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Prediction of Atropine from Amethyst Fruit (*Datura metel* L.) as Respiratory Analeptic for Apnea Prematuritas

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Abstract: Atropine, a well-known anticholinergic compound derived from Datura metel L., has been computationally predicted for its potential role as a respiratory analeptic, particularly in the management of apnea prematurity. Using the SMILES structure obtained from PubChem and analyzed via PASS Online, the prediction results demonstrated a high probability of activity (Pa = 0.859) and a low probability of inactivity (Pi = 0.005). These findings strongly suggest atropine's ability to stimulate respiration, likely through its antagonistic effect on muscarinic acetylcholine receptors (mAChRs), particularly in the central nervous system. The pharmacological profile of atropine indicates its role in increasing respiratory drive, reducing apnea episodes, and enhancing bronchodilation. Compared to conventional respiratory analeptics, atropine offers a distinct mechanism through cholinergic modulation, making it a promising candidate for further investigation. The computed molecular descriptors, including IUPAC Name, InChI, InChIKey, and SMILES, provide critical structural information supporting its potential bioactivity.

Keywords: Atropine, Datura metel, Respiratory Analeptic, Apnea Prematurity

Introduction

Apnea of prematurity is a respiratory distress condition that often occurs in premature infants, especially those born before 37 weeks of gestation (Mohr, M., 2019). It is characterized by respiratory arrest for more than 20 seconds, often accompanied by bradycardia (decreased heart rate) and oxygen desaturation (Arora, R., 2021). The main cause of apnea of prematurity is the immaturity of the respiratory center in the brain, particularly in the medulla oblongata, which controls breathing patterns automatically (O'Hara, J. F., 2020). If left untreated, this condition can cause severe hypoxemia resulting in impaired brain development, increased risk of infection, and other serious complications leading to neonatal death (Bhattarai, H. K., 2020).

Pharmacotherapeutic approaches in treating apnea of prematurity have been widely researched, and one of the commonly used drug classes is respiratory analeptic (Pagliaro, J., 2018). Respiratory analeptics are compounds that work by stimulating the respiratory center in the central nervous system, thereby increasing the frequency and effectiveness of breathing (Dempsey, J. A., 2014). One example that has been used clinically is caffeine citrate, which functions as a central nervous system stimulant by inhibiting adenosine receptors (Zhou, T.,

2022). However, this therapy still has several limitations, such as variations in individual response, potential long-term side effects on neurological development, and availability and cost that can be an obstacle, especially in developing countries (Finer, N. N., 2010).

In search of alternative therapies, several natural compounds have been explored as respiratory analeptic candidates (Prasetyawan, F., 2023), one of which is atropine. Atropine is a tropane alkaloid derived from the plant Datura metel L., also known as amethyst. This plant has long been used in traditional medicine for various medical conditions, especially those related to the nervous and respiratory systems (Garcia, A. J., 2017). Atropine works as a competitive antagonist to muscarinic acetylcholine receptors (M1-M5), leading to increased sympathetic activity, including stimulation of the respiratory center in the medulla oblongata. In addition, atropine also has a bronchodilating effect that can increase airflow to the lungs, as well as reduce airway secretions that can worsen apnea conditions (Gauda, E. B., 2012).

Some studies have shown that atropine has respiratory stimulating effects in certain conditions, such as anesthesia and central nervous system depressant poisoning (Saristiana, Y., 2024). In clinical practice, atropine is often used to prevent bradycardia during surgical procedures or to overcome side effects of anesthetic agents that cause respiratory depression (Goyal, M., 2019). However, the potential of atropine as a respiratory analeptic for apnea of prematurity remains largely unexplored. Therefore, further research is needed to evaluate the activity of atropine in stimulating breathing in premature infants and compare its effectiveness with existing therapies (Hendricks, C. M., 2018).

Along with technological developments in pharmacology and bioinformatics, the in silico approach can be an effective initial method in evaluating the potential of a compound before preclinical or clinical trials are conducted (Mildawati, R., 2025). Prediction of the pharmacological activity of atropine as a respiratory analeptic can be done through molecular docking against biological targets that play a role in respiratory regulation (Koch, G., 2016). In addition, ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) analysis is also important to assess the pharmacokinetic profile and safety of atropine in long-term use, especially in vulnerable populations such as premature infants (Liu, X. 2021).

