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# Molecular interactions of some natural ligands to explore their mechanism of actions as PDE-4B and 4D inhibitors in psoriasis: A molecular docking study

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Psoriasis is an autoimmune and inflammatory disease, that significantly affects human well-being. The chances of relapses of psoriasis are high even after steroidal therapy and other medicines. The proper treatment is unavailable due to a lack of understanding of the pathophysiology of this disease. Phosphodiesterase enzyme subtypes (PDE-4B and PDE-4D) have been implicated in the pathophysiology of psoriasis because this enzyme inhibitor elevates the level of C-Amp and hence reduces the features of inflammation. Recent researches also demonstrated the role of the Phosphodiesterase enzyme in psoriasis. Therefore, in this study, molecular docking analysis was carried out on twelve natural ligands that have been proven to be anti-psoriatic candidates *via* preclinical studies *via* different animal models but their mechanism of action was not explored yet. The chemical structures of the natural ligands were prepared using ChemSketch 2015 (Free version). The AutoDock Tool 1.5.6 was employed for the molecular docking studies. The results indicated that all ligands interacted with the targets in the active sites and Capsaicin and Hypericin inhibited PDE-4B and Gossypol inhibited PDE-4D enzymes, respectively, *via* interacting with responsible amino acids of the targets and demonstrating significant binding energies.

**Keywords:** Autoimmune, Inflammation, Molecular interactions, Natural ligands, Phosphodiesterase, Psoriasis

Psoriasis is a multi-factorial, autoimmune, and inflammatory dermatoses having ambiguous pathophysiology. It significantly impacted the affected person socially. In the current situation, environmental factors and a stressed atmosphere at the workplace might be major causes of psoriasis development. Psoriasis may have a psychological and social impact on a patient's life due to the loss of confidence while carrying out daily activities. Psoriasis is influenced by environmental factors like temperature and stressed conditions. Lack of comprehensiveness regarding the pathophysiology of psoriasis may lead to the unavailability of treatments, although various meticulous clinical trials and preclinical studies on natural products are in progress and some of them have shown promising antipsoriatic activity[1]. Amongst many targets, phosphodiesterase-4 is also believed to be one of the targets indulged in the pathophysiology of psoriasis. Moreover, this enzyme is also involved in different autoimmune disorders as this enzyme regulates the immune response by reducing cyclic AMP levels in cells. This enzyme is also expressed in non-immune cells such as keratinocytes and fibroblasts. Specifically, PDE-4B and PDE-4D are involved in psoriasis[2,3]. Since psoriasis is an inflammatory condition and PDE-4 is involved in the inflammatory conditions, PDE-4B and PDE-4D inhibitors were tried for the treatment of psoriasis under different clinical trials. It is evident from the histological and clinical studies that psoriasis is distinct from other inflammatory disorders in having changes in the architecture of epidermal and modification of keratinocytes differentiation and involvement of different immune cells in psoriasis[4]. Recent advances in the discovery of especially PDE-4B and 4D inhibitors lead to generate a hope for development of treatment of psoriasis as well as atopic dermatitis[5]. In the present study twelve natural compounds, namely Caffeine[6], Catechin and Epicatechin[7], Curcumin[8], Embelin[9], Gossypol[10,11], Hypericin[12], Luteolin[13], Quercetin[14], Capsaicin[15], Monoethyl Fumerate, and Dimethyl Fumerate[16], were included which have already shown antipsoriatic activity *via* different preclinical models in animals.

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## Methods and Materials

### Retrieval of Targets and their optimization

The three-dimensional crystallographic structures of phosphodiesterase enzyme-4 subtypes PDE-4B and PDE-4D (PDB IDs: 3O0J, and 3IAK, respectively) were retrieved from protein data bank (www.rcsb.org) involved in the pathophysiology of psoriasis. Further, these molecular targets were optimized by AutoDock tools version 4.2 which includes the removal of water molecules, native ligands, metal ions, and other hetero atoms as these molecules may provide a hindrance while carrying out the molecular docking study.

### Ligands preparation and their optimization

Chemsketch freeware (ACD 2015) was employed for preparing the structures of natural ligands (Fig. 1). After preparing the structures, they were subjected to clean to minimize the energy and subsequently converted into three-dimensional formats and exported in mol format. As per the compatibility with AutoDock tools, mol. format was converted into pdb format *via* Open Bable GUI v 3.1.1. For ligand preparation and optimization, open Babel was used, where steepest descent and conjugate gradient algorithms were used to prepare the ligand for docking studies.

### Molecular docking study

AutoDock v 4.2.6 software was used to carry out the molecular docking study by which binding modes and best conformers in terms of lowest binding energy (-kcal/mol) and binding to the targets can be identified. By using the Lamarckian genetic algorithm, the AutoDock tool carried out molecular docking between ligands, especially small ligands and macromolecules. To find out possible enzyme inhibitory mechanisms of investigational ligands, ligands were docked on entire molecular targets (blind docking) and further identified whether they made interactions in the active sites of or anywhere else in the enzymes. This version of AutoDock facilitates the automatic distribution of charges on the molecular target. Further, the active constituents (ligands) were loaded and their torsions along with rotatable bonds were assigned and the files

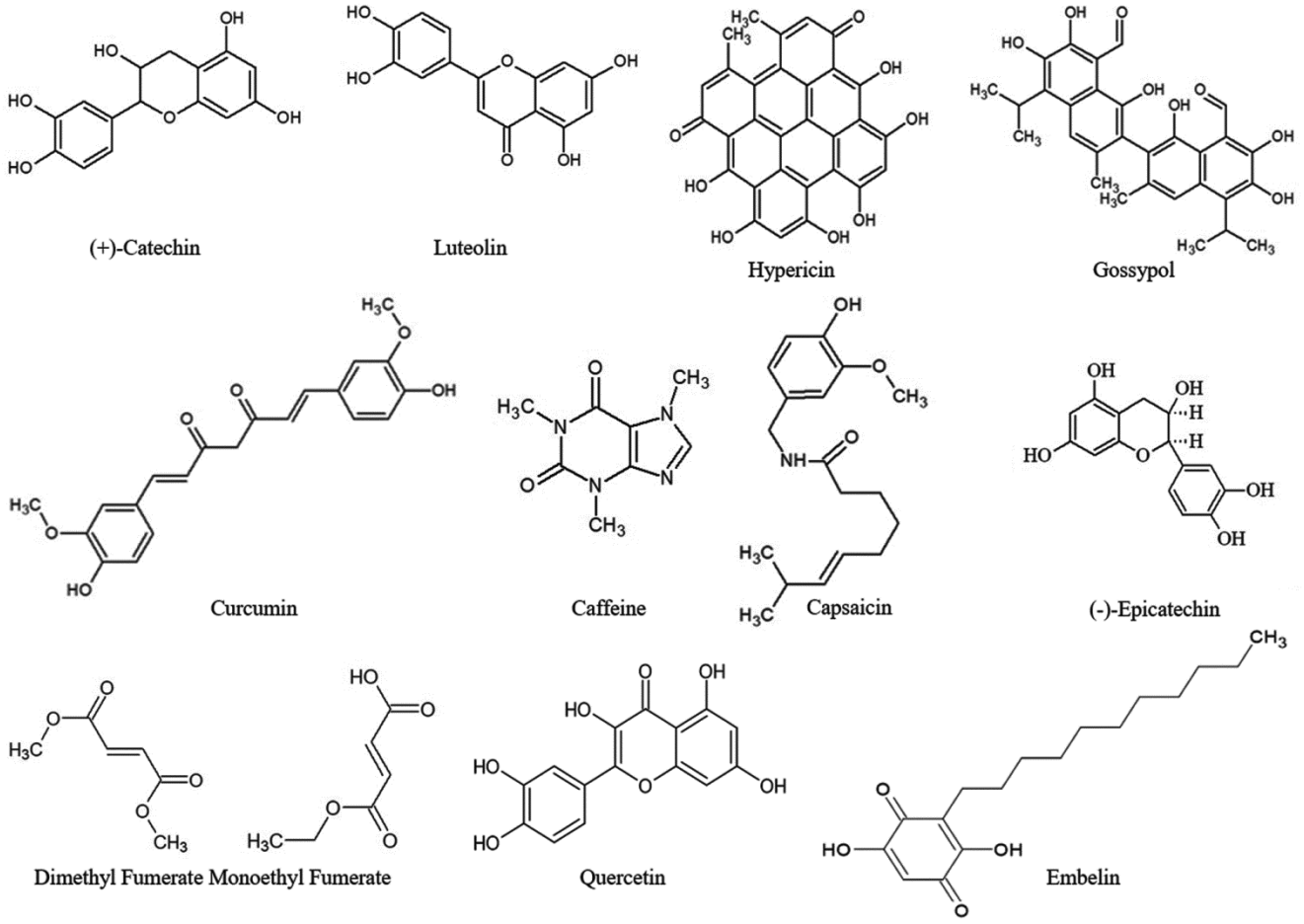



Fig. 1 — Structures of natural ligands

were saved as ligand.pdbqt. After refining, the macromolecule was saved as.pdb execution file. The macromolecule was loaded and stored as macromolecule.pdbqt after assigning hydrogen bonds and Gasteiger charges. The docking parameters were defined as coordinates of the center of the binding site and values for X, Y, and Z coordinates are given in (Tables 1 &2), and binding radius = 0.375 Å remains the same for all docking processes. Docked structures of the inhibitors were generated after a short number of evaluations. The 2D images of macromolecules and ligands interactions, to identify the active site and to verify further whether anti-inflammatory molecules were found to be present in the same active site or anywhere else, were obtained through Biovia Discovery Studio 4.5 Visualizer.

