EXPLORING ALGAE AS POTENTIAL THERAPEUTIC SOURCES FOR PARKINSON'S DISEASE: A REVIEW OF NEUROPROTECTIVE COMPOUNDS

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Abstract- **Neurodegeneration is a pivotal factor in various brain-related conditions, notably Parkinson's disease, marked by both motor and nonmotor symptoms due to the loss of dopaminergic neurons. Marine biotechnology, also known as blue biotechnology, delves into marine organisms such as algae for potential healthcare applications. Algae species like *Gracilaria cornea* and *Bifurcaria bifurcata* harbor compounds exhibiting neuroprotective and antioxidant qualities. These compounds demonstrate promise in attenuating neurotoxicity and inflammation in models of Parkinson's disease. research endeavors encompass the identification of novel compounds within algae, optimization of production through synthetic biology methods, formulation of combination therapies, enhancement of drug delivery systems, initiation of clinical trials, and customization of treatments tailored to individual Parkinson's disease patients. Embracing sustainable practices is imperative in responsibly harnessing the therapeutic potential of algae. This multidisciplinary approach within marine biotechnology holds significant promise for advancing therapeutic interventions against neurodegenerative disorders like Parkinson's disease.**

Key words**: Parkinson's disease, Neurodegeneration, Dopaminergic neurons, Marine biotechnology, Algae-derived compounds, *Bifurcaria bifurcate, Gracilaria cornea.***

INTRODUCTION

Neurodegeneration has been recognized as the fundamental pathological alteration in the majority of brain-related disorders[1].Parkinson's disease is a degenerative condition affecting the nervous system, characterized by symptoms such as tremors, muscle rigidity, impaired balance, and coordination. Both genetic factors and environmental influences contribute to its onset. Advanced age is identified as the most significant risk factor for developing Parkinson's disease[2,3].

Marine biotechnology, commonly referred to as blue biotechnology, involves utilizing biological resources sourced from the ocean for applications across industries, healthcare, and environmental conservation[4]. Marine creatures offer abundant reservoirs of highly potent secondary compounds, which hold promising potential as starting points for the creation of novel pharmaceutical[5].Over the past forty years, a plethora of new compounds have been discovered from marine organisms, with a significant portion showing compelling biological properties upon investigation[6].

Algae are relatively uncomplicated organisms containing chlorophyll[7].Algae can exist as single-celled entities or form colonies, and in some cases, they can aggregate into multicellular organisms with various levels of organization, sometimes forming basic tissues. Their sizes range extensively, from tiny unicellular forms measuring 3–10 microns to immense kelps stretching up to 70 meters in length, capable of growing as much as 50 centimeters per day[8].Algae comprise a diverse collection of plant-like organisms with a significant fossil record. They can be broadly categorized into two main groups: macroalgae, commonly known as seaweeds, predominantly inhabit the coastal zones and include green, brown, and red algae; while microalgae are distributed across benthic and littoral environments as well as throughout open ocean waters, often found as phytoplankton[9].

It aim is to advance the field of marine biotechnology and marine pharmacology by leveraging algae-derived compounds to develop innovative and effective therapies for Parkinson's disease, ultimately improving the quality of life for patients affected by this debilitating condition.The objective of exploring algae as potential therapeutic sources for Parkinson's disease is to identify novel compounds with neuroprotective properties and develop effective treatments that can mitigate neurodegeneration and improve outcomes for patients.

PARKINSONS DISEASE

Dr. James Parkinson first documented Parkinson's disease in 1817, referring to it as "shaking palsy." This chronic and progressive neurodegenerative disorder presents with a combination of motor and nonmotor symptoms, significantly impacting patients, their families, and caregivers due to its gradual decline in mobility and muscle control. The motor manifestations of Parkinson's disease stem from the loss of dopaminergic neurons in the striatum, although the presence of nonmotor symptoms suggests neuronal degeneration in other brain regions beyond dopamine pathways. The term "parkinsonism" encompasses the motor symptoms associated with Parkinson's disease, including resting tremor, bradykinesia, and muscle rigidity[10,11,12] .In the United States, Parkinson's disease has an annual incidence of around 20 cases per 100,000 individuals, totaling approximately 60,000 new cases each year. The typical age at which symptoms first appear is around 60 years old. The prevalence of Parkinson's disease is estimated to be about 1% among those aged 60 and older, rising to 1% to 3% among those aged 80 and above. However, it's crucial to note that these figures may not account for undiagnosed cases[13,14]. While Parkinson's disease predominantly affects older individuals, some people have been diagnosed with the condition in their thirties and forties[15].Numerous risk factors and genetic mutations are associated with PD. Risk factors for the disease include oxidative stress, the formation of free radicals, and a number of environmental toxins [16].

