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Research Article

IDENTIFICATION OF ANTI-ASTHMATIC DRUG FROM MEDICINAL PLANTS USING AN *IN SILICO* APPROACH

AAYUSHI SAHGAL, ABEER AIRAJUDDIN, SAMBARA PRAVALLIKA, VAEESHNAVI BUWA

Department of Sciences, St. Mary's College, Yousufguda, Hyderabad, Telangana, India. Email: Aayushi.sahagal26@gmail.com

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ABSTRACT

Objectives: Considering the limitations and side effects of current synthetic medications, herein, the exploration of the anti-inflammatory and antihistamine properties of medicinal plants is conducted to provide alternative treatment options for asthma and aims to identify potential anti-asthmatic drugs using an *in silico* approach.

Methods: A molecular docking study was performed to assess the binding affinities and interactions between the neuropeptide S receptor (NPSR) protein and 15 medicinal plants and flavonoids chosen from published literature. A Ramachandran Plot analysis was conducted to evaluate the stereochemical properties of the protein. Furthermore, to gain insights into the drug-likeness and pharmacokinetic properties of the identified ligands, ADMESAR analysis was performed to predict molecular properties and bioactivity of small molecules.

Results: Among the 15 medicinal plants investigated in this research, Kaempferol exhibited the least binding energy of −5.05, indicating a highly stable interaction with the NPSR protein. This exceptional stability suggests that Kaempferol has the potential to serve as an effective anti-asthmatic drug.

Conclusion: Asthma has no permanent cure, and the current synthetic medications raise long-term safety concerns. This study explored the use of medicinal plants and flavonoids, with Kaempferol showing promise as a potential anti-asthmatic drug candidate. This preliminary study could open avenues to further research and the use of medicinal plants in the treatment of asthma, potentially reducing reliance on synthetic drugs.

Keywords: Bioinformatics, Molecular docking, Asthma, Medicinal plants, Flavonoids, Kaempferol, Neuropeptide S receptor, Complementary and alternative medicine.

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INTRODUCTION

In everyday life, illnesses and other ailments are unavoidable, pushing man to find novel methods for treating them. One such disease that has been seen to affect people of all ages and that typically begins in childhood is asthma [1]. Asthma is a complex inflammatory condition, characterized by increased airway sensitivity and airflow limitation. According to reports from the Global Asthma Network and Global Initiative for Asthma, asthma is observed to impact anywhere from 1% to 18% of the population in different countries, leading to an astounding global prevalence of over 300 million individuals [2].

The immune system plays a central role in the development and progression of asthma's systemic effects. In individuals with asthma, the immune response to various triggers becomes dysregulated, leading to chronic inflammation throughout the respiratory tract. This immune response involves the activation of various immune cells, such as mast cells, eosinophils, and T-lymphocytes, which release pro-inflammatory mediators and cytokines [3]. As a result, not only the bronchial tubes but also the nasal passages and sinuses become sites of inflammation outcomes [4]. Moreover, this recognition of asthma's systemic nature and its link to the immune system highlights the heterogeneity of the condition, emphasizing the need for personalized approaches to its diagnosis, treatment, and management [5,6].

Even though a wide range of drugs is available for the treatment of asthma, including bronchodilators and corticosteroids, the relief offered by them is mostly symptomatic and short-lived. A permanent cure for asthma is yet to be found, and a personalized treatment may help reduce symptoms. Furthermore, the negative effects of these medications are highly concerning as a result; patients are turning to complementary and alternative forms of medicine (CAM) for treatment [7]. Medicinal plants have a long-standing tradition in the treatment of asthma and are prevalent in over 90% of traditional medicine recipes. They are sources of natural compounds with antihistamine, anti-inflammatory, bronchodilator, or immunomodulatory properties and have thus been used extensively as CAM. CAM has been practiced around the world and includes Ayurveda (Traditional Indian medicine), Hanbang (Traditional Korean medicine), and Kampo (Traditional Chinese and Japanese medicine) [8]. In addition, antioxidant supplements can be beneficial by reducing the severity of bronchoconstriction through the inhibition of pro-inflammatory processes and neutralization of excess reactive oxygen species and reactive nitrogen species [9].

The objective of this research paper is to investigate the therapeutic potential of medicinal plants as a source of anti-asthmatic compounds through molecular docking studies. Specifically, the study aims to target the neuropeptide S receptor (NPSR) protein, a protein known to play a critical role in the pathogenesis of asthma. By conducting *in-silico* docking simulations, we aim to identify potential compounds from medicinal plants that can interact with the target protein, thereby presenting a novel avenue for the development of an effective anti-asthmatic drug.

