EXPLORING ANTI-ALLERGIC PROPERTIES OF *JUSTICIA ADHATODA* PLANT FOR TREATMENT OF ALLERGIC RHINITIS USING NETWORK PHARMACOLGY AND MOLECULAR DOCKING

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CANDIDATE'S DECLARATION

I, Garima, Roll no. 2k22/MSCBIO/18 student of M.Sc. Biotechnology, hereby declare that the project Dissertation titled "Exploring anti-allergic properties of *Justicia adhatoda* for Allergic Rhinitis Treatment Using Network Pharmacology and molecular docking" which is submitted by me to the Department of Biotechnology, Delhi Technological University, Delhi, in partial fulfillment of the requirement for the award of the degree of Master of Science, is original and not copied from any source without proper citation. This work has not been previously formed the basis for the award of any Degree, Diploma associateship, Fellowship, or other similar title or recognition.

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Certified that **GARIMA** (2K22/MSCBIO/18) has carried out their search work presented in this thesis entitled **"Exploring anti-allergic properties of *Justicia adhatoda* for Allergic Rhinitis Treatment Using Network Pharmacology and Molecular docking"** for the award of **Masters of Science** from Department of Biotechnology, Delhi technological university, Delhi, under my supervision. The thesis embodies results of original work, and studies are carried out by the student herself and the content of the thesis don not form the basis for the award of any other degree to the candidate or to anybody else from this or any other University/Institution.

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Exploring anti-allergic properties of *Justicia adhatoda* plant for treatment of Allergic rhinitis using network pharmacology and molecular docking

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ABSTRACT

The most prevalent chronic sickness in the world, allergic rhinitis (AR), is brought on by immunoglobulin E (IgE)-mediated responses to inhaled allergens. Because of its severe burden and impairment, this disorder is of great global health concern. It frequently coexists with other respiratory conditions, such as asthma and conjunctivitis. Genetic predispositions and exposure to inhaled and occupational allergens are risk factors for allergic reactions (AR). AR's effects go beyond its physical manifestations; it also has a significant financial burden and negatively impacts social interactions, academic and professional performance, and general quality of life. The program Allergic Rhinitis and its Impact on Asthma (ARIA) divides asthma attacks into three categories: mild, moderate, and severe, as well as intermittent or chronic. A thorough clinical history is usually required for the diagnosis, which may include involve skin exams or serum-specific IgE antibody testing, especially in cases when patients have persistent symptoms or don't react to conventional therapies. This integrated strategy aids in comprehending the complex nature of the disease and customizing suitable therapeutic approaches to mitigate the significant effects of AR on patients and healthcare systems.

Medicinal plants' anti-inflammatory, antihistamine, and immunomodulatory qualities make them an effective alternative for treating a range of ailments. Adopting these natural resources offers a number of noteworthy benefits, which makes them a desirable strategy for healthcare. For generations, plants have been an essential part of many cultures' traditional healing methods. Natural selection has refined their wide range of medicinal chemicals over time, resulting in medicines that are frequently more effective and have fewer side effects than manmade drugs. This is mainly due to the fact that their organic provenance usually yields a safer profile. Furthermore, complex combinations of bioactive compounds found in medicinal plants sometimes have synergistic effects that might improve their overall therapeutic potential. Because of their synergistic effects, plants can cure multiple parts of a problem at once, providing a thorough and multifaceted approach. As a result, incorporating medicinal plants into healthcare not only draws from a rich and historic history of natural remedies, but it also corresponds with the increasing demand for therapies that are both potent and easy on the body.

Justicia adhatoda (JS) is a plant used in medicine for its known anti-inflammatory qualities, which are used to treat Allergic reactions and wounds and can be a promising target to treat Allergic rhinitis. In the framework of current study, network pharmacology study is used to identify the bioactive compounds of T. sinensis plant in order to better understand its molecular mechanism for the treatment of Allergic

rhinitis. In our study, we focused to explore compound-target-pathway network and discovered the active phytochemicals that target the particular genes that are responsible for the development of Allergic rhinitis.

Using a network pharmacology approach, the study methodically identified putative protein targets of *Justicia adhatoda* in Allergic Rhinitis. Target prediction with filtering data was performed using a variety of databases and web servers, including IMPPAT, Swiss ADME (bioavailability score ≥0.55), Molsoft (drug likeness ≥0.18), Swiss Target Prediction, STITCH, Gene card, and OMIM. The gene set was sorted with 2497 genes associated with disease and 401 genes associated with phytochemical which filtered out to be 2366 and 270 genes for disease and phytochemical respectively. Among the genes, are SRC gene which encode Src kinase as the target. Venn diagram comparing the genes of JA and AR, displaying common genes which came out to be 130. To analyze their correlation, a protein-protein interaction (PPI) network was constructed using STRING and displayed in Cytoscape. Immune response involvement is demonstrated by Kyoto Encyclopaedia of Genes and Genomes (KEGG) and Gene Ontology (GO) pathway enrichment analyses, with FcεRI being a critical step in allergic rhinitis. Target protein's with the highest binding energy of -9.3 score in molecular docking against PC kaempferol. Kaempferol ADME evaluation reveals no cytochrome enzyme inhibitor, suggesting it will not interfere with the metabolism of other drugs. Its pharmacokinetics predicted its molecular weight, bioavailability score, as well druglikness score. The selected candidate shows great promise for therapeutic intervention in AR, providing JA with fresh avenues for therapy.

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ABBREVIATIONS

JA - *Justicia adhatoda*

IgE - Immunoglobulin E

PC - Phytochemicals

IMPPAT - Indian Medicinal Plants, Phytochemistry And Therapeutics

OMIM - Online Mendelian Inheritance in Man

BBB - Blood Brain Barrier

GI - Gastrointestinal Absorption

GO - Gene Ontology

MF - Molecular Function

BP - Biological Processes

CC - Cellular Component

ADME - Absorption , Distribution, Metabolism , Excretion

PPI - Protein- protein Interaction

SRC – Tyrosine protein Kinase

CHAPTER I

INTRODUCTION

This study aims to shed lights on anti- allergic properties of medicinal plant *Justicia adhatoda* that can prove to be successful in treating allergic rhinitis disease. *Justicia adhatoda* contains phytochemicals with anti-inflammatory and immunomodulatory qualities that, by stabilizing mast cells and preventing the production of inflammatory mediators, can reduce the symptoms of allergic rhinitis. It has been proposed by network pharmacology and molecular docking analysis that particular phytochemicals in *Justicia adhatoda* target important proteins and processes linked to allergic rhinitis, hence lessening the intensity and frequency of allergic reactions. According to research, *Justicia adhatoda* provides a dual-action strategy by treating the underlying inflammatory processes and symptoms of autoimmune arthritis. Its anti-oxidant qualities also lessen oxidative stress, which makes inflammation worse. This all-encompassing approach demonstrates that *Justicia adhatoda* is a viable treatment for AR that deserves more investigation and clinical use.

1.1. Rationale

For a variety of compelling reasons, ayurvedic or herbal medicine is becoming more and more accepted as a useful choice for treating allergic rhinitis. First of, these therapies have proven to be successful in reducing allergic rhinitis symptoms.(Ceylan et al., 2020) Studies have demonstrated the anti-inflammatory, immunomodulatory, and antihistaminic properties of some Ayurvedic herbs, which may help lessen the symptoms of allergic rhinitis, such as itching, sneezing, and nasal congestion. Second, as compared to conventional drugs, Ayurvedic and herbal remedies usually have a positive safety profile with few side effects. They can therefore be used for an extended period of time, particularly by those looking for alternatives to traditional therapy. Furthermore, Ayurvedic medicine offers an extensive approach that takes into account the body's fundamental imbalances in addition to treating the symptoms.(Prakash Gupta et al., 2023) These therapies work to promote overall health, restore equilibrium, and stop the recurrence of allergic rhinitis symptoms while offering long-lasting relief. In addition, patients' inclination for natural cures and complementary therapies is increasing, which is indicative of a wider shift in healthcare towards integrative methods. As a result, in addition to conventional therapy choices, Ayurvedic or herbal remedies provide a thorough and patient-centered approach to managing allergic rhinitis(Guo et al., 2007; Jantrapirom et al., 2021; Sharma & Bhat, 2023).

A study conducted in 2005 by Juniper et al. evaluated the adverse effects of second-generation antihistamines on individuals suffering from allergic rhinitis(P. J. Bousquet et al., 2013). They discovered that although these drugs successfully lessened symptoms, tiredness, dry mouth, and gastrointestinal problems were frequent adverse

effects. Similarly, individuals taking antihistamines for allergic rhinitis reported side effects such weariness, headaches, and dry mouth in a research conducted by (Kuna et al., 2009). Intranasal corticosteroids are frequently administered to treat allergic rhinitis. However, a study by (Scadding et al., 2017) assessed the safety of fluticasone furoate nasal spray and discovered that patients frequently reported side symptoms such headache, epistaxis, and nasal irritation. Similar adverse effects, such as headache, epistaxis, and nose irritation, were noted in a different research by (Meltzer et al., 2013); however, they were all generally minor and well-tolerated. Decongestants are frequently used to treat allergic rhinitis by reducing nasal congestion. On the other hand, extended usage of decongestant nasal sprays may cause adverse effects like insomnia, anxiety, and rebound congestion, according to research by (Eccles et al., 2010). In a similar vein, individuals taking oral decongestants for allergic rhinitis reported side effects such as palpitations, sleeplessness, and hypertension in a research conducted by (Natan et al. 2013).

Ayurvedic therapies provide an extensive strategy for treating the root causes of allergic rhinitis in addition to its symptoms. Ayurveda believes that imbalances in the body's doshas (energies) are the cause of allergic rhinitis.(Jayandan et al., 2017) In contrast to traditional medicine, treatments use nutrition, lifestyle modifications, and herbal formulations to help restore balance. This results in a more all-encompassing management approach.(Sharma & Bhat, 2023). In addition to conventional medicines, many patients with allergic rhinitis use complementary and alternative medicine (CAM), including Ayurvedic treatments, for improved symptom control and overall well-being, according to a survey conducted. (Kessler et al., 2001)

Strong anti-inflammatory and immunomodulatory qualities found in several Ayurvedic herbs make them useful in the treatment of allergic rhinitis. The usefulness of herbs that lower inflammation and alter the immune system, such as ashwagandha and turmeric, was noted by Srivastava et al. (2010). This two-pronged approach relieves symptoms of allergic rhinitis while simultaneously dealing with the underlying inflammatory processes for longer-lasting relief. (Ziauddin et al., 1996)

1.2. Hypothesis and research pipeline

Justicia adhatoda has anti-inflammatory, bronchodilatory, and antioxidant properties that make it a promising natural treatment for allergic rhinitis. Its capacity to lessen oxidative stress and stabilize mast cells adds to its potential therapeutic uses. Even if the studies that are now available are encouraging, larger-scale clinical trials are required to completely determine the product's safety and efficacy. With the increasing popularity of integrative and alternative medicine, *Justicia adhatoda* could be a useful supplement to the list of allergy therapies. In our study we aim to conduct the study on phytochemicals of *Justicia adhatoda* by network pharmacology to check if they are able to target any pathways by binding to any protein in order to inhibit the release of inflammatory cytokines from mast cells to decrease the inflammation in nasal chamber and can relieve from the symptoms of allergic rhinitis.

In order to methodically discover possible protein targets of Justicia adhatoda in Allergic Rhinitis (AR), the study employed a network pharmacology technique. Target prediction required extensive data filtering across multiple databases and web servers, such as Gene card, OMIM, Molsoft (with a drug similarity criterion of ≥0.18), Swiss Target Prediction, IMPPAT, and Swiss ADME (ensuring a bioavailability score of ≥0.55). Protox II is used to check for the toxicity of PC and those PC which are inactive for all will be taken for further analysis. Genes linked to disease and genes related to phytochemicals are made up the original gene set. Using a venn diagram, illustrating is made to visualize shared genes between *Justicia adhatoda* and Allergic Rhinitis and used for further investigation refer Figure1.1.. A protein-protein interaction (PPI) network is created using STRING and displayed in Cytoscape in order to investigate their association. KEGG and GO pathway enrichment analysis will be made to the significance of immune response mechanisms in allergic rhinitis. The top genes ranked highest will be taken to be the target protein for further analysis.

Target proteins with the highest binding energy score found using molecular docking studies will be considered. An analysis of final phytochemical with the highest affinity against target protein will be done through ADME analysis which shows wheather the phytochemical pass BBB, is P-gp subtrate and GI absorption. The molecular weight, bioavailability score, and drug similarity score all included in the pharmacokinetic projections. All things are considered, these results indicate that the chosen candidate has great potential for therapeutic intervention in AR, providing *Justicia adhatoda* with new therapeutic options.

1.3. THESIS OUTLINE

Chapter 2 : A brief description of the literature study that has previously been done on the uses of medicinal plant to replace the contemporary medicine. It provides the insight into adverse effect of anti-inflammatory drugs and how plants such as JA has been used by scientist to relieve the symptoms of allergic rhinitis.

Chapter 3 : This chapter provides the steps of methodology used to perform and evaluate the potential PC of plant JA via network pharmacological screening and molecular docking. Each subsection focus on details of each steps needs and operations of online tools that are used to perform the procedure.

Chapter 4 : This chapter provides the outcome of each step that is followed in the previous section.

Chapter 5 : This chapter provides the significance and inference of the technical results obtained.

Chapter 6 : This section provides a summary of the results obtained from this study and mentions of the future prospects of current study.

