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# In Silico Studies and Anti Inflammatory Activity Evaluation of Phytochemicals as Potent Inhibitors of Rhinosinusitis

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**ABSTRACT**
An infection or an allergic reaction can cause sinusitis, which is defined as inflammation of the mucosal lining of one or more para-nasal sinuses. Sinusitis almost always develops as a side effect of the common cold in children. The nasal and sinus mucosa are both affected by inflammation and congestion even in simple viral upper respiratory infections like the common cold. As a result, these infections should be classified as rhino sinusitis. Here we have selected phytoconstituents from various medicinal plants. All the selected phytoconstituents will be evaluated for PASS prediction, GUSAR (Toxicity studies), SWISS ADME and Molecular Docking.In the present study, the phytochemical constituents were evaluated through In silico analysis. Initially the structure of these compounds and their sources were tabulated (see Table 1) and screened for their biological activity (see Table 2). 30 compounds with anti-inflammatory were chosen and predicted for toxicity and physicochemical properties and the results are tabulated in Table 3 & 4. Finally, docking simulation between the protein 1ALU and 1ICW, the chosen 20 compounds were done to optimize the best fit for the ligand in the active site of the target and the results are shown in Table 5. From the final results it was observed that, a docking score between -14 and -10showed the highest binding energy. With that being the case, Cubebene showed the highest binding energy of -14.156 kcal/molfor Interleukin-8 receptor and Linoleic acid showed highest binding energy of -11.0696 kcal/mol for Interleukin 6 receptor for sinusitis . The best 8 compounds were chosen based on the docking score and were visualized. The 2D ligand interactions, 3D docking poses and the hydrogen bond interactions are shown in Figure A,B,C,D,E,F and G,H.

**KEYWORDS:** Rhinosinusitis, Molecular docking, pass prediction, Target selection, Anti inflammatory activity.

## I. INTRODUCTION

### 1.1 SINUSITIS

An infection or an allergic reaction can cause sinusitis, which is defined as inflammation of the mucosal lining of one or more par nasal sinuses. Sinusitis almost always develops as a side effect of the common cold in children. The nasal and sinus mucosa are both affected by inflammation and congestion even in simple viral upper respiratory infections like the common cold. As a result, these infections should be classified as rhino sinusitis. Most of the time, this inflammation goes away on its own. Sinusitis is divided into three categories based on how long the symptoms last: acute (less than three weeks), sub-acute (three to ten weeks), and chronic (more than ten weeks). [1]

## EXPERIMENTAL

### Software and Hardware

The computer system with Intel ® Core ™ i7 11th Gen CPU processor having 16GB RAM and 1TB SSD And Geforce RTX 3070graphics card with Windows 11 as the operating system was used. All the computational studies were carried out in various softwares such as Argus lab, Chemdraw Ultra Version 12.0 and Discovery Studio Visualiser v21.1.1.0. Online tools like PASS Prediction, SwissADME, GUSAR Way to drug and chemical databases such as Protien Data Bank were used.

### Target Selection

The three-dimensional (3D) crystal structure ofInterleukin-6 (PDB ID: 1ALU) and Interleukin-8 (PDB ID: 1ICW) was obtained from the Protein Data Bank (www.rcsb.org/pdb) in PDB format.

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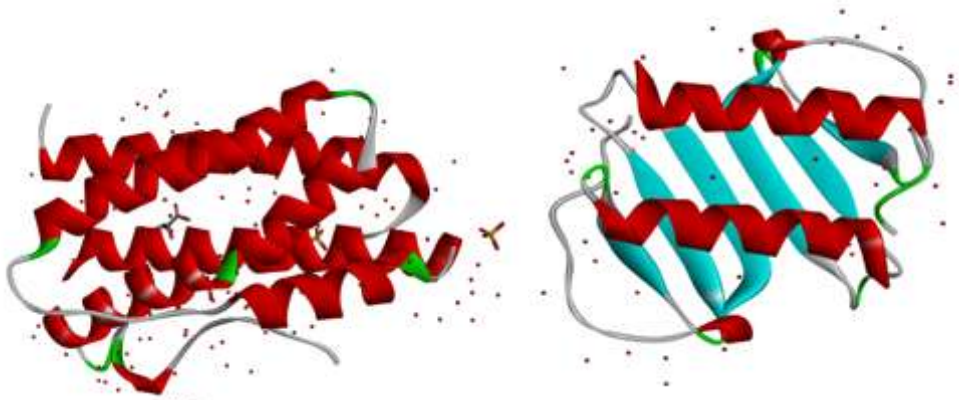

