Journal of Chemical Health Risks

www.jchr.org

JCHR (2025) 15(4), 905-910 | ISSN:2251-6727

Comparison of Efficacy of Nicotine Vs Plant based Alkaloid in Addiction - An In-Silico Study

Dr NishaJaisree S[1], Dr Pratibha Ramani[2], Dr Abilasha Ramasubramanian[3]

[1,2,3]Department of Oral Pathology Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai

(Received: 16 May 2025 Revised: 20 June 2025 Accepted: 12 July 2025)

KEYWORDS

Nicotine, Addiction, Plant based alkaloids.

ABSTRACT:

Introduction: Nicotine addiction remains a global health challenge, contributing significantly to preventable morbidity and mortality. While nicotine replacement therapies (NRTs) offer some relief, their limited success rates and potential carcinogenic risks underscore the need for safer, plant-derived alternatives. Phytotherapeutic agents like lobeline, a natural alkaloid from Lobelia species, have demonstrated neuropharmacological activity via interaction with nicotinic acetylcholine receptors (nAChRs).

Objectives: This study aims to evaluate and compare the binding affinity of lobeline, a plant-based alkaloid, with that of nicotine to nAChRs using in-silico docking models, and to highlight the therapeutic advantages of phytotherapeutic agents in addiction management.

Methods: Molecular docking simulations were performed using AutoDock 4.2 to predict binding interactions between ligands (lobeline and nicotine) and the $\alpha 4 \beta 2$ subunit of the nicotinic acetylcholine receptor. Ligand structures were retrieved from ZINC and ChEMBL databases, and receptor files were preprocessed for docking. Docked complexes were analyzed for binding affinity (ΔG), hydrogen bonds, and amino acid interactions using PyMOL and Discovery Studio.

Results: Lobeline demonstrated a higher binding affinity (-8.14 kcal/mol) compared to nicotine (-3.8 kcal/mol). Key amino acid residues involved in lobeline's interaction included Val, His, Ala, and Tyr, whereas nicotine interacted mainly with His. These findings suggest stronger and more specific binding for lobeline at the receptor site.

Conclusions: Lobeline, owing to its superior receptor-binding affinity and neuropharmacological advantages, presents a promising phytotherapeutic alternative to nicotine in addiction therapy. The results emphasize the potential role of plant-based compounds in developing safer and more effective interventions for nicotine dependence.

1. Introduction

Nicotine addiction is a major health concern worldwide, and there is a need for effective strategies and treatments to help individuals quit smoking [1]. The key receptor which drives nicotine addiction is the nicotinic acetylcholine receptor (nAChR), a ligand gated ion channel which is responsible for transmission of synapses in the central nervous system. The $\alpha 4 \beta 2$ subunit is responsible for modulating the reinforcing effects which aids in continuing substance use. It is one of the high affinity binding sites which mediates the addictive effects of nicotine. Some agonists and antagonists of nAChRs are used to treat neurodegenerative conditions such as dyskinesias, Tourette's syndrome, schizophrenia, attention deficit disorder, anxiety, and also in tobacco-use cessation [2].

Although several treatment modalities are available for habit cessation such as Nicotine replacement therapies including nicotine patches and gum, the abstinence rates for smoking remain low. This has led to the exploration of sustainable alternatives for smoking cessation. Plant based alternatives are a more sustainable option owing to fewer side effects and better efficacy [3]. Plant based alkaloids are more safe with less side effects and offer additional therapeutic benefits including antioxidant and anti inflammatory properties. They are more easily available and cost effective compared to conventional pharmacological agents for habit cessation [4]. Lobeline,

Journal of Chemical Health Risks
www.jchr.org
JCHR (2025) 15(4), 905-910 | ISSN:2251-6727

a natural alkaloid found in various species of the plant of genus Lobelia, which has been reported to have similar effects as nicotine on nicotinergic receptors in the brain [5]. Lobeline acts on various neurological targets and path ways including dopaminergic modulation, Nicotinic receptor interaction, and Vesicular mono amine transporter 2 [6]. It also has several therapeutic properties which aids its use to treat respiratory disorders, peripheral vascular disorders and Attention Deficit Disorders [7].

Computerized prediction models have several advantages as they help predict the binding energy and site without the use of In vitro studies, thereby reducing the time taken for prediction and costs involved [8]. The present study aims to compare the binding affinities of lobeline versus nicotine with nicotinic acetylcholine receptors using computerised predicting models.

