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Research Article

Lobeline: A Natural Alkaloid with Promising Neuroprotective Effect - A Novel Treatment Era

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Abstract:
Lobeline is an alkaloid that has actions like nicotine on nicotinic cholinergic receptors but is less potent. Lobeline, a natural alkaloid from the Lobelia genus, has emerged as a compound of interest due to its neuroprotective effects, particularly in the context of neurodegenerative diseases such as PD (Parkinson disease) anti-depressant, anti-epileptic. It has been proposed for a variety of therapeutic uses including in respiratory disorders, peripheral vascular disorders, insomnia, and smoking cessation. Neurodegenerative diseases are conventionally demarcated as disorders with selective loss of neurons. Recent studies have demonstrated that Lobeline exhibits significant protective properties against dopaminergic neuron death induced by neurotoxins like MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine). In animal models, Lobeline administration has been shown to alleviate behavioural deficits and reduce neurotoxin-induced immunoreactivity loss in key brain regions such as the substantia nigra and striatum, suggesting its potential utility in treating PD (Parkinson disease). Moreover, Lobeline's mechanism of action appears to involve the modulation of neurotransmitter systems, specifically through the inhibition of dopamine reuptake and the blockade of NMDARs (N-methyl-D-aspartate receptors), which are implicated in excitotoxicity. By preventing excessive calcium influx and oxidative stress associated with NMDARs (N-methyl-D-aspartate receptors) overactivity, Lobeline may offer a dual approach to neuroprotection both by enhancing dopaminergic signalling and by mitigating excitotoxic damage. In addition to its neuroprotective properties, Lobeline has shown promise in improving cognitive function and exhibiting antidepressant-like effects in preclinical studies. Its interaction with nicotinic acetylcholine receptors and modulation of BDNF (brain-derived neurotrophic factor) expression are likely contributors to these effects. In conventional medication therapies, several plants have been reported to bestow remedial effects. The present article reviews the potential efficacy of plant-derived alkaloid in particular Lobeline which possess potential therapeutic effects against PD (Parkinson's disease). Overall, the growing body of evidence supports Lobeline's potential as a therapeutic agent in the management of neurodegenerative disorders, warranting further investigation into its pharmacological mechanisms and clinical applications.

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Introduction:

Lobeline, a natural alkaloid primarily extracted from the Lobelia genus, Lobelia, named after the botanist Matthias de Lobel, comprises a large genus of flowering plants in the Campanulaceae family, with over 450 species predominantly found in tropical and temperate regions. Various species, such as Lobelia inflata, Lobelia nicotianaefolia, Lobelia cardinalis, Lobelia chinensis, Lobelia laxiflora, Lobelia trigona, Lobelia siphilitica, Lobelia sessilifolia, Lobelia polyphylla, and Lobelia pyramidalis, have been traditionally utilized in folk medicine for a range of ailments. For vertebrates to survive, oxygen must be transported from the environment into cells. Carbon dioxide and H+ must be created in the opposite direction of metabolism. Alkaloids are naturally occurring compounds containing carbon, hydrogen, nitrogen, and usually oxygen and are primarily found in plants, especially in certain flowering plants.[19]A single plant species usually comprises of few kinds of alkaloids but numerous families of plants such as Solanaceae (nightshades), Papaveraceae (poppies family), Ranunculaceae (buttercups) and Amaryllidaceae (amaryllis) are predominantly rich in several kinds of alkaloids Fig. 1 illustrates the role of alkaloids in a variety of NDDs and Fig. 2 illustrates neuroprotective effect of alkaloids. Phytochemical studies of these species have identified several novel bioactive secondary metabolites, highlighting their potential medicinal benefits and the importance of continued research into their therapeutic applications. has garnered significant attention in recent pharmacological research due to its neuroprotective properties.[1,18]