FIG 1: Protein Structure with PDB ID 1LAU and 1ICW

**PASS prediction**

The concept of biological activity spectrum served as a basis for developing PASS (prediction of activity spectra for substances) software product (http://way2drug.com/PassOnline/). PASS predicts simultaneously more than 780 pharmacological effects and biochemical mechanisms based on the structural formula of a substance. Also reported are the number of descriptors which are completely new compared with the descriptors of sub- stances from the PASS training set and comments on the interpretation of predictionresults.

- If Pa >0.7, the substance is very likely to exhibit the activity in experiment, but the chance of the substance being the analogue of a known pharmaceutical agent is also high.
- If 0.5 <Pa <0.7, the substance is likely to exhibit theactivity in experiment, but theprobability is less, and the substance is unlike known pharmaceutical agents.

If Pa <0.5, the substance is unlikely to exhibit the activity in experiment. However, if the presence of this activity is confirmed in the experiment the substance might be a new chemical entity.[2]

**Acute toxicity studies**

Acute toxicity refers to all those adverse effects that occurs after a single exposure to a substance, within a given time.[3,4] LD50 value is one of important characteristics of acute toxicity to quantify the short-term acute toxicity of a material. It corresponds to the dose causing 50% mortality within 24 hours of administration. For acute toxicity assessment, it is important to predict the oral, intraperitoneal and intravenous acute rodent toxicity. Mice and rats are the primarily used species used in these studies. There is a lot of LD50 data for mice and rats available in literature and databases.[4,10] The importance of in silico toxicity estimation paved the way for the development of various methods.LD50 values are given in Table 2 [3].

**SwissADME**

The physicochemical properties and drug-likeness of the designed set of compounds were predicted using the online tool SwissADME (http://www.swissadme.ch) in order to determine their design and therapeutic activity. The properties were evaluated based on the Lipinski's rule, in order to predict whether the compounds comply with the criteria of drug-likeness. The molecular properties such as molecular weight, partition coefficient, number of hydrogen bond donors, number of hydrogen bond acceptors and polar surface area were calculated.[5,12]

**Molecular docking**

Molecular docking is an attractive scaffold to understand drugbiomolecular interactions for the rational drug design and discovery, as well as in the mechanistic study by placing a molecule (ligand) into the preferred binding site of the target specific region of the DNA/protein (receptor) mainly in a non-covalent fashion to form a stable complex of potential efficacy and more specificity.[7,8] The information obtained from the docking technique can be used to suggest the binding energy, free energy and stability of complexes.[19,14] At present, docking technique is utilized to predict the tentative binding parameters of ligand-receptor complex beforehand. [6,13]

**A.Protein preparation**

The PDB structures of the protein will probably be missing hydrogens, partial charges,

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side chains. In order to make these structures suitable for modelling tasks and to resolve common structural issues, we will have to use the Protein Preparation Wizard that has processing, modification, and refinement tools. The target protein with the PDB ID: 1LAU and 1ICW were imported into Maestro and some typical operations were performed which may include:

(i) addition of hydrogen atoms
(ii) removal of heteroatoms, water molecules and unwanted chains
(iii) adding protons
(iv) optimizing protonation states.

The protein is preprocessed and during this step, bond orders were assigned, hydrogen atoms added and water molecules were removed. The H Bond network in the protein was optimized and minimized. This completes the protein preparation step.[15,16]

**B. Ligand preparation**

The structures drawn using ChemDraw Ultra 8.0 was saved in .mol2 format and imported into the LigPrep… window. There is no necessity to change the ionization state, desalt, or generate tautomers in this case. We need to sample ring conformations and generate 2 low energy ring conformations.[16,17] The ligand preparation took less than a minute and the prepared ligand is now in the file with .maegz extension. prepared ligands by generating possible tautomers and different protonation states as far as minimizing the structures themselves.[20]

**C. Evaluation of docking results**

At the end, the results are incorporated in the project table and was visualized using the pose viewer function of Biovia Discovery. Thus, the 3D interactions were obtained. Then the receptor with one of the poses in the Project table was selected and the 2D ligand interaction diagrams were visualized.[19, 18]

