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In Silico Investigation of *Dendrobium nobile* Compounds as Potential β_2-AR Activators for Asthma

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Abstract: *Asthma is a chronic respiratory disease characterized by airway inflammation and bronchoconstriction. Beta-2 Adrenergic Receptor (β_2-AR) is a primary target for bronchodilator therapy. This study aimed to investigate bioactive compounds from Dendrobium nobile as potential β_2-AR activators through in silico molecular interaction analysis. The methods included preparation of 24 ligands, drug-likeness screening using Lipinski's rules, molecular docking with the active conformation of β_2-AR (PDB ID: 3P0G), molecular interaction analysis, and ADMET prediction. The results showed that 19 compounds met the drug-likeness criteria. Molecular docking revealed that several compounds had stronger binding affinities than conventional agonists formoterol (-7.2 kcal/mol) and salmeterol (-6.4 kcal/mol), with kaempferol (-9.6 kcal/mol), apigenin (-9.3 kcal/mol), quercetin (-9.2 kcal/mol) and luteolin (-9.0 kcal/mol) as the top candidates. These ligands formed hydrogen bonds and hydrophobic interactions with key residues associated with receptor activation, such as Asp113, Ser203, Ser204 and Ser207. Furthermore, ADMET prediction indicated that promising ligands like luteolin and coniferin have low blood-brain barrier permeability, no hERG inhibition, and, in the case of coniferin, minimal cytochrome P450 interactions, suggesting a favorable safety and pharmacokinetic profile. In conclusion, this in silico study suggests that bioactive compounds from D. nobile, particularly luteolin and coniferin, may represent promising candidates for further development as β_2-AR activators and as plant-based bronchodilators.*

Keywords: Asthma, Beta-2 adrenergic receptor, *Dendrobium nobile*, molecular docking, natural compound

Abstrak: Asma merupakan penyakit pernapasan kronis yang ditandai oleh inflamasi saluran napas dan bronkokonstriksi. Reseptor Beta-2 Adrenergik (β_2-AR) merupakan target utama terapi bronkodilator. Penelitian ini bertujuan mengidentifikasi senyawa bioaktif dari *Dendrobium nobile* yang berpotensi sebagai aktivator β_2-AR melalui analisis interaksi molekuler secara *in silico*. Metode penelitian meliputi preparasi 24 ligan, penyaringan kelayakan obat berdasarkan aturan Lipinski, penambatan molekuler menggunakan konformasi aktif β_2-AR (PDB ID: 3P0G), analisis interaksi molekuler, serta prediksi ADMET. Hasil menunjukkan bahwa 19 senyawa memenuhi kriteria kelayakan obat. Analisis penambatan molekuler memperlihatkan beberapa senyawa memiliki afinitas ikatan lebih tinggi dibandingkan agonis konvensional, yaitu formoterol (-7,2 kkal/mol) dan salmeterol (-6,4 kkal/mol). Kaempferol (-9,6 kkal/mol), apigenin (-9,3 kkal/mol), quersetin (-9,2 kkal/mol), dan luteolin (-9,0 kkal/mol) merupakan kandidat terbaik. Senyawa-senyawa tersebut membentuk ikatan hidrogen dan interaksi hidrofobik dengan residu penting yang berperan dalam aktivasi reseptor, seperti Asp113, Ser203, Ser204, dan Ser207. Prediksi ADMET menunjukkan bahwa luteolin dan koniferin memiliki profil keamanan dan farmakokinetik yang baik. Dengan demikian, senyawa bioaktif *D. nobile*, khususnya luteolin dan koniferin, berpotensi dikembangkan lebih lanjut sebagai aktivator β_2-AR dan bronkodilator berbasis bahan alam.

Kata kunci: Asma, Reseptor Beta-2 Adrenergik, *Dendrobium nobile*, *molecular docking*, bahan alam

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1. Introduction

Beta-2 Adrenergic Receptors (β_2-ARs) play a crucial role in relaxing airway smooth muscles through bronchodilation and serve as the primary targets for β_2-AR agonist drugs used in lung diseases. These receptors are located on the membranes of various lung cells,

