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# IN-SILICO MOLECULAR DOCKING ANALYSIS OF POTENTIAL PHYTOTHERAPEUTICS FROM THE MEDICINAL HERB *CORALLOCARPUS EPIGAEUS* FOR TREATING URTICARIA

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## ABSTRACT

Urticaria commonly called by its name nettle rash characterized by the presence of redness, erythematous and oedematous papules. These marked inflammatory responses are majorly due to vasoactive mediators like histamine, released from mast cells. It was evident through several research outcomes that there was a remarkable increase in the expression of enzymes such as cyclooxygenase I and II that was observed in the patients with chronic urticaria. Hence management of pain and itching seems to be greater burden for patients reported with urticaria. Modern conventional medications such as anti-histamine, Analgesic and anti-inflammatory drugs including steroidal preparations currently used for clinical management of urticaria further worsen the condition by imparting unnecessary adverse events like ulcer, hypertension, dizziness, liver and kidney dysfunction etc. Herbal drugs become the essential components of siddha system of traditional medicine as its philosophy of healing greatly relies on healing by nature and also balancing the fundamental humors of the human body. India known for its herbal heritage of which flora comprises of several biologically significant herbs like *Corallocarpus epigaeus*. The main aim of the resent investigation is to screen the four bioactive phytocomponents such as Ascorbic acid, Beta sitosterol, Sesquiterpene, Tocopherol against the target Histamine 1 receptor-3RZE, Prostaglandin H2 synthases-1IGX, Cyclooxygenase I-3KK6, Cyclooxygenase 2-6COX along with their respective standard Cetirizine, Salycilic acid, Ibuprofen and Celecoxib. The results of the present investigation clearly shows that all the four bioactive compound screened In-silico has tendency to binding with the most significant active site amino acid residue present in the Histamine 1 receptor, Prostaglandin H2 synthases, Cyclooxygenase I and it was further observed that none of the compound has bound with Cyclooxygenase 2. From the results of the present investigation it was concluded that the phytotherapeutics present in the herb Corallocarpus epigaeus will be effective in management of urticaria.

**KEY WORDS:** ***Siddha system, Corallocarpus epigaeus, Urticaria, Histamine, Prostaglandin synthases, Cyclooxygenase, phytocomponents***

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## 1. Introduction

Urticaria is a kind of dermal inflammation characterized by edema and swelling due to leakage of fluid in response of vascular dilatation. Event of inflammation greatly triggered by mast cell degranulation and also due to release of inflammatory cytokines such as prostaglandins, leukotriene and chemokines hence pain and itching become impartial clinical symptoms of patient with urticarial [1]. National and regional guidelines for the diagnosis and treatment of urticaria have been previously published [2-4].

Anti-histamines and anti-inflammatory agents seems to be the first line drugs for treating urticarial which provides symptomatic relief where in usage of first generation antihistamine imparts side effect such as sedation, drowsiness, blurred vision, agitation, constipation and further. Further the chronic usage of anti-inflammatory and analgesic will often ends up in undesirable effects like ulceration, hypertension, dizziness and heart burn. Exploration of alternate therapeutic remedy from the herbal origin is the need of the hour in management of inflammatory disorders like urticaria.

People around the globe using herbal products as an alternative remedy in addition to modern medicine for their basic health care needs. India is rich in green diversity and comprises of almost 7% of the world's flowering plants [5-6].

Ethnomedicinal studies in the Eastern Ghats of Tamil Nadu have been carried out previously by a number of researchers [7]. However, there is not much information available on ethnoveterinary medicine in the Eastern Ghats of India. The genus corallocarpus contains about 43 species of tendril-bearing climbing herbs, distributed in tropical Africa, Persian gulf region, and India [8].

Corallocarpus epigaeus: The herb belongs to the family Cucurbitaceae. The plant is indigenously known as murdonda, Nagadonda in telugu, Akasgaddah in hindi and Akasagarudan in tamil. The plant is reported to contain a sesquiterpene [9]. The roots and rhizomes are having many traditional claims especially in syphilitic cases, old venereal complaints, and chronic dysentery [10]. It is also an effective remedy for diabetes [11], herpes, and Anthelmintic [13], rheumatism and snake bite. Decoction of powder root has given benefit in cases of chronic mucous enteritis.

