Section A-Research paper

PLANT-BASED ALPHA-ALKALOIDS: A POTENTIAL BRAND-NEW TREATMENT FOR DEPRESSION

Shilajit Das, Avijit Majumder*, Bhavani Pentela

Department of Pharmacology, Noida Institute of Engineering and Technology (Pharmacy Institute)

19, Institutional Area, Knowledge Park II, Greater Noida, Uttar Pradesh 201306, India

Abstract

It has proven to categorise and treat depression as a range of mood disorders. Due to its widespread applicability and medicinal efficacy coupled with minimal adverse responses, ayurvedic drugs are utilised more frequently than synthetic ones around the world. This has led to the initiation of scientific investigations associating the antidepressant activity. The most common forms of medications used for the treatment of depression are antidepressants. Antidepressant medications come in a wide variety, and the only things that set them apart from one another are how they work in the brain, how much they cost, and how many side effects they have. The alkaloids obtained from various plants' seeds, bark, & roots are only a few of the elements that have been utilised traditionally in medicine. The primary focus of this review is the clinical behaviour of a plant-based alkaloid (the primary intermediate metabolites) as a potential brand-new treatment for depression.

Keywords: Alkaloids; antidepressants; neurotransmission; MAO Inhibitors; hippocampus.

Correspondence: Avijit Majumder, Email- avijitmazum@yahoo.com, Orcid Id: 0000-0002-3053-8106

Department of Pharmacology, Noida Institute of Engineering and Technology, Greater Noida, Uttar Pradesh, India.

1. Introduction

Approximately 264 million people worldwide are affected by depression which is proved to be a prevalent mental illness [1]. As optimal hormone concentrations are necessary for brain function and emotion regulation, hormones like dopamine as well as norepinephrine can contribute to depression [2]. Major depressive disorder typically manifests in persons in their

twenties, with a second peak occurring in their fifties. Depression is twice as common in women as in men [3] .Being separated or divorced is another risk factor for developing major depressive illness [4]. Depression is the major cause of suicide largely recorded in the United States of America [5]. There was also a huge rise of depression cases during the time of COVID-19 pandemic all over the world especially USA [6]. Alkaloids contain some mixtures with neutral and even mildly acidic characteristics [7, 8]. Most commercial interest is focused on about 30 alkaloids, mostly as medications, flavours, or poisons [9-12]. Alkaloids also possess hypertensive, sedative and tranquilizing properties [13].

2. Plant Alkaloids as Antidepressants

The literature has documented the antidepressant effects of many plant alkaloids. When examined on a 5-Hydroxy-tryptamine system found in the hippocampus of rats, Brazilian researchers extracted strictosidinic acid coming from *Psychotria myriantha* that displayed effects resembling those of an antidepressant. During the forced swim test, it was found that berberine therapy greatly decreased immobility and boosted climbing activity [14]. However, the elevated plus maze test revealed increased open-arm exploration, confirming that the antidepressant action had no effect on swimming time. Anonaine, liriodenine, 1, 2-dimethoxy-5, 6, 6a, 7, tetrahydro-4H-dibenzoquinoline, 3, 8, and 9-tetraol, as well as nornuciferine, were among the alkaloids identified from *Annona cherimolia* [15].The findings demonstrated that prolonged administration of this plant to mice resulted in an effect resembling that of an antidepressant. A dose-dependent shortening of the inactivity period throughout the mouse forced swim test served as evidence of the antidepressant-like effects associated with the carboline alkaloid substances harmane, norharmane, and harmine [16]. *Ziziphus apetala's* Mauritine A, which inhibits 11-hydroxysteroid dehydrogenase in vitro with significant effectiveness, has also been found to have depressive properties [17]. The effectively obtained diterpene alkaloid compounds (songorine, napelline, mesaconitine & hypaconitine) from *Aconitum baicalens* have demonstrated an antidepressant-like impact in an animal model of depression [18]. *Boerhaavia diffusa* Linn was used to produce Punaravine, which was isolated by Dhingra and Valecha in 2014. In both stressed and unstressed mice in various settings, it demonstrated considerable antidepressant activity [19]. Evodiamine was cleansed through E*vodia fructus* & discovered that it could increase immobility time and reverse decreases in preference of sucrose, the crossing numbers, 5-Hydroxytryptamine as well as other variables [20]. Mesembrine, a component of *Sceletium tortuosum*, was discovered to have antidepressant effects in animal tests, according to American researchers [21].