including airway smooth muscle cells, epithelial cells, endothelial cells, mast cells, and type II epithelial cells. They are predominantly found in structures such as the alveolar wall, pulmonary artery smooth muscle, tracheal smooth muscle, and bronchial epithelium, where they contribute to regulating airway tone and fluid clearance (Yang *et al.* 2021). The β_2-AR, also known as ADRB2 (the gene encoding this receptor), is a prototypical G protein-coupled receptor (GPCR) composed of seven transmembrane α-helices. It has an extracellular N-terminus and an intracellular C-terminus, a structure that enables it to transduce extracellular signals, such as adrenaline and noradrenaline, into intracellular responses (Plazinska *et al.* 2015). Because of its function in airway relaxation and its expression on airway smooth muscle cells, β_2-AR serves as the primary pharmacological target in asthma and COPD therapy (Amrani & Bradding 2017; Thomsen *et al.* 2012). Genetic polymorphisms in the ADRB2 gene have also been investigated as potential biomarkers for predicting patient response to β_2-AR agonist treatment (Slob *et al.* 2018). Advances in pharmacology focusing on selective binding to β_2-ARs in lung tissue have led to the replacement of older treatments with β_2-AR agonists, which are now considered first-line therapies (Billington *et al.* 2016). These drugs have shown clear clinical benefits by easing symptoms, improving treatment outcomes, enhancing patients' quality of life, and lowering mortality rates (Lim & Priefer 2022).

These β_2-AR agonists are primarily used to treat asthma, a chronic respiratory disease characterized by airway inflammation, bronchoconstriction, and reversible airflow obstruction. Common symptoms include wheezing, shortness of breath, chest tightness, and coughing. It affects people across all age groups, particularly children and the elderly. The global burden of asthma continues to grow, with an estimated 100 million individuals projected to be affected by 2025 (Rodriguez Del Rio *et al.* 2022). One of the main treatments involves β_2-AR agonists, which act as bronchodilators to relieve airway constriction. These include short-acting β_2-agonists (SABAs) such as salbutamol and terbutaline, as well as long-acting β_2-agonists (LABAs) like formoterol and salmeterol. Although generally effective, these drugs can cause adverse effects including tremors, arrhythmias, hypokalemia, and reduced therapeutic response with chronic use (Hall 2006; Usmani *et al.* 2023). In regions with limited healthcare access, the high cost of conventional drugs and their potential side effects contribute to poor asthma management and higher mortality. Consequently, natural bioactive compounds are increasingly being explored as alternative therapies or complementary therapeutic sources. These compounds often serve as valuable starting points for drug development due to their structural diversity (Lee *et al.* 2022).

Dendrobium nobile, a species of orchid commonly known as an ornamental plant, possesses various health benefits. This orchid contains a range of bioactive compounds, including alkaloids such as dendrobine, dendroxine, dendramine, dendrine, dendrobine N-oxide, nobilonine, dendrochrysine, and moscatiline. It also contains bibenzyls, phenanthrenes such as phenanthrene, flavonoids such as quercetin, kaempferol, apigenin, luteolin, rutin, and isorhamnetin, as well as polysaccharides. These compounds have been associated with diverse pharmacological activities, including antioxidant, anti-inflammatory, antidiabetic, immunomodulatory, and anticancer properties (Fan *et al.* 2023; Zhang *et al.* 2023). Furthermore, *Dendrobium* is widely distributed throughout Indonesia, particularly in the eastern regions such as Papua and Maluku, where it represents a significant component of the country's genetic resources (Hartati *et al.* 2021). Several species from this genus have long been used in traditional medicine, not only in China and India but also by local Indonesian communities, indicating their potential as accessible and affordable therapeutic agents (Aswandi & Kholibrina 2021).

These diverse pharmacological properties suggest the potential of *D. nobile* in treating conditions characterized by underlying inflammation, including respiratory diseases. Its anti-inflammatory effects, demonstrated in conditions like arthritis and dermatitis, are often mediated by the inhibition of key signaling pathways such as NF-κB and MAPK (Jain *et al.* 2024). Given that these same pathways are also central drivers of inflammation in asthma, it is plausible that *D. nobile* could confer similar benefits in the airway. Despite this broader anti-inflammatory potential, its specific role as a β_2-AR activator for bronchodilation in asthma treatment remains underexplored. *In silico* approaches, such as molecular docking and dynamics simulations, offer a powerful strategy to identify bioactive compounds capable of binding to β_2-AR and eliciting bronchodilatory effects (Ahmad *et al.* 2021). These methods

allow for the rapid screening of phytochemicals, reducing the time and cost of drug development compared to traditional experimental approaches (Shaker *et al.* 2021). Nevertheless, the interaction of *D. nobile* constituents with β_2-AR, particularly in the context of asthma therapy, remains unexplored. This study aims to investigate the potential of *D. nobile* bioactive compounds to enhance β_2-AR activity as a novel bronchodilatory approach in asthma therapy. The findings are expected to provide new insights into the development of plant-based interventions for respiratory health and support the exploration of Indonesia's abundant natural resources to develop an affordable and effective alternative to synthetic asthma medications.