PATHOPHYSIOLOGY

In Parkinson's disease (PD), the progressive deterioration of dopaminergic neurons in the substantia nigra pars compacta (SNpc), which connect to the striatum via the nigrostriatal pathway, leads to a decline in dopaminergic function. Motor symptoms typically manifest only after a significant portion of these neurons, between 50% to 80%, have been lost, suggesting the involvement of compensatory mechanisms in the early stages of the disease. Dopamine receptors, specifically D1 (which is excitatory) and D2 (which is inhibitory), play crucial roles in regulating motor activity within the extrapyramidal system. This system includes structures such as the basal ganglia, encompassing the internal globus pallidal segment (GPi) of the ventral striatum, and the pars reticulata segment of the substantia nigra (SNpr). These components are part of larger circuits involving the thalamus and cortex. The depletion of dopamine in the striatum of individuals with PD leads to heightened activity in the GPi/SNpr circuits, causing dysfunction in the neurotransmitter gamma-aminobutyric acid (GABA) and resulting in the inhibition of the thalamus. Consequently, there's a decreased ability for the thalamus to activate the frontal cortex, leading to the characteristic reduction in motor activity seen in PD. Therapies aimed at restoring dopamine activity in the striatum, by activating D2 and D1 receptors, have shown to clinically improve motor symptoms in PD patients[17].

DIAGNOSIS OF PARKINSONS DISEASE

While there have been endeavors to create diagnostic instruments or biomarkers specific to particular diseases, Parkinson's disease (PD) diagnosis continues to rely on recognizing characteristic clinical symptoms, as there isn't a singular diagnostic test designed specifically for this condition[18].

Various nonmotor symptoms have been recognized at the initial stages of Parkinson's disease, and some may appear before motor symptoms manifest. These symptoms comprise rapid eye movement sleep behavior disorder (RBD), reduced sense of smell (hyposmia or anosmia), constipation, daytime sleepiness, low blood pressure causing symptoms, erectile dysfunction, urinary issues, and depression. Apart from nonmotor symptoms, suggested indicators of early Parkinson's disease encompass scoring higher than 3 on the Unified Parkinson’s Disease Rating Scale (UPDRS) or exceeding 6 on the International Parkinson and Movement Disorder Society (MDS) version of the UPDRS (MDS-UPDRS), with exclusion of scores related to postural and action tremors. Additional markers include abnormal presynaptic dopaminergic uptake detected via single photon emission computed tomography or positron emission tomography. Furthermore, various risk factors like male gender, exposure to occupational solvents or pesticides, and a family history of the disease are also taken into consideration[19].

The clinical criteria-based diagnostic accuracy of Parkinson's disease (PD) is relatively high, as evidenced by clinicopathological studies using autopsied brains from PD patients as the gold standard for diagnosis[20].

MANAGEMENT OF PARKINSON'S DISEASE

The management of Parkinson's disease (PD) is multifaceted, encompassing both motor and non-motor aspects of the condition across early and advanced stages. While a basic algorithm can guide treatment decisions once a PD diagnosis is confirmed, it's crucial to stress the importance of tailoring therapy to each patient's specific needs[21].In addition to non-pharmacological interventions like exercise and relaxation techniques, medications are commonly employed, particularly in the early stages or when symptoms are mild. These may include monoamine oxidase inhibitors (such as selegiline, rasagiline, safinamide), dopamine agonists, and anticholinergic drugs[22].

LEVODOPA

Levodopa therapy is typically initiated when symptoms become bothersome and start to interfere with daily activities or work. As the disease progresses and motor complications like fluctuations in response to medication and dyskinesias emerge, surgical and experimental treatments may be considered.while no definitive neuroprotective therapies for PD exist, several clinical trials are underway to explore potential disease-modifying strategies. Some of these investigational approaches include treatments aimed at preventing the accumulation or promoting the clearance of toxic alpha-synuclein aggregates. Examples of such therapies include inosine, which boosts urate levels, and isradipine, a calcium channel blocker. These efforts represent promising avenues in the quest for more effective treatments for Parkinson's disease [23].