METHODS

Preparation of target proteins

The NPSR protein is a member of the G protein-coupled receptor (GPCR) family that is activated by the neuropeptide S (NPS). NPSR and NPS are proteins that are widely expressed in the central nervous system (CNS) and are known to play important roles in asthma pathogenesis, locomotor activity, wakefulness, anxiety, and food intake. Furthermore,

mutations in NPSR have been connected to asthma susceptibility (for asthma susceptibility) [10].

The NPSR protein file, Q6W5P4 (NPSR1_HUMAN), was obtained from the Universal Protein Resource Database (https://www.uniprot.org/) [11] and prepared for docking studies using the ITASSER (https://zhanggroup.org/Iterative Threading Assembly Refinement/) [12] tool. To assess the protein's stereochemical and structural properties, a Ramachandran Plot was generated using the Z-lab server (https://zlab.umassmed.edu/bu/rama/)[13] and PROCHECK [14] was used to generate plot statistics.

Selection of medicinal plants as potential ligands
After a thorough review of literature, 15 potential medicinal plants and flavonoids were selected based on their anti-inflammatory, antihistamine, and anti-allergic properties [15,16]. The 3D structures (Table 1) of these ligands were obtained from the PUBCHEM database (https://pubchem.ncbi.nlm.nih.gov/) [17] in structured data format and converted to protein data bank (PDB) format using the OpenBabel-2.4.1 software [18].

Analysis of ligand suitability as drug
The drug likeness of the potential ligands was evaluated using the Lipinski filter and ADMESAR analysis (http://www.swissadme.ch/) [19,20] which describes the properties of a molecule important for drug pharmacokinetics, including Absorption, Distribution, Metabolism, and Excretion (ADME). The Lipinski rule of 5 states that: (i) The molecular weight of the compound should be < 500 daltons, (ii) the lipophilicity (expressed as iLogP) should be <5, (iii) the number of hydrogen bond acceptors should be <10, (iv) the number of hydrogen bond donors should be <5, and (v) the molar refractivity should be between 40 and 130. The selected compounds were also analyzed for their permeability to the blood-brain barrier and gastrointestinal absorption using Brain Or Intestinal Estimated Permeation Method (BOILED-Egg). The BOILED Egg analysis can be used for a variety of functions, ranging from evaluation of the drug candidates for their development to the exploration for drug discovery [21].

Screening for ligands for molecular docking
Compounds selected from SWISS ADME were subjected to further screening based on their binding energies using python prescription (PyRx), a virtual screening software used for computational drug discovery [20].

Molecular docking studies
To predict the interaction between the selected medicinal plants and the NPSR protein, a molecular docking study was conducted using AutoDock Tools 1.5.7 software. Experiments were carried out with default parameters to ensure accurate results. The extended PDB format, PDB Format File Plus Charges (Q) (PDBQT) files, for ligands and proteins, which included the atomic partial charges, atom types, grid boxes, and grid parameter files, were generated using the graphical user interface of AutoDock Tools. The NPSR protein was prepared by removing water molecules, assigning polar hydrogens, and stored in PDBQT format. The autogrid procedure was performed to generate the grid map by embedding the protein into a three-dimensional grid box. The grid size was set to 126x126x126 (XYZ) with a grid spacing of 0.708 Å and the grid center was designated at the dimensions (X, Y, and Z): 70.581, 70.364, and 70.322. Docking was carried out using the Lamarckian genetic algorithm with 10 runs, and the most favorable configuration was selected from the cluster root mean square deviation table [22].

Analysis of docking results
The conformation with the lowest binding energy of each ligand was extracted from the docking log file (DLG) files and analyzed on Autodock Tools. Protein-ligand docked complexes were saved in PDBQT format and subsequently converted into PDB format using OpenBabel-2.4.1 and visualized in PyMOL 2.5.1 [23].

RESULTS

Pre docking procedure

Protein file preparation

Information on the NPSR protein PDB file is mentioned in Table 1 and the Ramachandran plot analysis showing stereochemical properties is shown in Fig. 1 and Table 2.

Ligand library generation
Physiochemical properties of all 15 compounds obtained from PubChem open chemistry database are listed in Table 3.