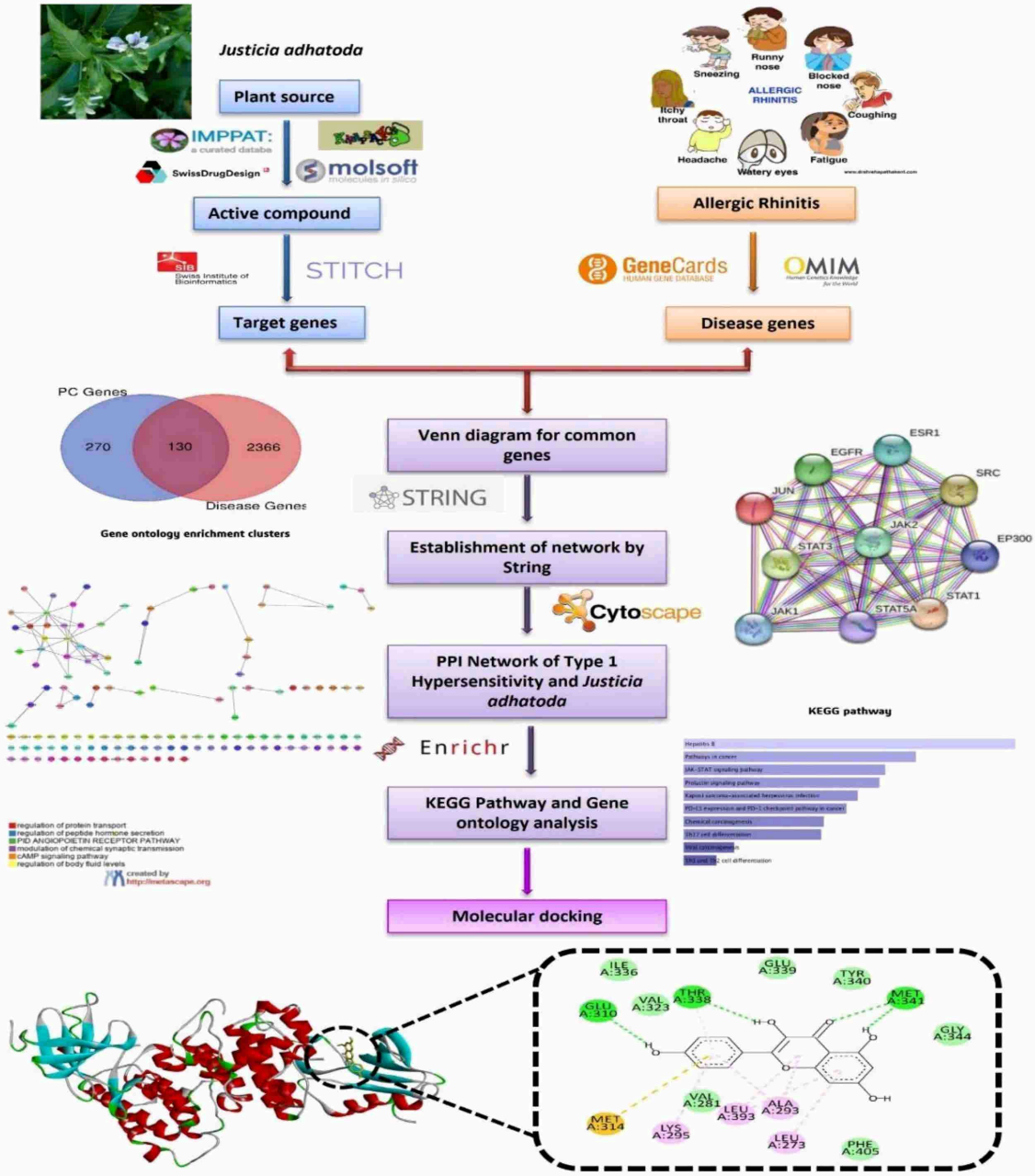


Figure 1.1. : Graphical representation of hypothesis and research pipeline. Target prediction required a significant amount of data filtering from numerous online sites and databases, including Swiss Target Prediction, IMPPAT, Gene card, OMIM, Molsoft, and Swiss ADME. To evaluate toxicity, Protox II was employed, and a venn diagram was utilized to illustrate the genes that Justicia adhatoda and Allergic Rhinitis had in common. To explore associations, a protein-protein interaction network was constructed with Cytoscape and STRING. Immune response mechanisms in allergic rhinitis were highlighted by KEGG and GO pathway enrichment analysis, with top-ranked genes chosen as target proteins for additional investigation.

CHAPTER II

LITERATURE REVIEW

About 20% of people globally suffer from allergy-related diseases, and the incidence of these conditions is rising as a result of industrialization, contemporary lifestyles, and environmental pollution. The most prevalent of them, Type I allergies are distinguished by an intricate immunological reaction. Immunoglobulin E (IgE) and the high-affinity IgE receptor (FcεRI) on mast cells and basophils are involved in this reaction. One of the most common conditions under Type I Hypersensitivity, allergic rhinitis (AR) affects a great number of individuals globally (Pawankar et al., 2012). The symptoms of allergic responses (AR) are caused by IgE-mediated reactions to inhaled allergens. Sneezing, nasal congestion, nasal itching, and rhinorrhea (nasal discharge) are some of these symptoms. The increasing prevalence of allergy reactions (AR) highlights the need to enhance understanding and treatment of allergic disorders in context of changing environmental and lifestyle factors.(Eguiluz-Gracia et al., 2019; Mims, 2014)

2.1. Allergic rhinitis

Type 2 cells are pivotal in causing mucosal inflammation in immune responses, particularly in allergic conditions. These cells, part of the adaptive immune system, play a crucial role in the pathophysiology of allergic rhinitis. Allergic rhinitis can be triggered by seasonal allergens such as pollens and molds, as well as perennial indoor allergens like dust mites, pets, vermin, and certain molds (Kubo, 2017; Sicherer & Eggleston, n.d.). The condition significantly impacts quality of life, leading to sleep disturbances, reduced productivity at work or school, and decreased participation in outdoor activities, particularly among children. There is a strong association between allergic rhinitis and asthma; indeed, most individuals with asthma also suffer from rhinitis. Up to 40% of people with seasonal or perennial allergic rhinitis either already have asthma or later develop it. This indicates a significant increase in the likelihood of developing asthma. Moreover, allergic conjunctivitis and allergic rhinitis usually combine, increasing the overall burden of allergic disorders. The interaction of several allergy disorders emphasizes the necessity of all-encompassing patient outcomes management approaches(J. Bousquet et al., 2008; Brożek et al., 2010).

When someone is exposed to an allergen to which they are sensitized, the allergen binds to IgE antibodies on mucosal mast cells, causing cross-linking, which causes nasal symptoms to appear within minutes. Neuroactive and vasoactive substances such prostaglandin D2, histamine, and cysteinyl leukotrienes are released as a result of this cross-linking (Fig.2.1.). The acute symptoms of allergic rhinitis are caused by these substances (Meltzer & Bukstein, 2011). Th2 inflammation in the nasal mucosa develops in the following hours as a result of several chemokines and cytokines secreted by mast cells, as well as contributions from epithelial cells, dendritic cells, T cells, innate lymphoid cells, eosinophils, and basophils (Modena et al., 2016). This process involves a complex interplay among these cell types, which perpetuates and amplifies

the inflammatory response. Consequently, nasal symptoms can persist for hours following allergen exposure due to ongoing mucosal inflammation. Additionally, the inflamed mucosa becomes more reactive to other allergens, strong odors, and various irritants, a phenomenon known as priming or nonspecific nasal hyperresponsiveness. This heightened reactivity means that the nasal mucosa remains sensitive and can respond excessively to a wide range of stimuli beyond the initial allergen.(Borish & Joseph, 1992; Fiocchi, 1997; Sin & Togias, 2011)

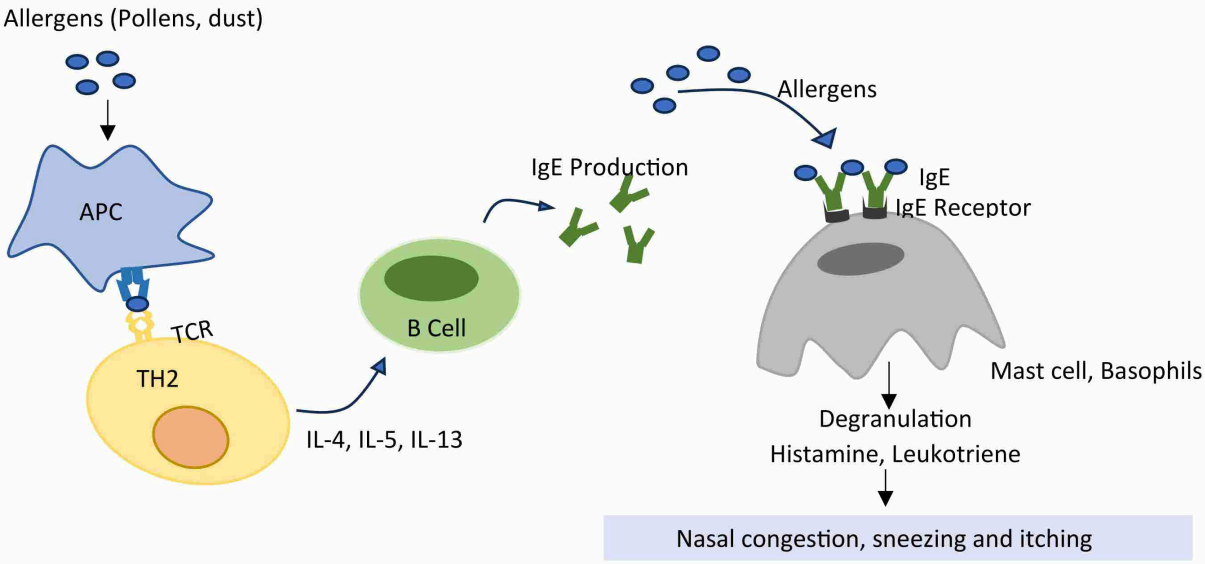


Figure 2.1. Mechanism of release of inflammatory molecules in allergic rhinitis disease upon exposure to allergens.

2.2. Using plants remedies to avoid adverse effects

The pharmacological characteristics of first-generation antihistamines, such diphenhydramine (Benadryl), are linked to a number of serious adverse effects. It is well recognized that these drugs lead to drowsiness, exhaustion, and altered mental state. Their propensity to pass the blood-brain barrier, which sets them apart from second-generation antihistamines that are less prone to do so, is the main cause of these side effects. First-generation antihistamines can therefore have effects on the central nervous system, which might impair cognition and cause sleepiness. Daily activities that demand complete concentration and cognitive function, such as operating machinery, driving, and completing other duties, might be greatly impacted by this sedative effect. Furthermore, these drugs may impair children's academic achievement because they lower alertness and cognitive function(Espada-Sánchez et al., 2023;Sur and plesa, 2015).

Anti-inflammatory drugs are frequently used to treat allergic responses, including corticosteroids, anti-leukotrienes, and antihistamines. These medications work by either obstructing the action of mediators implicated in the allergic response or by preventing certain inflammatory genes from expressing. However, these treatments have limitations due to the possibility of adverse effects and their inability to completely prevent allergic reactions. Despite these advancements, there is still a need for more research to develop therapies that are both effective and have minimal side effects. One promising area of study is the application of herbs with strong immunomodulatory effects, as demonstrated in Indian medicine. These herbal medicines may offer supplemental or alternative approaches to treating allergic diseases, given their demonstrated ability to modulate immunological responses. This potential avenue of research could lead to the development of new treatments that effectively manage allergic reactions while minimizing the risk of adverse effects.(Jantrapirom et al., 2021; Papapostolou & Makris, 2022; Sharma & Bhat, 2023a)

A large fraction of people worldwide suffer from allergic rhinitis, a common allergy illness marked by symptoms like rhinorrhea, sneezing, itching, and congestion in the nasal passages. Traditionally, Ayurvedic medicine in particular has used a variety of herbal therapies to treat allergy-related disorders (Sharma & Bhat, 2023b). Around 75–80% of the world's population still receives their primary care from herbal medicine, especially in underdeveloped nations. This preference is mostly caused by the fact that herbal remedies are more widely accepted in society, work better with the body, and typically have less negative effects than synthetic medications(Jamshidi-Kia et al., 2018).

The use of herbal medicine has increased significantly in wealthy nations in recent years as well, indicating a growing interest in complementary and alternative remedies. After initial pharmacological screening, thorough characterisation is crucial for modern medications (Pan et al., 2014). This entails an evaluation of their toxicity as well as in-depth research on their pharmacokinetic and pharmacodynamic characteristics. Comprehending these characteristics aids in guaranteeing the effectiveness and security of the medications. As a result, the current correspondence reviews the medicinal plant *Justicia adhatoda*. It sometimes referred to as Vasaka or Malabar nut, is one such plant that has drawn interest due to its possible medical uses in the treatment of allergic rhinitis (Biharee et al., 2024). This plant contains a wide variety of phytochemical elements that have been identified as having significant properties such as antitussive, abortifacient, antimicrobial, insecticidal, hepatic and cardiovascular protection, anticholinesterase, antioxidant, and anti-inflammatory properties.

2.3. Effects of Justicia adhatoda

Justicia adhatoda, traditionally known in Indian Ayurvedic medicine as Vasaka or Malabar nut, is a medicinal herb that has shown significant potential in the treatment of allergic rhinitis. This condition, marked by symptoms such as nasal congestion, sneezing, and itching, may be effectively alleviated by the bioactive components of *Justicia adhatoda*, specifically vasicine and vasicinone.(P. Singh et al., 2011) These

compounds exhibit strong anti-inflammatory and bronchodilatory properties, which contribute to their therapeutic effects. By inhibiting the production of inflammatory mediators and stabilizing mast cells, which play a crucial role in allergic reactions, vasicine and vasicinone help reduce the symptoms of allergic rhinitis.(Rudrapal et al., 2023)

Research has demonstrated that vasicine and vasicinone can relax airway muscles, making breathing easier and thereby reducing nasal congestion. Additionally, these compounds significantly mitigate itching and sneezing by blocking the release of histamines and other inflammatory chemicals (Liu et al., 2015). *Justicia adhatoda* also possesses antioxidant properties, which help reduce oxidative stress—a condition often heightened in allergic responses that can worsen inflammation. By scavenging free radicals, the antioxidants in *Justicia adhatoda* diminish oxidative damage and its harmful effects. (Malathi. et al , 2018)

As a result, *Justicia adhatoda* treats the underlying inflammatory processes linked to allergic rhinitis in addition to relieving symptoms. It is a potentially useful natural therapeutic option due to its dual activity. Its comprehensive strategy, which addresses both acute symptoms and more general inflammatory problems, highlights its promise as a comprehensive and successful treatment for allergic rhinitis, calling for more investigation and clinical use. (Chavan and Chowdhary, 2014)

Justicia adhatoda's varied activities demonstrate its promise as a versatile medicinal agent. Its significance in both conventional and modern medicine is shown by the fact that it has been traditionally used in many cultures and that its pharmacological qualities have been confirmed by science. For this plant to reach its full medicinal potential and be successfully incorporated into modern medical procedures, more study and clinical trials are necessary (Ilavenil et al., 2024).

Justicia adhatoda is an Indian medicinal plant that has been used traditionally to treat respiratory ailments because of its quinazolin alkaloids. The herbal medication is still widely used in Indian traditional medicine and is considered safe by the WHO when manufactured locally, but its use in European medicine for the treatment of respiratory disorders has significantly decreased.(Ramawat & Goyal, 2008). It's interesting to note that in Germany, where applying *Justicia adhatoda* extracts topically to treat allergic rhinitis has become more popular, the trend is very different. This rising demand in the German market is indicative of a resurgence of interest in holistic and natural methods of treating allergic rhinitis, a common ailment that causes symptoms including itching, sneezing, and congestion in the nose. Because of its anti-inflammatory and mast cell-stabilizing qualities, *Justicia adhatoda* extracts have demonstrated efficacy in reducing these symptoms (Baral, P.K., 2018).

According to a study, allergic rhinitis is the most common chronic illness in children, with symptoms often appearing in one in five by the time they are two or three years old. The health, conduct, and academic performance of a kid can all be greatly impacted by these allergy symptoms. Serious diseases like asthma, recurrent middle ear infections, sinusitis, sleep disturbances, and persistent cough can develop from

allergic rhinitis if treatment is not received. The study assessed *Justicia adhatoda*, an Indian herbal remedy, for treating pediatric allergic rhinitis. The results showed that children between the ages of 7 and 9 had the highest frequency of allergic rhinitis, with a greater incidence in boys. The main cause was found to be dust exposure. Surprisingly, *Justicia adhatoda*, a rather uncommon medicine, reduced the severity, duration, and frequency of symptoms in approximately 93% of the instances, improving the disease. Only two of the thirty patients had a poor recovery, while the other 28 showed a notable improvement.(Oza, 2022)

CHAPTER 3

METHODOLOGY

3.1. Screening of active compounds from phytochemical data set

Literature review was done on our plant to check for its active phytochemicals and if it has role in suppressing Allergic rhinitis. First of all we need to get the phytochemicals of the plant.