## II. RESULTS AND DISCUSSION

In the present study, the phytochemical constituents were evaluated through In silico analysis. Initially the structure of these compounds and their sources were tabulated (see Table 1) and screened for their biological activity (see Table 2). 30 compounds with anti-inflammatory were chosen and predicted for toxicity and physicochemical properties and the results are tabulated in Table 3 & 4. Finally, docking simulation between the protein 1ALU and 1ICW, the chosen 20 compounds were done to optimize the best fit for the ligand in the active site of the target and the results are shown in Table 5. From the final results it was observed that, a docking score between -14 and -10showed the highest binding energy. With that being the case, Cubebene showed the highest binding energy of -14.156 kcal/molfor Interleukin-8 receptor and Linoleic acid showed highest binding energy of -11.0696 kcal/mol for Interleukin 6 receptor for sinusitis . The best 8compounds were chosen based on the docking score and were visualized. The 2D ligand interactions, 3D docking poses and the hydrogen bond interactions are shown in Figure A,B,C,D,E,F and G,H

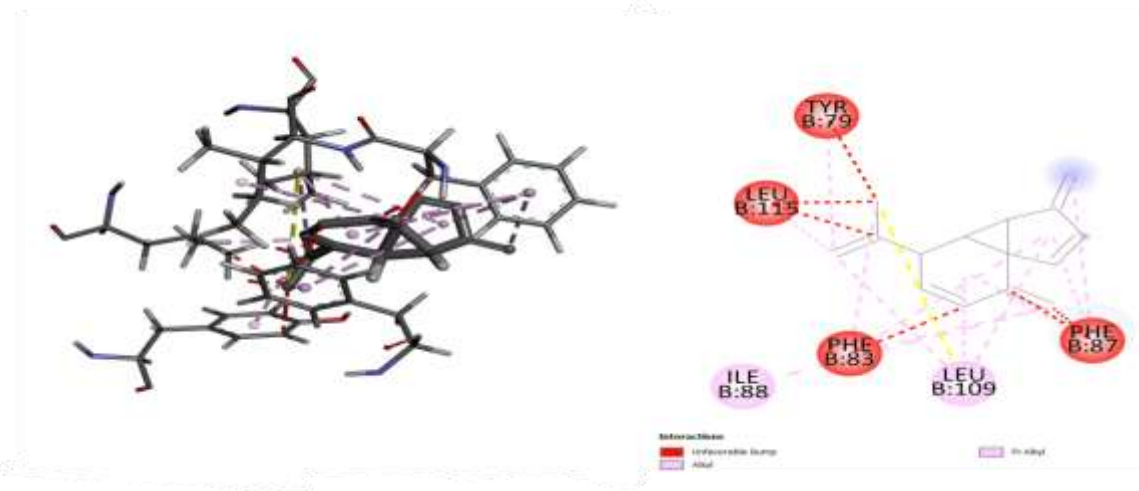


**FIG A: 3D & 2D Docking Poses For Cubebene with Interleukin-8 (PDB ID: 1ICW)**

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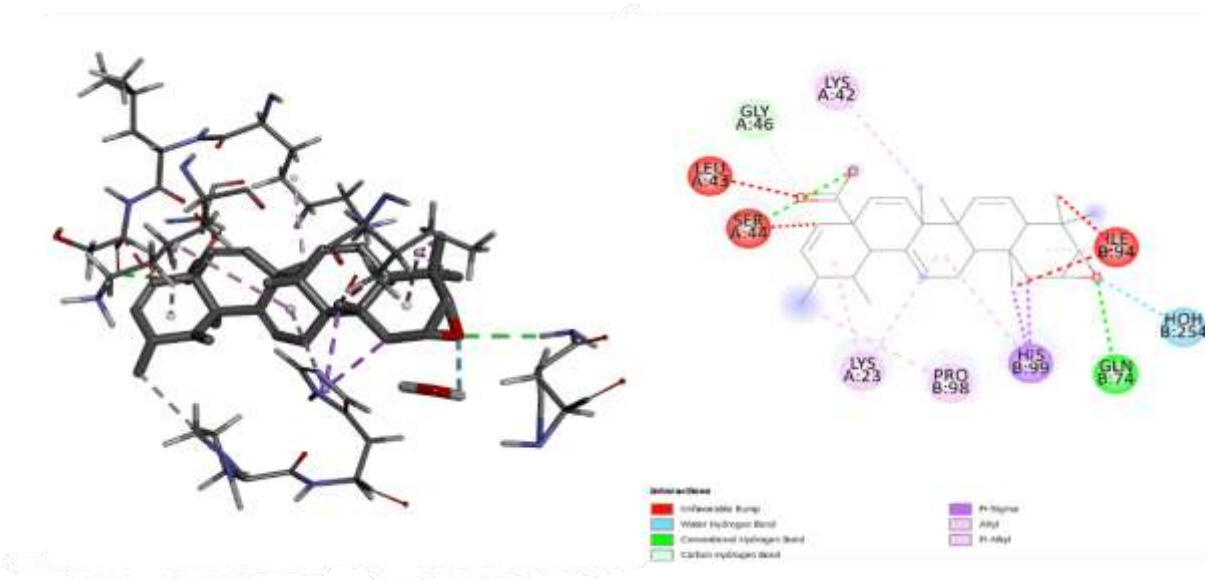