Molecular docking is a key tool in structural molecular biology and computer-assisted drug design. The goal of ligand-protein docking is to predict the predominant binding mode(s) of a ligand with a protein of known three-dimensional structure. Successful docking methods search high-dimensional spaces effectively and use a scoring function that correctly ranks candidate dockings [14].

The main aim of the present investigation is to screen the anti- allergic potential of the bioactive phytotherapeutics ascorbic acid, Beta sitosterol, sesquiterpene and tocopherol from the herb Corallocarpus Epigaeus against Histamine 1 receptor with PDB 3RZE, Prostaglandin H2 synthases- PDB 1IGX, Cyclooxygenase I- PDB 3KK6, Cyclooxygenase 2- PDB 6COXalong with the standard along with standard cetirizine, salycilic acid, ibuprofen and celecoxib using auto-dock computational docking analysis.

## 2. Materials and Methods

### 2.1 Software's required

Several docking tools were been used in recent times which works behind structure-based drug design strategies one among which is auto dock a componential software tools used to analyze the protein Dipeptidyl peptidase-4 (DPP-4) and to study the binding energy properties with the following lead component such as Ascorbic acid, Beta sitosterol, Sesquiterpene and Tocopherol along with standard Cetirizine, Salycilic acid, Ibuprofen and Celecoxib. Histamine 1 receptor-3RZE, Prostaglandin H2 synthases-1IGX, Cyclooxygenase I-3KK6, Cyclooxygenase 2-6COX was obtained from protein data bank (www.pdb.org/pdb/). To get insight the intermolecular interactions, the molecular docking studies were done for the above mentioned phytoconstituents along with standard at the active site 3D space of receptor of interest using auto dock – docking tool module.

### 2.2. Ligand preparation

The ligands such as Ascorbic acid, Beta sitosterol, Sesquiterpene and Tocopherol along with standard Cetirizine, Salycilic acid, Ibuprofen and Celecoxib were built using Chemsketch and optimized using

Docking server online web tool as shown in Figure 1 and 2 for docking studies by using Geometry optimization method MMFF94 and charge calculation was carried out based on Gasteiger method at PH 7 as shown in Table 1.

**Table 1: Ligand Properties of the selected Lead Molecules**

| S.No | Name of the Compounds | Molar weight g/mol | H Bond Donor | H Bond Acceptor | Rotatable bonds |
|---|---|---|---|---|---|
| 1 | Ascorbic Acid | 176.124 g/mol | 4 | 6 | 2 |
| 2 | Beta Sitosterol | 414.718 g/mol | 1 | 1 | 6 |
| 3 | Sesquiterpene | 480.777 g/mol | 0 | 2 | 20 |
| 4 | Tocopherol | 430.717 g/mol | 1 | 2 | 12 |
| 5 | Cetirizine | 461.808 g/mol | 1 | 5 | 8 |
| 6 | Salicylic acid | 138.122 g/mol | 2 | 3 | 1 |
| 7 | Celecoxib | 381.373 g/mol | 1 | 7 | 3 |
| 8 | Ibuprofen | 206.285 g/mol | 1 | 2 | 4 |

**Fig 1: 2D Structure of lead 1.Ascorbic acid 2. Beta sitosterol 3.Sesquiterpene 4.Tocopherol 5.Cetirizine 6.Salycilic acid 7.Ibuprofen and 8.Celecoxib**