Table 1 — Results of Molecular docking study of natural products with PDE-4B receptor

| S. N | Ligands | Binding Energy at active site (-kcal/mol) PDE-4B | Amino acids involved in H-bonding in active site |
|---|---|---|---|
| 1 | Caffeine | -5.34 | NIL |
| 2 | Capsaicin | -5.73 | Gln443 |
| 3 | Catechin | -6.95 | Tyr233, His274, Asp275, Thr345, Asp392 |
| 4 | Curcumin | -7.08 | His274, Asp275, Thr345 |
| 5 | Dimethyl Fumarate | -4.96 | Arg331, Arg335 |
| 6 | Embelin | -4.23 | Glu304, Thr345, Met347 |
| 7 | Epicatechin | -6.93 | His234, Asp392, Met431, Gln443 |
| 8 | Gossypol | -7.96 | Tyr233, His234 |
| 9 | Hypericin | -9.33 | Tyr233, His238, Asp392 |
| 10 | Luteolin | -7.16 | Tyr233, His238, His274, Asp275, Thr407, Gln443 |
| 11 | Monoethyl Fumarate | -5.38 | Arg335 |
| 12 | Quercetin | -6.25 | His234, Asp275, Gly280, His307 |

Table 2 — Results of Molecular docking study of natural products with PDE-4D receptor

| S. N | Ligands | Binding Energy at active site (-kcal/mol) PDE-4D | Amino acids involved in H-bonding in active site |
|---|---|---|---|
| 1 | Caffeine | -5.16 | Gln369 |
| 2 | Capsaicin | -4.90 | NIL |
| 3 | Catechin | -6.94 | Asp318, Gln369 |
| 4 | Curcumin | -6.88 | Gln369 |
| 5 | Dimethyl Fumarate | -3.82 | Asn321, Gln369 |
| 6 | Embelin | -4.28 | Thr333, Gln369 |
| 7 | Epicatechin | -6.22 | His164, Asp201, Asn321, Gln369 |
| 8 | Gossypol | -9.3 | Tyr159, Asn209, Glu230, Gln369 |
| 9 | Hypericin | -9.0 | Asn209, Asp318 |
| 10 | Luteolin | -6.94 | His200, Asp201, His204, Gly206, Thr271, Asp318, Glu339 |
| 11 | Monoethyl Fumarate | -3.14 | Arg257 |
| 12 | Quercetin | -6.85 | Tyr159, His164, Glu230, His233, Asp318 |

## Results and Discussion

Phosphodiesterase enzyme has been implicated in a variety of inflammatory diseases which degrades cyclic AMP in different types of inflammatory cells and non-inflammatory cells eosinophils, macrophages, and neutrophils 5. However, in psoriasis lot of knowledge about the expression of phosphodiesterase enzymes is yet to be deciphered. Drugs that elevate the level of C-AMP may have an antagonistic effect on the production of inflammatory molecules therefore inhibition of the Phosphodiesterase enzyme is a prominent strategy of treatment of inflammatory diseases such as atopic dermatitis and psoriasis3. There are four isoforms of Phosphodiesterase (PDE) *i.e*. PDE-4A, PDE-4B, PDE-4C, and PDE-4D were found in which two isoforms *viz*. PDE-4B and PDE-4D were found to be over-expressed in psoriasis (in peripheral blood mononuclear cells). Apremilast, which was approved for the treatment of moderate to severe plaque psoriasis as well as psoriatic arthritis, is a small and novel molecule that is orally administered for this purpose 17. Based on the above description, molecular docking study analysis were carried out to find out the binding modes and possible mechanism of action of natural ligands in PDE-4B and PDE-4D enzymes. The active site of PDE-4B comprised Tyr233, His234, His278, Met347, Asp392, Leu393, Ile410, Phe414, Met431, Ser442, Gln443, and Phe446 whereas the active site of PDE-4D comprised Tyr159, Met273, His276, Leu319, Asn321, Tyr329, Trp332, Thr333, Ile336, Phe340, Met357, Gln369 and Phe372 (Fig. 2). Figures 3 and 4 demonstrated the interactions among the natural ligands and PDE-4B and PDE-4D, respectively.

The efficacy of the topically administered Caffeine was tested in the patients affected by psoriasis vulgaris in a randomized, double-blind, and placebo-controlled study[6]. The production of TNF-α is one of the prime factors in the pathogenesis of psoriasis and Embelin has reportedly been implicated as a beneficial candidate in the treatment of psoriasis as it reduces the TNF-α level[9]. When thelight was irradiated with a 500-watt

halogen lamp, psoriasis was induced in the mice but when Hypericin ointment was applied with PEG or Solketal® or 10 mg/kg Hypericin was administered intraperitoneally, no photosensitization occurred[12]. Weng *et al.* 2014 investigated the antipsoriatic potential of Luteolin, in which pretreatment with Luteolin (10-100 µM) significantly inhibited TNF-α induced mRNA expression as well as the release of three mediators involved in the inflammatory process like IL-6, IL-8, and VEGF in a concentration-dependent manner[13]. Harries *et al.* 2005 showed the efficacy of fumaric acid esters (FAEs) used in the treatment of severe psoriasis. In this study, they identified patients who received fumaric acid esters for psoriasis treatment at one UK regional referral central between the duration June 1999 to October 2003[16]. Tea contains a variety of flavonoids *i.e.* catechins have extensively been reported to be efficacious in various skin ailments including psoriasis. Aljuffali *et al.* 2022 demonstrated in their research that nanocapsulation of tea catechins enhances their skin permeability and subsequently their efficacy therapeutically[7]. Arora *et al.* 2015 reported the efficacy of the combination of the extract of four medicinal plants against psoriasis induced by Imiquimod. In the preparation of extract, four plants were used which are *Tinospora cardifolia*, *Curcuma longa*, *Celastrus paniculata*, and *Aloe vera*. This extract reduced the over-expression of cytokines on the psoriatic skin when administered orally or topically[18]. Dodue *et al.* 2005 reported the synthesis of atropisomers of gossypol and further evaluated for anti-proliferative and antioxidant activity using MTT viability assay and thiobarbituric acid test, respectively. Data obtained through this study indicated that gossypol showed moderate antioxidant activity ($IC_{50}$ = 13.1 µM) and (-) – gossypol was found to be a most potent antiproliferative agent. Therefore, this study concluded that gossypol as either a racemic mixture or the individual atropisomers has the potential to treat psoriasis[19]. Vijayalakshmi *et al.* 2014 evaluated the antipsoriatic activity of the traditionally used plant Cassia tora L. In this study leaves of this plant were used to prepare ethanolic extract and further three flavanoids namely Luteolin-7-O-β-glucopyranoside, Quercetin-3-O-β-D-glucoronide, and Formononetin-7-O-β-D-glucoside were isolated form ethanolic extract and identified using HPLC. This ethanolic extract and isolated compounds were subjected to evaluate antipsoriatic properties at the dose of 400 mg/kg using ultraviolet Brays photo-dermatitis in rat model. Ethanolic extract and isolated flavonoids exhibited a significant ($P$< 0.01) reduction of epidermal thickness when compared to standard. The study concluded that isolated herbal molecules from Cassia tora possessed the antipsoriatic property[20]. In the current study, molecular docking analysis of natural ligands with PDE-4B revealed that most of the natural ligands were found in the active pocket of enzyme PDE-4B except DMF, MEF, Quebrachitol, and 2,3-Dihydro-3,5-dihydroxy-6-methyl-4H-pyran-4-one. Freund *et al.*2012 described the novel binding of Boron-based Phosphodiesterase inhibitors to the PDE-4 binding center.