Wattanathorn and colleagues believed piperine, a major alkaloid found in *Piper nigrum*, to be useful [22].

2.1.Berberine

Reserpine's enhanced immobility duration was reversed by berberine (5 & 10 mg/kg, ip) [23].The generation of kynurenine in the cells of A549 was greatly reduced by berberine, a recently discovered indoleamine oxygenase inhibitor. Through the Phosphoinositide 3-kinase/protein kinase B/nuclear component-E2-related factor 2-dependent pathway, berberine reduced reactive oxygen species levels and boosted nerve growth factor-mediated neurite outgrowth in several depression models. Berberine has been proven to shield rats from a variety of chronic depressive and stress-related symptoms in high doses. This implies that berberine might have medical uses [24].

Figure 1

2.2.Strictosidinic Acid

It is an important alkaloid which helps in the cure of depression. Strictosidinic acid derived from *Psychotria myriantha* helps to increase dopamine levels in rats. It helps in the treatment of depression by reducing 3, 4-dihydroxyphenylacetic acid expression [25].These are also referred to as one of the monoamine oxidase-A Inhibitors which are effective as antidepressants. Alkaloids have also served as excellent approaches for the engineered MAO inhibitors [26].Increased monoamine neurotransmitters in the brain and a reduction in depressive symptoms may result from MAO inhibition.

Figure 2

2.3.Curcumin

Antidepressant and anxiolytic effects in rats were frequently noticed when curcumin was given before the stressor, as indicated by alterations in behaviour, hunger, socialisation, and weight loss [27-33].

Figure 3

2.4. Hirsutine

U. rhynchophylla extract contains an alkaloid known as Hirsutine. *Uncaria* species are exempted from hirsutine. They have vasodilatory and central depressing characteristics.

Hirsutine is also effective in protection against neuronal death [34]. Numerous advantageous pharmacological effects on the central nervous system, including depression, are produced by *U. rhynchophylla* and its principal constituents, including hirsutine [35]. Hirsutine alleviates depressive-like behaviour in mice having depression [36].Hirsutine improved cognitive function as well as suppressed depression in an effective manner [37].

Figure 4

2.5. Nornuciferine

Nornuciferine along with other alkaloids had proven to have anti-depressive effect [38]. It comes from the plant *Annona cherimolia*. Neferine (10 mg/kg) & 8-hydroxy-2-(di-n-propylamino) tetralin (0.1 mg/kg) dosages combined to produce an antidepressant-like compact. When whole lotus plumule sizes extract alkaloids are present, nitric oxide (NO), a further contributor in the emergence of depression accompanied by inflammation, is created less frequently (60.1% neferine, 17.8% isoliensinine ,12.0% liensinine, and 4.54% nuciferine) [39].

Figure 5

2.6. Harmine

Harmine is obtained from the plants of *Peganum harmala* on mid to long term administration, improves the depressive state of rats [40]. Intraperitoneally given doses for harmaline (0.31, 0.625, & 1.25 mg/kg) reduced depressed and anxiety-like behaviour in Acute Radiation Syndrome mice. MAO-A total distribution volume (VT), a protein-level measure, has been shown to vary in major depression according to positron emission tomography investigations of harmine [41].Ayahuasca, an Amazonian beverage contains harmine, which shows to have potential psychotherapeutic action along with depression [42].

Figure 6

2.7. Piperine

The alkaloid piperine is obtained from the plant *Piper nigrum*. Piperine (PIP) has drawn increased attention for its potential to cure a number of CNS conditions, including depression, alzheimer's, epilepsy, anxiety, and parkinson's disease in the recent past[43]. PIP has reportedly demonstrated a range of CNS actions, including anti-epileptic, anti-depressant, and in a number of neurodegenerative conditions [44]. In the case of animal models of depression

brought on by corticosterone, piperine may have antidepressant properties. Piperine also shown antidepressant-like effects in mice exposed to mild chronic stress. Piperine treatment increased Brain Derived Neurotrophic Factor proteins and mRNA levels in the mouse hippocampus, decreasing the depressed reactions to corticosterone [45].

