

**SYSTEMATIC REVIEW ON PHYTOCHEMICAL AND
PHARMACOLOGICAL PROFILE OF *LOBELIA
NICOTIANAEOFOLIA* ROTH E & S**

Abrar Tamboli, Imran Khan, Ketan Bhutkar, Rukhsana Rub*

Department of Pharmacognosy, M.C.E Society's Allana College
of Pharmacy, 2390, K.B. Hidayatullah Road, Azam
Campus, Camp, Pune-411 001, MS, India.

Summary

Lobelia nicotianaefolia is a hairy biennial or perennial herb found in many parts of India at altitudes of 700-2200m and is a native of Indo-Malaysian regions and Sri Lanka. The plant was primarily used to treat cold and respiratory problems. *Lobelia nicotianaefolia* is a rich source of alkaloids, the main alkaloid being lobeline and others include lobelanine, lobelanidine, as well as fourteen piperidine alkaloids, which comprise the total alkaloidal content of the plant to 1.04-1.18%. Lobeline has been found to be effective in respiratory disorders like asthma, pneumonia, asphyxia in newborn infants. Also the research work on effect of lobeline on psychological disorders like drug abuse, smoking cessation and learning disorder like Alzheimer disease is in process. The present review elaborately summarizes the ethnomedical, phytochemical and pharmacological review.

Keywords: *Lobelia nicotianaefolia*, Lobeline, drug abuse
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***Author for correspondence:** Prof. Rukhsana A. Rub,
Head, Department of Pharmacognosy,
Allana College of Pharmacy,
2390, K.B. Hidayatullah Road, Azam campus, Camp,
Pune-411001
Maharashtra, India.
Email: hailrukhsar@yahoo.com
Mobile No. +91-9890937888.

Introduction

Indian Lobelia consists of dried roots and dried above ground parts of *Lobelia nicotianaefolia* Roth E & S, Family Lobeliaceae.



Figure1. *Lobelia nicotianaefolia* Roth E & S

The generic name lobelia was given to the plant by Carl von Linne, the Swedish botanist and taxonomist popularly known as Linnaeus-considered the father of modern botany and classification. *Lobelia nicotianaefolia* is a hairy biennial or perennial herb found in many parts of India at altitudes of 700-2200m that reaches a height upto three meters ^[1, 2]. Globally this species is distributed in South India, North East India and in the Indo-Malaysian regions and Sri Lanka. Within India it is distributed in the Western Ghats of Maharashtra, Karnataka, Kerala and Tamil Nadu. This species is distributed in Indo-Malaysia. Within India, it is distributed in the Western Ghats of Maharashtra, Karnataka, Kerala and Tamil Nadu ^[3, 4].

Ethnomedical Review

Leaf paste mixed with a pinch of lime is applied to foul smelling wounds for speedy healing^[5]. Infusion of leaves is used as an antispasmodic, roots are used in scorpion sting, antiseptic to asthma^[6].

Root extract has been used in tonsillitis and stomachache. Leaf extract is also used in ringworm and eczema as an external liniment. Apart from these, plant is used in epilepsy and snakebites. It is an effective pesticide. Leaf extract is used against leach. Leaf yields a good litter. Flowers are beautiful and used for decorations^[7]. The plant is used to treat cold and respiratory problems^[8]. Decoction of flowers and leaves are antispasmodic and are used in asthma, bronchitis and fever. In ayurveda, plant is used for sciatica and back pain. Roots are useful in the treatment of eye diseases.^[9,10]

Phytochemical Review

1. *Lobelia nicotianaefolia* is a rich source of alkaloids of the Lobeline group & used as a substitute for *Lobelia inflata*. The plant has been recorded to contain several alkaloids with the main alkaloid lobeline apparently observed, revealed higher concentrations. The total alkaloids content ranges, from 1.04-1.18%^[11].
2. The active principle of lobelia is an acrid, irritating, unstable alkaloid, called *lobeline*, first obtained by Wm. Procter, Jr. The chemical formula of lobeline is $C_{22}H_{27}NO_2$, for a molecular mass of 337.47. In proper nomenclature, lobeline is 2-[6-(2-Hydroxy-2-phenylethyl)-1-methyl-2-piperidinyl]-1-phenylethanone^[12].
3. Lobeline separates from alcohol, ether or benzene in shining needles with melting point 130. It is readily soluble in hot alcohol or benzene, sparingly soluble in light petroleum or ether. The hydrochloride forms rosettes of needles and is soluble in chloroform. On warming with water, lobeline produces acetophenone. With benzoyl chloride it yields benzoyl lobeline hydrochloride^[12].