2. Objectives

The objectives of the present study includes identification of key receptor involved in addiction pathway and structure of the ligand for molecular docking and use of computational models to predict the binding energy of the ligand to the receptor and compare the same with that of nicotine.

3. Methods

Ligand and Receptor Preparation:

The three-dimensional structures of the ligand, lobeline, and its respective target receptor were retrieved in suitable file formats to facilitate molecular docking studies. The receptor structure was downloaded in Protein Data Bank (PDB) format from the RCSB Protein Data Bank, while the ligand structure (lobeline) was obtained in Sybyl mol2 format from the chemical database, ZINC15. Prior to docking, both structures underwent preprocessing to prepare them for simulation. This included the removal of crystallographic water molecules, which could otherwise interfere with ligand binding, and the addition of polar hydrogen atoms to ensure proper hydrogen bonding during interaction modeling. Furthermore, Gasteiger partial charges were assigned to all atoms using AutoDockTools, and both ligand and receptor files were converted into the PDBQT format, which is the required input for AutoDock docking simulations.

Molecular Docking Procedure

Molecular docking simulations were performed using AutoDock 4.2, a widely recognized tool for studying ligand－receptor interactions. The docking procedure began with the preparation of a grid box that encompassed the active or predicted binding site of the receptor. This grid defines the region within which the ligand will search for optimal binding conformations. Grid parameters, including box dimensions and spacing, were adjusted to ensure complete coverage of the binding pocket and surrounding residues of interest.

AutoDock’s Lamarckian Genetic Algorithm (LGA) was used to explore the conformational space and predict optimal ligand binding poses. The docking parameters included 100 genetic algorithm runs, a population size of 150, a maximum of 2,500,000 energy evaluations, and 27,000 generations per run. These parameters were selected to maximize the diversity and accuracy of docking outcomes. During the simulation, AutoDock calculated the binding free energy (ΔG) for each pose, ranking them according to interaction energy and clustering them based on RMSD values [9, 10].

Post-Docking Analysis and Visualization

Following docking, the results were analyzed to identify the best-docked conformation based on the lowest binding energy and highest frequency of occurrence in cluster analysis. Visualization of the docked complexes was performed using PyMOL and Discovery Studio Visualizer to examine the molecular interactions between lobeline and its receptor. Key interactions, including hydrogen bonds, $\pi - \pi$ stacking, and hydrophobic contacts, were identified and recorded. These interactions provide insights into the strength and specificity of the ligand−receptor binding.

To ensure the validity of the docking protocol, where available, re-docking of the co-crystallized ligand was conducted and compared against the experimental pose. The Root Mean Square Deviation (RMSD) between the predicted and experimental binding orientations was calculated; an RMSD value below 2.0 Å was considered indicative of a reliable docking procedure.

Journal of Chemical Health Risks

www.jchr.org

JCHR (2025) 15(4), 905-910 | ISSN:2251-6727

4. Results

The two dimensional and three dimensional conformation of Lobeline was obtained from Chembl data base (Figure 1).

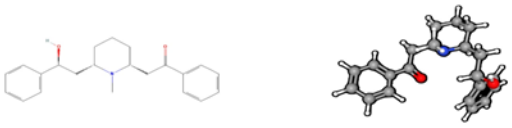
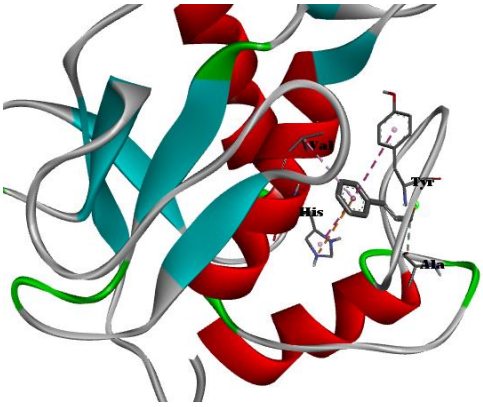


