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Review Article

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Ethnomedicinal and pharmacological potential of marine macroalgae for CNS disorders: An overview

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ABSTRACT

Marine macroalgae or seaweeds have created a favourable implication in the area of biomedical sciences, due to the present of potential bioactive substances. Extensive studies are reported on neuropharmacological effects of terrestrial plants and their constituents but there is inadequate information on the potential application of marine macroalgae for behavioural and neurological disorders. This review will emphasize on recent studies and/or updates on bioactive compounds or extracts from marine macroalgae and their potential toward CNS disorders.

KEYWORDS: Marine macroalgae, Seaweed, CNS disorders

INTRODUCTION

Most medicines are obtained from natural sources and researchers are still searching the tropical rainforest for potentially high-priced medicinal products. Many products of sea origin were used as food supplement since early 20th century, like cod liver and shark liver oil. It was only in early years of 1950s that researchers began to scientifically probe marine flora for medicines. Till now, around 10,000 bioactive compounds have been explored from marine sources. The quest still continues to discover new bioactive compounds from oceans (Colwell, 2002; Proksch *et al.*, 2002).

Marine plants involve marine algae, mangroves, sea grasses and sand dune plants. Almost 90 percent of marine plants are marine algae (Dhargalkar & Pereira, 2005). Marine algae are of two types, macroalgae (seaweeds) and microalgae. Marine macroalgae are found in the coastal area between high tide to low tide or in the subtidal region. Marine macroalgae are of three types: Green algae (Chlorophyta), Brown algae (Phaeophyta) and Red algae (Rhodophyta) (Garson, 1989; El Gamal, 2010). Green algae (Chlorophyta) found in the fresh as well as marine habitats. It contains chlorophyll a & b as photosynthetic pigments. The photosynthetic product of these algae is starch, with ulvan being the major polysaccharide component. Brown algae (Phaeophyta) are found only in marine habitat. Photosynthetic pigments of these algae are carotenoid, fucoxanthin (pigment responsible for brown colour), chlorophyll a & c, carotene and xanthophylls. The cell walls are made of cellulose and alginic acid. The photosynthesis of brown algae produced Laminarian, fucane and Manitol. Red algae (Rhodophyta) are exclusively marine (except for few species). Red algae contain phycoerythrin and phycothcyanin (pigment responsible for red colour), chlorophyll a and b-carotene. The primary polysaccharides of these algae are agars and carrageenans (Bold & Wynne, 1978).

The macroalgae are used for human consumption in China and Japan. The countries like Singapore, Malaysia, Thailand, Indonesia, Korea used marine macroalgae in soup, salad or jelly. Marine macroalgae are loaded with proteins, soluble dietary fibers, minerals, polyunsaturated fatty acids, vitamins, antioxidants and essential amino acids (Dhargalkar & Pereira, 2005). Extensive studies are reported on the therapeutic prospective of marine macoalgae toward various diseases. We have previously published a review paper on therapeutic potential of various *Sargassum* species and their health benefits (Yende *et al.*, 2014). In present review article, CNS potential of various marine macroalgae are explored.

CNS Potential of Marine Macroalgae

As per WHO report, out of approximately 450 million people suffering from a mental or behavioural disorder, small number of them receive basic treatment, this accounts for 12.3 percent of the global burden of disease and will increase to 15 percent by the year 2020 (Herrera-Ruiz *et al.*, 2006). From last few

decades, synthetic drugs have been increasingly prescribed as most effective in the treatment and management of neurological and psychologic disorders, although extensive use of these synthetic drugs lead to a variety of unwanted pharmacological effects. However, synthetic drugs primarily alleviate the symptoms and give temporary relief. Therefore, development of cheap, effective and safe agents from plants and other natural sources becomes necessary to overcome these untoward effects. For long time, natural products have abundant use throughout the world for treatment and prevention of human diseases. The medicines from natural product obtained from various sources like marine plants and organisms, terrestrial plants, microorganisms, vertebrates and invertebrates (Newman *et al.*, 2000). Large numbers of studies are reported on neuropharmacological effects of terrestrial plants and their constituents but there is inadequate information on the potential application of components from marine plants for neuropsychiatric disorders. Recently, in the field of marine pharmacognosy, the development of marine natural products is promising as an important field for neuropharmacology. Currently, several drugs derived from marine organisms (worm and snail) are in the phase of clinical trials or used for treatment of schizophrenia, neuropathic pain and Alzheimer's disease (Alicino *et al.*, 2012). By considering various pharmacologically active components and previous reports on neuropharmacological effects of marine herbs (Smit, 2004), they can be considered as a promising source for development of novel neuropsychological drugs.