4. Lobeline; primary alkaloid, but atleast 14 piperidine-type alkaloids have been identified, including lobelanine and lobelanidine. Lobeline, lobelanine, and lobelanidine are found in the greatest proportions. Lobelamine, norlobelanine, lelobanidine, norlelobanidine, norlobelanidine, lobinine, norlobeline (=isolobelanine), lelobanidine, lovinine, isolobinine, lobinanidine are present in lesser amounts^[13].
5. In addition to the alkaloids, lobelia also contains a bitter glycoside (lobelacrin), chelidonic acid, lipids (fats), gum, resin, a pungent volatile oil (labelianin), chlorophyll, lignin, salts of lime and potassium, with ferric oxide. Another constituent of lobelia, beta-amyirin palmitate, has been studied for its antidepressant effects^[14].
6. Also gum, resin, chlorophyll, fixed oil, lignin, salts of lime and potassium, with ferric oxide, manganese and vitamins A and C are present in the leaves. Lobelacrine, formerly considered to be the acrid principle, is probably lobelate of lobeline^[15].
7. Apart from *L.nicotianaefolia*, the pyrrolidine alkaloids radicamine A and B have been isolated from *L. chinensis*. A bioactive (α -glucosidase inhibitor) homonojirimycin glycoside has been isolated from *L. sessilifolia*^[16].
8. Typical lobelia alkaloids belong to three groups, the basic structure of these alkaloids shown in Figure 2. The main ring is derived from lysine via piperidine, while the two benzene rings it contains are derived from phenylalanine via the shikimic acid pathway^[17].
9. Lobeline is a tertiary base and a keto-alcohol on reduction with sodium amalgam in acetic acid, lobeline furnishes lobelanidine by reduction of the benzoyl group to CHOH. C₆H₅. and is oxidized by chromic oxide in acetic acid to lobelanine by the conversion of the C₆H₅. CHOH group to CO.C₆H₅ (Fig.2).

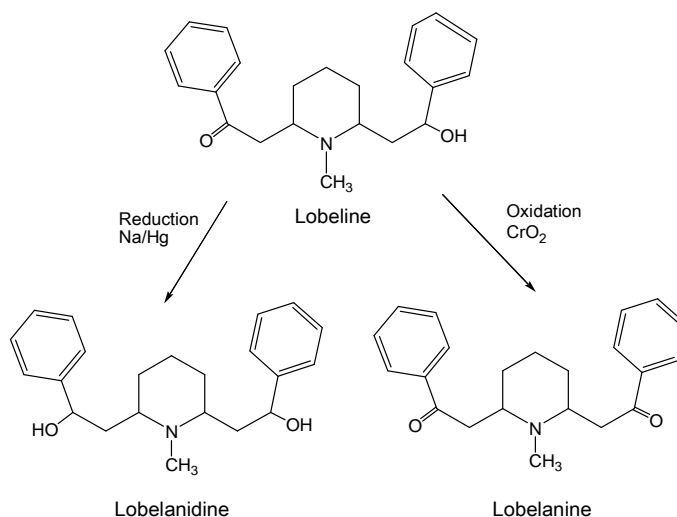


Figure 2. Structure of lobeline, lobelanidine and lobelanine.

Pharmacological Review

The primary bioactive component of *Lobelia nicotianaefolia* is an alkaloid lobeline, although the minor alkaloids have been shown to have similar but distinct pharmacology in a number of nicotinic cholinergic systems. Lobeline has a complex pharmacological profile. The following points focus on the pharmacological activities of lobeline.

