DEPRESSION AND ROLE OF MARINE BIOMATERIALS: A REVIEW

Vandita Namola*1, Parminder Ratan2 and Preeti Kothiyal3

*Correspondence for Author
Vandita Namola
Research Scholar, Division of Pharmaceutical Sciences, Shri Guru Ram Rai Institute of Technology, Uttarakhand Technical University. Dehradun (Uttarakhand), India.

1Research Scholar, Division of Pharmaceutical Sciences, Shri Guru Ram Rai Institute of Technology, Uttarakhand Technical University. Dehradun (Uttarakhand), India.

2Assistant Professor, Division of Pharmaceutical Sciences, Shri Guru Ram Rai Institute of Technology and Sciences, Uttarakhand Technical University, Dehradun (Uttarakhand), India.

3Professor and Director, Division of Pharmaceutical Sciences, Shri Guru Ram Rai Institute of Technology and Sciences, Uttarakhand Technical University, Dehradun (Uttarakhand), India.

ABSTRACT

Depression is the most common disorder nowadays seen in adults, old age and even children. It is one of the largest causes of morbidity, and is often accompanied with low mood, loss of appetite, insomnia. The major factors contributing to depression is deficiency of monoamines such as serotonin, noradrenaline, dopamine in various regions of the brain. The rapidly growing number of patients suffering from depression has lead to an enormous increase in the research on antidepressant drugs, and as it is well known that synthetic drugs have various side effects therefore research on natural sources for treatment of depression is going on and marine sources being the most diverse of all natural sources is being studied extensively. Marine Biomaterials such as Bryostatin , and other biomaterials obtained from crustaceans , seaweed , algae are currently being researched as antidepressant leads. Hence, the objective of this review is to discuss various marine biomaterials that can serve as potent antidepressants.

KEYWORDS: Depression, Monoamines, MAO, Marine biomaterials.

INTRODUCTION

Depression is a heterogenous group of brain disorders characterized by a wide range of symptoms that result in psychomotor and cognitive impairments. Depression is accompanied
with, loss of interest or pleasure, decreased energy, feelings of guilt or low self-worth, disturbed sleep or appetite, and poor concentration.\[1\] Moreover, depression often comes with symptoms of anxiety. These problems can become chronic or recurrent and lead to substantial impairments in an individual’s ability to take care of his or her everyday responsibilities.\[2\]

Depression is characterized by feelings of intense sadness and despair, mental slowing and loss of concentration, pessimistic worry, lack of pleasure and self-deprecation. Physical changes also occur, particularly in severe depression, including: insomnia or hypersomnia; altered eating patterns, with anorexia and weight loss or sometimes overeating; decreased energy and libido; and disruption of the normal circadian and ultradian rhythms of activity, body temperature, and many endocrine functions. Depressed patients usually respond to antidepressant drugs, or, in severe or treatment-resistant cases, to electroconvulsive therapy (ECT). This method remains the most rapid and effective treatment for severe acute depression.\[2,3\]

Depression is the second largest cause of morbidity worldwide as estimated by WHO. Various environmental factors such as stress, trauma and various genetic factors contribute to the progression of the disease.\[3,4\] There are various hypothesis of the pathophysiology of depression, amongst which the most widely accepted hypothesis of depression is the monoamine hypothesis according to which the depression is caused by the deficit of NE/5-HT, at various sites in the brain.\[5\]

**Epidemiology**

The world mental health surveys conducted indicates that major depression is experienced by 10-15% people in their lifetime and about 5% suffer from major depression in any given year. Lifetime prevalence of all depressive disorders taken together is over 20%, that is one in five individuals. In Indian context, a recent large sample survey with rigorous methodology reported an overall prevalence of 15.9% for depression.\[6\]