Effects of Marine Macroalgae in Behavioural Diseases

CNS depressant effects of the *Himanthalia elongata* extract was studied in mice (Table 1). *H. elongate* extract at dose of 300 mg/kg significantly prolonged sleep duration treated with barbiturate and delay pentylenetetrazol induced mortality. It also showed significant reductions in motor activity (Anca *et al.*, 1990).

Kamat *et al.* (1994) evaluated CNS activity of 69 marine plants of Indian coastal region. Among these, extract of *Caulerpa sertularioides* and *Sargassum tenerrimum* possesses CNS depressant activity. The methanolic extract of *C. sertularioides* and *S. tenerrimum* prolonged pentobarbital induced sleep and decreased spontaneous locomotor activities. Further, authors reported that *Ulva fasciata*, *Chnoospora implexa*, *Gelidiella acerosa*, *Centroceras clavulatum*, *Hypnea musciformis* and *Hypneac ervicornis* showed increase spontaneous locomotor score and possess CNS stimulant activity.

Methanol extract of *Laminaria ochroleuca* was studied for CNS activities. The result of the study revealed that, *L. ochroleuca* significantly and dose dependently reduced spontaneous motor activity, reduced exploratory behaviour, reduced time on rota rod, reduced d-amphetamine-induced hyper-motility, decreased rectal temperature and decreased the reaction time in the hot plate analgesic test. Also, the extract showed significant enhancement in sleeping time induced by pentobarbital. Whereas, extract doesn't showed any protection against pentylenetetrazole induced convulsions (Vázquez-Freire *et al.*, 1994). Further, neuropharmacological effect of methanol extract of brown seaweed *Cystoseira usneoides* was studied. The extract significantly decreased spontaneous locomotor activity, reduced exploratory behaviour, reduced d- amphetamine induced hypermotility, reduced body temperature. Also, extracts showed significant effect on pentobarbital induced sleep and pentylenetetrazole induced seizures. Further, administration of extracts shows modification in level of dopamine, 3, 4-dihydroxy phenylacetic acid, 3-methoxytyramine and homovanilic acid in rat striatum (Vázquez-Freire *et al.*, 1995).

The effects of phlorotannins and eckstolonol (a major phlorotannin ingredient) obtained from ethanol extract of *Ecklonia cava* were evaluated for sleep wake profiles in C57BL/6N mice by measuring electroencephalograms (EEG) and Electromyograms (EMG) (Figure 1). Further, hypnotic mechanism of eckstolonol (1) was investigated by injecting Flumazenil. The results of this study revealed that, eckstolonol administration showed significant decrease in sleep latency and increase in non-rapid eye movement sleep (NREMS). Hypnotic effect of eckstolonol was completely abolished by pre-treatment with flumazenil. In conclusions, phlorotannins enhanced NREMS by modulating $GABA_A$ receptor at benzodiazepine site. The results obtained in this study propose that phlorotannins can be used as potential sedative–hypnotics to cure insomnia (Cho *et al.*, 2014). Further, Yoon and Cho (2018) conducted similar study on triphlorethol A (2), major phlorotannin constituents and compared with zolpidem, a distinguished hypnotic drug. The result of this study showed significant sleep-promoting effect of triphlorethol A at a dose of 50 mg/kg.

