Marine Algae as a Source of Prevention and Relief in Those with Depression and Dementia

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Abstract

Although not as common as those in young adults, the prevalence of late-onset depression has been reported to be increasing in its global incidence. Late-onset depression is generally a product of cognitive deficit and decline, rather than genetic history. Past studies have shown links between the development of depression, dementia, and vascular diseases especially with respect to the nutritional constituents as causative factors. Individuals with depression and dementia tend to be deficient in folate, polyunsaturated fatty acids, and vitamin B₁₂. Folate and vitamin B₁₂ are essential to the metabolism of neurotransmitters necessary in mood regulation (dopamine, serotonin, and noradrenalin), as well as the conversion of homocysteine to cysteine. High levels of homocysteine may result in damage to neuronal pathways and DNA, increasing the risk of dementia. Another risk factor of dementia is the rapid metabolism of neurotransmitter acetylcholine (ACh) due to the enzyme acetylcholinesterase (AChE).

Various types of seaweeds have been found to contain properties and nutrients to alleviate such symptoms and risk factors. These remedies include high levels of polyunsaturated fatty acids, folate, vitamin B₁₂, AChE inhibition and fucoidan. Fucoidan is a compound found in seaweeds that has anti-inflammatory and neuroprotective properties. Further research with the incorporation of seaweeds into common diets may allow for natural prevention and treatment.

Keywords: Marine algae, Late-onset depression, Alzheimer’s disease, Nutritional deficiencies, Fucoidan, Acetylcholinesterase inhibition
INTRODUCTION
The prevalence of Major Depressive Disorder has been reported to have a drastic increase, since the systematic epidemiologic studies of it began in the 20th century.[1] Because the diagnosis of depression is often relative to bias and subjectivity, studies and statistics can often be difficult to analyze. A community-based longitudinal survey, which is less susceptible to bias, studied the prevalence of major depressive disorder in American adults. This survey showed an increase in prevalence from 3.33% in 1991-92 to 7.06% in 2001-02.[1] Major Depressive Disorder is best defined as a serious mood disorder that affects the cognitive and emotional thinking of one. Those with Major Depressive Disorder often experience a lack in concentration, sleep, appetite, and interest, and an increase in irritability, pessimism, anxiety, and fatigue.[2] There are many factors to be considered in diagnosis and treatment, those most widely examined being genetics, biological factors, environmental factors, and psychological factors. Major Depressive Disorder can also occur concurrently with other medical conditions that may pre-exist or develop in a patient.[2] Although the rates of Major Depressive Disorder are still higher in young people than senior citizens, there is an increasing rate of late-onset depression. Late-onset depression is reported to be less likely to originate from genetic history than cognitive deficits and decline.[3,4] Past studies have predicted between a 9-68% prevalence in depression and dementia. Depression has been viewed as both a risk factor and a prodrome to the condition, and a history of depression doubles the chance of developing symptoms of dementia.[5-7]

Dementia is best defined as an umbrella term that encapsulates a number of symptoms caused by the degeneration of the brain. People who have dementia have difficulty in cognitive functions such as memory, problem solving, emotional control, and impaired intellectual functioning.[8] The most common diseases that exhibit symptoms of dementia include, but are not limited to, Alzheimer’s disease and vascular dementia.[8] Alzheimer’s disease is caused by a build-up of proteins from amyloid plaques and tau tangles in the brain, leading to a decline in neuron function and eventually, neuronal death. While the reasoning behind the cause of Alzheimer’s is still unclear, it is known that early-onset Alzheimer’s is a result of genetic mutation, while late-onset is a result of a number of factors such as lifestyle, genetics, and environment that may alter brain chemistry.[9] Deficiencies in the neurotransmitter acetylcholine (ACh), have been associated with Alzheimer’s Disease. Acetylcholinesterase (AChE) is the enzyme responsible for breaking down brain neurotransmitter ACh. The inhibition of AChE seems to be a positive approach to treating Alzheimer’s disease.[10,11] This
article specifically focuses on depression and its correlation to Alzheimer’s disease with sea
weeds as target herbal supplements for their prevention.

Connections between depression and dementia
There are six main hypotheses behind the correlation of depression and dementia: i) The
medication used in treatment for depression poses risks for developing dementia, ii)
Depression and dementia share common risk factors, iii) Depression as prodrome to
dementia, iv) Depression as a reaction to the early cognitive declines, v) Motivational deficits
caused by depression leading to a lack of use of the brain manifested in dementia, and vi)
Depression leading to a damage of the hippocampus. Although comprehensible, these
hypotheses are all in need of further investigation and many do not have enough evidence to
be conclusive.\[12\] From these hypotheses, it can be assumed that there are established
connections between late-onset depression and dementia, but the further specifics must be
examined.