Figure 1 showing 2 Dimensional and 3 Dimensional images of Lobeline

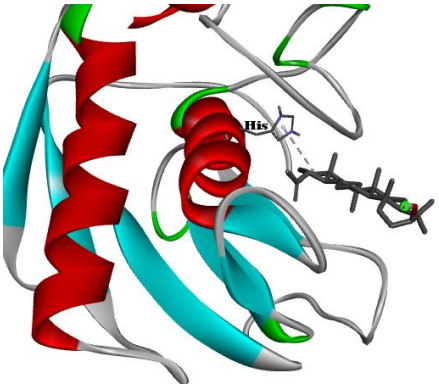
Comparing the binding affinities of Lobeline and Nicotine, lobeline showed the better affinity value of -8.14 kcal/mol than nicotine. The interaction between the ligand and receptor was confirmed through the increase in negative value of binding affinity (Figure 2 & 3)

Figure 2 showing interaction of Lobeline with Nicotinic Acetylcholine Receptor



Binding Affinity Value	-8.14 kcal/mol
Amino acid interaction between Lobeline and Nicotinic acetylcholine receptor	Val, His, Aln, and Tyr

Figure 3 showing interaction of Nicotine with Nicotinic Acetylcholine Receptor



Binding Affinity Value	-3.8 kcal/mol
Amino acid interaction between Nicotine and Nicotinic acetylcholine receptor	His

5. Discussion

Nicotine acts via mesocorticolimbic dopamine (DA) system, which originates in the ventral tegmental area (VTA) and projects to the nucleus accumbens (NAcc) and other forebrain regions. It has also been demonstrated that the rewarding qualities of the substance used depends on the activation of this mechanism [11]. Nicotine's activation of nAChRs has physiological effects on cells that are crucial for the development and spread of cancer. Through receptor-mediated processes, it directly activates signal transduction pathways, enabling injured epithelial cells to survive. Research indicates that the nitrosation of nicotine may result in the production of NNN (N’-nitrosonornicotine) and NNK(Nicotine-derived nitrosamine ketone). Owing to the presence of nicotine in tobacco and nicotine replacement products in large concentrations, this effect of nicotine may be significant. NNN and NNK have a high carcinogenic potential [12, 13].

When compared to nicotine, Lobeline shows contrasting effects and demonstrates a more favorable pharmacodynamic profile by modulating dopaminergic neurotransmission through inhibition of dopamine uptake, acting as antagonists of nAChRs thereby altering dopamine release without mimicking the agonist behaviour of nicotine [6].

Journal of Chemical Health Risks

www.jchr.org

JCHR (2025) 15(4), 905-910 | ISSN:2251-6727

Lobeline has a wide array of medicinal implications and was traditionally used in homeopathic practices for treating respiratory disorders [14]. Literature states that lobeline acts through multiple mechanisms, including cholinergic N receptors, opioid receptors, and monoamine transporters. Specifically, it has demonstrated significant potential as a medicinal substance for treating mental addiction and illnesses of the nervous system, including depression, Parkinson's disease, and Alzheimer's disease [15]. Studies have indicated that Lobeline also affects glutamatergic activity and implies a broader neurotransmitter regulatory capacity, which reveals its role in cognitive enhancement and neurological disorder treatment [16]. The interaction spectrum includes μ-opioid receptors, which indicates the role of Lobeline to reduce opioid reinforcement [14]. Studies have indicated that Lobeline interacts with voltage gated potassium channels and impact the excitability in cardiac and neural tissues [17].

In silico analysis of CYP2A6 gene variants revealed that several missense mutations may influence nicotine metabolism and dependence. Identifying such high-risk polymorphisms supports the rationale for exploring personalized, plant-based therapeutic alternatives to conventional nicotine cessation therapies [18].

The phytotherapeutic agents have multiple biological targets and enhance their effectiveness in complex diseases including addiction, cancer and neurological diseases [19]. They are less toxic and well tolerated on long term usage thereby serving as effective methods to treat chronic conditions [20]. Studies have shown that plant based alkaloids can be combined with synthetic pharmacological agents inorder to enhance their therapeutic efficacy, reduce side effects via synergistic effects [21]. They can be incorporated into various forms including capsules, extracts, topical agents and medicated chewing gums [22]. Since the alkaloids are derived from renewable natural sources, they aim to provide a sustainable alternative with reduced environmental impact when compared to synthetic pharmacological agents [23, 24].