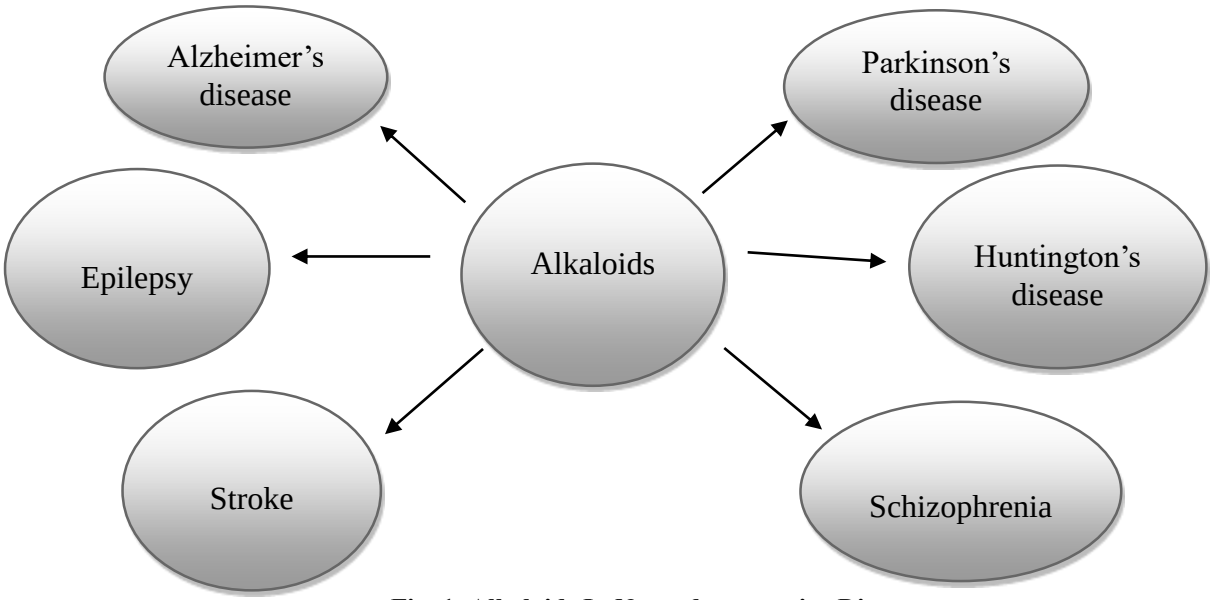

Fig. 1: Alkaloids In Neurodegenerative Diseases

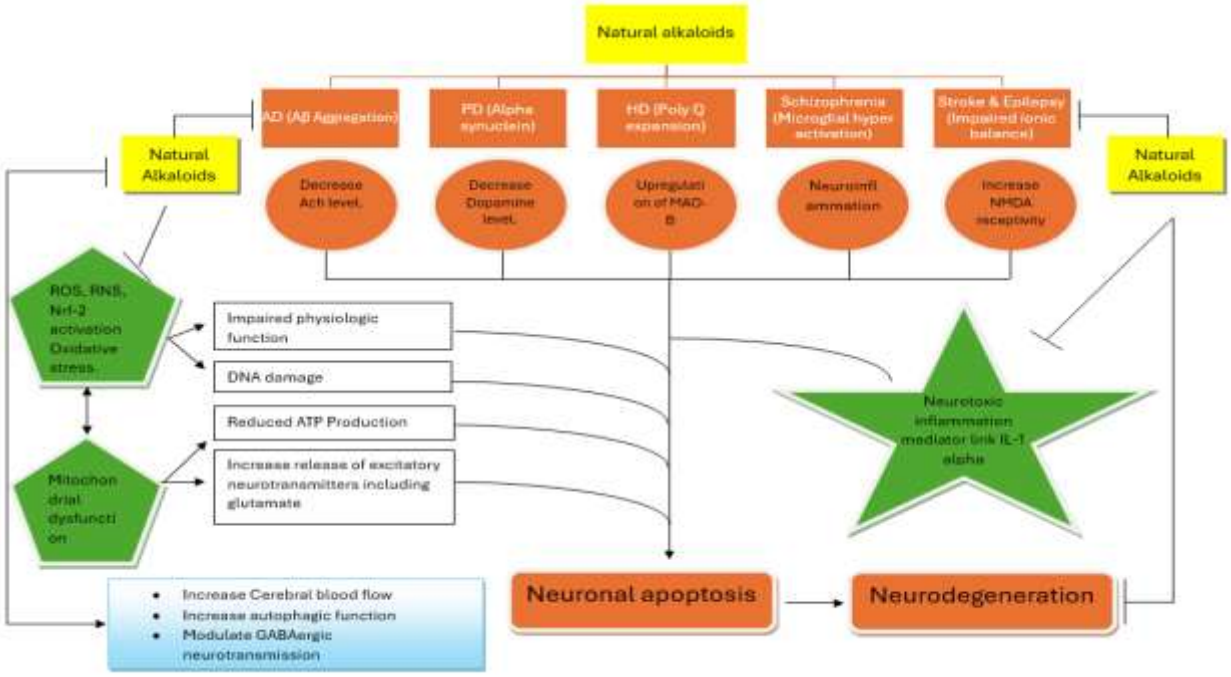

Fig. 2: Neuroprotective effects of Alkaloids

Lobeline acts as a competitive antagonist at nAChRs (Nicotinic acetylcholine receptors), particularly the α4β2 subtype. This interaction is crucial for its antidepressant-like effects. Research has shown that nAChRs (Nicotinic acetylcholine receptors) antagonists can produce antidepressant-like behaviours in various animal models.

Originally recognized for its use in traditional medicine, Lobeline has been investigated for its potential therapeutic effects against various neurodegenerative disorders, including Parkinson's disease and epilepsy. Studies have shown that Lobeline can protect dopaminergic neurons from neurotoxin-induced damage, particularly in models using MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), a well-known neurotoxin that mimics PD (Parkinson disease) pathology.[2,3] The mechanisms underlying Lobeline's neuroprotective effects are multifaceted. Research indicates that Lobeline acts as a modulator of the NMDARs (N-methyl-D-aspartate receptors), blocking excitotoxicity associated with excessive glutamate signalling. This action not only prevents neuronal death but also enhances synaptic plasticity and cognitive function.[4] Additionally, Lobeline has been shown to interact with nAChRs (Nicotinic acetylcholine receptors), further contributing to its antidepressant-like effects and potential cognitive enhancement.[5]

