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MOLECULAR DOCKING STUDIES ON DRUG TARGET SITES FOR ATMOSPHERIC DUST ALLERGY

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Abstract

Allergy describes a constellation of clinical diseases that affect up to 30% of the world's population. The underlying pathophysiology involves immunoregulatory dysfunctions similar to those noted in highly stressed populations. Histamine is a major mediator in allergic reactions and the histamine H1 receptor is responsible for many of the symptoms of allergic reactions such as rhinorrhoea, contraction of bronchial and gastrointestinal smooth muscle, and many forms of itch. H1 receptor antagonists are used extensively for the treatment of allergic disorders to the extent that "anti-histamines" would be universally recognized as a treatment for hayfever, for example, but not for asthma. This work aims to find the binding sites between the phytochemicals from coleus barbatus and the human histamine h1 receptor protein. The protein 3D structure is retrieved from the PDB database. The active sites of the histamine h1 protein are derived from Castp. Binding molecules or ligands are derived from the literature and phytochemical databases. From PubChem, the 2D structures of the ligands are taken. Molecular docking is done by swissdock server and the final ADMET studies are done with the help of SwissADME. It is observed that alpha-ionone shows the best docking result among all the phytochemicals and also obeys the Lipinski rule of 5 and ADMET.

Keywords: *Allergy, histamine h1 receptor protein, PDB, PubChem, Cast p, Swissdock, Swiss ADME, Lipinski rule of five.*

INTRODUCTION

Drug design

Drug design often referred to as rational drug design or simply rational design, is the inventive process of finding new medications based on the knowledge of a biological target. The drug is most commonly an organic small molecule that activates or inhibits the function of a biomolecule such as a protein, which in turn results in a therapeutic benefit to the patient. In the most basic sense, drug design involves the design of molecules that are complementary in shape and charge to the biomolecular target with which they interact and therefore will bind to it. Drug design frequently but not necessarily relies on computer modeling techniques. This type of modeling is sometimes referred to as computer-aided drug design. Finally, drug design that relies on the knowledge of the three-dimensional structure of the biomolecular target is known as structure-based drug design. In addition to small molecules, biopharmaceuticals including peptides and especially therapeutic antibodies are an increasingly important class of drugs, and computational methods for improving the affinity, selectivity, and stability of these protein-based therapeutics have also been developed. *(Madsen et.al; 2002)*

The phrase "drug design" is to some extent a misnomer. A more accurate term is ligand design (i.e., the design of a molecule that will bind tightly to its target). Although design techniques for the prediction of binding affinity are reasonably successful, many other properties, such as bioavailability, metabolic half-life, side effects, etc. must first be optimized before a ligand can become a safe and efficacious drug. These other characteristics are often difficult to predict with rational design techniques. Nevertheless, due to high attrition rates, especially during clinical phases of drug development, more attention is being focused early in the drug design process on selecting candidate drugs whose physicochemical properties are predicted to result in fewer complications during development and hence more likely to lead to an approved, marketed drug. Furthermore, in vitro experiments complemented with computation methods are increasingly used in early drug discovery to select compounds with more favorable ADME (absorption, distribution, metabolism, and excretion) and toxicological profiles. *(Madsen et.al; 2002.*

Types of drug design

The drug discovery cycle highlights both ligand-based (indirect) and structure-based (direct) drug design strategies. There are two major types of drug design. The first is referred to as ligand-based drug design and the second, is structure-based drug design. *(Madsen et.al; 2002)*

Ligand-based

Ligand-based drug design (or indirect drug design) relies on knowledge of other molecules that bind to the biological target of interest. These other molecules may be used to derive a pharmacophore model that defines the minimum necessary structural characteristics a molecule must possess to bind to the target. In other words, a model of the biological target may be built based on the knowledge of what binds to it, and this model in turn may be used to design new molecular entities that interact with the target. Alternatively, a quantitative structure-activity relationship (QSAR), in which a correlation between the calculated properties of molecules and their experimentally determined biological activity, may be derived. These QSAR

relationships in turn may be used to predict the activity of new analogs. *(Madsen et.al; 2002)*

Structure-based

Structure-based drug design (or direct drug design) relies on knowledge of the three- dimensional structure of the biological target obtained through methods such as x-ray crystallography or NMR spectroscopy. If an experimental structure of a target is not available, it may be possible to create a homology model of the target based on the experimental structure of a related protein. Using the structure of the biological target, candidate drugs that are predicted to bind with high affinity and selectivity to the target may be designed using interactive graphics and the intuition of a medicinal chemist. Alternatively, various automated computational procedures may be used to suggest new drug candidates. *(Madsen et.al; 2002)*

Current methods for structure-based drug design can be divided roughly into three main categories. The first method is the identification of new ligands for a given receptor by

searching large databases of 3D structures of small molecules to find those fitting the binding pocket of the receptor using fast approximate docking programs. This method is known as virtual screening. A second category is the de novo design of new ligands. In this method, ligand molecules are built up within the constraints of the binding pocket by assembling small pieces in a stepwise manner. These pieces can be either individual atoms or molecular fragments. The key advantage of such a method is that novel structures, not contained in any database, can be suggested. A third method is the optimization of known ligands by evaluating proposed analogs within the binding cavity. *(Madsen et.al; 2002)*

Drug targets

A biomolecular target (most commonly a protein or a nucleic acid) is a key molecule involved in a particular metabolic or signaling pathway that is associated with a specific disease condition or pathology or to the infectivity or survival of a microbial pathogen. Potential drug targets are not necessarily disease-causing but must by definition be disease- modifying. In some cases, small molecules will be designed to enhance or inhibit the target function in the specific disease-modifying pathway. Small molecules (for example receptor agonists, antagonists, inverse agonists, or modulators; enzyme activators or inhibitors; or ion channel openers or blockers) will be designed that are complementary to the binding site of the target. Small molecules (drugs) can be designed so as not to affect any other important "off-target" molecules (often referred to as antitargets) since drug interactions with off-target molecules may lead to undesirable side effects. Due to similarities in binding sites, closely related targets identified through sequence homology have the highest chance of cross- reactivity and hence the highest side effect potential. *(Anderson et.al; Sep 2003)*

Most commonly, drugs are organic small molecules produced through chemical synthesis, but biopolymer-based drugs produced through biological processes are becoming increasingly more common. In addition, mRNA-based gene silencing technologies may have therapeutic applications. *(Anderson et.al; Sep 2003)*

Molecular docking

Molecular docking analysis has been one of the most basic and important strategies for drug discovery. It allows the prediction of molecular interactions that hold together a protein and a ligand in the bound state.

Phytochemicals

Phytochemicals are chemical compounds produced by plants, generally to help them resist fungi, bacteria, and plant virus infections, and also consumption by insects and other animals. The name comes from the Greek φυτόν (phyton) 'plant'. Some phytochemicals have been used as poisons and others as traditional medicine.

As a term, phytochemicals are generally used to describe plant compounds that are under research with unestablished effects on health and are not scientifically defined as essential nutrients. Regulatory agencies governing food labeling in Europe and the United States have guided for the industry to limit or prevent health claims about phytochemicals on the food products or nutrition labels.

Functions of phytochemicals

The phytochemical category includes compounds recognized as essential nutrients, which are naturally contained in plants and are required for normal physiological functions, so must be obtained from the diet of humans. Some phytochemicals are known phytotoxins that are toxic to humans; for example, aristolochic acid is carcinogenic at low doses. Some phytochemicals are antinutrients that interfere with the absorption of nutrients. Others, such as some polyphenols and flavonoids, may be pro-oxidants in high ingested amounts. Non-digestible dietary fibers from plant foods, often considered a phytochemical, are now generally regarded as a nutrient group having approved health claims for reducing the risk of some types of cancer and coronary heart disease.

Eating a diet high in fruits, vegetables, grains, legumes, and plant-based beverages has long- term health benefits, but no evidence taking dietary supplements of non-nutrient phytochemicals extracted from plants similarly benefits health. Phytochemical supplements are neither recommended by health authorities for improving health nor approved by regulatory agencies for health claims on product labels.

Lipinski's rule of five

Lipinski's rule of five, also known as Pfizer's rule of five or simply the rule of five (RO5), is a rule of thumb to evaluate drug likeness or determine if a chemical compound with a certain pharmacological or biological activity has chemical properties and physical properties that would make it a likely orally active drug in humans. The rule was formulated by Christopher

A. Lipinski in 1997, based on the observation that most orally administered drugs are relatively small and moderately lipophilic molecules. *(Lipinski et.al; March 2001)*

The rule describes molecular properties important for a drug's pharmacokinetics in the human body,

including their absorption, distribution, metabolism, and excretion ("ADME"). However, the rule does not predict if a compound is pharmacologically active. *(Lipinski et.al;March 2001)*

The rule is important to keep in mind during drug discovery when a pharmacologically active lead structure is optimized step-wise to increase the activity and selectivity of the compound as well as to ensure drug-like physicochemical properties are maintained as described by Lipinski's rule. Candidate drugs that conform to the RO5 tend to have lower attrition rates during clinical trials and hence have an increased chance of reaching the market. *(Lipinski et.al; March 2001)*

1.6.2. Components of the rule

Lipinski's rule states that, in general, an orally active drug has no more than one violation ofthe following criteria:

- No more than 5 hydrogen bond donors (the total number of nitrogen–hydrogen and oxygen-hydrogen bonds)
- No more than 10 hydrogen bond acceptors (all nitrogen or oxygen atoms)
- A molecular mass of fewer than 500 daltons
- An octanol-water partition coefficient (log P) that does not exceed 5. *(Lipinski et.al;March 2001)*

ADME Studies

ADME is the abbreviation for Absorption, Distribution, Metabolism, and Excretion. ADME studies are designed to investigate how a chemical (e.g. a drug compound) is processed by a living organism. Toxicology tests are often a part of this process, yielding the acronym ADMET. *(Gleichmann et. al.;2020)*

Pharmacokinetics is a specific branch of pharmacology that studies what the body does to a drug. Pharmacokinetic studies evaluate:

- The rate that which a chemical is absorbed and distributed
- The rate and pathways of drug metabolism and excretion
- The plasma concentration of a drug over time
- ADME is the four steps of pharmacokinetics.

Absorption

Absorption describes how a chemical enters the body. Absorption relates to the movement of a chemical from the administration site to the bloodstream. There are four main routes of administration:

- Ingestion through the digestive tract
- Inhalation via the respiratory system
- Dermal application to the skin or eye

- Injection through direct administration into the bloodstream

Only injected compounds enter directly into the systemic circulation. For drugs administered through ingestion, inhalation, or dermal contact, the chemicals must cross a membrane before entering the bloodstream. There are 4 ways through which a chemical can cross a membrane and enter the bloodstream.

- Passive diffusion: When a molecule moves from an area of high concentration to an area of low concentration. This is the most common way a drug is absorbed.
- Facilitated diffusion: When a molecule moves from an area of high concentration to one of low concentration with the help of carrier proteins in the membrane.
- Active diffusion: An energy-dependent process during which a molecule requiresenergy in the form of ATP to cross a membrane.
- Endocytosis: When a larger drug is transferred through a membrane via invagination of the membrane. *(Gleichmann et. al.;2020)*

Distribution

Once a drug has been absorbed, it moves from the absorption site to tissues around the body. This distribution from one part of the body to another is typically accomplished via the bloodstream, but it can also occur from cell to cell. Researchers examine where the chemical travels, the rate at which it arrives at certain sites, and the extent of the distribution to help determine efficacy. Some compounds move easily, while others do not. Factors such as blood flow, lipophilicity, tissue binding, and molecular size influence distribution. *(Gleichmann et. al.;2020)*

Metabolism

Drug metabolism is the biotransformation of a drug by organs or tissues (primarily the liver, kidney, skin, or digestive tract) so that the drug can be excreted. To facilitate removal via feces or urine, the drug compound is altered to become more water-soluble. Chemical

metabolism can result in toxicity, for instance by creating damaging byproducts or a toxic metabolite. Scientists map out the specific metabolic pathways of a drug candidate, something called adverse outcome pathways (AOPs). AOPs provide data needed to determine the potential safety or toxicity of a drug. Drug metabolism and interaction data provide researchers with the information they need to determine the likelihood of drug-drug interactions (DDIs). Anticipating drug interactions is essential for safe pharmaceutical development. *(Gleichmann et. al.;2020)*

Excretion

Excretion is the process by which the metabolized drug compound is eliminated from the body. Researchers want to know how rapidly the drug is excreted and what pathway it takes to exit the body. Most drug excretion occurs in feces or urine. Other excretion methods include through the lungs or in sweat through the skin. Molecular size and charge influence the excretion pathway. Not every drug compound is fully excreted. When the chemical or metabolic by-products bioaccumulate, adverse effects can occur. Lipid-soluble compounds are more prone to bioaccumulate compared to water-soluble compounds. *(Gleichmann et. al.;2020)*

Importance of ADME studies

In drug discovery and development, researchers must examine the activity of a drug in the body to assess safety and toxicity. Drug metabolism and pharmacokinetic studies, such as ADME and toxicology studies, are critical steps in this process. The data collected tells researchers if a drug is viable and provides specific targets for future research and development. Advances in the field have precipitated the rise of personalized ADME approaches, where factors such as a patient's genome or even the time of day during which drugs are administered are considered. Computational techniques are often used to assist these more precise studies. *(Gleichmann et. al.;2020).*

Atmospheric dust allergy

Allergy describes a constellation of clinical diseases that affect up to 30% of the world's population. It is characterized by the production of allergen-specific IgE which bind to mast cells and initiates a cascade of molecular and cellular events that affect the respiratory tract (rhinitis and asthma) skin (dermatitis, urticaria), and multi-systems (anaphylaxis) to a variety of allergens including pollens, mold spores, animal danders, insect stings, foods, and

drugs. The underlying pathophysiology involves immunoregulatory dysfunctions similar to those noted in highly stressed populations. The relationships in terms of potential for intervention are discussed. Most allergies are inherited, which means they are passed on to children by their parents. People inherit a tendency to be allergic, although not to any specific allergen. If your child develops an allergy, you or your partner likely have allergies.

Allergies are your body's reaction to a substance it views as a harmful "invader." Forexample, coming into contact with what is normally a harmless substance, such as pollen, might cause your immune system to react. Substances that cause these reactions are called allergens. Allergy symptoms range from mild – rash or hives, itchiness, runny nose, watery/red eyes – to life-threatening. Treatments include antihistamines, decongestants, nasal steroids, asthma medicines, and immunotherapy. An "allergic reaction" is the way your body responds to the allergen. A chain of events occurs that results in an allergic reaction. If you are prone to allergies, the first time you're exposed to a specific allergen (such as pollen), your body responds by

producing allergic (IgE) antibodies. The job of these antibodies is to find the allergens and help remove them from your system. As a result, a chemical called histamine is released and causes symptoms of allergies. Nasal allergy symptoms and hay fever are referred to as “allergic rhinitis”. Seasonal allergic rhinitis is a nasal allergy that changes with the seasons because of pollen from plants (trees, grasses, or weeds). Seasonal symptoms arise during the pollinating seasons for particular plants. Because a person can be allergic to more than one thing, the symptoms may get worse at different times throughoutthe year or maybe constant. More than 50 million Americans (1 in 6) experience all types of allergies, including indoor/outdoor allergies, food, and drug, latex, insect, skin, and eye allergies. The number of people who have allergies continues to increase across all ages, sex, and racial groups.

