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Docking studies: Search for possible phytoconstituents for the treatment of histamines

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ABSTRACT

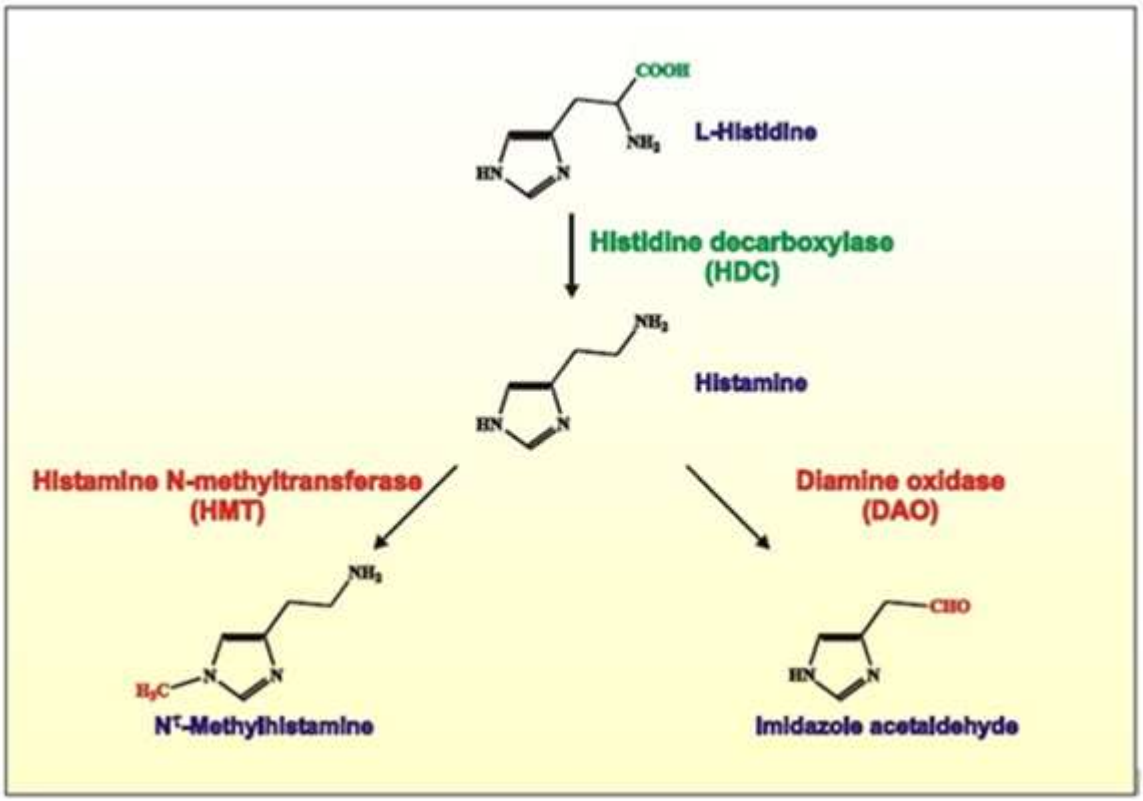
Binding interactions of drugs using docking studies is an important component of computer aided drug design. Histamine N-methyltransferase plays a significant role in degrading histamine and in regulating the airway response to histamine. It has a key enzyme in allergy and immune responses host defense against infection. Abnormal release of histamine, which is present in relatively high concentration in the lungs, causes serious allergic vasoconstriction and anaphylactic manifestation in human beings.. They were docked with the inhibitor binding cavity of the enzyme Histamine N-methyltransferase to understand the mode of binding interactions. A library of naturally occurring flavanoids like Apigenin, Acacetin, Baicalin, Chrysin, Luteolin and quercetin, Myricetin were docked into the active site cavity of target protein, HMT (PDB: 2AOT). Promethazine, a known Histamine N-methyltransferase inhibitor was used as standard. All the naturally occurring flavanoids showed comparable negative binding energies pointing towards the potent antihistamine. The results showed that all the selected flavonoids showed lesser binding energy ranging between -8.32 kcal/mol to -6.80kcal/mol when compared with that of the standard(-6.60 kcal/mol). These molecular docking analyses could contribute for the further development of Histamine N-methyltransferase inhibitors for the prevention and treatment of human allergic bronchospasm.

