

# Computational investigation of *Coleus barbatus* phytochemicals as inhibitors for the treatment of Atmospheric dust allergy

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**Abstract:** Up to 30% of the world's population suffers from a constellation of clinical illnesses referred to as allergies. The histamine H1 receptor is involved for several allergic reaction symptoms including rhinorrhea, contraction of bronchial and gastrointestinal smooth muscle, various itching patterns. Histamine is a key mediator in allergic reactions. This research attempts to identify the binding sites between the human histamine h1 receptor protein and *Coleus barbatus* phytochemicals. The 3D structure of the protein was retrieved from the PDB database. The target's active sites are taken from Castp. Ligands, also known as binding molecules, are gathered from literature and phytochemical databases. The ligands' 2D structures were derived from PubChem. SwissADME assists with the final ADMET investigations, and Swiss Dock server used for molecular docking. Coleone E is seen to have the best docking results of all the phytochemicals, and it also complies with the Lipinski rule of 5 and ADMET. Recent natural medications have been shown in docking tests to have higher binding affinities and lower energies, which internally aid in more precisely binding with the target. So these phytochemicals can replace the chemically synthesized drugs which cause the side effects.

**Key Words:** Allergy, Histamine H1 receptor, Castp, Swiss Dock, Swiss ADME, Lipinski rule of five.

## 1. INTRODUCTION:

The recent developments of fast reliable docking, virtual screening, and other algorithms gave rise to the discovery of many novel ligands of histamine receptors that could be used for the treatment of allergic inflammatory disorders, central nervous system pathologies, pain, cancer, and obesity. Furthermore, the pharmacological profiles of ligands indicate that these receptors may be considered targets not only for selective but also for multi-target drugs that could be used for the treatment of complex disorders such as Alzheimer's disease. Therefore, analysis of protein-ligand recognition in the binding site of histamine receptors and also other molecular targets has become a valuable tool in the drug design toolkit.<sup>[1]</sup>

Many studies have demonstrated that exposure to outdoor air pollutants can exacerbate pre-existing asthma [2,3], but it is unclear whether outdoor air pollutants increase the incidence of asthma or allergic diseases in children. While a limited number of studies have described associations between asthma and ozone [4,5], there is growing evidence that air pollutants specifically associated with traffic exposure may be of greater importance to asthma and allergic disease development [6–19].

## 2. LITERATURE REVIEW:

*Coleus forskohlii* is an important medicinal plant native to India. It has been used in traditional Ayurvedic medicine for curing various disorders and this is the only source of diterpenoid forskolin. A tuberous roots are found to be a rich source of forskohlin (coleonol) used as a potential drug for hypertension, congestive heart failure, eczema, colic, respiratory disorders, painful urination, insomnia and convulsions. Clinical studies of the plant further support these traditional uses, indicating therapeutic benefits in asthma, angina, psoriasis and prevention of cancer metastases,

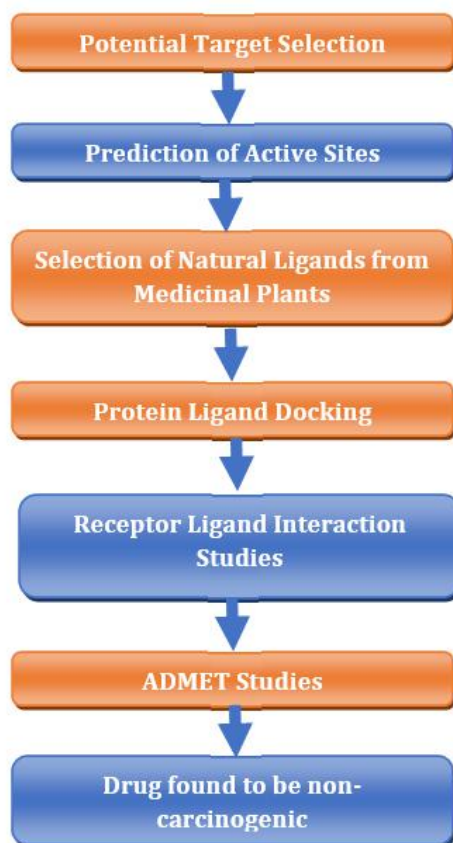
where decreased intracellular cAMP level is believed to be a major factor in the development of the disease process. This article gives a comprehensive look on Coleus as a natural product and aims to present it in a brief manner for the researchers, scientist, botanists, pharmacognosists and herbalists to refresh their knowledge about coleus.<sup>[20]</sup>