H1 Receptors

Histamine H1 receptors are expressed widely in the body, in particular in tissues such as smooth muscle, endothelial cells, adrenal medulla, heart, and central nervous system. Histamine is a major mediator in allergic reactions and the histamine H1 receptor is responsible for many of the symptoms of allergic reactions such as rhinorrhoea, contractionof bronchial and gastrointestinal smooth muscle, and many forms of itch. H1 receptor antagonists are used extensively for the treatment of allergic disorders to the extent that "anti-

histamines" would be universally recognized as a treatment for hay fever, for example, but not for asthma. *(Kim et.al; 2007)*

Histamine H1 receptors occur throughout the central nervous system, with a particularly high density in regions involved in arousal and waking, such as the thalamus and cortex and the cholinergic, noradrenergic, dopaminergic, and serotonergic nuclei. H1 receptor activation causes excitation in most brain regions (brain stem, thalamus, hypothalamus, cortex, amygdala, striatum) through Gq11 protein and direct block of leak K+ conductance orphospholipase C, inositol trisphosphate (IP3), and diacylglycerol (DAG) mediation. IP3 releases Ca2+ from internal stores and activate several Ca2+-dependent processes, including the opening of a cation channel of the transient receptor potential canonical (TRPC) type or the stimulation of a Na+−Ca2+-exchanger. Furthermore, the elevated intracellular Ca2+ can stimulate NO synthase and consequently guanylate cyclase. On the other hand, Ca2+- dependent K+ channels can be opened, leading to hyperpolarization and inhibition, for instance, in hippocampal pyramidal neurons. *(Kim et.al; 2007)*

H1 receptor antagonists are classic antihistaminics and are widely prescribed for allergies. Their well-known sedative actions have prompted early suggestions for the involvement of endogenous histamine in sleep-waking regulation. There is strong evidence for H1 receptors being the main mediators of histamine waking action. In H1 receptor knockout (KO) mice, however, the sleep-the waking pattern is hardly changed, but the waking response to H3 receptor antagonists, which relieve the autoinhibition of histamine release, is abolished. Most antipsychotic and antidepressive pharmaceuticals occupy H1 receptors, but this is not part of the therapeutic effect. Genetic and molecular studies have recently attributed an important role in peripheral and central immunity to histamine receptors. The H1 receptor is identical to an

autoimmune locus receptor (Bordetella pertussis-induced histamine sensitization; Bphs), with relevance to inflammatory brain diseases (eg, multiple sclerosis). Through action on astrocytes, histamine regulates the permeability of the blood-brain barrier and the immigration of immune cells in the otherwise privileged CNS. Histidine decarboxylase (HDC) KO mice, compared to wild type, produce more pro-inflammatory signals and display a particularly marked experimental autoimmune encephalitis. *(Kim et.al; 2007)*

Antihistamines and allergic disease

Histamine is a heterocyclic amine that is synthesized by decarboxylation of the dietary amino acid l-histidine in many different cells and functions as a local hormone (autacoid) and in the brain, where it acts as a neurotransmitter.

Histamine is released from mast cells and basophils by degranulation after activation of the cell either by a direct physical or chemical injury or by cross-linking of attached IgE molecules of complement proteins. After release from these cells, histamine is rapidly metabolized. The effects of histamine are mediated by four distinct types of G protein- coupled receptors known as H1, H2, H3, and H4. In general, H1 receptors are involved in the 'defensive' actions of histamine and contribute to immune regulation and acute and chronic allergic inflammation.

Histamine H1 receptors are normally in equilibrium between the active and inactive state. At rest, even in the absence of histamine, the H1 receptor exerts a basal or constitutive level of activity. Histamine preferentially binds to the receptor in its active state and shifts the equilibrium further towards the active state. Histamine H1 receptors act through intracellular Ca2+ as a second messenger and are coupled to inositol phospholipid intracellular signaling pathways. This activates the ubiquitous gene transcription factor nuclear factor κB, which stimulates the production of pro-inflammatory cytokines (particularly tumor necrosis factor α and interleukins IL-6 and IL-8) and increases the expression of epithelial and endothelial adhesion molecules. The following are the major consequences of H1 receptor stimulation:

- Capillary and venous dilation can produce marked hypotension. In the skin, histamine contributes to the wheal-and-flare response; an axon reflex via H1 receptors is responsible for the spread of vasodilation or flare from the oedematous wheal.
- Increased capillary permeability, which produces local edema. This can lead to urticaria, angioedema, and laryngeal edema. The consequent loss of fluid from the circulating blood volume contributes to hypotension.
- Smooth muscle contraction, especially in bronchioles (producing bronchospasm) and the intestine (producing abdominal pain).
- Skin itching (produced by histamine in combination with kinins and prostaglandins).
- Pain due to stimulation of nociceptors.
- Increased antigen-presenting cell capacity, upregulation of Th1 cells, and chemotaxis of eosinophils and neutrophils into affected tissues.

AIM AND OBJECTIVE

This project aims to find the best phytochemicals from *Coleus barbatus* for human histamine H1 receptor protein.

Objective

- To find the active sites.
- To find binding between phytochemicals and h1 receptor protein.
- AMDET studies.
- To get better ligands that can be more effective than commercially availablemedicines which causes side effects

REVIEW OF LITERATURE

Kumar *et al* ., (2014), Studied Phytochemical Screening from Leaf Extracts of The Plant Coleus Forskohlii (Brig) Collected from The Ananthagiri Forest Area, Rangareddy District, Andhra Pradesh, India. The medicinally important plants of Coleus forskohlii were collected from the forest areas of Ananthagiri, Rangareddy District. This plant belongs to the family of Lamiaceae. A total of fourteen (14) phytochemicals were screened from the leaf extracts of the above plant. The analysis was studied in different solvents like methanol, acetone, petroleum ether, and chloroform including the aqueous extracts. The phytochemical analysis revealed the presence of alkaloids, saponins, tannins, flavonoids, terpenoids, coumarins, quinines, cardiac glycosides, Xanthoproteins, glycosides, steroids, phenols, resins, acarboxylic acid group in varying concentrations.

Basu *et al* ., (2017) Studied on Molecular-Docking-Based Anti-Allergic Drug Design. Allergens are foreign proteins that when coming in contact with the part (s) of the human body stimulate the production of immunoglobulin types of proteins (antibodies). These allergens react with antibodies (immunoglobulin type E or IgE) producing allergic reactions, also known as immediate-type hypersensitivity reactions. As much as 20% of the general population may be affected by grass pollen as a major cause of allergic disease. EXPB class of proteins is known in the immunological literature as group-1 grass pollen allergens Molecular docking method can be used to identify the predicted interaction of pollen allergen EXPB1 (Zea m 1), a beta-expansin and group-1 pollen allergen from maize with IgE molecules of human. The World Health Organization recognized allergen immunotherapy, as therapeutic for allergic diseases. RNA Interference (RNAi) is a biological process in which RNA molecules e.g. Small Interfering RNAs (siRNAs) inhibit gene expression, by cleavage and destruction of specific mRNA molecules. The use of Small Interfering RNA (siRNA) is a novel method in the induction of RNA Interference (RNAi), which is a potent method for therapeutics of allergic reactions. Due to various effects of STAT 6 proteins during hypersensitivity reactions caused by pollen allergens, mRNA of the STAT6 gene is selected as the target gene for allergy therapeutics via Post-Transcriptional Gene Silencing (PTGS). Using molecular docking study a specific sense siRNA is identified as an anti-allergic drug to treat allergic asthma during the immediate type of hypersensitivity reaction, caused by Zea m 1 pollen allergen.

G. Ferreira *et al* ., (2015) studied Molecular Docking and Structure-Based Drug Design Strategies

Pharmaceutical research has successfully incorporated a wealth of molecular modeling methods, within a variety of drug discovery programs, to study complex biological and chemical systems. The integration of computational and experimental strategies has been of great value in the identification and development of novel promising compounds. Broadly used in modern drug design, molecular docking methods explore the ligand conformations adopted within the binding sites of macromolecular targets. This approach also estimates the ligand-receptor binding free energy by evaluating critical phenomena involved in the intermolecular recognition process. Today, as a variety of docking algorithms are available, an understanding of the advantages and limitations of each method is of fundamental importance in the development of effective strategies and the generation of relevant results.

Jakhar *et al* ., (2020), studied on Relevance of Molecular Docking Studies in Drug Designing. Molecular Docking is used to position the computer-generated 3D structure ofsmall ligands into a receptor structure in a variety of orientations, conformations, and positions. This method is useful in drug discovery and medicinal chemistry providing insights into molecular recognition. Docking has become an integral part of Computer-Aided Drug Design and Discovery (CADDD). Traditional docking methods suffer from limitations of semi-flexible or static treatment of targets and ligands. Over the last decade, advances in the field of computational, proteomics, and genomics have also led to the development of different docking methods which incorporate protein-ligand flexibility and their different binding conformations. Receptor flexibility accounts for more accurate binding pose predictions and a more rational depiction of protein binding interactions with the ligand. Protein flexibility has been included in generating protein ensembles or dynamic docking methods. Dynamic docking considers solvation, and entropic effects and also fully explores the drug-receptor binding and recognition from both energetic and mechanistic points of view. Although in the fast-paced drug discovery program, dynamic docking is computationally expensive but is being progressively used for screening large compound libraries to identify the potential drugs.

Nataraj *et al* ., (2017) studies Software for molecular docking. The molecular docking methodology explores the behavior of small molecules in the binding site of a target protein. As more protein structures are determined experimentally using X-ray crystallography or nuclear magnetic resonance (NMR) spectroscopy, molecular docking is increasingly used as a tool in drug discovery. Docking against homology-modeled targets also becomes possible for proteins whose structures are not known. With the docking strategies, the draggability of the compounds and their specificity against a particular target can be calculated for further lead optimization processes. Molecular docking programs perform a search algorithm in which the conformation of the ligand is evaluated recursively until the convergence to the minimum energy is reached. Finally, an affinity scoring function, ΔG [U total in kcal/mol], is employed to rank the candidate poses as the sum of the electrostatic and van der Waals energies. The driving forces for these specific interactions in biological systems aim toward complementarities between the shape and electrostatics of the binding site surfaces and the ligand or substrate.

Daniel *et al* ., (1996) studied Molecular docking toward drug discovery. Fuelled by advances in molecular structure determination, tools for structure- based drug design are proliferating rapidly. Lead discovery through searching of ligand databases with molecular docking techniques represents an attractive alternative to high-throughput random screening. The size of commercial databases imposes severe computational constraints on molecular docking, compromising the level of calculational detail permitted for each putative ligand. We describe alternative philosophies for docking which effectively address this challenge. Concerning the dynamic aspects of molecular recognition, these strategies lie along a spectrum of models bounded by the Lock-and-Key and Induced-Fit theories for ligand binding. We explore the potential of a rigid model in exploiting species specificity and

of a tolerant model in predicting absolute ligand binding affinity.

Saikia *et al* ., (2019) studied Molecular Docking: Challenges, Advances and its Use in Drug Discovery Perspective. Molecular docking is a process through which small molecules are docked into the macromolecular structures for scoring their complementary values at the binding sites. It is a vibrant research area with dynamic utility in structure-based drug designing, lead optimization, and biochemical pathway, and drug designing is the most attractive tool. Two pillars for a successful docking experiment are correct pose and affinity prediction. Each program has its advantages and drawbacks concerning its docking accuracy, ranking accuracy, and time-consuming so a general conclusion cannot be drawn. Moreover, users don't always consider sufficient diversity in their test sets which results in certain programs outperforming others. In this review, the prime focus has been laid on the challenges of docking and troubleshooters in existing programs, the underlying algorithmic background of docking, preferences regarding the use of docking programs for best results illustrated with examples, comparison of performance for existing tools, and algorithms, state of art in docking, recent trends of diseases and current drug industries, evidence from clinical trials and post-marketing surveillance are discussed.

Stanzione *et al* ., (2021) studied on Use of molecular docking computational tools in drug discovery. Molecular docking has become an important component of the drug discovery process. Since first being developed in the 1980s, advancements in the power of computer hardware and the increasing number of and ease of access to small molecule and protein structures have contributed to the development of improved methods, making docking more popular in both industrial and academic settings. Over the years, the modalities by which docking is used to assist the different tasks of drug discovery have changed. Although initially developed and used as a standalone method, docking is now mostly employed in combination with other computational approaches within integrated workflows. Despite its invaluable contribution to the drug discovery process, molecular docking is still far from perfect. This chapter will provide an introduction to molecular docking and the different docking procedures with a focus on several considerations and protocols, including protonation states, active site waters, and consensus, that can greatly improve the docking results.

Li *et al* ., (2019) studied An Overview of Scoring Functions Used for Protein-Ligand Interactions in Molecular Docking. Currently, molecular docking is becoming a key tool in drug discovery and molecular modeling applications. The reliability of molecular docking depends on the accuracy of the adopted scoring function, which can guide and determine the ligand poses when thousands of possible poses of ligand are generated. The scoring function can be used to determine the binding mode and site of a ligand, predict binding affinity, and identify the potential drug leads for a given protein target. Despite intensive research over the years, accurate and rapid prediction of protein-ligand interactions is still a challenge in molecular docking. For this reason, this study reviews four basic types of scoring functions, physics-based, empirical, knowledge-based, and machine learning-based scoring functions, based on an up-to-date classification scheme.

Holgate *et al* ., (2008) studied Treatment strategies for allergy and asthma. Allergic diseases have reached epidemic proportions worldwide. An understanding of the cellular and soluble mediators that are involved in allergic inflammatory responses not only helps in understanding the mechanisms of current treatments but is also important for the identification of new targets that are amenable to both small-molecule and biological interventions. There is now considerable optimism with regards to tackling the allergy epidemic in light of improvements in systemic and mucosal allergen-specific immunotherapy, the identification of key cytokines and their receptors that drive T-helper-2- cell polarization, a clearer understanding of the pathways of leukocyte recruitment, and the signaling pathways that

are involved in cell activation and mediator secretion, and new approaches to vaccine development.

Mehta *et al* ., (2021) studied Molecular Modeling of Histamine Receptors—Recent Advances in Drug Discovery. The recent developments of fast reliable docking, virtual screening, and other algorithms gave rise to the discovery of many novel ligands of histamine receptors that could be used forthe treatment of allergic inflammatory disorders, central nervous system pathologies, pain, cancer, and obesity. Furthermore, the pharmacological profiles of ligands indicate that these receptors may be considered targets not only for selective but also for multi-target drugs that could be used for the treatment of complex disorders such as Alzheimer's disease. Therefore, analysis of protein-ligand recognition in the binding site of histamine receptors and also othermolecular targets has become a valuable tool in the drug design toolkit.

Dias *et al* ., (2008) Molecular Docking Algorithms. Using virtual screening of small molecule databases, it is possible to identify new potential inhibitors against a target of interest. Molecular docking is a computer simulation procedure to predict the conformation of a receptor-ligand complex. Each docking program makes use of one or more specific search algorithms, which are the methods used to predict the possible conformations of a binary complex.

Rawiya *et al* ., (2010) Plectranthus barbatus: A Review of Phytochemistry, Ethnobotanical Uses, and Pharmacolog.y. Plectranthus barbatus Andr. is one of the most important species of the genus Plectranthus L′ Herit. (Lamiaceae), with a wide variety of traditional medicinal uses in Hinduand Ayurvedic traditional medicine as well as in the folk medicine of Brazil, tropical Africa, and China. In addition to essential oil, abietane diterpenoids and 8,13-epoxy-land-14-en-11- one diterpenoids are the main constituents found in Plectranthus barbatus. The major ethnobotanical uses are for intestinal disturbance and liver fatigue, respiratory disorders, heart diseases, and certain nervous system disorders. Forskolin as one of the major constituents with its unique adenylyl cyclase activation that underlies the wide range of pharmacological properties could explain the different traditional uses of Plectranthus barbatus. Forskolin is involved in several patented pharmaceutical preparations used as over-the-counter drugs for the treatment of several ailments. However, the water-insoluble nature of forskolin limits its clinical usefulness. Forskolin thus served as a prototype for the development of 6-(3- dimethylaminopropionyl) forskolin hydrochloride (NKH477) as a potent water-soluble forskolin derivative that finds use in the therapy for several diseases, especially in the cardiovascular system.

DISEASE AND PHYTOCHEMICALINFORMATION

Disease Information

The Pathophysiology of Allergic Responses

Allergic disease is estimated to affect around 15-20% of the population of the western world, with a two- to three-fold increase being seen in the past 20-30 years (Royal College of Physicians, 2003). It is a condition that has a huge impact on the lives of those who experience it. A range of immune cells and mediators are responsible for the symptoms of allergy, which can occur both early and late in the overall response. An understanding of the pathophysiology of allergic disease can assist in the management, treatment, and therefore theprevention of allergy. Despite its increasing prevalence, there is a shortage of allergists in the UK with just one consultant allergist per two million of the population compared with oneper 100,000 of the population for other specialties. *(Bousquet et al, 2001)*

Allergic rhinitis

Allergic rhinitis is characterized by the presence of two or more of the following symptoms:

- Nasal itch;
- Sneezing;
- Blockage;
- Rhinorrhoea (a persistent watery discharge).