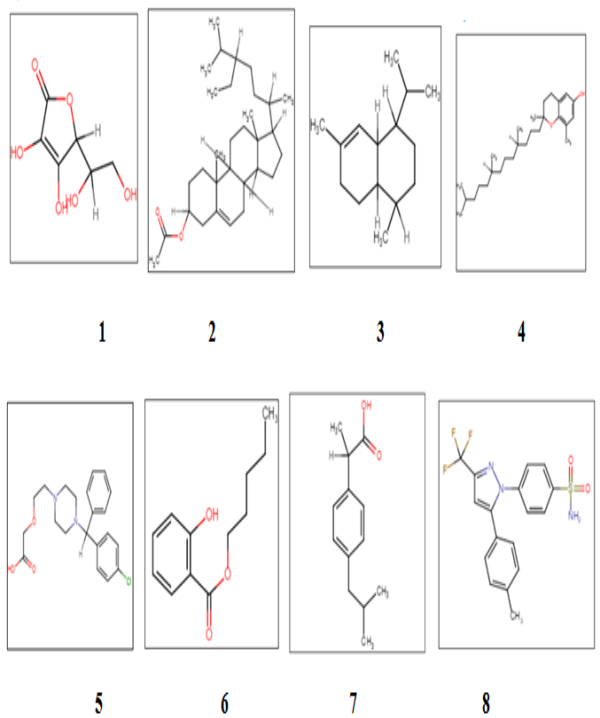
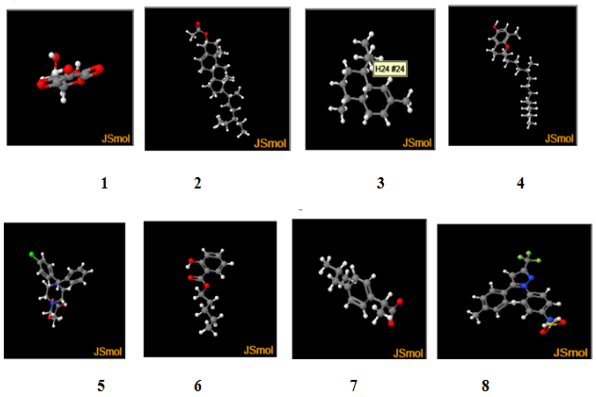



**Fig 2: 3D Structure of lead 1.Ascorbic acid 2. Beta sitosterol 3.Sesquiterpene 4.Tocopherol 5.Cetirizine 6.Salycilic acid 7.Ibuprofen and 8.Celecoxib**




### 2.3. Active Site Prediction

Active site of enzyme was obtained by LIGSITE web server by using the automatic identification of pockets on protein surface given 3D coordinates of protein. The potential ligand binding sites in Histamine 1 receptor, Prostaglandin H2 synthases, Cyclooxygenase I, Cyclooxygenase 2 target protein is identified using grid space of 1 and probe of radius 5.0 angstrom [15]. Ligand site prediction was performed by using online tool GHECOM and the respective pockets calculations [16-17].

### 2.4. Docking Methodology

Docking calculations were carried out using Docking Server [18- 19]. Gasteiger partial charges were added to the ligand atoms. Non-polar hydrogen atoms were merged, and rotatable bonds were defined. Docking calculations were carried out based on the binding free energy on the following compounds like Ascorbic acid, Beta sitosterol, Sesquiterpene and Tocopherol along with standard Cetirizine, Salicylic acid, Ibuprofen, Celecoxib band their binding affinity towards the target protein with Histamine 1 receptor, Prostaglandin H2 synthases, Cyclooxygenase I, Cyclooxygenase 2 as shown in figure 3 to 6. Essential hydrogen atoms, Kollman united atom type charges, and solvation parameters were added with the aid of Auto Dock tools. Affinity (grid) maps of Å grid points and 0.375 Å spacing were generated using the Autogrid program. Auto Dock parameter set and distance-dependent dielectric functions were used in the calculation of the van der Waals and the electrostatic terms, respectively. Docking simulations

were performed using the Lamarckian genetic algorithm (LGA) and the Solis and Wets local search method [20]. Initial position, orientation, and torsions of the ligand molecules were set randomly. All rotatable torsions were released during docking. Each docking experiment was derived from 2 different runs that were set to terminate after a maximum of 250000 energy evaluations. The population size was set to 150. During the search, a translational step of 0.2 Å, and quaternion and torsion steps of 5 were applied [21].