Analysis of drug-likeliness
There were 10 ligands that showed drug-likeness, namely, *A. marmelos*, *Crocus sativus,* Curcumin, *Ginkgo biloba*, *Glycyrrhiza glabra,* Kaempferol, Luteolin, Oroxylin A, Quercetin, and Resveratrol. Molecules that showed even one violation of the Lipinski rule were disregarded. The results are summarized in Table 4. Furthermore, the Boiled Egg analysis revealed that the ligands: *C. sativus*, Curcumin, Kaempferol, Luteolin, Oroxylin A, and Quercetin were shown to be well absorbed but could not penetrate the brain barrier and are not effluated by the CNS by the P-glycoprotein (PGP-), whereas *A. marmelos* and Resveratrol were capable of being pumped out through PGP transporters [24], and *G. glabra* is the only ligand which is predicted to cross the brain barrier, while the rest of them are not subject to active reflux.

Screening of ligands using PyRx
The ligands that followed Lipinski's rule of 5 from the SWISS ADME analysis were selected and used against the NPSR protein for screening purposes. The binding energies of all the ligands were compared and it was found that seven ligands with similar energies of −6.7 and above could be used for docking studies. The selected ligands are as follows: *C. sativus* (−7), Curcumin (−6.8), *G. biloba* (−7.1), Kaempferol (−7.4), Luteolin (−6.8), Oroxylin A (−6.8), and Quercetin (−6.7) Table 5.

Docking studies
A molecular docking study was performed to predict the interaction of the selected medicinal plants with the NPSR protein (NPSR) using AutoDock Tools 1.5.7 software. *C. sativus*, Curcumin, *G. biloba*, Kaempferol, Luteolin, Oroxylin A, and Quercetin were selected after the analysis of their binding energies from PyRx and were subjected to docking against the protein. The parameters were set to default for accurate results. The conformations with the lowest binding energies of all ligands were extracted from the DLG files, and the ligand Kaempferol was selected for its lowest binding energy of −5.05. This showed that the protein-ligand

Table 1: Extracted protein information

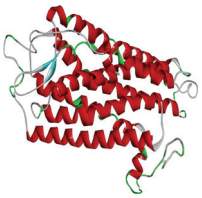
Protein ID	Macromolecule	Method	Organism	Length	Structure
Q6W5P4	Neuropeptide S receptor	X-ray crystallography	*Homo sapiens* (Human)	371AA	

Table 2: Plot statistics

Placement of residues	Amount	Percentages
Residues in most favored regions [A,B,L]	246	72.1
Residues in additional allowed regions [a,b,1,p]	70	20.5
Residues in generously allowed regions [~a,~b,~1,~p]	18	5.3
Residues in disallowed regions	7	2.1
Number of non-glycine and non-proline residues	341	100
Number of end-residues (excl. Gly and Pro)	2	
Number of glycine residues (shown as triangles)	14	
Number of proline residues	14	
Total number of residues	371	

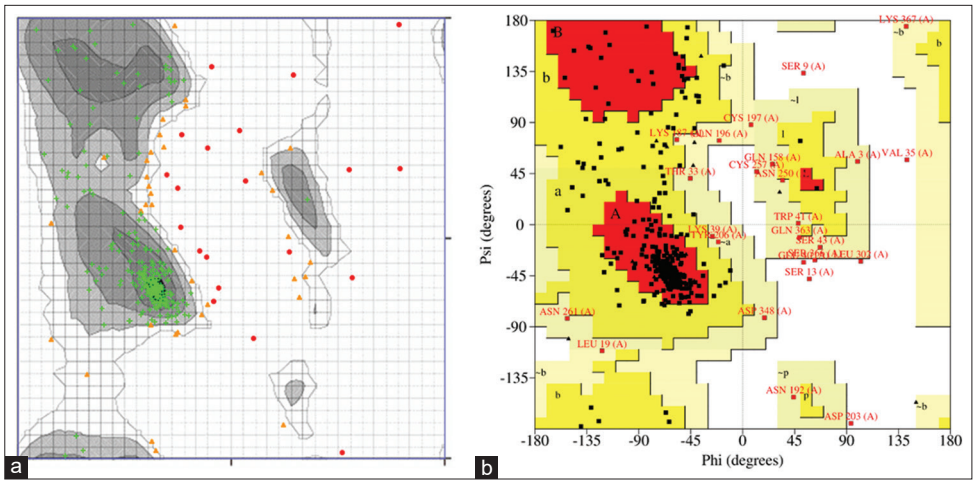


Fig. 1: a. Ramachandran Plot analysis – The chart is color-coded: BLACK, DARK GREY, and LIGHT GREY represent highly preferred conformations (Delta≥−2). WHITE with BLACK grids represent preferred conformations (−2>Delta≥−4). WHITE with GREY grids represent questionable conformations (Delta<−4). Highly preferred observations are shown as GREEN crosses: 285 (83.578%). Preferred observations are shown as BROWN triangles: 36 (10.557%). Questionable observations are shown as RED circles: 20 (5.685%). b. Plot statistics analysis using PROCHECK server