While there are many causes of rhinitis, it is thought that allergy is the most common, implicated in 50% of all cases *(Skoner, 2001).* The symptoms of allergic rhinitis are often accompanied by conjunctivitis and asthma *(Strachan, 1995).*

Guidelines published in 2001 state that up to 80% of patients with asthma have co-existing rhinitis and that 60-70% of patients with rhinitis also have asthma *(Bousquet et al, 2001).*

Seasonal allergy

The symptoms of allergic disease can occur both seasonally and perennially and are causedby a variety of allergens. Offending allergens can often be identified by matching the timing of symptoms experienced by the patient and the prevalence of allergens at particular times of the year. In the UK, tree pollen is the predominant allergen between February and April and can cause severe symptoms affecting both the upper and lower airways - particularly the pollen of the silver birch. Interestingly, silver birch pollen shares cross-reactivity with some fruits and vegetables such as apples, potatoes, and celery, consumption of which can lead to symptoms such as itching and swelling of the lips, oral mucosa, and soft palate. This ‘oral allergy syndrome’ affects up to 70% of people with birch pollen allergy. Summertime hay fever is most commonly caused by grass pollen allergy and symptoms are experienced from May to July in the UK. As some patients experience their most severe symptoms early in the morning and in the evening, it may be helpful to avoid the outdoors at these times and keep windows closed. The most frequently experienced symptoms occur in the upper airways but the allergen can fragment, reducing in size and reaching the lower airways and resulting in seasonal asthma symptoms. Other seasonal allergens include weed pollens, prevalent during late summer, and molds and fungi, which provoke symptoms usually between July and October.

Perennial allergy

Many allergens provoke symptoms all year round. For example, pet allergy, in particular cat allergen, causes perennial symptoms in sensitized individuals, and severe symptoms can be experienced in both the upper and lower airways. Cat allergen exists in high concentrations in the homes of cat owners, but it has also been shown that a level high enough to provoke symptoms can be carried into public places. Studies have shown that cat allergens can be found in many unusual places, including bus and train seats, cinemas,

and schools. Probably

the most prevalent perennial allergen is that of the house-dust mite. These spider-like creatures are invisible to the naked eye and inhabit bedding and other soft furnishings. Allergic symptoms are caused by the digestive juices in mites' feces. Many patients may associate symptoms with exposure, experiencing, for example, sneezing and a blocked nose after making the bed.

Pathophysiology of allergy

Atopy is the predisposition for producing the antibody IgE, which is defined by the presence of one or more positive skin prick tests (SPT) to common aeroallergens *(Durham andChurch, 2001)*. Allergy is the clinical expression of atopy - the physical symptoms of allergy- related to exposure. The immune response is dependent on the body's two subsets of T- lymphocytes, known as T helper cells TH1 and TH2. In the normal immune response, TH1 cells release a range of mediators to help the body to defend against invasion from parasites, bacteria, and viruses.

In atopic individuals, TH2 cells and their mediators encourage the immune system to recognize allergens as an invader and mount a response against them. Strachan (2000) suggests that because of reduced natural exposure to bacteria and viruses as children, as a result of living in an increasingly sterile environment, allergy is increasing and immune responses are more likely to develop along the TH2 pathway. This principle is widely accepted and is known as the hygiene hypothesis. For allergy to exist, allergen sensitization must first occur. Antigen-presenting cells, such as macrophages and dendritic cells that are present on the mucosal surfaces of the body, detect the allergen. This can occur in many ways, including inhalation into the nose and lungs, through the skin, and the gastrointestinal tract. The antigen-presenting cells come into contact with the allergen which, in people predisposed to atopy, is perceived to be an invader. The allergen is then absorbed, processed, and displayed on the surface of the antigen-presenting cell. This cell then migrates to the T- lymphocyte (T-cell) and presents the allergen, which then stimulates the B-cell to produce antibodies specific to the allergen. These specific antibodies, IgE, are then released, and attach themselves to high-affinity receptors on the surfaces of mast cells in the mucosal surfaces and on basophils in the blood. After the period of sensitization described above, there is a period of latency, and on subsequent re-exposure to the allergen the allergicresponse is triggered: allergen cross-links with the IgE on the surfaces of the mast cell or basophil, causing the cell to 'degranulate' or release inflammatory mediators. These include

largely histamine and other mediators, including cysteinyl leukotrienes, prostaglandins, and kinins. They have different actions in terms of symptoms in different organs.

Allergy in the lung

It is increasingly clear that the pathological event underlying most cases of asthma is chronic inflammation and that the most commonly identified cause of this is the inhalation of allergens *(Platts-Mills et al, 2001)*. Asthma symptoms can occur immediately (early-phase response) or some hours after allergen exposure (late-phase response). Many immune cells and mediators are involved in the asthmatic response and all play

a role in the evolution of both the early and late responses. The early asthmatic response After allergen exposure, inflammatory mediators, including large quantities of histamine, are released from mast cells on the mucosal surfaces. Histamine causes immediate bronchoconstriction and bronchospasm, resulting in narrowing of the small airways (bronchioles). Cysteinyl leukotrienes, also released from mast cells, are also potent bronchoconstrictor of airway smooth muscle, amplifying the action of histamine. Cysteinyl leukotrienes also increasemicrovascular permeability, resulting in edema and narrowing of the airways, and stimulationof the secretion of mucus in the lower respiratory tract *(O'Byrne et al, 2001).*

Prostaglandins, released by mast cells, are also involved in the early-phase response. In the management of allergy, it is important to match the drug with the symptom. In research, inhaled allergen challenge is used to provoke symptoms in allergic volunteers to mimic natural environmental exposure and measure bronchial hyperreactivity. Pre-treatment with a combination of a leukotriene receptor antagonist and an antihistamine can almost completely prevent the early-phase asthmatic response after a controlled allergen challenge, although once the early asthmatic response has occurred introduction of an inhaled bronchodilator is recommended *(British Thoracic Society, 2003)*.

The late asthmatic response A characteristic of the late-phase asthmatic response is the infiltration of the airways with inflammatory cells and mediators, in particular eosinophils, which results in airway narrowing and associated bronchial hyper-responsiveness. Atopic individuals have increased levels of the cytokine inflammatory mediator interleukin 5 (IL-5), which is produced by immune cells such as mast cells and T-lymphocytes. This mediator stimulates the production of eosinophils and also attracts them to the site of inflammation. Eosinophils play an important role in the pathophysiology of asthma, and their migration into the lungs is associated with inflammation and bronchoconstriction. They produce a host of

enzymes, proteins, and mediators that are directly associated with epithelial tissue damage in asthma. This damage contributes to the chronic changes seen, such as airway remodeling and associated airway hyperresponsiveness.

The allergic nose

As with the lung, the allergic response in the nose can be separated into early and late phases. The early-phase reaction After sensitization to an allergen has occurred, and on subsequent re-exposure, cross-linking of allergen on IgE displayed on the surfaces of mast cells in the nasal mucosa causes degranulation. The proinflammatory mediators within are released and act upon cells, nerve endings, and the vasculature in the nose *(Bousquet et al, 1996)*. Histamine plays the biggest role in this process, acting upon nerve endings to produce the symptoms of itch and sneezing, and on the small veins and capillaries, causing vascular permeability, which results in nasal blockage, which is one of the primary symptoms of allergic rhinitis.

The late-phase reaction After the early response in the nose following allergen exposure, inflammatory cells continue to be recruited. These cells and their mediators sensitize the nose to both allergen exposure and non-specific stimuli. This nasal hyperresponsiveness is a characteristic of the late-phase response; sufferers describe allergy-like symptoms on exposure to a range of stimuli, including strong smells such as bleach,

hairspray, and tobacco smoke. During this phase 'priming' occurs, where nasal cells are ready to respond to stimuli so that often a smaller amount of allergen is needed to provoke allergic symptoms. As with the asthmatic late response, eosinophils play an important role in the late-phase response in the nose, with the enzymes and proteins released causing tissue damage and further inflammation. Again, matching drug to symptom is crucial in the management of allergic rhinitis, with the early phase of the allergic response, which is largely due to histamine, being treated with a long-acting antihistamine. The later, more chronic symptoms, should be treatedwith a topical nasal corticosteroid. This combination is the preferred and first-line treatment for allergic rhinitis.

Dust Allergy Symptoms

Allergy symptoms are classified as mild, moderate, or severe:

- Mild reactions include local symptoms (affecting a specific area of your body) such as a rash or hives, itchiness, watery/red eyes, hay fever, and runny nose. Mild reactions do not spread to other parts of your body.
- Moderate reactions include symptoms that spread to other parts of your body. Symptoms may include itchiness, hives, and/or swelling, and trouble breathing.
- A severe allergic reaction, known as anaphylaxis, is a rare, life-threatening emergencyin which your body's response to the allergen is sudden and affects the whole body. Anaphylaxis may begin with severe itching of your eyes or face. Within minutes, more serious symptoms appear, including throat swelling (which could cause problems with swallowing and breathing), abdominal pain, cramps, vomiting, diarrhea, hives, and swelling (angioedema). You may also have mental confusion or dizziness, since anaphylaxis may cause a drop in blood pressure.

Factors causing allergic effects

Dust mites

Dust mites – sometimes called bed mites – are the most common cause of an allergy to house dust. Dust mites live and multiply easily in warm, humid places. They prefer temperatures at or above 70 degrees Fahrenheit with humidity of 75 to 80 percent. They die when the humidity falls below 50 percent. They are not usually found in dry climates. Dust mite particles are often found in pillows, mattresses, carpeting, and upholstered furniture. They float into the air when anyone vacuums, walks on a carpet, or disturbs bedding and they settleonce the disturbance is over. Dust mites are a common cause of asthma in children. A house does not need to be visibly dirty to trigger a dust mite allergy reaction. The particles are too tiny to be seen and often cannot be removed using normal cleaning procedures. A vigorous cleaning can make an allergic person's symptoms worse.

Cockroaches

Cockroaches live in all types of buildings and neighborhoods. Some people develop allergy symptoms when they are around cockroaches. Tiny particles from the cockroach are a common component of

household dust and maybe the true cause of a dust allergy.

Mold

Mold is a fungus that makes spores that float in the air. When people with a mold allergy inhale the spores, they get allergy symptoms. There are many different kinds of mold. Molds

live everywhere—on logs and fallen leaves, and in moist places like bathrooms and kitchens. Tiny mold particles and spores are a common component of household dust and maybe the true cause of a dust allergy.

Pollen

Pollen comes from trees, grasses, flowers, and weeds. People can be allergic to different types of pollen. For instance, some people are allergic to pollen from only beech trees; others are allergic to pollen from only certain kinds of grasses. Pollen is a common component of household dust and maybe the true cause of a dust allergy.

Animal hair, fur, and feathers

Pets can cause problems for allergic patients in several ways. Their dander (skin flakes), saliva, and urine can cause an allergic reaction, especially when combined with household dust. In households with birds, feathers and bird droppings can also become embedded in household dust and cause problems for people who are allergic to them.

Treatment

If you think you may have an allergy to any of the components of house dust, see an allergist. To pinpoint the cause of your symptoms, the allergist will ask detailed questions about your work and home environments, family medical history, frequency and severity of symptoms, exposure to pets, and other possible triggers. Sometimes the medical interview will reveal a likely culprit—for instance, a girl who gets a stuffy nose every time she plays with a friend's cat might have an allergy to cats or the dust infused with cat hair in her friend's house. Often an allergist will need to conduct a skin test to determine exactly what is triggering an allergic reaction. Skin tests involve using a small, sterile probe to prick the skin with extracts from common allergens, such as tree pollen and pet dander, and observing the reaction. A positive reaction may indicate that you are allergic to that substance. Occasionally, your allergist mayorder a blood test and a skin test to confirm an allergy. *(Bousquet et al, 1996)*

Common Medications

Milder symptoms:

- Antihistamines eg: Allegra, Zyrtec
- Decongestanats eg: Sudafed, Contact
- Nasal Steroid/ Nasal Sprays eg: Flonase, Nasonex
- Cromolyn Sodium
- Nasal AntihistaminsesAsthma Medications:
- Inhaled bronchodilators
- Inhaled steroids
- Oral Bronchodilators (theophylline)
- Oral Anti-Leukotrines

Eg: Montelukast (Singular) Zafirlukast (Accolatle)Zileuton (Zyflo)

- Vaccine Type

Eg: Omalizumab (Xolair) Dupliumb (Dupixent) Reslizumab (Linqair) Benralizumb (Fasenra) Mepolizumab (Nucala)

- Immunotherapy

Eg: allergy shot therapy/allergy oral immunotherapy

Management

To manage a dust allergy, it's best to avoid the things most likely to cause an allergic reaction. Here are some simple steps to reduce exposure to indoor dust:

- Opt for wood flooring over wall-to-wall carpets when possible, especially in bedrooms. Clean your house regularly, using a central vacuum or a vacuum with a HEPA filter. If you are allergic, wear an N95 filter mask while dusting, sweeping, or vacuuming. Use "mite-proof" cases on your mattresses and pillows. Wash all bed linens regularly, using hot water. Keep a HEPA air cleaner running in the allergic person's bedroom.
- Keep pets out of the allergic person's bedroom at all times.
- Keep all unrefrigerated food covered; dispose of food waste in a tightly sealed garbage can.
- If cockroaches are a known problem, use roach traps and schedule regular visits by z professional pest control service.
- Install a high-efficiency media filter with a MERV rating of 11 or 12 in the furnace and the air conditioning unit. Leave the fan on to create a "whole house" air filter that removes particulates. Change the filter at least every three months (with the change ofthe seasons) to keep the air clean year-round. Have your heating and air conditioning units inspected and serviced every six months.

- Get in the habit of using a hygrometer to measure the humidity in your home; keep the humidity level below 55 percent. If you live in a humid or sticky climate, you may find it helpful to use a dehumidifier. You may use a vent fan for removing moisture in bathrooms and the kitchen. Repairing all water leaks will also help keep moisture away.

Medical Plant – Phytochemical Information

Coleus barbatus

Coleus barbatus, also known by the synonyms Plectranthus barbatus and incorrectly *Coleus forskalaei* (and other spellings of this epithet), is a tropical perennial plant related to the typical coleus species. It produces forskolin, an extract useful for pharmaceutical preparations and research in cell biology. *Coleus barbatus* was first described by Henry Cranke Andrews in 1810 as Plectranthus barbatus. It was transfered to Coleus by Bentham in 1830. Although Coleus was previously sunk into Plectranthus, the original binomial was revived in a major study of the subtribe Plectranthinae in 2019. There has been some confusion over the synonyms of this species.

Figure 1:*Coleus barbatus*

Coleus is a plant that has been used since ancient times to treat heart disorders such as high blood pressure and chest pain (angina), as well as respiratory disorders such as asthma. Forskolin is a chemical found in the roots of the coleus plant. When taken by mouth, coleus is used to treat allergies, dry eye, skin conditions such as eczema and psoriasis, obesity, painful menstrual periods, irritable bowel syndrome (IBS), urinary tract infections (UTI), bladder infections, advanced cancer, blood clots, sexual problems in men, trouble sleeping

(insomnia), and convulsions. Healthcare providers sometimes give coleus intravenously (by IV) for heart failure. Some people breathe in (inhale) coleus powder for asthma. Coleus drops are used in the eyes to treat glaucoma. Herbal product manufacturers are now producing Coleus extracts that contain high levels of forskolin. These preparations are being promoted for the same conditions for which forskolin has been traditionally used. However, currently, there is no reliable scientific information that shows Coleus extracts taken by mouth are effective.