2. Methodology

The active conformation of β_2-AR (PDB ID: 3P0G) was retrieved from the Protein Data Bank and prepared using BIOVIA Discovery Studio 2019. Twenty-four bioactive compounds from Dendrobium nobile were obtained from PubChem, converted and energy-minimized using PyRx and OpenBabel. Drug-likeness was assessed with SwissADME according to Lipinski's Rule of Five. Molecular docking was conducted using AutoDock Vina in PyRx 0.8, and the docking protocol was validated through re-docking of the co-crystallized agonist BI-167107, producing an RMSD of 1.493 Å. The best ligand conformations were selected based on binding affinity and analyzed for protein-ligand interactions using BIOVIA Discovery Studio and UCSF ChimeraX. ADMET properties of all compounds were predicted using pkCSM to evaluate their pharmacokinetic and toxicity profiles.

2.1. Protein targets selection and preparation

The three-dimensional (3D) crystallographic structure of the β_2-AR in its active conformation (PDB ID: 3P0G), which comprises two chains (Figure 1), was retrieved from the Protein Data Bank (PDB), following the approach described in previous studies (Masureel *et al.* 2018). This specific active conformation was selected because it is co-crystallized with BI-167107, a high-affinity agonist, making it the most relevant structure for identifying potential β_2-AR activators. The structure was resolved at 3.50 Å and consists of 405 modeled amino acid residues. For docking purposes, only chain A was retained to focus on the primary binding site. Prior to docking, the receptor structure was refined by removing the co-crystallized nanobody, BI-167107 ligand, and water molecules using BIOVIA Discovery Studio 2019 (Maheswari & Salamun, 2023). The presence of the co-crystallized agonist in this structure provides a reference for docking validation and defines the key residues involved in agonist binding, including Asp113, Ser203, Ser204, and Ser207, which are established as critical for receptor activation (Rasmussen *et al.* 2011).

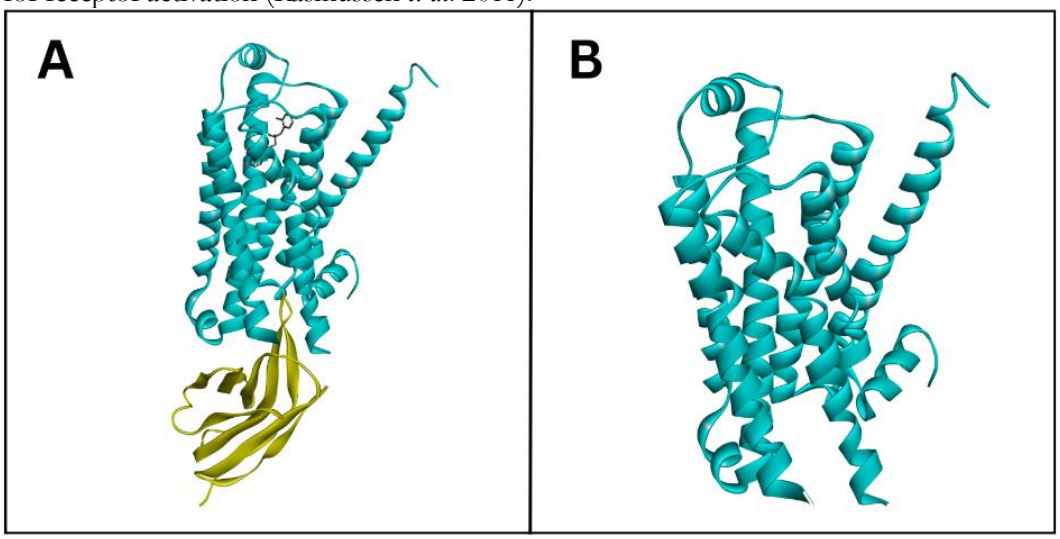


Figure 1. Three-dimensional structure of human β_2-adrenergic receptor (β_2-AR). **a)** β_2-AR (chain A, cyan) in complex with a co-crystallized nanobody (chain B, yellow). **b)** β_2-AR structure after removal of the nanobody.

