INTRODUCTION

Histamine is a small molecule derived from the decarboxylation of the amino acid called histidine. These histamine molecules are synthesized in all tissues but are mainly abundant in the skin, gastrointestinal tract, and lungs. The prominent source of this histamine is mast cells and other immune cells. When the allergen or antigen cross-links with IgE on the surface of immune cells, it responds by the liberating histamine molecules. Histamine [1-7], a chemical messenger, exerts many numerous physiological processes in hypersensitivity responses, gastric acid secretion, neurotransmission, immunomodulation, cell differentiation, and embryonic development through four distinct receptors: H1R, H2R, H3R, and H4R, which belong to class of G-protein–coupled receptors (GPCR) [8-14]. Histamine is best known as a mediator of allergic reactions and now recognized to participate in numerous other pathologic processes. The sensitivity of histamine depends on the type of receptor. It is mainly expressed in mast cells, monocytes, eosinophils, dendritic, and T-cells. Histamine 4 receptor, a type of G-protein coupled histamine receptor family identified in recent times, commonly known as H4R. The histamine receptors are differentially expressed in various cell types which when binds to a small biogenic amine molecule called histamine leads to various pathophysiological regulatory role in cellular events. H4R is expressed in numerous cells and tissues of immune system, especially in the hematopoietic sources; in other words, it is present in bone marrow, spleen, thymus, lung, and colon. As it is highly expressed in peripheral blood cells and intestinal tissues, the activation of the H4 receptor by the binding of histamine molecule enhances the activity of several chemotactic tracts and leads to chemotaxis, eosinophil, and neutrophil trafficking which causes inflammation. This in turn makes H4 receptor a potential target of allergic and inflammatory disorders. Hence, the unexplored biochemical activities and necessity to inhibit the histamine binding attracted biologist, thus serving as a novel target for pharmacological modulation of histamine–transferred immune signals. The unexplored biochemical activities attract biologist, and it serves as a novel target for pharmacological modulation of histamine-transferred immune signals. H4R shows 35% homology to H3R. H4R [7, 15-20] mainly distributes in hematopoietic cells and plays a key role in nociceptive responses, autoimmunodegree disorder, allergic conditions, colon cancer, and breast cancer. H4R belongs to the super family of GPCR. In connection with efforts rendered in finding out novel inhibitors for H4R, we perform virtual screening and docking studies, and with the best ligands, we have created a pharmacophore model, and quantitative structure activity relationship (QSAR) studies were performed.

METHODS

Homology modeling

The crystal structure of histamine 4 is not available in protein data bank (PDB). Hence, we developed the optimized model of H4R with the help of Easy Modeler. Hence, the crystal structure of histamine 1 which has been identified very recently is downloaded from the PDB (PDB ID 3RZE). This is used as template to construct the H4R model. The H4R sequence is retrieved from Gen Bank (Accession no QH3EN8). The model that is generated is then energy minimized. The optimized model is then validated using structure analysis and verification server.

Molecular docking

Preparation of the target protein using 'protein preparation wizard'. Pre-processing and heteronate for co-crystallized ligand were generated using Epik; protonation state and optimization of H-bonding of the protein side chains were assigned using protassign, energy
minimized (impref minimization) using optimized potential for liquid simulations (OPLS) 2001 force field. Receptor grid has been prepared with default parameters and without any constraints.

**Ligand preparation**

The ligands required for docking exported as a single file and are prepared by using the tool LigPrep utility of Schrodinger suite with default parameters, the ligand energy minimized by using OPLS 2005 (macromodel multiple minimization) and water as solvent. Ligand docking was performed using OPLS force field. To predict the binding affinity and preeminent docked structures, the combined ligand docking and energy grid scores were ranked by using Emodel and glide scores.

**Ligand docking**

Flexible docking was performed using the extra precision feature of glide 5.0 module implemented in the Schrodinger LLC. Visualization and analysis of protein-ligand complexes were performed using PyMOL ver.0.99 software (DeLano Scientific LLC, CA, USA), and the best-docked ligand will be classified based on the glide score.

**Phase methodology dataset and biological activity**

We take 11 natural antihistamines from literature studies, and their inhibitory concentration (IC\(_{50}\)) values are converted into p IC\(_{50}\) using following formula: p IC\(_{50}\) = -\(\log_{10}\) IC\(_{50}\) (Table 1).

**Creating pharmacophore sites and common pharmacophore hypothesis (CPH) generation**

The molecules are divided into actives and inactives according to the p IC\(_{50}\) values. The phase consists of the pharmacophore features such as hydrogen bond acceptor (A), hydrogen bond donor (D), hydrophobic/non-polar group (H), negatively ionizable (N), positively ionizable (P), and aromatic ring (R) which is used to create the pharmacophore sites for the ligands. The CPH is examined using scoring hypothesis.