**Monoamine hypothesis**

This theory is attributed to the ability of the NE and 5-HT uptake inhibiting or monoamine oxidase –A, (Monoamine oxidase inhibitors (MAOIs) block the degradation of the monoamine neurotransmitters serotonin, norepinephrine, and dopamine by inhibiting the enzyme monoamine oxidase), leading to increased concentrations of these neurotransmitters in the brain and an increase in neurotransmission inhibiting drugs to facilitate NE/5-HT
neurotransmission, the monoaminergic system is involved in the regulation of broad range of brain functions which includes cognition, sleep, appetite, mood, attention and reward processing and these functions are seen to be impaired in patients suffering from depression. In case of depression the level of MAO increases in the brain where it acts as a metabolizing enzymes for serotonin, noradrenaline and dopamine. Inhibition of monoamine oxidase increases availability of monoamines at the presynaptic neurons which forms the basis of action of various antidepressant drugs.

**Fig 1: Site of action of various antidepressant drugs and their mechanism of action (monoamine theory)**

There are evidences in support of this theory which are as follows.

- Low CSF levels of 5-hydroxyindole acetic acid (5-HIAA), which is a metabolite of 5-HT in patients suffering from depression.
- Low CSF levels of 3-methoxy-4-hydroxyphenyl glycol (MHPG), which is a metabolite of NE.
- Lower tryptophan availability in patients of depression.

**HPA axis theory of depression**
Hypothalamic pituitary adrenal axis (HPA) plays an important role in development of response towards various internal and external stimuli which includes psychological stressors.\[^8\] Hyperactivity of HPA axis is one the most important theories of depression, also there is an increased concentration of cortisol (in response to ACTH) in patients which is considered a marker of HPA axis activation.\[^9\]

The hyperactivity of HPA axis is seen in patients suffering from depressive disorders which is marked by an increase cortisol level in plasma, urine and cerebrospinal fluid of patients of depression. Mechanisms thought to be involved in HPA axis hyperactivity in depression is impaired feedback inhibition of the HPA axis by circulating glucocorticoids.\[^10\]

![Fig.2 Schematic diagram of the hypothalamic-pituitary-adrenal (HPA) axis that describes the regulation and negative feedback (-) of cortisol via glucocorticoid receptors (GRs) and mineralocorticoid receptors (MRs).\[^9\]](image)

Other hypothesis in support are.
1) Downregulation of β1, β2 and α2 adrenoreceptors.\[^7\]
2) Neuroendocrine abnormalities such as increase in cortisol level due to corticosteroid receptor expression and various biochemical markers are associated with depressive disorders.
and an increase or decrease in these markers forms the pathogenesis of the disorder. The plethora of potential biological markers of major depression including neurotrophic factors, serotonergic markers, biochemical markers, immunological markers and neuropsychological markers.[7,8]

![Diagram of biological markers of depression](image)

Fig. 3 Biological markers of depression. Both genetic and environmental factors during neurodevelopment or later in life influence nervous system function and plasticity and modulate immune and endocrine cascades associated with pathophysiology of depression. Nervous, immune and endocrine systems have feedback regulations and are linked to each other. For example: an increase of cortisol may activate monocytes to increase pro-inflammatory cytokines which may lead to a deficiency of 5-HT due to the favoured metabolism of tryptophan by increased activity of IDO to the neurotoxins kynurenine and quinolinic acid. Such regulations can be measurable and may be used as indicators (robust, good or weak) of the presence, severity and prognosis of depression as well as prediction of drug/other treatment and are characterized as biological markers of depression. Li, limbic areas; _ increase; ¡, decrease; s, serum; c, CSF; sa, saliva; l, lymphocytes; b, blood; t, thrombocytes.[8]
Classification

Depression is classified according to various classification systems, the 2 most well accepted international systems are diagnostic and statistical manual (DSM-IV) of American psychiatric association and international classification of disease and related health problems (ICD-10) of WHO.\[9,10\]

Depression is broadly classified into unipolar and bipolar depression also known as mono and bipolar dichotomy.
- Unipolar depression is a type of depression in which the mood swings are unidirectional and is very common form of depression often associated with stressful life events sometimes accompanied with anxiety and restlessness.
- Bipolar depression is less common endogenous depression, unrelated to stress and results in oscillating depression and maniac symptoms in a period of few weeks.\[11-14\]

