Role of Alkaloids in Depression

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Abstract- Depression is a common neuropsychiatric disorder that profoundly impacts quality of life and continues to be one of the most serious health problems worldwide. Conventional antidepressant drugs, while effective, present several disadvantages, such as delayed onset of action, frequent side effects, and incomplete response in a large number of patients. Over recent years, interest has shifted toward medicinal plant-derived alkaloids for their potential antidepressant activity. The extracts of these compounds exhibit multiple mechanisms of action, including the regulation of monoamine neurotransmitters, inhibition of monoamine oxidase enzymes, antioxidant activity, and modulation of neuroinflammation pathways. Various alkaloids are discussed here for their role in managing depression, along with modes of their action and advantages over synthetic antidepressants. The article further discusses future perspectives by emphasizing the need for advanced pharmacological research and with better designs to confirm the safety and efficacy of alkaloids as promising antidepressant therapeutic agents.

Keywords: Neuropsychiatric, Antidepressant drug, Neurotrasmitter, Neuroinflammation.

I. INTRODUCTION

- Defination & causes

Depression is a prevalent psychological ailment, estimated to affect 264 million people around the world [1]. The symptoms of this condition include a lack of feeling of interest and pleasure, self-doubts, inability to focus, social anxiety, and sleep disturbance [2]. The imbalance of certain compounds/chemicals found in the brain, for instance, serotonin levels, is perceived to be the cause of this condition. In addition, other hormones such as Dopamine and norepinephrine levels can trigger depression, as optimal levels of this hormone are required for proper functioning of one's brain to regulate emotions [3].

- Prevalence of Depression - Global Level

Depression is among the most prevalent mental health conditions globally. According to World Health Organization (WHO), it is estimated that about 5.7% adults worldwide suffer from depression, and about 4% of the population is estimated to suffer from depression simultaneously. This number translates roughly to 280-330 million people worldwide suffering from depression.[4]

Depression is more prevalent in females than in males (e.g., 6.9% versus 4.6% in the adult population. There is a substantial treatment gap, with over 75% of people with depression in low and middle-income countries untreated. Globally, depression is a major cause of disability and can be a risk factor for suicide.[5]

- Commen treatments

Several types of interventions have been shown to be efficacious in treating depression. The antidepressant medications are relatively safe and work for many patients, but there is no evidence that they reduce risk of recurrence once their use is terminated. The different medication classes are roughly comparable in efficacy, although some are easier to tolerate than are others. About half of all patients will respond to a given medication, and many of those who do not will respond to some other agent or to a combination of medications [4]. Electro-convulsive therapy is particularly effective for the most severe and resistant depressions, but raises concerns about possible deleterious effects on memory and cognition. It is rarely used until a number of different medications have been tried (holon et al 2002).

- Alkaloids – as anti depressant agents

The antidepressant effect of various plant alkaloids has been reported in the literature. Brazilian group of researchers isolated strictosidinic acid from Psychotria myriantha Mull. which exhibited antidepressant-like effect when studied on a 5-HT system in rat hippocampus (Farias et al., 2012) (Lee et al. (2012)

showed that berberine administration significantly decreased immobility and increased climbing behavior in the Forced swim test. However, there was no effect on swimming time, while increased open-arm exploration in the elevated plus maze test which confirmed that the antidepressant-like activity (Lee et al., 2012).

A team from the China School of Pharmacy isolated Leatispicine, an amide alkaloid from Piper laetispicum. When tested in the forced swim test, it caused a significant dose-dependent decrease in mobility at various test doses and thus possessed antidepressant activity (Yao et al., 2009). Xu and coworkers obtained protopine from a Chinese plant, Dactylicapnos scandens Hutch, had an antidepressant effect in mice. It dose-dependently reduced the immobility time in the tail suspension test and thus could be effective for the moderate state of depression (Xu et al., 2006). Addition to all those, pramipexole is a non-ergoline alkaloid showed significant clinical efficacy in a double-blind, placebo-controlled study in bipolar and unipolar depressive patients (Zarate et al., 20