IMPPAT an open-source databases that provide information on natural products, were used to compile a list of phytochemicals found in JA. The Indian Medicinal Plants, Phytochemistry, and Therapeutics (IMPPAT) database is a bioinformatics platform offering extensive data on Indian medicinal plants. It provides crucial information on phytochemicals, their medicinal uses, and molecular mechanisms, facilitating drug discovery and development. IMPPAT includes detailed records on plant species, their chemical compositions, biological activities, and pharmacological data. This resource is invaluable for pharmacology, biotechnology, and traditional medicine, promoting scientific research and the development of integrated medicine and phytotherapy. A total of 78 PC were collected from IMPPAT tool.(Vivek-Ananth et al., 2023)

Using canonical SMILES and Pubchem Id, a phytochemical (PC) was located, assigned an individual identification number, and its chemical properties were retrieved from the PubChem database. Further out of total, PC are selected on the basis of some selection criteria. Among the selection criteria were drug likeness scores which was taken out from Molsoft which is an online tool is a crucial asset in pharmaceutical research, providing a user-friendly platform to assess chemical compounds for drug candidacy, molecular weight and bioavailability scores from Swiss ADME. Swiss ADME is a vital tool in drug discovery, offering detailed analysis of small molecule pharmacokinetics. It examines absorption, distribution, metabolism, and excretion (ADME) parameters, providing insights into a compound's potential as a medication candidate. Using advanced computer models, Swiss ADME predicts key pharmacokinetic characteristics such as water solubility, cytochrome P450 metabolism, blood-brain barrier permeability, and gastrointestinal absorption. This early assessment aids in understanding a compound's metabolism, bioavailability, and potential toxicity, facilitating optimization and informed decision-making. By minimizing the risk of failure in later development stages, Swiss ADME significantly contributes to the development of safer and more effective medicines.

3.2. Target prediction for *Justicia adhatoda* and allergic rhinitis

Screening hits that could be AR targets was necessary for predicting compound targets. To identify the genes related to JA, Swiss Target Prediction and STITCH was used to predict targets. After we got the list for genes associated with PC was sorted, set of genes were selected for further analysis after duplicate data was eliminated from the

list and identified as target genes. Disease Target genes were obtained with associated allergy terms, including genes from GeneCards and the OMIM tool and the list of disease genes is collected separately.(Luo et al., 2019).

3.3. Identification of common genes associated with JA and AR.

A Venn diagram was made by putting all the selected genes for phytochemical to first column and all the selected genes for disease to second column. By running the program, a Venn diagram was made which is used to identify common genes between the disease and JA which will be utilized for the further analysis and network building.

3.4. Construction of network

STRING predicts protein interactions, enriches pathways, and covers diverse species. Cytoscape visualizes and analyzes complex networks, integrates biological data, and offers extensive plugins. Together, they enable researchers to explore protein-protein interactions, analyze network properties, and gain insights into biological processes in various organisms. For common genes as therapeutic genes that were targeted by both Allergic rhinitis and *Justicia adhotoda* , a protein-protein interaction network (PPI) was constructed using the STRING Tool [1]. Following the selection of species, the PPI was visualized with the highest confidence (0.900) in Cytoscape (TSV file). A set of genes can be identified by employing Cytoscape software (v3.8.0) to analyze the topological characteristics of the network (Doncheva et al., 2019).

3.5. Gene ontology and KEGG pathway

KEGG compiles biological pathways, diseases, and drugs, enhancing comprehension of cellular functions. GO categorizes genes and gene products, supplying standardized biological annotations. These resources are vital in bioinformatics for deciphering molecular functions, biological processes, and cellular components. DAVID provides tools for functional annotation and enrichment analysis, aiding in therapeutic gene assessment via SR plot with highest p-value. Gene ontology plot and KEGG plot is mage by putting all the top 10 hub genes in enrichr tool that will give the top cellular and metabolic pathways regulated by the genes (Zhang et al., 2021).

3.6. Preparation of protein file for docking

For docking, first we need to prepare the protein file. 3D structure of protein c-Srv kinase is downloaded from PDB (pdb id: 3F3V) in 3d SDF file. The protein was visualized in PyMol for further modification. Removal of water molecules, associated ligands with protein structure and addition of polar hydrogen was done. Prepared protein file was saved in the system for further docking.

3.7. Molecular docking using Pyrx

Molecular docking, facilitated by PyRx software, predicts the binding interactions between specific target proteins and chosen phytochemicals. The efficacy of drug discovery hinges on understanding how drug molecules interact with target proteins, enabling the identification of precise drug candidates. Docking is done by first loading the target protein to program and transform it into macromolecule. All the selected ligand are loaded into software using Open Babel. Then converting selected ligands into pdbqt format for energy minimization process. Docking is done using

Vina Wizard by selecting all the pdbqt files of ligand. Prior to run docking process, grid box around the protein binging site is made with dimensions (in Angstrom) X: 62.3106, Y: 77.1286 and Z: 90.7164. Following docking, binding affinities for each Ligand against macromolecule is stored. Docking studies were conducted using PI3K and the five selected phytoconstituents with the PyRx software for autodocking, validating the process. Each docked ligand's output file is saved for later 2D analysis that shows the interactions and hydrogen bonds that occur between the ligand and macromolecule.

3.8. ADME and toxicity analysis

Swiss ADME is a web tool used to predict pharmacokinetics and drug-likeness of compounds. Drug development and discovery professionals use a set of standards known as Compounds with no blood-brain barrier permeability, bioavailability score of 0.55 and high GI absorption. In AMDE analysis, the absence of cytochrome enzyme inhibition indicates a low risk of drug-drug interactions and potential safety. An online tool ProTox 3.0 is used to forecast a chemical compound's level of toxicity. In order to estimate the possible toxic effects, it makes use of machine learning algorithms and a database. This aids in the identification and mitigation of safety risks in chemical research, including drug development.

CHAPTER 4

RESULTS

4.1. Active phytochemical analysis from *Justicia adhatoda* plant and allergic rhinitis therapeutic gene analysis.

From the IMPPAT we sorted out 78 phytochemicals (Appendix 1, List of phytochemicals of *Justicia adhatoda* taken from IMPPAT tool for treatment of Allergic rhinitis). For the Selected phytochemicals based on the drug likeness scores from Molsoft ≥ 0.18, bioavailability scores ≥ 0.17 from Swiss ADME (Table 4.1.), and PC sorted using the Protox-2. These predict potential side effects determined, such as immunogenicity, carcinogenicity, mutagenicity and cytogenetic (Table4.2.).

Table 4.1. : List of phytochemicals obtained after going through selection criteria of drug likeness and Bioavailability score.

S.No	Phytochemical name	MW	Pubchem ID	Drug Likeness	Bio availability Score
1	beta-Sitosterol	414.71	222284	0.78	0.55
2	Kaempferol	286.24	5280863	0.5	0.55
3	Quercetin	302.24	5280343	0.52	0.55
4	Luteolin	286.24	5280445	0.38	0.55
5	Vasicinone	202.21	442935	0.38	0.55
6	Sitogluside	576.85	5742590	0.5	0.55
7	beta-Sitosterol-d-glucoside	576.85	12309060	0.5	0.55
8	beta-Sitosterol-beta-D-glucoside	576.85	12309055	0.5	0.55
9	Vasicinolone	218.21	158720	0.88	0.55
10	Vasicinol	204.23	442934	0.61	0.55
11	Anisotine	349.38	442884	0.79	0.55
12	Ascorbic acid	176.12	54670067	0.74	0.56
13	Neoandrographolide	480.59	9848024	0.23	0.55
14	Vasicolinone	305.37	627712	0.9	0.55
15	Vasicoline	291.39	626005	0.7	0.55
16	Isovitexin	432.38	162350	0.59	0.55
17	Vasicine	188.23	667496	0.33	0.55
18	Ephedrine	165.23	9294	0.54	0.55

Table 4.1. (Continued)					
19	Vitexin	432.38	5280441	0.6	0.55
20	Fenretinide	391.55	5288209	1.08	0.55

Table 4.2. : List of Phytochemicals after analysis of Toxicity from PROTOX-II

S.No.	**Phytochemical name**	**Pubchem ID**	**Carcinogenecity**	**Immunogenecity**	**Mutagenecity**	**Cytotoxicity**
1	beta-Sitosterol	222284	Inactive	Active	Inactive	Inactive
2	Kaempferol	5280863	Inactive	Inactive	Inactive	Inactive
3	Quercetin	5280343	Active	Inactive	Active	Inactive
4	Luteolin	5280445	Active	Inactive	Active	Inactive
5	Vasicinone	442935	Inactive	Active	Inactive	Inactive
6	Sitogluside	5742590	Inactive	Active	Inactive	Inactive
7	beta-Sitosterol-d-glucoside	12309060	Inactive	Active	Inactive	Inactive
8	beta-Sitosterol-beta-D-glucoside	12309055	Inactive	Inactive	Inactive	Inactive
9	Vasicinolone	158720	Inactive	Inactive	Inactive	Inactive
10	Vasicinol	442934	Yes	Inactive	Active	Inactive
11	Anisotine	442884	Inactive	Inactive	Inactive	Inactive
12	Ascorbic acid	54670067	Inactive	Active	Inactive	Active
13	Neoandrographolide	9848024	Inactive	Active	Active	Inactive
14	Vasicolinone	627712	Inactive	Inactive	Inactive	Inactive
15	Vasicoline	626005	Inactive	Inactive	Active	Inactive
16	Isovitexin	162350	Inactive	Inactive	Inactive	Inactive

Table 4.2. (Continued)						
17	Vasicine	667496	Inactive	Inactive	Inactive	Inactive
18	Ephedrine	9294	Inactive	Inactive	Active	Inactive
19	Vitexin	5280441	Inactive	Inactive	Inactive	Inactive
20	Fenretinide	5288209	Inactive	Inactive	Inactive	Inactive

After the Phytochemicals sorted out on the basis of carcinogenicity, immunogenicity, Mutagenicity and cytotoxicity showing inactive for all. With the help of STITCH and Swiss target prediction, a list of genes for phytochemicals were taken out and saved. A similar list for disease genes is also prepared with the help of OMIM and gene card tools. Genes searched with the term "Allergic Rhinitis" and the file containing set of genes is downloaded. Duplicated were removed and a venn diagram was prepared taking Phytochemical genes and disease genes. Venn diagram identify all the 130 common genes between Phytochemicals and Disease (Figure4.1). These genes are used for further analysis.

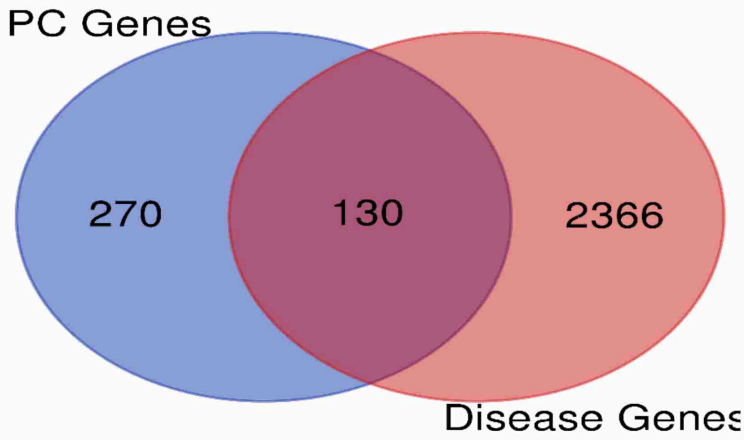


Figure 4.1. : Venn diagram of common genes between Phytochemicals and Disease

4.2. PPI network for therapeutic gene

Upon getting the 130 common genes using venn diagram (refer Appendix 2, List of common genes between *justicia adhatoda* and allergic rhinitis disease). Using the STRING database to build the PPI network by entering the list of common genes into the database. To make sure that only interactions with the highest level of confidence are included, set the confidence score criterion to 0.9. We got the interaction data from STRING so to can visualize and analyze it more. Next we used the Cytoscape tool for network visualization (Figure 4.2.). To find important nodes (genes) and their interactions, we import the interaction data from STRING into Cytoscape and do a network analysis. Seek out strongly linked nodes (hubs) that may be important for the pathophysiology of the disease or for the medicinal benefits of phytochemicals. Not only does Cytoscape make it easier to identify these important genes, but it also makes it possible to investigate their functions and interactions in a larger biological framework.

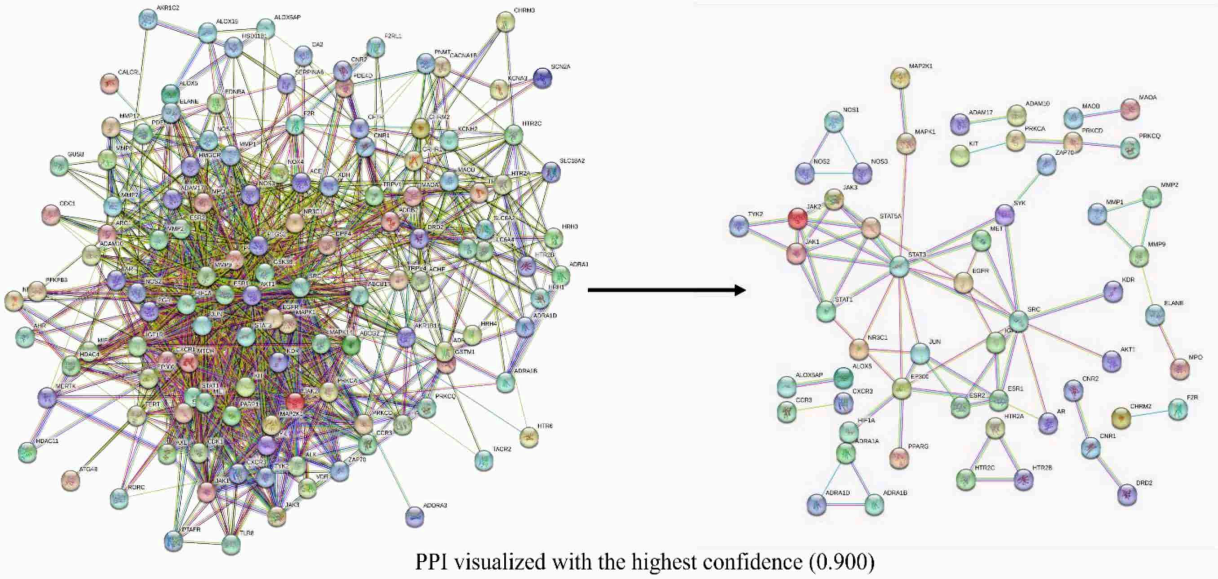


Figure 4.2. : Visualization of PPI network of common genes with the highest confidence of 0.9