**FIG B: 3D & 2D Docking Poses for Ursolic Acid with Interleukin-8 (PDB ID: 1ICW)**

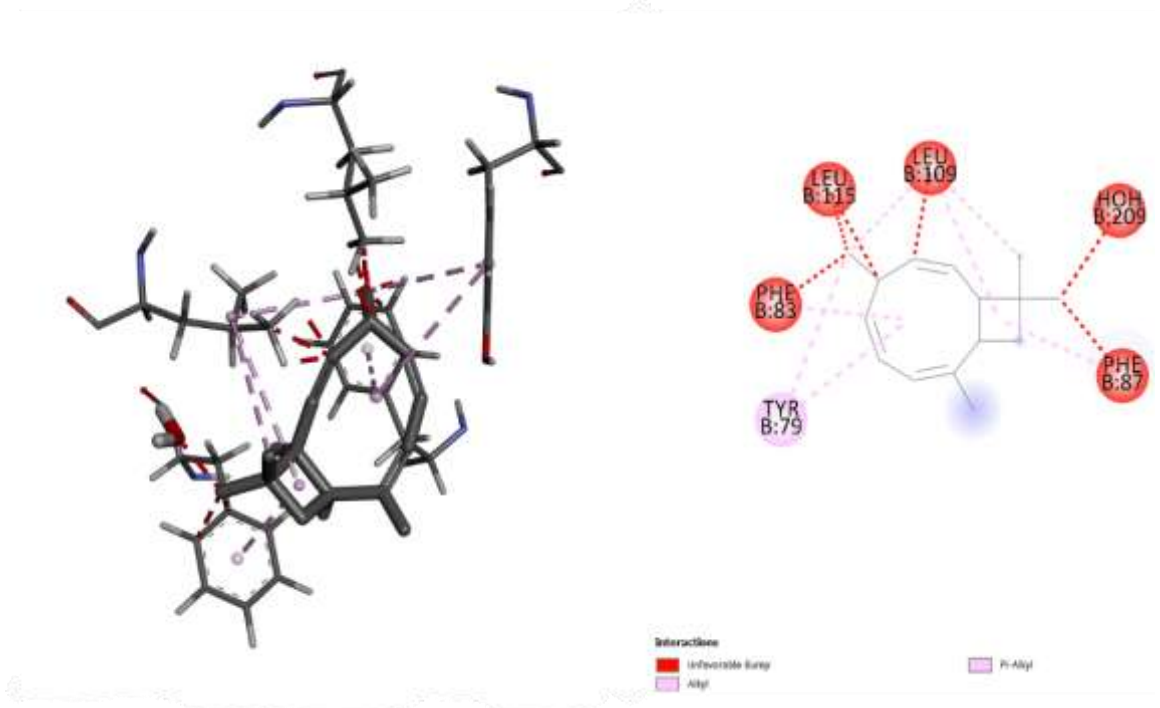


**FIG C: 3D & 2D Docking Poses of Caryophyllene with Interleukin-8 (PDB ID: 1ICW)**

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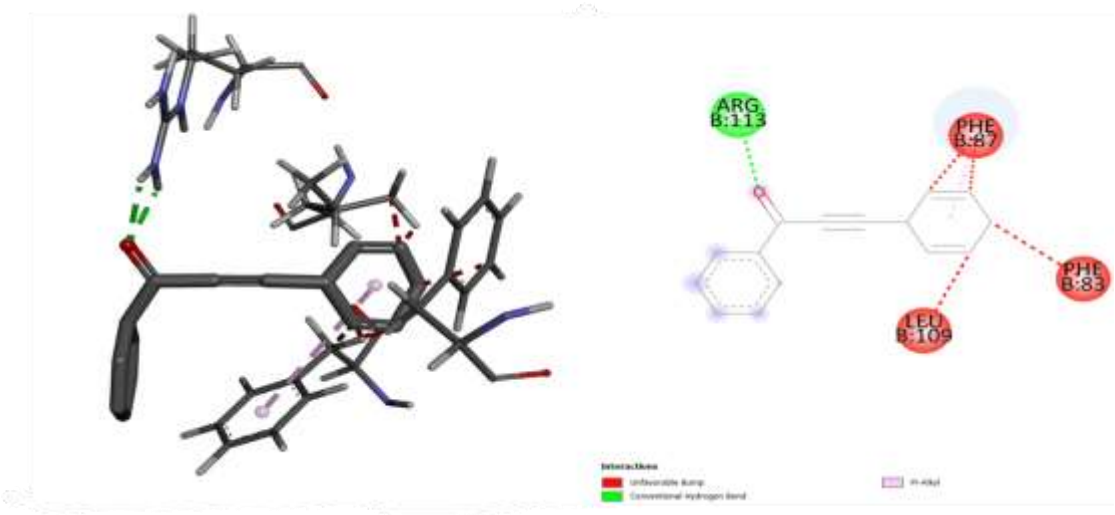