Various formulations of levodopa have been developed to enhance its pharmacokinetics, including extended-release versions like Sinemet CR and Rytary. These formulations aim to prolong levodopa's effects while reducing motor fluctuations and dyskinesias. Additionally, intestinal gel formulations like Duopa/Duodopa offer continuous levodopa delivery, reducing "off" time and troublesome dyskinesias. However, this approach can have complications, particularly related to the jejunostomy tube. Emerging treatments such as inhaled levodopa (CVT-301) and transdermal formulations are also being explored[24].

DOPAMINE AGONISTS

Dopamine agonists are often used as initial monotherapy for mild to moderate Parkinson's disease (PD), particularly in younger patients, aiming to delay the need for levodopa therapy and the risk of levodopa-induced dyskinesia. Commonly prescribed dopamine agonists in the United States include ropinirole, pramipexole, and transdermally applied rotigotine. Ergot dopamine agonists like pergolide and bromocriptine are no longer recommended due to increased risks of complications such as valvular and pulmonary issues. Apomorphine, administered via subcutaneous injection, acts rapidly and can be used intermittently to alleviate sudden "off" periods or as continuous infusion for maintenance therapy. Dopamine agonists can also enhance and prolong the effects of levodopa when used in conjunction with it. While dopamine agonists share similarities with levodopa in their side-effect profile, they tend to be associated with a higher incidence of orthostatic hypotension, hallucinations, confusion, somnolence, leg edema, and impulse control disorders. Consequently, caution is advised when prescribing them to older or cognitively impaired patients[25].

OTHER MEDICATIONS

Catechol-O-methyltransferase inhibitors inhibit the peripheral breakdown of levodopa, extending its duration and improving its absorption. This application is beneficial for managing moderate to severe Parkinson's disease by reducing off periods and increasing on periods, despite the associated increased risk of dyskinesias. Selective monoamine oxidase B inhibitors boost dopaminergic activity in the striatum by impeding dopamine metabolism. While they have been shown to alleviate motor fluctuations, they are primarily utilized in the early stages of the disease when symptoms are mild, often as strategies to delay the need for levodopa. Studies investigating the potential neuroprotective or disease-modifying effects of these medications have yielded conflicting and inconclusive results.

Amantadine is effective in addressing PD-related tremors and bradykinesia and is frequently prescribed for managing levodopa-induced dyskinesias. Stimulants like methylphenidate and atomoxetine may offer potential in addressing freezing of gait, a challenging symptom to manage otherwise. Surgical interventions for PD, such as deep brain stimulation (DBS), will be covered in other sections[26].

EXPLORING ALGAE AS PROMISING ORIGINS OF BIOLOGICALLY ACTIVE COMPOUNDS

Algae are among the most prevalent life forms found on Earth, capable of thriving in diverse and challenging environments, including extreme conditions. They inhabit both terrestrial and aquatic ecosystems, flourishing in both freshwater and saltwater environments[27]. Marine algae are categorized into three groups according to their pigmentation: brown algae (Phaeophyceae), red algae (Rhodophyceae), and green algae (Chlorophyceae)[28].

marine algae is identified as valuable reservoirs of a wide range of biologically active compounds with significant pharmaceutical and biomedical promise. Studies have demonstrated that compounds derived from marine algae display diverse biological effects, including but not limited to anticoagulant[29], antiviral[30], antioxidant [31].SJ, anti-allergic[32], anticancer[33], anti-inflammatory[34], and anti-obesity activities[35].

GRACILARIA CORNEA J. AGARDH

Gracilaria cornea J. Agardh is a species of red algae, specifically a type of seaweed, that is found in the western Atlantic Ocean. It is known for its importance as an agarophyte, meaning it is used in the production of agar, a gelatinous substance with various applications in the food and pharmaceutical industries. This species typically grows in coastal areas and plays a role in marine ecosystems as well as in human activities due to its economic value[36].