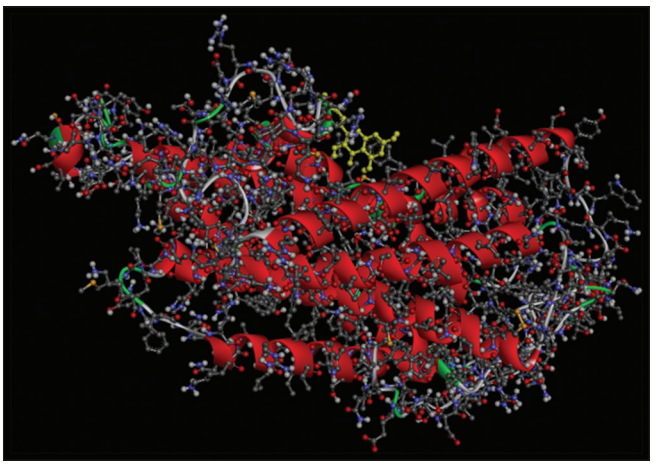


Fig. 2: Visualization of AutoDock results using PyMOL 2.5.1

complex (NPSR protein and Kaempferol) formed the most stable complex of all (Fig. 2), making it a potential anti-asthmatic drug.

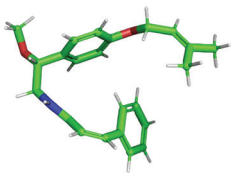
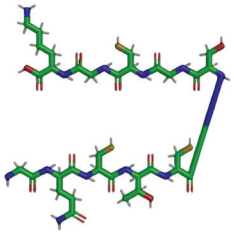
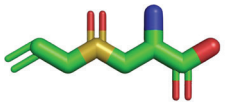
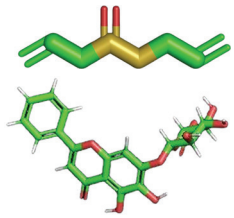
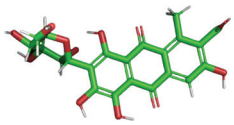
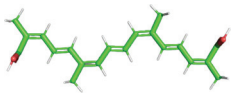
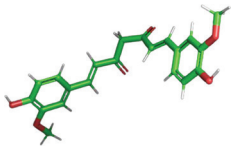
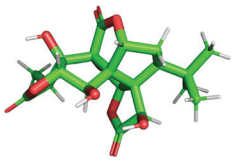
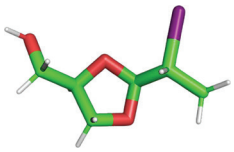
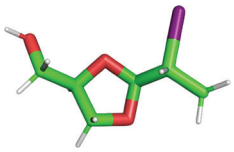
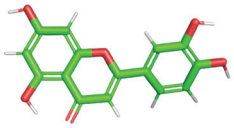
DISCUSSION

Research indicates that individuals with asthma often experience inflammation and heightened sensitivity in the nasal passages and sinuses, which is known as "rhinosinusitis [25]." This interconnected inflammation between the upper and lower airways is referred to as the "united airway concept." Such inflammation in the nasal passages and sinuses can exacerbate asthma symptoms and vice versa, leading to a more complex and severe manifestation of the disease [26]. Moreover, the impact of asthma extends beyond the respiratory system, as systemic inflammation can manifest in other distant parts of the body. People with asthma may show increased markers of inflammation in their blood, suggesting a broader immune system response. This systemic inflammation has been associated with a higher risk of cardiovascular diseases and other inflammatory conditions, highlighting the potential influence of asthma on overall health.