1. Lobeline: Mixed agonist-antagonist.

Pharmacological literature exists for lobeline, which has long been classified as a nicotinic receptor ligand viz. lobeline activated inward currents in bovine chromaffin cells voltage clamped at negative holding potentials as that of nicotine and tetramethylammonium ^[18]. Responses obtained in superior cervical ganglion (SCG) neurones when compared with different nicotinic agonists then cytisine was found to be the most potent agonist and lobeline the least potent. ^[19]. However, several studies show that there is a large diversity of nicotinic receptor subtypes that differ in subunit composition and

function and that lobeline's actions are only partly caused by agonism at nicotinic receptors. Lobeline inhibits nicotine-evoked $^{86}\text{Rb}^+$ efflux from rat thalamic synaptosomes indicating that lobeline also as an antagonist at $\alpha 4\beta 2$ nicotinic receptors. Likewise, lobeline also inhibits [^3H] methyllycaconitine binding to rat brain membranes indicating that there is an interaction with the $\alpha 7$ nicotinic receptor subtype. Also, lobeline has been reported to be an antagonist at human $\alpha 7$ nicotinic receptors expressed in *Xenopus* oocytes [20,21,22]. Parker et al. has performed saturation and competition assays to determine the affinities of six different neuronal nAChR subunit combinations for Acetylcholine (ACh), Anabasine, Cytisine, 1,1-dimethyl-4-phenylpiperizinium (DMPP), Epibatidine, Lobeline, and Nicotine. These subunit combinations were found to vary in affinities for lobeline as well as for other nicotinic ligands [23].

2. Relation between Nicotine & Lobeline

Many similar effects for nicotine and lobeline, like tachycardia and hypertension, anxiolytic activity and improvement of learning and memory have been recorded [24, 25]. Nicotine and lobeline, when injected intradermally, did not provoke an axon reflex sweating [26]. Nicotine and lobeline were used as smoking cessation therapies, both were assessed for their ability to inhibit choline uptake into brain. Although nicotine did not significantly reduce choline permeability-surface area products, lobeline did inhibit brain [^3H]choline uptake [27]. However, the study conducted by Benwell et al. exhibited that lobeline fail to stimulate the mesolimbic dopamine (DA) system and locomotion in the rat in a nicotine-like way, also it exerted a short-lived antagonism of the stimulant effects of nicotine. Low doses of lobeline selectively and maximally attenuated nicotine-evoked locomotor stimulation while higher doses inhibit nicotine-evoked responses proves that lobeline does not increase locomotor activity [28]. Lobeline evoked dopamine release, but the effect was large and delayed with respect to nicotine; Noradrenaline (NA) release was not increased but rather depressed at high concentrations of lobeline from rat striatal slices [29]. Lobeline induces DA release by potent inhibition of DA uptake into

synaptic vesicles, and a subsequent alteration in presynaptic DA storage which was calcium-independent and insensitive to mecamylamine, a non-competitive nicotinic receptor antagonist that blocks the ion channel of the receptor. In addition, at weak concentrations that had no effect alone, lobeline blocked nicotine-evoked DA release, indicating that it acts as an antagonist at nicotinic acetylcholine receptor (nAChR) [24]. Application of lobeline releases norepinephrine (NE) from the cytoplasm which may be due to the vesicular uptake inhibition and a reversal of the plasma membrane carrier. Lobeline antagonized the high voltage activated calcium current in a dose-dependent manner in rat sympathetic neurons using the patch-clamp technique [30]. This suggests that blockade of the pre- and postsynaptic Voltage dependent Ca^{2+} channel (VDCC) contributes to the complex action of lobeline. Thus, the effects of lobeline on N-methyl-D-aspartate (NMDA), serotonin and NE release may be attributed to the complex action of lobeline. All of this suggests that nicotine and lobeline act on nAChR via a non-common CNS mechanism. Thus, the pharmacological effect of lobeline can either be mediated by minor subset populations of nAChR or through a non-nicotinic mechanism. It is also possible that lobeline causes an allosteric effect at the nAChR, leading to a modification of its properties [30, 31, 32].