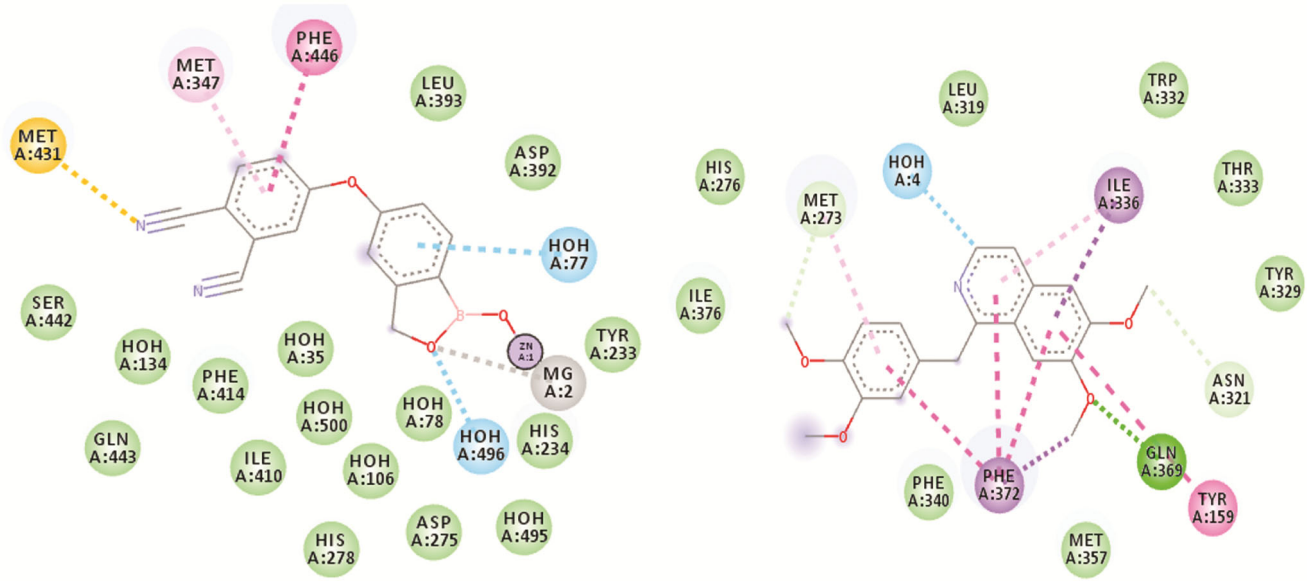
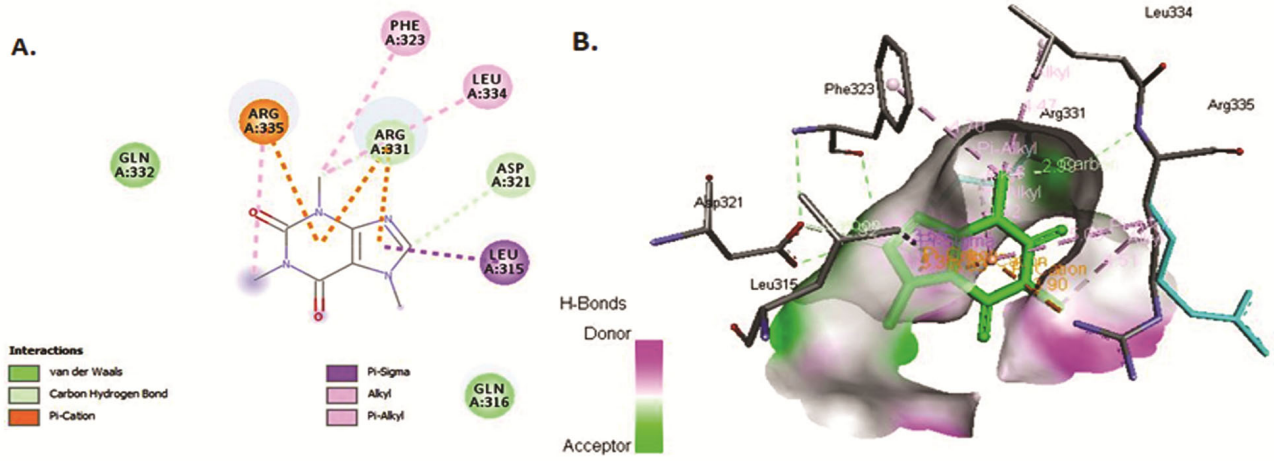
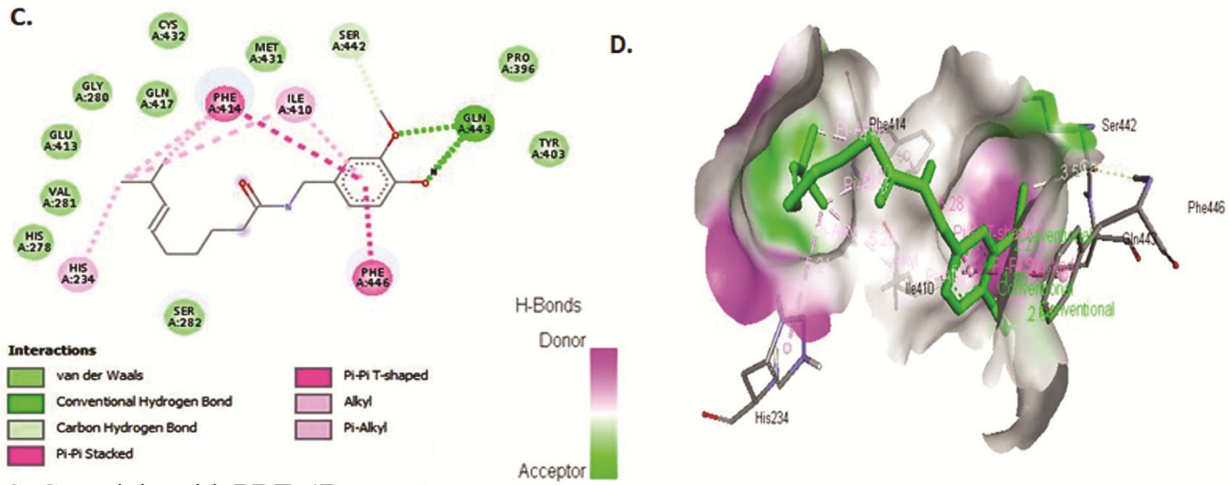