Cho *et al.* (2012) reported that, ethanol extract of *Ecklonia cava* at 1000 mg/kg showed increased in pentobarbital-induced sleep. Also, at 500 mg/kg it showed marked anticonvulsant activity in mice against picrotoxin induced seizure. The anxiolytic effects of sulphated polysaccharides isolated from *Gracilaria cornea* (red algae) was evaluated using elevated plus maze (EPM), hole board, open field and rotarod test. Also, its mechanism through benzodiazepine receptor was evaluated. It observed that, isolated sulphated polysaccharides at 10 mg/kg showed significant modification all the parameters observed in the EPM test. Further, it showed non-significant change in motor activity observed in open field test and rotarod test. Also, at 10 mg/kg it significantly increased number of head dips when tested using the hole board test. An increased expression of alpha 2-gamma-aminobutyric acid type A (alpha 2-GABA(A)) receptor in the hippocampus was observed in diazepam treated as well as with isolated sulphated polysaccharides treated group. In conclusion, sulphated polysaccharides from *G. cornea* (10 mg/kg) showed an anxiolytic effect, observed via alpha 2-GABA(A) receptor (Monteiro *et al.*, *2016)*.

The neuropharmacological properties of seaweeds from the genus *Turbinaria*, *Sargassum*, *Dictyota*, *Ulva* and *Padina* were studied using behavioural and electrophysiological techniques. The extracts of these seaweeds were evaluated as anti-cholinergic and anti-glutamatergic agents using snail receptors. Further, results showed sedative as well as anxiolytic action of *Dictyota´s* extracts and anticonvulsant effects for *Sargasum, Turbinaria, Dictyota* and *Padina* extract (Nuñez *et al.*, 2006).