**FIG D: 3D & 2D Docking Poses of Chalone with Ingterleukin-8 (PDB ID: 1ICW)**

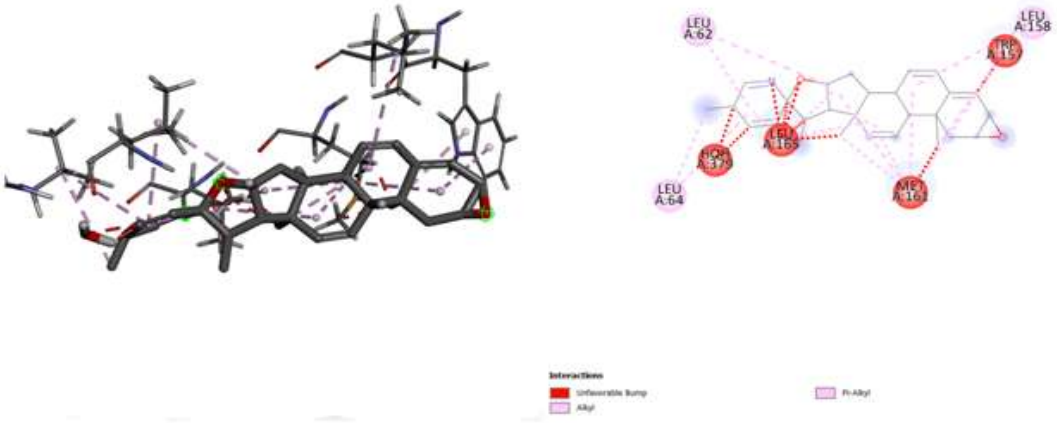


**FIG E: 3D & 2D Docking Poses of Solasodine with Interleukin-6 (PDB ID: 1ALU)**

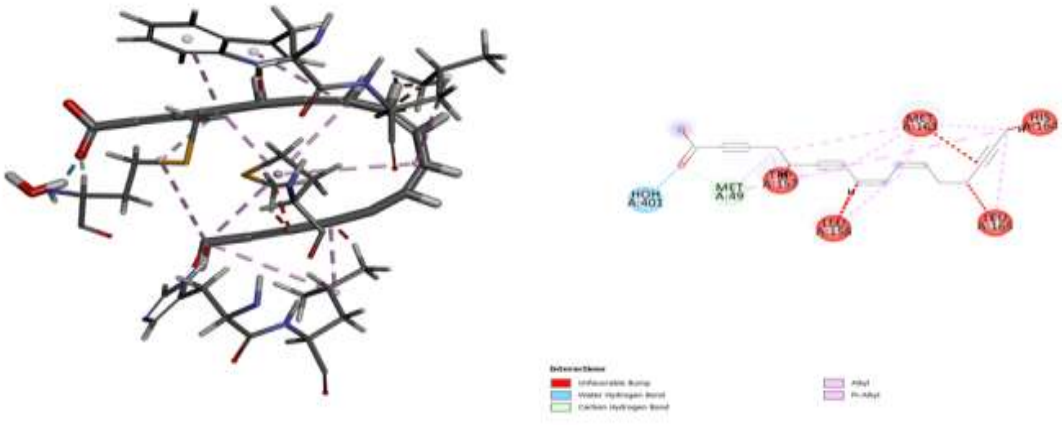


**FIG F: 3D & 2D Docking Poses of Ursolic acid with