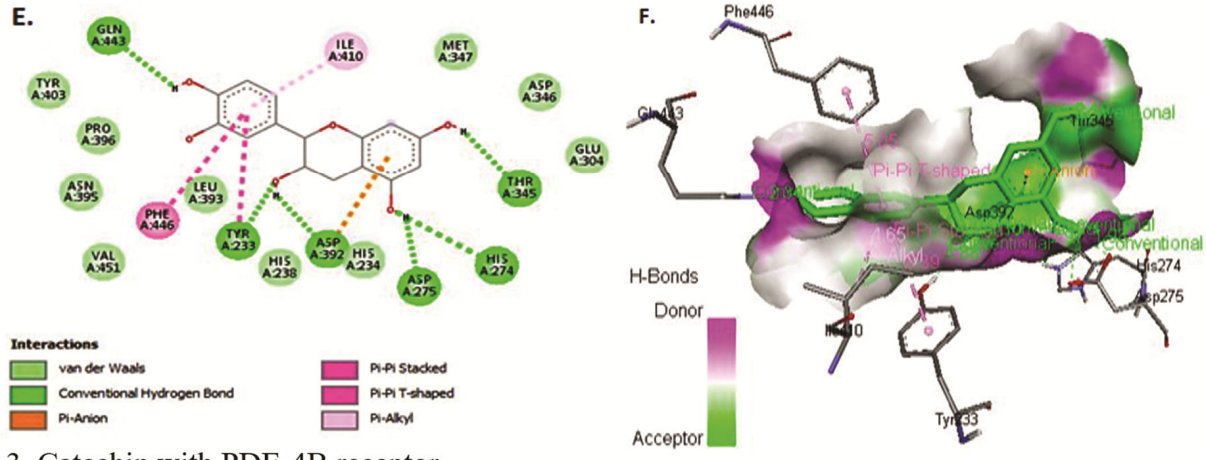

Fig. 2 — Active sites of PDE-4B and PDE-4D, respectively




1. Caffeine with PDE-4B receptor

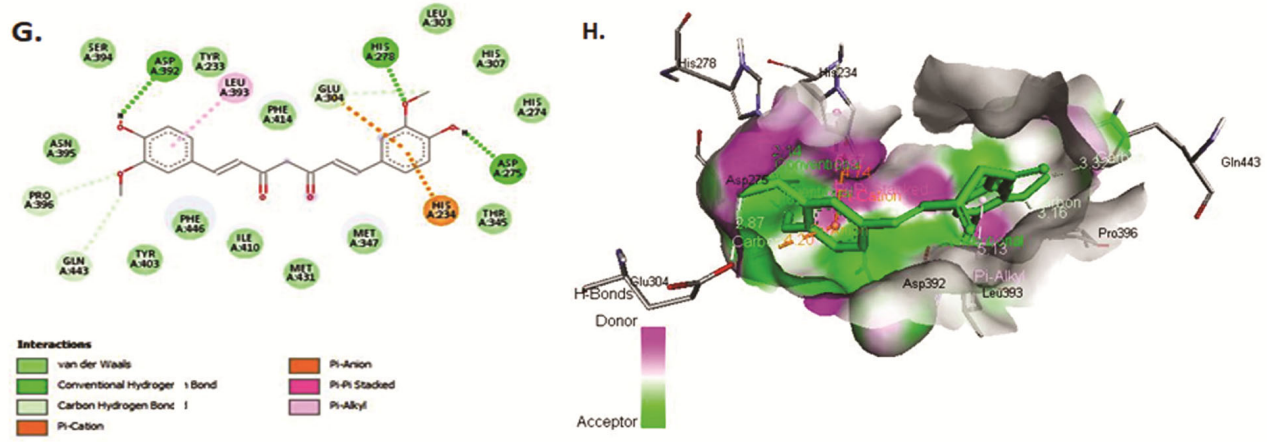



2. Capsaicin with PDE-4B receptor

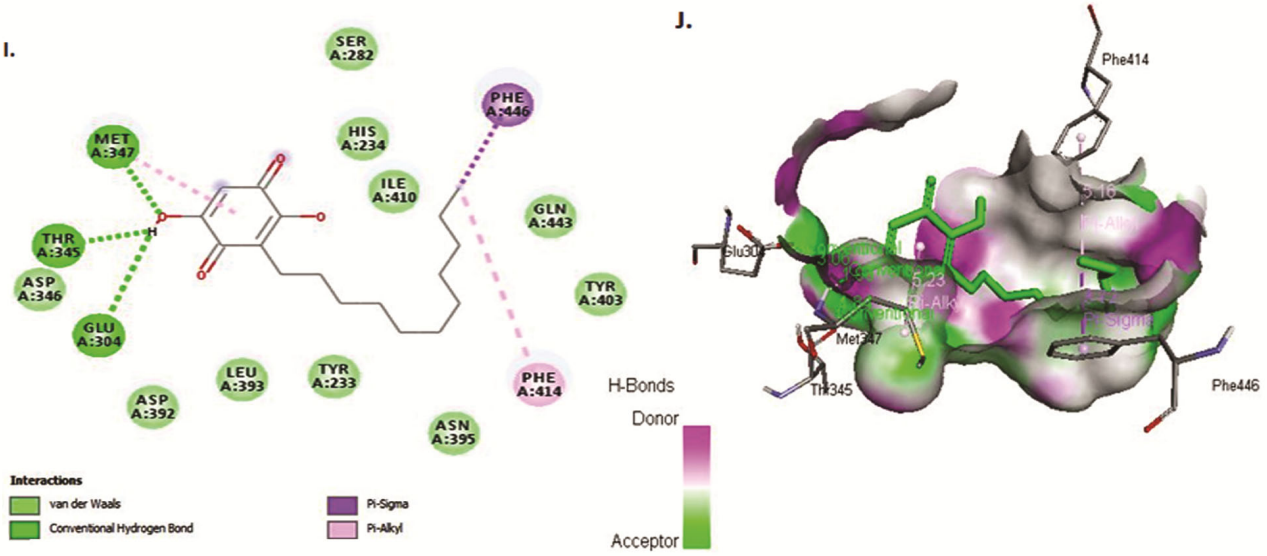



3. Catechin with PDE-4B receptor

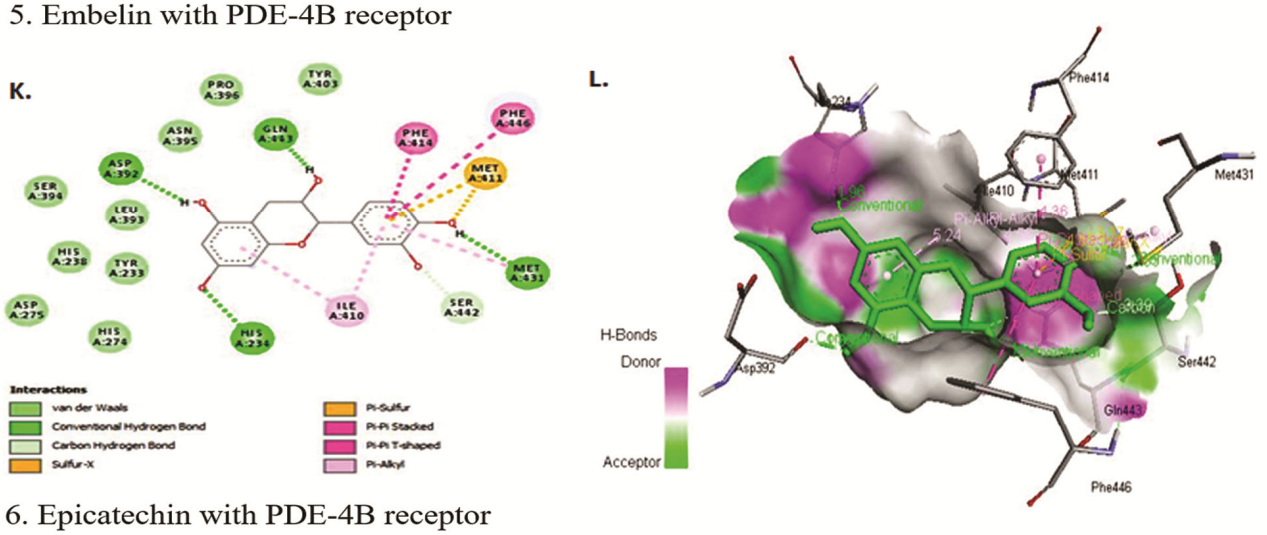
Fig. 3 — 2D and 3D interactions of natural products with PDE-4B receptor (*contd.*)