Conclusion

In conclusion, the findings of this study could play a crucial role in diversifying the available smoking cessation strategies. Lobeline is proven to be more effective than nicotine in aiding smoking cessation, it could offer a natural and potentially safer alternative for individuals trying to quit smoking. This study opens up new possibilities for innovative approaches to addressing nicotine dependence and may ultimately lead to improved outcomes for individuals seeking to quit smoking.

References

1. Govindasamy R, Venkidasamy B, Thiruvengadam M. Current strategies for overcoming smoking addiction: a major cause of oral cancer. Recent Pat Anticancer Drug Discov. 2024;19(2):123-125. doi:10.2174/1574892818666230220102507.
2. Huang X, Zheng F, Crooks PA, Dwoskin L, Zhan CG. Modeling multiple species of nicotine and deschloroepibatidine interacting with α 4 β 2 nicotinic acetylcholine receptor: from microscopic binding to phenomenological binding affinity. J Am Chem Soc. 2005 Oct 19;127(41):14401 − 14414. doi:10.1021/ja052681+.
3. Mitra R, Rai A, Kumar A, Mitra JK. Role of Herbal Medication in Tobacco Cessation Treatment: A Systematic Review and Meta-analysis. Addict Health. 2023 Jan;15(1):63-70. doi: 10.34172/ahj.2023.1290. Epub 2023 Jan 29. PMID: 37560083; PMCID: PMC10408736.
4. Aryal B, Raut BK, Bhattarai S, Bhandari S, Tandan P, Gyawali K, Sharma K, Ranabhat D, Thapa R, Aryal D, Ojha A, Devkota HP, Parajuli N. Potential Therapeutic Applications of Plant-Derived Alkaloids against Inflammatory and Neurodegenerative Diseases. Evid Based Complement Alternat Med. 2022 Mar 9;2022:7299778. doi: 10.1155/2022/7299778. PMID: 35310033; PMCID: PMC8926539.
5. Piper ME, Smith SS, Schlam TR, et al. A Randomized Placebo-Controlled Clinical Trial of 5 Smoking Cessation Pharmacotherapies. Arch Gen Psychiatry. 2009;66(11):1253 − 1262. doi:10.1001/archgenpsychiatry.2009.142
6. Shah H, Mehta N, Patani P, Chandarana S. Lobeline: A natural alkaloid with promising neuroprotective effect − a novel treatment era. Afr J Biomed Res. 2024 Dec;27(4):6255 − 6261. Available from: https://africanjournaloebiomedicalresearch.com/index.php/AJBR