2.2. Ligand preparations

A set of 24 bioactive compounds from *D. nobile* was selected based on their previously reported biological activities (Jain *et al*. 2024). These compounds were retrieved from the PubChem database in 3D conformations and downloaded in Simple Data Format (SDF). The structures were imported into PyRx version 0.8 and converted using OpenBabel (Maheswari & Salamun, 2023). Energy minimization was performed using the Universal Force Field (UFF) to optimize the molecular geometry prior to docking analysis.

2.3. Drug-likenes screening

To evaluate the drug-likeness of the selected compounds, their physicochemical propertieswere analyzed using the SwissADME web-tool (http://www.swissadme.ch /index.php). Swiss-ADME predicts various molecular descriptors, such as lipophilicity (LogP), molecular weight, and the number of hydrogen bond donors and acceptors. Lipinski's Rule of Five was applied to evaluate drug-likeness based on physicochemical criteria relevant to inhaled drug candidates (Choy & Prausnitz 2011). The ligand structures were uploaded in SMILES format, and the tool generated relevant drug-likeness parameters for further evaluation.

2.4. Molecular Docking

Molecular docking was performed using AutoDock Vina in PyRx version 0.8 (Maheswari & Salamun 2023). Blind docking was employed to enable exploration of the entire receptor surface and potential binding cavities. To validate the docking protocol, the co-crystallized ligand BI-167107 was extracted from the 3P0G structure and re-docked into the binding pocket using the same parameters. The RMSD between the predicted and experimental binding poses was calculated using UCSF ChimeraX version 1.9 and obtained a value of 1.493 Å, which is below the acceptable threshold of 2.0 Å, confirming the reliability of the docking protocol (Pettersen *et al*. 2021). All ligands and the target protein were converted to PDBQT format using AutoDock Tools. The docking protocol generated multiple binding poses for each ligand, from which the best-ranked conformations based on binding affinity were selected. Visualization and interaction analysis of protein-ligand complexes were conducted using BIOVIA Discovery Studio 2019 (Maheswari & Salamun 2023).

2.5. Molecular interaction analysis

The protein-ligand complexes obtained from docking simulations were visualized and analyzed using BIOVIA Discovery Studio 2019. Key molecular interactions between the protein and ligands were identified and characterized to elucidate the binding modes of the ligands within the active site of the target protein. Representative snapshots were captured to illustrate the key binding interactions.

2.6. Prediction of ADMET properties

ADMET profiles of the compounds were analyzed using pkCSM (http://biosig.unimelb.edu.au/pkcsm/), a tool that applies graph-based machine learning to predict pharmacokinetic properties and toxicity (Abdullahi *et al*. 2022). The evaluation focused on fundamental ADMET properties relevant to early-stage drug discovery, such as intestinal absorption, blood-brain barrier permeability, cytochrome P450 enzyme interactions, and toxicity potential. Each compound was submitted in SMILES format.

3. Results

3.1. Drug-likeness screening

Of the 24 bioactive compounds from *D. nobile* screened for drug-likeness, 19 compounds complied with Lipinski's Rule of Five (Table 1). The five excluded compounds primarily violated the criteria for molecular weight and topological polar surface area. All compliant compounds conformed to Lipinski's Rule of Five, with molecular weights below 500 g/mol and fewer than 10 hydrogen bond acceptors. This high pass rate underscores the drug-like potential of *D. nobile*'s phytochemical profile.

Table 1. Physicochemical properties of compounds calculated based on the Lipinski's rules