Uses & Effectiveness

Insufficient Evidence to Rate Effectiveness for **Asthma**. It is not known if coleus is beneficial for treating asthma because research findings are inconsistent. Some research shows that inhaling a chemical from coleus called forskolin might improve breathing. Some research shows that taking forskolin by mouth might reduce asthma attacks, but other research shows no benefit. Dry eye. Early research suggests that taking a specific combination supplement (Kronk, SOOFT Italia) containing coleus for 30 days moderately decreases dry eye symptoms compared to a placebo. Erectile dysfunction (ED). Early research suggests that injecting coleus into the base of the penis along with the drugs phentolamine, papaverine, and prostaglandin E1 improves sexual function in men with ED.

High blood pressure. Early research shows that taking coleus root tuber or coleus whole root tablets for 2 months slightly decreases blood pressure in elderly people with high blood pressure. A heart condition is called idiopathic congestive cardiomyopathy. Some research shows that giving forskolin, a chemical found in coleus, by injection improves the function of the heart in people with a heart condition called congestive cardiomyopathy.

Glaucoma. Early research suggests that taking a specific combination supplement *(Kronk Soft Italia SpA, Montegiorgio, Italy)* containing forskolin may slightly decrease eye blood pressure in people with glaucoma. Other research shows that taking a different specific product *(Gangliolife, SOOFT Italia)* in addition to prescription drug therapy decreases eye blood pressure in people with glaucoma.

Obesity. Early research shows that taking a specific coleus supplement does not decrease weight, but modestly decreases body fat in overweight and obese men. However, other early research has found no benefit for weight or fat loss.

- Allergies.
- Blood clots.
- Cancer.
- Chest pain.
- Insomnia.
- Irritable bowel syndrome (IBS).
- Period pains.
- Seizures.
- Skin.
- Urinary tract infections (UTIs) and bladder infections.

- Other conditions.

Phytochemical Composition

- Essential oil

Contains the following: Alpha-Humulene, Alpha-Phellandrene, Alpha-Pinene, Alpha- Terpinene, Alpha-Terpineol, Alpha-Terpinolene, Beta-Caryophyllene, Beta-Pinene, Borneol, Borneol-Acetate, Camphene, Camphor, Car-3-Ene, Carvacrol, Copaene, Gamma-Terpinene, Linalool, Linalyl-Acetate, Myrcene, P-Cymene, Piperitone, Terpinene-4-Ol.

Stem Contains the following: (+)-Ferruginol, 20-Deoxocarnosol, 6-Alpha-Hydroxy-Carnosol, arbatusol, Cariocal, Coleus-Barbatus-Seco-Abientane-Diterpene-1, Coleus-Barbatus-Seco- Diterpene-2.

Root Contains the following: 1,9-Dideoxycoleonol, 1,9-Dideoxyforskolin, 1-Acetoxy-Coleosol 1- Deoxyforskolin, 6-Beta-7-Beta-Dihydroxy-8,13-Epoxy-Labd-14-En-11-One, 7beta,9alpha-Trihydroxy-8,13-Epoxy-Labd-14-En-11-One, 6beta-Hydroxy-8,13- Epoxy-Labd-14-En-11-One, 7-Beta-Acetoxy-1-Alpha-6-Beta-Dihydroxy-8,13-Epoxy- Labd-14-En-11-One, 7-Beta-Acetoxy-6-Beta-Hydroxy-8,13-Epoxy-Labd-14-En-11-One, 7beta-Acetoxy-6beta,9alpha-Dihydroxy-8,13-Epoxy-Labd-14-En-11-One, 8,13-Epoxy-Labd-14-En-11-One, 9-Alpha-Hydroxy-8,13-Epoxy-Labd-14-En-11-One, Caffeic-Acid, Coleforsin, Coleforsine, Coleol, Coleonol-B, Coleonol-C, Coleonol-D, Coleonolic-Acid, Coleonone, Coleoside, Coleoside-B, Coleosol, Crocetin-Dialdehyde, Deacetyl-Forskolin, Deoxycoleonol, Forskolin.

Leaf Contains the following: (+)-Ferruginol, 16(R)-Plectrinon-A, 3beta-Hydroxy-3- Deoxybarbatusin, 6beta-Hydroxy-Carnosol, Allyl-Royleanone, Barbatusin, Barbatusol, Coleon-E, Coleon-F, Coleon-O, Coleonol, Cyclobutatusin, Plectrin, Plectrinon-B Shoot Contains the following: Crocetin-Dialdehyde, Forskolin.

MATERIALS

Database

RCSB PDB

The Protein Data Bank (PDB) is a database for the three-dimensional structural data of large biological molecules, such as proteins and nucleic acids. The data, typically obtained by X- ray crystallography, NMR spectroscopy, or, increasingly, cryo-electron microscopy, andsubmitted by biologists and biochemists from around the world, are freely accessible on the Internet via the websites of its member organizations (PDBe, PDBj, RCSB, and BMRB).

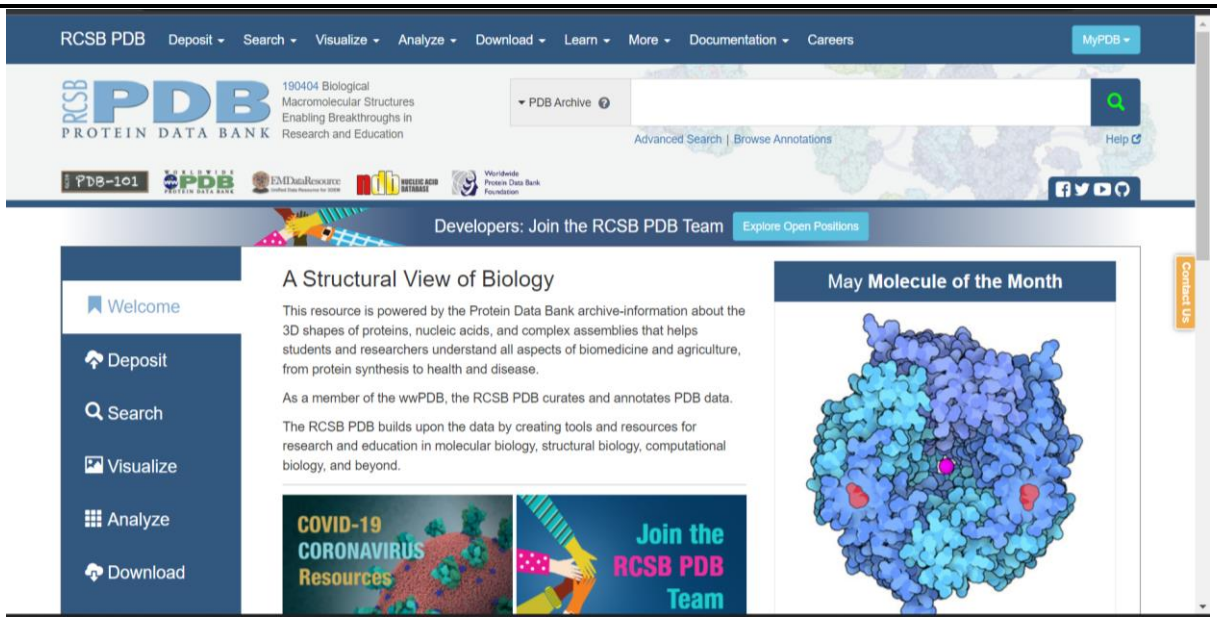


Figure 2: Home Page of PDB

CASTp

Computed Atlas of Surface Topography of Proteins (CASTp) aims to provide a comprehensive and detailed quantitative characterization of topographic features of the protein, which is now updated to version 3.0. Since its release in 2006, the CASTp server has had ~ 45 000 visits and fulfills ~ 33 000 calculation requests annually. CASTp has been proven as a confident tool for a wide range of research, including investigations of signaling receptors, discoveries of cancer therapeutics, understanding of the mechanism of drug actions, studies of immune disorder diseases, analysis of protein–nanoparticle interactions,

inference of protein functions and development of high-throughput computational tools. This server is maintained by Jie Liang's lab at the University of Illinois at Chicago.

For the calculation strategy of CASTp, alpha-shape and discrete-flow methods are applied to the protein binding site, also the measurement of pocket-size by the program of CAST by *Liang et al. in 1998*, then updated by *Tian et al. in 2018*.

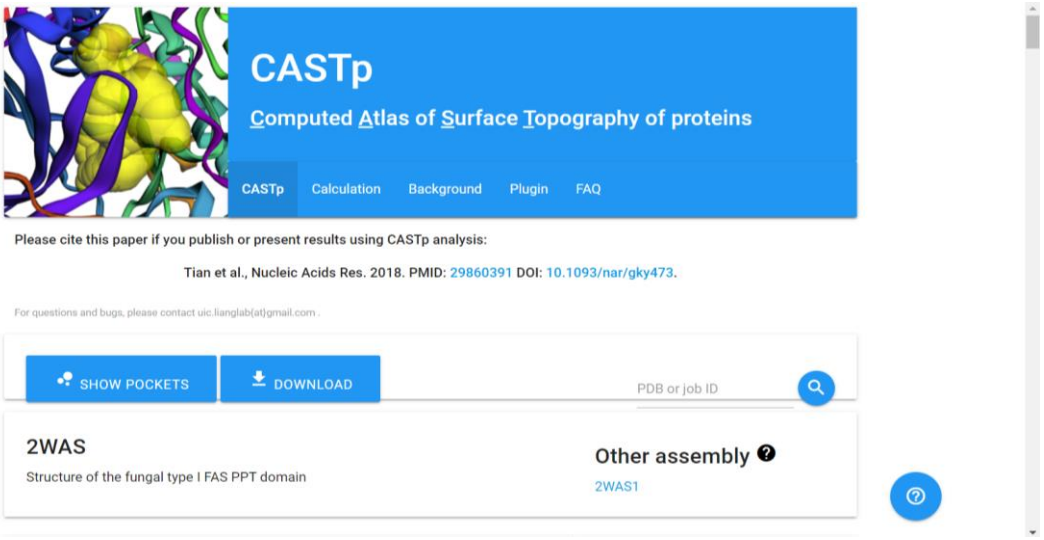


Figure 3: Home Page of Cast p

PubChem

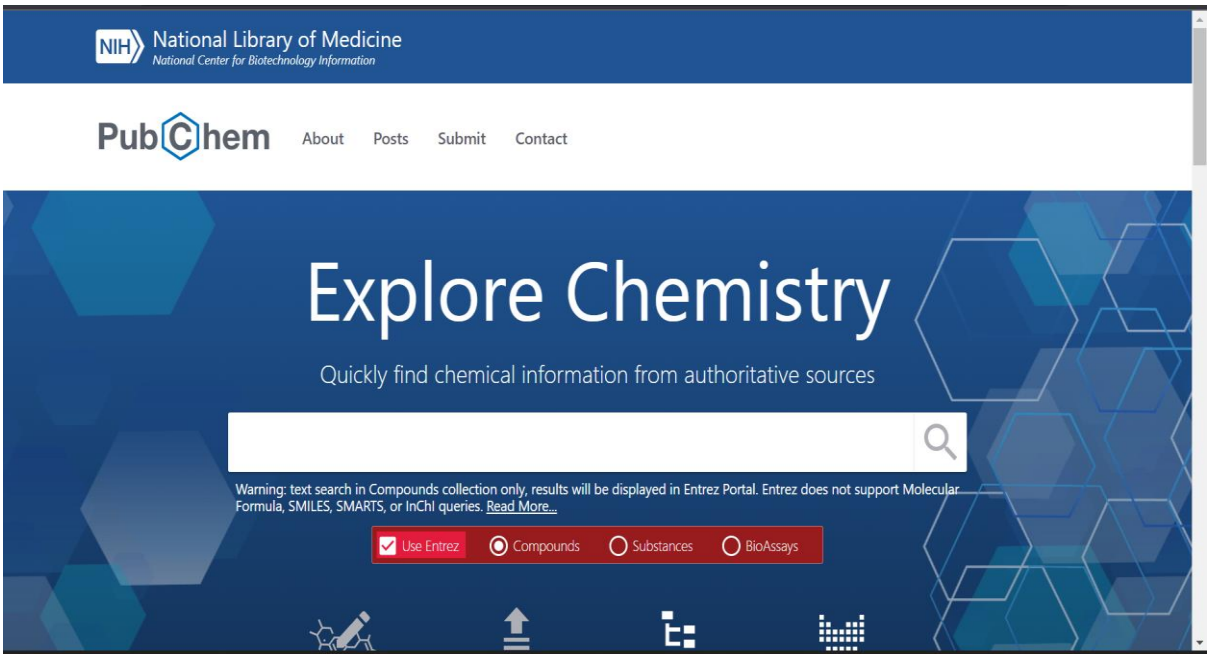


Figure 4: Home Page of PubChem

PubChem is a database of chemical molecules and their activities against biological assays. The system is maintained by the National Center for Biotechnology Information (NCBI), a component of the National Library of Medicine, which is part of the United States National Institutes of Health (NIH). PubChem can be accessed for free through a web user interface. Millions of compound structures and descriptive datasets can be freely downloaded via FTP. PubChem contains multiple substance descriptions and small molecules with fewer than 100 atoms and 1,000 bonds. PubChem contains its online molecule editor with SMILES/SMARTS and InChI support that allows the import and export of all common chemical file formats to search for structures and fragments. Each hit provides information about synonyms, chemical properties, and chemical structure including SMILES and InChI strings, bioactivity, and links to structurally related compounds and other NCBI databaseslike PubMed. In the text search form, the database fields can be searched by adding the fieldname in square brackets to the search term. A numeric range is represented by two numbers separated by a colon.

Swissdock

SwissDock is a webserver dedicated to carrying out protein-ligand docking simulation intuitively and elegantly. Most life science processes involve, at the atomic scale, recognition between two molecules. The SwissDock website is available onlineat http://www.swissdock.ch.

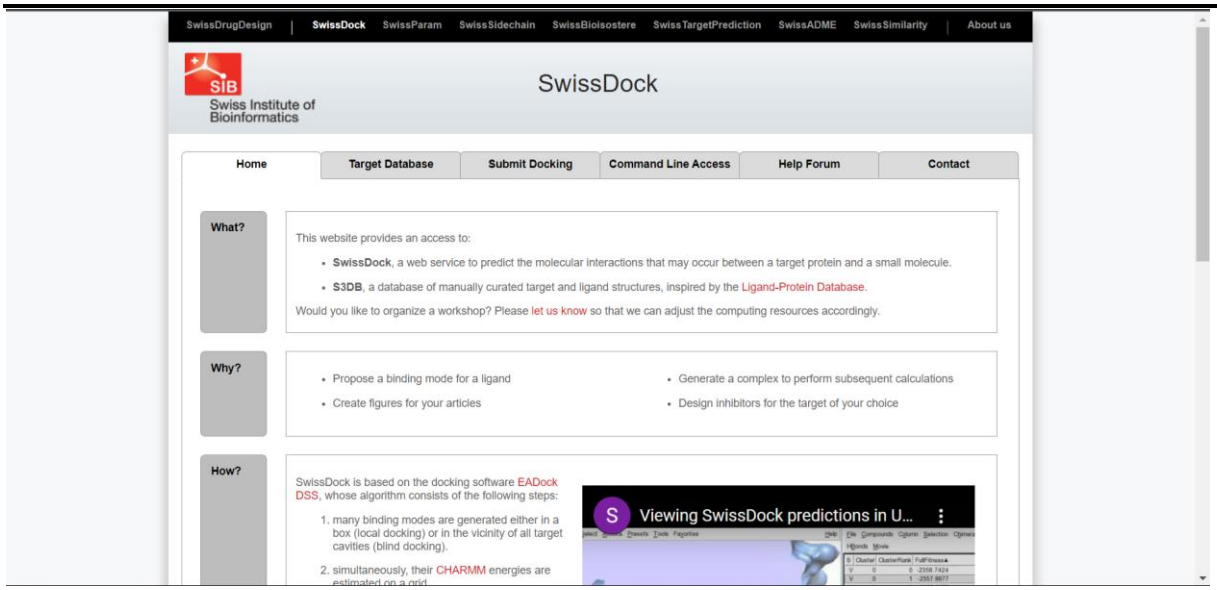


Figure 5: Home Page of Swissdock

SwissADME

ADME is an abbreviation in pharmacokinetics and pharmacology for "absorption,distribution, metabolism, and excretion", and describes the disposition of a pharmaceutical compound within an organism. The four criteria all influence the drug levels and kinetics of drug exposure to the tissues and hence influence the performance and pharmacologicalactivity of the compound as a drug. Sometimes, liberation and/or toxicity are also considered,yielding LDME, ADMET, or ADMET.