The medicinally important plants of *Coleus forskohlii* were collected from the forest areas of Ananthagiri, Rangareddy District. This plant belongs to the family of Lamiaceae. A total of fourteen (14) phytochemicals were screened from the leaf extracts of the above plant. The analysis was studied in different solvents like methanol, acetone, petroleum ether, and chloroform including the aqueous extracts. The phytochemical analysis revealed the presence of alkaloids, saponins, tannins, flavonoids, terpenoids, coumarins, quinines, cardiac glycosides, Xanthoproteins, glycosides, steroids, phenols, resins, a carboxylic acid group in varying concentrations.<sup>[21]</sup>

Allergens are foreign proteins that when coming in contact with the part(s) of the human body stimulate the production of immunoglobulin types of proteins (antibodies). These allergens react with antibodies (immunoglobulin type E or IgE) producing allergic reactions, also known as immediate-type hypersensitivity reactions. As much as 20% of the general population may be affected by grass pollen as a major cause of allergic disease. EXPB class of proteins is known in the immunological literature as group-1 grass pollen allergens. Molecular docking method can be used to identify the predicted interaction of pollen allergen EXPB1 (*Zea m 1*), a beta-expansin and group-1 pollen allergen from maize with IgE molecules of human. The World Health Organization recognized allergen immunotherapy, as therapeutic for allergic diseases. RNA Interference (RNAi) is a biological process in which RNA molecules e.g. Small Interfering RNAs (siRNAs) inhibit gene expression, by cleavage and destruction of specific mRNA molecules. The use of Small Interfering RNA (siRNA) is a novel method in the induction of RNA Interference (RNAi), which is a potent method for therapeutics of allergic reactions. Due to various effects of STAT 6 proteins during hypersensitivity reactions caused by pollen allergens, mRNA of the STAT6 gene is selected as the target gene for allergy therapeutics via Post-Transcriptional Gene Silencing (PTGS). Using molecular docking study a specific sense siRNA is identified as an anti-allergic drug to treat allergic asthma during the immediate type of hypersensitivity reaction, caused by *Zea m 1* pollen allergen.<sup>[22]</sup>

### 3. MATERIALS AND METHODS:

- I. **Structure retrieval - PDB ([www.rcsb.org](http://www.rcsb.org))**
- II. Protein Data Bank is a database for the three dimensional structural data for large biomolecules. The target protein Aldose Reductase three dimensional structure was retrieved from PDB.
- III. **Structure visualization-RASMOL:** RasMol ([RasMol- www.rasmol.org/](http://www.rasmol.org/)), a molecular graphics program used for the visualization of Biomolecules. Aldose Reductase three dimensional structure was visualized using Rasmol.
- IV. **Prediction of Active site – Castp:** (Cast p <http://sts.bioe.uic.edu/castp>) It is a online tool used to predict the binding pockets of the protein Histamine H1 receptor.
- V. **2D Structure of Inhibitors – Pubchem :** (Pubchem - <https://pubchem.ncbi.nlm.nih.gov/>) The phytochemicals in Coleus barbetus was obtained from the online chemical database Pubchem. The inhibitors should obeys Lipinski's Rule of Five.
- VI. **File Format Conversion – Open Babel: (Open Babel – [www.cheminfo.org](http://www.cheminfo.org))** The file format of Ligands are converted by using open source software Open Babel.
- VII. **Docking: SWISS DOCK** ([swiss Dock-http://www.swissdock.ch/](http://www.swissdock.ch/)). Docking was done with the SWISS DOCK Server. In docking Ligands binds to the active sites. The results are obtained on the basis of pose energy.
- VIII. **ADMET Studies:** Swiss ADMET (Swiss ADMET – [www.swissadme.ch](http://www.swissadme.ch)) Absorption, distribution, metabolism, excretion and Toxicity studies for the phytochemicals in Coleus barbetus are analysed using this tool.



#### 4. RESULT:

##### 1. Retrieval of human 3D structure of Aldose Reductase

The Histamine H1 (PDB ID: 3RZE) human Protein 3D structure was downloaded from the Protein Data Bank for further analysis.