4. Curcumin with PDE-4B receptor

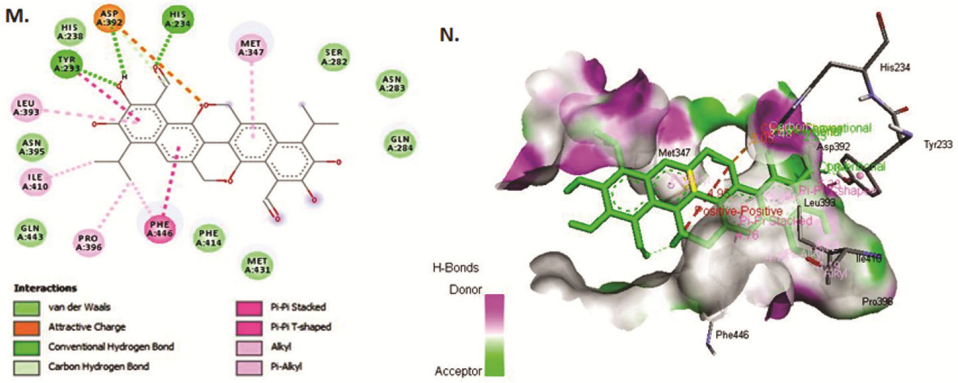



5. Embelin with PDE-4B receptor

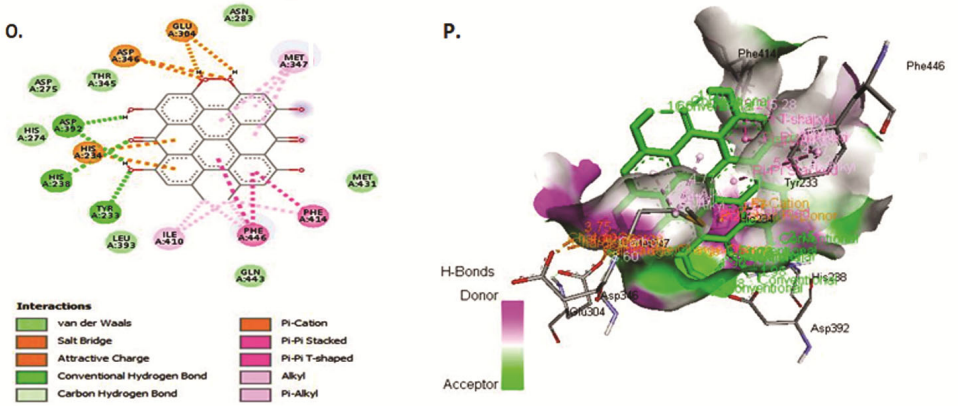



6. Epicatechin with PDE-4B receptor

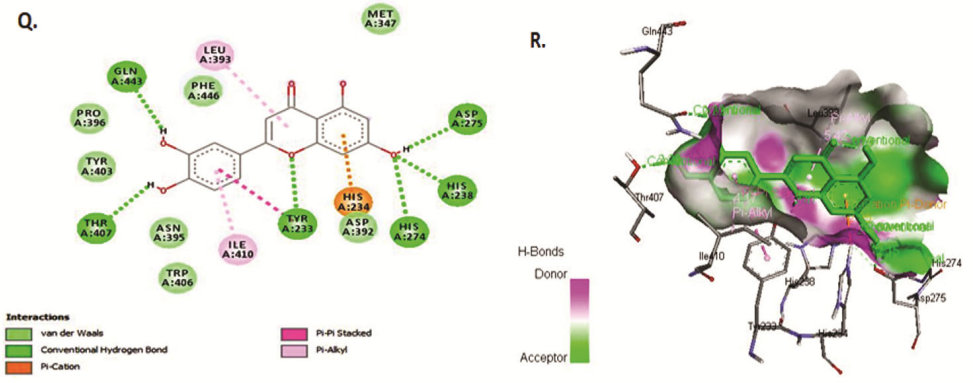
Fig. 3 — 2D and 3D interactions of natural products with PDE-4B receptor (*contd.*)




7. Gossypol with PDE-4B receptor

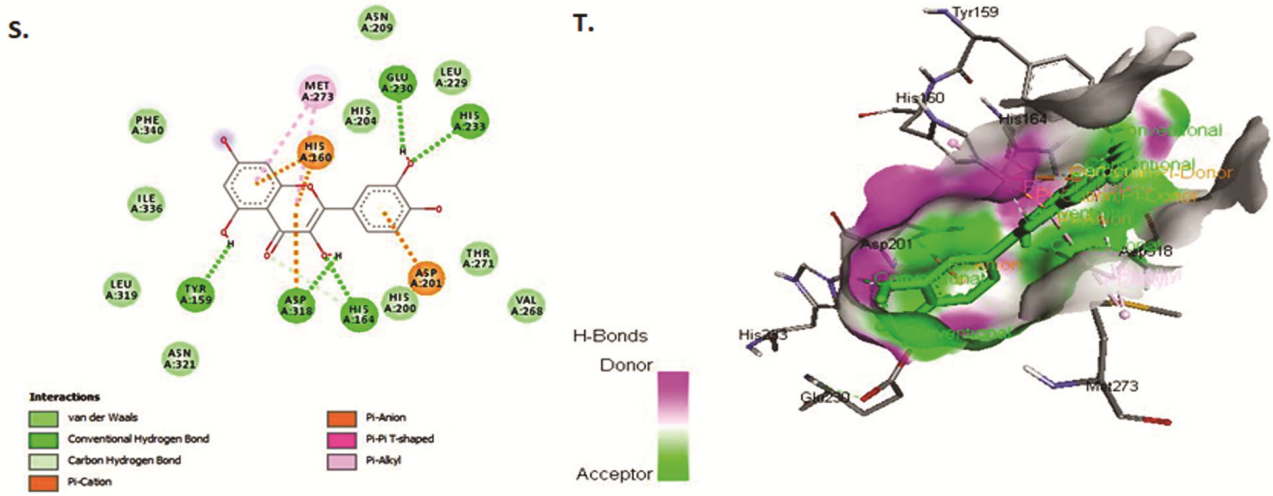



8. Hypericin with PDE-4B receptor

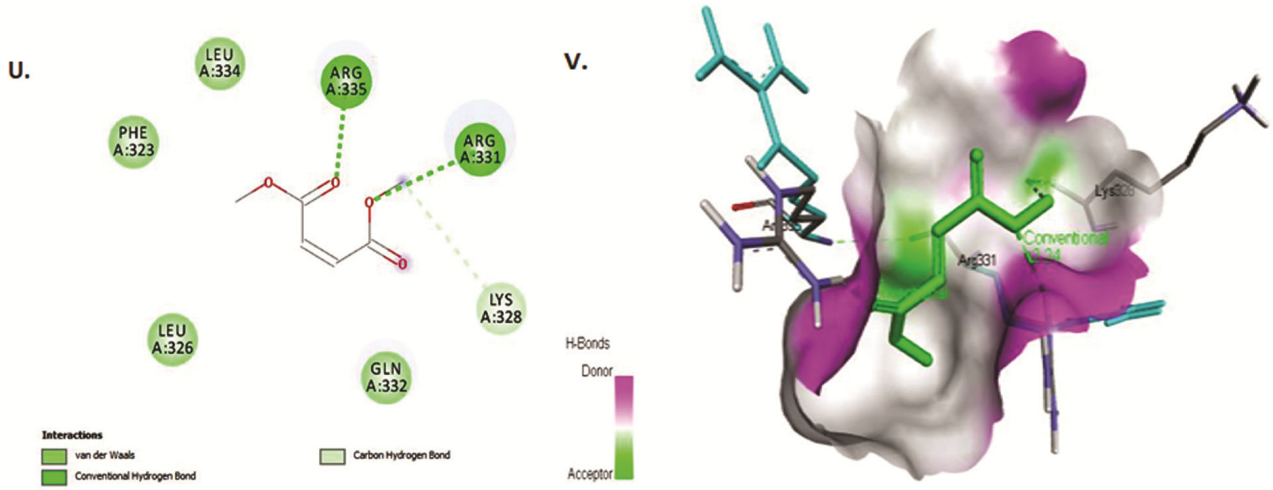



9. Luteolin with PDE-4B receptor

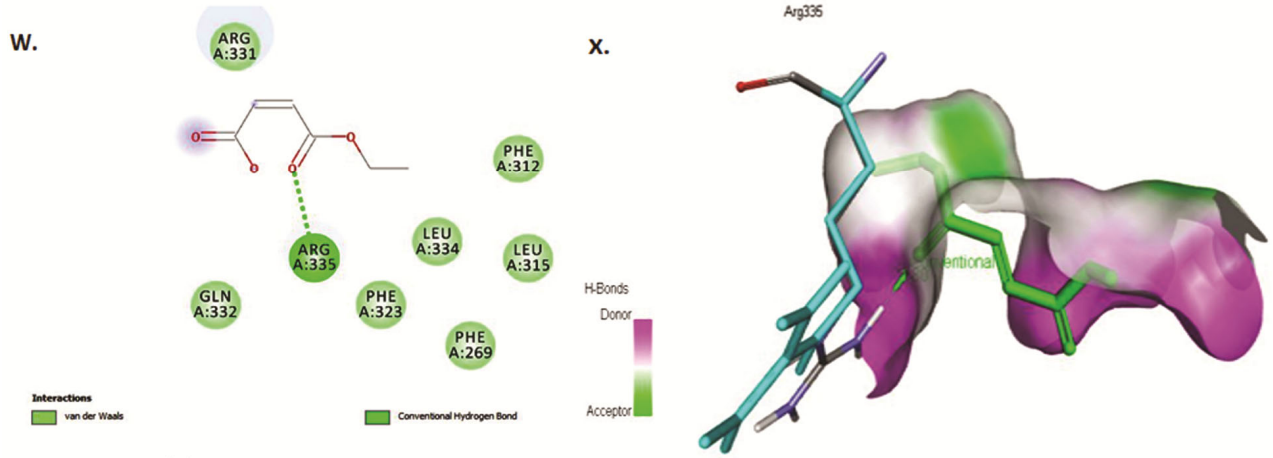
Fig. 3 — 2D and 3D interactions of natural products with PDE-4B receptor (*contd.*)