Key words: Docking, Flavanoids, Histamine, Histamine N-methyltransferase.

INTRODUCTION

Antihistamines a class of drugs, which blocks the effect of a histamine that is produced by the body, especially the mast cells, in response to an allergic reaction due to antibodyantigen interaction followed by degranulation of mast cell. They are used to treat symptoms of allergic reactions such as the sneezing and runny nose of hay fever, itching, swelling and other allergic rashes.. Histamine is broken down by histamine *N*-methyl transferase (HMT)and diamine oxidase.

A recent study reveals that histamine *N*-methyltransferase plays a significant role in degrading histamine and in regulating the airway response to histamine. It may be termed as key enzyme involved in allergy and immune responses host defense against infection. It is mainly known for its pathogenic action against allergy related asthma/human allergic bronchospasm.



Flavanoids represent an awfully important group of organic compounds exhibit significant biological activity, including anti-inflammatory and pharmacological effect. Researchers are underway to study the effect of several flavonoids in diseases such as pneumonia, cancer, amoebic dysentery, worm infestations and allergic disorders through bioinformatics studies of docking flavonoides on different proteinstructures involved in these diseases.

Molecular modelling techniques are used to predict how any proteininteracts with small drug like molecules. The ability of a protein to interact with small molecules governs a significant part of the protein's dynamics which may enhance/ inhibitits biological function. This plays an important role in the rational design of drugs. Present study aims to demonstrate the successful use of docking techniques to study the interaction of Histamine *N*-methyltransferase enzyme with naturally occurring flavonoids.

MATERIALS AND METHODS

I. Preparation of protein molecule

The experimental structure of Histamine N- Methyl tranferase (HMT)(PDB ID: 2AOT) as shown in Figure 1 was retrieved from the RCSB protein data bank as a PDB file. The protein molecules were prepared mainly by using the software Swiss PDB viewer.

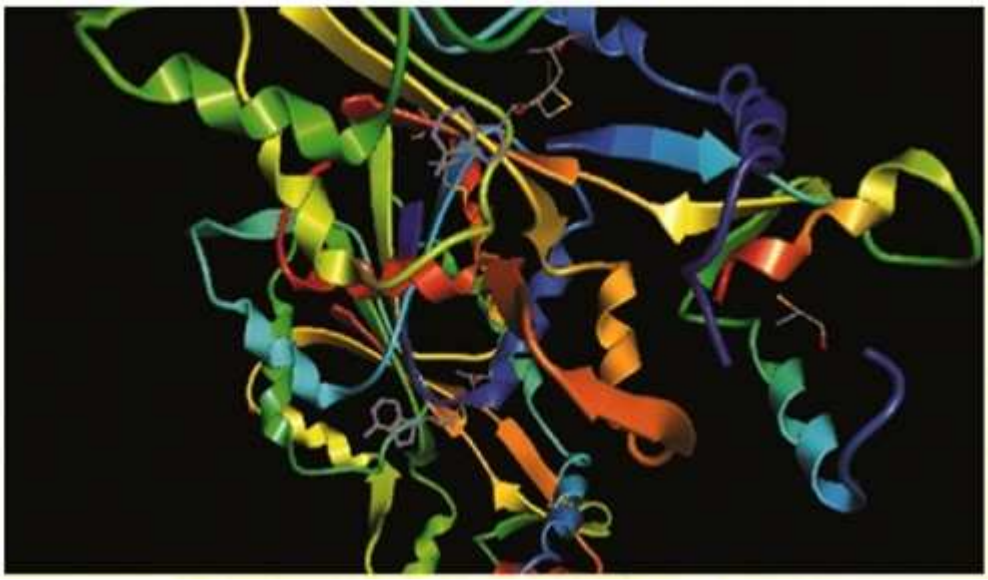
II. Preparation of ligand

The ligand compoundsnaturally occurring flavanoids like Apigenin, Acacetin, Baicalin, Chrysin, Luteolin and quercetin, Myricetin were drawn using ACD/ Chemsketch (12.0) (Alex, 2009) and saved in mol 2 format.