There is not one independent cause of depression, and depression can be a result of many
different factors. Along with environmental and genetic factors, nutritional deficits are also
highly influential to mental health. The most common deficiencies that lead to depression are
those in folate, vitamin B\(_{12}\), and long chain omega-3 fatty acids (EPA and DHA).\[13\] Patients
diagnosed with depression are more likely to have a point mutation in the gene that codes for
an enzyme that metabolizes folate, predisposing them to a folate deficiency.\[13,14\] This
mutation is known as the 677C-T polymorphism in the methylenetetrahydrofolate reductase
(MTHFR) gene.\[14\] Folate and vitamin B\(_{12}\) are essential in metabolizing the neurotransmitters
dopamine, noradrenalin, and serotonin, which are crucial for mood regulation and central
nervous system function.\[15\] Those with deficiencies in folate and vitamin B\(_{12}\) are also at risk
of high homocysteine levels as they are essential to the conversion from homocysteine to
cysteine.\[13\] A rise in homocysteine levels are also linked to the 677C-T polymorphism in
MTHFR (see Fig. 1).\[14\] A buildup of homocysteine levels can cause damage to nerve cells in
the brain, damage in DNA, an increase the production of reactive oxygen species, as well as
an increase in apoptosis (programmed cell death).\[13,15\] High levels of homocysteine have also
been linked to atrophy in parts of the brain most commonly associated with depressive
symptoms.\[15\] A cross-sectional study surveyed 732 Korean adults over 65 years of age. The
results of this study indicated that deficiencies in folate, vitamin B\(_{12}\), and higher levels of
homocysteine were all significant risk factors for late-onset depression.\[15,16\] High levels of
homocysteine have also shown high risk of vascular disease, another risk factor of depression.\cite{13,17,18}

![Diagram: Effects of 677C-T polymorphism in MTHFR gene and its linkage to depression]

**Fig. 1: Effects of 677C-T polymorphism in MTHFR gene and its linkage to depression**

**Relationship between vascular disease, depression, and dementia**

Links between vascular disease and depression have also been widely studied in the past. A large contributor to vascular disease is a deficiency in polyunsaturated fatty acids (PUFAs). PUFAs help lower inflammation which alleviate symptoms and risks of vascular disease, and if applicable, possibly alleviate symptoms of depression. EPA and DHA are long chain omega-3 fatty acids and are these are the PUFAs most relevant to mental health as they contribute to membrane fluidity and regulate dopamine and serotonin levels.\cite{13,19,20} A study that examined the DHA concentrations in breast milk of women in 23 countries showed a correlation between high fish consumption and DHA levels, and lowered postpartum depression rates.\cite{13,21} While linolenic acid (omega-6) and a-linolenic acid (short chain omega-3) can be found in many vegetable sources, long-chain omega-3s are only found in marine sources.\cite{13} Chemical structures of some active constituents found in marine plants and reported to be useful in prevention and treatment of dementia are shown in Fig. 2.
Long chain omega-3 PUFAs have also been examined by several epidemiology studies in suggestion to protective roles against Alzheimer’s disease. There have been both positive and negative results to these studies.[22-25] It is widely known that PUFAs are essential to functional and structural roles in neuron membranes and the regulation of gene expression and inflammation.[22,26] Vascular disease risk factors have also been proven to accelerate Alzheimer’s disease.[27-29]

**Mediterranean diet reported as treatment of depression**

With evidence linking depression as a risk factor for dementia, and similar nutritional deficiencies in depression and dementia, the implementation of certain diets have been in consideration. A popular diet pattern used in past studies is the Mediterranean Diet. The Mediterranean Diet is defined by a consumption of whole grains, plants, olive oil, fish, and wine.[30] These food groups provide ample amounts of nutrients often found to be deficient in those with depression and dementia. Folate is most commonly found in dark leafy green vegetables, vitamin B12 is found in animal sources, and PUFAs can be found in plant and fish oils.[31] Thus, this particular diet has shown positive effects on reducing cardiovascular risk, cancers, cognitive deficits and declines, and overall health.[30] European studies have found a lower prevalence of depression and lower suicide rates in Mediterranean countries than in Northern European countries.[31] The Seguimiento Universidad de Navarra/University of Navarra Follow-up (SUN) Project surveyed the mental health of former students in comparison to their adherence to the Mediterranean Diet. The resulting population totaled to be 10,094 and was sorted into three groups based off of their level of adherence. Those with higher adherence were found to have higher energy levels and be more physically active.
Inverse relationships were found between those with high adherences to the Mediterranean Diet and risks of developing depressive symptoms.\textsuperscript{[31]} Similarly, a study conducted in Chicago, Illinois, a group of older adults (65 years and older), with no evidence of depression were subjected to the Mediterranean Diet from 1993-1996 with follow-up interviews every three years for up to twelve years. The study showed a decrease from 7.4\% to 6.4\% in the annual depressive symptom rate. Moreover, those with the highest adherence to the diet had annual depressive symptom rates, 98.6\% lower than those who adhered to the diet the least.\textsuperscript{[30]}