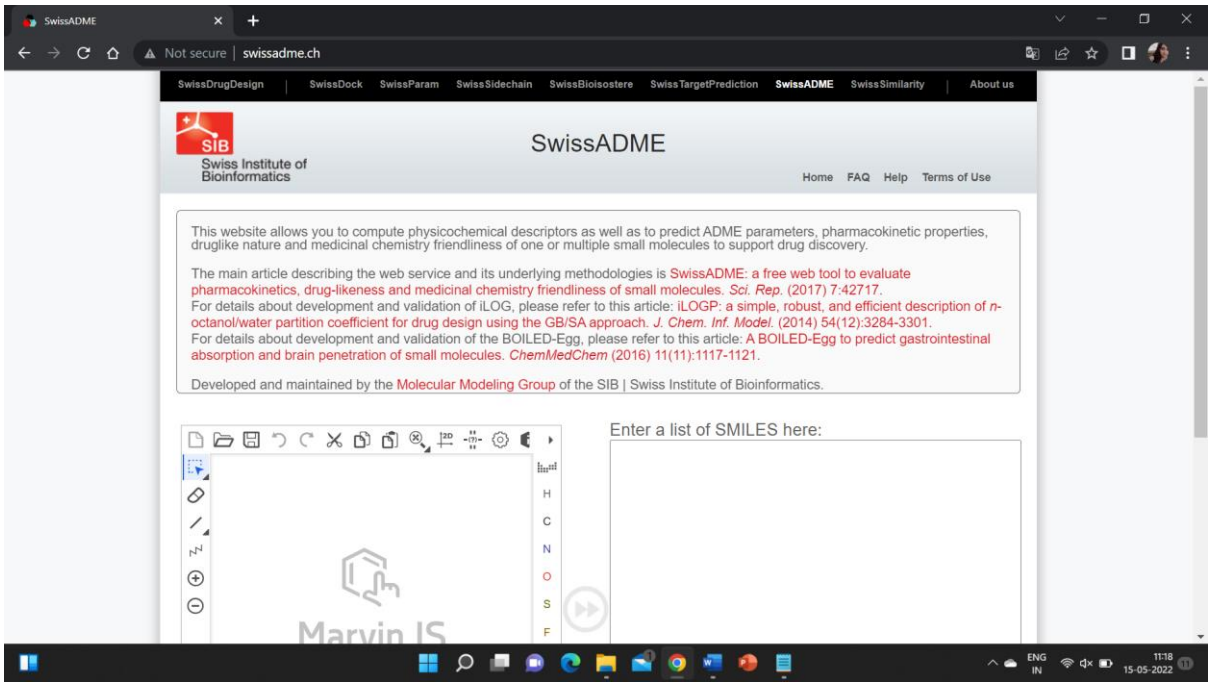
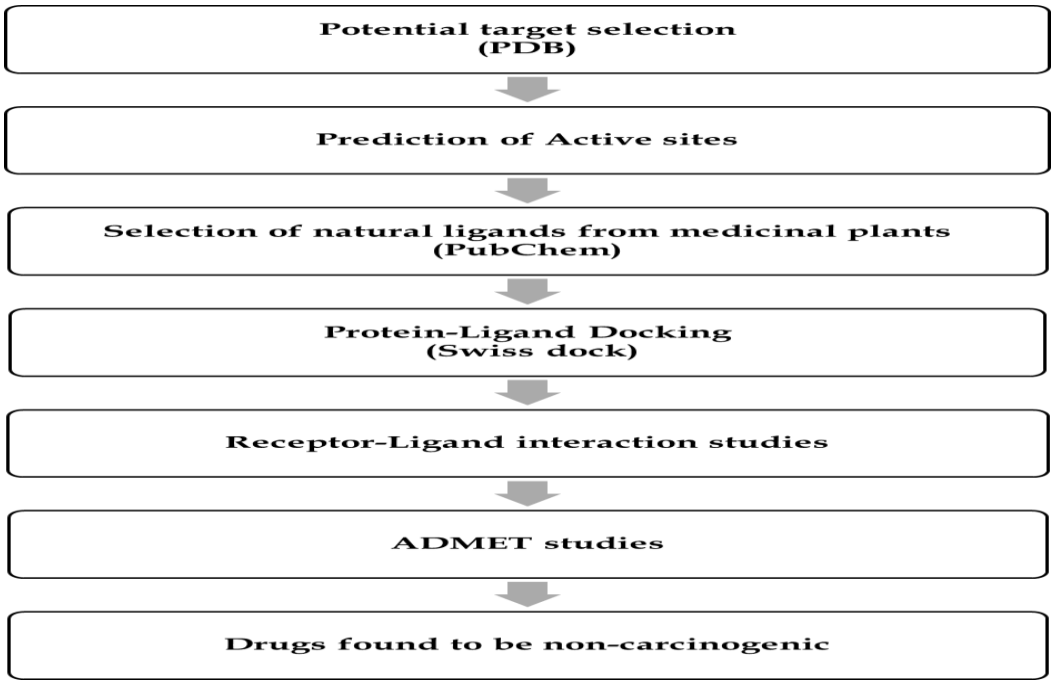


Figure 6: Home Page of Swiss ADME

Methodology



RESULT

Target – histamine H1 receptor protein

The Target is histamine H1 receptor protein visualized in the swissdock server. This PDB Structure is in .pdb file format for docking studies. The target-receptor details are given below:

Details of the target site

Target Name	Target Type	PDB ID
Histamine h1 receptor protein	Successful target	3RZE

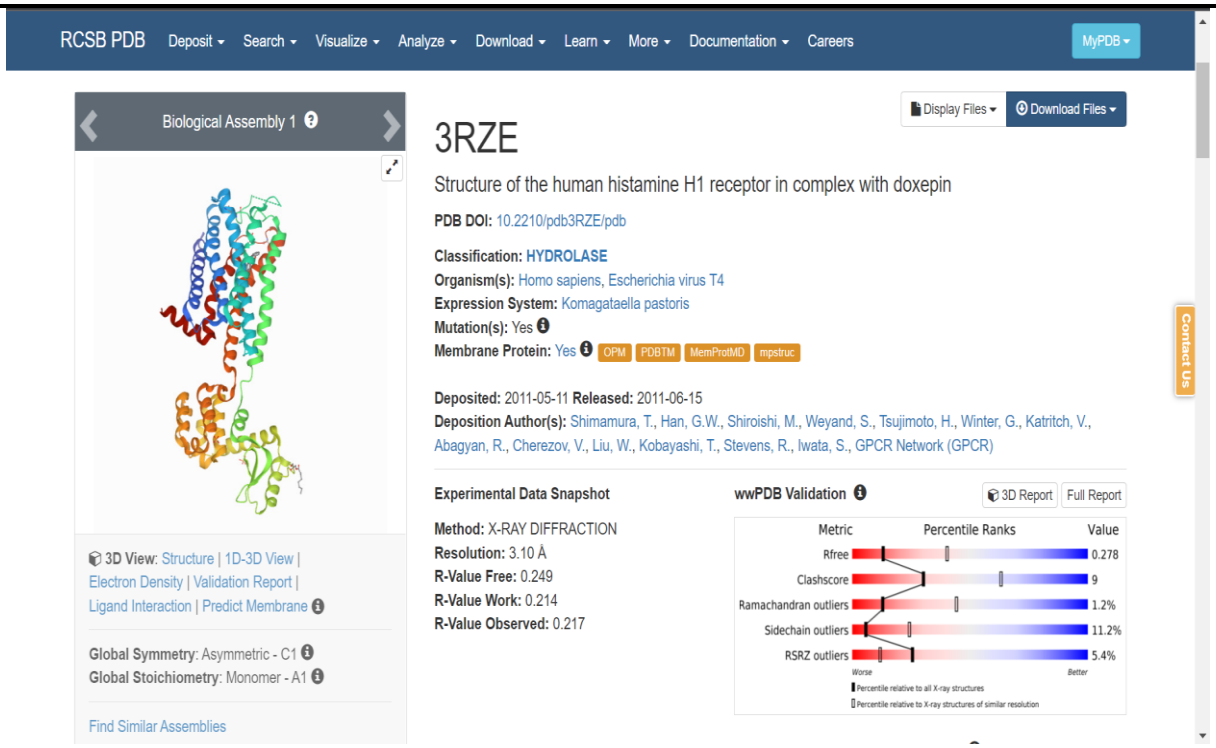


Figure 7: 3D Structure of Histamine H1 Receptor protein

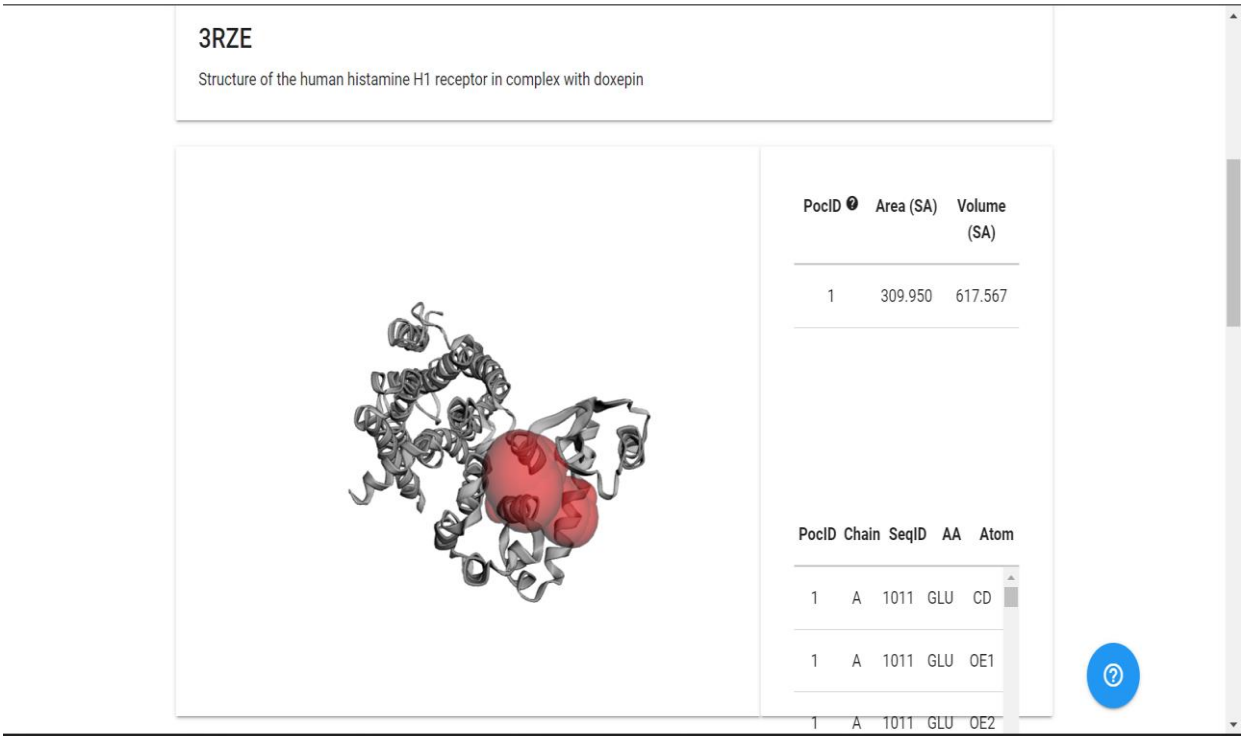


Figure 7: active site

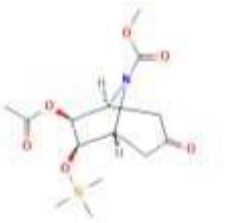
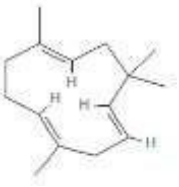
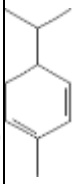
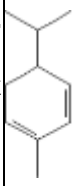
The active sites are represented in red colur. A total of 66 active sites amino acids are found in histamine h1 receptor protein. Some are listed below:

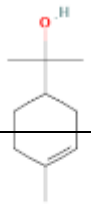
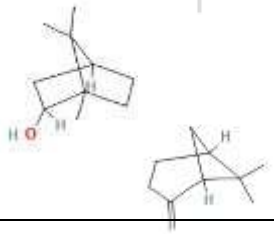
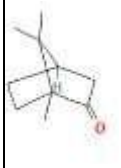
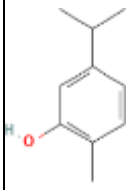
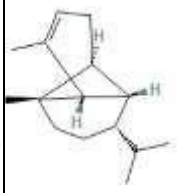
:**GLU**	1022A
TYR	1024A
THR	1026A
ILE	1029A
GLY	1030A
HIS	1031A
LEU	1032A
THR	1034A
ASP	1070A
ALA	1073A
ALA	1074A
VAL	1103A
PHE	1104A
GLN	1105A
MET	1106A
GLY	1107A
GLU	1108A
TRP	1138A
GLN	1141A
THR	1142A
ARG	1142A

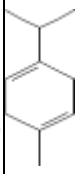
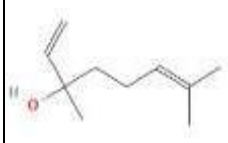
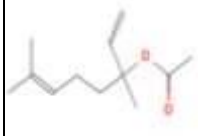
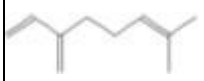
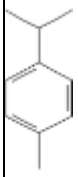
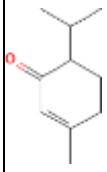
Table 2: active site residue

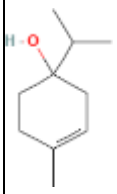
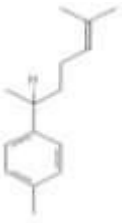
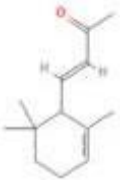
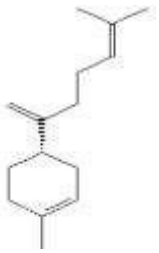
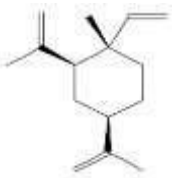
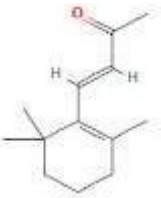
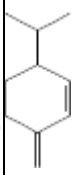
Ligand-Phytochemicals

The ligands were screened by the Lipinski rule of five (RO5). They are listed below:

SL: NO:	MPOUNDNAME	PROPERTIES	2D STRUCTURE
1.	7-Beta-Acetoxy-8	Molecular FormulaC14H23NO6Si Molecular Weight 329.42 Hydrogen Bond Donor Count0 Hydrogen Bond Acceptor Count 6Rotatable Bond Count 5	
2.	Alpha-Humulene Humulene	Molecular Formula C15H24 Molecular Weight 204.35 Hydrogen Bond Donor Count0 Hydrogen Bond Acceptor Countn0 Rotatable Bond Count0	
3.	Alpha-Phellandrene	Molecular Formula C10H16 Molecular Weight 136.23 Hydrogen Bond Donor Count0 Hydrogen Bond Acceptor Count 0 Rotatable Bond Count1	
4.	Alpha-Pinene	Molecular Formula C10H16 Molecular Weight 136.23 Hydrogen Bond Donor Count0 Hydrogen Bond Acceptor Count 0Rotatable Bond Count 0	
5.	Alpha-Terpinene	Molecular Formula C10H16 Molecular Weight 136.23 Hydrogen Bond Donor Count0 Hydrogen Bond Acceptor Count 0Rotatable Bond Count 1	
6.	Alpha-Terpineol	Molecular Formula C10H18O Molecular Weight 154.25 Hydrogen Bond Donor Count 1 Hydrogen Bond Acceptor Count 1Rotatable Bond Count 1	