The limitations and potential side effects of synthetic medications have led researchers to shift their focus toward exploring natural sources for the development of effective anti-asthmatic drugs. Medicinal plants offer a promising pathway due to their long history of traditional use in various cultures and the growing body of scientific evidence supporting their therapeutic properties [27]. Previous research and traditional knowledge from indigenous Indian practices have shown how the use of plants is referenced to treat a wide range of human ailments. India is home to approximately 45,000 plant species, several thousand of which are claimed to possess medicinal properties. Some of the medicinal plants that have been found to have anti-asthmatic properties are as follows: *Aerva lanta*, *Bacopa monnieri, Cassia sophera, Euphorbia hirta, Gakani, Hemidesmus indicus, Olea europea,* and *Piper betel* [28].

In this research endeavor, medicinal plants were considered potential ligands, aiming to neutralize the undesirable effects associated with asthma. A diverse set of medicinal plants and flavonoids were meticulously chosen based on their specific attributes, which include anti-inflammatory, antihistamine, immunomodulatory, and anti-allergic properties. Among these, *A. marmelos*, *Agaricus bisporus*, *Allium sativum*, Baicalin, *Boswellia serrata*, *C. sativus*, Curcumin, *G. glabra*, *G.*

Table 3: Medicinal plants used in the treatment of asthma

S. No.	Medicinal Plant	PubChem ID	Molecular Formula	Molecular Weight	Structure
1.	*Aegle marmelos*	CID131752933	$C_{23}H_{27}NO_3$	365.47	
2.	*Agaricus bisporus*	CID102059656	$C_{33}H_{58}N_{12}O_{14}S_3$	943.08	
3.	*Allium sativum*	...	...	488.90	
4.	Baicalin	CID64982	$C_{21}H_{18}O_{11}$	446.36	
5.	*Boswellia serrata*	CID11168203	$C_{32}H_{48}O_5$	492.39	
6.	*Crocus sativus*	...	...	328.40	
7.	Curcumin	CID969516	$C_{21}H_{20}O_6$	368.38	
8.	*Ginkgo biloba*	CID6324617	$C_{20}H_{24}O_{10}$	424.40	
9.	*Glycyrrhiza glabra*	...	...	258.05	
10.	Kaempferol	CID5280863	$C_{15}H_{10}O_6$	286.24	
11.	Luteolin	CID5280445	$C_{15}H_{10}O_6$	286.24	

(Contd...)

Table 3: *(Continued)*

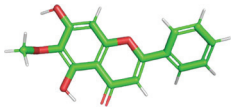
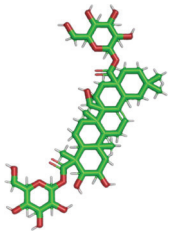
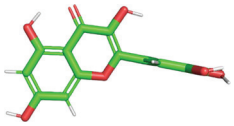
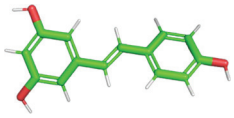
S. No.	Medicinal Plant	PubChem ID	Molecular Formula	Molecular Weight	Structure
12.	Oroxylin A	CID5320315	$C_{16}H_{12}O_5$	284.26	
13.	*Panax ginseng*	...	...	842.96	
14.	Quercetin	CID5280343	$C_{15}H_{10}O_7$	302.24	
15.	Resveratrol	CID445154	$C_{14}H_{12}O_3$	228.24	

Table 4: Analysis of Potential Ligands using Lipinski's rule of 5

S. No.	Name of the Ligand	Molecular weight (g/mol)	H-bond acceptors	H-bond donors	Molar refractivity	Lipophilicity (iLOGP)	Drug likeness
1.	*Aegle marmelos*	365.47	3	1	109.58	4.04	Yes
2.	*Agaricus bisporus*	943.08	16	15	223.96	0.78	No
3.	*Allium sativum*	488.90	1	0	144.32	6.43	No
4.	Baicalin	446.36	11	6	106.72	1.59	No
5.	Boswellia	492.39	13	9	112.39	-1.31	No
6.	*Crocus sativus*	328.40	4	2	98.48	3.33	Yes
7.	Curcumin	368.38	6	2	102.80	3.27	Yes
8.	*Ginkgo biloba*	424.40	10	3	93.29	1.19	Yes
9.	*Glycyrrhiza glabra*	258.05	3	1	45.14	1.99	Yes
10.	Kaempferol	286.24	6	4	76.01	1.70	Yes
11.	Luteolin	286.24	6	4	76.01	1.86	Yes
12.	Oroxylin A	284.26	5	2	78.46	2.61	Yes
13.	*Panax ginseng*	842.96	17	11	204.70	2.86	No
14.	Quercetin	302.24	7	5	78.03	1.63	Yes
15.	Resveratrol	228.24	3	3	67.88	1.71	Yes

