78,79,110]
4	<i>Dictyota dichotoma</i>	Brown	Diterpenes, fucoxanthin	Antioxidant, Anti-obesity, Antithrombotic	[80,213]
5	<i>Hormophysa cuneiformis</i>	Brown	Alkaloids, phenolics, sulfated polysaccharides	Anticancer, Antioxidant	[32,33]
6	<i>Colpomenia sinuosa</i>	Brown	Polyphenols, diterpenes, carotenoids	Anticancer, Antioxidant, Antidiabetic	[35,62]
7	<i>Sargassum tenerrimum</i>	Brown	Fucoidans, flavonoids	Antioxidant, Antidiabetic, Anti-inflammatory	[36,73]
8	<i>Padina boergesenii</i>	Brown	Sterols, tannins	Anti-inflammatory, Antioxidant, Antibacterial	[37,99]
9	<i>Turbinaria ornata</i>	Brown	Phytosterols, polyphenols	Antioxidant, Antidiabetic	[38,120]
10	<i>Sargassum polycystum</i>	Brown	Fucoidan, mannitol	Antioxidant, Neuroprotective	[39,103]

**Anti-Obesity Activities of Red Algae:**

*Hypnea musciformis* also improves lipid metabolism and reduces oxidative stress, and lowers cholesterol levels. A high intake of it may thus have a preventive effect on the sequelae of obesity-related diseases [170-172]. *Gracilaria edulis* has hypoglycemic and antioxidant effects that can aid in the control of blood glucose and oxidative stress, which can contribute to the anti-obesity potential of this seaweed [173-175]. *Gracilaria dura* inhibits the activity of  $\alpha$ -amylase and  $\alpha$ -glucosidase, leading to decreased carbohydrate absorption. Its polyphenols and flavonoids also help fight inflammation and oxidative stress associated with obesity [176,177].

In vitro studies have demonstrated that *Hypnea cervicornis* exhibits enzyme-inhibitory, lipid-modulating, and antioxidant activities. A regulatory action on appetite has also been proposed, although human research remains outstanding [178-180]. Other mechanisms involved in anti-obesity effects include inhibition of enzymes and antioxidant activities that are also exhibited by *Gelidiella acerosa*. It might also participate in appetite regulation, or in satiety [181,182]. *Kappaphycus alvarezii*, through modulation of gut microbiota, inhibition of digestive enzymes, and regulation of lipid metabolism. In addition, its antioxidative and anti-inflammatory effects also favour its application in the treatment of obesity [183-185].

**Anti-Obesity Activities of Brown Algae:**

*Sargassum wightii* has been proposed as a potential candidate for functional foods to prevent obesity, with its components rich in polyphenols and fucoxanthin able to regulate lipid metabolism, insulin sensitivity, and inflammation [186-188]. *Sargassum polycystum* reduced weight gain and fat accumulation in rats fed a high-fat diet [189,190].

*Padina tetrastomatica* was found to reduce lipogenesis and increase thermogenesis in hypertrophied 3T3-L1 adipocytes. *Padina tetrastomatica* and barley were demonstrated to be safe and effective in mouse models [191,192]. Fucoxanthin and fucoxanthin in *Turbinaria ornata* influenced adipocyte differentiation and lipid metabolism. It has also been demonstrated to have very strong protective effects in similar situations that are related to oxidative stress from obesity [193,194]. They isolated an FTO-binding compound from *Turbinaria conoides*, which is a derivative of oxygenated fucoxanthin. Sulfated polysaccharide bioactivity of this seaweed has also been associated with antioxidant defence against obesity [195,196].

*Dictyota dichotoma* contains fucoxanthin and phenol with strong antioxidant potential. They have been linked to their anti-obesity properties, and are considered a natural remedy [197,198]. *Fucus vesiculosus* (Bladderwrack) has been used for medicinal purposes for thousands of years. Its fucoxanthin and phlorotannins have anti-obesity, antidiabetic and thermogenic activity. Bound extracts rich in phlorotannins have also shown anti-hyperlipidemic effects, which can be involved in preventing atherosclerosis [199,200]. *Lobophora variegata* is a prolific source of sulfated polysaccharides and phlorotannins. Although there is little direct evidence of anti-obesity activity, it exhibits significant antioxidant and anti-inflammatory action, which is interesting to be further, developed for therapeutic use [201, 202].