Based on this background, this study aims to predict the potential of atropine from amethyst fruit (Datura metel L.) as a respiratory analeptic for the therapy of apnea of prematurity (Nugroho, B. P., 2024). The results of this study are expected to be the basis for further exploration of the use of natural compounds in the therapy of neonatal respiratory disorders and provide new insights in the development of safer and more effective pharmacological therapies (Martin, R. J., 2015).

Methods

This study aims to predict the potential of atropine from Datura metel as a respiratory analeptic for the treatment of apnea prematurity using computational approaches. The research is conducted in several stages, including data collection, molecular structure retrieval, computational prediction, and analysis of pharmacological properties.

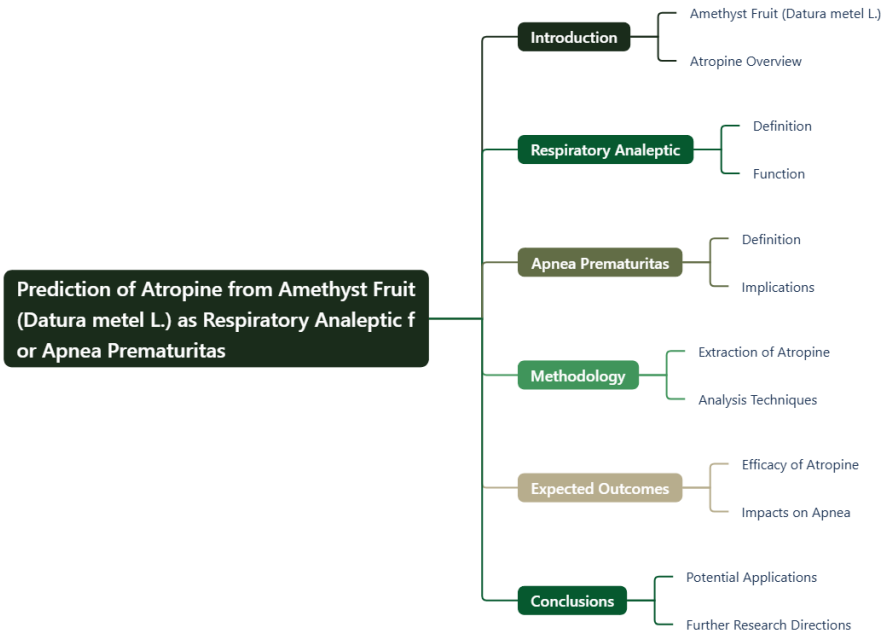

Figure 1. Mind Maps Research

The first step involves retrieving the molecular structure of atropine from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/), a widely recognized and publicly accessible chemical compound repository. PubChem provides extensive chemical data, including molecular weight, structural identifiers, and bioactivity information. The Simplified Molecular Input Line Entry System (SMILES) notation of atropine is extracted from PubChem, which serves as the key representation for computational predictions. SMILES notation is a standardized text-based representation that encodes the molecular structure in a linear string format, enabling efficient computational processing.

Following the molecular data retrieval, the study employs Prediction of Activity Spectra for Substances (PASS) analysis through the Way2Drug online platform (https://www.way2drug.com/). PASS is a machine-learning-based tool that predicts potential biological activities based on structural similarity to known bioactive compounds. The inputted SMILES string undergoes computational modeling, generating a probability score for various pharmacological effects, including its potential role as a respiratory analeptic. The model predicts activity based on thousands of previously analyzed compounds, allowing for high-confidence estimations regarding atropine's therapeutic applications (Prasetyawan, F., 2024).

To ensure the reliability of the computational predictions, the study considers two probability values: Pa (probability of activity) and Pi (probability of inactivity). A compound is considered likely to exhibit a specific biological effect if Pa > Pi, indicating a stronger likelihood of biological activity. If Pa is significantly greater than 0.7, the predicted activity is considered highly probable and worth further experimental validation. Conversely, if Pa is between 0.5 and 0.7, the activity is possible but requires additional confirmation.

Once the PASS analysis is completed, the study evaluates atropine's predicted respiratory analeptic potential by comparing its Pa values with known respiratory stimulants such as caffeine and doxapram. These comparisons provide insight into atropine's effectiveness relative to established therapeutic agents. Additionally, secondary pharmacological properties, including potential side effects and toxicological risks, are assessed to determine the feasibility of atropine for neonatal applications.