Table 5: Analysis of ligands using PyRx

S. No.	Ligand	PubChem ID	Binding energy
1.	*Aegle marmelos*	CID131752933	−6.2
2.	*Crocus sativus*	...	−7
3.	Curcumin	CID969516	−6.8
4.	*Ginkgo biloba*	CID6324617	−7.1
5.	*Glycyrrhiza glabra*	...	−4.4
6.	Kaempferol	CID5280863	−7.4
7.	Luteolin	CID5280445	−6.8
8.	Oroxylin A	CID5320315	−6.8
9.	Quercetin	CID5280343	−6.7
10.	Resveratrol	CID445154	−6.3

PyRx: Python Prescription

biloba, Kaempferol, Luteolin, Oroxylin A, *Panax ginseng*, Quercetin, and Resveratrol have shown promising potential in addressing the complexities of asthma by targeting multiple aspects of the condition. The exploration of these natural compounds as potential anti-asthmatic drugs not only offers a more holistic and potentially safer approach to asthma management but also aligns with the increasing global interest in traditional and herbal medicine.

With advantages of cost-effectiveness, time efficiency, scalability, and the ability to explore challenging scenarios, the *in silico* approach has revolutionized scientific research, offering valuable insights and innovative solutions to intricate problems before transitioning to real-world experiments. It complements wet-lab experiments and the combination of *in-silico* predictions with wet-lab validation enhances research quality and fosters a more comprehensive understanding of biological processes and drug development. Docking of the NPSR protein revealed that Kaempferol exhibited the lowest binding energy, indicating a potentially favorable interaction with the receptor. This low binding energy suggests greater stability of the Kaempferol-receptor complex. The negative Gibbs free energy associated with this binding indicates that the interaction is thermodynamically favorable, further supporting its potential as a drug candidate for the treatment of asthma. Moreover, during the assessment of the compounds' drug-likeness based on Lipinski's rule of 5, they were found to meet the criteria for suitability for human consumption.

This preliminary study holds the potential to inspire further research and exploration of the application of these natural compounds in the treatment of asthma. By incorporating these plants, there could be a reduction in the reliance on synthetic drugs and a corresponding

decrease in their associated side effects. The objectives of medicine are the same regardless of which group it belongs to, that is, the welfare of patients. One can look forward to an era of integrated medicine and hope that research in alternative medicine will aid in the safe and effective treatment of asthma rather than just managing it.

The future offers promising directions for research. To validate the efficacy and safety of the potential compounds, comprehensive *in vitro* and *in vivo* experiments can be conducted. Further, understanding the essential chemical features responsible for their anti-asthmatic activity through structure-activity relationship studies will aid in designing more potent and selective drugs [29]. Implementing high-throughput screening methods will accelerate the identification of novel anti-asthmatic candidates from a broader range of medicinal plants and compounds. Exploring the synergistic effects of combining multiple medicinal plant compounds can lead to more effective and comprehensive anti-asthmatic treatments with enhanced efficacy and reduced side effects. In addition, assessing the pharmacokinetics and pharmacodynamics of these compounds will optimize dosage regimens and pave the way for clinical trials to evaluate their safety and efficacy in asthma patients. Mechanistic studies will unravel the underlying molecular pathways of action, contributing to the development of targeted therapies. Moreover, formulating appropriate dosage forms and delivery systems will ensure optimal bioavailability and patient compliance [30]. By fostering global collaboration and integrating traditional herbal knowledge with modern scientific approaches, researchers can advance anti-asthmatic drug discovery and potentially revolutionize asthma management with safer, more effective, and more affordable treatment options.

CONCLUSION

Asthma is a lung disorder that currently has no permanent cure and can only be managed by treating its symptoms. Although synthetic medications exhibit remarkable efficacy against asthma, their long-term usage raises numerous concerns. Herbal medicine has long been thought to be one of the oldest forms of treatment used by mankind and according to the findings of this study, a variety of medicinal plants and flavonoids showed counterbalancing effects on inflammation, oxidative stress, allergic response, tracheal smooth muscle cell constriction, and airway remodeling. While the binding strength of these medicinal plants may need to be improved for their application as drugs, this preliminary study serves as a foundation for further research potentially reducing reliance on synthetic drugs and mitigating their adverse effects.

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CONFLICTS OF INTERESTS

The authors declare no conflicts of interest.

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