Figure 7

2.8. Evodiamine

Evodiamine was used in combination with berberine in order to improve depressive disorder [46]. Evodiamine ameliorating paclitaxel may offer an intriguing alternative for the treatment of CINP since it reduces inflammatory responses and maintains mitochondrial anti-oxidant capacities. [CINP-Chemotherapy induced neuropathic pain][47].The methanolic extract of *Calycatome villosa* contained alkaloids, saponins, carbohydrates, phytosterols, phenols, and tannins, according to preliminary phytochemical analysis. In a different trial, they combined berberine and evodiamine, two organic bioactive substances having antidepressant properties, into a nasal formulation [48].

Figure 8

2.9. Mesembrine

Previously categorised as *Sceletium tortuosum*, *Mesembryanthemum tortuosum L.* (Aizoaceae) is still frequently referenced to by that name in literature. A high level of mesembrine-type alkaloids in the plant is thought to be the reason for its psychedelic effects. These phytochemical components known as mesembrine-type alkaloids are responsible for these pharmacological actions [49].The distinctive neuro-psycho-pharmacological activities of the mesembrine, mesembrenone, mesembrenol, & mesembranol alkaloids found in *Sceletium tortuosum*, which may be the basis for the above-mentioned therapeutic qualities. *Centella asiatica* & *Mesembryanthemum tortuosum* are two herbs that are widely utilised in South Africa due to their anxiolytic & anti-depressant properties [50]. Due to the psychotropic mood-enhancing effects of mesembrine alkaloids, *Sceletium* plants have recently become more popular in mainstream culture alongside as recreational drugs [51]. Mesembrine has been sold as a consumer product due to binding studies demonstrating that it is a more powerful blocker of serotonin transporter (SERT) in comparison to fluoxetine (Prozac) [52].

Figure 9

2.10. Mesaconitine

According to a study, the antidepressant effects of napelline, hypaconitine, mesaconitine, & songorine are due in part to their ability to control serotonin function. Mesaconitine may have effects on the brain's central noradrenergic pathway and the serotonin system, acting similarly to tricyclic antidepressants and norepinephrine reuptake inhibitors, which raise norepinephrine levels in depression brought on by stress [53]. By increasing the activity of the serotonergic system, the diterpene alkaloid mesaconitine from *Aconitum baicalense* has demonstrated antidepressant properties in animal depression models [54]. Numerous neurological diseases, including nicotine dependency, Alzheimer's disease, schizophrenia, Parkinson's illness, and depression, have been linked to the effects of the α7 and α4β2* receptors [55].

Figure 10

2.11. Songorine

Songorine, a C20 diterpenoid alkaloid & 12-keto counterpart of napelline, was produced by *Aconitum soongaricum*, and it has been associated with a wide spectrum of biological functions. In vivo investigations on songorine have revealed stimulatory effects that have been linked to the dopaminergic system [56]. During sepsis, songorine encourages cardiac mitochondrial biogenesis through Nuclear factor erythroid 2-related factor 2 activation, hence assisting in reducing depression [57].

Figure 11

2.12. Mitragynine

Mitragynine, the primary alkaloid discovered in *Mitragyna speciosa* (kratom), may be used to alleviate depression and pain [58]. The pharmacology of modern [Chemotherapy induced peripheral neuropathy] CIPN pharmacotherapies such antidepressants is similar to that of mitragynine, which has a distinct, mixed pharmacological profile integrating opioid, adrenergic, & serotonergic features [59]. According to certain reports, mitragynine alters hippocampus synaptic transmission [60].

Figure 12

2.13. Others

Other less renowned alkaloids which also help in depression are Mauritine A, Punaravine, Protopine, Akuammine.