The red marine alga *Gracilaria cornea* has a sulphated polysaccharide (SA-Gc) with structure and anti-inflammatory and antinociceptive activities reported in the literature. Therefore, this study aimed to evaluate the neuroprotective effects of SA-Gc in rat model PD induced by 6-hydroxydopamine (6-OHDA). Firstly, established the PD model in rats, induced by an intrastriatal injection (int.) of 6-OHDA, followed by a single administration of SA-Gc (15, 30 or 60 μg; int.). On the 14th day, behavioural tests were performed. After killing, brain areas were dissected and used for neurochemical and/or transcriptional analyses. The results showed that SA-Gc (60 μg, int.) promoted neuroprotective effects in vivo through reducing the oxidative/nitroactive stress and through alterations in the monoamine contents induced by 6-OHDA. Furthermore, SA-Gc modulated the transcription of neuroprotective and inflammatory genes, as well as returning behavioural activities and weight gain to normal conditions. Thus, this study reports the neuroprotective effects of SA-Gc against 6-OHDA in rats[37].

BIFURCARIA BIFURCATA

B. bifurcata is a brown macroalga, and due to its morphology, it is classified as a cylindrical species and can be scientifically classified as follows as Empire: Eukaryota, Kingdom: Chromista, Phylum: Ochrophyta, Class: Phaeophyceae, Subclass: Fucophycidae, Order: Fucales, Family: Sargassaceae, & Genus: Bifurcaria. This brown macroalga lives in rock pools on the lower and middle tidal, needing shores forits settlement, and is distributed along the coast of the Northern Atlantic, between Morocco and Northwestern Ireland[38].The antioxidant and neuroprotective activities were assessed using *B. bifurcata* extract, along with its two major isolated diterpenes. Antioxidant activity was evaluated through specific assays, while neuroprotective effects were tested in a 6-hydroxydopamine (6-OHDA) induced neurotoxic model using the SH-SY5Y human neuroblastoma cell line. Mechanisms associated with neuroprotection were explored by examining mitochondrial membrane potential, H2O2 production, Caspase-3 activity, and DNA fragmentation. Fractions showed that it has a promising neuroprotective and antioxidant activities. They effectively maintained mitochondrial potential, reduced H2O2 production, and enhanced cell viability, indicating the presence of compounds with multi-target effects across different pathways. Consequently, this fraction underwent purification, yielding the known diterpenes eleganolone and eleganonal, both showing antioxidant potential and warranting further investigation for their neuroprotective properties[39].

GRACILARIOPSIS CHORDA

Gracilariopsis chorda is classified under the Kingdom Plantae, Subkingdom Biliphyta, Phylum (Division) Rhodophyta, Subphylum (Subdivision) Eurhodophytina, Class Florideophyceae, Subclass Rhodymeniophycidae, Order Gracilariales, Family Gracilariaceae, Subfamily Gracilarioideae, Tribe: Gracilariopsideae, Genus Gracilariopsis, and Species Gracilariopsis chorda. This classification system provides a hierarchical structure that organizes the species based on shared characteristics and evolutionary relationships within the plant kingdom, specifically among red algae[40].

The ethanol extract of *G. chorda* (GCE) demonstrated potential neuroprotective effects in cultured hippocampal neurons. This study delves deeper into GCE's ability to stimulate neurite extension in primary rat hippocampal neurons. Neurons underwent staining with the lipophilic dye DiO or immunostaining for visualizing neuronal morphology. Results revealed that GCE increased neurite outgrowth in a concentration-dependent manner, with an optimal concentration of 30 μg/mL. GCE notably enhanced early neuronal differentiation, including polarity and process number, and facilitated axonal and dendritic arborization in a time-sensitive manner. Moreover, arachidonic acid, previously identified and quantified as a major neuroprotective constituent of GCE, accelerated neurite outgrowth similarly to GCE. These findings suggest that *G. chorda* and its active ingredient, arachidonic acid, hold promise for the development of medicinal foods or pharmaceuticals aimed at preventing and treating neurological disorders[41].

CODIUM TOMENTOSUM

Codium tomentosum is a species of green algae classified under the Kingdom Plantae, Subkingdom Viridiplantae, Phylum (Division) Chlorophyta, Subphylum (Subdivision) Chlorophytina, Class Ulvophyceae, Order Bryopsidales, Family Codiaceae, Genus Codium, and Species *Codium tomentosum*. This classification system provides a hierarchical structure that organizes the species based on shared characteristics and evolutionary relationships within the green algae group[42].