Bioactive compounds	PubChem ID	Chemical Formula	Lipinski Rules					
			MW	LogP	NHA	NHD	NRB	TPSA
Kaempferol	5280863	$C_{15}H_{10}O_6$	286.24	1.9	6	4	1	111.13
Apigenin	5280443	$C_{15}H_{10}O_5$	270.24	3.02	5	3	1	90.9
Chlorogenic acid	1794427	$C_{16}H_{18}O_9$	354.31	-0.42	9	6	5	164.75
Methylhesperidin	5284419	$C_{29}H_{36}O_{15}$	624.59	-0.69	15	7	8	223.29
Quercetin	5280343	$C_{15}H_{10}O_7$	302.24	1.54	7	5	1	131.36
Luteolin	5280445	$C_{15}H_{10}O_6$	286.24	2.53	6	4	1	111.13
Phenanthrene	995	$C_{14}H_{10}$	312.36	5.49	2	0	3	26.3
Coniferin	5280372	$C_{16}H_{22}O_8$	342.34	-1.28	8	5	6	128.84
Isorhamnetin-3-O-Neohespeidoside	11665412	$C_{28}H_{32}O_{16}$	624.54	-0.41	16	9	7	258.43
β-Eudesmol	91457	$C_{15}H_{26}O$	222.37	3.74	1	1	1	20.23
Isorhamnetin	5281654	$C_{16}H_{12}O_7$	316.26	1.87	7	4	2	120.36
Ferulic acid	445858	$C_{10}H_{10}O_4$	194.18	1.51	4	2	3	66.76
Caffeic acid	689043	$C_9H_8O_4$	180.16	1.15	4	3	2	77.76
Gallic acid	370	$C_7H_6O_5$	170.12	0.7	5	4	1	97.99
α-bisabolol	1549992	$C_{15}H_{26}O$	222.37	3.79	1	1	4	20.23
Germacrene D	5317570	$C_{15}H_{24}$	204.35	4.74	0	0	1	0
Shikimic acid	8742	$C_7H_{10}O_5$	174.15	-1.72	5	4	1	97.99
4-Hydroxybenzoic acid	135	$C_7H_6O_3$	138.12	1.58	3	2	1	57.53
Salicylic acid	338	$C_7H_6O_3$	138.12	2.26	3	2	1	57.53
Cis-Aconitic acid	643757	$C_6H_6O_6$	174.11	-0.97	6	3	4	111.9
Trigonelline	5570	$C_7H_7NO_2$	137.14	0.51	2	0	1	44.01
Galactinol	11727586	$C_{12}H_{22}O_{11}$	342.3	-5.69	11	9	3	200.53
5'-Deoxy-5'-(Methylthio) Adenosine	439176	$C_{11}H_{15}N_5O_3S$	297.33	-0.27	6	3	3	144.61
Moscatiline	11740968	$C_{21}H_{24}O_7$	338.41	3.56	7	0	10	80.29

3.2. Molecular docking and protein-ligand interaction analysis

The selected compounds were evaluated from the drug-likeness screening using molecular docking. Simultaneously, docking was also performed between β_2-AR and the selected β_2-AR agonists. The results revealed that several compounds exhibited stronger predicted binding affinities for β_2-AR than the reference drugs formoterol (-7.2 kcal/mol) and salmeterol (-6.4 kcal/mol) (Table 2). Kaempferol exhibited the strongest affinity (-9.6 kcal/mol), followed by apigenin (-9.3 kcal/mol), quercetin (-9.2 kcal/mol), and luteolin (-9.0 kcal/mol). Based on these reference values, twelve compounds with binding energies lower than -6.9 kcal/mol were identified as top candidates for further analysis (Table 2).

Furthermore, the binding of these four lead compounds involved key activation residues, such as Asp113 and Ser203 similar to those occupied by formoterol (Figure 2).

Table 2. Analysis of molecular interaction for the bioactive compounds with β_2-AR

Compounds	Binding energy (kcal/mol)	No. of hydrogen bond formed	Residues involved in hydrogen bond formation	Residues involved in hydrophobic interaction
Kaempferol	-9.6	2	Lys305, Asn312	Trp109, Ile309, Phe193
Apigenin	-9.3	2	Lys305, Trp313	Trp109, Asp113, Ile309, Phe193
Quercetin	-9.2	5	Asp113, Tyr316	Trp109, Ile309, Phe193
Luteolin	-9	7	Asp113, Val114, Thr118, Ser203, Ser204, Ser207, Asn293	Val114, Val117, Phe289, Phe193
Phenanthrene	-9	0	-	Phe193
Coniferin	-8.4	2	Ser203, Asp113	Phe193
β-Eudesmol	-7.9	1	Asp113	Ile309, Trp109, Phe193, Tyr308
Isorhamnetin	-7.6	4	Thr195, Asn293, His296, Phe193	Ala201, His178, His296
Ferulic acid	-7.2	1	Ser203	Phe290, Val114, Val117
Caffeic acid	-7.1	4	Asn312, Ala200, Ser204, Asp113	Phe289, Val114, Val117
Gallic acid	-7	2	Asn293, Ser203	Val114, Phe290, Val117
α-bisabolol	-6.9	1	Phe193	Trp109, Val114, Phe193, Ile309, Trp313, Tyr316
Moscatilin	-6.9	4	Thr177, His178, Thr195, Asn293	-
Germacrene D	-6.7	-	-	Leu53, Cys327, Arg333, Leu340, Phe336
Shikimic acid	-6.5	3	Thr195, His296, Asn293	-
4-Hydroxy benzoic acid	-6.5	4	Tyr308, Val114, Thr118, Ser207	Val114, Phe290, Val117, Asn293
Salicylic acid	-6.4	2	Ser203, Ser207	Val114, Phe290, Val117
Cis-Aconitic acid	-5.7	3	His296, Thr195, Asn293	-
Trigonelline	-5.6	3	His93, Trp313, Gly90	Ile309
Formoterol	-7.2	5	Thr195, His296, Tyr308, Phe193, Asn293	His178, His296
Salmeterol	-6.4	2	His296, Phe193	Phe194, His296, His178