Figures 13-16

3. Mechanism of Action of Alkaloids as Antidepressants

Table 1

4. Conclusion

According to our review of the literature, alkaloids may have some therapeutic potential as natural antidepressants. The treatment of patients with any therapeutic option is inefficient; first-line antidepressant drugs have a documented failure rate ranging from 30–40% and a very sluggish onset of action. In various therapeutic classes, a number of alkaloids are being used in clinical practise and producing excellent results. In our review, we discovered enough scientific data to draw the conclusion that potentially plant-based alkaloids can be employed as a foundation for the creation of novel antidepressants.

5. Author's Contribution

Shilajit prepared the overall studies related to the manuscript and drafted it. Bhavani helped with the study design. Avijit approved the final work done .The final manuscript was read and approved by all authors.

6. Conflict of Interest

None.

7. Ethical Statement

None.

8. References

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Table 1

PLANT NAME	FAMILY	CHEMICAL CONSTITUENT	MECHANISM OF ACTION
Berberis aristata	**Berberidaceae**	**Berberine**	**Serotonergic, dopaminergic and noradrenergic, interventions**
Psychotria myriantha	**Rubiaceae**	**Strictosidinic acid**	**MAO inhibition**
Curcuma longa	**Zingiberaceae**	**Curcumin**	**Increase the levels of BDNF and others**
Uncaria rhynchophylla	**Rubiaceae**	**Hirsutine**	**Increase the levels of NE and 5-HT**
Annona cherimolia	**Annonaceae**	**Nornuciferine**	**Increase in monoaminergic turnover**
Peganum harmala	**Zygophyllaceae**	**Harmine**	**Preventing the function of MAO and a number of cell-surface receptors, such as serotonin receptor 2A**
Piper nigrum	**Piperaceae**	**Piperine**	**MAO enzyme inhibition, increased amounts of 5-HT and BDNF in the brain**
Evodia fructus	**Rutaceae**	**Evodiamine**	**Effects on BDNF-TrkB signalling and monoamine transmitters in the hippocampal region**

Sceletrium tortuosum	**Mesembryanthemaceae**	**Mesembrine**	**Inhibits the reuptake of 5-HT**
Aconitum baicalense	**Ranunculaceae**	**Mesaconitine**	**Improved serotonergic system**
Aconitum soongaricum	**Ranunculaceae**	**Songorine**	**Excitatory synaptic transmission**
Mitragyna speciosa	**Rubiaceae**	**Mitragynine**	**Reducing the release of corticosterone**
Ziziphus apetala	**Rhamnaceae**	**Mauritine A**	**11-β-hydroxysteroid dehydrogenase inhibition**
Boerhaavia diffusa	**Nyctaginaceae**	**Punaravine**	**Inhibition of MAO and a drop in plasma corticosterone**
Dactylicapnos scanens	**Papaveraceae**	**Protopine**	**Serotonin transporter with noradrenaline transporter inhibition**
Rhazya stricta	**Apocynaceae**	**Akuammine**	**MAO inhibition**