While the Mediterranean Diet has been studied and proven to be beneficial to those with cognitive decline and depressive symptoms, deficit gaps are filled by a variety of foods. Variety in diet is essential and aids in keeping balance and adequacy in diet, however, further reading in this topic prompted the search for marine plants that could provide ample amounts of those nutrients commonly deficit in those with depression and dementia, specifically folate, vitamin B\textsubscript{12}, and long-chain omega-3 fatty acids. Past studies have shown the versatility and functionality of marine algae. Marine algae has been tested to have high amounts of folate, vitamin B\textsubscript{12}, vitamin B\textsubscript{6}, and PUFAs.\textsuperscript{[32]} The under-exploited marine plant has antioxidant, anticoagulant, anti-inflammatory, and neuroprotective properties (see Table 1). Dried green and purple laver have been the most popular selections of edible seaweed and also contain high amounts of vitamin B\textsubscript{12}.\textsuperscript{[33, 34]} Vitamin B\textsubscript{12} is most commonly found in animal sources and therefore are more difficult to obtain with lower meat consumption.\textsuperscript{[33]} Surveys conducted by NHANES indicated a peak in meat consumption from ages 20-49 and a decrease in meat consumption in older age.\textsuperscript{[35]} The decrease in meat consumption may create deficiencies in vitamin B\textsubscript{12} and other nutrients that may be risk factors to depression and dementia.

Table 1: Marine plants reported for prevention and treatment of depression and dementia

<table>
<thead>
<tr>
<th>Scientific Name</th>
<th>Physical Characteristic of Algae</th>
<th>Pharmacological properties reported</th>
<th>in-vitro/in-vivo reported study</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Neorhodomela aculeate</td>
<td>red</td>
<td>Anti-oxidation</td>
<td>IC\textsubscript{50} = 90 \textmu g mL\textsuperscript{-1} Rats subjected to H2O2-induced lipid peroxidation.\textsuperscript{[36]}</td>
</tr>
<tr>
<td>2. Ecklonia cava</td>
<td>brown</td>
<td>Anti-inflammation</td>
<td>IC\textsubscript{50} not reported Tested E. cava pretreatment on lipopolysaccharide (LPS)-stimulated</td>
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<tr>
<td>3. Ulva conglobata</td>
<td>green</td>
<td>Anti-inflammation</td>
<td>IC$_{50}$ not reported. Tested anti-inflammatory properties of <em>U. conglobata</em> on interferon gamma (IFN-γ)-induced BV2 cells.\cite{38}</td>
</tr>
<tr>
<td>4. Sargassum macrocarpum</td>
<td>brown</td>
<td>Neurite outgrowth</td>
<td>IC$_{50} = 9$ μM. Successful PC12D cell survival tested against protein kinase A (PKA) inhibitor and U0126.\cite{39}</td>
</tr>
<tr>
<td>5. Eisenia bicyclis</td>
<td>brown</td>
<td>BACE1 inhibition from isolated phlorotannins</td>
<td>dixinodehydroeckol- IC$<em>{50} = 5.35$ μM; eckol- IC$</em>{50} = 12.20$ μM; phlorofuroeckol-A- IC$<em>{50} = 2.13$ μM; dieckol- IC$</em>{50} = 2.21$ μM; triphloroethol A- IC$<em>{50} = 11.68$ μM; 7-phloroethol- IC$</em>{50} = 8.59$ μM. Conducted by molecular docking simulation.\cite{40}</td>
</tr>
<tr>
<td>6. Ulva fasciata</td>
<td>green</td>
<td>AChE inhibition</td>
<td>IC$_{50} = 4.83$ mg mL$^{-1}$. Microplate assay based on the modified Ellman's version.\cite{41}</td>
</tr>
<tr>
<td>7. Dictyota humifusa</td>
<td>brown</td>
<td>AChE inhibition</td>
<td>IC$_{50} = 4.75$ mg mL$^{-1}$. Microplate assay based on the modified Ellman’s version.\cite{41}</td>
</tr>
<tr>
<td>8. Hypnea valentiae</td>
<td>red</td>
<td>AChE inhibition</td>
<td>BChE inhibition</td>
</tr>
<tr>
<td>9. Ulva reticulate</td>
<td>green</td>
<td>AChE inhibition</td>
<td>BChE inhibition</td>
</tr>
<tr>
<td>10. Padina gymnospora</td>
<td>brown</td>
<td>AChE inhibition</td>
<td>BChE inhibition</td>
</tr>
<tr>
<td>11. Gracilaria edulis</td>
<td>red</td>
<td>AChE inhibition</td>
<td>IC$_{50} = 3$ mg mL$^{-1}$. Studied <em>in vitro</em> and analyzed using Ellman's colorimetric method.\cite{42}</td>
</tr>
<tr>
<td>12. Enteromorpha intestinalis</td>
<td>green</td>
<td>BChE inhibition</td>
<td>IC$_{50} = 7$ mg mL$^{-1}$. Studied <em>in vitro</em> and analyzed using Ellman's colorimetric method.\cite{42}</td>
</tr>
<tr>
<td>13. Dictyota dichotoma</td>
<td>brown</td>
<td>BChE inhibition</td>
<td>IC$_{50} = 6.5$ mg mL$^{-1}$. Studied <em>in vitro</em> and analyzed using Ellman's colorimetric method.\cite{42}</td>
</tr>
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Scientific studies reported on using marine plants as prevention and treatment of depression and dementia