Interleukin-6 (PDB ID: 1ALU)**

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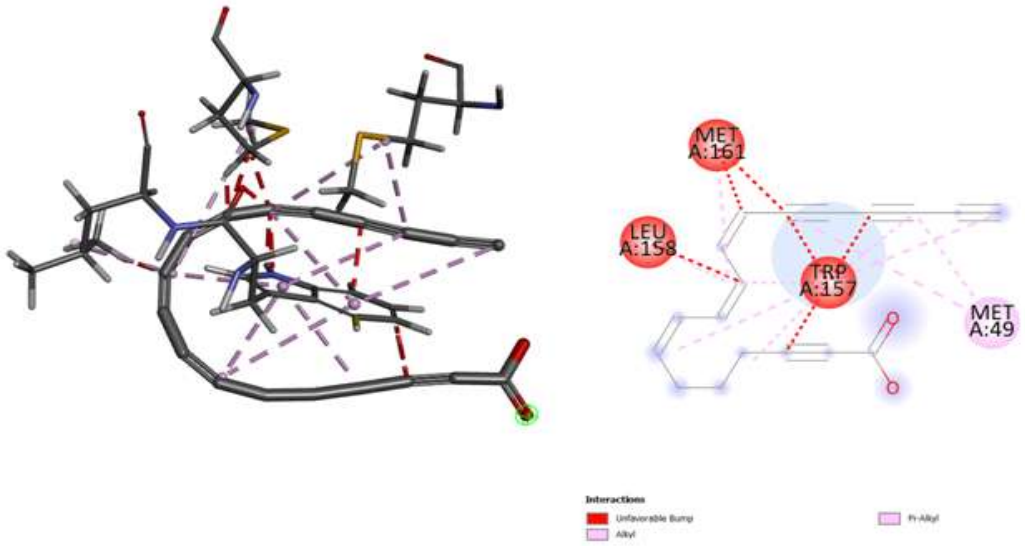



**FIG G: 3D & 2D Docking Poses of Linoleic acid with Interleukin-6 (PDB ID: 1ALU)**

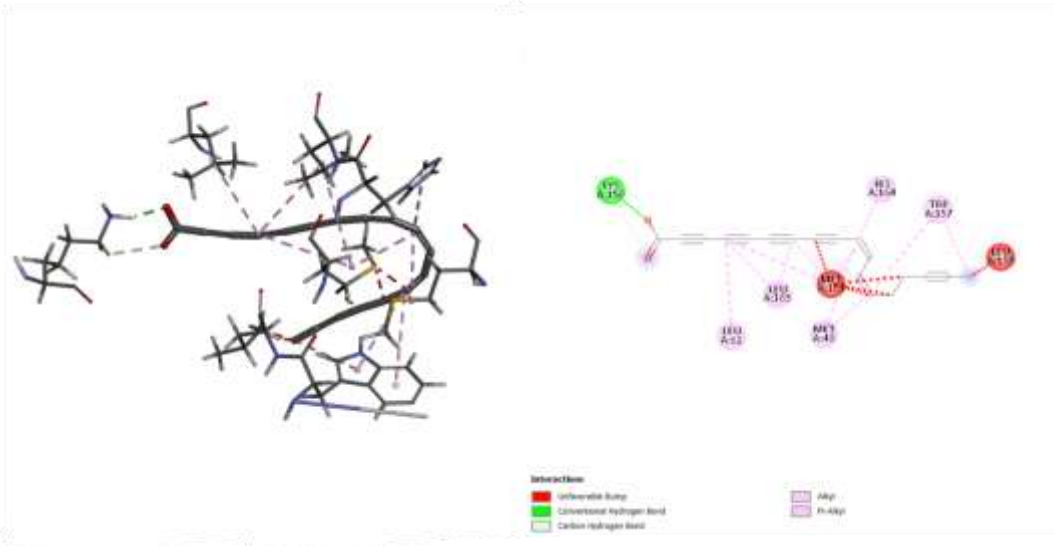
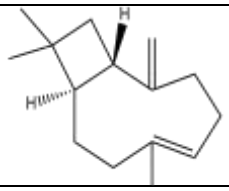