7.	Beta-Pinene	Molecular Formula C10H16 Molecular Weight 136.23 Hydrogen Bond Donor Count0 Hydrogen Bond Acceptor Count 0 Rotatable Bond Count 0	
8.	Borneol	Molecular Formula C10H18O Molecular Weight 154.25 Hydrogen Bond Donor Count1 Hydrogen Bond Acceptor Count 1 Rotatable Bond Count0	
9.	Camphene	Molecular Formula C10H16 Molecular Weight 136.23 Hydrogen Bond Donor Count0 Hydrogen Bond Acceptor Count 0 Rotatable Bond Count0	
10.	Camphor	Molecular Formula C10H16O Molecular Weight 152.23 Hydrogen Bond Donor Count0 Hydrogen Bond Acceptor Count 1 Rotatable Bond Count0	
11.	Carvacrol	Molecular Formula C10H14O Molecular Weight 150.22 Hydrogen Bond Donor Count1 Hydrogen Bond Acceptor Count 1 Rotatable Bond Count1	
12.	Copaene	Molecular Formula C15H24 Molecular Weight 204.35 Hydrogen Bond Donor Count0 Hydrogen Bond Acceptor Count 0 Rotatable Bond Count1	

13.	Gamma-Terpinene	Molecular Formula C10H16 Molecular Weight 136.23 Hydrogen Bond Donor Count0 Hydrogen Bond Acceptor Count 0 Rotatable Bond Count1	
14.	Linalool	Molecular Formula C10H18O or (CH3)2C=CH(CH2)2C(CH3)(OH)CH =CH2 Molecular Weight 154.25 Hydrogen Bond Donor Count1 Hydrogen Bond Acceptor Count 1 Rotatable Bond Count4	
15.	Linalyl-Acetate	Molecular Formula C12H20O2 or CH3COOC10H17 Molecular Weight 196.29 Hydrogen Bond Donor Count 0 Hydrogen Bond Acceptor Count 2 Rotatable Bond Count 6	
16.	Myrcene	Molecular Formula C10H16 Molecular Weight 136.23 Hydrogen Bond Donor Count0 Hydrogen Bond Acceptor Count 0 Rotatable Bond Count 4	
17.	P-Cymene	Molecular Formula C10H14 or CH3C6H4CH(CH3)2 Molecular Weight 134.22 Hydrogen Bond Donor Count0 Hydrogen Bond Acceptor Count 0 Rotatable Bond Count 1	
18.	Pipertone	Molecular Formula C10H16O Molecular Weight 152.23 Hydrogen Bond Donor Count0 Hydrogen Bond Acceptor Count 1 Rotatable Bond Count1	

19.	Terpinene-4-Ol	Molecular Formula C10H18O Molecular Weight 154.25 Hydrogen Bond Donor Count1 Hydrogen Bond Acceptor Count 1 Rotatable Bond Count1	
20.	Alpha-Curcumene	Molecular Formula C15H22 Molecular Weight 202.33 Hydrogen Bond Donor Count0 Hydrogen Bond Acceptor Count 0 Rotatable Bond Count4	
21.	Alpha-Ionone	Molecular Formula C13H20O Molecular Weight 192.30 Hydrogen Bond Donor Count0 Hydrogen Bond Acceptor Count 1 Rotatable Bond Count2	
22.	Beta-Bisabolene	Molecular Formula C15H24 Molecular Weight 204.35 Hydrogen Bond Donor Count0 Hydrogen Bond Acceptor Count 0 Rotatable Bond Count4	
23.	Beta-Elemene	Molecular Formula C15H24 Molecular Weight 204.35 Hydrogen Bond Donor Count0 Hydrogen Bond Acceptor Count 0 Rotatable Bond Count3	
24.	Beta- Ionone	Molecular Formula C13H20O Molecular Weight 192.30 Hydrogen Bond Donor Count0 Hydrogen Bond Acceptor Count 1 Rotatable Bond Count2	
25.	Beta-Phellandrene	Molecular Formula C10H16 Molecular Weight 136.23 Hydrogen Bond Donor Count0 Hydrogen Bond Acceptor Count 0 Rotatable Bond Count1	

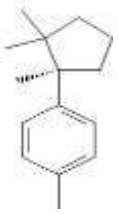
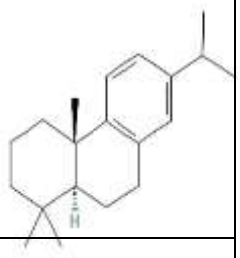
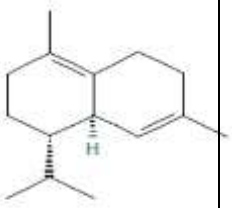
26.	Cuparene	Molecular Formula C15H22 Molecular Weight 202.33 Hydrogen Bond Donor Count0 Hydrogen Bond Acceptor Count 0 Rotatable Bond Count1	
27.	Dehydroabietane	Molecular Formula C20H30 Molecular Weight 270.5 Hydrogen Bond Donor Count0 Hydrogen Bond Acceptor Count 0 Rotatable Bond Count1	
28.	Delta-Cadinene	Molecular Formula C15H24 Molecular Weight 204.35 Hydrogen Bond Donor Count0 Hydrogen Bond Acceptor Count 0 Rotatable Bond Count1	

Table 3: Ligand-Phytochemicals

Molecular Docking

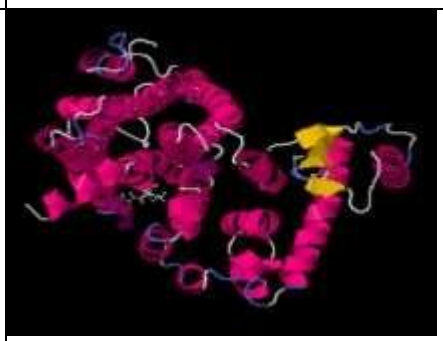
The phytochemicals are docked with target histamine h1 receptor protein. The best phytochemicals are screened according to the docking score value. The least score value ligand s is taken as the best phytochemical. The ligands and the docking score values are listed below:

Sl no:	Ligand	Docking score
1	7-Beta-Acetoxy-8	No interaction
2	Alpha-Humulene / Humulene	-5.35
3	Alpha-Phellandrene	-5.29
4	Alpha-Pinene	-5.37
5	Alpha-Terpinene	No interaction
6	Alpha-Terpineol	-6.44
7	Beta-Pinene	-5.13
8	Borneol	-5.38
9	Camphene	-6.46
10	Camphor	-6.58
11	Carvacrol	-6.16

12	Copaene	No interaction
13	Gamma-Terpinene	No interaction
14	Linalool	-6.42
15	Linalyl-Acetate	No interaction
16	Myrcene	-6.83
17	P-Cymene	-6.27
18	Pipertone	No interaction
19	Terpinene-4-Ol	No interaction
20	Alpha-Curcumene	-6.97
21	Alpha-Ionone	-7.10
22	Beta-Bisabolene	No interaction
23	Beta-Elemene	No interaction
24	Beta- Ionone	-6.75
25	Beta-Phellandrene	-6.16
26	Cuparene	No interaction
27	Dehydroabietane	No interaction
28	Delta-Cadinene	No interaction

Table 4: Molecular Docking Score

The best docking results are as follows:

Sl.No	Ligand name	Molecular docking
1	Alpha – Ionone	
2	Alpha- Curcumene	

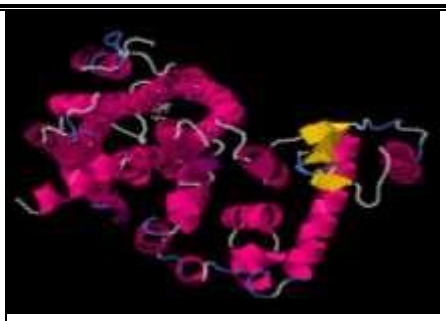
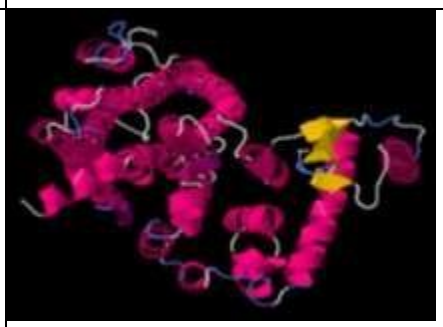
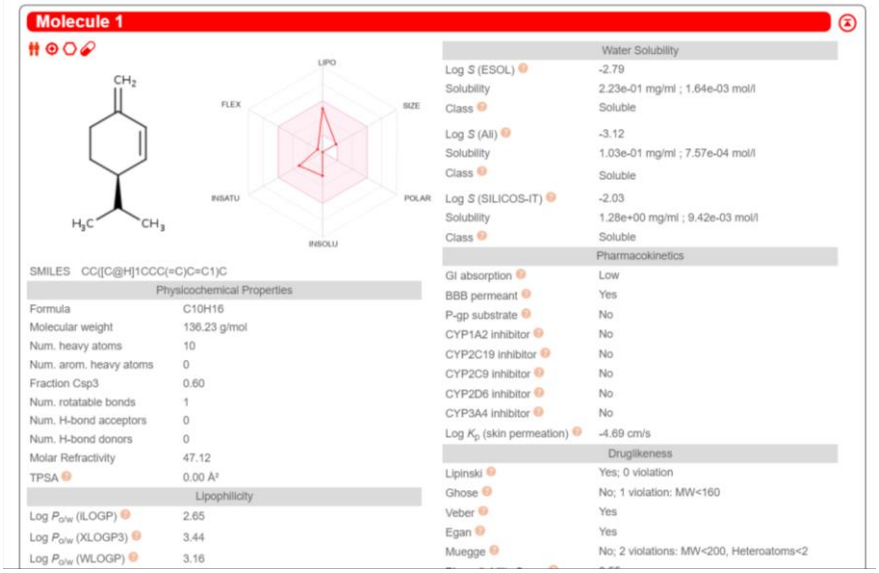
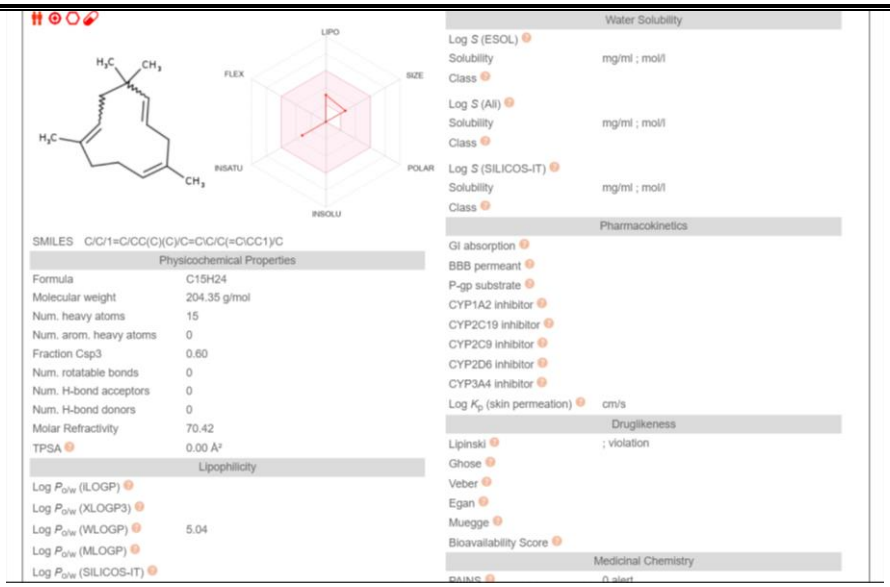
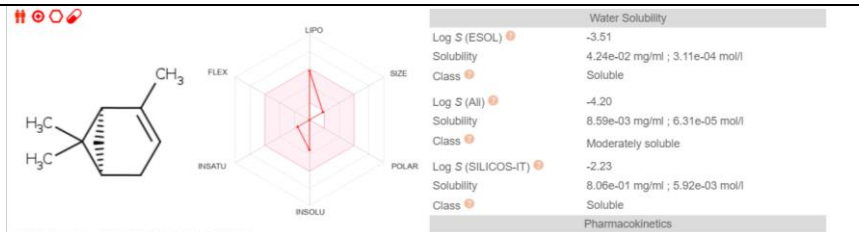
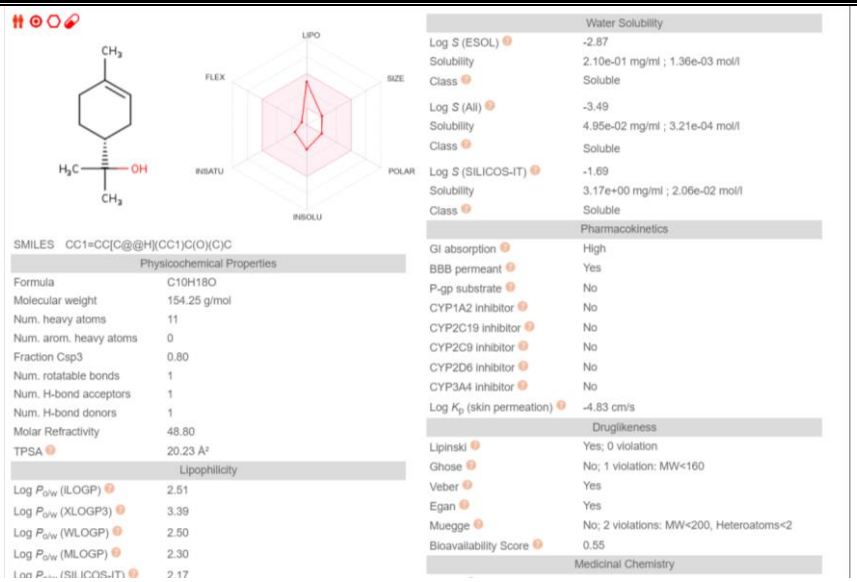
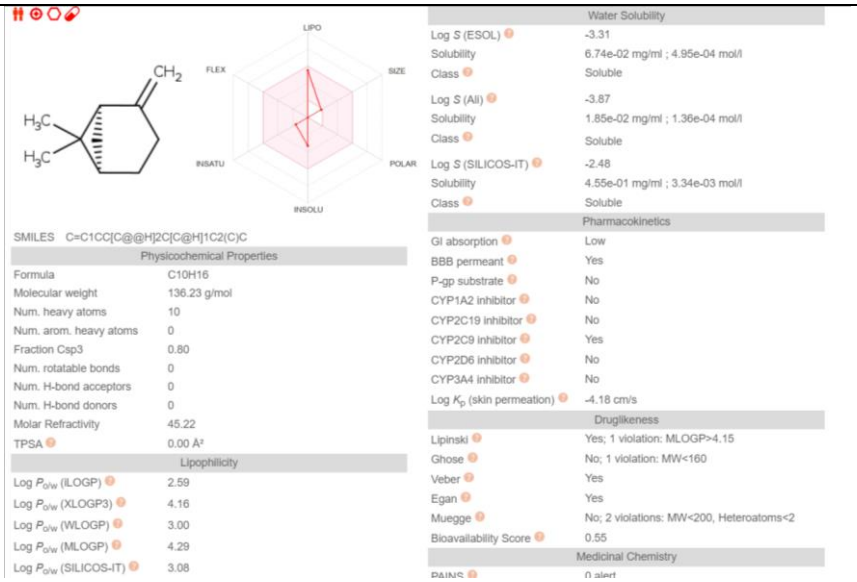
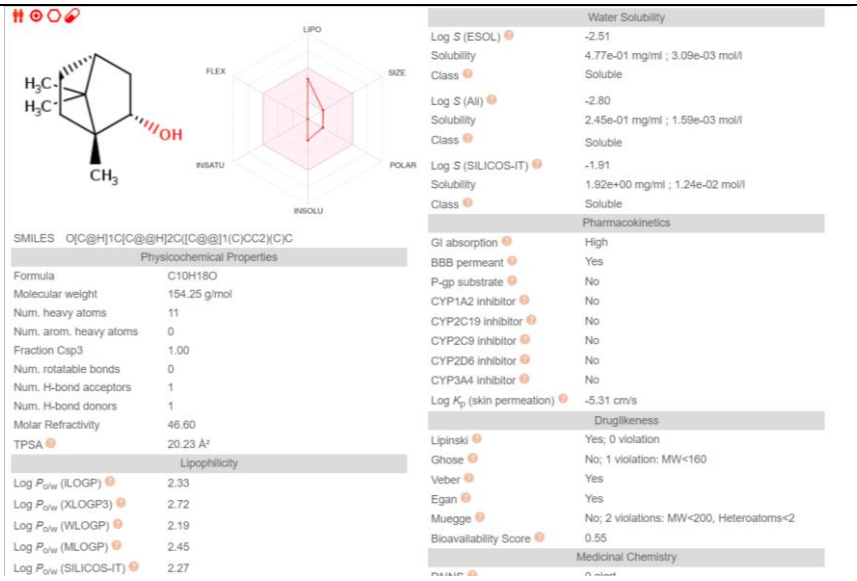
3	Myrcene	
4	Beta-Ionone	
5	Camphor	