III. Argus Lab:

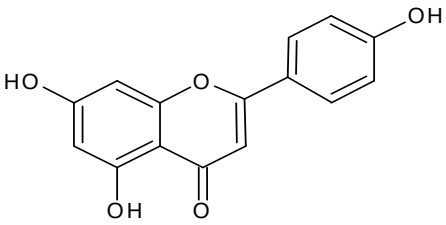
- *ArgusLab4.0* has fast become a favorite introductory molecular modeling package with academics mainly because of its user-friendly interface and intuitive calculation menus (Thompson, 2004)..
- Flexible ligand docking is possible with ArgusLab, where the ligand is described as a torsion tree and grids are constructed that overlay the binding site
- The N-lowest energy poses are retained and the final set of poses undergoes coarse minimization, re-clustering and ranking.
- Argus Lab 4.0 was used10 to perform all the docking techniques. The crystal structure used for the present study was found to be complexed with inhibitor diphenhydramine, was downloaded from Protein Data Bank (http://www.rscb.org/) as PDB files.

Fig1: Histamine N-Methyl transferase(HMT) – (2AOT)

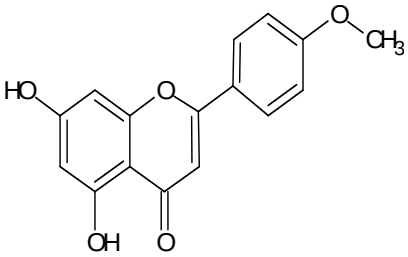


STRUCTURE OF LIGANDS: (Natural flavones)

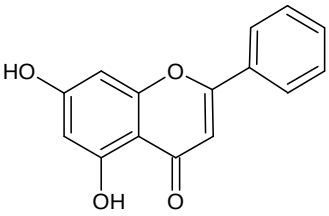
Apigenin



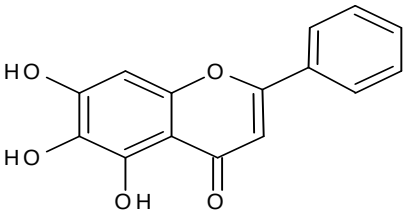
Acacetin



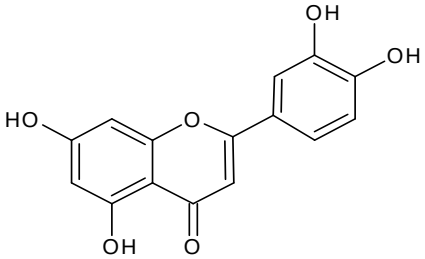
Chrysin



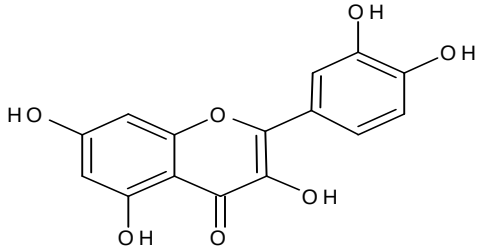
Baicalein



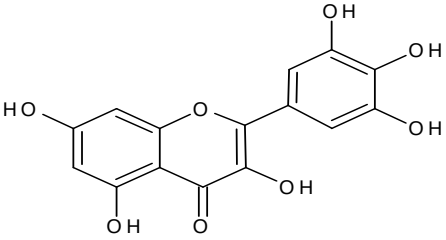
Luteolin



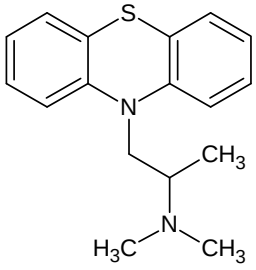
Quercetin



Myricetin



Promethazine(std)



IV. Docking of natural flavones to Histamine N-Methyl transferase:

- Docking of natural flavones withHistamine N-Methyl transferase was performed using ARGUS LAB4.0.
- The best docking solutions ARGUS LAB score for each compound was considered.
- A library of naturally occurring flavanoids like Apigenin, Acacetin, Baicalin, Chrysin, Luteolin and quercetin, Myricetin were docked into the active site cavity of target protein, HMT (PDB: 2AOT).
- Promethazine, a known Histamine *N*-methyltransferase inhibitor was used as standard.