10. Quercetin with PDE-4D receptor

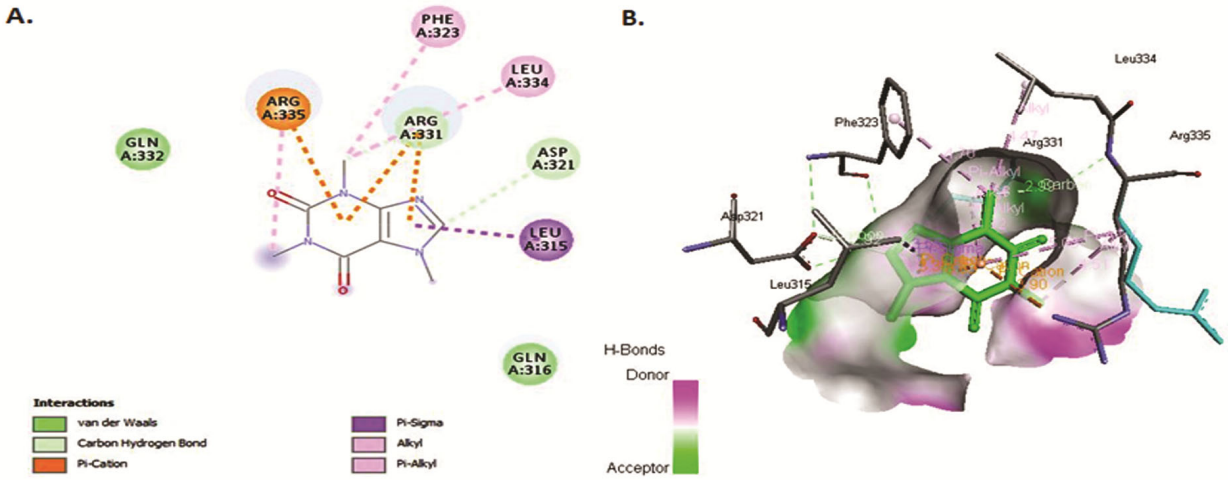



11. DMF with PDE-4B receptor

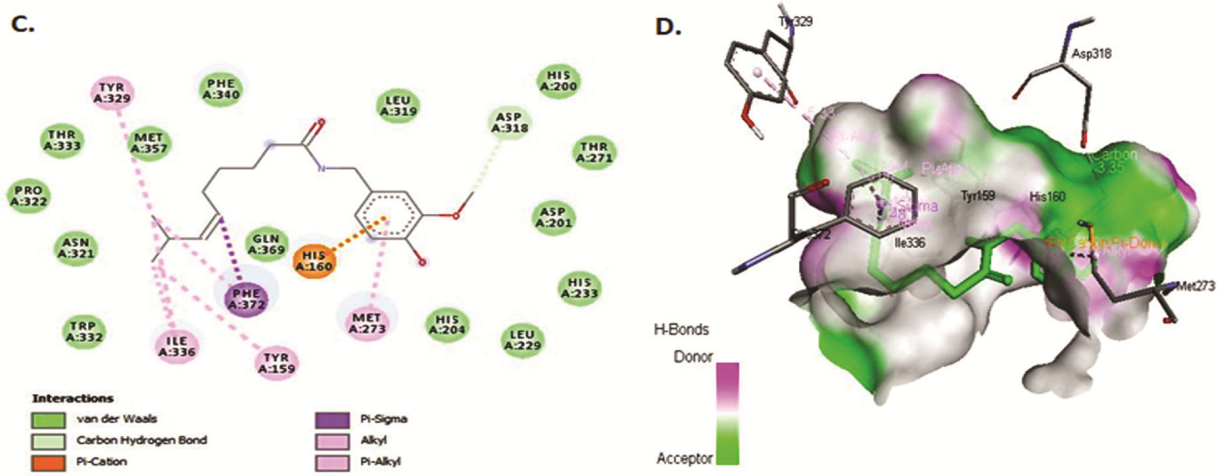



12. MEF with PDE-4B receptor

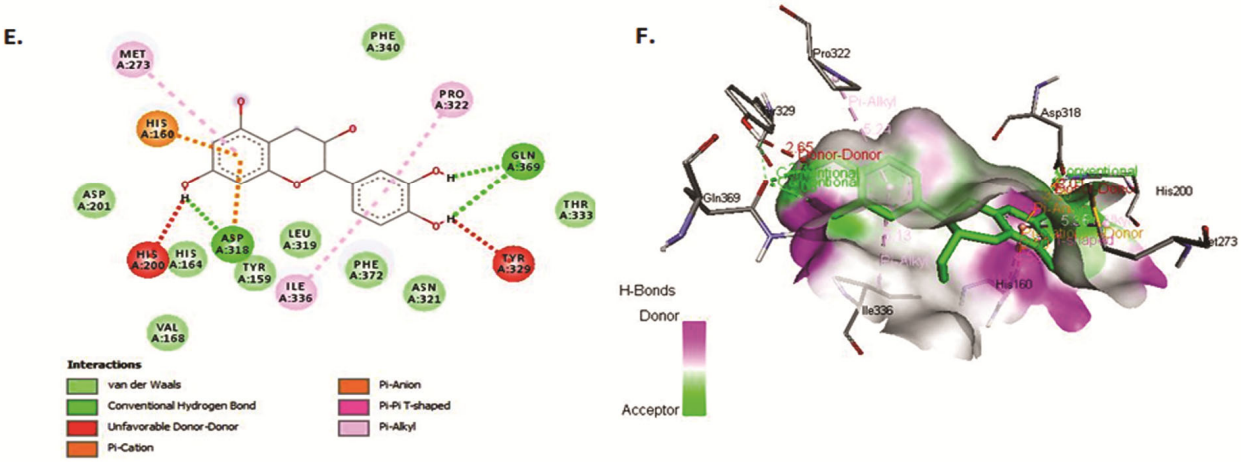
Fig. 3 — 2D and 3D interactions of natural products with PDE-4B receptor




1. Caffeine with PDE-4D receptor

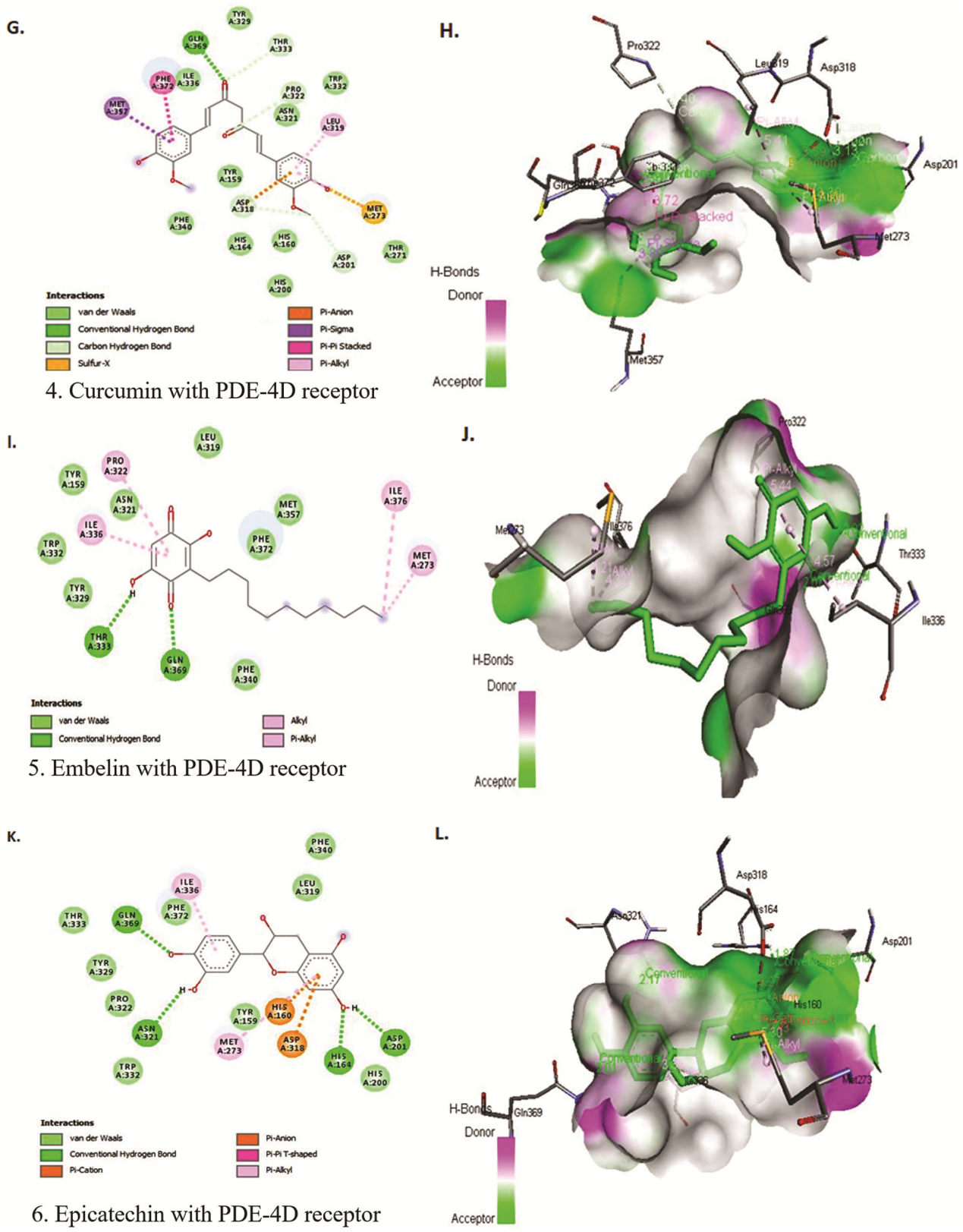



2. Capsaicin with PDE-4D receptor




3. Catechin with PDE-4D receptor

Fig. 4 — 2D and 3D interactions of natural products with PDE-4D receptor (*contd.*)