**FIG H: 3D & 2D Docking Poses of Linolenic acid with Interleukin-6 (PDB ID: 1ALU)**

**TABLE 1.Group of Compounds Showing Best Activity**

| SN0 | PLANT SOURCE | PHYTOCONSTITUENTS | STRUCTURE |
|---|---|---|---|
| 1. | Peppermint oil | Caryophyllene |  |

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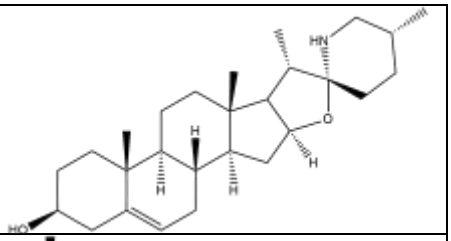
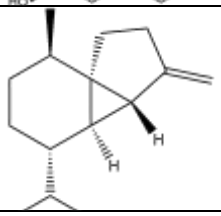
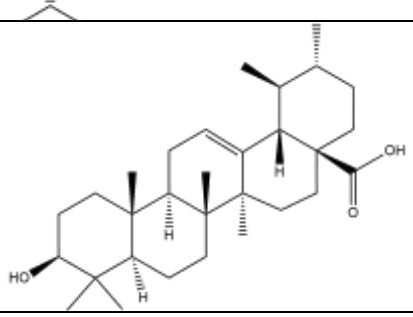
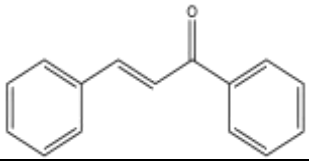
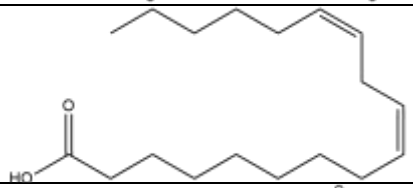
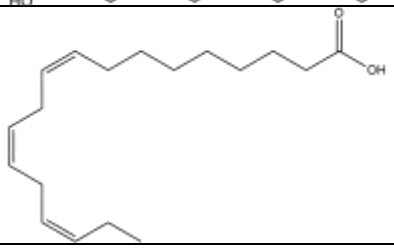
| | | | |
|---|---|---|---|
| 2. | Thuthuvalai | Solasodine |  |
| 3. | Eucalyptus | Cubebene |  |
| 4. | Rosmarinus officinalis L | Ursolic acid |  |
| 5. | Liqurice | Chalcone |  |
| 6. | Oenothera biennis | Linoleic acid |  |
| 7. | Oenothera biennis | Linolenic acid |  |

**TABLE 2. Pass data for antiinflamattory activity of designed compounds**

| Compound Name | Pa | Pi |
|---|---|---|
| Caryophyllene | 0.745 | 0.011 |
| Solasodine | 0.921 | 0.004 |
| Cubebene | 0.923 | 0.004 |
| Chalcone | 0.676 | 0.019 |

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| | | |
|---|---|---|
| Linoleic Acid | 0.730 | 0.012 |
| Linolenic Acid | 0.804 | 0.006 |
| Ursolic Acid | 0.864 | 0.005 |
| Ibuprofen (Standard drug) | 0.901 | 0.004 |