Journal of Chemical Health Risks

www.jchr.org

JCHR (2025) 15(4), 905-910 | ISSN:2251-6727

7. Martin CA, Nuzzo PA, Ranseen JD, Kleven MS, Guenthner G, Williams Y, Walsh SL, Dwoskin LP. Lobeline Effects on Cognitive Performance in Adult ADHD. J Atten Disord. 2018 Dec;22(14):1361-1366. doi: 10.1177/1087054713497791. Epub 2013 Aug 21. PMID: 23966351; PMCID: PMC4062608.
8. Saini R, Vadadumm S, Dermawan D, Bavabeedu SS, Khudayveran M, Mosaddad SA, Heboyan A. In silico docking of medicinal herbs against P. gingivalis for chronic periodontitis intervention. Int Dent J. 2025;75(2):1113 − 1115. doi:10.1016/j.identj.2024.06.019.
9. Yadalam PK, Neelakandan A, Arunraj R, Anegundi RV, Ardila CM. Exploring the interplay between Porphyromonas gingivalis KGP gingipain, herpes virus MicroRNA-6, and Icp4 transcript in periodontitis: Computational and clinical insights. PLoS One. 2024 Oct 31;19(10):e0312162. doi: 10.1371/journal.pone.0312162. PMID: 39480863; PMCID: PMC11527181.
10. Rajimon KJ, Deepthi S, Rajendran Nair D, Srinivasaragavan D, Thomas R. Integrated experimental and computational study of a fluorescent Schiff base: Synthesis, characterization, electronic structure properties, and biological potentials of (1E,1′ E)-1,1′ -(1,4-phenylene) bis(N-(2-chlorophenyl) methanimine) with a focus on molecular docking and dynamics simulation. Chem Phys Impact. 2024;8:100435. doi:10.1016/j.chphi.2023.100435.
11. Vezina P, McGehee DS, Green WN. Exposure to nicotine and sensitization of nicotine-induced behaviors. Prog Neuropsychopharmacol Biol Psychiatry. 2007;31:1625−1638.
12. International Agency for Research on Cancer. Tobacco smoke and involuntary smoking. IARC Monogr Eval Carcinog Risk Hum. 2007;89:455−7.
13. Stepanov I, Carmella SG, Briggs A, Hertsgaard L, Lindgren B, Hatsukami D, et al. Presence of the carcinogen N’-nitrosonornicotine in the urine of some users of oral nicotine replacement therapy products. Cancer Res. 2009;69:8236−40.
14. Stansbury, Jill & Saunders, Paul & Zampieron, Eugene. (2013). The Use of Lobelia in the Treatment of Asthma and Respiratory Illness. Journal of Restorative Medicine. 2. 94-100. 10.14200/jrm.2013.2.0109.
15. Miller DK, Lever JR, Rodvelt KR, Baskett JA, Will MJ, Kracke GR. Lobeline, a potential pharmacotherapy for drug addiction, binds to mu opioid receptors and diminishes the effects of opioid receptor agonists. Drug Alcohol Depend. 2007 Jul 10;89(2-3):282-91. doi: 10.1016/j.drugalcdep.2007.02.003. Epub 2007 Mar 21. PMID: 17368966.
16. Remya C, Dileep KV, Variyar EJ, Omkumar RV, Sadasivan C. Lobeline: A multifunctional alkaloid modulates cholinergic and glutamatergic activities. IUBMB Life. 2023 Oct;75(10):844-855. doi: 10.1002/iub.2762. Epub 2023 Jun 19. PMID: 37335270.
17. Marhaba Hojahmat, David B. Horton, Seth D. Norrholm, Dennis K. Miller, Vladimir P. Grinevich, Agripina Gabriela Deaciuc, Linda P. Dwoskin, Peter A. Crooks, Lobeline esters as novel ligands for neuronal nicotinic acetylcholine receptors and neurotransmitter transporters, Bioorganic & Medicinal Chemistry, Volume 18, Issue 2, 2010, Pages 640-649,ISSN 0968-0896, https://doi.org/10.1016/j.bmc.2009.12.002.
18. Venkadesan K, Leelavathi L, Priyadharsini JV, Arumugham IM, Kumar SR. Pathogenic missense mutations in nicotine-metabolizing cytochrome P450 2A6 gene − an in silico study. J Int Clin Dent Res Organ. 2024 Jan-Jun;16(1):55-65. doi:10.4103/jicdro.jicdro_75_23.
19. Dwoskin LP, Crooks PA. A novel mechanism of action and potential use for lobeline as a treatment for psychostimulant abuse. Biochem Pharmacol. 2002 Jan 15;63(2):89-98. doi: 10.1016/s0006-2952(01)00899-1. PMID: 11841781.
20. Puri V, Kanojia N, Sharma A, Huanbutta K, Dheer D, Sangnim T. Natural product-based pharmacological studies for neurological disorders. Front Pharmacol. 2022 Nov 7;13:1011740. doi: 10.3389/fphar.2022.1011740. PMID: 36419628; PMCID: PMC9676372.
21. Vezikov LV, Simpson M. Plant Alkaloids Toxicity. [Updated 2023 Apr 29]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from:

https://www.ncbi.nlm.nih.gov/books/NBK587364/

22. Ali H, Ali D, Almutairi BO, Kumar G, Karga GA, Masi C, Sundramurthy VP. Synergistic Effect of Conventional Medicinal Herbs against Different Pharmacological Activity. Biomed Res Int. 2022 Jun 29;2022:7337261. doi: 10.1155/2022/7337261. Retraction in: Biomed Res Int. 2024 Jan 9;2024:9836173. doi: 10.1155/2024/9836173. PMID: 35813228; PMCID: PMC9259343.
23. Rajalekshmi R, Agrawal DK. Therapeutic Efficacy of Medicinal Plants with Allopathic Medicine in Musculoskeletal Diseases. Int J Plant Anim Environ Sci. 2024;14(4):104-129. doi: 10.26502/ijpaes.4490170. Epub 2024 Dec 23. PMID: 39866300; PMCID: PMC11765655.
24. Chaachouay, N.; Zidane, L. Plant-Derived Natural Products: A Source for Drug Discovery and Development. Drugs Drug Candidates 2024, 3, 184-207. https://doi.org/10.3390/ddc3010011