Figures

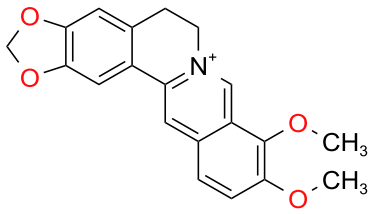

Fig 1: Berberine

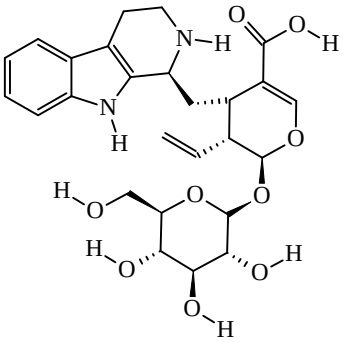

Fig 2: Strictosidinic acid

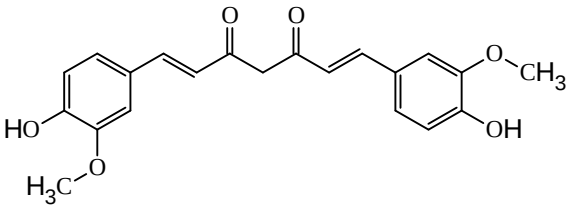

Fig 3: Curcumin

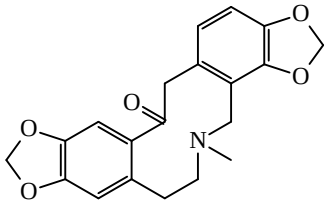

Fig 4: Hirsutine

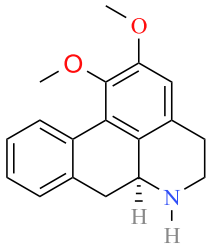

Fig 5: Nornuciferine

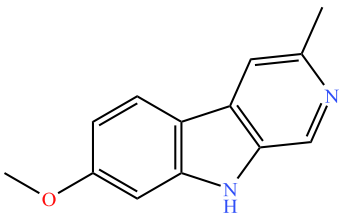

Fig 6: Harmine

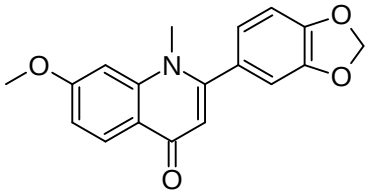

Fig 7: Piperine

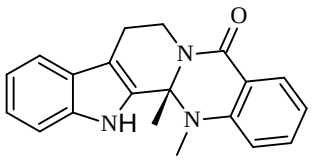

Fig 8: Evodiamine

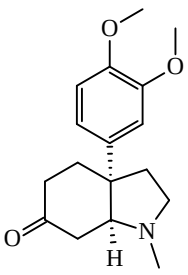

Fig 9: Mesembrine

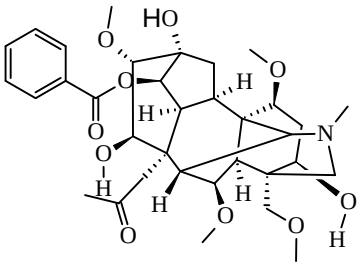

Fig 10: Mesaconitine

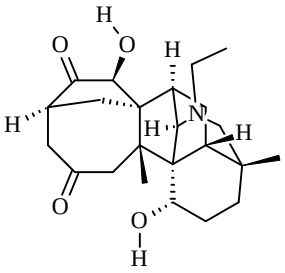

Fig 11: Songorine

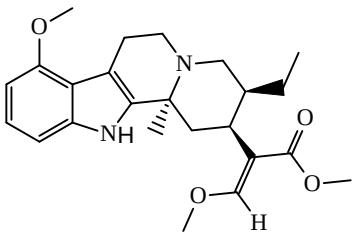

Fig 12: Mitragynine

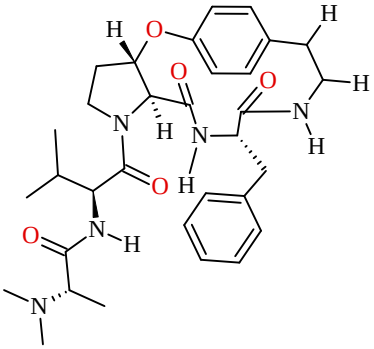

Fig 13: Mauritine A

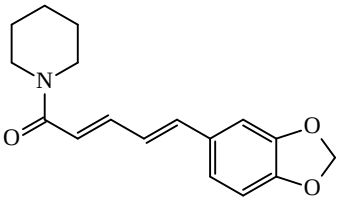

Fig 14: Punaravine

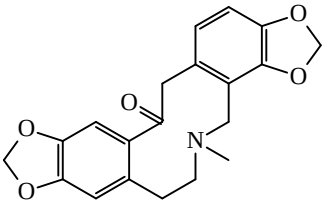

Fig 15: Protopine

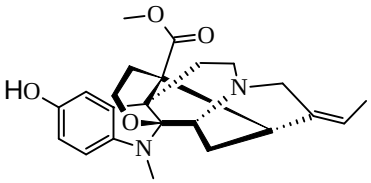

Fig 16: Akuammine