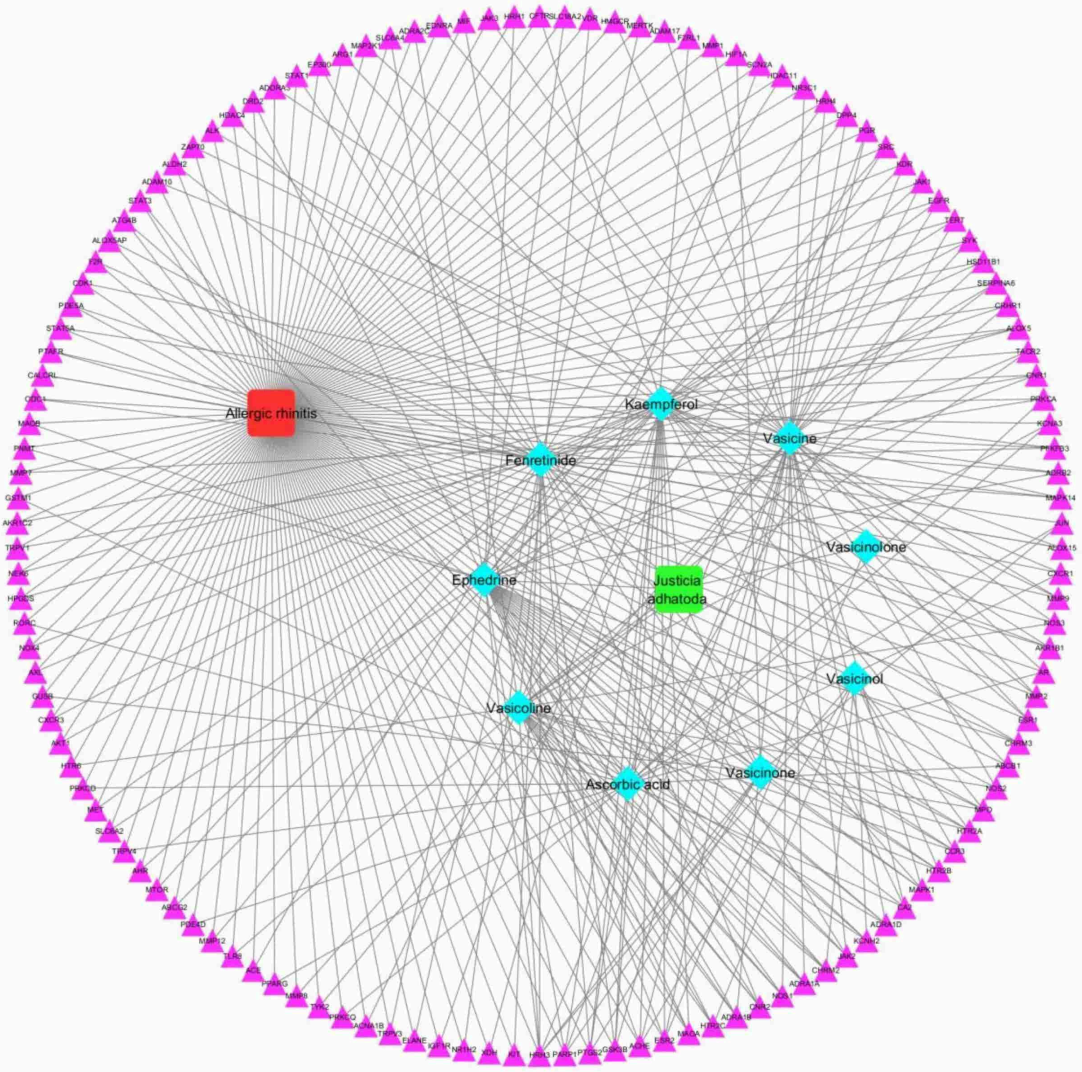


Figure 4.3. Network of plants, its active phytochemicals and common gene targets associated with in disease. Different categories are represented by different color of nodes. Cyan color is used for active phytochemicals, green is used for plant JA, pink color represents common target and allergic rhinitis is represented by red.

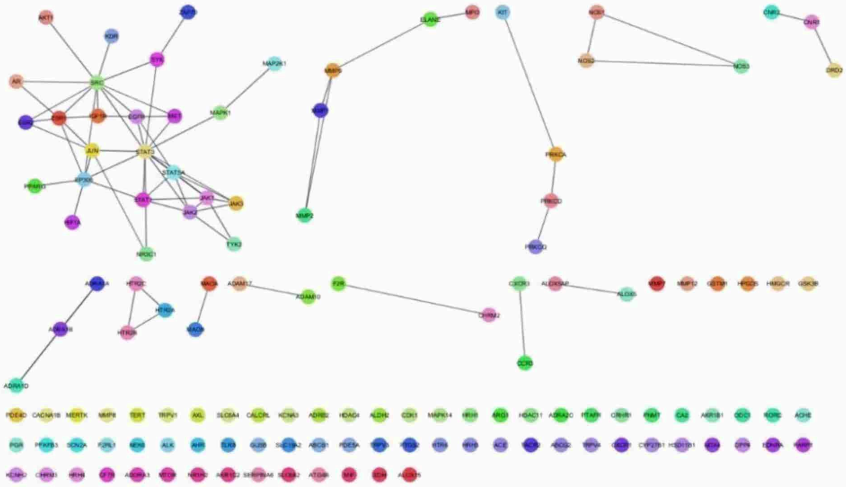


Figure 4.4. : Visualization of PPI network by Cytoscape obtained from STRING showing interaction between different genes, number of nodes:130 and number of edges: 74

After visualization of PPI network by Cytoscape, a Hub gene network is created. A hub gene network, which is a collection of nodes (genes) that are crucial to the functioning of the biological network, is generated from Protein-Protein Interaction (PPI) data in Cytoscape (Figure 4.4.). High levels of connectivity, or the ability to interact with numerous other genes, are characteristics of hub genes, which makes them important regulators or hubs in the network. Through the identification of these hub genes, we can identify critical genes that may be required to sustain biological function and network stability. Visualizing a hub gene network in Cytoscape might highlight important genes that may mediate the effects of phytochemicals on allergic reactions, which is relevant for a study on common genes between phytochemicals and allergic rhinitis. Hub gene is made by Cytohubba plugin by degree method in cytoscape showed 10 most interacting genes from the list of common genes (Fig4.5.).

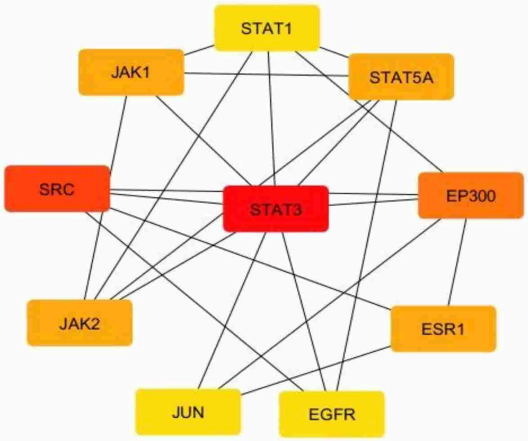


Figure 4.5. : Top 10 Hub most interacting genes made by cytohubba pluggin within cytoscape

Ranking the top 10 hub genes using the degree method in Cytoscape involves quantifying the number of direct interactions each gene has within the Protein-Protein Interaction (PPI) network (Table 4.3.). The genes are ordered by degree values, and the top 10 genes are those with the greatest number of interactions. These top-ranked hub genes are likely important actors in the underlying biological processes and could be main targets for therapeutic intervention or additional functional investigations in the context of examining common genes between phytochemicals and allergic rhinitis. Therefore all the data has been analyzed and we choose SRC gene as the target gene for our further analysis.

Table 4.3. : Top 10 gene ranking by degree method from cytoscape

Rank	Name	Score
1	STAT3	13
2	SRC	11
3	EP300	7
4	ESR1	6
4	JAK1	6
4	JAK2	6
4	STAT5A	6
8	STAT1	5
8	JUN	5
8	EGFR	5

4.3. Enrichment analysis

GO enrichment analysis shows positive regulation of Interleukin-9-mediaated signalling pathway for biological process (BP), extrinsic side of cytosolic side for plasma membrane for cellular process(CP) and protein tyrosine kinase activity for molecular function (MF) (Fig 4.6.). KEGG pathway showed that our genes also has an involvement in JAK-STAT pathway. Studies also showed the involvement of these pathways in Allergic rhinitis which is discussed later.

Figure 4.6. : Gene ontology analysis showing (a) cellular pathway process (b) Biological pathway process and (c) Molecular functions of genes for disease. (d) KEGG pathway showing metabolic and cellular pathways regulated by our top 10 Hub genes.

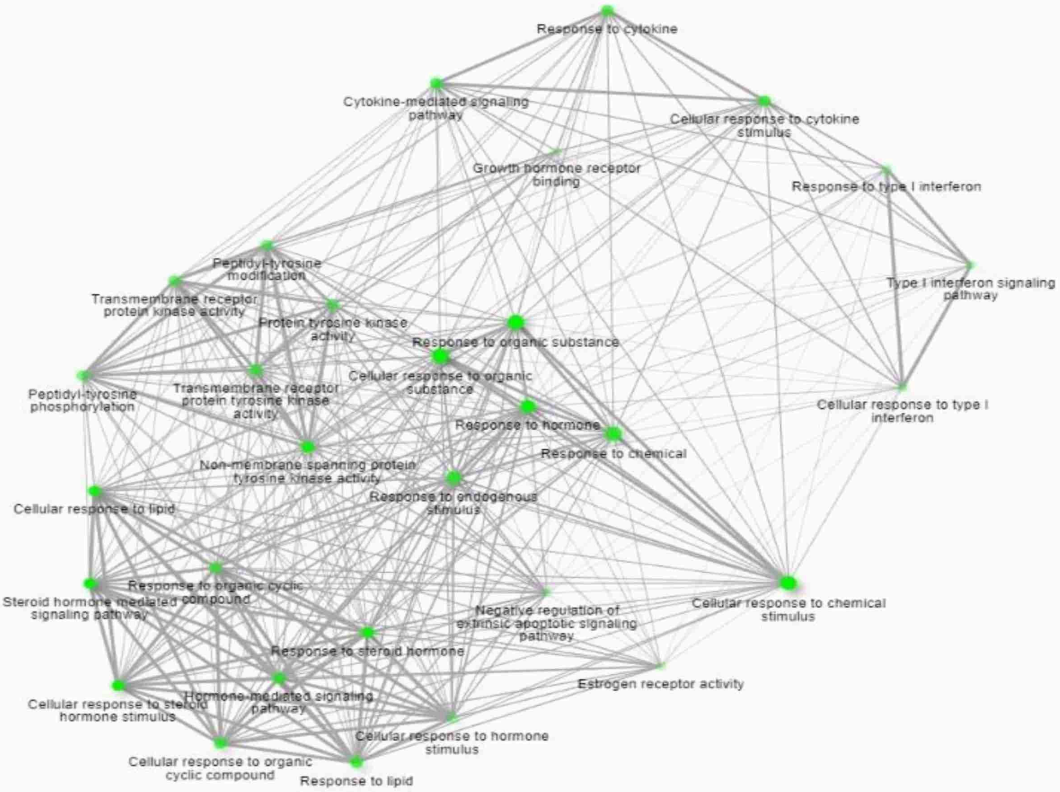


Figure 4.7. : Pathways related to hub genes and their connection with each other. Color of green symbol define its degree with respect to their size more relevant pathway more bigger will be the circle.

To find Gene Ontology (GO) terms or other functional categories that are strongly enriched among the hub genes, the program will perform enrichment analysis. Enrichment bar graph is made by SynGo tool using Hub genes. A carefully selected collection of genes linked to synaptic processes and functions can be found in the SynGO database. The y-axis of the bar graph usually shows the enriched phrases, while the x-axis shows the p-values, enrichment scores, or other metrics. The bar graph shows highest expression of hub genes in Type I interferon signaling Pathway (Fig4.8.) (Dos Santos, M., & Hannon, E. (2021). SynGO: An Evidence-Based, Expert-Curated Knowledge Base for Synapse Biology. Frontiers in Molecular Neuroscience, 14, 45.)

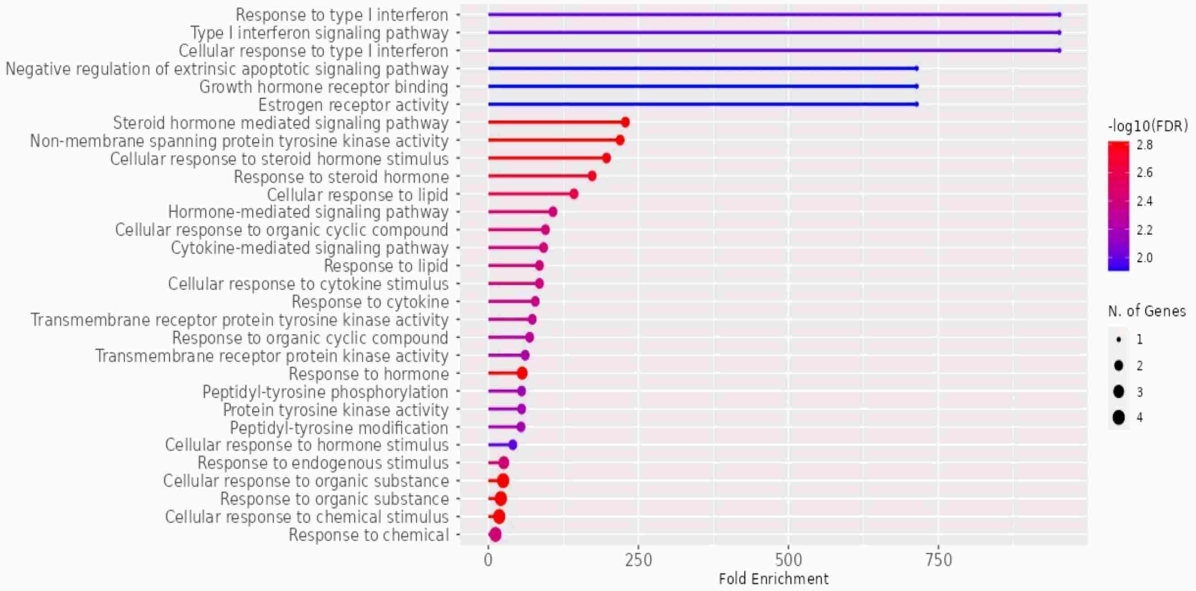


Figure 4.8. : Enrichment bar graph displaying the pathways regulated by top hub genes.