3. Smoking Cessation

The most promising area in this field is the ability of lobeline to be a substitute of nicotine. As we have seen earlier, lobeline produces several physiological effects similar to those produced by nicotine. The use of lobeline as a smoking deterrent was reported in 1936, but several later studies led to a dispute between positive and negative reports. Numerous countries have sold drugs containing lobeline such as Nicoban, Bantron, CigArest, NicFite and Smoker's Choice. In 1993, however, the FDA claimed the inefficacy of these products and removed them from the market. In a recent patent, studies on a new formulation of drugs to deliver an effective amount of lobeline to sublingual mucosa were done. Sublingual formulation of lobeline sulfate does not appear to be an effective smoking cessation aid [33, 34]. Lobeline was a component of OTC products

for withdrawal from tobacco addiction for many years. Results from clinical studies of the efficacy of lobeline have been mixed and a meta-review found that none of the available studies have been controlled adequately or were of sufficient duration to prove its efficacy. The FDA removed lobeline from the market because of lack of demonstrated efficacy as part of its OTC review process in 1993 ^[35-36].

4. Drug Abuse

A novel mechanism of action proposed for lobeline, namely that it inhibited DA uptake into rat striatal synaptic vesicles by acting at the tetrabenzine binding site on vesicular monoamine transporter-2 (VMAT2). The induced inhibition of synaptic vesicular DA transport modified the concentration of DA in the cytosol and vesicles and, consequently, altered dopaminergic neurotransmission. The concentration of dopamine in the synaptic cleft and the activation of postsynaptic dopamine receptors diminished. Thus, by acting as an indirect antagonist of DA receptors, lobeline antagonizes the effect of psychostimulants which produce their effects, in part, by activation of the dopaminergic system. Experimental work has provided evidence that lobeline may be useful in the treatment of amphetamine abuse, based on the blockade of amphetamine-induced dopamine release in rat striatum. Lobeline attenuated the self-administration of amphetamine, but not sucrose, by rats. In several rodent models, lobeline had a selective effect on amphetamine-induced behavior and neurochemistry. The addiction liability of lobeline in humans has not been established. Systemic administration of lobeline also did not produce a significant depletion of striatal DA and Dihydroxyphenylacetic acid (DOPAC) content, suggesting that its inhibitory effect is not the result of a neurotoxic effect of the alkaloid. Lobeline was shown to attenuate self-administration of heroine in rats. Lobeline was effective in the treatment of alcohol abuse in both rats and mice. Lobeline augmented cocaine-induced hyperactivity after repeated administration in rats. Hu et al. proposed that the potassium large conductance calcium-activated channel KCNMA1 may be a protein targeted

by Lobeline which is said to be effective in treating drug abuse. Lobeline has been reported as a useful agent to treat dependency on drugs such as cocaine, amphetamine, caffeine, phenylcycline, opiates, barbiturates, benzodiazepines, cannabinoids, hallucinogens, and, especially, nicotine suggesting huge potential for lobeline to be used in pharmacotherapy for drug abuse^[22, 23, 37-42].

5. Respiratory Effects

For a very long time, the most important use for this drug has been in the treatment of respiratory problems. For this class of disease, no remedy was more highly valued by physicians in the late 19th century. The effect of lobeline on the heart appeared to be complex in character, consisting of initial stimulation both of the vagus nucleus in the medulla and the ganglion cells of the vagus in the nodes of the heart. The effect of lobeline on the blood-pressure shows an initial fall, due probably to cardiac inhibition, followed by a marked rise, after which the blood-pressure returns to normal; however in case of larger doses BP fall below normal level. Indeed, lobeline was known as a powerful respiratory stimulant causing a considerable increase in the pulmonary ventilation. This important property has been explained by the activation of the carotid and aortic body chemoreceptor at therapeutic doses. Larger doses may induce a cough. Lobeline relaxes the tissues and favors expectoration when a large quantity of mucus is secreted. The potent action of this alkaloid on the respiratory system has therefore been used with success in numerous applications. Chronic pneumonia, asthma, bronchitis and laryngitis are all conditions in which lobeline has been of great service. Lobeline has also been advantageous for the treatment of victims who have been electrocuted or asphyxiated by toxic gases. In animals narcotized by morphine, lobeline increases the rate of respiration and leads to adequate ventilation. Vomiting, micturition and defecation may occur when large doses are employed. Reflex respiratory effects, sensations and cough of lobeline attributed to J receptors even to rapidly adapting receptors (RARs). There was hypothesis that right handers and left handers may differ in sensory perceptions and respiratory