**Scoring function**

The measurement of quality of alignment is done by means of survival score given as:

\[ S = W_{\text{site}}S_{\text{site}} + W_{\text{vec}}S_{\text{vec}} + W_{\text{vol}}S_{\text{vol}} + W_{\text{sel}}S_{\text{sel}} + W_{\text{m rew}} \]

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where \( W \) denotes weights, \( S \) denotes scores, \( S_{\text{site}} \) represents alignment score, \( S_{\text{vec}} \) represents vector score which is the averages of the cosine of the angles formed by corresponding pairs of vector features in aligned structures, \( S_{\text{vol}} \) represents volume score which is based on overlap of Vander Waals models of non-hydrogen atoms in each pair of structures, and \( S_{\text{sel}} \) represents selectivity score, and this accounts for what fraction of molecules is likely to match the hypothesis regardless of their activity toward the receptor. The default values for \( W_{\text{site}}, W_{\text{vec}}, W_{\text{vol}}, \) and \( W_{\text{sel}} \) are 1.0, whereas the default value for \( W_{\text{sel}} \) is 0.0. We have used the default values in all the cases for our hypothesis generation.

**Table 1: Compounds with IC\(_{50}\) values**

| Compounds       | IC\(_{50}\) |
|-----------------|------------|
| Hesperidin      | 9.5        |
| Vitexin         | 46.5       |
| Rutin           | 12.3       |
| Chlorogenic acid| 45.5       |
| Quercetin       | 15.4       |
| Myricetin       | 2.12       |
| Fisetin         | 3.7        |
| 3-methyl quercetin | 2.75    |
| Luteolin        | 18.6       |
| Catechin        | 49         |
| Kaempferol      | 0.84       |

\( IC_{50} \): Inhibitory concentration

**RESULTS AND DISCUSSION**

**Homology modeling**

The Ramachandran plot obtained from procheck showed that 90.9% of the residues were found to be in the most favored regions, indicating that our model was good (a good quality model would be expected to have over 90% in the most favored regions), and only 0.3% of the residues were found to be present in disallowed region. Thus, out of 390 residues, 328 residues were found in most favored regions, and only one residue was in the disallowed region (Fig. 1) [21-23].

**Molecular docking studies**

The active sites are predicted based on literature studies and the amino acids include Asp94, Tyr95, Glu182, Thr316, Thr319, and Phe344 [24]. The interactions of H4R with both natural and synthetic ligands are analyzed. In case of synthetic ligands, the common amino acids that interacted with histamine were Tyr95 and Thr323 (Table 2). In case of natural ligands, the common amino interactions were Tyr95, Glu182, Thr323, and Ser362 (Table 3).

In light of good docking score (glide score) and a number of hydrogen bonds shown by docking analysis in the comparison, following compounds show better efficiency: Hesperidin, vitexin, and dismosin such as 13.71 kcal\(^{-1}\), −11.34 kcal\(^{-1}\), and −10.87 kcal\(^{-1}\), respectively (Fig. 2). These natural compounds showing their best efficiency could be thus used as potential leads in drug designing. Furthermore, the natural compounds are found to be better inhibitors of H4R when compared to synthetic ligands based on the glide score. Thus, natural compounds can be more effective when used in the treatment of disease when compared to synthetic compounds [25].

**Atomic three-dimensional QSAR (3D-QSAR) generation**

The QSAR models were developed from a series of molecules, of varying activity, that have all been aligned to a CPH that is associated with a single reference ligand. All hypotheses that successfully generated and scored were then used to build pharmacophore-based 3D-QSAR models with grid spacing 1.0 A. PHASE supports only external validation, using a factual test set for which structures and activities are not considered for developing QSAR models. The developed 3D-QSAR models are validated by predicting activities of test set molecules which are measured in terms of Q-square values. The predictive ability of the developed models is measured by means of the Pearson correlation coefficient r value.
Table 2: Docking result of chemical inhibitors

| Name               | Cid number | Glide score | Glide score | H-bond length | Amino acid interaction |
|--------------------|------------|-------------|-------------|---------------|------------------------|
| Diphenhydramine    | 3100       | -6.75       | 2.353, 2.314| TYR 95, TYR 319|                        |
| A-943931           | 25068753   | -6.72       | 2.315, 2.341, 2.410| TYR 95, GLU 182|                        |
| Thioperamide       | 3035905    | -6.32       | 1.813       | THR 323, TYR 340|                        |
| [N]-10191584       | 104445295  | -5.73       | 2.584, 1.669| SER 179, THR 323|                        |
| [N]-7777210        | 4908365    | -5.67       | 1.756       | TYR 95             |                        |
| Cetirizine         | 2678       | -5.42       | 2.623, 1.717| THR 323, SER 320|                        |
| Clemastine         | 269876     | -1.65       | No interaction| No interaction|                        |
| Loratadine         | 3957       | -0.44       | No interaction| No interaction|                        |
| Histamine          | 774        | -6.54       | No interaction| No interaction|                        |