Although marine animals such as fish are the most common sources of omega-3, the omega-3 in their bodies are obtained by consuming marine vegetation.[32, 43] A cross-sectional study was conducted in Japan on 1,745 pregnant women. The women were given questionnaires to survey their lifestyle and diet habits, depressive symptoms, and family history. The prevalence of depression within the 1,745 pregnant women was 19.3%. The women were placed into quartiles based on their seaweed consumption. The results from this study showed an independent correlation between high seaweed consumption and low depressive symptoms.[44] In another study, rats were exposed to repeated restraint stress to increase their susceptibility to depression. Half of the study group animals were given a placebo saline solution while the others were given fucoidan, a complex sulfated polysaccharide derived from brown seaweeds. The rats were subjected to forced swim tests to induce depressive symptoms. Their body weights and serum levels of corticosterone were used to test the efficacy of the fucoidan. An increase in body weight was observed in those given the fucoidan as opposed to those given saline, indicating the possibility of treatments for depression using fucoidan. Fucoidan has notable antioxidant, anti-inflammatory, and anticoagulant properties, as well as neuroprotective effects.[45]

Fucoidan has also been shown to have properties protecting against neuronal death. A past study subjected rats to beta-amyloid to induce cholinergic neuronal death. Not only was fucoidan able to prevent neuronal death, it was also able to block the activation of capase-9 and capase-3, neuronal pathways that signal apoptosis.[10,46] In addition to this, one of the most realistic approaches to treating symptoms of Alzheimer’s disease is the inhibition of the AChE enzyme.[10,47] AChE inhibition has been found as a property present in many marine algae species. A study published in 2009 measured the inhibitory function of 27 Korean marine plants. Extracts from *Ecklonia stolonifera*, a species of brown algae was found to have the highest amount of inhibitory activity. More specifically, AChE inhibition has been linked to the structure of the pholor-tannins present in these marine plants as they are able to block substrates associated with metabolizing AChE. Similar to AChE inhibitory, butyrylcholinesterase (BChE) activity inhibition has also seen to improve symptoms of Alzheimer’s Disease. A balance of the inhibition of the two mechanisms seems to be the ideal approach in treatment. Two species of marine algae found in Tamil Nadu, India, *Hypnea valentiae* (red) and *Ulva reticulate* (green), have been reported to inhibit both AChE and
BChE activities. The combination of marine red, green and brown algae may have the greatest potential in neuroprotection by inhibition of AChE activity. Pharmaceutical research is being conducted to find inhibitory functions of both AChE and BChE. In 1993, Tacrine became the first drug to be introduced with AChE inhibition. It has since been abandoned due to its severe side effects, including hepatotoxicity. Rivastigmine has inhibitory functions of both AChE and BChE and is available in capsule and liquid dosage formulations. However, its side effects include nausea, vomiting, abdominal pain, anorexia, diarrhea, headache, syncope, and dizziness. The severity of these side effects can be reduced by delivery through a transdermal patch. Conversely, many types of commonly consumed marine algae possess AChE and BChE inhibitory activity and do not produce harmful side effects.

**CONCLUSIONS**

Research of marine algae is still a widely under-explored area. Their properties as of acting as anti-inflammatory, anti-coagulant, and anti-oxidant, with high amounts of folate, vitamin B_{12}, and PUFAs are highly beneficial to those in risk of vascular disease, depression, dementia, and perhaps all three in conjunction. A push to incorporate a variety of marine algae into common diets lacking in said nutrients, such as the Western Diet as a method of prevention should be further explored. Further research should also be conducted to better our understanding of marine vegetation as it is abundant and under exploited.

**REFERENCES**