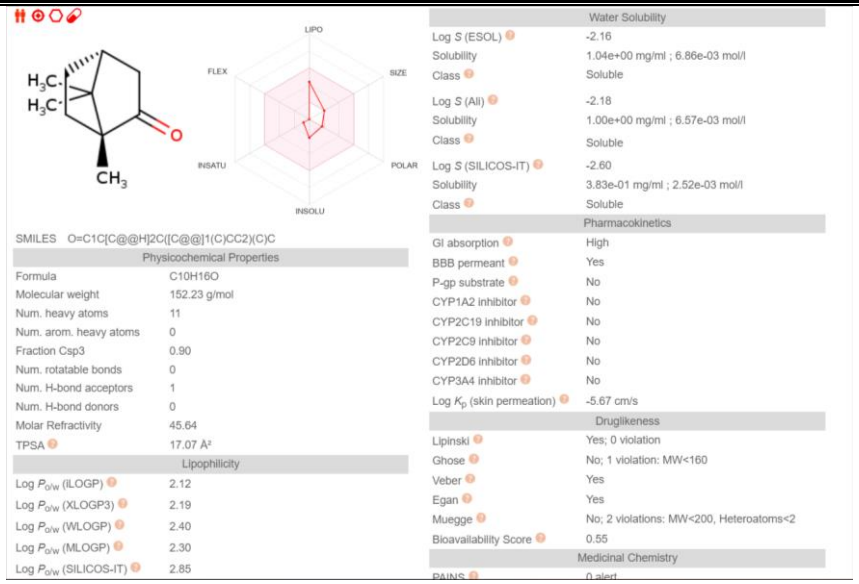
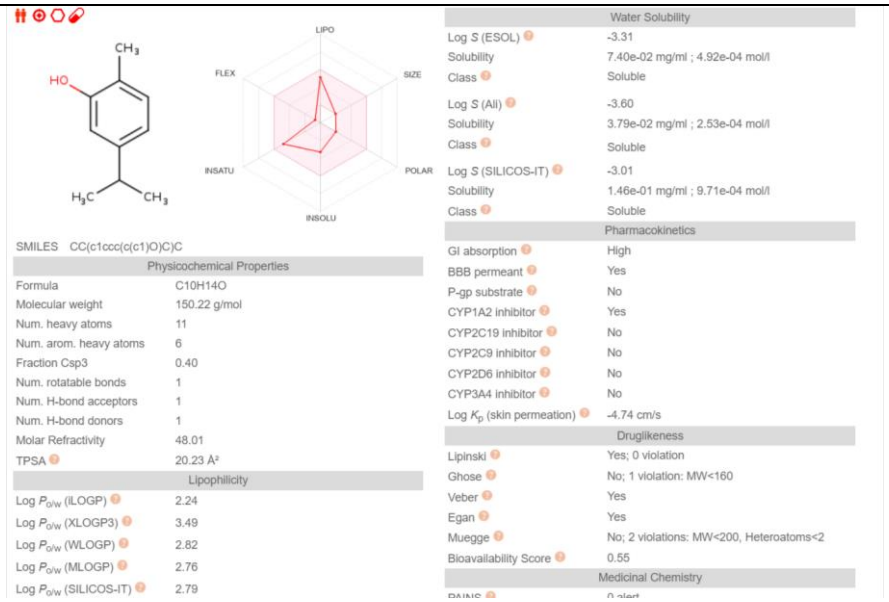
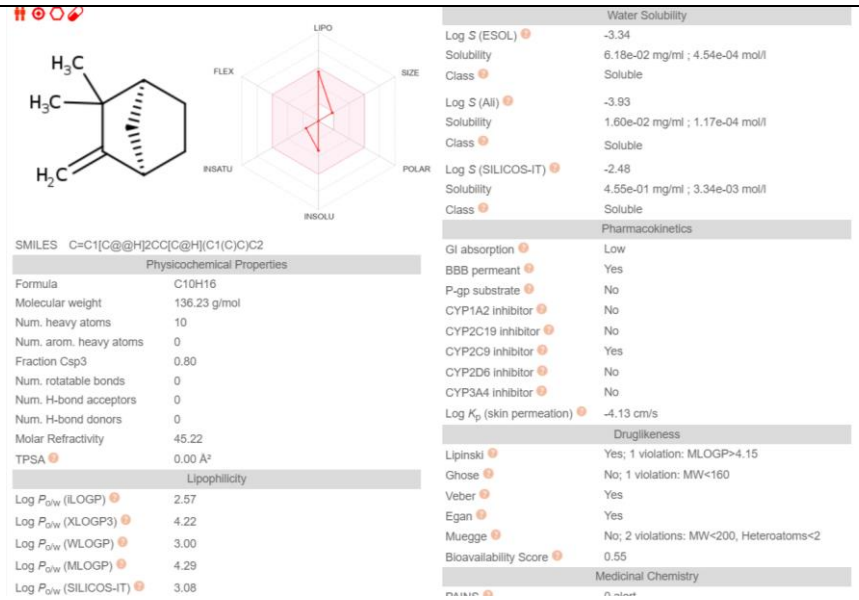
Table 5: Docking Result

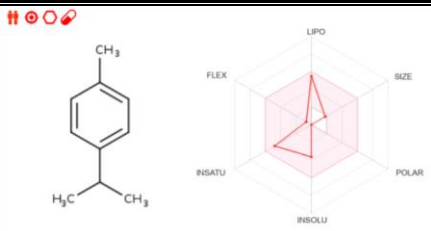
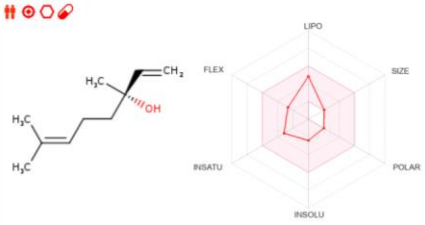
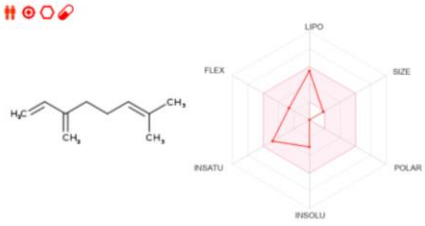
The yellow colour region shows that the ligand binds to the active sites.

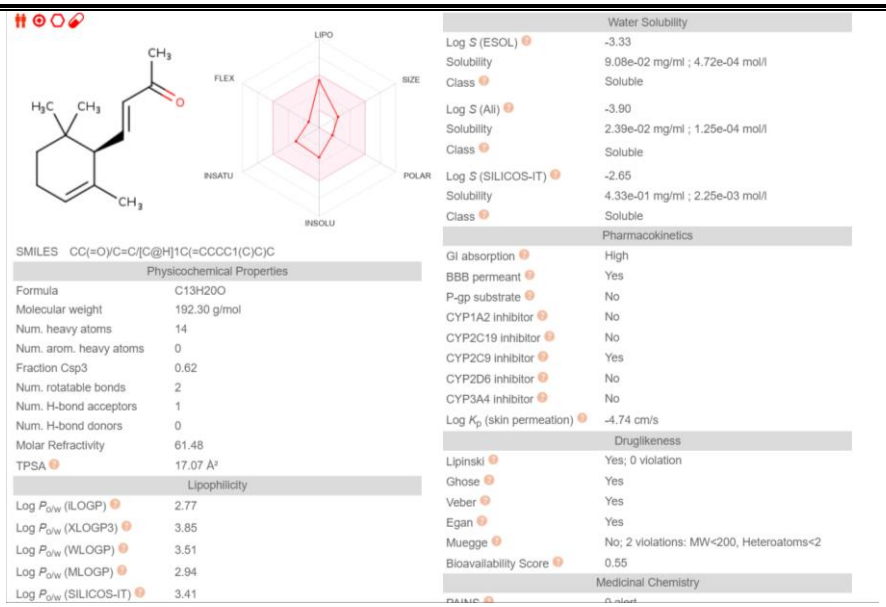
Sl.No	PHYTOCHEMICALS	ADME CHARACTERISTICS
1	Beta phellandrene	

2	Alpha humulene	 SMILES C/C/1=C/CC(C)(C)/C=C\C/C(=C\CC1)/C **Physicochemical Properties** Formula C15H24 Molecular weight 204.35 g/mol Num. heavy atoms 15 Num. arom. heavy atoms 0 Fraction Csp3 0.60 Num. rotatable bonds 0 Num. H-bond acceptors 0 Num. H-bond donors 0 Molar Refractivity 70.42 TPSA 0.00 Å² **Lipophilicity** Log $P_{o/w}$ (ILOGP) Log $P_{o/w}$ (XLOGP3) Log $P_{o/w}$ (WLOGP) 5.04 Log $P_{o/w}$ (MLOGP) Log $P_{o/w}$ (SILICOS-IT) **Water Solubility** Log *S* (ESOL) Solubility mg/ml ; mol/l Class Log *S* (Ali) Solubility mg/ml ; mol/l Class Log *S* (SILICOS-IT) Solubility mg/ml ; mol/l Class **Pharmacokinetics** GI absorption BBB permeant P-gp substrate CYP1A2 inhibitor CYP2C19 inhibitor CYP2C9 inhibitor CYP2D6 inhibitor CYP3A4 inhibitor Log K_p (skin permeation) cm/s **Druglikeness** Lipinski ; violation Ghose Veber Egan Muegge Bioavailability Score **Medicinal Chemistry** PAINS 0 alert
3	Alpha phellandrene	 SMILES CC1=CC[C@@H](C=C1)C(C)C **Physicochemical Properties** Formula C10H16 Molecular weight 136.23 g/mol Num. heavy atoms 10 Num. arom. heavy atoms 0 Fraction Csp3 0.60 Num. rotatable bonds 1 Num. H-bond acceptors 0 Num. H-bond donors 0 Molar Refractivity 47.12 TPSA 0.00 Å² **Lipophilicity** Log $P_{o/w}$ (ILOGP) 2.65 Log $P_{o/w}$ (XLOGP3) 3.21 Log $P_{o/w}$ (WLOGP) 3.16 Log $P_{o/w}$ (MLOGP) 3.27 Log $P_{o/w}$ (SILICOS-IT) 2.55 **Water Solubility** Log *S* (ESOL) -2.64 Solubility 3.11e-01 mg/ml ; 2.29e-03 mol/l Class Soluble Log *S* (Ali) -2.88 Solubility 1.79e-01 mg/ml ; 1.31e-03 mol/l Class Soluble Log *S* (SILICOS-IT) -1.78 Solubility 2.27e+00 mg/ml ; 1.67e-02 mol/l Class Soluble **Pharmacokinetics** GI absorption Low BBB permeant Yes P-gp substrate No CYP1A2 inhibitor No CYP2C19 inhibitor No CYP2C9 inhibitor No CYP2D6 inhibitor No CYP3A4 inhibitor No Log K_p (skin permeation) -4.85 cm/s **Druglikeness** Lipinski Yes; 0 violation Ghose No; 1 violation: MW<160 Veber Yes Egan Yes Muegge No; 2 violations: MW<200, Heteroatoms<2 Bioavailability Score 0.55 **Medicinal Chemistry**
4	Alpha pinene	 SMILES CC1=CC[C@@H]2C[C@H]1C2(C)C **Physicochemical Properties** Formula C10H16 Molecular weight 136.23 g/mol Num. heavy atoms 10 Num. arom. heavy atoms 0 Fraction Csp3 0.80 Num. rotatable bonds 0 Num. H-bond acceptors 0 Num. H-bond donors 0 Molar Refractivity 45.22 TPSA 0.00 Å² **Lipophilicity** Log $P_{o/w}$ (ILOGP) 2.63 Log $P_{o/w}$ (XLOGP3) 4.48 Log $P_{o/w}$ (WLOGP) 3.00 Log $P_{o/w}$ (MLOGP) 4.29 **Water Solubility** Log *S* (ESOL) -3.51 Solubility 4.24e-02 mg/ml ; 3.11e-04 mol/l Class Soluble Log *S* (Ali) -4.20 Solubility 8.59e-03 mg/ml ; 6.31e-05 mol/l Class Moderately soluble Log *S* (SILICOS-IT) -2.23 Solubility 8.06e-01 mg/ml ; 5.92e-03 mol/l Class Soluble **Pharmacokinetics** GI absorption Low BBB permeant Yes P-gp substrate No CYP1A2 inhibitor No CYP2C19 inhibitor No CYP2C9 inhibitor Yes CYP2D6 inhibitor No CYP3A4 inhibitor No Log K_p (skin permeation) -3.95 cm/s **Druglikeness** Lipinski Yes; 1 violation: MLOGP>4.15 Ghose No; 1 violation: MW<160 Veber Yes Egan Yes Muegge No; 2 violations: MW<200, Heteroatoms<2 Bioavailability Score 0.55 **Medicinal Chemistry**

5	Alpha terpinol	 SMILES CC1=CC[C@@H](CC1)C(O)(C)C Physicochemical Properties Formula C10H18O Molecular weight 154.25 g/mol Num. heavy atoms 11 Num. arom. heavy atoms 0 Fraction Csp3 0.80 Num. rotatable bonds 1 Num. H-bond acceptors 1 Num. H-bond donors 1 Molar Refractivity 48.80 TPSA 20.23 Å² Lipophilicity Log $P_{o/w}$ (iLOGP) 2.51 Log $P_{o/w}$ (XLOGP3) 3.39 Log $P_{o/w}$ (WLOGP) 2.50 Log $P_{o/w}$ (MLOGP) 2.30 Log $P_{o/w}$ (SILICOS-IT) 2.17 Water Solubility Log S (ESOL) -2.87 Solubility 2.10e-01 mg/ml ; 1.36e-03 mol/l Class Soluble Log S (Ali) -3.49 Solubility 4.95e-02 mg/ml ; 3.21e-04 mol/l Class Soluble Log S (SILICOS-IT) -1.69 Solubility 3.17e+00 mg/ml ; 2.06e-02 mol/l Class Soluble Pharmacokinetics GI absorption High BBB permeant Yes P-gp substrate No CYP1A2 inhibitor No CYP2C19 inhibitor No CYP2C9 inhibitor No CYP2D6 inhibitor No CYP3A4 inhibitor No Log K_p (skin permeation) -4.83 cm/s Druglikeness Lipinski Yes; 0 violation Ghose No; 1 violation: MW<160 Veber Yes Egan Yes Muegge No; 2 violations: MW<200, Heteroatoms<2 Bioavailability Score 0.55 Medicinal Chemistry
6	Beta pinene	 SMILES C=C1CC[C@@H]2C[C@H]1C2(C)C Physicochemical Properties Formula C10H16 Molecular weight 136.23 g/mol Num. heavy atoms 10 Num. arom. heavy atoms 0 Fraction Csp3 0.80 Num. rotatable bonds 0 Num. H-bond acceptors 0 Num. H-bond donors 0 Molar Refractivity 45.22 TPSA 0.00 Å² Lipophilicity Log $P_{o/w}$ (iLOGP) 2.59 Log $P_{o/w}$ (XLOGP3) 4.16 Log $P_{o/w}$ (WLOGP) 3.00 Log $P_{o/w}$ (MLOGP) 4.29 Log $P_{o/w}$ (SILICOS-IT) 3.08 Water Solubility Log S (ESOL) -3.31 Solubility 6.74e-02 mg/ml ; 4.95e-04 mol/l Class Soluble Log S (Ali) -3.87 Solubility 1.85e-02 mg/ml ; 1.36e-04 mol/l Class Soluble Log S (SILICOS-IT) -2.48 Solubility 4.55e-01 mg/ml ; 3.34e-03 mol/l Class Soluble Pharmacokinetics GI absorption Low BBB permeant Yes P-gp substrate No CYP1A2 inhibitor No CYP2C19 inhibitor No CYP2C9 inhibitor Yes CYP2D6 inhibitor No CYP3A4 inhibitor No Log K_p (skin permeation) -4.18 cm/s Druglikeness Lipinski Yes; 1 violation: MLOGP>4.15 Ghose No; 1 violation: MW<160 Veber Yes Egan Yes Muegge No; 2 violations: MW<200, Heteroatoms<2 Bioavailability Score 0.55 Medicinal Chemistry
7	Borneol	 SMILES O[C@H]1C[C@@H]2C([C@@]1(C)CC2)(C)C Physicochemical Properties Formula C10H18O Molecular weight 154.25 g/mol Num. heavy atoms 11 Num. arom. heavy atoms 0 Fraction Csp3 1.00 Num. rotatable bonds 0 Num. H-bond acceptors 1 Num. H-bond donors 1 Molar Refractivity 46.60 TPSA 20.23 Å² Lipophilicity Log $P_{o/w}$ (iLOGP) 2.33 Log $P_{o/w}$ (XLOGP3) 2.72 Log $P_{o/w}$ (WLOGP) 2.19 Log $P_{o/w}$ (MLOGP) 2.45 Log $P_{o/w}$ (SILICOS-IT) 2.27 Water Solubility Log S (ESOL) -2.51 Solubility 4.77e-01 mg/ml ; 3.09e-03 mol/l Class Soluble Log S (Ali) -2.80 Solubility 2.45e-01 mg/ml ; 1.59e-03 mol/l Class Soluble Log S (SILICOS-IT) -1.91 Solubility 1.92e+00 mg/ml ; 1.24e-02 mol/l Class Soluble Pharmacokinetics GI absorption High BBB permeant Yes P-gp substrate No CYP1A2 inhibitor No CYP2C19 inhibitor No CYP2C9 inhibitor No CYP2D6 inhibitor No CYP3A4 inhibitor No Log K_p (skin permeation) -5.31 cm/s Druglikeness Lipinski Yes; 0 violation Ghose No; 1 violation: MW<160 Veber Yes Egan Yes Muegge No; 2 violations: MW<200, Heteroatoms<2 Bioavailability Score 0.55 Medicinal Chemistry