Fig2: ACACETIN

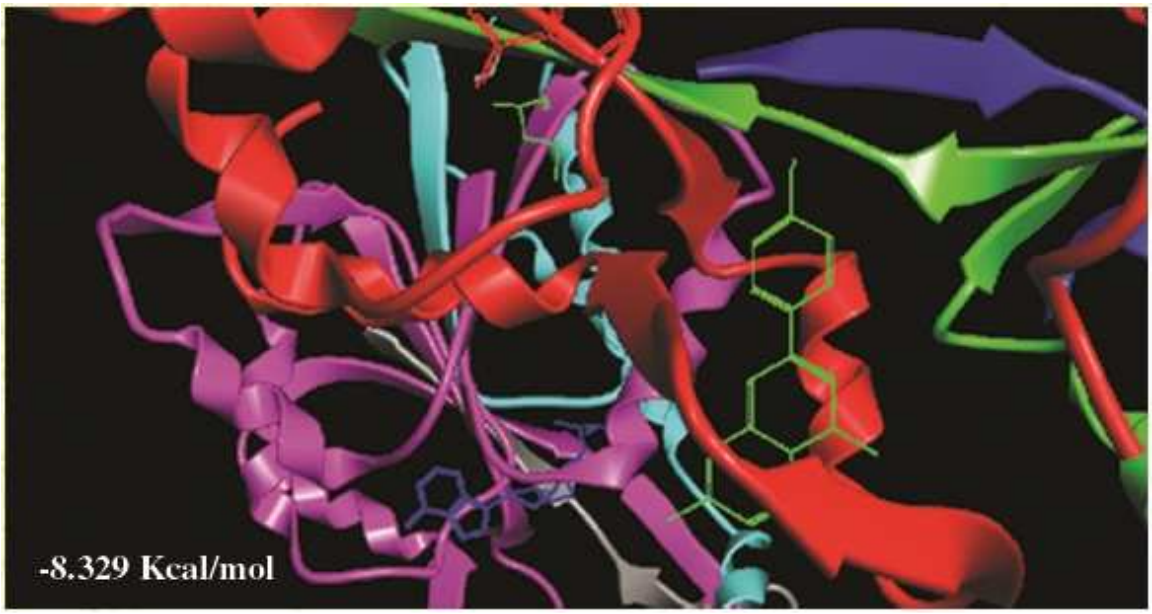


Fig3:BAICALIN

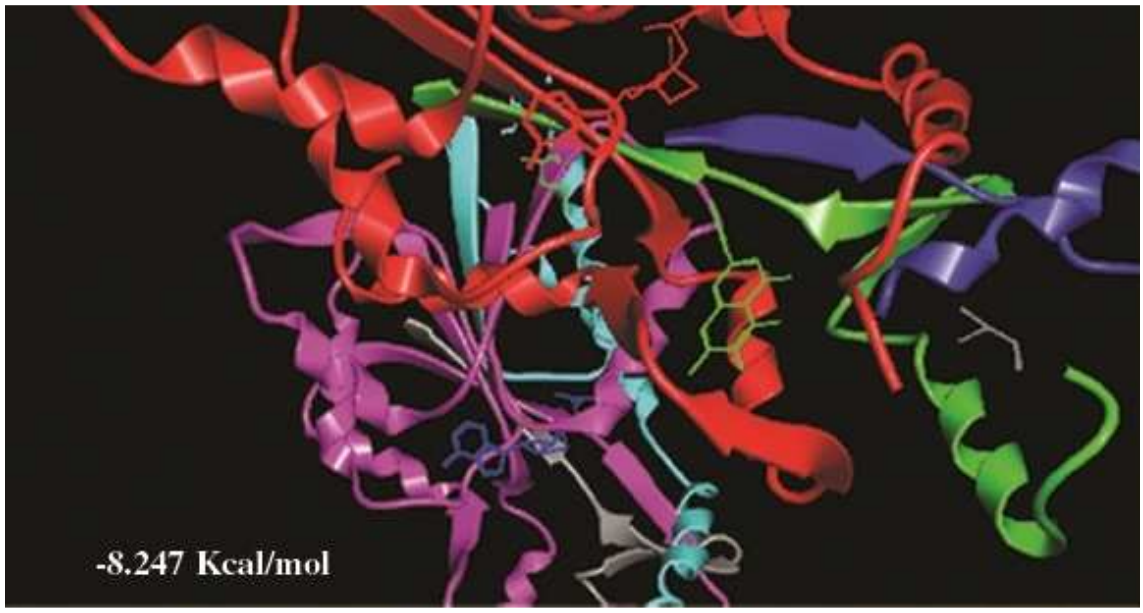
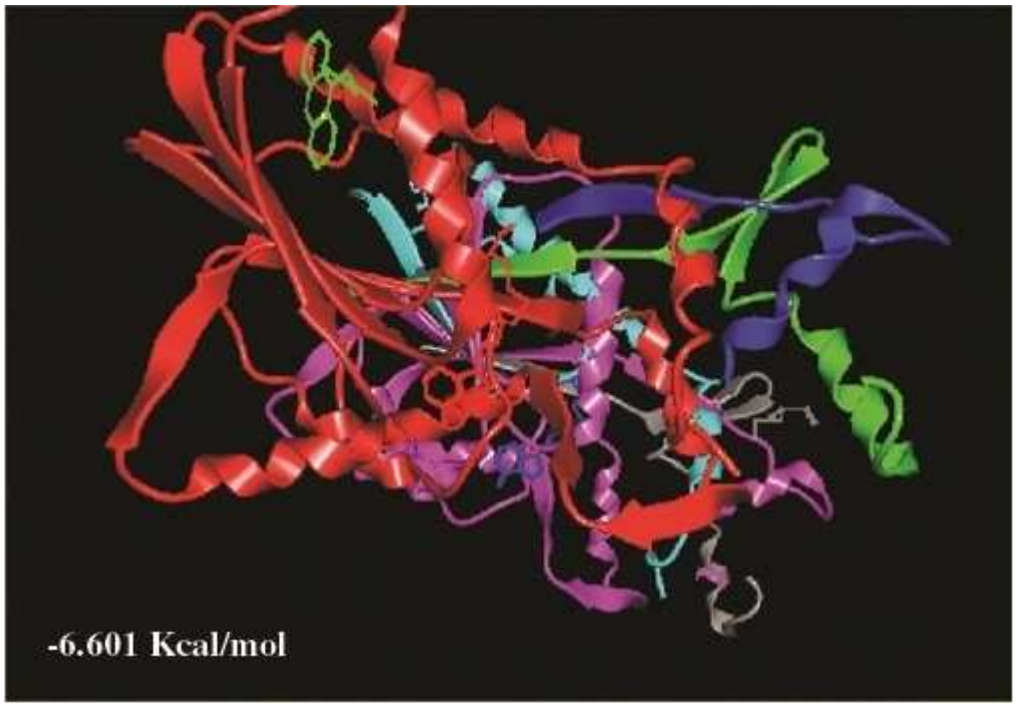


Table 1. ARGUS LAB scores and interactions of Promethazine drug and natural flavones with HMT.

NATURAL FLAVONES	ARGUS LAB Kcal/mol
Acacetin	**-8.329**
Apigenin	-7.670
Baicalin	**-8.247**
Chrysin	-7.980
Luteolin	-7.426
Quercetin	-6.802
Myricetin	-6.710
Promethazin(Standard)	**-6.601**

Fig4: PROMETHAZINE:



RESULTS AND DISCUSSION

➢ All the 7natural flavone (ligands) showed binding in the HMT active site with the binding scores between -8.329 and 6.710 kcal/mol, Table 1. These data clearly indicated their potency as anti-histamine heterocycles.
➢ Compound Acacetin(-8.329)and baicalin(-8.247)showed the highest binding score with HMT enzyme active site cavity with comparison to other ligands including well known anti histamines such as promethazine(-6.60).
➢ These molecular docking analysis could contribute for the further development of Histamine *N*-methyltransferase inhibitors for the prevention and treatment of human allergic bronchospasm.

CONCLUSION

❖Flavone derivatives could be a unique class of histamine inhibitors. As many flavanoids are naturally occurring and possess anti inflammatory and anti oxidant activity thus may show synerjistic effect along with H1-Histamine inhibition.
❖ The close overlapping shown in fig (2&3) defines the best choice of docking package according to result obtained in this work.
❖The data may open the now way of investigation of some novel potential antihistamines.
❖The negative binding scores, green procedure of synthesis, easy work up and isolation led chromen analogues as potential candidates for further research.

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