In preclinical study, it was explored the effects of Lobeline on adult ADHD (Attention-deficit/hyperactivity disorder).[6] The research involved nine adults (5 females and 4 males, ages 23–41, with a mean age of 31.11 ± 7.08 years). Participants underwent a 7-day regimen that included oral administration of methylphenidate capsules at doses of 0, 15, or 30 mg, followed by sublingual Lobeline tablets at doses of 0, 7.5, 15, or 30 mg one hour later. Placebo doses for both forms of medication were also administered. The findings revealed that Lobeline led to a modest improvement in working memory, although it did not significantly enhance attention in the participants with ADHD (Attention-deficit/hyperactivity disorder).

The effects of Lobeline, extracted from Lobelia nicotianaefolia, were examined in the context of seizures induced by chemoconvulsants. The researchers compared Lobeline's efficacy to that of diazepam, a well-known anticonvulsant. The aim was to evaluate Lobeline's potential as an alternative treatment for seizure disorders. The researchers found that Lobeline exhibited significant anticonvulsant activity, particularly at the 20 mg/kg dose, enhancing brain GABA (gamma-aminobutyric acid) levels within 45 minutes post-administration. Saline served as the negative control.[7] Also, in the study of Buttler that shows improvement in sensation after injection of Lobeline into the right antecubital vein were studied in 8 subjects after bilateral lung transplantation and 10 control subjects.[6]

Therapeutic efficacy of Lobeline:

Lobeline is a piperidine alkaloid isolated from e leaves and tops of wild tobacco Lobelia inflata and exhibits neuroprotective effects. It is a lipophilic alkaloidal component of Indian tobacco. Lobeline inhibits nicotine-evoked dopamine release and [3H] nicotine binding, thus acting as a potent antagonist at both $\alpha_3\beta_2$ and $\alpha_4\beta_2$ neuronal nicotinic receptor subtypes. However, Lobeline does not release dopamine from its presynaptic terminal, but appears to induce the metabolism of dopamine intraneuronally. Revaluation of the mechanism by which Lobeline alters dopamine function reveals that its primary mechanism is inhibition of dopamine uptake and promotion of dopamine release from the storage vesicles within the presynaptic terminal, via an interaction with the tetrabenazine-binding site on the vesicular monoamine transporter (VMAT2). Thus, Lobeline appears to perturb the fundamental mechanisms of dopamine storage and release. Based on its neurochemical mechanism, the ability of Lobeline to functionally antagonize the neurochemical and behavioural effects of the psychostimulants amphetamine and methamphetamine was examined. Lobeline was found to inhibit the amphetamine-induced release of dopamine in vitro, and amphetamine-induced hyperactivity, drug discrimination, and self-administration. [1]

Lobeline: Anti- Parkinson activity:

PD (Parkinson disease) involves the dopaminergic neuronal loss in substantia nigra pars compacta (SNpc) and is second most common neurodegenerative disorder. Parkinson's disease is one of the most prevalent neurodegenerative disorders, affecting millions worldwide. The hallmark of PD (Parkinson Disease) is the loss of dopaminergic neurons, leading to motor symptoms such as tremors, rigidity, bradykinesia, and postural instability. The pathophysiology of PD (Parkinson Disease) involves complex interactions among genetic predispositions, environmental factors, and neuroinflammatory processes. The adult hippocampal DG (dentate gyrus) receives inputs from dopaminergic neurons in SN. So, deterioration of dopaminergic neurons may directly affect adult hippocampal neurogenesis. LB (Lewy bodies) are associated with the pathology of PD (Parkinson Disease) and α-synuclein is the chief component of LB (Lewy bodies) which become aggregated in PD (Parkinson Disease).[1] Current treatments primarily focus on symptomatic relief through dopaminergic therapies like levodopa; however, these treatments do not halt disease progression and can lead to long-term complications.[8]

Research has demonstrated that Lobeline exhibits protective effects against neurotoxin-induced dopaminergic neuron death, particularly in models using MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine). In a study, Lobeline was shown to significantly reduce behavioural deficits and neurotoxin-induced immunoreactivity loss in the substantia nigra and striatum regions when administered prior to MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) exposure.[5] These findings suggest that Lobeline may protect dopaminergic neurons by modulating neurotransmitter systems and reducing oxidative stress.[3] One of the critical mechanisms through which Lobeline exerts its

neuroprotective effects is by acting as an antagonist to NMDARs (N-methyl-D-aspartate receptors). Excitotoxicity resulting from excessive glutamate signalling through NMDARs is a significant contributor to neuronal damage in PD (Parkinson Disease).[4] Lobeline's ability to block NMDARs (N-methyl-D-aspartate receptors) activity helps prevent calcium overload in neurons, thereby reducing oxidative stress and subsequent cell death.[3] This action positions Lobeline as a promising candidate for mitigating excitotoxic damage associated with PD (Parkinson Disease). Lobeline, has also been shown to inhibit DAT (dopamine transporter) activity. By blocking DAT-mediated dopamine reuptake, Lobeline increases extracellular dopamine levels, which can enhance dopaminergic signalling in the brain.[7] This mechanism may provide symptomatic relief for patients with PD (Parkinson Disease) by improving motor function and potentially alleviating some non-motor symptoms associated with the disease.

Another study, Lobelia cardinalis was identified as containing nAChRs (Nicotinic acetylcholine receptors) binding activity with anti-inflammatory and neuroprotective properties for Parkinson and Alzheimer disease.[9]

Furthermore, the anticonvulsant activity of the Lobeline isolated from the Lobelia nicotianaefolia in chemo convulsant-induced seizures and its biochemical mechanism by investigating relationship between seizure activities and altered GABA (gamma amino butyric acid) in brain of mice in PTZ (Pentylenetetrazol) seizure models. GABA (gamma amino butyric acid) is the major inhibitory neurotransmitter in the central nervous system and even slight deficiencies in GABAergic transmission may lead to hyperexcitability and pathological neuronal discharges leading to epilepsy. This study showed that isolated Lobeline (20mg/ kg) exhibited potent anticonvulsant activity against PTZ (Pentylenetetrazol) induced seizures. Also, a biochemical evaluation suggested significant increase in brain GABA (gamma amino butyric acid) level at 20 mg/kg i.p. of isolated Lobeline. Hence, in conclusion we can say that Lobeline reduces epileptic seizures by enhancing the GABA (gamma amino butyric acid) release supporting the GABAergic mechanism.[8]