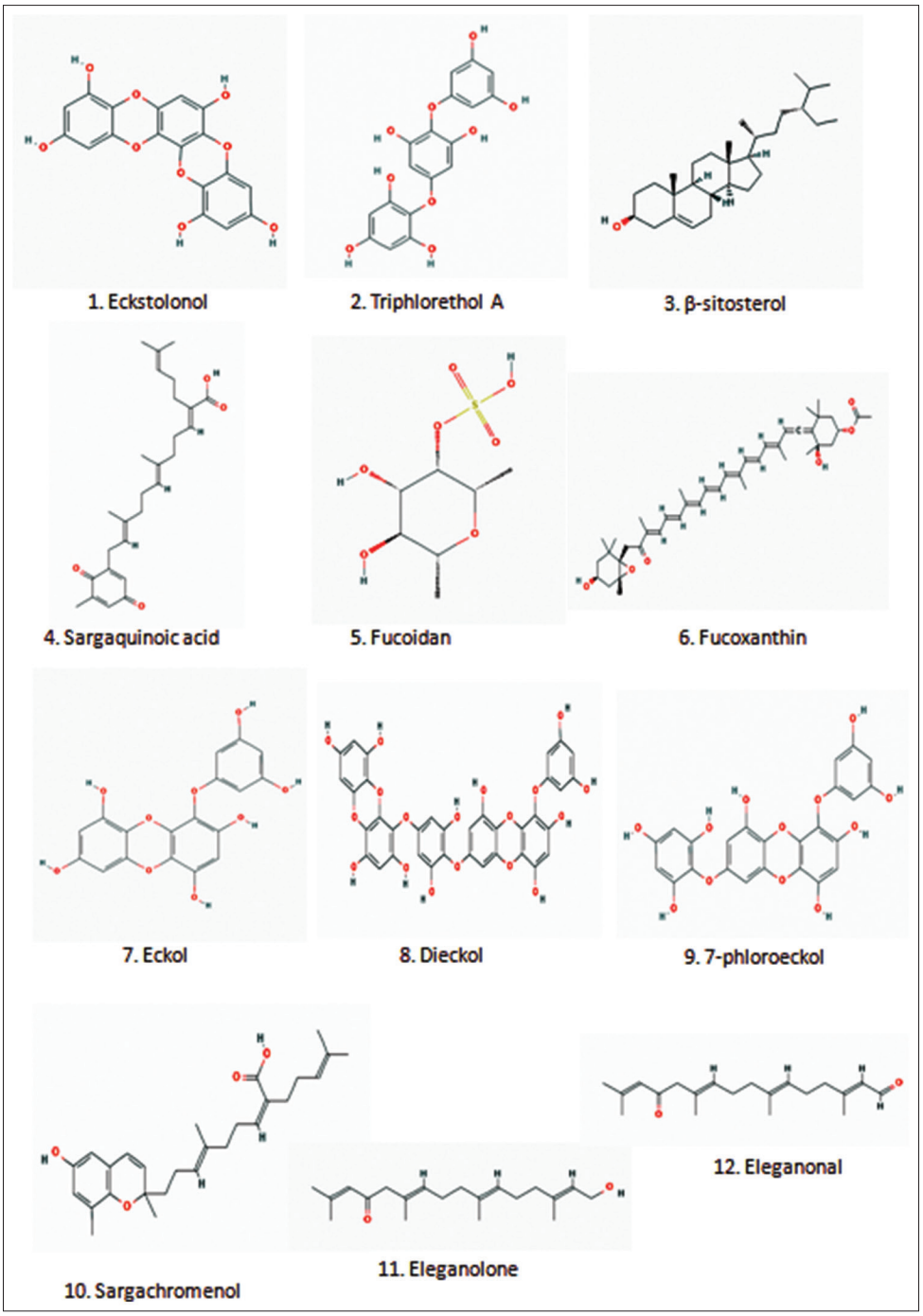

Figure 1: Chemical structures of some phytoconstituents of marine macroalge (Source-https://pubchem.ncbi.nlm.nih.gov/)

Antidepressant activity, anticonvulsant activity and anxiolytic effect of extracts of *Sargassum ilicifolium* was screened using animal experimental models. The results of these studies showed that ethanol and chloroform extract at 400 mg/kg and 600 mg/kg exhibited significant antidepressant, anxiolytic and anticonvulsant activity (Yende & Harle, 2013; Yende *et al.*, 2016a; Yende *et al.*, 2018). Further, cognitive enhancing and antioxidant activities of *Sargassum ilicifolium* and *Padina tetrastromatica* are reported in scopolamine treated mice (Yende *et al.*, 2021). Yende *et al.* (2016b) reported anticonvulsant activity and anxiolytic effect of *Padina tetrastromatica*. Ethanol extract at 400 and 600 mg/kg and chloroform extract at 600 mg/kg of *P. tetrastromatica* showed significant anxiolytic effect in elevated plus maze and light/dark exploration tests. Whereas, chloroform extract at 600 mg/kg showed significant activity against maximal electroshock and pentylenetetrazole induced convulsion in mice.

A study was carried out as antidepressant like effect of *Sargassum swartzii*, *Stoechospermum marginatum* and *Nizamuddinia zanardinii* using forced swimming test in rats. It was found that, oral injection of methanolic extracts (30–60 mg/kg) showed reduction in immobility time, without any significant change in locomotion in open field