**Fig 3:Target protein Histamine 1 receptor with PDB code 3RZE**

**Fig 4:Target protein Prostaglandin H2 synthases with PDB code 1IGX**

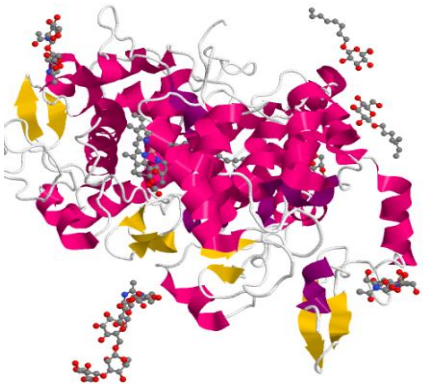


**Fig 5:Target protein Cyclooxygenase 2 with PDB code 6COX**

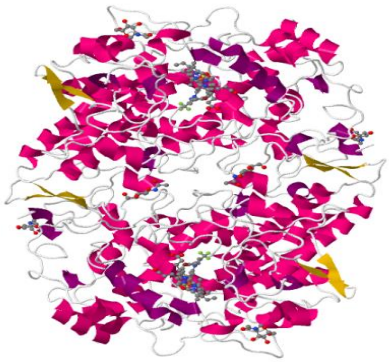
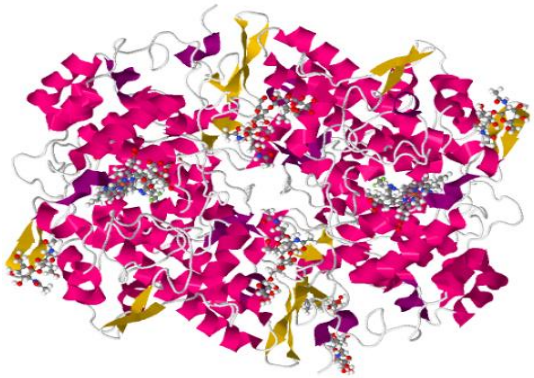


**Fig 6:Target protein Cyclooxygenase I with PDB code 3KK6**



## 3. Results

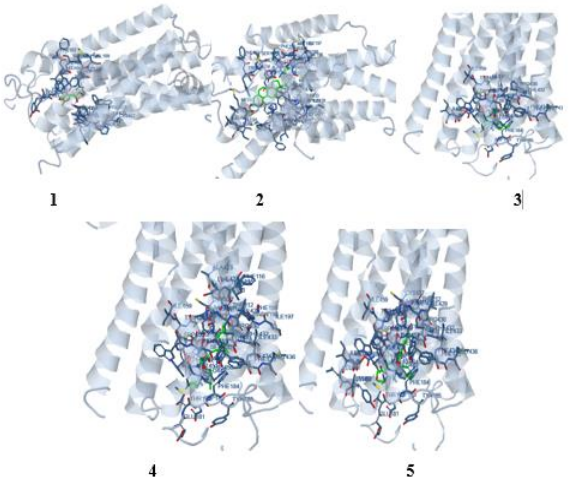
### 3.1. Dock score of Ligands with Histamine 1 receptor

Amino acid 428 TRP is the most significant residue involved in mediating histamine 1 receptor activity. Binding of lead compounds with this core residue may has H1 receptor blocking activity out of four compound's Ascorbic Acid, Beta Sitosterol and Tocopherol has tendency to bind with Amino acid 428 TRP, similar to that of the standard cetirizine. Hence these compounds possess promising Histamine 1 receptor blocking activity. Whereas lead Sesquiterpene was unable to bind with Amino acid 428 TRP and hence it doesn't has histamine 1 receptor blocking activity. The docking score with respect to Binding Free energy, Inhibition constant including Total Interaction Surface were listed in table 2 and illustrated in figure 7.

**Table 2: Summary of the molecular docking studies of compounds against Histamine 1 receptor**

| Compound | Docking Score (Est Free Binding Energy k Cal/ mol) | Inhibition constant Ki µM (*mM)(** nm) | Electrostatic energy Kcal/mol | Intermolecular energy Kcal/mol | Total Interaction Surface |
|---|---|---|---|---|---|
| Ascorbic Acid | -4.85 | 278.87 | -0.14 | -4.7 | 427.58 |
| Beta Sitosterol | -8.31 | 811.62** | -0.01 | -10.08 | 773.35 |
| Sesquiterpene | -7.44 | 3.51 | 0 | -7.74 | 634 |
| Tocopherol | -6.05 | 36.65 | -0.04 | -9.72 | 994.11 |
| Cetirizine | -5.58 | 81.77 | -0.19 | -8.95 | 782.54 |