Several studies have explored the efficacy of Lobeline in preclinical models of PD (Parkinson's disease):

1. Behavioral Studies: In a series of experiments involving rotarod and swim tests following MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) administration, Lobeline treatment resulted in improved locomotor activity compared to control groups. These behavioral improvements correlate with reduced neuronal loss in key areas affected by PD (Parkinson Disease).[3]

2. Neurochemical Assessments: Immunohistochemical evaluations have shown that Lobeline treatment significantly decreases the loss of TH (tyrosine hydroxylase) immunoreactivity in the substantia nigra and striatum following MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) exposure. This suggests that Lobeline preserves dopaminergic neuron integrity and function.[10]

3. Oxidative Stress Reduction: Lobeline has been reported to mitigate oxidative stress markers in neuronal tissues exposed to neurotoxins. Studies indicate that Lobeline reduces DNA damage and oxidative stress induced by seizures in animal models, further supporting its role as an antioxidant.[11]

Lobeline: Antidepressant-Like Effects and Mechanisms of Action:

Antidepressant therapies typically target neurotransmitter systems, particularly serotonin (5-HT), NE (norepinephrine), and DA (dopamine). The monoamine hypothesis posits that depression results from deficiencies in these neurotransmitters. More recent theories emphasize the role of neuroplasticity and neurotrophic factors, such as BDNF (brain-derived neurotrophic factor), in mediating antidepressant effects.

Lobeline's pharmacological profile suggests it may influence multiple neurotransmitter systems, particularly through interactions with nAChRs (nicotinic acetylcholine receptors) and modulation of noradrenergic signalling pathways.[12]

1. Interaction with Nicotinic Acetylcholine Receptors: Research has shown that nAChRs (nicotinic acetylcholine receptors) antagonists can produce antidepressant-like behaviours in various animal models, In a study examining Lobeline's effects on mice subjected to chronic unpredictable stress, Lobeline administration significantly reduced immobility time in the FST (forced swim test), indicating an antidepressant-like effect. Additionally, Lobeline's ability to attenuate stress-induced increases in plasma corticosterone levels suggests it may modulate the HPA (hypothalamic-pituitary-adrenal) axis, a key player in the body's response to stress.[2,10]

2. Modulation of Neurotransmitter Levels: Lobeline has been shown to influence levels of norepinephrine and serotonin in the brain. In preclinical studies, Lobeline treatment resulted in significant reductions in norepinephrine levels in the prefrontal cortex following forced swim stress. This modulation of neurotransmitter levels may contribute to its observed antidepressant-like effects. Moreover, Lobeline's interaction with dopaminergic pathways is noteworthy. By inhibiting dopamine reuptake and promoting dopamine release from vesicles via VMAT2 (vesicular monoamine transporter 2), Lobeline enhances dopaminergic signalling (Drug Bank). This mechanism could play a role in alleviating depressive symptoms associated with dopaminergic dysfunction.[2]

Preclinical Evidence Supporting Antidepressant-Like Effects:

a) Behavioral Studies:

- **Forced Swim Test (FST):** In studies utilizing the FST—a widely accepted model for assessing antidepressant activity—Lobeline administration significantly reduced immobility time compared to control groups. This reduction indicates an increase in active coping strategies among treated mice, suggesting an antidepressant-like effect.[2]

- **Tail Suspension Test (TST)**: The TST is another behavioral assay used to evaluate antidepressant efficacy. While Lobeline did not significantly alter immobility time in this test, its effects on other behavioral measures suggest a complex interaction with mood regulation mechanisms.[10]

- **Novelty Suppressed Feeding Test (NSFT)**: Repeated treatment with Lobeline significantly reduced feeding latency in the NSFT, further supporting its potential as an antidepressant by indicating reduced anxiety-related behaviours.[10]

b) Neurochemical Assessments: Research has demonstrated that Lobeline influences various neurochemical pathways associated with mood regulation:

- **Corticosterone Levels**: Lobeline pretreatment significantly attenuated forced swim stress-induced increases in plasma corticosterone levels, indicating a modulatory effect on HPA **(**hypothalamic-pituitary-adrenal**)** axis activity.[10]

- **Norepinephrine and Serotonin Levels**: High-performance liquid chromatography assessments revealed that Lobeline administration resulted in altered norepinephrine levels.