responses to J receptor stimulation with intravenous injections of lobeline in incremental doses but it proved wrong by the studies performed by Jaju et al. They have proved that handedness did not influence J receptor responses to lobeline. In adrenalectomized rats, lobeline was profoundly effective in preventing pulmonary edema when they pretreated with cortisone but unresponsive in case of lung edema. Injection of lobeline into asphyxiated adult and newborn rhesus monkeys during primary apnoea caused them to gasp earlier than normal time whereas in horses, lobeline infusion caused marked hyperpnea followed by a period of tachypnea. In demonstrating the bronchoconstrictor effect of lobeline, healthy patients found to have three times more ventilation than the normal subjects but patients with mitral stenosis showed only minute change along with the appearance of cough in 30% of total patients. Moreover, it was useful in the case of the paralysis of respiratory centers after drug poisoning with alcohol, soporifics or morphine or after narcosis. Lastly, it has also been used to treat asphyxia in newborn infants^[33, 43-49].

6. Memory and Learning

Lobeline has been studied for its ability to improve learning and memory. Lobeline was found to improve learning on the radial-arm maze hence may be useful in the development of novel treatments for learning deficits^[50]. This pharmacological profile may be of great importance in the treatment of learning disorders like Alzheimer's disease, the most common cause of dementia in the elderly. Lobeline also appears to improve the performance of rats in sustained attention tasks. This disorder afflicts children as well as adults and is characterized by inattention, restlessness, impulsiveness and hyperactivity^[33]. Lobeline also has been found to have activity along with nicotine in anxiolytic models^[51]. Lobeline slightly improved the learning rate of lesioned animals. On the other hand, lobeline did not significantly modify the performance of saline injected animals. The deficit in the acquisition of a trace eyeblink classical conditioning was reverted by the systemic administration of carbachol, a nonselective cholinergic

muscarinic agonist, but not by lobeline^[52]. Lobeline useful as a pharmacotherapy for Substance Use Disorder (SUD) and Attention Deficit Hyperactivity Disorder (ADHD) but successful treatment of these disorders may require chronic lobeline treatment^[53].

7. Analgesia

A role for spinal nicotinic receptor subtypes in nonopioid analgesia has been found using the frog alkaloid epibatidine, and lobeline inhibited its analgesic properties by blocking antinociception and nociception but potentiated epibatidine induced agitation^[54].

8. Future Prospectus

Lobeline and its analogues could represent a novel class of therapeutic agents with a great potential for the treatment of psychostimulant abuse. Lobelane, a molecule formed from deoxygenation of the lobeline molecule, has a shorter duration of action compared to lobeline^[55]. Though, Lobeline failed significantly in treating smoking cessation, efforts have to make in developing analogs with a more desirable profile and a dosage regimen with a higher probability for success. As lobeline was found to be mixed agonist-antagonist at nAChR, it might be effective in treating neuropsychiatric disorders like Alzheimer's disease, Parkinson's disease, Schizophrenia and epilepsy. Till date, lobeline was not used in Tourette's syndrome; which is a chronic neurological disorder characterized by involuntary verbalizations and obsessive compulsive behaviors.

Conclusion

Lobelia is one of the most important plants mentioned in different traditional systems of medicine. The plant has been extensively used in treating respiratory disorders as well as in agro field. Lobeline is a principle phytoconstituent; also 14 piperidine-type alkaloids have been identified, including lobelanine and lobelanidine. Lobeline, lobelanine, and

lobelanidine are found in the greatest proportions while Lobelamine, norlobelamine, lelobanidine, norlelobanidine, norlobelanidine, lobinine, norlobeline, lelobanidine, lovinine, isolobinine, lobinanidine are present in lesser amounts which make total alkaloid content up to 1.04-1.18%. Pharmacological profile of lobeline highlights its distinguishing features from nicotine and its interaction with nicotinic receptors in brain. From pharmacological review, it is certain that lobeline has huge potential as a pharmacotherapy for drug abuse, also in treating respiratory problems. Lobeline and its analogues have great future in treating number of neuropsychiatric disorders like Alzheimer's disease, schizophrenia and epilepsy. Thus, more extensive research is needed in this area.

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