Among the twelve ligands with stronger binding affinities, the majority formed both hydrogen bonds and hydrophobic interactions (Table 2). Phe193 emerged as the most frequently involved residue in hydrophobic contacts. Asp113, a known key residue in β_2-AR activation, formed hydrogen bonds with quercetin, luteolin, coniferin, β-eudesmol, and apigenin. Val114 and Thr118 participated in hydrogen bonding with luteolin, while Ser203, Ser204, and Ser207 formed interactions with luteolin and coniferin.

Notably, luteolin demonstrated the most extensive interaction profile, forming hydrogen bonds with seven residues, including Asp113, Val114, Thr118, Ser203, Ser204, Ser207, Asn293, along with hydrophobic interactions with Phe193, Phe289, and Val117. Kaempferol interacted via hydrogen bonds with Lys305 and Asn312, and hydrophobically with Trp109, Ile309, and Phe193. Apigenin formed hydrogen bonds with Lys305 and Trp313, and hydrophobic contacts with Trp109, Asp113, Ile309, and Phe193. In contrast, phenanthrene interacted solely through hydrophobic contact with Phe193.

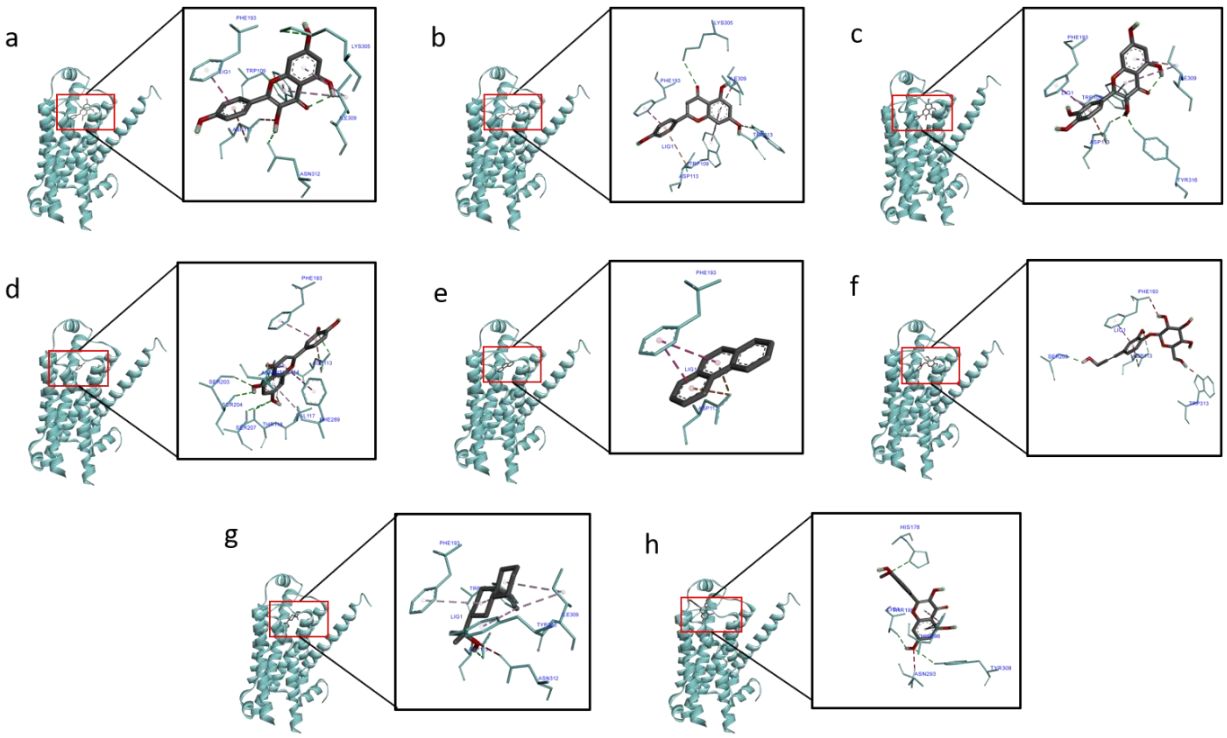


Figure 2. The visualization of molecular docking between β_2-AR (cyan) with **a)** Kaempferol, **b)** Apigenin, **c)** Quercetin, **d)** Luteolin, **e)** Phenanthrene, **f)** Coniferin, **g)** β-eudesmol, **h)** Isorhamnetin. Dashed lines represent interaction type, with the dark and light green lines representing hydrogen bonds and the pink line representing hydrophobic interaction.