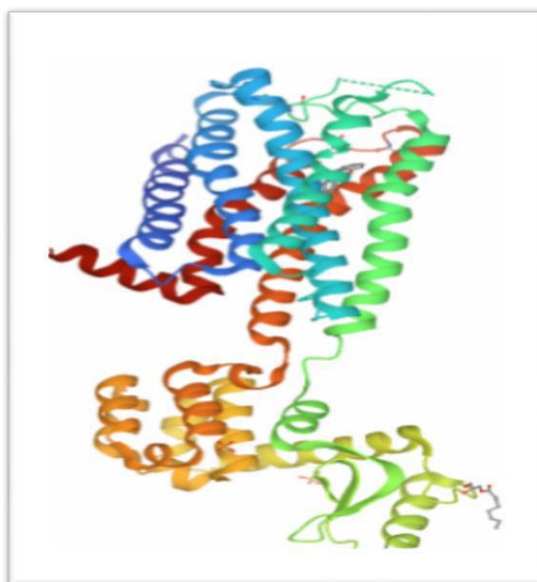


Figure 1: Histamine H1

##### 2. Binding Site Prediction – CASTp:

The PDB ID :3RZE given as input to CASTp and the binding site of the protein was predicted. Some of the amino acid present in the pockets are GLU 1011A, ASP 1020A, THR 1021A, GLU 1022A, TYR 1024A, THR 1026A, ILE 1029A, GLY 1030A, HIS 1031A, LEU 1032A, THR 1034A, ASP 1070A, ALA 1073A, ALA 1074A, VAL 1103A, PHE 1104A, GLN 1105A, MET 1106A, GLY 1107A, GLU 1108A, TRP 1138A,

GLN 1141A, THR 1142A, ARG 1142A. Totally 66 amino acids are present in the binding site of the protein Histamine H1.



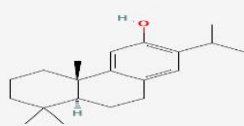
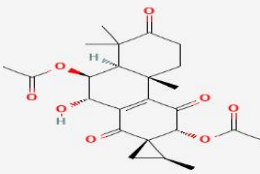
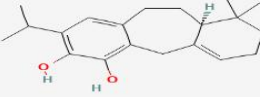
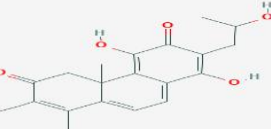
Figure 2: Binding Site Present in Aldose Reductase

### 3. Retrieval of Ligands from PUBCHEM:

The Histamine H1 Inhibitors are collected from literatures and downloaded from PUBCHEM. Phytochemicals from the leaf of Medicinal Plant Coleus barbetus such as (+)-Ferruginol, Barbatusin, Barbatusol, Coleon-E, Coleon-F, Coleon-O, Coleonol, Plectrin are downloaded for further studies. Canonical Smilies of phytochemicals are retrieved and using Open Babel it is converted into .Mol2 file format for Docking studies.

### 4. Molecular Docking Studies:

The docking studies was carried out using Swiss Dock Server. The protein side chain molecules were deleted using the the proper visualization of them with the use of numerous tool controls. The investigation used a different .Mol2 dataset that contained the binding site molecules. Then, docking studies were carried out after loading the protein and ligand .mol2 files. Details about the best docked conformation and its binding energy are provided below. The different binding configurations were then examined, and the list of optimum poses was generated, downloaded and saved for further studies.

Phytochemical	Structure	Docking Score
(+)-Ferruginol,		-7.17
Barbatusin,		-7.04
Barbatusol,		-7.03
Coleon-E,		-7.19

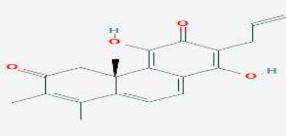
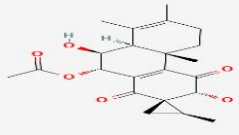
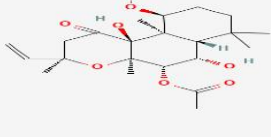
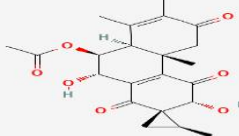



Coleon-F,		-6.97
Coleon-O,		-7.01
Coleonol,		-7.1
Plectrin		-7.13

Table 4.1 Phytochemicals 2D Structure and Docking Score

		
Docking Interactions of Coleon E in binding Site	Docking Interactions of (+)-Ferruginol in binding Site	Docking Interactions of Plectrin in binding Site

4.2 Best Docking Score Molecules

5. ADMET Studies using Swiss Dock

All the Ligands are undergone ADMET Studies using Swiss ADME Server. The Pharmacokinetic properties are studied.