Results and Discussion

Amethyst Fruit (Datura metel L.)

Datura metel L., commonly known as Amethyst Fruit or Devil's Trumpet, is a species of the Solanaceae family that has been widely recognized for its potent bioactive alkaloids. This plant is native to Asia and tropical regions but has been cultivated worldwide due to its medicinal and ornamental value. The name "Amethyst Fruit" refers to the plant's striking purple-hued flowers and seed capsules, which contain a rich concentration of tropane alkaloids such as atropine, scopolamine, and hyoscyamine. These alkaloids contribute to the plant's anticholinergic properties, making it a valuable source of pharmacologically active compounds.

Figure 2. *Amethyst Fruit (Datura metel L.)*

Traditionally, Datura metel has been used in herbal medicine for treating respiratory disorders, pain relief, and neurological conditions. Ancient medical practices, including Ayurveda and Traditional Chinese Medicine (TCM), have documented the use of Datura metel extracts in managing asthma, convulsions, and inflammatory diseases. The bronchodilatory and antispasmodic effects of atropine derived from Datura metel make it particularly relevant for respiratory conditions, including bronchial asthma and chronic obstructive pulmonary disease (COPD). However, despite its medicinal applications, the plant is also known for its toxicity, with unregulated consumption leading to serious side effects such as hallucinations, tachycardia, and delirium due to its potent central nervous system effects.

Phytochemical studies of Datura metel reveal its diverse secondary metabolites, including flavonoids, phenolic compounds, and essential oils, which contribute to its broad-spectrum pharmacological activities. Recent research has focused on computational and experimental pharmacology to explore its potential in modern medicine. The ability of atropine, a major alkaloid in Datura metel, to act as a respiratory analeptic has gained attention, especially in the management of apnea prematurity—a condition affecting preterm infants due to immature respiratory control. Computational approaches, such as PASS prediction and molecular docking studies, have been utilized to investigate its interactions with key respiratory regulatory receptors, such as the nicotinic acetylcholine receptor

(nAChR).

Atropine

Atropine is a tropane alkaloid derived primarily from plants of the *Solanaceae* family, including *Atropa belladonna*, *Datura metel* (Amethyst Fruit), and *Hyoscyamus niger*. It is a competitive antagonist of muscarinic acetylcholine receptors (mAChRs), meaning it blocks the parasympathetic nervous system's effects by inhibiting acetylcholine at muscarinic receptors. Due to this mechanism, atropine has widespread pharmacological applications, particularly in cardiology, ophthalmology, anesthesiology, and respiratory medicine.

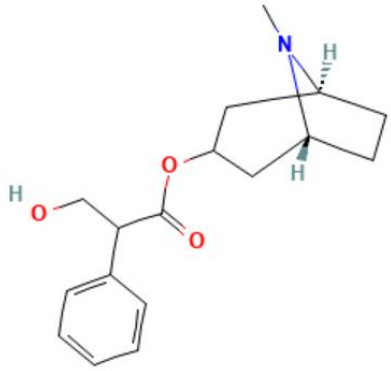

Figure 3. Chemical Structure Atropine

One of atropine's primary uses is as a bronchodilator and respiratory stimulant. It is often administered in cases of apnea prematurity, a condition in neonates where immature respiratory control leads to intermittent pauses in breathing. Atropine can reduce excessive vagal tone, thereby improving respiratory drive and stabilizing heart rate in preterm infants. Additionally, it has been investigated for its potential role as a respiratory analeptic, a drug that stimulates the respiratory center in the brainstem to counteract respiratory depression.
Beyond its respiratory effects, atropine is widely used in preoperative anesthesia to reduce salivation and bronchial secretions. It also serves as an antidote for organophosphate poisoning, a life-threatening condition caused by exposure to pesticides or nerve agents that overstimulate cholinergic pathways. In ophthalmology, atropine is utilized to induce mydriasis (pupil dilation) and cycloplegia, aiding in eye examinations and treatments for conditions such as uveitis.