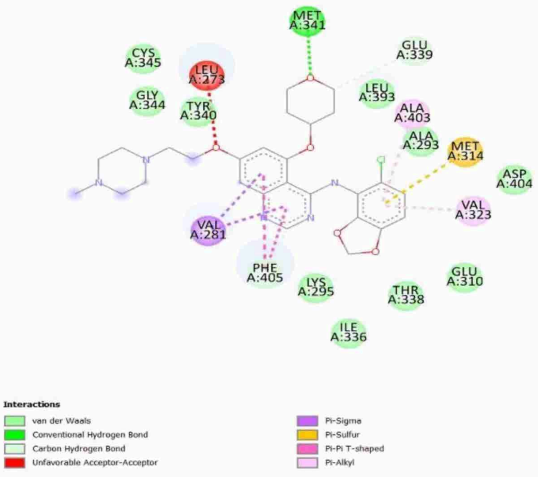
4.4. Molecular docking using PyRx

Docking is performed using PyRx, for all the 10 selected phytochemicals. Using PyRx software, all of these drugs were docked with Src kinase prortein which is encoded by gene SRC. We created a grid box around the binding site of each protein with dimensions (in Angstrom) X: 62.3106, Y: 77.1286 and Z: 90.7164. We evaluated our all the 10 docked ligands with the reference Drug saracatinib which is Src kinase inhibitor. The binding energy (kcal/mol) and amino acids of the ligand binding site were measured and recorded after our ligands were docked with the target protein. Out of the 10 phytochemicals taken, only two PC showed binding affinity higher or equivalent to the drug/inhibitor (Table 4.4.). The binding energies of these target compound which were identified as, kaempferol, and Fenretinide, are -9.3, and -8.8 Kcal/Mol , respectively (Table). The findings demonstrate that these target compound had a comparatively high binding energy compared to standard drug and could bind to Src kinase in a manner identical it. Among the active compound Kaempferol showed the highest binding affinity of -9.3kcal/mol with protein Src kinase encoded by selected gene SRC. The conformations of PC showing highest binding affinities were saved in pdb files and visualized with the help of Discovery studio demonstrating residues involved in bond formation in 2D view.

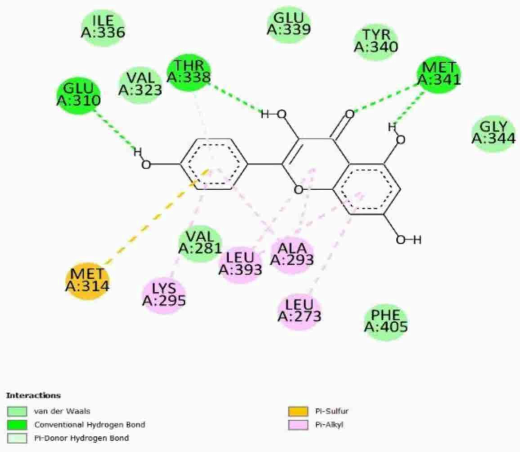
Table 4.4. : Interaction between best suited Phytochemicals as ligand and selected protein as the receptor.

S.No.	Pubchem ID	Phytochemicals	Binding Affinity (Kcal/Mol)	Interacting Residues
1.	10302451	Drug	-8.8	M:341, C:345, G:344, Y:340, L:393, A:293, D:404, E:310, T:338, I:336 K:295
2.	5280863	Kaempferol	-9.3	T:338, E:310, V:323, I:336, E:339, Y:340, M:341, G:344, F:405, V:281
3.	5288209	Fenretinide	-8.8	M:341, D:348, Y:340, I:294, I:336, T:338, E:310, M:314, D:404, V:323, G:344, K:343, C:345
4.	158720	Vasicinolone	-7.8	G:344, L:273, F:405, E:310, K:295, M:314, V:323, E:339, Y:340, M:341, T:338, Y:340, D:404
5.	442935	Vasicinone	-7.3	E:339, V:323, T:338, I:336, M:314, D:310, F:405, K:295, V:218, L:273, M:341, Y:340
6.	442934	Vasicinol	-6.9	E:310, V:281, F:405, L:393, A:293, L:273, G:344, Y:340, M:341, E:339, T:338, K:295, M:314

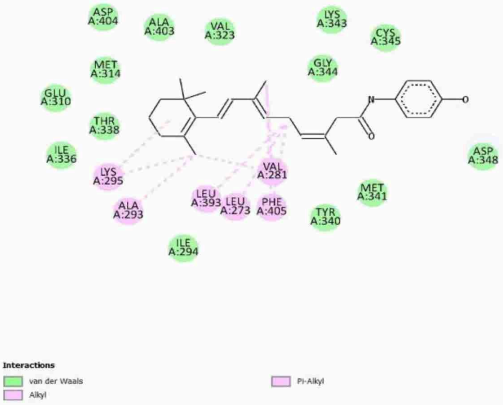
7.	626005	Vasicoline	-6.9	M:341, L:393, G:344, G:274, L:407, V:281, D:348, Y:340
8.	667496	Vasicine	-6.9	E:339, M:341, T:338, K:295, E:310. V:281, F:405, L:273,Y340
9.	54670067	Ascorbic acid	-5.6	T:521, V:461, D:518, R:460, E:517, P:464, Y:463, K:427, V:467
10.	9294	Ephedrine	-5.9	D:404, V:281, L:273, A:293, M:341, Y:340, E:339, T:338



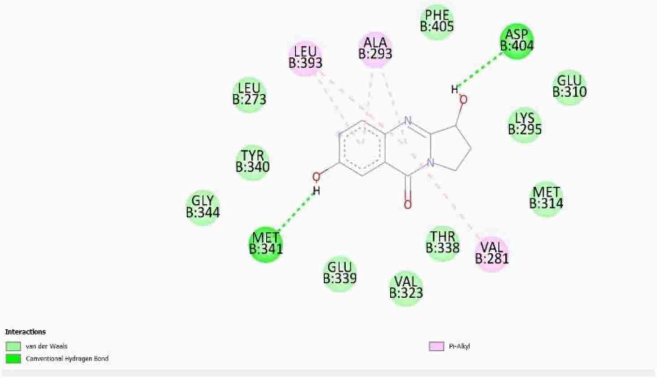
(a) Drug (Saracatinib)



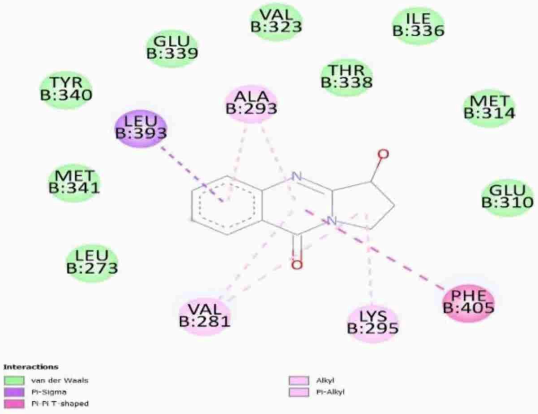
(b) Kaempferol



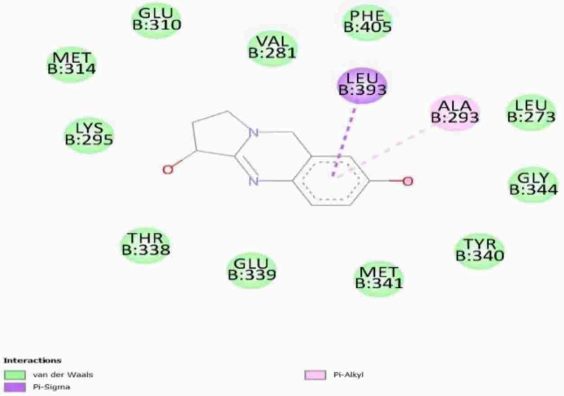
(c) Fenretinide



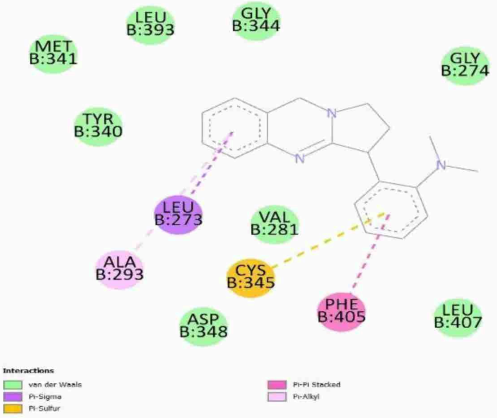
(d) Vasicinolone



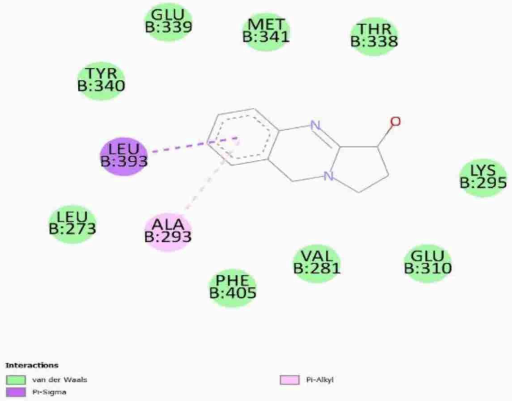
(e) Vasicinone



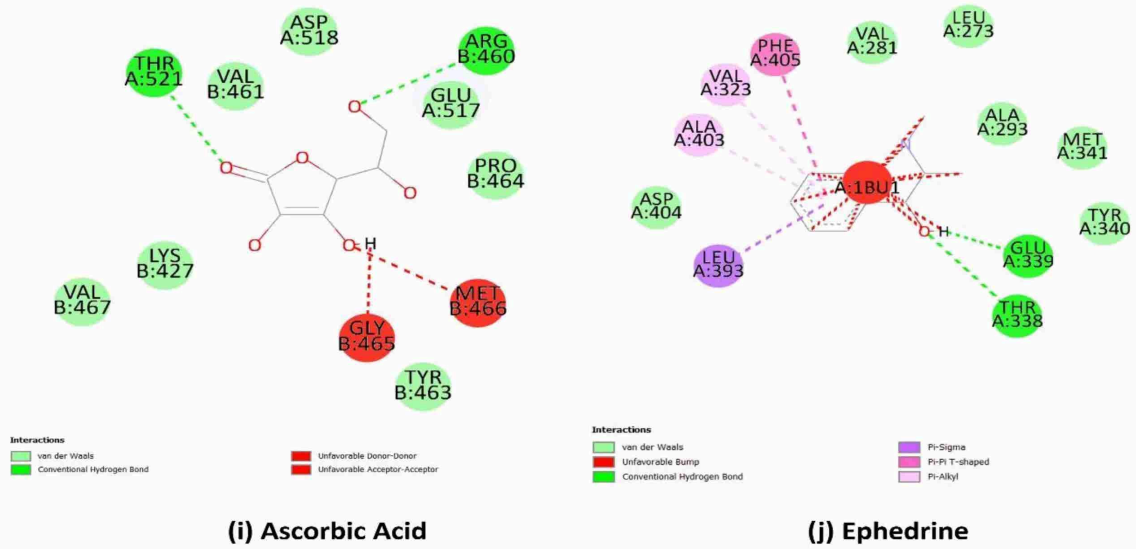
(f) Vasicinol



(g) Vasicoline

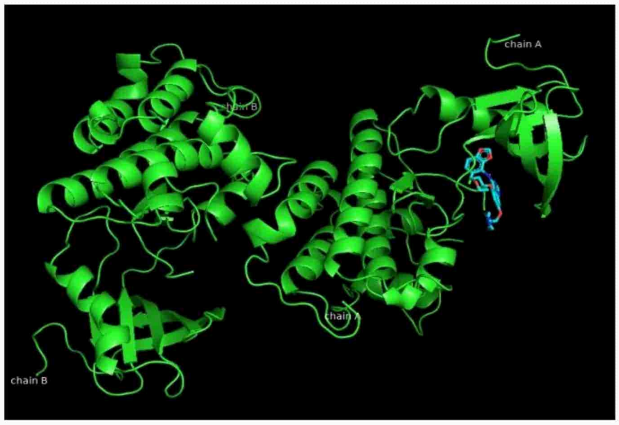


(h) Vasicine

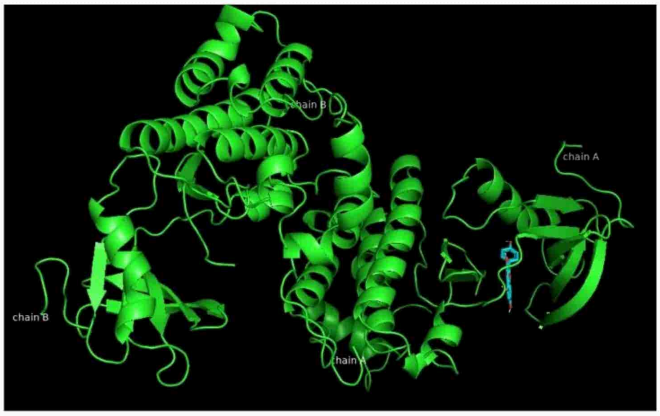


(i) Ascorbic Acid **(j) Ephedrine**

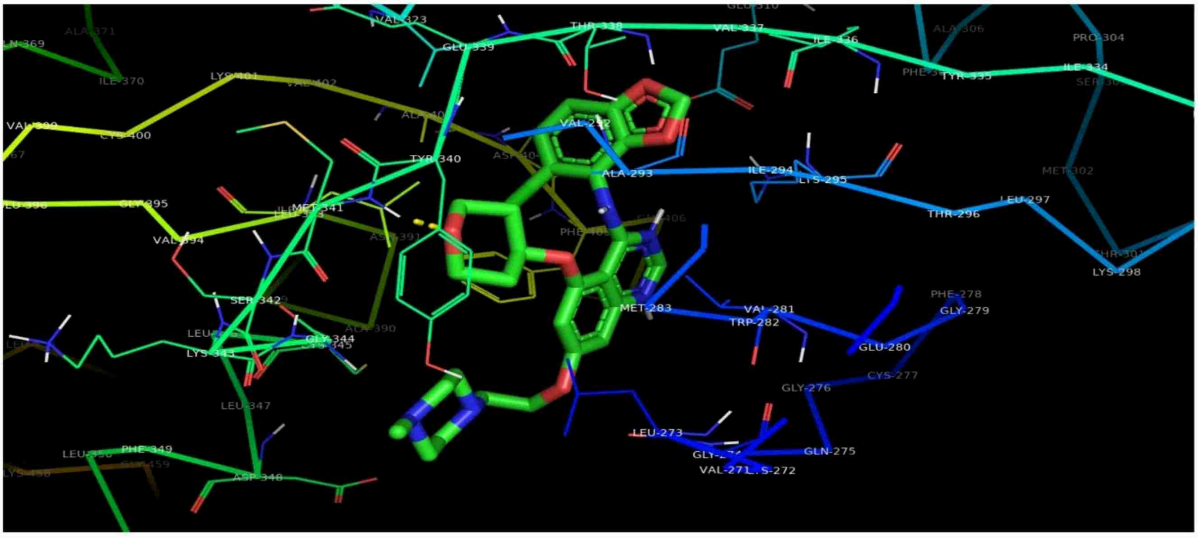
Figure 4.9. : 2D structures of selected ligands interacting with a receptor Src kinase (a) Drug (b) Kaempferol (c) Fenretinide (d) Vasicinolone (e) Vasicinone (f) Vasicinol (g) Vasicoline (h) Vasicine (i) Ascorbic acid (j) Ephedrine. These interactions involve various bonds as shown in the diagram with the different colour lines depicting different bonds of interacting residues.