Table 3: Docking result of natural ligands

| Name               | Compound ID (PubChem) | Glide score | Interaction | H-bond length |
|--------------------|-----------------------|-------------|-------------|---------------|
| Hesperidin         | 10621                 | -1.371      | Thr323, Glu182, Phe169, Ser331, Pro335 | 1.845, 1.491, 1.780, 1.843, 1.940 |
| Vitexin            | 5280441               | -11.34      | Gln182, Thr323 | 1.763, 2.573 |
| Diosmin            | 5281613               | -10.87      | Thr323, Phe169 | 2.037, 1.802 |
| Rutin              | 5280805               | -10.43      | Gln182, Tyr95, Thr323 | Glu182 (1.713,2.013), Tyr95 (1.812,2.384), Thr323 (2.094,1.429, 2.358) |
| Alloin             | 12305761              | -9.82       | Ser162, Thr323, Thr319, Phe169 | Ser162 (1.994,2.495), 1.711, Tyr319 (1.983, 2.329,2.614), 2.183 |
| Chlорогенный кислота | 1794427              | -9.22       | Ser162, Glu163, Ser179, Thr323, Ser320 | 2.315, 1.733, 1.629, 2.172, 2.039 |
| Quercetin          | 5280343               | -9.06       | Phe169, Tyr95, Tyr319, Glu182 | 1.991, 2.090, 2.558, Glu182 (1.808,1.676) |
| Myricetin          | 5281672               | -8.95       | Thr323, Glu182, Ser162 | 1.869, Glu182 (1.650, 1.718), 2.362 |
| Fisetin            | 5281614               | -8.61       | Phe169, Gln182, Tyr95, Tyr319 | 1.987, Glu182 (1.8,1.672), 2.1, 2.566 |
| Hydroyxypeucedanin hydrate | 17536             | -8.48       | Thr323, Tyr95 | 1.866, Tyr95 (2.614, 1.971, 1.893) |
| 3-метилкуверсетин  | 5281654               | -8.29       | Gln163, Thr323, Glu182, Tyr95 | 1.829, 1.928, 1.643, 3.272, 2.375 |
| Luteolin           | 5280445               | -8.23       | Ser162, Glu182, Tyr319 | 2.012, 1.725, 2.510 |
| Catechin           | 9064                  | -8.13       | Thr323, Glu163, Tyr95, Tyr319, Glu182 | 2.151, 1.817, 2.451, 2.328, Glu182 (1.636, 1.673) |
| Kaempferol         | 5280863               | -8.04       | Ser162, Glu182, Tyr95, Tyr319 | 2.574,19182.112, Tyr319 (2.402,2.101) |
| Byakangelin        | 10211                 | -7.95       | Gln182, Tyr95 | 1.991, Tyr95 (1.965, 2.089, 2.676) |
| Baijalin           | 5281605               | -7.67       | Phe169 | 2.214 |
| Piceatannol        | 667639                | -7.65       | Gln182, Ser162 | Glu182 (1.737,1.638), 2.108 |
| Apigenin           | 5280443               | -7.63       | Gln182, Phe169 | 1.709, 2.169 |
| Acacetin           | 5280442               | -7.63       | Thr323, Phe169 | 2.622, 2.004 |
| Ginkgol           | 5271805               | -7.53       | Thr178, Phe169, Ser337 | 2.246, 2.226, 1.804 |
| 3-Метилкуверсетин  | 5280681               | -7.44       | Gln182, Tyr95, Tyr319 | Glu182 (1.937,2.100), 2.030, 2.611 |
| Cetirizine         | 2678                  | -7.35       | Ser179, Thr323 | 2.203, 2.205 |
| 8-Гинерол          | 168114                | -7.22       | Gln163, Tyr95 | 1.618, 1.894 |
| Xanthotoxol        | 65090                | -7.15       | Tyr95 | 1.926, 2.047 |
| Xanthotoxin        | 4114                 | -6.44       | Tyr95, Tyr319 | 2.078, 2.202 |
| Diphenhydramine    | 3100                  | -6.27       | Tyr95 | Tyr95 (2.159, 2.246) |
| Flavone            | 10680                | -6.02       | Tyr95, Tyr319 | 2.342, 2.308 |

Pharmacophore hypothesis
Pharmacophore modeling studies were done using IC50 values of the top scoring natural antihistamines, and subsequently a pharmacophore compound consisting of 7 essential pharmacophoric features of three Hydrogen bond Donor, two hydrogen bond Acceptor and two hydrophobic ring structure was developed (Fig. 3, Table 4).