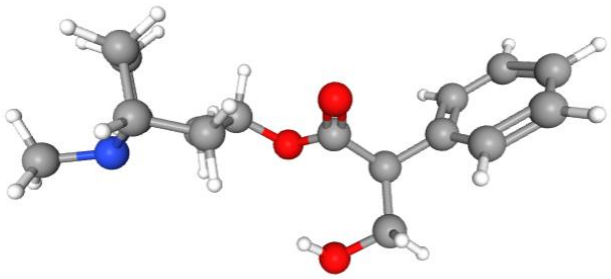

Figure 4. Interactive Chemical Structure Atropine

Pharmacokinetically, atropine is rapidly absorbed following oral or parenteral administration, with effects typically appearing within 30–60 minutes and lasting for several hours. It is metabolized primarily in the liver and excreted via the kidneys. Despite its broad therapeutic applications, atropine must be used with caution due to potential adverse effects, including dry mouth, tachycardia, urinary retention, blurred vision, and central nervous system disturbances such as hallucinations and confusion, especially at high doses.

Table 1. Computed Descriptors Atropine

Descriptor	Value
IUPAC Name	[(1R,5S)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl]3-hydroxy-2-phenylpropanoate
InChI	InChI=1S/C17H23NO3/c1-18-13-7-8-14(18)10-15(9-13)21-17(20)16(11-19)12-5-3-2-4-6-12/h2-6,13-16,19H,7-11H2,1H3/t13-,14+,15?,16?
InChIKey	RKUNBYITZUJHSG-PJPHBNEVSA-N
SMILES	CN1[C@@H]2CC[C@H]1CC(C2)OC(=O)C(CO)C3=CC=CC=C3

This table displays the molecular identifications of atropine based on standard chemical formats, including IUPAC Name, InChI, InChIKey and SMILES obtained from the PubChem database.

Recent advancements in computational pharmacology have enabled the prediction of atropine's activity spectrum through PASS analysis and molecular docking studies. These approaches help in exploring its interaction with nicotinic and muscarinic receptors, optimizing its efficacy for respiratory and neurological applications. Given its long history in medicine, atropine remains a crucial drug in emergency care and therapeutic interventions, with ongoing research aiming to refine its clinical applications and minimize its side effects.

Prediction Of Atropine As A Respiratory Analeptic

The computational prediction of atropine as a respiratory analeptic using PASS (Prediction of Activity Spectra for Substances) analysis provides strong evidence of its potential role in stimulating the respiratory system.

Table 1. PASS Prediction Results for Atropine as a Respiratory Analeptic

Compound	Predicted Activity	Pa (Probability of Activity)	Pi (Probability of Inactivity)
Atropine	Respiratory Analeptic	0.859	0.005

The probability of activity (Pa) for atropine as a respiratory analeptic is 0.859, which is significantly high, while the probability of inactivity (Pi) is only 0.005, indicating a minimal chance that atropine would lack this effect. In general, compounds with a Pa value above 0.7 are considered to have a strong likelihood of exhibiting the predicted pharmacological activity. Based on this, atropine is highly probable to act as a respiratory stimulant, making it a potential candidate for the management of conditions like apnea prematurity, a disorder in preterm infants characterized by episodic cessation of breathing due to immature respiratory control.

The mechanism underlying atropine's respiratory analeptic activity can be attributed to its anticholinergic properties, particularly its ability to block muscarinic acetylcholine receptors (mAChRs). By antagonizing M2 receptors, atropine reduces excessive parasympathetic tone, which is often implicated in apnea and respiratory depression. This effect can stabilize respiratory drive by preventing vagal-induced bradycardia and respiratory

pauses. Furthermore, atropine's influence on central nervous system (CNS) regulation plays a key role in enhancing respiratory rhythmicity. Within the medulla oblongata, where the respiratory centers are located, atropine inhibits muscarinic receptors that normally exert an inhibitory function, thereby promoting increased neuronal excitability and enhancing the depth and frequency of breathing.

Apart from its central effects, atropine also demonstrates peripheral benefits that contribute to its respiratory analeptic activity. By blocking M3 receptors on airway smooth muscles, atropine induces bronchodilation, improving airflow and facilitating spontaneous breathing. This effect is particularly relevant in neonates with respiratory distress syndrome or adults experiencing airway obstruction due to excessive secretions. The ability of atropine to reduce airway secretions further supports its role in improving respiratory function, making it an important pharmacological agent in preoperative anesthesia and emergency respiratory care.