chain A
chain B
chain A
chain B

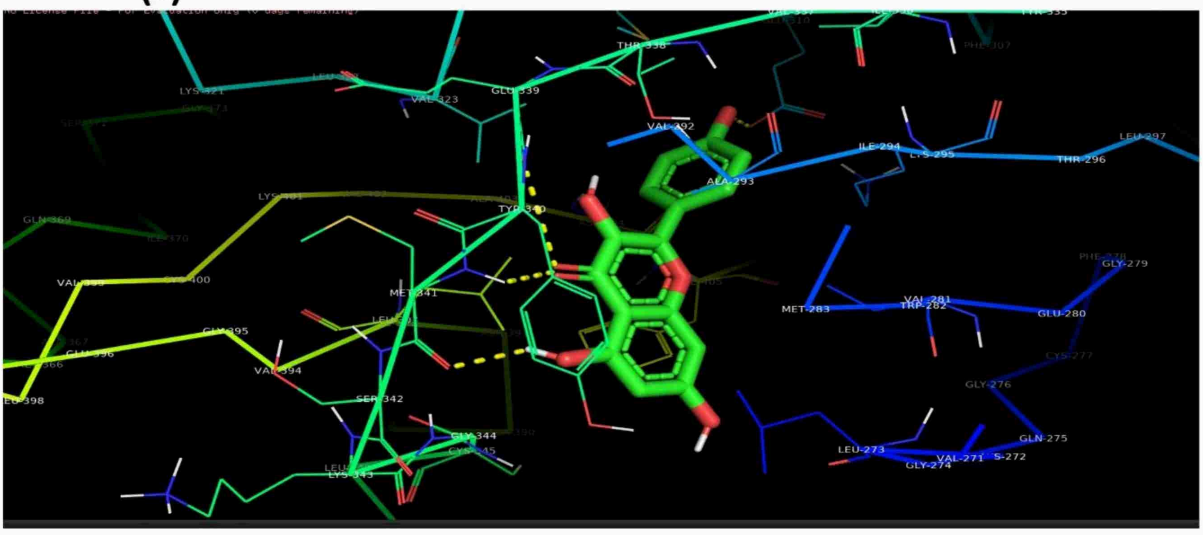
(a)


chain B
chain A
chain B
chain A

(b)


VAL-423
GLU-339
ILE-370
LYS-400
TYR-340
ALA-293
ILE-294
LYS-295
THR-296
LEU-297
LYS-298
MET-341
VAL-394
SER-342
MET-283
VAL-281
TRP-282
PHE-278
GLY-279
GLU-280
GLY-276
CYS-277
LEU-273
GLN-275
VAL-271
S-272
LEU-347
PHE-349
ASP-348

(c)


THR-338
VAL-423
GLU-339
VAL-292
ILE-294
LYS-295
THR-296
LEU-297
ALA-293
TYR-340
MET-341
VAL-400
GLY-395
VAL-394
SER-342
MET-283
VAL-281
TRP-282
GLU-280
GLY-279
GLY-276
LEU-273
GLN-275
VAL-271
S-272
GLY-274

(d)

Figure 4.10. : Docked conformations of (a) Drug with src protein (b) Kaempferol with src protein, Residues of protein involved in bond formation with (c) Drug and (d) Kaempferol

4.5. Active compound analysis

ADME analysis of all the docked Phytochemicals is done to check the active compounds. Out of 9 compounds, 7 compounds showed no BBB permeation. All the compounds showed high GI absorption, means that when a phytochemical is administered orally, the gastrointestinal tract absorbs a sizable amount of it. This indicates that the substance can effectively enter the systemic circulation, which may lead to its potential efficacy at lower dosages. Except 3 compounds, all of them showed P-gp substrate no meaning, it is less likely to be pumped out of cells and reach higher effective quantities in the bloodstream, this predicts improved bioavailability. Also, even in cells with strong P-gp expression, the chemical retains its effectiveness due to its reduced susceptibility to P-gp-mediated drug resistance (Table 4.5). Furthermore, there may be greater predictability in the phytochemical's distribution and removal, as well as a possible longer retention period in the target tissues. Last but not least, P-gp has a lesser chance of drug-drug interactions, which lessens the possibility of changed pharmacokinetics when taken with other drugs.

Table 4.5. : List of Phytochemicals for active compound analysis with their structures.

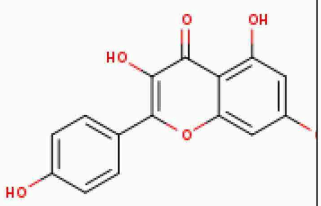
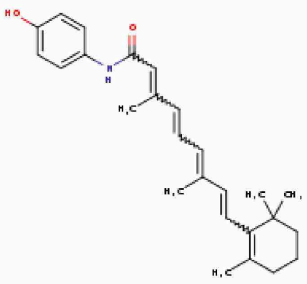
S.No.	Phytochemical	Structure	BBB permeation	GI absorption	P-gp substrate
1.	Kaempferol		No	High	No
2.	Fenretinide		No	High	No

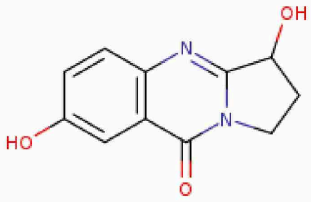
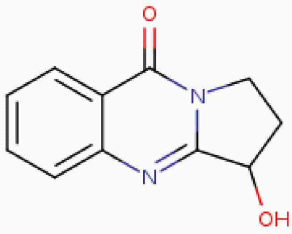
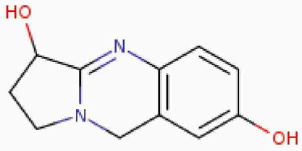
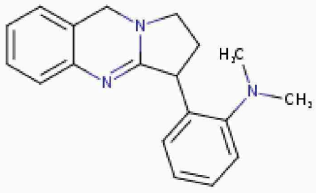
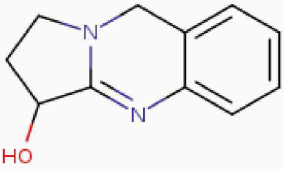
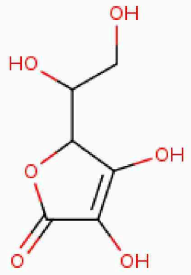
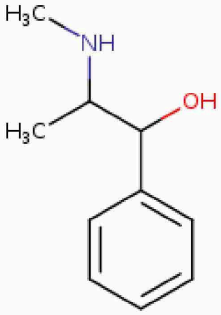
Table 4.5. (Continued)					
3.	Vasicinolone		No	High	No
4.	Vasicinone		No	High	No
5.	Vasicinol		No	High	Yes
6.	Vasicoline		Yes	High	Yes
7.	Vasicine		No	High	Yes

Table 4.5. (Continued)					
8.	Ascorbic acid		No	High	No
9.	Ephedrine		Yes	High	No

CHAPTER 5

DISCUSSION

Tyrosine kinases are essential for the intracellular signals that receptors transmit. Because many receptors lack intrinsic tyrosine kinase activity, they depend on cytosolic and/or membrane-associated tyrosine kinases for the first generation of signals. Src family kinases, often associated with receptors, start cytosolic signals that are subsequently transduced to the nucleus and other cytosolic compartments, eliciting distinct physiological reactions (Sun et al., 2021; Wong, 2005).

The Src family kinases, comprising c-src kinase, were identified structurally as the first non-receptor tyrosine kinases and are crucial in allergic rhinitis. A C-terminal regulatory tail, an N-terminal membrane localization motif, a Src homology3 (SH3) domain, a Src homology2 (SH2) domain, and a kinase domain make up the conserved domain structure of these kinases. They assist in the activation and transmission of signaling pathways upon stimulation of the T cell receptor (TCR). Following TCR activation, c-src kinase phosphorylates immunoreceptor tyrosine-based activation motifs (ITAMs) on CD3ζ subunits, creating docking sites for other kinases and adaptor proteins.(Ulanova et al., 2005).

The role of c-src kinase in mediator release and mast cell activation in allergic rhinitis is crucial. When an allergen binds to IgE antibodies on mast cells, the activation of c-src kinase sets off signaling cascades that ultimately result in the degranulation of mast cells. Histamine and leukotrienes, two inflammatory mediators, are released when c-src kinase phosphorylates downstream targets. Furthermore, c-src kinase promotes the release of pre-formed mediators by aiding in the fusion of secretory granules with the plasma membrane, which exacerbates symptoms of early-phase allergic rhinitis. By comprehending the function of c-src kinase in mediating mediator release and mast cell activation, allergic rhinitis therapy might be improved. According to a study by (Hata et al. ,2011), allergic rhinitis sufferers' nasal tissues have activated Src family kinases, which aid in the release of inflammatory cytokines and chemokines. When these kinases were inhibited, allergic inflammation was significantly reduced (Xia et al., 2013).

Justicia adhatoda shows promise as a herbal medicine for creating a multi-target medication that is both safe and effective against allergic rhinitis. Based on network pharmacology analysis, these studies predict 9 phytochemicals among which 2 PC showed highest affinity greater than Drug saracatinib against src kianse, making it potential herbal remedy. According to these network analyses, JA acts as a therapeutic against AR by modifying a number of genes, including STAT3, SRC, EP300, ESR1, JAK1, JAK2, STAT5A, STAT1, JUN and EGFR.

Gene enrichment analysis and KEGG analyzed for the common set of genes we got in Hub genes. GO enrichment analysis shows positive regulation of Interleukin-9-

mediaated signalling pathway for biological process (BP). A study showed that patients with peanut allergies and allergic rhinitis have been shown to have elevated levels of IL-9. Mice that do not have mast cells that produce IL-9 do not exhibit intestinal mastocytosis or signs of food allergies. Research utilizing mice that overexpress IL-9 suggests that IL-9 is also a major factor in gastrointestinal allergies (Chakraborty et al., 2019). Studies have revealed that higher levels of IL-9 are present in patients with allergic rhinitis, suggesting that this protein plays a role in the inflammatory response typical of this illness. Research has shown elevated levels of IL-9 in these individuals' serum and nasal lavage fluids, indicating a relationship between the severity of allergic rhinitis and IL-9 expression (Kakinoki, Y. et al. ,(2001). Increased expression of IL-9 in nasal mucosa of patients with allergic rhinitis. GO also showed extrinsic side of cytosolic side for plasma membrane for cellular process (CP) and protein tyrosine kinase activity for molecular function (MF). KEGG pathway showed that our genes also has an involvement in JAK-STAT pathway. The signal transducer and activator of transcription (STAT)-Janus kinase (JAK) pathway is an additional important mechanism implicated in allergic inflammation. According to a study by (Banerjee et al.,2017), JAK inhibitors have the ability to decrease the cytokine signaling associated with allergic rhinitis, underscoring the possibility of using tyrosine kinase activity targeting in treatment approaches.

Among the 10 Hub genes with top ranking, we took SRC gene for our analysis. Docking results of 9 phytochemicals show high binding affinities for src protein and out of the 9 PC, two PC Kaempferol and Fenretinide show highest affinity of -9.3 and -8.8 Kcal/Mol. So we can conclude that binding of kaempferol and fenretinide can bind to src kinase and can reduce the mast cell degranulation that can reduce the symptoms of Allergic rhinitis.

In conclusion, molecular docking studies shed light on how Justicia adhatoda phytochemicals lessen allergic rhinitis symptoms by blocking SRC protein activation. Because they particularly target the SRC protein's A chain, these phytochemicals present a viable therapeutic approach for the treatment of allergic rhinitis (Francini et al., 2015). When these phytochemicals occupy the active site in the A chain, they effectively block the signaling pathways that lead to inflammation. These phytochemicals can inhibit the ATP-binding site or other critical regions required for the kinase's activity once they attach to the SRC protein. Because of this inhibition, the SRC kinase is unable to transfer phosphate groups, which is necessary for starting the signaling cascades that activate mast cells and produce inflammatory mediators including histamine and leukotrienes.(Nipunika et al., 2022a)

When the SRC kinase's ATP-binding site or other critical areas are blocked, the enzyme's enzymatic activity is disrupted, which stops the phosphorylation of downstream substrates. The signaling pathway is disrupted, which stops the series of actions that usually lead to mast cell degranulation and the production of inflammatory chemicals (Máñez & Del Carmen Recio, 2002). Consequently, there is a decrease in the total inflammatory response. The production of inflammatory mediators and mast cell activation are markedly reduced when SRC kinase activity is inhibited. As a result, allergic rhinitis sufferers report less inflammation and a reduction in symptoms such rhinorrhea, sneezing, congestion in the nose, and itching. Phytochemicals from Justicia

adhatoda offer a dual-action strategy by addressing the underlying mechanisms of allergic responses and the symptoms of allergic rhinitis(Oza, 2022; Zhang et al., 2021).

This comprehensive strategy aids in both the acute symptom management and the prevention of allergy episode recurrence. With less side effects and a more patient-centered approach, the usage of Justicia adhatoda and its bioactive ingredients, such as vasicine and vasicinone, shows great promise as an alternative to traditional treatments for allergic rhinitis. The information that is now available indicates that these phytochemicals have a promising function in the treatment of allergic rhinitis, but more investigation and clinical trials are required to confirm their safety and efficacy in broader patient groups(Arvinder et al., 2015; Nipunika et al., 2022b).

With out study we can conclude that our plant *justicia adhatoda* can be used in a medicinal treatment for allergic rhinitis. More research is necessary to validate the clinical efficacy of *Justicia adhatoda* and its mechanisms against Allergic rhinitis.

CHAPTER 6

CONCLUSION

Similar to other allergic disorders, allergic arthritis is caused by complicated immunological pathways that are mainly mediated by immunoglobulin E (IgE) and result in the activation of basophils and mast cells(Leung, 1998). Pro-inflammatory mediators are released, leading to chronic inflammation in allergic arthritis and aggravating joint pain, edema, and stiffness. Anti-inflammatory medications, immunosuppressants, and biologics are frequently used in traditional treatments; although beneficial, these medications have a number of drawbacks and adverse effects(Barden et al., 2016). This makes it necessary to investigate alternative therapies, of which Justicia adhatoda appears to be a potential contender with improved safety profiles and efficacy. Clinical data indicate that Justicia adhatoda can greatly enhance the quality of life for individuals suffering with allergic arthritis. Studies on its impact on respiratory disorders, for example, have shown improvements in symptoms including discomfort, edema, and stiffness in the joints. Although the main focus of these trials was on respiratory benefits, allergic arthritis can directly benefit from the anti-inflammatory and immunomodulatory effects that were shown.(Batool et al., 2017)

The phosphorylation of downstream substrates is stopped by the SRC kinase's enzymatic activity being disturbed when its ATP-binding site or other important regions are blocked. By blocking the signaling route that triggers mast cell degranulation and the production of pro-inflammatory chemicals, this disruption lowers the level of inflammation overall. Mast cell activation and the generation of inflammatory mediators are markedly reduced when SRC kinase activity is inhibited. Because of this, those who have allergic rhinitis report feeling less irritated and having less symptoms, including sneezing, rhinorrhea, nasal congestion, and itching. Justicia adhatoda phytochemicals provide a dual-action approach by targeting allergic rhinitis symptoms as well as the underlying processes of allergic reactions.