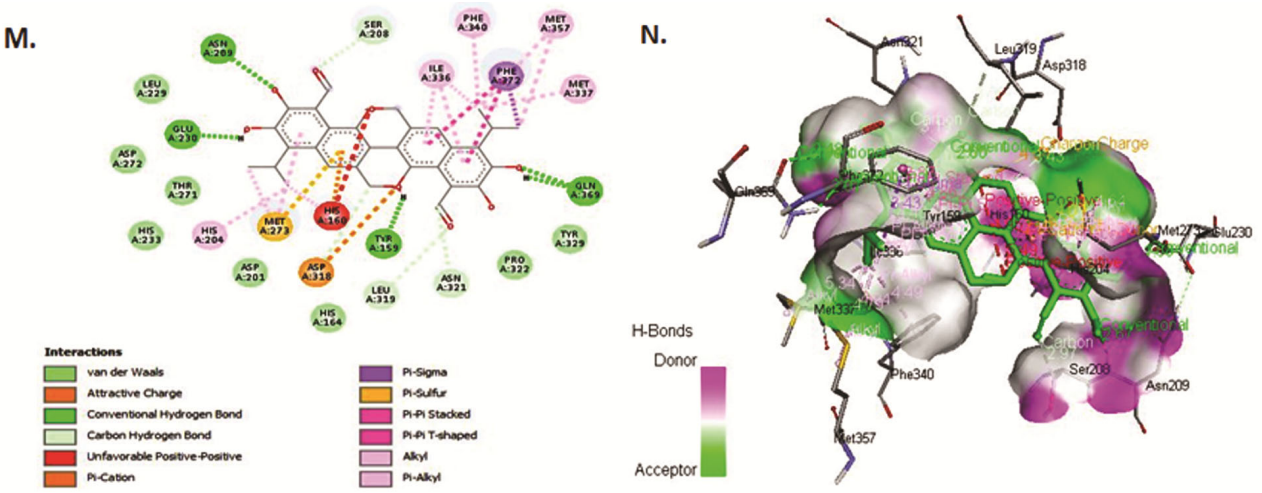



4. Curcumin with PDE-4D receptor

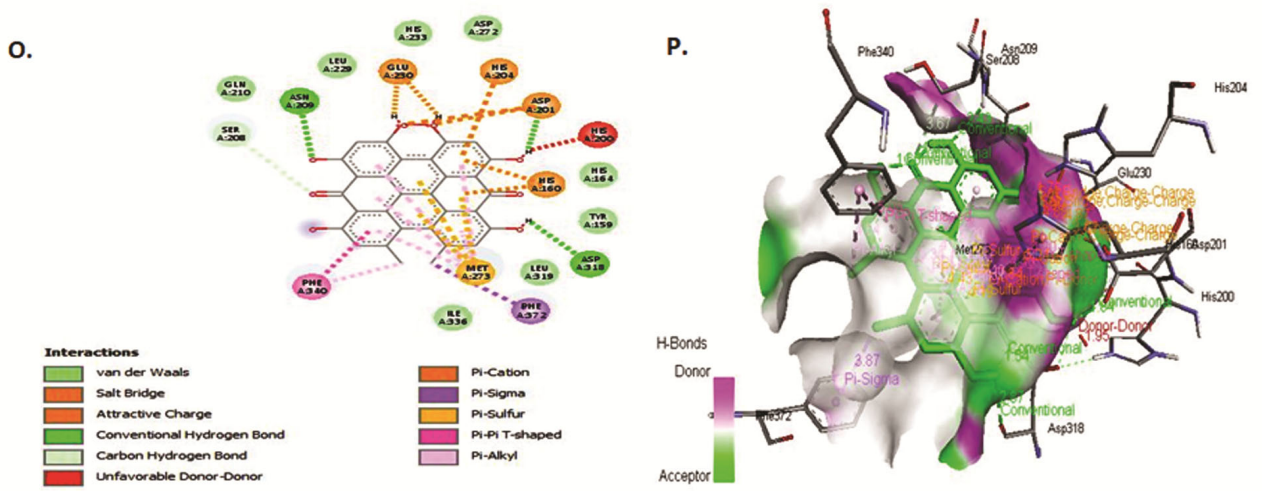
5. Embelin with PDE-4D receptor

6. Epicatechin with PDE-4D receptor

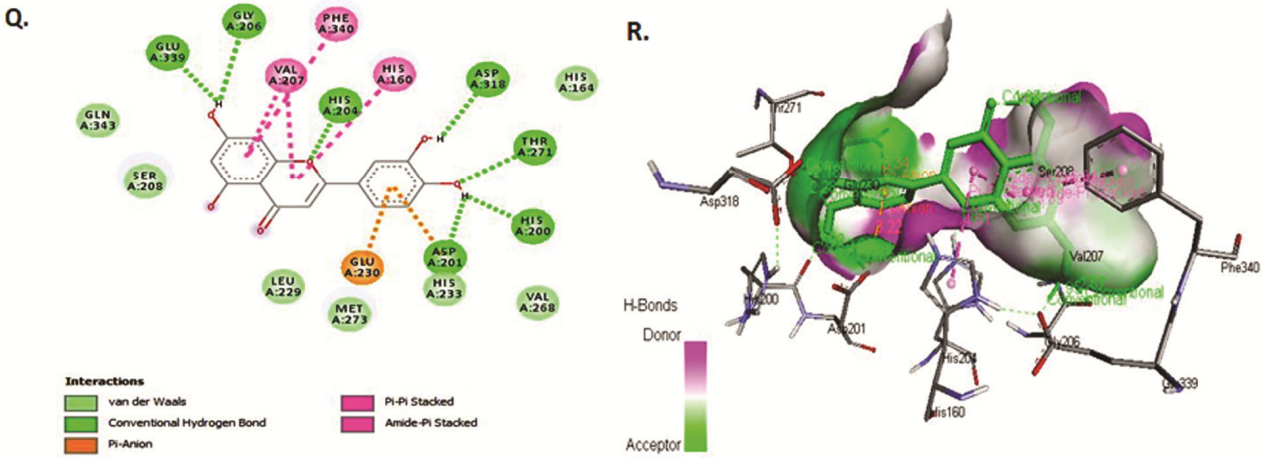
Fig. 4 — 2D and 3D interactions of natural products with PDE-4D receptor (*contd.*)