The other types of depression are\[14-16\]

<table>
<thead>
<tr>
<th>S.NO</th>
<th>Depression</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Major depressive disorder</td>
<td>An individual with major depressive disorder has persistent low mood,anhedonia,negative cognition,and disturbances in sleep, apetite and psychomotor functions.</td>
</tr>
<tr>
<td>2.</td>
<td>Dysthymia (minor depression)</td>
<td>It is a low grade persistent depression lasting for 2 years or more in which a person is reported to have low mood for a long duration.</td>
</tr>
<tr>
<td>3.</td>
<td>Bipolar depression</td>
<td>It is a condition in which depression alters with a state or phase of mania or hypomania.</td>
</tr>
<tr>
<td>4.</td>
<td>Melancholic depression</td>
<td>It is characterized by a loss of pleasure in most of the activities,depressed mood is more pronounced in early morning often accompanied with excessive weight loss and psychomotor retardation.</td>
</tr>
<tr>
<td>5.</td>
<td>Atypical depression</td>
<td>It is associated with hypersomnia, increased apetite,weight gain and social impairment.</td>
</tr>
<tr>
<td>6.</td>
<td>Catatonic depression</td>
<td>It is a rare and severe form of depression involving motor and behavioural disturbances exhibiting bizarre movements .if the individual has depression without mania then it is unipolar depression ,if maniac or hypomanic episodes are present then diagnosis is bipolar depression.</td>
</tr>
</tbody>
</table>

Oxidative stress in depression

Oxidative stress is the imbalance between production of reactive oxygen species and their insufficient destruction by the antioxidant defence system Oxidative stress has been
implicated in the pathophysiology of several neuropsychiatric diseases, including Major Depressive Disorders. Total antioxidant capacity (TAC) and total oxidant status (TOS) are altered in depressive patients.[17]

Major depressive disorder is accompanied by an increase in oxidative stress and a decrease in antioxidant status, which damages neurons and alters level of biomarkers such as glutathione, catalase, malondialdehyde, prolidases and studies have also revealed association of inflammation with depressive disorders.[18-19] Various studies have demonstrated that potency of oxidative stress is directly linked to severity of depression.

Oceans cover more than 70% of earth’s total surface which makes the diversity in marine ecosystem an evident one. The biodiversity in marine ecosystem is far more than the terrestrial ecosystem which makes it a vast source from which various useful therapeutics can be discovered.[20] Marine organisms remain the largest unexploited natural resource for obtaining therapeutic agents. Marine organisms are constituted by materials with a vast range of properties and characteristics that may justify their potential application within the biomedical field.[21-23] The secondary metabolites of marine organisms are highly potent and bioactive.[24-26] The potency of bioactive metabolites is mainly due to the constant ecological/environmental pressure and the defence mechanism they have evolved to protect themselves from the predators.[26-27] Drugs derived from these marine sources such as marine algae, fungi are currently in use as anticancer, antiviral, immunomodulators, antioxidant and anti-inflammatory agents.[28-30] Apart from algae and marine fungi various sea weeds are useful as memory boosting agents as well as also finding way in neuropsychiatric disorders such as anxiety and depression.[31-32]

**Marine biomaterials in depressive disorders**

**Marine sponges with antidepressant activity**[33]

Sponges are the most primitive of all multicellular organisms and are excellent research subjects due to their fibrous skeletons and mineralized spicules Anna J. Kochanowska *et al* studied activity of metabolites from three Florida sponges, namely, *Verongula rigida*, *Smenospongia aurea*, and *S. cerebriformis*. All three species were investigated chemically, revealing similarities in secondary metabolites. Isolated compounds were evaluated in the Porsolt forced swim test (FST) and the chick anxiety-depression continuum model. Structural similarity of indole alkaloids and the endogenous monoamine serotonin, many efforts has
been directed toward isolation and synthesis of serotonin-like molecules, which could possibly possess affinity to different 5HT receptors. Brominated marine indole alkaloids have been previously reported by Hu et al. to possess high affinity for human serotonin receptors the isolated compounds, 5,6-dibromo-N,N-dimethyltryptamine exhibited significant antidepressant-like action in the rodent Forced swim test (FST) model by significantly reducing the immobility period at 20 mg/kg dose, while 5-bromo-N,N-dimethyltryptamine caused significant reduction of locomotor activity indicative of a potential sedative action. The current study provides ample evidence that marine natural products with the diversity of brominated marine alkaloids can provide potential leads for antidepressant and anxiolytic drugs.