The crystal energy is minimized using the OPLS 2005 force field energy. The ligands are built using Maestro build panel and prepared by a LigPrep 2.2 module, which uses OPLS 2005 force field to produce the lowest energy conformer of ligands. The training and test set were selected randomly, and the seed value for activity threshold given was 8.432 to ensure that the assignment is randomly done (Fig. 4).

Due to various difficulties in the crystallization of GPCR protein, the crystal structure of H4R is not yet solved. The crystal structure of human histamine H1R is reported very recently. Hence, we developed a homology model of H4R based on the crystal structure of H1R [15]. Then, several synthetic and natural ligands including agonists and antagonists are docked in the H4R model [15]. The synthetic and natural

| Rank | Feature label | Score | Type | Number | Source |
|------|---------------|-------|------|--------|--------|
| 1    | R27           | -1.26 | R    | 26     | Aromatic ring |
| 2    | D18           | -0.96 | D    | 17     | H phobe |
| 3    | D20           | -0.96 | D    | 19     | H Bond |
| 4    | R26           | -0.94 | R    | 25     | Ring chem score |
| 5    | A9            | -0.78 | A    | 8      | H Bond |
| 6    | D23           | -0.48 | D    | 22     | H Bond |
| 7    | A11           | -0.26 | A    | 10     | PhobEn+H Bond |
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various allergic and inflammatory diseases. The pharmacophore-based 3D-QSAR model generated from natural antihistamines can provide intricate structural knowledge about a new class of anti-allergic and anti-inflammatory drug research. The developed pharmacophore model can help us in virtual screening of finding new potent ligands against allergy which can help us in the better therapy of allergic conditions.

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Table 5: Statistical data for best QSAR model by the PLS method for natural antihistamines

| Hypothesis ID | Survival score | $R^2$ value | RMSE values | F | $Q^2$ value | Pearson-R values |
|---------------|----------------|-------------|-------------|---|-------------|------------------|
| AAARR. 4      | 3.906          | 0.8533      | 0.4914      | 29.1 | 0.45        | 0.8954           |
| AADDR. 112     | 3.906          | 0.759       | 0.3363      | 15.7 | 0.483       | 0.8868           |
| ADRRR. 4       | 3.914          | 0.7308      | 0.2788      | 13.6 | 0.4989      | 0.9673           |
| AARRR. 16      | 3.914          | 0.8962      | 0.6611      | 34.5 | 0.451       | 0.7932           |

QSAR: Quantitative structure activity relationship, RMSE: Root-mean-square error, $R^2$: The coefficient of determination, $Q^2$: Cross-validated $R^2$, F: F test score, R: Correlation between experimental and predicted activity for the test set.

CONCLUSION

In light of good glide score, it can be concluded that the natural antihistamines such as hesperidin, vitexin, and diosmin show better efficiency when compared to synthetic compounds and could be used as potential leads in drug designing against H4 receptor to treat various allergic and inflammatory diseases. The pharmacophore-based 3D-QSAR model generated from natural antihistamines can provide intricate structural knowledge about a new class of anti-allergic and anti-inflammatory drug research. The developed pharmacophore model can help us in virtual screening of finding new potent ligands against allergy which can help us in the better therapy of allergic conditions.

Fig. 2: Interaction of the three top scored natural ligands in the binding pocket of target molecules

Fig. 3: The pharmacophore hypothesis where the red ball denotes hydrogen bond donor and brown ring denotes ring feature

Fig. 4: The scatter plots of quantitative structure activity relationship model applied to all compounds in the training and test set

ligands are collected from literature searches and Duke’s phytochemical database, respectively. The interaction of ligands with the model is analyzed, and based on the docking score, potential ligand is identified. Pharmacophore modeling studies are done using IC50 values of 11 natural antihistamines which are collected from the literature. Thus, a five-point pharmacophore model is developed. The pharmacophore hypothesis is then used to yield a statistically significant 3D-QSAR model with a good correlation coefficient and predictive power [23-32] (Table 5).

CONCLUSION

In light of good glide score, it can be concluded that the natural antihistamines such as hesperidin, vitexin, and diosmin show better efficiency when compared to synthetic compounds and could be used as potential leads in drug designing against H4 receptor to treat various allergic and inflammatory diseases. The pharmacophore-based 3D-QSAR model generated from natural antihistamines can provide intricate structural knowledge about a new class of anti-allergic and anti-inflammatory drug research. The developed pharmacophore model can help us in virtual screening of finding new potent ligands against allergy which can help us in the better therapy of allergic conditions.

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