7. Gossypol with PDE-4D receptor

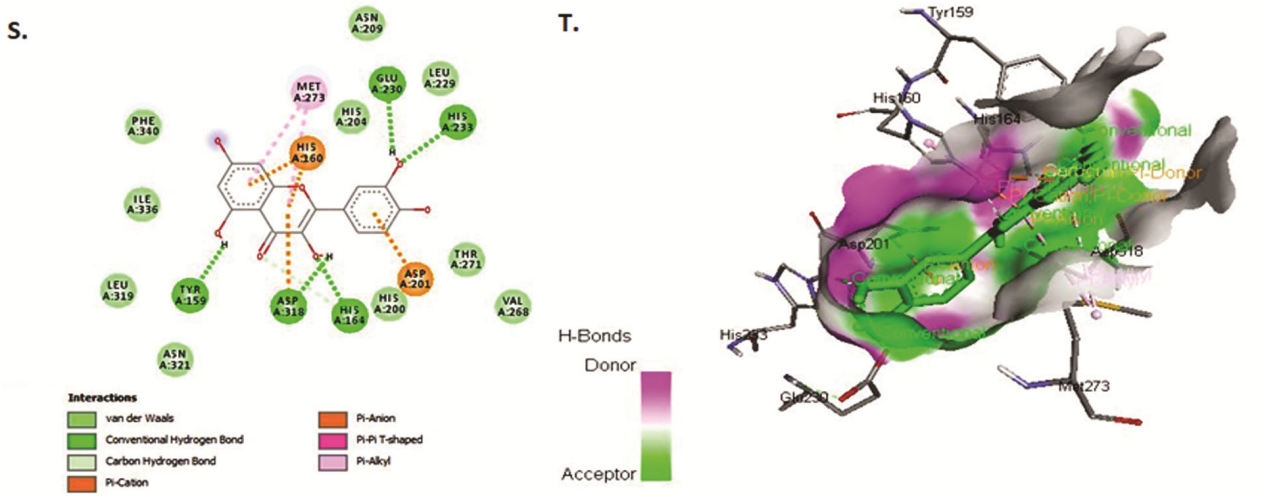



8. Hypericin with PDE-4D receptor

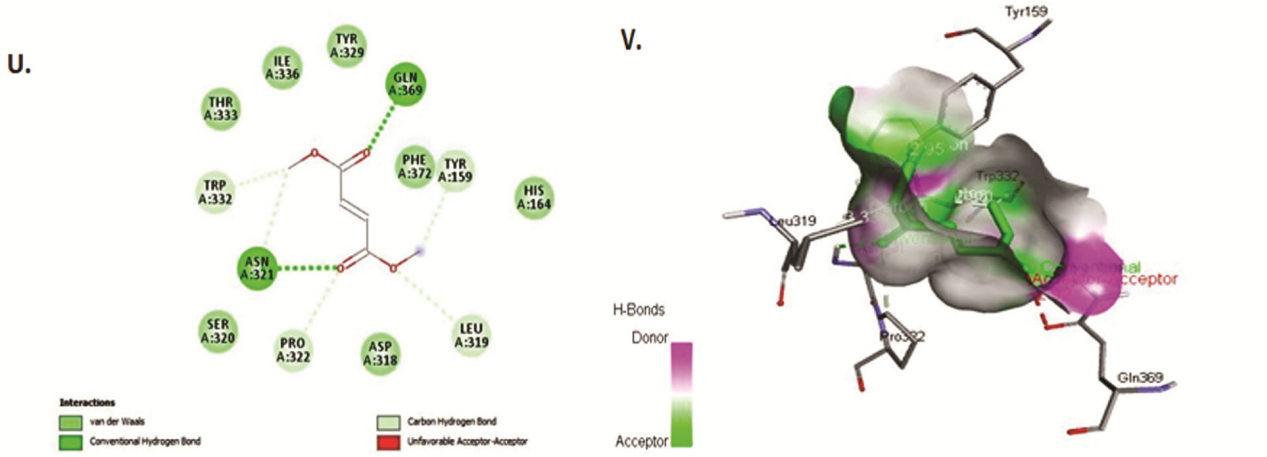



9. Luteolin with PDE-4D receptor

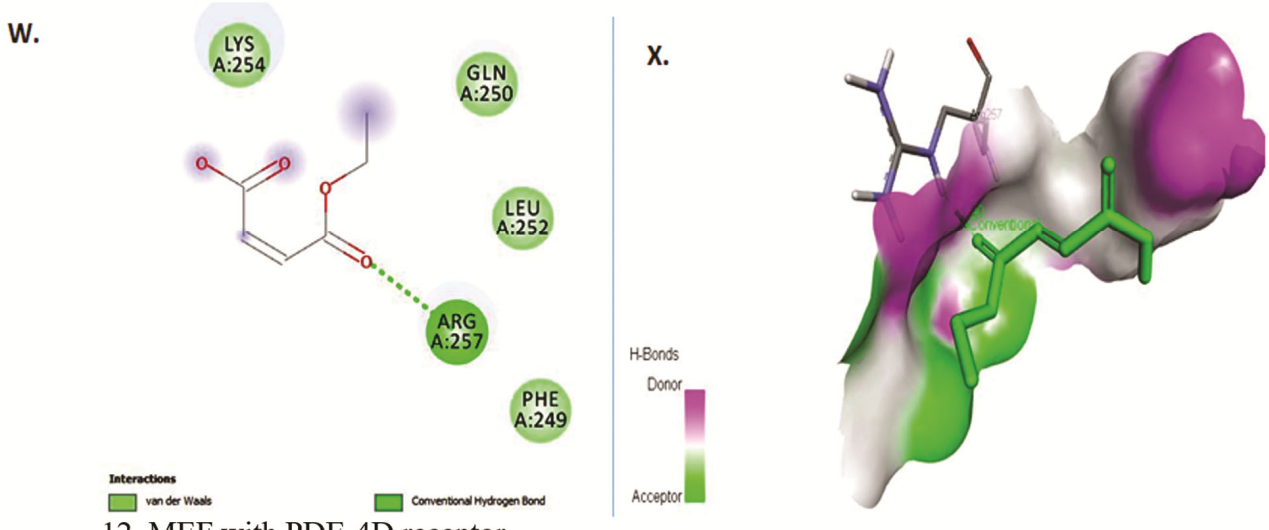
Fig. 4 — 2D and 3D interactions of natural products with PDE-4D receptor (*contd.*)




10. Quercetin with PDE-4D receptor




11. DMF with PDE-4D receptor




12. MEF with PDE-4D receptor

Fig. 4 — 2D and 3D interactions of natural products with PDE-4D receptor

According to them, Ligand AN2898 bound to the active site of PDE-4 in a unique way which was different from other inhibitors because other inhibitors formed a hydrogen bond with the side chain of Gln443, while AN2898 did not form such a hydrogen bond. Another inhibitor AN4800 also formed a similar hydrogen bond with Gln 443 and showed better inhibition of PDE-4 than AN2898[21]. In our study, only four ligands *viz*. Luteolin, Emodin, Epicatechin, and Capsaicin, made this signature hydrogen bond interaction with PDE-4B, out of them Luteolin also exhibited appreciable binding affinity *i.e.* -7.16 kcal/mol but more specifically Capsaicin formed hydrogen bonds with amino acids residues with quite better binding affinities. Hypericin showed the highest binding energy *i.e.* -9.33 kcal/mol but could not form a prerequisite hydrogen bond with Gln443 to inhibit the enzyme. Gossypol also exhibited better binding affinity than antioxidant natural ligands but could not manage to interact with Gln443. Overall; natural ligands which managed to interact with Gln443 *via* hydrogen bond and exhibited better affinity might inhibit this enzyme PDE-4B and follow this type of mechanism of action.

Huai *et al*. 2003 described the binding of Roliprams with PDE-4D and discussed the inhibition of PDE-4D selectively. According to their study, Gln369 residue plays an important role in the inhibition of the PDE-4D enzyme after binding with ligands through hydrogen bonds. Roliprams interacted with residues Ile336, Met337, Phe340, Met357, Ser368, Gln369, and Phe372[22]. In our study, molecular docking analysis with PDE-4D revealed that all the natural ligands included in the study were found to be in interacted conditions in the active site of PDE-4D. Surprisingly, most of them could afford necessary hydrogen bonds with residue Gln369, except Hypericin, Luteolin, MEF, and Quercetin. All the natural ligands could interact with active pocket residues through hydrophobic interaction which is also an important criterion for inhibition of PDE-4D selectively. In the current study, Gossypol showed maximum binding energy and some hydrogen bond interactions with Tyr159, Asn209, Glu230 and required H-bond interaction with Gln369 whereas Capsaicin could not form any hydrogen bond and made only hydrophobic interactions entirely and also exhibited the lowest binding affinities towards the enzyme PDE-4D. Herbal PDE inhibitors such as theophylline can cause potential adverse effects like nausea, vomiting, tachycardia, fatigue, and CNS effects (Seizures and dizziness)[23]. The elaboration of the mechanism of action *via* molecular docking study might be useful in the development of lead molecules. Similarly, Agrawal *et al.* deciphered the P38-MAPK inhibitory mechanism of selected antipsoriatic natural ligands using a molecular docking study[24]. With the help of SAR or QSAR of lead compounds, new chemical entities can be designed. Generally molecular docking method is adopted for deciphering the binding modes and to predict the mechanism of action. However, there are some limitations including the presence or absence of water molecules, stability of ligand-target complex, and generation of actual binding energy.

## Conclusion

In these molecular docking studies, Capsaicin, in terms of proper molecular interactions with poor binding affinity, and Hypericin in terms of binding affinity and molecular interactions other than required hydrogen bond formation with GLN443, demonstrated to be an inhibitor of PDE-4B enzyme Whereas Gossypol in terms of binding affinity and prerequisite molecular interactions by forming H-bond with Gln369 demonstrated to be an inhibitor of PDE-4D enzyme.

## Acknowledgement

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## Conflict of interest

All authors declare no conflict of interest.

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