While bronchodilatory effects are generally advantageous in respiratory disorders, Justicia adhatoda also demonstrates the ability to relax smooth muscles. This can be especially helpful in cases of allergic arthritis, as stiff joints and muscles are common symptoms. Justicia adhatoda's ability to relax muscles can help with joint mobility and discomfort management.

Even though Justicia adhatoda has a bright future, more thorough clinical studies are required to confirm its safety and effectiveness in the setting of allergic arthritis. To confirm the results of exploratory studies and anecdotal evidence, large-scale randomized controlled trials should be the main focus of future study. Additionally, enhancing the usage of Justicia adhatoda in therapeutic settings would require an understanding of the precise molecular pathways by which it exerts its effects. Finally, Justicia adhatoda offers an effective supplementary or substitute therapy for allergic

arthritis. It is a versatile therapeutic agent due to its anti-inflammatory, immunomodulatory, bronchodilatory, and antioxidant qualities. Enhancing patient results could be possible by including Justicia adhatoda into treatment plans in addition to conventional Ayurvedic principles. With further research aimed at clarifying its advantages and working processes, *Justicia adhatoda* has the potential to significantly influence the treatment of allergic arthritis.

REFERENCES

Arvinder, K., Davinder, K., & Saroj, A. (2015). Evaluation of antioxidant and antimutagenic potential of Justicia adhatoda leaves extract. *African Journal of Biotechnology*, *14*(21), 1807–1819. https://doi.org/10.5897/AJB2015.14486

Barden, A. E., Moghaddami, M., Mas, E., Phillips, M., Cleland, L. G., & Mori, T. A. (2016). Specialised pro-resolving mediators of inflammation in inflammatory arthritis. *Prostaglandins, Leukotrienes and Essential Fatty Acids*, *107*, 24–29. https://doi.org/10.1016/j.plefa.2016.03.004

Batool, R., Salahuddin, H., Mahmood, T., & Ismail, M. (2017). Study of anticancer and antibacterial activities of Foeniculum vulgare, Justicia adhatoda and Urtica dioica as natural curatives. *Cellular and Molecular Biology*, *63*(9), 109–114. https://doi.org/10.14715/cmb/2017.63.9.19

Biharee, A., Chaudhari, L., Bhartiya, S., Kori, S. K., Chaudhary, A., Dubey, D., & Yadav, A. (2024). A Comprehensive Study on Natural Products and their Bioactive Constituents to Cure Respiratory Diseases. *The Natural Products Journal*, *14*(2). https://doi.org/10.2174/2210315513666230612111133

Borish, L., & Joseph, B. Z. (1992). Inflammation and the allergic response. *Medical Clinics of North America*, *76*(4), 765–787. https://doi.org/10.1016/S0025-7125(16)30325-X

Bousquet, J., Khaltaev, N., Cruz, A. A., Denburg, J., Fokkens, W. J., Togias, A., Zuberbier, T., Baena-Cagnani, C. E., Canonica, G. W., Van Weel, C., Agache, I., Aït-Khaled, N., Bachert, C., Blaiss, M. S., Bonini, S., Boulet, L. -P., Bousquet, P. -J., Camargos, P., Carlsen, K. -H., … Williams, D. (2008). Allergic Rhinitis and its Impact on Asthma (ARIA) 2008*. *Allergy*, *63*(s86), 8–160. https://doi.org/10.1111/j.1398-9995.2007.01620.x

Bousquet, P. J., Demoly, P., Devillier, P., Mesbah, K., & Bousquet, J. (2013). Impact of allergic rhinitis symptoms on quality of life in primary care. *International Archives of Allergy and Immunology*, *160*(4), 393–400. https://doi.org/10.1159/000342991

Brożek, J. L., Bousquet, J., Baena-Cagnani, C. E., Bonini, S., Canonica, G. W., Casale, T. B., van Wijk, R. G., Ohta, K., Zuberbier, T., & Schünemann, H. J. (2010). Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 Revision. *Journal of Allergy and Clinical Immunology*, *126*(3), 466–476. https://doi.org/10.1016/j.jaci.2010.06.047

Ceylan, M. E., Kuzucu, İ., & Bayar Muluk, N. (2020). Herbal Remedy Alternatives for Allergic Rhinitis. In *All Around the Nose* (pp. 327–331). Springer International Publishing. https://doi.org/10.1007/978-3-030-21217-9_37

Chakraborty, S., Kubatzky, K. F., & Mitra, D. K. (2019). An Update on Interleukin-9: From Its Cellular Source and Signal Transduction to Its Role in Immunopathogenesis. *International Journal of Molecular Sciences*, *20*(9), 2113. https://doi.org/10.3390/ijms20092113

Daina, A., Michielin, O., & Zoete, V. (2017). SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. *Scientific Reports*, *7*(1), 42717. https://doi.org/10.1038/srep42717

Doncheva, N. T., Morris, J. H., Gorodkin, J., & Jensen, L. J. (2019). Cytoscape StringApp: Network Analysis and Visualization of Proteomics Data. *Journal of Proteome Research*, *18*(2), 623–632. https://doi.org/10.1021/acs.jproteome.8b00702

Eccles, R., Meier, C., Jawad, M., Weinmüllner, R., Grassauer, A., & Prieschl-Grassauer, E. (2010). Efficacy and safety of an antiviral Iota-Carrageenan nasal spray: a randomized, double-blind, placebo-controlled exploratory study in volunteers with early symptoms of the common cold. *Respiratory Research*, *11*(1). https://doi.org/10.1186/1465-9921-11-108

Eguiluz-Gracia, I., Layhadi, J. A., Rondon, C., & Shamji, M. H. (2019). Mucosal IgE immune responses in respiratory diseases. *Current Opinion in Pharmacology*, *46*, 100–107. https://doi.org/10.1016/j.coph.2019.05.009

Espada-Sánchez, M., Sáenz de Santa María, R., Martín-Astorga, M. del C., Lebrón-Martín, C., Delgado, M. J., Eguiluz-Gracia, I., Rondón, C., Mayorga, C., Torres, M. J., Aranda, C. J., & Cañas, J. A. (2023). Diagnosis and Treatment in Asthma and Allergic Rhinitis: Past, Present, and Future. *Applied Sciences*, *13*(3), 1273. https://doi.org/10.3390/app13031273

Fiocchi, C. (1997). Intestinal inflammation: a complex interplay of immune and nonimmune cell interactions. *American Journal of Physiology-Gastrointestinal and Liver Physiology*, *273*(4), G769–G775. https://doi.org/10.1152/ajpgi.1997.273.4.G769

Francini, C. M., Fallacara, A. L., Artusi, R., Mennuni, L., Calgani, A., Angelucci, A., Schenone, S., & Botta, M. (2015). Identification of Aminoimidazole and Aminothiazole Derivatives as Src Family Kinase Inhibitors. *ChemMedChem*, *10*(12), 2027–2041. https://doi.org/10.1002/cmdc.201500428

Guo, R., Pittler, M. H., & Ernst, E. (2007). Herbal medicines for the treatment of allergic rhinitis: a systematic review. *Annals of Allergy, Asthma & Immunology : Official Publication of the American College of Allergy, Asthma, & Immunology*, *99*(6), 483–495. https://doi.org/10.1016/S1081-1206(10)60375-4

Ilavenil, K. K., Senthilkumar, V., Kasthuri, A., & Sivaraman, S. (2024). Nanoparticles (MgO) utilising Justicia adhatoda and an evaluation of their antimicrobial properties. *Materials Today: Proceedings*. https://doi.org/10.1016/j.matpr.2024.05.144

Jamshidi-Kia, F., Lorigooini, Z., & Amini-Khoei, H. (2018). Medicinal plants: Past history and future perspective. *Journal of Herbmed Pharmacology*, *7*(1), 1–7. https://doi.org/10.15171/jhp.2018.01

Jantrapirom, S., Hirunsatitpron, P., Potikanond, S., Nimlamool, W., & Hanprasertpong, N. (2021). Pharmacological Benefits of Triphala: A Perspective for Allergic Rhinitis. *Frontiers in Pharmacology*, *12*. https://doi.org/10.3389/fphar.2021.628198

Jayandan, J. S., Misra, R., & Kundagol, M. C. (2017). A REVIEW ON IMMUNOMODULATION AND IMMUNOPROTECTION IN ALLERGIC ASTHMA: AN AYURVEDIC APPROACH. *International Journal of Research in Ayurveda & Pharmacy*, *8*(2), 73–77. https://doi.org/10.7897/2277-4343.08286

Kessler, R. C., Davis, R. B., Foster, D. F., Van Rompay, M. I., Walters, E. E., Wilkey, S. A., Kaptchuk, T. J., & Eisenberg, D. M. (2001). Long-term trends in the use of complementary and alternative medical therapies in the United States. *Annals of Internal Medicine*, *135*(4), 262–268. https://doi.org/10.7326/0003-4819-135-4-200108210-00011

Kubo, M. (2017). Innate and adaptive type 2 immunity in lung allergic inflammation. *Immunological Reviews*, *278*(1), 162–172. https://doi.org/10.1111/imr.12557

Kuna, P., Bachert, C., Nowacki, Z., Van Cauwenberge, P., Agache, I., Fouquert, L., Roger, A., Sologuren, A., & Valiente, R. (2009). Efficacy and safety of bilastine 20 mg compared with cetirizine 10 mg and placebo for the symptomatic treatment of seasonal allergic rhinitis: a randomized, double-blind, parallel-group study. *Clinical and Experimental Allergy : Journal of the British Society for Allergy and Clinical Immunology*, *39*(9), 1338–1347. https://doi.org/10.1111/J.1365-2222.2009.03257.X

Leung, D. Y. M. (1998). Molecular Basis of Allergic Diseases. *Molecular Genetics and Metabolism*, *63*(3), 157–167. https://doi.org/10.1006/mgme.1998.2682

Liu, W., Shi, X., Yang, Y., Cheng, X., Liu, Q., Han, H., Yang, B., He, C., Wang, Y., Jiang, B., Wang, Z., & Wang, C. (2015). In Vitro and In Vivo Metabolism and Inhibitory Activities of Vasicine, a Potent Acetylcholinesterase and Butyrylcholinesterase Inhibitor. *PLOS ONE*, *10*(4), e0122366. https://doi.org/10.1371/journal.pone.0122366

Luo, P., Tian, L.-P., Ruan, J., & Wu, F.-X. (2019). Disease Gene Prediction by Integrating PPI Networks, Clinical RNA-Seq Data and OMIM Data. *IEEE/ACM Transactions on Computational Biology and Bioinformatics*, *16*(1), 222–232. https://doi.org/10.1109/TCBB.2017.2770120

Máñez, S., & Del Carmen Recio, M. (2002). *Modulation of protein phosphorylation by natural products* (pp. 819–890). https://doi.org/10.1016/S1572-5995(02)80049-7

Meltzer, E. O., Bernstein, D. I., Prenner, B. M., Berger, W. E., Shekar, T., & Teper, A. A. (2013). Mometasone furoate nasal spray plus oxymetazoline nasal spray: short-term efficacy and safety in seasonal allergic rhinitis. *American Journal of Rhinology & Allergy*, *27*(2), 102–108. https://doi.org/10.2500/AJRA.2013.27.3864

Meltzer, E. O., & Bukstein, D. A. (2011). The economic impact of allergic rhinitis and current guidelines for treatment. *Annals of Allergy, Asthma & Immunology*, *106*(2), S12–S16. https://doi.org/10.1016/j.anai.2010.10.014

Mims, J. W. (2014). Epidemiology of allergic rhinitis. *International Forum of Allergy & Rhinology*, *4*(S2). https://doi.org/10.1002/alr.21385

Modena, B. D., Dazy, K., & White, A. A. (2016). Emerging concepts: mast cell involvement in allergic diseases. *Translational Research*, *174*, 98–121. https://doi.org/10.1016/j.trsl.2016.02.011

Nipunika, M. M., Abeysinghe, D. C., & Dharmadasa, R. M. (2022a). Distribution of Bioactive Compounds and Antioxidant Capacity of Different Parts of <i>Justicia adhatoda</i> L. (Acanthaceae). *World Journal of Agricultural Research*, *10*(2), 60–63. https://doi.org/10.12691/wjar-10-2-4

Nipunika, M. M., Abeysinghe, D. C., & Dharmadasa, R. M. (2022b). Distribution of Bioactive Compounds and Antioxidant Capacity of Different Parts of <i>Justicia adhatoda</i> L. (Acanthaceae). *World Journal of Agricultural Research*, *10*(2), 60–63. https://doi.org/10.12691/wjar-10-2-4

Oza, Dr. N. (2022). To Study The Role Of Justicia Adhatoda In Management Of Allergic Rhinitis In Children. *National Journal of Integrated Research in Medicine*, *13*(6), 30–32. https://doi.org/10.1159/000093586

P. Singh, T., M. Singh, O., & B. Singh, H. (2011). Adhatoda vasica Nees: Phytochemical and Pharmacological Profile. *The Natural Products Journale*, *1*(1), 29–39. https://doi.org/10.2174/2210315511101010029

Pan, S.-Y., Litscher, G., Gao, S.-H., Zhou, S.-F., Yu, Z.-L., Chen, H.-Q., Zhang, S.-F., Tang, M.-K., Sun, J.-N., & Ko, K.-M. (2014). Historical Perspective of Traditional Indigenous Medical Practices: The Current Renaissance and Conservation of Herbal Resources. *Evidence-Based Complementary and Alternative Medicine*, *2014*, 1–20. https://doi.org/10.1155/2014/525340

Papapostolou, N., & Makris, M. (2022). Allergic Asthma in the Era of Personalized Medicine. *Journal of Personalized Medicine*, *12*(7). https://doi.org/10.3390/JPM12071162

Pawankar, R., Canonica, G. W., Holgate, S. T., & Lockey, R. F. (2012). Allergic diseases and asthma. *Current Opinion in Allergy & Clinical Immunology*, *12*(1), 39–41. https://doi.org/10.1097/ACI.0b013e32834ec13b

Prakash Gupta, J., Sharma, R., Sahay Shukla, G., Agarwal, R., Goyal, M., & Pal Tyagi, V. (2023). INTEGRATION OF AYURVEDA IN MODERN PHARMACOLOGY. *International Journal of Advanced Research*, *11*(04), 551–557. https://doi.org/10.21474/IJAR01/16693

Ramawat, K. G., & Goyal, S. (2008). The Indian Herbal Drugs Scenario in Global Perspectives. In *Bioactive Molecules and Medicinal Plants* (pp. 325–347). Springer Berlin Heidelberg. https://doi.org/10.1007/978-3-540-74603-4_18

Rudrapal, M., Vallinayagam, S., Aldosari, S., Khan, J., Albadrani, H., Al-Shareeda, A., & Kamal, M. (2023). Valorization of Adhatoda vasica leaves: Extraction, in vitro analyses and in silico approaches. *Frontiers in Nutrition*, *10*. https://doi.org/10.3389/fnut.2023.1161471