**Antihypertensive Activity:**

High blood pressure is both a major global health problem and one of the main risk factors for cardiovascular diseases, stroke and kidney failure. Red (Rhodophyta) and brown (Phaeophyceae) marine macroalgae are being increasingly appreciated as potential natural sources of antihypertensive agents. Most of them contain bioactive compounds such as sulfated polysaccharides, peptides, phlorotannins, polyphenols, among others, and exhibit ACE inhibition, vasodilator and antioxidant activity, among others, modulating pathways [203,204].

*Gracilaria* and *Hypnea* are reported species of red algae that harbour inhibitory peptides and antioxidant substances. The same is true for brown seaweeds like *Sargassum*, *Ecklonia* and *Fucus* species that are abundant in phlorotannins and other compounds that preserve vascular tissues ([205]). These findings suggest that marine algae could be promising natural sources for functional food and drugs to regulate hypertensive condition [206].

**Antihypertensive Activity of Red Algae:**

The high antihypertensive phenolic and carotenoid content with ACE-inhibitory and antioxidant activities of *Hypnea musciformis* is noteworthy and is indicative of a possible application of the seaweed in an anti-hypertensive therapy. While in vivo evidence is scarce, its ethanolic extracts have been shown to exhibit antioxidant activity and to enhance endothelial dysfunction [207]. Similar results have been reported for *G. edulis*, having been observed with ACE inhibitory and antioxidant activities, which are believed to be attributed to its sulfated polysaccharides. They reduce oxidative damage to blood vessel walls and are suggested to be involved in the regulation of blood pressure [208]. It has been shown that *G. verrucosa* directly lowers blood pressure in rats. Its ethanol extract also decreased systolic and diastolic blood pressure by ~14.6% and 15.1% when 125mg/kg was administered, possibly due to inhibition of ACE inhibition [209].

*Gracilaria dura* is rich in polyphenols and terpenoids that are known for their antioxidant and inhibitory activities, supporting its suggested vascular-protective and antihypertensive effect [210]. *Gelidiella* has acidic polysaccharides and peptides containing sulfate, which participate in the actions of ACE-inhibitory and antioxidant, which explains its role in antihypertensive capacity. *Kappaphycus alvarezii*, containing kappa-carrageenan, indirectly regulates blood pressure through anti-inflammatory and antioxidative effects on the vascular endothelium [211,212].

**Antihypertensive Activity of Brown Algae:**

Chloroform extract of *Sargassum wightii* has been known to exhibit a tentative ACE inhibitory activity at an  $IC_{50}$  value of approximately 0.084 mg/mL. Its fractions also have a potent anti-inflammatory action by means of COX and 5-LOX inhibition, and have been reported to protect the vasculature [213]. The phlorotannins isolated from *Ecklonia stolonifera*, including eckol, dieckol, and phlorofucoxekol A, displayed ACE-inhibition activities with  $IC_{50}$  values of 70.82  $\mu$ M, 34.25  $\mu$ M, and 12.74  $\mu$ M, respectively. Dieckol is a non-competitive inhibitor and is useful in the long-term control of vascular tone [214].

*Ecklonia cava* has the effect of inhibiting ACE and the release of NO in endothelial cells. The dieckol from this species is a potent ACE-inhibitor that the endothelium releases [215]. Peptides from the enzymatic hydrolysis of *Undaria pinnatifida* (wakame) that inhibit ACE decrease systolic BP in humans, which confirms their use as candidates for clinical use [216]. Phlorotannins and enzyme-hydrolysed extracts from *Fucus spiralis* have demonstrated significant ACE-inhibition potential ( $IC_{50}$ ~0.5 mg/mL). These double-action molecules would regard vascular protection and their role in functional food development [214].

**Anticoagulant and Antithrombotic Activities:**

Cardiovascular disease is one of the major causes of mortality all over the world, and thrombosis and abnormal blood coagulation are the essential factors of its pathogenesis. The risks associated with the use of conventional anticoagulant or antithrombotic compounds, such as haemorrhage, toxicity, etc., have led to the exploration of safer alternatives existing in nature. Red (Rhodophyta) and brown (Phaeophyceae) algae have been recognised as good sources of bioactive molecules with anticoagulant and antithrombotic properties. These seaweeds are highly enriched with sulfated polysaccharides, such as carrageenans, agarans and fucoidans that are thrombin inhibitory, slowing coagulation and promoting fibrinolysis, similar to heparin but with reduced undesirable side effects [217,218].