**Anxiolytic and antidepressant activity of the seaweed**[34]

Seaweed indicates the class of marine algae comprising of red, brown and green algae. Riaz bushra et al explored neuropharmacological activities of the brown seaweed *Iyengaria stellata*. Ethanolic extract of this seaweed was screened for various CNS screening tests such as open field test, head dip test, passive avoidance test, forced swim test and morris water maze test. The screening of *Iyengaria stellata* on CNS parameters have been conducted and revealed that the locomotor activity decreased after administration of the seaweed extract. In forced swim test also the immobility period significantly decreased throughout the study, it was suggested that *Iyengaria stellata* possess significant anxiolytic and antidepressant activity due to its adrenergic activity, also it has memory boosting effects as well as mild nociceptive actions.

**Antidepressant activity of semi synthetic derivatives obtained from natural sources**

Miao-Kun Sun et al (2006) reviewed Drugs such as bryostatin with a chemical structure of macrocyclic polypeptides. It is a powerful protein kinase c agonist having the ability to activate the isoenzymes at very low concentrations.[35] This review rules out the therapeutic uses of bryostatin in various disorders including Alzheimer’s disease, depression. This study also gives a detail insight on the pharmacokinetics and possible side effects and toxicity of bryostatins. The human plasma membrane serotonin transporter is a substrate for PKC. PKC activation or phosphatase inhibition downregulate uptake of 5-HT. This effect is probably mediated by reduction of the expression of 5-HT transporter, an important role of PKC activity in mood regulation is the observation that bryostatin-1, at appropriate doses, has
antidepressant activity in rats in an open space swim model of induced depressive behavior, bryostatin-1, at 100 nmoles/kg i.v., significantly reduced non-searching immobility in rats.\[36\]

Jeffrey A. Diers et al identified the antidepressant drug leads through the evaluation of marine natural products with neuropsychiatric pharmacophores. Selected marine natural products or their semi-synthetic derivatives: 1) aaptamine 2) isoaaptamine 3) 8,9-demethylaaptamine 4) 5,6-dibromo-N,N-dimethyltryptamine and 5) manzamine A were evaluated for antidepressant-like effects in mice using the forced swim test (FST), locomotor activity and tail suspension test (TST). These marine bioactive compounds were extracted from various sponges. This study demonstrated that aaptamine and 5,6-dibromo-N,N-dimethyltryptamine exhibited antidepressant like activity in the FST, and have the potential to be antidepressant drug leads.\[37\]

CONCLUSION
In the past few decades marine biomolecules have emerged as novel lifestyle drugs. Antidepressive marine biomolecules have special benefits. They act as biochemical replenishers for maintaining healthy bioenergetic profile and physiological balancer of neurotransmitters. Various marine flora and fauna have contributed significantly in search of antidepressant leads. Marine sponges, seaweeds, crustaceans and phytoplanktons are extensively being studied for antidepressant activity, but for these drugs to reach the drugstore shelves an extensive research is required which will open the possibility for use of marine sources of drugs in depression.

ACKNOWLEDGEMENT
Author is thankful to Prof (Dr.) Preeti Kothiyal (Director, Shri Guru Ram Rai Institute of Technology and sciences, division of pharmaceutical sciences, Dehradun) and Mrs. Parminder Ratan (Assistant Professor, Shri Guru Ram Rai Institute of Technology and sciences, division of pharmaceutical sciences, Dehradun) for their kind support and guidance.

REFERENCES