The unique pharmacological profile of Lobeline may allow it to be used in combination with existing antidepressants to enhance therapeutic outcomes. For instance, combining Lobeline with SSRIs (selective serotonin reuptake inhibitors) could potentially improve efficacy by targeting multiple neurotransmitter systems.[10]

Antiepileptic Activity of Lobeline:

Epilepsy is a chronic neurological disorder characterized by recurrent seizures resulting from abnormal electrical activity in the brain. It affects millions of people worldwide and can significantly impact quality of life. The pathophysiology of epilepsy is complex and involves various factors, including genetic predispositions, structural brain abnormalities, and imbalances in neurotransmitter systems, particularly. GABA (gamma-aminobutyric acid) and glutamate. Current antiepileptic drugs (AEDs) primarily target either sodium channels or GABAergic pathways to inhibit neuronal excitability. However, many patients experience inadequate seizure control or adverse side effects from existing medications. Therefore, there is a pressing need for novel therapeutic agents with improved efficacy and safety profiles.[13]

The efficacy of Lobeline as an anticonvulsant has been primarily assessed using PTZ (Pentylenetetrazol)-induced seizure models. In these studies, Lobeline was administered at various doses (5, 10, 20, and 30 mg/kg) prior to PTZ (Pentylenetetrazol) exposure. Results indicated that doses of 10 mg/kg and above significantly delayed seizure onset and reduced the severity of seizures compared to control groups. The protective effects were further corroborated by biochemical evaluations showing increased GABA (gamma-aminobutyric acid) levels following Lobeline treatment. These findings suggest that Lobeline's enhancement of GABAergic transmission plays a critical role in its anticonvulsant activity.[7]

In addition to PTZ (Pentylenetetrazol) models, Lobeline's anticonvulsant properties have also been evaluated using strychnine-induced seizures. Strychnine acts as a glycine receptor antagonist, leading to increased excitability and convulsions. Lobeline administration effectively antagonized strychnine-induced seizures, further supporting its broad-spectrum anticonvulsant activity.[7]

Given its multifaceted mechanisms of action and promising preclinical findings, Lobeline holds potential as a therapeutic agent for treating epilepsy. Its ability to enhance GABAergic transmission while modulating cholinergic signaling provides a unique approach to managing seizure disorders. Lobeline, may also be explored as an adjunct therapy alongside existing antiepileptic drugs (AEDs). Combining Lobeline with traditional antiepileptic medications could enhance therapeutic efficacy while potentially reducing side effects associated with higher doses of conventional drugs.

Lobeline has also been reported to block NMDARs (N-methyl-D-aspartate receptors), which are critical for glutamate signaling. Excessive activation of NMDARs (N-methyl-D-aspartate receptors) can lead to excitotoxicity and neuronal damage. By inhibiting NMDARs (N-methyl-D-aspartate receptors), Lobeline helps protect neurons from glutamate-induced excitotoxicity while simultaneously promoting a balanced neurotransmitter environment conducive to increased GABA (gamma-aminobutyric acid) levels.[14]

The Potential of Lobeline in Alzheimer's Disease (AD):

Alzheimer's disease is characterized by the accumulation of amyloid-beta plaques and neurofibrillary tangles composed of hyperphosphorylated tau protein. The accumulation of amyloid oligopeptides in the brain is the primary cause of Alzheimer's disease pathogenesis.[17] These pathological features lead to neuronal loss, synaptic dysfunction, and ultimately cognitive decline.[15] The cholinergic hypothesis posits that a deficiency in ACh (acetylcholine) contributes to cognitive impairment in AD. Current treatments, such as cholinesterase inhibitors (e.g., donepezil), aim to increase ACh