Scadding, G. K., Kariyawasam, H. H., Scadding, G., Mirakian, R., Buckley, R. J., Dixon, T., Durham, S. R., Farooque, S., Jones, N., Leech, S., Nasser, S. M., Powell, R., Roberts, G., Rotiroti, G., Simpson, A., Smith, H., & Clark, A. T. (2017). BSACI guideline for the diagnosis and management of allergic and non-allergic rhinitis (Revised Edition 2017; First edition 2007). *Clinical and Experimental Allergy : Journal of the British Society for Allergy and Clinical Immunology*, *47*(7), 856–889. https://doi.org/10.1111/CEA.12953

Sharma, R., & Bhat, P. (2023a). Management of allergic rhinitis with Rajanyadi Churna and Guduchi Kwatha- A case report. *Journal of Ayurveda and Integrative Medicine*, *14*(4). https://doi.org/10.1016/J.JAIM.2023.100740

Sharma, R., & Bhat, P. (2023b). Management of allergic rhinitis with Rajanyadi Churna and Guduchi Kwatha- A case report. *Journal of Ayurveda and Integrative Medicine*, *14*(4), 100740. https://doi.org/10.1016/j.jaim.2023.100740

Sicherer, S. H., & Eggleston, P. A. (n.d.). Environmental Allergens. In *Allergic Diseases* (pp. 39–50). Humana Press. https://doi.org/10.1007/978-1-59745-382-0_4

Sin, B., & Togias, A. (2011). Pathophysiology of Allergic and Nonallergic Rhinitis. *Proceedings of the American Thoracic Society*, *8*(1), 106–114. https://doi.org/10.1513/pats.201008-057RN

Sun, Y., Yang, Y., Zhao, Y., Li, X., Zhang, Y., & Liu, Z. (2021). The role of the tyrosine kinase Lyn in allergy and cancer. *Molecular Immunology*, *131*, 121–126. https://doi.org/10.1016/j.molimm.2020.12.028

Ulanova, M., Duta, F., Puttagunta, L., Schreiber, A. D., & Befus, A. D. (2005). Spleen tyrosine kinase (Syk) as a novel target for allergic asthma and rhinitis. *Expert Opinion on Therapeutic Targets*, *9*(5), 901–921. https://doi.org/10.1517/14728222.9.5.901

Vivek-Ananth, R. P., Mohanraj, K., Sahoo, A. K., & Samal, A. (2023). IMPPAT 2.0: An Enhanced and Expanded Phytochemical Atlas of Indian Medicinal Plants. *ACS Omega*, *8*(9), 8827–8845. https://doi.org/10.1021/acsomega.3c00156

Wong, W. F. (2005). Inhibitors of the tyrosine kinase signaling cascade for asthma. *Current Opinion in Pharmacology*, *5*(3), 264–271. https://doi.org/10.1016/j.coph.2005.01.009

Xia, Y. C., Harris, T., Stewart, A. G., & Mackay, G. A. (2013). Secreted Factors from Human Mast Cells Trigger Inflammatory Cytokine Production by Human Airway Smooth Muscle Cells. *International Archives of Allergy and Immunology*, *160*(1), 75–85. https://doi.org/10.1159/000339697

Zhang, Y., Huang, Y., Chen, W., & Xu, Z. (2021). Identification of key genes in allergic rhinitis by bioinformatics analysis. *Journal of International Medical Research*, *49*(7), 030006052110295. https://doi.org/10.1177/03000605211029521

Ziauddin, M., Phansalkar, N., Patki, P., Diwanay, S., & Patwardhan, B. (1996). Studies on the immunomodulatory effects of Ashwagandha. *Journal of Ethnopharmacology*, *50*(2), 69–76. https://doi.org/10.1016/0378-8741(95)01318-0

APPENDIX I

Table IV.1 List of phytochemicals of *Justicia adhatoda* taken from IMPPAT tool for treatment of Allergic rhinitis

S.No.	Phytochemical name	Pubchem ID	S.No.	Phytochemical name	Pubchem ID
1.	29-Methyl-1-triacontanol	85683337	40.	Tricosane	12534
2.	beta-Sitosterol	222284	41.	Dodecane	8182
3.	Flavone	10680	42.	Methyl 2-(methylamino)-5-(1,2,3,9-tetrahydropyrrolo[2,1-b]quinazolin-3-yl)benzoate	5316460
4.	Pentadecanoic acid	13849	43.	4-Hydroxybenzoic acid	135
5.	Kaempferol	5280863	44.	Tetracontane	20149
6.	Quercetin	5280343	45.	Tetradecane	12389
7.	Luteolin	5280445	46.	beta-Eudesmol	91457
8.	Tritriacontane	12411	47.	Vasicine	667496
9.	Tridecanoic acid	12530	48.	Ephedrine	9294
10.	Vasicinone	442935	49.	4-Hydroxycinnamic acid	637542
11.	alpha-Amyrin	73170	50.	17-Octadecynoic acid	1449
12.	Sophoraflavonoloside	5282155	51.	Caryophyllene oxide	1742210
13.	Sitogluside	5742590	52.	Phytol	5280435
14.	beta-Sitosterol-d-glucoside	12309060	53.	Vitexin	5280441
15.	beta-Sitosterol-beta-D-glucoside	12309055	54.	Fenretinide	5288209
16.	Syringic acid	10742	55.	3-Methyl-4-(2,6,6-trimethyl-2-cyclohexen-1-yl)-3-buten-2-one	5372174
17.	Octanal	454	56.	5-Octadecenal	545652
18.	Pyrrolo(2,1-b)quinazolin-9(1H)-one, 2,3-dihydro-3,7-dihydroxy-, (3S)-	158720	57.	D-Galactose	6036

Table I.1. (continued)					
19.	Heptacosane	11636	58.	Myristic acid	11005
20.	Verbenone	29025	59.	Heptadecanoic acid	10465
21.	Vasicinol	442934	60.	Tetracosanoic acid	11197
22.	Anisotine	442884	61.	Hexacosanoic acid	10469
23.	Ascorbic acid	54670067	62.	Lauric acid	3893
24.	Eicosane	8222	63.	Eicosadienoic acid	6439848
25.	Undecanal	8186	64.	Docosanoic acid	8215
26.	Deoxyvasicinone	68261	65.	trans-2-Icosenoic acid	6438157
27.	1-Tetradecanol	8209	66.	Arachidic acid	10467
28.	1-Octene	8125	67.	Oleic acid	445639
29.	Neoandrographolide	9848024	68.	Erucic acid	5281116
30.	Palmitic acid	985	69.	Linolenic acid	5280934
31.	Quinazoline	9210	70.	Linoleic acid	5280450
32.	Pyrrolo[2,1-b]quinazolin-9(1H)-one, 3-[2-(dimethylamino)phenyl]-2,3-dihydro-	627712	71.	2,3-Dihydro-3-hydroxypyrrolo(2,1-b)quinazolin-9(1H)-one hydrochloride	157315
33.	Benzenamine, N,N-dimethyl-2-(1,2,3,9-tetrahydropyrrolo[2,1-b]quinazolin-3-yl)-	626005	72.	Betaine	247
34.	Isovitexin	162350	73.	2',4'-Dihydroxychalcone 4'-glucoside	6857762
35.	Hentriacontane	12410	74.	Triacontane	12535
36.	1-Pentadecanol	12397	75.	alpha-Carotene	6419725
37.	Pentacosane	12406	76.	Vasicol	273474418
38.	Heneicosane	12403	77.	Desmethoxyaniflorine	274926634
39.	Nonacosane	12409	78.	Vasnetine	274303670

APPENDIX 2

Table IV.2 List of common genes between *justicia adhatoda* and allergic rhinitis disease

S.No.	Gene Symbols	Protein Name
1.	ABCB1	ATP binding cassette subfamily B member 1
2.	ABCG2	ATP binding cassette subfamily G member 2 (JR blood group)
3.	ACE	angiotensin I converting enzyme
4.	ACHE	acetylcholinesterase (Yt blood group)
5.	ADAM10	ADAM metallopeptidase domain 10
6.	ADAM17	ADAM metallopeptidase domain 17
7.	ADORA3	adenosine A3 receptor
8.	ADRA1B	adrenoceptor alpha 1B
9.	ADRA1A	adrenoceptor alpha 1D
10.	ADRA1D	adrenoceptor alpha 1D
11.	ADRA2C	adrenoceptor alpha 2C
12.	ADRB2	adrenoceptor beta 2
13.	AHR	aryl hydrocarbon receptor
14.	AKR1B1	aldo-keto reductase family 1 member B
15.	AR	aldo-keto reductase family 1 member B
16.	AKR1C2	aldo-keto reductase family 1 member C2
17.	AKT1	AKT serine/threonine kinase 1
18.	ALDH2	aldehyde dehydrogenase 2 family member
19.	ALK	ALK receptor tyrosine kinase
20.	ALOX15	arachidonate 15-lipoxygenase
21.	ALOX5	arachidonate 5-lipoxygenase
22.	ALOX5AP	arachidonate 5-lipoxygenase activating protein
23.	ATG4B	autophagy related 4B cysteine peptidase
24.	AXL	AXL receptor tyrosine kinase
25.	CA2	carbonic anhydrase 2
26.	CACNA1B	calcium voltage-gated channel subunit alpha1 B
27.	CALCRL	calcitonin receptor like receptor
28.	CCR3	C-C motif chemokine receptor 3
29.	CDK1	cyclin dependent kinase 1
30.	CFTR	CF transmembrane conductance regulator
31.	CHRM2	cholinergic receptor muscarinic 2
32.	CHRM3	cholinergic receptor muscarinic 3

Table II.1. (Continued)		
33.	CRHR1	corticotropin releasing hormone receptor 1
34.	CXCR1	C-X-C motif chemokine receptor 1
35.	CXCR3	C-X-C motif chemokine receptor 3
36.	VDR	cytochrome P450 family 27 subfamily B member 1
37.	HRH1	DEAH-box helicase 8
38.	DPP4	dipeptidyl peptidase 4
39.	DRD2	dopamine receptor D2
40.	EDNRA	endothelin receptor type A
41.	EGFR	epidermal growth factor receptor
42.	ELANE	elastase, neutrophil expressed
43.	EP300	E1A binding protein p300
44.	ESR1	estrogen receptor 1
45.	ESR2	estrogen receptor 2
46.	F2R	coagulation factor II thrombin receptor
47.	F2RL1	F2R like trypsin receptor 1
48.	GSK3B	glycogen synthase kinase 3 beta
49.	GSTM1	glutathione S-transferase mu 1
50.	GUSB	glucuronidase beta
51.	HDAC11	histone deacetylase 11
52.	HDAC4	histone deacetylase 4
53.	HIF1A	hypoxia inducible factor 1 subunit alpha
54.	HMGCR	3-hydroxy-3-methylglutaryl-CoA reductase
55.	HPGDS	hematopoietic prostaglandin D synthase
56.	HRH3	histamine receptor H3
57.	HRH4	histamine receptor H4
58.	HSD11B1	hydroxysteroid 11-beta dehydrogenase 1
59.	HTR2A	5-hydroxytryptamine receptor 2A
60.	HTR2B	5-hydroxytryptamine receptor 2B
61.	HTR2C	5-hydroxytryptamine receptor 2C
62.	HTR6	5-hydroxytryptamine receptor 6
63.	IGF1R	insulin like growth factor 1 receptor
64.	JAK1	Janus kinase 1
65.	JAK2	Janus kinase 2
66.	JAK3	Janus kinase 3
67.	JUN	Jun proto-oncogene, AP-1 transcription factor subunit
68.	KCNA3	potassium voltage-gated channel subfamily A member 3
69.	KCNH2	potassium voltage-gated channel subfamily H member 2
70.	KDR	kinase insert domain receptor
71.	KIT	KIT proto-oncogene, receptor tyrosine kinase

72.	MAOA	monoamine oxidase A
73.	MAOB	monoamine oxidase B
74.	MAP2K1	mitogen-activated protein kinase kinase 1
75.	MAPK1	mitogen-activated protein kinase 1
76.	MAPK14	mitogen-activated protein kinase 14
77.	MERTK	MER proto-oncogene, tyrosine kinase
78.	MMP1	matrix metallopeptidase 1
79.	MMP12	matrix metallopeptidase 12
80.	MMP2	matrix metallopeptidase 2
81.	MMP7	matrix metallopeptidase 7
82.	MMP8	matrix metallopeptidase 8
83.	MMP9	matrix metallopeptidase 9
84.	MPO	myeloperoxidase
85.	MTOR	mechanistic target of rapamycin kinase
86.	NOS1	nanos C2HC-type zinc finger 1
87.	NOS2	nanos C2HC-type zinc finger 2
88.	NOS3	nanos C2HC-type zinc finger 3
89.	NEK6	NIMA related kinase 6
90.	NOX4	NADPH oxidase 4
91.	NR1H2	nuclear receptor subfamily 1 group H member 2
92.	NR3C1	nuclear receptor subfamily 3 group C member 1
93.	PARP1	poly(ADP-ribose) polymerase 1
94.	CNR2	protocadherin alpha 6
95.	CNR1	protocadherin alpha cluster, complex locus
96.	PDE4D	phosphodiesterase 4D
97.	PDE5A	phosphodiesterase 5A
98.	PNMT	phosphatidylethanolamine N-methyltransferase
99.	PFKFB3	6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3
100.	PGR	progesterone receptor
101.	PPARG	peroxisome proliferator activated receptor gamma
102.	PRKCA	protein kinase C alpha
103.	PRKCD	protein kinase C delta
104.	PRKCQ	protein kinase C theta
105.	PTAFR	platelet activating factor receptor
106.	PTGS2	prostaglandin-endoperoxide synthase 2
107.	MET	RNA guanine-7 methyltransferase
108.	RORC	RAR related orphan receptor C
109.	MIF	S100 calcium binding protein A8
110.	SCN2A	sodium voltage-gated channel alpha subunit 2
111.	SERPINA6	serpin family A member 6

112.	SLC18A2	solute carrier family 18 member A2
113.	ODC1	solute carrier family 25 member 21
114.	SLC6A2	solute carrier family 6 member 2
115.	SLC6A4	solute carrier family 6 member 4
116.	XDH	sorbitol dehydrogenase
117.	SRC	SRC proto-oncogene, non-receptor tyrosine kinase
118.	STAT1	signal transducer and activator of transcription 1
119.	STAT3	signal transducer and activator of transcription 3
120.	STAT5A	signal transducer and activator of transcription 5A
121.	SYK	spleen associated tyrosine kinase
122.	TACR2	tachykinin receptor 2
123.	TERT	telomerase reverse transcriptase
124.	ARG1	tubulointerstitial nephritis antigen like 1
125.	TLR8	toll like receptor 8
126.	TRPV1	transient receptor potential cation channel subfamily V member 1
127.	TRPV3	transient receptor potential cation channel subfamily V member 3
128.	TRPV4	transient receptor potential cation channel subfamily V member 4
129.	TYK2	tyrosine kinase 2
130.	ZAP70	zeta chain of T cell receptor associated protein kinase 70

LIST OF PUBLICATIONS

CONFERENCES

Conference paper presented in Scopus indexed conference at ICAEM 20254 organized by International School of Technology and sciences for women in collaboration with Samarkand State University, Uzbekistan held on 20 April.

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