8	Camphor	 SMILES O=C1C[C@@H]2C([C@@]1(C)CC2)(C)C **Physicochemical Properties** Formula C10H16O Molecular weight 152.23 g/mol Num. heavy atoms 11 Num. arom. heavy atoms 0 Fraction Csp3 0.90 Num. rotatable bonds 0 Num. H-bond acceptors 1 Num. H-bond donors 0 Molar Refractivity 45.64 TPSA 17.07 Å² **Lipophilicity** Log $P_{o/w}$ (iLOGP) 2.12 Log $P_{o/w}$ (XLOGP3) 2.19 Log $P_{o/w}$ (WLOGP) 2.40 Log $P_{o/w}$ (MLOGP) 2.30 Log $P_{o/w}$ (SILICOS-IT) 2.85 **Water Solubility** Log *S* (ESOL) -2.16 Solubility 1.04e+00 mg/ml ; 6.86e-03 mol/l Class Soluble Log *S* (Ali) -2.18 Solubility 1.00e+00 mg/ml ; 6.57e-03 mol/l Class Soluble Log *S* (SILICOS-IT) -2.60 Solubility 3.83e-01 mg/ml ; 2.52e-03 mol/l Class Soluble **Pharmacokinetics** GI absorption High BBB permeant Yes P-gp substrate No CYP1A2 inhibitor No CYP2C19 inhibitor No CYP2C9 inhibitor No CYP2D6 inhibitor No CYP3A4 inhibitor No Log K_p (skin permeation) -5.67 cm/s **Druglikeness** Lipinski Yes; 0 violation Ghose No; 1 violation: MW<160 Veber Yes Egan Yes Muegge No; 2 violations: MW<200, Heteroatoms<2 Bioavailability Score 0.55 **Medicinal Chemistry** PAINS 0 alert
9	Carvacrol	 SMILES CC(c1ccc(c(c1)O)C)C **Physicochemical Properties** Formula C10H14O Molecular weight 150.22 g/mol Num. heavy atoms 11 Num. arom. heavy atoms 6 Fraction Csp3 0.40 Num. rotatable bonds 1 Num. H-bond acceptors 1 Num. H-bond donors 1 Molar Refractivity 48.01 TPSA 20.23 Å² **Lipophilicity** Log $P_{o/w}$ (iLOGP) 2.24 Log $P_{o/w}$ (XLOGP3) 3.49 Log $P_{o/w}$ (WLOGP) 2.82 Log $P_{o/w}$ (MLOGP) 2.76 Log $P_{o/w}$ (SILICOS-IT) 2.79 **Water Solubility** Log *S* (ESOL) -3.31 Solubility 7.40e-02 mg/ml ; 4.92e-04 mol/l Class Soluble Log *S* (Ali) -3.60 Solubility 3.79e-02 mg/ml ; 2.53e-04 mol/l Class Soluble Log *S* (SILICOS-IT) -3.01 Solubility 1.46e-01 mg/ml ; 9.71e-04 mol/l Class Soluble **Pharmacokinetics** GI absorption High BBB permeant Yes P-gp substrate No CYP1A2 inhibitor Yes CYP2C19 inhibitor No CYP2C9 inhibitor No CYP2D6 inhibitor No CYP3A4 inhibitor No Log K_p (skin permeation) -4.74 cm/s **Druglikeness** Lipinski Yes; 0 violation Ghose No; 1 violation: MW<160 Veber Yes Egan Yes Muegge No; 2 violations: MW<200, Heteroatoms<2 Bioavailability Score 0.55 **Medicinal Chemistry**
10	Camphene	 SMILES C=C1[C@@H]2CC[C@H](C1(C)C)C2 **Physicochemical Properties** Formula C10H16 Molecular weight 136.23 g/mol Num. heavy atoms 10 Num. arom. heavy atoms 0 Fraction Csp3 0.80 Num. rotatable bonds 0 Num. H-bond acceptors 0 Num. H-bond donors 0 Molar Refractivity 45.22 TPSA 0.00 Å² **Lipophilicity** Log $P_{o/w}$ (iLOGP) 2.57 Log $P_{o/w}$ (XLOGP3) 4.22 Log $P_{o/w}$ (WLOGP) 3.00 Log $P_{o/w}$ (MLOGP) 4.29 Log $P_{o/w}$ (SILICOS-IT) 3.08 **Water Solubility** Log *S* (ESOL) -3.34 Solubility 6.18e-02 mg/ml ; 4.54e-04 mol/l Class Soluble Log *S* (Ali) -3.93 Solubility 1.60e-02 mg/ml ; 1.17e-04 mol/l Class Soluble Log *S* (SILICOS-IT) -2.48 Solubility 4.55e-01 mg/ml ; 3.34e-03 mol/l Class Soluble **Pharmacokinetics** GI absorption Low BBB permeant Yes P-gp substrate No CYP1A2 inhibitor No CYP2C19 inhibitor No CYP2C9 inhibitor Yes CYP2D6 inhibitor No CYP3A4 inhibitor No Log K_p (skin permeation) -4.13 cm/s **Druglikeness** Lipinski Yes; 1 violation: MLOGP>4.15 Ghose No; 1 violation: MW<160 Veber Yes Egan Yes Muegge No; 2 violations: MW<200, Heteroatoms<2 Bioavailability Score 0.55 **Medicinal Chemistry**

11	p-cymene	 SMILES Cc1ccc(cc1)C(C)C **Physicochemical Properties** Formula C10H14 Molecular weight 134.22 g/mol Num. heavy atoms 10 Num. arom. heavy atoms 6 Fraction Csp3 0.40 Num. rotatable bonds 1 Num. H-bond acceptors 0 Num. H-bond donors 0 Molar Refractivity 45.99 TPSA 0.00 Å² **Lipophilicity** Log $P_{o/w}$ (iLOGP) 2.51 Log $P_{o/w}$ (XLOGP3) 4.10 Log $P_{o/w}$ (WLOGP) 3.12 Log $P_{o/w}$ (MLOGP) 4.47 Log $P_{o/w}$ (SILICOS-IT) 3.29 **Water Solubility** Log S (ESOL) -3.63 Solubility 3.12e-02 mg/ml ; 2.33e-04 mol/l Class Soluble Log S (Ali) -3.81 Solubility 2.10e-02 mg/ml ; 1.56e-04 mol/l Class Soluble Log S (SILICOS-IT) -3.57 Solubility 3.58e-02 mg/ml ; 2.67e-04 mol/l Class Soluble **Pharmacokinetics** GI absorption Low BBB permeant Yes P-gp substrate No CYP1A2 inhibitor No CYP2C19 inhibitor No CYP2C9 inhibitor No CYP2D6 inhibitor Yes CYP3A4 inhibitor No Log K_p (skin permeation) -4.21 cm/s **Druglikeness** Lipinski Yes; 1 violation: MLOGP>4.15 Ghose No; 1 violation: MW<160 Veber Yes Egan Yes Muegge No; 2 violations: MW<200, Heteroatoms<2 Bioavailability Score 0.55 **Medicinal Chemistry**
12	Linalool	 SMILES C=C[C@](CCC=C(C)C)(O)C **Physicochemical Properties** Formula C10H18O Molecular weight 154.25 g/mol Num. heavy atoms 11 Num. arom. heavy atoms 0 Fraction Csp3 0.60 Num. rotatable bonds 4 Num. H-bond acceptors 1 Num. H-bond donors 1 Molar Refractivity 50.44 TPSA 20.23 Å² **Lipophilicity** Log $P_{o/w}$ (iLOGP) 2.70 Log $P_{o/w}$ (XLOGP3) 2.97 Log $P_{o/w}$ (WLOGP) 2.67 Log $P_{o/w}$ (MLOGP) 2.59 Log $P_{o/w}$ (SILICOS-IT) 2.35 **Water Solubility** Log S (ESOL) -2.40 Solubility 6.09e-01 mg/ml ; 3.95e-03 mol/l Class Soluble Log S (Ali) -3.06 Solubility 1.35e-01 mg/ml ; 8.75e-04 mol/l Class Soluble Log S (SILICOS-IT) -1.84 Solubility 2.20e+00 mg/ml ; 1.43e-02 mol/l Class Soluble **Pharmacokinetics** GI absorption High BBB permeant Yes P-gp substrate No CYP1A2 inhibitor No CYP2C19 inhibitor No CYP2C9 inhibitor No CYP2D6 inhibitor No CYP3A4 inhibitor No Log K_p (skin permeation) -5.13 cm/s **Druglikeness** Lipinski Yes; 0 violation Ghose No; 1 violation: MW<160 Veber Yes Egan Yes Muegge No; 2 violations: MW<200, Heteroatoms<2 Bioavailability Score 0.55 **Medicinal Chemistry**
13	Myrcene	 SMILES C=CC(=C)CCC=C(C)C **Physicochemical Properties** Formula C10H16 Molecular weight 136.23 g/mol Num. heavy atoms 10 Num. arom. heavy atoms 0 Fraction Csp3 0.40 Num. rotatable bonds 4 Num. H-bond acceptors 0 Num. H-bond donors 0 Molar Refractivity 48.76 TPSA 0.00 Å² **Lipophilicity** Log $P_{o/w}$ (iLOGP) 2.89 Log $P_{o/w}$ (XLOGP3) 4.17 Log $P_{o/w}$ (WLOGP) 3.48 Log $P_{o/w}$ (MLOGP) 3.56 Log $P_{o/w}$ (SILICOS-IT) 3.05 **Water Solubility** Log S (ESOL) -3.05 Solubility 1.22e-01 mg/ml ; 8.96e-04 mol/l Class Soluble Log S (Ali) -3.88 Solubility 1.80e-02 mg/ml ; 1.32e-04 mol/l Class Soluble Log S (SILICOS-IT) -2.42 Solubility 5.24e-01 mg/ml ; 3.85e-03 mol/l Class Soluble **Pharmacokinetics** GI absorption Low BBB permeant Yes P-gp substrate No CYP1A2 inhibitor No CYP2C19 inhibitor No CYP2C9 inhibitor No CYP2D6 inhibitor No CYP3A4 inhibitor No Log K_p (skin permeation) -4.17 cm/s **Druglikeness** Lipinski Yes; 0 violation Ghose No; 1 violation: MW<160 Veber Yes Egan Yes Muegge No; 2 violations: MW<200, Heteroatoms<2 Bioavailability Score 0.55 **Medicinal Chemistry**

14	Alpha-ionone	

DISCUSSION

Natural products have been used for medical purposes since ancient times and we are well known as sources of a variety of human ailments. The therapeutic properties of these herbs and medicinal plants have prompted researchers to look at natural products as a possible source of drug molecules. In this study; only one plant is taken to derive the medical compounds as ligands hypothesized to be responsible for much of the disease's protection.

Coleus barbatus is the plant that is used to treat allergic and other irritant problems. From early times it is used for various treatments as it is having a high medical value. It has anti- allergic, anti-inflammatory, and even anti-cancerous properties. The stem, roots, leaves, shoot, and essential oils are used to treat various disease conditions.

As it is known that allergies can lead to asthma and even higher conditions such as eosinophilia and leukemia. It is better to treat from the earlier stage. Anti-histamines are given to suppress the action of the histamine H1 receptor. Many medications that are taken, can be additive or even cause hormonal imbalance. The use of the phytochemicals lowers the chance of side effects caused by the chemically synthesized antihistamines.

The ligands derived from the plant are docked with the protein molecule using software or servers to find out the efficiency of each ligand. Swissdock is the server that is used to dock the Histamine H1 receptor protein with the ligands. Alpha-ionone, alpha-curcumene, myrcene, Beta-ionone, and Camphor are having the best docking score thus implying that these ligands are more suitable for drug designing. Swiss ADME studies are done for thesemolecules, all the molecules obey the Lipinski rule of 5. These all components are having anti-cancerous effects thus proving that they are non-carcinogenic.

CONCLUSION AND FUTURE WORK

Treatment for allergic symptoms is limited as the medicines are given for suppressing the symptoms. Suppression of symptoms may cause may other side effects. Anti-histamines that are used to treat the disease have a high chance of causing side effects such as addiction and hormonal imbalance. Once taking the synthetically produced antihistamines leads to the usage of the medicines continuously as it has only suppression action and not a complete cure.

Phytochemicals that are produced by the plant *Coleus barbatus* are helpful for the curing of allergic conditions as they have anti-allergic activity. Using phytochemical-based medicines does not cause additive effects in the body and does not produce any side effects. Using thisas medicine also helps to prevent the body from various reactions and keeps the body healthy.The analysis of the docking result shows efficiency of the natural bioactive compound to control the Histamine. The binding energy of the ligand protein interaction also confirmed that the ligand tightly fits to the molecule. This study can provide a clue for atmospheric dust allergy and design of new combined drugs APPENDIX

- A drug is defined as any chemical substance intended for use in the medical diagnosis, cure, treatment, or prevention of disease.
- Target is frequently used in pharmaceutical research to describe the native protein in the body whose activity is modified by a drug resulting in a desirable therapeutic effect.
- Pharmacology is the branch of medicine and biology concerned with the study of drugaction.
- In silico is an expression used to mean performed on a computer or via computer simulation.
- Phytochemicals are defined as chemical compounds that occur naturally in plants.
- Ligands are defined as an atom, ion, or molecule that donates or shares one or more ofits electrons through a covalent bond with a central atom or ion.
- Toxicity is defined as the sum of adverse effects or the degree of danger posed by asubstance to living organisms.
- Molecular docking is the study of how two or more molecular structures (e.g., drug and enzyme or protein) fit together. In a simple definition, docking is a molecular

modeling technique that is used to predict how a protein (enzyme) interacts with smallmolecules (ligands).

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