**Anticoagulant and Antithrombotic Activities of Red Algae:**

*Gracilaria corticata* has been demonstrated to exert a dose-dependent anticoagulant effect through the inhibition of thrombin and factor Xa and also a marked prolongation of aPTT, suggesting a heparin-like action [219]. *Hypnea valentiae* also showed potent anti-thrombotic activity through inhibiting platelet aggregation and fibrin formation; its sulfated galactans could inhibit thrombus formation in preclinical models [220]. Sulfated polysaccharides fraction from *Gelidiella acerosa* has anticoagulant and antiplatelet effects since they can prolong coagulation time and thrombin activity [221,222]. Likewise, simultaneously, *Grateloupia indica* shows aPTT and inhibition of thrombin and, therefore, its galactans may be low-MW heparins [223].

*Portieria hornemannii*, found in tropical Indian waters, is the species that most profiles as an anti-coagulant, enhancing protein C activity and also inhibiting thrombin [224]. *Acanthophora spicifera* has been shown to

impact the intrinsic pathway of blood coagulation, presenting in vitro and in vivo prolonged blood clotting time [225]. *Halymenia floresii* affects the intrinsic and extrinsic factors of the coagulation cascade, as well as the sulfated polysaccharides of this alga, which cause a reduction in the binding of fibrinogen and final strength of the forming clot [226].

#### **10.2 Anticoagulant and Antithrombotic Activities of brown algae:**

Fucoidans with potential anticoagulant activity are predominantly found in brown algae. Another instance is the fucoidan-rich extract of *Sargassum tenerrimum* implicated to have a strong influence on the formation of thrombin and fibrinolytic activity [227]. *Turbinaria ornata* has shown potent anticoagulant and fibrinolytic activity, as well as inhibited platelet activation and potentiated endogenous anticoagulant activity in its high degree of sulfated fucoidans [228]. Another species, *Sargassum wightii*, the fucoidans of which were shown to be active at the level of both thrombin and factor Xa, can prolong PT and aPTT remarkably, indicating its strong antithrombotic value [229]. Fibrin clots have been confirmed to be weakened, and the fibrinolysis is favoured by sulfated fucans of the tropical brown macroalga *Turbinaria conoides*, which is commonly found distributed [230].

*Padina tetrastrum* shows moderate anti-coagulation activity by inhibiting thrombin and enhancing tPA for the degradation of the clot [231]. *Dictyota dichotoma* demonstrated dose-dependent anticoagulant activity due to its sulphated polysaccharide with high fucosa content [232]. Meanwhile, *Stoechospermum marginatum* also shows anticoagulant activities by suppressing the binding activities of fibrinogen to thrombin, which leads to delayed clotting [233].

#### **Analgesic and Antipyretic Activities:**

The analgesic and antipyretic effect is a prerequisite for the symptomatic treatment of inflammation and infection. Despite the latter, natural products continue to be a key source of such therapeutics, with red and brown taxa of Indian Ocean-derived marine macroalgae having received significant recent attention as suppliers of these agents. The bioactive components of seaweed, including terpenoids, sulfated polysaccharides, flavonoids and phenolics, are reported to act by inhibiting the synthesis of prostaglandins, the content of pain-related inflammatory mediators, and the behaviour of nociceptive signals in animals. The products obtained from the algae present a low toxicity and therefore they are more biocompatible and eco-sustainable compared to chemical synthetic drugs, and they represent an interesting frontier in alternative medicines [234].

#### **Analgesic and Antipyretic Activities of Red Algae:**

The analgesic and antipyretic activities of *Hypnea musciformis* were reported to be most potent. Mice with decreased writhing tested in the acetic acid model, as well as prolonged latencies in the hot-plate test after methanolic extracts, displayed evidence of peripheral and central pain attenuation. It also showed fever-reducing activity in yeast-induced pyrexia in animal models, most likely due to inhibiting prostaglandin synthesis. The analgesic profile and antipyretic property imitate that of the standard reference drugs *Gracilaria dura*. In vivo models have demonstrated its diminished pain and fever effect attributable to its high concentration of terpenoids and phenolic compounds with established anti-inflammatory properties.