3.3. ADMET profiling

The ADMET properties of compounds with stronger binding affinity than reference drugs were predicted (Table 3). For Caco-2 permeability, phenanthrene (1.391) and β-eudesmol (1.508) showed higher values than formoterol (1.074) and salmeterol (1.089). All Dendrobium-derived compounds except β-eudesmol were predicted as P-glycoprotein substrates and inhibitors. Most compounds showed low blood-brain barrier permeability, except phenanthrene and β-eudesmol.

Regarding cytochrome P450 interactions, kaempferol, apigenin, luteolin, quercetin, and isorhamnetin were predicted as CYP1A2 inhibitors. Phenanthrene acted as CYP3A4 substrate and inhibitor of CYP1A2, CYP2C19, and CYP2C9. Coniferin showed no interaction with any tested CYP enzymes, while β-eudesmol was a CYP3A4 substrate without inhibitory effects.

In toxicity profiling, isorhamnetin, quercetin, coniferin, and β-eudesmol showed no mutagenic potential in the AMES test. Kaempferol, apigenin, luteolin, and phenanthrene tested positive for AMES toxicity. No compounds, including references, were identified as hERG I inhibitors.

Table 3. ADMET properties of bioactive compounds from *D. Nobile*

Compound	Caco-2 Permeability (log Papp)	P-gp Substrate	P-gp Inhibitor	BBB Permeability (logBB)	CYP Substrate	CYP Inhibitor						AMES Toxicity	hERG I Inhibitor
					2D6	3A4	1A2	2C19	2C9	2D6	3A4		
Kaempferol	0.270	Yes	No	-0.886	No	No	Yes	No	No	No	No	Yes	No
Apigenin	1.062	Yes	No	-0.708	No	No	Yes	No	No	No	No	Yes	No
Luteolin	0.270	Yes	No	-0.886	No	No	Yes	No	No	No	No	Yes	No

Compound	Caco-2 Permeability (log Papp)	P-gp Substrate	P-gp Inhibitor	BBB Permeability (logBB)	CYP Substrate	CYP Inhibitor					AMES Toxicity	hERG I Inhibitor
Phenanthrene	1.391	Yes	No	0.545	No	Yes	Yes	Yes	No	No	Yes	No
Quercetin	-0.057	Yes	No	-1.339	No	No	Yes	No	Yes	No	No	No	No
Isorhamnetin	0.027	Yes	No	-1.174	No	No	Yes	No	No	No	No	No	No
Coniferin	0.478	Yes	No	-1.110	No	No	No	No	No	No	No	No	No
β-Eudesmol	1.508	No	No	0.634	No	Yes	No	No	No	No	No	No	No
Formoterol	1.074	Yes	No	-0.832	No	Yes	No	No	No	No	No	No	No

4. Discussion

This *in silico* study indicates that the initial drug-likeness screening proved to be a crucial filter, with 19 out of 24 compounds complying with Lipinski's Rule of Five, confirming this species as a rich source of lead-like molecules. The five excluded compounds, such as Methylhesperidin, Isorhamnetin-3-O-Neohesperidoside, Galactinol, Chlorogenic acid, and 5'-Deoxy-5'-(Methylthio) Adenosine, failed primarily due to excessive molecular weight and topological polar surface area (TPSA), parameters critically linked to poor membrane permeability and rapid mucociliary clearance in the lungs (Choy & Prausnitz 2011). This justifies their exclusion from further analysis as inhaled bronchodilator candidates, though their high polarity may suit other therapeutic applications.

Several test ligands demonstrated stronger binding affinities compared to the reference drugs (Table 2). Among the compounds with the strongest binding, flavonoids dominated the top ranks, showing binding energies below -9.0 kcal/mol. Kaempferol showed the strongest binding affinity at -9.6 kcal/mol, followed by apigenin (-9.3 kcal/mol), quercetin (-9.2 kcal/mol) and luteolin (-9.0 kcal/mol). These compounds exhibited substantially more negative binding energies than the conventional β_2-AR agonists formoterol (-7.2 kcal/mol) and salmeterol (-6.4 kcal/mol). Notably, luteolin formed extensive interactions with key activation residues, suggesting it may exhibit agonist-like properties.