(acetylcholine) levels but often provide only modest benefits.[16]

Lobeline has been shown to inhibit DAT (dopamine transporter) activity, leading to increased extracellular dopamine levels. This modulation may enhance dopaminergic signaling in the brain, which could be beneficial for cognitive function. The interplay between dopamine and ACh (acetylcholine) is critical for maintaining cognitive processes such as attention and memory.[7] Lobeline acts as a competitive antagonist at nAChRs (nicotinic acetylcholine receptors), particularly the $\alpha_4\beta_2$ subtype. This interaction is crucial for its potential cognitive-enhancing effects. Research has shown that nAChRs (nicotinic acetylcholine receptors) antagonists can exhibit antidepressant-like properties and may also enhance cognitive function by modulating cholinergic signaling. By influencing nAChRs (nicotinic acetylcholine receptors) activity, Lobeline may help restore cholinergic signaling disrupted in AD.[1]

Oxidative stress plays a significant role in the pathophysiology of Alzheimer's disease. Lobeline has demonstrated antioxidant properties that may help protect neurons from oxidative damage. In preclinical models, Lobeline administration has been associated with reduced markers of oxidative stress and DNA damage. By mitigating oxidative stress, Lobeline may help preserve neuronal integrity and function.[6,11] In animal models, Lobeline has shown promise in enhancing cognitive function. For instance, studies have indicated that Lobeline administration improves performance in tasks assessing learning and memory.[6] These findings suggest that Lobeline may have potential as a cognitive enhancer in conditions like Alzheimer's disease, evidence regarding Lobeline's effects on amyloid-beta accumulation is limited, its ability to modulate neurotransmitter systems suggests a potential role in mitigating amyloid-related toxicity. Enhanced cholinergic signaling through nAChRs (nicotinic acetylcholine receptors) modulation could influence amyloid precursor protein processing and clearance mechanisms.[15]

Lobeline exhibits significant potential for managing Alzheimer's disease through its interactions with nicotinic acetylcholine receptors, dopaminergic modulation, and neuroprotective effects against oxidative stress.[16] While preclinical evidence supports its efficacy, further research is necessary to establish its safety profile and effectiveness in human populations. As the search for novel therapeutic agents continues, Lobeline represents a promising candidate worthy of further investigation.[20]

Conclusion:

Lobeline, a piperidine alkaloid derived from the Lobelia genus, presents a multifaceted approach to addressing the challenges posed by neurodegenerative diseases like epilepsy, Alzheimer, Parkinson and mania. This review has highlighted Lobeline's potential through various mechanisms of action, including its modulation of cholinergic and dopaminergic systems, enhancement of GABAergic transmission, and neuroprotective effects against oxidative stress and excitotoxicity. In conclusion, Lobeline's multifaceted mechanisms of action position it as a promising candidate for the management of various neurodegenerative diseases. There are several drugs, which have been used for NDDs till date, but they do not possess the efficacy to amend the disease progression. Numerous natural alkaloids retain mounting effects in the treatment of several NDDs. Along with modulating neurotransmitter system, natural alkaloids also possess anti-amyloid, anti-inflammatory, and antioxidant properties as well as anti-depressive and anti-convulsing efficacy. Thus, natural alkaloids possess multiple mechanistic approaches in the treatment of NDDs. It has been suggested that the selection of natural alkaloids in the treatment of NDDs is safe as compared to synthetic drug. There is a vital requirement to design clinical trials for such compounds that are not even entered in the clinical trials till date, because the natural alkaloids are encouraging hope in slowing the development and progression of NDDs. Its ability to modulate cholinergic and dopaminergic systems, enhance GABAergic transmission, and provide neuroprotection against oxidative stress makes it a compelling focus for future research aimed at developing more effective therapeutic strategies for this debilitating condition. As we advance our understanding of Lobeline's pharmacological properties, it holds the potential to contribute significantly to the landscape of various neurodegenerative disease treatment options. From above studies, Lobeline seems to be an active natural alkaloid against several neuroprotective effects.

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