Table 1: CNS activity of extracts or components of marine macroalgae

Algal source	Extract/Component	Activity	Reference
H. elongata		CNS depressant effects Sedative – Hypnotic activity	(Anca *et al.*, 1990)
C. sertularioides, *S. tenerrimum* *U. fasciata,* *C. implexa,* *G. acerosa,* *C. clavulatum,* *H. musciformis* *H. ervicornis*	Methanolic extract	CNS depressant activity, Sedative – Hypnotic activity CNS stimulant activity	(Kamat *et al.*, 1994)
L. ochroleuca	Methanol extract	CNS depressant activity	(Vázquez-Freire *et al.*, 1994)
C. usneoides	Methanol extract	Neuropharmacological effect	(Vázquez-Freire *et al.*, 1995)
E. cava	Phlorotannins and eckstolonol	Hypnotic activity	(Cho *et al.*, 2014)
	Triphlorethol A	Hypnotic activity	(Yoon & Cho, 2018)
	Ethanol extract	Sedative- hypnotic activity, Anticonvulsant activity	(Cho *et al.*, 2012)
G. cornea	Sulphated polysaccharides	Anxiolytic effect	(Monteiro *et al.*, 2016)
Genus *Turbinaria, Sargassum, Dictyota, Ulva and Padina*		Neuropharmacological activities	(Nuñez *et al.*, 2006)
S. ilicifolium	Ethanol and Chloroform extract	Antidepressant activity, Anticonvulsant activity, Anxiolytic activity	(Yende *et al.*, 2016a; Yende & Harle, 2013; Yende *et al.*, 2018)
P. tetrastromatica	Ethanol and Chloroform extract	Anticonvulsant activity, Anxiolytic activity	(Yende *et al.*, 2016a; 2016b)
S. swartzii, S.marginatum, and N. azanardinii	Methanolic extract	Antidepressant activity	(Siddiqui *et al.*, 2017)
S. horneri	Total sterols and β-sitosterol	Antidepressant activity	(Zhao *et al.*, 2016)
U. pinnatifida	Ethanol extract	Neuroprotective activity	(Choi *et al.*, 2018)
G. gracilis	Methanolextract	Anti AChE activity, Anti BuChE activity	(Natarajan *et al.*, 2009)
S. sagamianum	Farnesylacetone derivatives, sargaquinoic acid and sargachomenol	Anti AChE activity, Anti BuChE activity	(Choi *et al.*, 2007)
S. fusiforme	Fucoidan	Neuroprotective activity	(Hu *et al.*, 2016)
S. siliquastrum, *S. horneri*	Fucoxanthin	Antioxidant activity, anti AChE activity	(Heo *et al.*, 2008)
E. stolonifera	Eckol, dieckol, eckstolonol, phlorofucofuroeckol,2-phloroeckol and 7-phloroeckol	Anti AChE activity, Anti BuChE activity	(Yoon *et al.*, 2008)
E. cava	Dieckol, phlorofucofuroeckol and phlorotannins	Anti AChE activity	(Myung *et al.*, 2005)
S. macrocarpum, *S. fulvellum*	Sargachromenol, sargaquinoic acid, Pheophytin A	Neuroprotective activity, Enhanced nerve growth factor in rat pheochromocytoma (PC12) cell line	(Kamei & Tsang 2003; Ina *et al.*, 2007)
U. conglobata	Methanol extracts	Neuroprotective activity	(Jin *et al.*, 2006)
B. bifurcate	Eleganolone and Eleganonal	Antioxidant and neuroprotective activity	(Silva *et al.*, 2019)

test. Further this study extended by investigating involvement of monoaminergic system using inhibitors of brain serotonin, dopamine and adrenaline. The results of this study suggested the involvement of monoamine system in antidepressant like activity of the methanolic extracts (Siddiqui *et al.*, 2017). A similar study was reported by Zhao *et al.* (2016) where total sterols and β-sitosterol (3) was isolated from brown algae *Sargassum horneri* and its antidepressant-like activity was investigated. It was found that, total sterols and β-sitosterol significantly decreased immobility time when evaluated using forced swimming test and tail suspension test. Further, it significantly increased brain norepinephrin, serotonin and the serotonin metabolite, 5- hydroxyindoleacetic acid level.

Effects of Marine Macroalgae on Neurological Disorders

It was reported that ethanol extracts of *U. pinnatifida* enhanced cognitive impairment when evaluated using passive avoidance test. The extract increased latency time and restored spine density and morphology in hippocampal neurons of scopolamine-induced rats (Choi *et al.*, 2018). Natarajan et al, reported that methanol extract of *Sargassum* and *Gracilaria gracilis* showed strong inhibition on acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) activity (Natarajan *et al.*, 2009). Also, two farnesylacetone derivatives from *Sargassum sagamianum* possess moderate inhibition on acetylcholinesterase and butyrylcholinesterase activity (Ryu *et al.*, 2003). Further sargaquinoic acid (4) and sargachomenol (meroterpenes) isolated from *S. sagamianum* Yendo showed marked anti acetylcholinesterase and anti butyrylcholinesterase activity (Choi *et al.*, 2007).

Fucoidan (5) (sulphated polysaccharides) isolated from brown algae, was shown protective effect on Aβ-induced cholinergic neuronal loss in rat. It may be due to inhibition of the Aβ-

induced ROS generation, or due to activation of caspase-9 and caspase-3 (mediators of terminal stages of neuronal apoptosis) (Jhamandas *et al.*, 2005). A fucoidan extracted from *Sargassum fusiforme*, showed improvement in spatial learning and memory when screened using scopolamine and ethanol induced cognitive deficit (Hu *et al.*, 2016).