GI absorption ? High	GI absorption ? High	GI absorption ? High
BBB permeant ? No	BBB permeant ? Yes	BBB permeant ? No
P-gp substrate ? Yes	P-gp substrate ? No	P-gp substrate ? Yes
CYP1A2 inhibitor ? No	CYP1A2 inhibitor ? No	CYP1A2 inhibitor ? No
CYP2C19 inhibitor ? No	CYP2C19 inhibitor ? Yes	CYP2C19 inhibitor ? No
CYP2C9 inhibitor ? No	CYP2C9 inhibitor ? Yes	CYP2C9 inhibitor ? No
CYP2D6 inhibitor ? No	CYP2D6 inhibitor ? Yes	CYP2D6 inhibitor ? No
CYP3A4 inhibitor ? No	CYP3A4 inhibitor ? No	CYP3A4 inhibitor ? No
Log K <sub>p</sub> (skin permeation) ? -7.76 cm/s	Log K <sub>p</sub> (skin permeation) ? -3.28 cm/s	Log K <sub>p</sub> (skin permeation) ? -8.89 cm/s
Coleon E	(+)-Ferruginol	Plectrin

5.1 Best Docking Compounds with Pharmacokinetic properties.

5. DISCUSSION:

Since the beginning of time, natural remedies have been utilized to treat many human illnesses, and we are well recognised for producing many of them. Due to the medical benefits of these herbs and plants, scientists are now



considering natural products as potential sources for pharmacological molecules. In this work, a single plant is used to create the therapeutic molecules known as ligands, which are thought to be mostly responsible for the disease's protection. Asthma and even more serious illnesses like eosinophilia and leukaemia can result from allergies, as is well recognised. It is preferable to start treating at a younger stage. Antihistamines are used to block the histamine H1 receptor's activity. Numerous drugs might interact with one another or possibly lead to hormonal imbalance. The likelihood of adverse effects brought on by chemically produced antihistamines is reduced by the usage of phytochemicals.

The herb *Coleus barbatus* used to treat allergy and other irritating issues. Due to its strong medical value, it has been utilised for a variety of treatments since ancient times. It has anti-inflammatory, anti-allergic, and even anti-cancerous qualities. A variety of illness disorders are treated using the stem, roots, leaves, shoots, and essential oils. In the present work some of the phytochemicals from the leaves are used. To determine each ligand's effectiveness, the plant-derived ligands are docked with the protein molecule utilising software or servers. The best docking scores indicate that Coleone E, (+)-Ferruginol and Plectrin are better ligands for drug creation. These compounds have undergone Swiss ADME investigations, and each molecule complies with the Lipinski rule of 5. The *Coleus barbatus* plant produces phytochemicals that have anti-allergic activity, which are useful for treating allergic disorders. Using medications based on phytochemicals has no negative side effects and has no additional effects on the body. Utilising this as medicine also assists in protecting the body from adverse reactions and maintains overall health. The effectiveness of the natural bioactive molecule to regulate histamine is demonstrated by the docking result analysis. The ligand's close fit to the molecule was further supported by the binding energy of the ligand-protein interaction. This study may offer insight into allergic reactions to airborne dust and potential medication combinations.

## 6. CONCLUSION:

Since the medications are administered to suppress the symptoms, there is little treatment available for allergic symptoms. Other negative consequences could result from the suppression of symptoms. The use of antihistamines to treat the condition increases the risk of negative effects like addiction and hormonal imbalance. Since synthetic antihistamines simply reduce symptoms rather than provide a full cure, taking them once encourages continued use of the medication. The *Coleus barbatus* plant produces phytochemicals that have anti-allergic activity, which are useful for treating allergic disorders. Using medications based on phytochemicals has no negative side effects and has no additional effects on the body. Utilising this as medicine also assists in protecting the body from adverse reactions and maintains overall health. The effectiveness of the natural bioactive molecule to regulate histamine is demonstrated by the docking result analysis. The ligand's close fit to the molecule was further supported by the binding energy of the ligand-protein interaction. This study may offer insight into allergic reactions to airborne dust and potential medication combinations.

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