**Fig 7: Possible ligand binding pockets on the surface of target against Histamine 1 receptor with PDB code 3RZE. Pockets calculated by GHECOM.1.Ascorbic acid 2.Beta sitosterol 3.Sesquiterpene 4.Tocopherol and 5. Cetirizine**



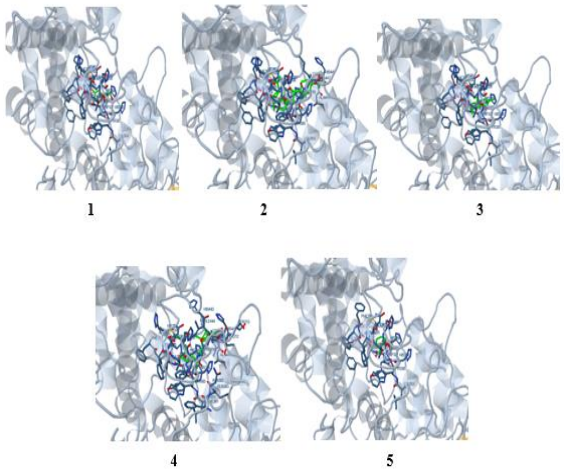

### 3.2. Dock score of Ligands with Prostaglandin H2 synthases

Amino acids such as 202 ALA, 206 THR, 385 TYR, 338 HIS and 390 LEU are the core residues involved in mediating the Prostaglandin Synthase enzyme activity. Binding of lead compounds with this core residue may inhibit the enzyme activity .Out of four compound's Beta Sitosterol and sesquiterpene has 6 interactions similar to that of the standard Salicylic acid. Other compounds such as Ascorbic Acid and Tocopherol have 5 and 4 interactions similar to that of the standard. Hence these compounds possess promising Prostaglandin Synthase enzyme inhibition activity. The docking score with respect to Binding Free energy, Inhibition constant including Total Interaction Surface were listed in table 3 and illustrated in figure 8.

**Table 3: Summary of the molecular docking studies of compounds against Prostaglandin H2 synthases**

| Compounds | Docking Score (Est Free Binding Energy k Cal/ mol) | Inhibition constant Ki µM (*mM)(**nm) | Electrostatic energy Kcal/mol | Intermolecular energy Kcal/mol | Total Interaction Surface |
|---|---|---|---|---|---|
| Ascorbic Acid | -5.39 | 111.03 | -0.07 | -5.37 | 459.97 |
| Beta Sitosterol | -5.65 | 72.64 | 0 | -9.11 | 922.79 |
| Sesquiterpene | -8.74 | 398.87** | 0 | -9.04 | 594.84 |
| Tocopherol | -7.15 | 5.72 | 0.01 | -10.22 | 883.92 |
| Salicylic acid | -5.24 | 145.22 | -0.04 | -5.82 | 395.57 |

**Fig 8: Possible ligand binding pockets on the surface of target against Prostaglandin H2 synthases receptor with PDB code 1IGX. Pockets calculated by GHECOM.1.Ascorbic acid 2.Beta sitosterol 3.Sesquiterpene 4.Tocopherol and 5. Salicylic acid**