Moderate antipyretic and weak analgesic activities were observed in the rodent by the *Kappaphycus alvarezii*. These bioactivities have been attributed to sulfated galactans. Seaweed *Gracilaria corticata* procured from the Tamil Nadu coast was found to possess antipyretic activity in pyrexial rats. Its methanolic extract was found to have an antipyretic, equal to paracetamol, dose-dependent activity; a property that identifies this plant as a likely febrifuge [235,236].

#### **Analgesic and Antipyretic Activities of brown algae:**

Vinegar writhing and hot-plate tests have shown significant dose-dependent analgesic activity of *Sargassum ilicifolium*. This extract also showed central and peripheral antinociceptive and antipyretic activities in a carrageenan-induced paw oedema and yeast-induced fever model. *Sargassum wightii* showed significant anti-inflammatory and antipyretic activities. Fractions of fucoidan isolated from algae were able to inhibit prostaglandin-induced body hyperthermia and reduce nociceptive responses in rats [235-237].

The flavonoids and sterols identified in *Padina tetrastrum* support its pharmacological applicability to alleviate both fever and pain, which is used traditionally. Phytochemical screening revealed the presence of these active constituents, thus reinforcing the interest in the plant as a potential pharmacologically derived process [238]. *Turbinaria conoides* was used as an antipyretic in paediatrics. Suppression of inflammatory mediators by cyclohexane extracts has been supported by a study in which a marked decrease in body temperature was observed in experimental models ( $P < 0.01$ ) [239]. The analgesic and antipyretic activity could be mediated through the anti-inflammatory action of *Stoechospermum marginatum*. GC-MS screening reveals the existence of some bioactive compounds, which could modify pain and fever pathways [240].

### Conclusion:-

Macroalgae are the source of a significant number of bioactive compounds, such as sulfated polysaccharides, phlorotannins, polyphenols, carotenoids, sterols, peptides, etc., particularly those from Indian red and brown macroalgae, which have structural diversity and have been reported. A wide range of pharmacological properties have been reported in vitro and in vivo, such as anticancer, antidiabetic, antioxidant, anti-inflammatory, antimicrobial, and neuroprotective. Anti-obesity, antihypertensive, anticoagulant, analgesic and antipyretic effects. These bioactive substances act through diverse molecular mechanisms at the redox level, inhibition of enzymatic or other biologically relevant ligands, induction of anti- and pro-apoptotic signalling, suppression of the inflammatory pathway, and regulation of cellular metabolism.

Crucially, these marine resources are renewable from the Indian coast and may offer biocompatibility and multiple therapeutic potentials, thereby highlighting them as propitious targets for potential pharmaceutical, nutraceutical, and cosmeceutical applications. However, the rendition of these findings to the clinic is limited due to difficulty in bioactive compound yields, lack of standardised extraction procedures, poor bioavailability, and absence of human trials.

### Future Prospects:

Emerging limitations for clinical and commercial translation of Indian red and brown macroalgae warrant their incorporation into future investigations. For enhanced reproducibility of the bioactive yield as a function of season and location, extraction and purification methodologies must be standardised. Technology of formulations, such as nanoencapsulation, controlled release, and targeted delivery systems, could largely improve stability and bioavailability of algal derivatives, and therefore, their therapeutic options. Likely, the application of a combinatorial strategy integrating omics-based platforms such as genomics, metabolomics and proteomics, novel compounds and their mode of action could become identifiable.

Additional studies, following in vivo validation and systematic clinical studies to prove the effectiveness, the safety, and optimal dose in humans, are needed and are currently underway. Large-scale aquaculture or sustainable methods towards biotechnological growth without exhausting natural resources will be needed for future industrial demand of these compounds. In addition, the use of these bioactive-rich seaweeds for the development of functional foods, nutraceuticals and cosmeceuticals might be of interest as a preventive healthcare approach. Thus, Indian reds and browns have the potential to be developed as important resources for marine-based drug discovery and global health prospectors, providing a means to bridge the current gap between laboratory-based research and implementation.

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