Fucoxanthin (6), a carotenoid extracted from *Sargassum siliquastrum* significantly inhibit free radical formation and apoptosis induced by H_2O_2. It shows reduction in oxidative damage and inflammation in microglial cells (Heo *et al.*, 2008). Recently, Lin et al, reported that, Fucoxanthin obtained from *Sargassum horneri*, significantly reversed impairments of memory induced by scopolamine. Further, it significantly increased choline acetyltransferase activity and Brain derived neurotrophic fact (BDNF) expression. Also, fucoxanthin shows anti AChE activity in scopolamine treated mice (Lin *et al.*, 2016).

Phlorotannins, algal polyphenols, are prominent therapeutically active compounds. Yoon *et al.* (2008) isolated Eckol (7), dieckol (8), eckstolonol (1), phlorofucofuroeckol,2-phloroeckol and 7-phloroeckol (9) from *Ecklonia stolonifera* Okamura, these compounds exhibit dose-dependent inhibition in AChE and BuChE. Also, anti-AChE activity of Dieckol, phlorofucofuroeckol and phlorotannins from *Ecklonia cava* was reported (Myung *et al.*, 2005). Further, anti neuro inflammatory activity of dieckol extracted from *E. Cava* was also evaluated (Jung *et al.*, 2009).

Tsang *et al.* (2005) isolated sargachromenol (10), a plastoquinone (terpens) from *Sargassum macrocarpum*. It was found that, sargachromenol enhanced nerve growth factor (NGF) dependent neurogenesis. This study was carried out in rat pheochromocytoma (PC12) cell line,which is an experimental model for the neuroprotective study of neurotrophic factors, like NGF. Further, it was reported that sargaquinoic acid (4) extracted from *S. macrocarpum*, increased neuritis outgrowth when studied in PC12D cells (Kamei & Tsang, 2003). Also, Pheophytin A (Chlorophylls) obtained from *Sargassum fulvellum* significantly increased neuritis outgrowth in PC12 cells (Ina *et al.*, 2007).

The neuroprotective activity of *Ulva conglobata* on glutamate-induced neurotoxicity in the murine hippocampal HT22 cell line and the anti-inflammatory effects on interferon gamma (IFN-γ)-induced microglial activation in BV2 cells was evaluated. It was found that, methanol extracts of *U. conglobate* showed significant attenuation in the neurotoxicity induced by glutamate in HT22 cells and inhibit nitric oxide production induced by IFN- γ in BV2 cells. Further, it suppressed the expression of the cyclooxygenase 2 and nitric oxide synthase (pro inflammatory enzyme), which suggest that *U. conglobate* possesses neuroprotective activity associated with neuroinflammation (Jin *et al.*, 2006).

Seven fractions (F1–F7) and two major diterpenes, eleganolone (11) and eleganonal were extracted from dichloromethane extract of *Bifurcaria bifurcate* and evaluated for antioxidant and neuroprotective activity. The neuroprotective activity was evaluated by 6-hydroxydopamine induced neurotoxicity model using human neuroblastoma cell line. It was observed that, fractions F4 and F5 showed the potent neuroprotective and antioxidant activities, whereas, fractions F4, eleganolone (11) and eleganonal (12) showed exhibited antioxidant activity (Silva *et al.*, 2019).

CONCLUSION

In extensive studies of marine macroalgae, CNS depressant/stimulant activities, sedative-hypnotic activities, anticonvulsant, antidepressant, anxiolytic effects, antioxidant, anticholinestrase and neuroprotective activities have also been reported. This scientific evidence shows that marine macroalgae have significant CNS potential. Further, the extensive pharmacological actions coupled with compounds derived from these seaweeds such as phlorotannins, alginates, β-sitosterol, fucoidan, sargachromenol, sargaquinoic acid, flucoxanthin *etc* increases the prospective to expand the neuropharmacological potential and health beneficial values of marine macroalgae. In conclusion, marine macroalgae are a valuable resource for the formation of novel ingredients which can be useful for the treatment of CNS disorders.

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