**TABLE 3. Acute Toxicity Profile of Designed Compounds**

| S.no | Compound Name | Rat IP LD50 (mg/kg) | Rat IV LD50 (mg/kg) | Rat Oral LD50 (mg/kg) | Rat SC LD50 (mg/kg) |
|---|---|---|---|---|---|
| **1.** | Caryophyllene | 393,800 in AD | 36,710 in AD | 2321,000 in AD | 390,600 in AD |
| **2.** | Chalcone | 601,300 in AD | 72,190 in AD | 3608,000 in AD | 1764,000 in AD |
| **3.** | Cubebene | 426,400 in AD | 42,950 in AD | 1020,000in AD | 398,400 in AD |
| **4.** | Linoleic Acid | 7739,000 out of AD | 674,800 in AD | 5259,000 in AD | 6663,000 in AD |
| **5.** | Linolenic Acid | 7208,000 out of AD | 588,700 in AD | 6838,000 in AD | 5257,000 in AD |
| **6.** | Solasodine | 964,000 in AD | 8,274 in AD | 2582,000 in AD | 415,500 in AD |
| **7.** | Ursolic Acid | 1459,000 in AD | 5,376 in AD | 265,000 out of AD | 146,500 in AD |
| **8.** | Ibuprofen (Standard drug) | 657,600 in AD | 224,100 in AD | 1082,000 in AD | 566,400 in AD |

**TABLE 4. Predicted Physicochemical Properties and Drug Likeness of Designed Compounds**

| SNO | COMPOUND NAME | MOL.WT | HBD | HBA | logP | TPSA | Lipinski rule |
|---|---|---|---|---|---|---|---|
| **1.** | Caryophyllene | 204.35 | 0 | 0 | 3.28 | 0.00 | Yes; 1 violation |
| **2.** | Solasodine | 413.64 | 2 | 3 | 4.26 | 41.49 | Yes; 1 violation |
| **3.** | Cubebene | 204.35 | 0 | 0 | 3.38 | 00.0 | Yes; 1 violation |
| **4.** | Ursolic Acid | 456.70 | 2 | 3 | 3.95 | 57.53 | Yes; 1 violation |
| **5.** | Chalcone | 208.26 | 0 | 1 | 2.53 | 17.07 | Yes; 0 violation |
| **6.** | Linoleic Acid | 280.45 | 1 | 2 | 6.86 | 37.30 | Yes; 1 violation |
| **7.** | Linolenic Acid | 278.44 | 1 | 2 | 5.84 | 37.30 | Yes; 1 violation |
| 8. | Ibuprofen (Standard drug) | 206.28 | 1 | 2 | 2.17 | 37.30 | Yes; 0 violation |

**TABLE 5. Docking Scores of Selected Compounds**

| SNO | COMPOUND NAME | BINDING ENERGY | BINDING ENERGY |
|---|---|---|---|

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| | | INTERLEUKIN-8 | INTERLEUKIN-6 |
|---|---|---|---|
| 1. | Caryophyllene | -11.9869 kcal/mol | -9.68869 kcal/mol |
| 2. | Solasodine | -10.4113 kcal/mol | -10.5702 kcal/mol |
| 3. | Cubebene | -14.156 kcal/mol | -9.49557 kcal/mol |
| 4. | Ursolic Acid | -12.4167 kcal/mol | -10.2245 kcal/mol |
| 5. | Chalcone | -11.8763 kcal/mol | -10.1946 kcal/mol |
| 6. | Linoleic Acid | -10.7096 kcal/mol | -11.0696 kcal/mol |
| 7. | Linolenic Acid | -10.4617 kcal/mol | -10.2712 kcal/mol |
| 8. | Ibuprofen (Standard) | -9.71536 kcal/mol | -8.42993 kcal/mol |

## III. CONCLUSION

A series of phytochemical constituents were selected and evaluated for their pharmacological activity against Sinusitis, We have performed various studies like predicting their Biological activity (PASS prediction), toxicity prediction (GUSAR), physicochemical evaluation Swiss ADME and molecular docking analysis (Argus lab). Compounds Caryophyllene, Cubebene, urosolic acid, Chalcone, showed maximum potency and binding affinity towards the protein (IL8 receptor). For sinusitis, the constituents Solasodine, Linoliec acid, Linolinic acid, ursolic acid, have shown good binding affinity towards the protein (IL6 receptor). From the above results, we can conclude that the compunds binded to IL8 receptor are more potent than compounds binded to IL6 and these compounds have the ability to bind to the receptor and can be able to treat disease. In future, the compounds with the highest binding affinity will be selected for synthesis, invitro and invivo studies against the sinusitis.

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