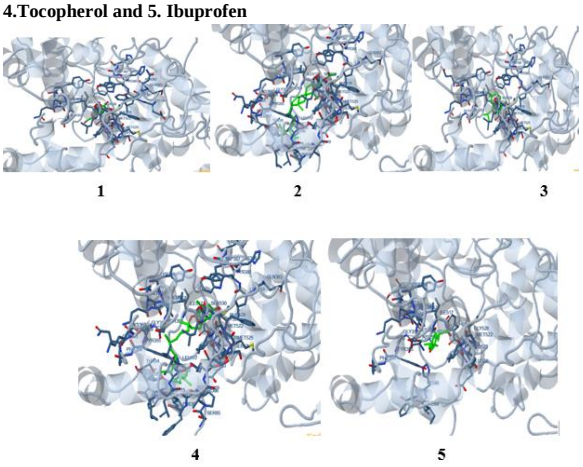

### 3.3. Dock score of Ligands with Cyclooxygenase I

Amino acids such as 192 GLN, 352 LEU and 523 ILE are the core residue involved in mediating the Cyclooxygenase I enzyme activity .Binding of lead compounds with this core residue may inhibit the enzyme activity .Out of four compound's Ascorbic Acid and Beta Sitosterol has 2 interactions similar to that of the standard Ibuprofen. Other compounds such as Ascorbic Acid and Beta Sitosterol have one interaction similar to that of the standard. Hence these compounds possess promising Cyclooxygenase I enzyme inhibition activity. The docking score with respect to Binding Free energy, Inhibition constant including Total Interaction Surface were listed in table 4 and illustrated in figure 9.

**Table 4: Summary of the molecular docking studies of compounds against Cyclooxygenase I**

| Compounds | Docking Score (Est Free Binding Energy k Cal/ mol) | Inhibition constant Ki µM (*mM) (**nm) | Electrostatic energy Kcal/mol | Intermolecular energy Kcal/mol | Total Interaction Surface |
|---|---|---|---|---|---|
| Ascorbic Acid | -4.71 | 350.89 | -0.02 | -4.74 | 490.52 |
| Beta Sitosterol | -3.4 | 3.23* | 0.02 | -10.6 | 960.29 |
| Sesquiterpene | -8.02 | 1.33 | -0.01 | -8.31 | 623.25 |
| Tocopherol | -8.04 | 1.28 | 0.03 | -11.94 | 1022.49 |
| Ibuprofen | -6.51 | 16.99 | 0 | -7.71 | 648.81 |

**Fig 9: Possible ligand binding pockets on the surface of target against Cyclooxygenase I receptor with PDB code 3KK6 .Pockets calculated by GHECOM.1.Ascorbic acid 2.Beta sitosterol 3.Sesquiterpene 4.Tocopherol and 5. Ibuprofen**



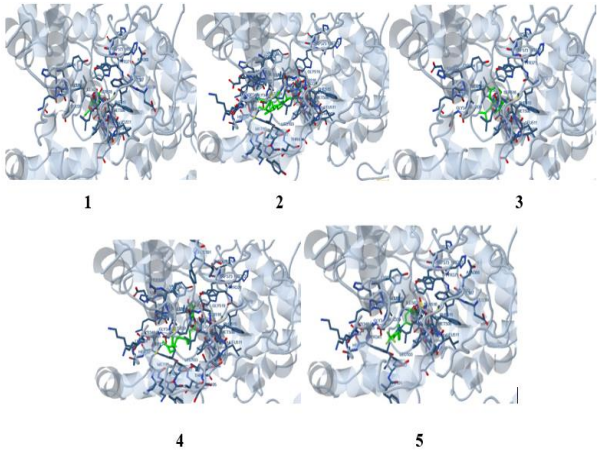

### 3.4.Dock score of Ligands with Cyclooxygenase II

Amino acids such as 90 HIS, 352 LEU, 353SER and 387 TRP are the core residues involved in mediating the Cyclooxygenase II enzyme activity .Binding of lead compounds with this core residue may inhibit the enzyme activity. From the result obtained from the current docking analysis it was observed that none of the compounds has tendency to bind with the above mentioned core residue and hence it was concluded that none of the four compounds has tendency to inhibit the Cox II enzyme when compare to the standard celecoxib. The docking score with respect to Binding Free energy, Inhibition constant including Total Interaction Surface were listed in table 5 and illustrated in figure 10.