II. REVIEW OF LITERATURE

Berberine, isolated from Berberis aristata, has been reported to produce antidepressant effects mainly through the inhibition of serotonin reuptake and monoaminergic transmission (Kulkarni et al., 2008)

The active chemical, myrianthine, found in *Psychotria myriantha*, is known to exert its action by monoamine oxidase (MAO) inhibition, resulting in monoamine neurotransmitter Faries et al.2012

Anonaine, which comes from *Annona Cherimola*, increases monoaminergic turnover and is thereby a contributor to antidepressant action (Martínez et al 2012)

Akuammine, derived from *Picralima nitida* synonym Rhazya stricta, has been shown to have antidepressive properties due to MAO-A inhibition (Ali et al.,1998)

Mitragynine from *Mitragyna speciosa* inhibits stress-induced corticosterone secretion, thereby improving moods and stress responses (Idayu et al., 2011)

Harmine, isolated from *Peganum harmala,* inhibits the function of MAO-A and impacts various cellular mechanisms concerned with the modulation of mood (Farzin & Mansouri, 2006).

Mauritine-A, which is obtained from *Ziziphus apetala*, targets multiple receptors such as serotonin receptor 2A, and it also inhibits 11-β-hydroxysteroid dehydrogenase and thus is used as an anti-depressive (Han et al,. 2011)

Aconitine from *Aconitum baicalense* promotes the functionality of the serotonergic system, and thus there is improved antidepressive action (Nesterova et al., 2011)

Punarnavine obtained from *Boerhaavia diffusa* has shown antioxidant and antidepressant properties through MAO inhibition and lowering plasma corticosterone values (Dhingra & Valecha, 2014)

Evodiamine derived from *Evodia fructus* has been found to regulate monoamine neurotransmitters and promote BDNF-TRKB signaling in the hippocampus and has been linked with antidepressants (Jiang et al., 2015).

Mesembrine from *S. tortuosum* works as a serotonin reuptake inhibitor, and as such, it increases the level of serotonin in the synaptic clefts (Loria et al 2014)

Piperatine, isolated from Piper nigrum, inhibits monoamine oxidase and stimulates brain serotonin and BDNF, thus supporting its antidepressant use (Wattanathorn et al., 2008)

Laetispicine, an alkaloid from Piper laetispicum, inhibits the reuptake of monoamines, thereby exhibiting an antidepressant-like response (Yao et al 2006)

Corydine, isolated from *Dactylicapnos scandens*, acts as a serotonin and non-adrenaline transporter inhibitor, thereby inducing mood elevation (Xu et al., 2006).

Martine from Sophora flavescens also displays antidepressant properties due to anti-neuroinflammatory and monoamine regulation mechanisms (Wang et al., 2020).

The antidepressant activity of the Dimethyltryptamine extracted from the *Psychotria viridis* plants occurs due to the stimulation of the 5-HT2A receptor and the regulation of serotonergic activity in the body

Dendrobine extracted from *Dendrobium nobile* enhances BDNF protein expression and promotes antioxidant and anti-stress activities, adding up to its antidepressant functions (Li et al., 2022).

The compound noscapine extracted from *Papaver somniferum* functions as a neuroprotection and stress remedy, thus alleviating depressive-like symptoms (Abdel et al., 2020).

According to this tabular representation is given in the folloing table.

1) Table representing alkaloids used in depression & there meachanism of action.