The molecular docking results revealed specific interactions with key residues in the β_2-AR binding pocket. Among the twelve ligands with superior binding, the majority formed both hydrogen bonds and hydrophobic interactions. The top-performing compounds were found to interact with key residues known to be critical for β_2-AR activation and agonist function (Isin *et al.* 2012; Soriano-Ursúa *et al.* 2013). Phe193 emerged as the most frequently involved residue in hydrophobic contacts, interacting with kaempferol, apigenin, luteolin, quercetin, coniferin, β-eudesmol, and phenanthrene. This suggests Phe193 serves as a crucial hydrophobic anchor within the binding site (Soriano-Ursúa *et al.* 2013). Furthermore, Asp113, a known key residue in β_2-AR activation, formed hydrogen bonds with quercetin, luteolin, coniferin, β-eudesmol, and apigenin. The engagement of Asp113 is particularly significant as this residue is known to be associated with ligand binding and may contribute to agonist-induced receptor activation and signal transduction (Mizoguchi *et al.* 2023). The serine cluster (Ser203, Ser204, Ser207) also participated in interactions with luteolin and coniferin. These residues are known to be critical for forming a stable agonist-receptor complex and stabilizing the active conformation (Bandaru *et al.* 2017). Among all, luteolin exhibited the most promising profile, engaging seven residues via hydrogen bonds (Asp113, Val114, Thr118, Ser203, Ser204, Ser207, Asn293) and three via hydrophobic contacts (Phe193, Phe289, Val117). This comprehensive binding mode provides a structural explanation for its superior binding affinity and strongly positions it as a top lead candidate for further development. In contrast, the minimal interaction profile of phenanthrene, which relied solely on hydrophobic contact with Phe193, highlights the importance of multifaceted interactions for effective agonist function.

Our ADMET profiling further reinforced the therapeutic potential of the candidates by revealing favorable pharmacokinetic and safety properties (Table 3). Notably, both coniferin and luteolin demonstrated low blood-brain barrier permeability, a desirable trait for inhaled bronchodilators to minimize potential CNS-mediated side effects commonly associated with β_2-agonists (Barisione *et al.* 2010). Furthermore, the absence of hERG inhibition indicates a reduced risk of cardiotoxicity, a well-established critical safety

consideration in drug development (Parker *et al.* 2022). This combination of a promising in silico safety profile with strong target engagement positions coniferin and luteolin as well-rounded candidates for safer pulmonary therapy.

In this study, coniferin and luteolin emerged as the most promising leads. Beyond their strong β_2-AR binding and favorable ADMET profile, they offer complementary therapeutic advantages. Coniferin's minimal CYP interaction suggests a low risk of metabolic drug-drug interactions. Meanwhile, luteolin is a known anti-inflammatory agent (Ntalouka & Tsirivakou 2023), a property highly relevant for addressing the underlying inflammation in asthma. While other compounds like kaempferol and quercetin showed strong binding, their potential to inhibit CYP enzymes warrants caution. Similarly, β-eudesmol's predicted BBB permeability necessitates further safety investigation. Overall, the combination of strong target engagement, favorable pharmacokinetics, and additional beneficial properties positions coniferin and luteolin as the prime candidates for prioritization in subsequent in vitro and in vivo studies. The need for such well-rounded candidates is underscored by the limitations of current β_2-AR agonist therapies. Despite their efficacy as bronchodilators, drugs like formoterol have been associated with adverse events, including pneumonia and altered bone mineral density, particularly when combined with inhaled corticosteroids in COPD patients (Tashkin 2020). Therefore, the discovery of natural compounds like coniferin and luteolin, which exhibit not only superior binding affinity but also a potentially safer and multifunctional profile, addresses a critical unmet need in respiratory medicine.

This study suggests the potential of bioactive compounds from *D. nobile* as β_2-AR agonists involved in bronchodilation. Notably, several compounds, particularly luteolin and coniferin, exhibited strong binding affinities that surpassed those of conventional drugs such as formoterol and salmeterol, alongside favorable pharmacokinetic profiles. These findings highlight the potential of these natural compounds as safer and more affordable plant-based alternatives for asthma therapy. However, this study has limitations. The investigation was confined to 24 reported compounds and requires further computational validation through molecular dynamics simulations, along with additional analyses. Furthermore, subsequent in vitro studies are essential to verify the agonistic potential and pharmacological efficacy of the identified candidates.

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