**Table 5: Summary of the molecular docking studies of compounds against Cyclooxygenase II**

| Compounds | Docking Score (Est Free Binding Energy k Cal/ mol) | Inhibition constant Ki µM (*mM) (**nm) | Electrostatic energy Kcal/mol | Intermolecular energy Kcal/mol | Total Interaction Surface |
|---|---|---|---|---|---|
| Ascorbic Acid | -4.52 | 485.94 | -0.03 | -4.48 | 490.45 |
| Beta Sitosterol | -4.6 | 425.55 | 0.04 | -6.42 | 640.33 |
| Sesquiterpene | -7.87 | 1.69 | -0.01 | -8.17 | 623.53 |
| Tocopherol | -5.54 | 87.08 | 0 | -9.03 | 955.53 |
| Celecoxib | -7.86 | 1.73 | -0.04 | -9.7 | 775.42 |

**Fig 10: Possible ligand binding pockets on the surface of target against Cyclooxygenase II receptor with PDB code 6COX. Pockets calculated by GHECOM.1.Ascorbic acid 2.Beta sitosterol 3.Sesquiterpene 4.Tocopherol and 5. Celecoxib**




## 4. Discussion

Computational docking is widely used for study of protein-ligand interactions and for drug discovery and development. Typically the process starts with a target of known structure, such as a crystallographic structure of an enzyme of medicinal interest. Docking is then used to predict the bound conformation and binding free energy of small molecules to the target [22].

Molecular docking has become an increasingly important tool for drug discovery. The Auto Dock Tools (ADT) graphical user interface was used to calculate Kollman charges for the protein and to add polar hydrogen. Molecular docking is a computational procedure that attempts to predict non-covalent binding of macromolecules or, more frequently, of a macromolecule (receptor) and a small molecule (ligand) efficiently, starting with their unbound structures, structures obtained from MD simulations, or homology modeling, etc [23].

COX-1 and COX-2 have similar structures and catalytic activities. The amino acid sequences for the substrate binding and catalytic sites are almost identical, but COX-2 has valine substituted for isoleucine at positions 434 and 523 [24-25].

Out of four compound's ascorbic acid and Beta sitosterol has 2 interactions similar to that of the standard Ibuprofen. Other compounds such as has one interaction similar to that of the standard on cyclooxygenase I receptor. Further it was also

noticed from the results obtained from the current docking analysis it was observed that none of the compounds has tendency to bind with the above mentioned core residue and hence it was concluded that none of the four compounds has tendency to inhibit the Cox II enzyme when compare to the standard celecoxib.

In recent time prostaglandin synthases have become an important drug target for the researchers working in the field of inflammation associated diseases like urticaria. As the enzyme prostaglandin synthase involved in catalyzing the production of prostaglandin which sensitize the nerve ending for modulate the amplitude of pain responses. It was observed from the results of the present investigation that the leads Beta sitosterol and sesquiterpene has 6 interactions similar to that of the standard Salicylic acid. Other compounds such as ascorbic acid and tocopherol have 5 and 4 interactions similar to that of the standard binding affinity towards prostaglandin H2 synthases [26].

Mast cell contributes to the major release of histamine which mediates most of the vascular event including vasodilation, flushing and redness. In turn histamine considerably triggers the episode of itching which is considerably the most important pathological hall mark of urticarial [27]. Use of antihistamine renders some potential side effects which include drowsiness, fatigue, headache, nausea and dry mouth. Results of the present investigation has revealed that lead molecules such as ascorbic acid, Beta Sitosterol and tocopherol has tendency to bind with Amino acid 428 TRP, similar to that of the standard cetirizine. Hence these compounds possess promising Histamine 1 receptor blocking activity.

Computational docking minimizes the time consuming process of molecular analyses for selecting a suitable ligand which could be then applied for wet lab investigations [28]. Wickbery and Co-workers used Bioinformatics to narrow down suitable ligands for biomedical research and drug design as structure based design shows precisely the location and orientation of bound inhibitors and their physico-chemical properties.

## 5. Conclusion

Molecular docking of bioactive components like Ascorbic acid, Beta sitosterol, Sesquiterpene and Tocopherol present in Corallocarpus Epigaeus has been successfully validated against target receptors. The results of the study clearly justifies that all the four phytotherapeutics present in the herb Corallocarpus Epigaeus would have significant biding affinity towards the such as Histamine 1 receptor, Prostaglandin H2 synthases and Cyclooxygenase I. whereas none of the compound would exert the expected binding affinity on Cyclooxygenase II receptor. From this it was concluded that the herb Corallocarpus Epigaeus may act as a better therapeutic lead for clinical management of symptoms pertains to urticaria.

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## 6. References

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