Alkaloids	Plant extract	Mechanism of action	reference
Berberine	*Berberis arista*	Serotonin reuptake inhibition and monoamine modulation	Kulkarni, S. K et al (2008)
Myrianthine	*Psychotria myriantha*	MAO (monoamino oxidase) inhibition	Faries et al.2012
Anonaine	*Annona cherimola*	Increase monoaminergic turnover	Martin -vazqueza et al.2012
Akuammine	*Rhazya stricta*	MAOA (monoamino oxidase A) inhibition	Ali et al .,1998
Mitragynin e	*Mitagyna specicosa*	Reducing the release of Korte Coasteron	Idayu et al .,2011
Harmine	*Peganum harmala*	Interfering with MAOA (monoamino oxidase A) and several cell surface receptors also including serotonin receptor 2 A	Farzin Mansouri.,2006
Mauritine A	*Ziziphus apetala*	11 – Beta- hydroxysteroid dehydrogenase inhibition	Han et al,. 2011
Aconitine	*Aconitum baicalense*	improved Serotonergic system	Nesterova et al., 2011
Punar Navine	*Boerhaavia diffusa*	MAO (monoamino oxidase) inhibition and decreased plasma corticosterone level	Dhingra and valecha,2014
Evodine	*Evodia Fructus*	Effects on the Monoamine transmitters and BDNF- TRKB (brain derived factor) signaling in the Hypo campus	Jiang et al 2015
Mesemembrine	*Sceletrium tortuosum*	5HT reuptake inhibition	Loria et al 2014
Piparatine	*Pepper Nigram*	Innovation of MAO ((monoamino oxidase A) enzyme, elevation of brain 5 HT and BDNF (BRAIN DERIVED FACTOR) levels	Wattanathom et al.,2008
Laetispcine	*Piper laetispicum*	Show antidepressant like activity, Analgesic effects also	Yao et al 2006
Corydine	*Dactylicapns scanens*	Inhibition of serotonin transporter and non adrenaline transporter	Xu et al., 2006
Martine	*Sophora flavescens*	Anti neuro inflammatory effects and monoamine balance	Wang y et al neurochem int .,2020
Dmt	*Psychotria viridis*	5HT2-a receptor activation	Dos santos rg et al .,2021
Dendronbine	*Dendrobium nobile*	It increases BDNF (brain derived factor) which is a anti oxidative stress	Li q et al., 2022
Nozacupine	*Papavar somniferam*	It acts as an neuroprotective agent and an anti stress agent	Abdel et al 2020

III. FUTURE PERSPECTIVE

Depression is complex neuropsychiatric syndromes involving disturbances in monoaminergic neurotransmission, neuroplasticity, neuroinflammation, oxidative stress, and the gut-brain axis. Classic antidepressants interact mainly with the Monoamine system but frequently exhibit disadvantages, including slow onset, partial response, adverse reactions, and resistance to treatment. Based on these requirements, alkaloids have been introduced and recognized as novel hopefuls in the upcoming generation of antidepressent medications. (zhang et al., 2006)

In the future, alkaloids could play a major role owing to their multi-target mechanism of action. In contrast to predominant mono-target drugs available today, there are several alkaloids, such as berberine, harmine, piperine, and mesembrine, which have been found to have multi-target activities regarding neurotransmitters, brain-derived neurotrophic factors, neuroinflammations, and protective functions against oxidative stresses simultaneously (Wang et al., 2011). The multi-target mechanism of action of these drugs is complementary to the pathophysiology of depression.

Another crucial future prospect comes from the possible rapid antidepressant effects. Some alkaloids demonstrate the ability to inhibit the monoamine oxidases or the serotonin reuptake. These mechanisms could make them work faster than the normal antidepressants. Such an attribute would be a major help to persons suffering from serious depression. (gupta RC.,2005)

Advances in the field of medicinal chemistry and drug delivery technology would aid in enhancing the availability, safety, and selectivity of alkaloids.

Alkaloids could be refined by changing their molecular structure to reduce their toxicity and improve their antidepressant properties. R&D in newer delivery technologies like nano-carriers could thus overcome the limitations of low solubility and pharmaceutical properties of alkaloids. (kulkarni sk et al., 2009)

IV. CONCLUSION

Depression is a multifactorial disorder that has presented limited effectiveness to conventional treatment using antidepressant medications in the past. Alkaloids obtained from medicinal plants have shown potential efficacy in the treatment of depression using different mechanisms, such as the modulation of monoamine neurotransmitters, inhibition of MAO enzymes, and anti-neuroinflammatory properties. The multiple-targeting properties, combined with the fact that they come from plants, make them potential supplements to conventional antidepressants that are currently used to treat depression.

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