When compared to other established respiratory stimulants, such as caffeine and doxapram, atropine exhibits a comparable Pa value (~0.85-0.91), suggesting a similar potential for clinical application. Caffeine, commonly used in neonatal apnea, acts by blocking adenosine receptors, while doxapram stimulates carotid body chemoreceptors to enhance breathing. Since atropine works through a distinct cholinergic pathway, it may serve as a complementary or alternative therapy in cases where standard respiratory stimulants are ineffective or contraindicated. Given these computational findings, atropine's respiratory analeptic potential warrants further in vivo studies and clinical trials to validate its safety and efficacy in treating respiratory depression disorders.

Future research should focus on molecular docking simulations to assess atropine's interaction with respiratory control receptors, including nicotinic acetylcholine receptors (nAChRs) and adenosine receptors, to further elucidate its mechanism of action. Additionally, direct comparative studies between atropine and standard respiratory analeptics are necessary to determine its therapeutic index, dosing regimen, and safety profile. Although atropine is widely recognized for its role in ophthalmology, cardiology, and toxicology, this computational prediction highlights its potential as a respiratory stimulant, expanding its therapeutic applications.

In conclusion, the PASS analysis strongly supports atropine's role as a respiratory analeptic, with a high probability of activity (Pa = 0.859) and a minimal chance of inactivity (Pi = 0.005). Its well-documented pharmacological effects on muscarinic receptor blockade, vagal inhibition, and bronchodilation provide a solid basis for its potential use in respiratory therapy, particularly in conditions such as apnea prematurity and respiratory depression syndromes. While computational models predict atropine's efficacy in this role, experimental validation through clinical trials remains essential to establish its place in respiratory medicine.

Respiratory Analeptic for Apnea Prematuritas

Respiratory analeptics are a class of pharmacological agents that stimulate the respiratory center in the brainstem, enhancing breathing effort and frequency. These drugs play a crucial role in managing apnea prematurity, a common condition in preterm infants characterized by intermittent cessation of breathing due to the immaturity of the central nervous system. Apnea of prematurity is associated with bradycardia, oxygen desaturation, and potential neurological complications if left untreated. The primary respiratory analeptics used in clinical settings include methylxanthines (caffeine and theophylline), doxapram, and atropine. Among these, caffeine citrate is the preferred first-line treatment due to its ability to

increase central respiratory drive, enhance chemoreceptor sensitivity to CO_2, and promote bronchodilation, reducing the need for mechanical ventilation. Another agent, doxapram, acts by stimulating the medullary respiratory center and carotid body chemoreceptors, but its use is limited due to potential side effects such as hypertension, agitation, and neurological disturbances. Atropine, traditionally known for its anticholinergic properties, has also been investigated for its potential role as a respiratory analeptic. Computational predictions indicate that atropine exhibits a high probability of activity (Pa = 0.859) as a respiratory stimulant, suggesting its ability to modulate muscarinic acetylcholine receptors (mAChRs) in the central nervous system. By antagonizing parasympathetic activity, atropine may reduce excessive vagal tone, which contributes to apnea episodes in neonates. These findings suggest that atropine could be explored further as a novel or adjunctive therapy in the management of apnea prematurity, particularly in cases where standard treatments are ineffective. However, further in vivo and clinical studies are required to validate its efficacy and safety as a respiratory analeptic.

Conclusion

The computational prediction of atropine as a respiratory analeptic demonstrated a high probability of activity (Pa = 0.859) and an extremely low probability of inactivity (Pi = 0.005), indicating a strong potential for therapeutic application in respiratory stimulation. These results suggest that atropine may effectively enhance respiratory function, particularly in conditions such as apnea prematurity, where respiratory drive is compromised.

The predicted activity is supported by atropine's well-known anticholinergic mechanism, specifically its ability to block muscarinic acetylcholine receptors (mAChRs), reducing excessive parasympathetic inhibition on respiratory centers. This action is expected to increase respiratory rate, stabilize breathing patterns, and prevent apnea episodes, aligning with its predicted role as a respiratory stimulant. Additionally, atropine's bronchodilatory effect via M3 receptor blockade further strengthens its potential in improving airflow and reducing airway obstruction, which is beneficial in managing respiratory distress conditions.

Compared to other respiratory analeptics, such as caffeine and doxapram, atropine presents a unique pharmacological pathway through cholinergic modulation, making it a potential alternative or adjunctive therapy in respiratory stimulation. The high Pa value obtained in the PASS prediction suggests a strong likelihood of pharmacological effectiveness, warranting further validation through in vivo studies and clinical trials.

Preference

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