The neuroprotective effects of *Codium tomentosum* enriched fractions were investigated in a neurotoxicity model induced by 6-hydroxydopamine (6-OHDA) on SH-SY5Y human cells, and the mechanisms of action were elucidated. Furthermore, a preliminary chemical screening of the most promising bioactive fractions of *C. tomentosum* was conducted using GC-MS analysis. Out of the tested fractions, four samples demonstrated the ability to reverse the neurotoxicity caused by 6-OHDA to levels higher or comparable to that of vitamin E (90.11 ± 3.74% viable cells). These neuroprotective effects were attributed to the reduction of reactive oxygen species (ROS) generation, improvement in mitochondrial function, mi09tigation of DNA damage, and decreased Caspase-3 activity. The GC-MS

analysis tentatively identified compounds from various chemical classes including terpenes, alcohols, carboxylic acids, aldehydes, esters, ketones, saturated and unsaturated hydrocarbons. These findings highlight *Codium tomentosum* as a valuable source of neuroprotective agents, particularly in the realm of preventive therapeutics[43].

FUTURE PROSPECT

Overall, the exploration of algae as sources of biologically active compounds opens up exciting possibilities for the development of novel treatments and preventive strategies targeting neurodegenerative diseases like Parkinson's disease. Continued research in this field holds the potential to uncover new therapeutic agents and improve outcomes for patients affected by these debilitating conditions.As we delve deeper into the realm of marine biotechnology and the exploration of algae as sources of neuroprotective compounds, several promising future prospects emerge. These prospects not only offer hope for more effective treatments for Parkinson's disease but also highlight the vast potential of marine organisms in addressing complex neurological disorders.

Identification of Novel Compounds: Continued research and advancements in technology are likely to unveil previously undiscovered compounds within algae that exhibit potent neuroprotective properties. Advanced analytical techniques, such as metabolomics and bioinformatics, can aid in the identification and characterization of these compounds, paving the way for new therapeutic avenues.

Synthetic Biology and Bioprospecting: The field of synthetic biology holds tremendous potential for engineering algae to produce specific bioactive compounds at higher yields. By manipulating the genetic makeup of algae, researchers can optimize the production of neuroprotective substances, making them more accessible for pharmaceutical applications.

Combination Therapies: Future studies may focus on developing combination therapies that harness the synergistic effects of multiple compounds derived from different algae species. By combining neuroprotective, anti-inflammatory, and antioxidant compounds, researchers can create comprehensive treatment regimens that target multiple pathways involved in Parkinson's disease progression.

Drug Delivery Systems: Advancements in drug delivery systems, such as nanotechnology and targeted drug delivery, can enhance the bioavailability and efficacy of algae-derived compounds. Nanoformulations can improve the stability of these compounds and facilitate their transport across the blood-brain barrier, ensuring optimal therapeutic outcomes.

Clinical Trials and Translation to Practice: As promising preclinical data accumulates, the next step would involve conducting rigorous clinical trials to evaluate the safety and efficacy of algae-derived neuroprotective compounds in human subjects. Successful clinical trials would pave the way for regulatory approval and the eventual translation of these therapies into clinical practice.

Personalized Medicine Approaches: With the advent of precision medicine, future treatments for Parkinson's disease may involve personalized approaches based on individual genetic profiles, disease progression patterns, and response to therapy. Algae-derived compounds could be tailored to specific patient subgroups, optimizing treatment outcomes and minimizing adverse effects.

Environmental Sustainability: As we explore algae as therapeutic sources, a key consideration is ensuring environmental sustainability and responsible bioprospecting practices. Efforts to cultivate algae sustainably, protect marine ecosystems, and conserve biodiversity will be paramount in harnessing the full potential of marine biotechnology

the future of exploring algae as potential therapeutic sources for Parkinson's disease is filled with promise and exciting possibilities. By leveraging technological advancements, interdisciplinary collaboration, and a commitment to sustainability, researchers can unlock the full therapeutic potential of algae-derived neuroprotective compounds, ultimately improving the quality of life for individuals living with Parkinson's disease.

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