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Computational Guided Identification of Potential Anti-Psoriatic Phytoconstituents from *Psoralea Corylifolia*

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Abstract

Phosphodiesterase 4B (PDE4B) inhibitors increase cAMP levels and are used commonly as a therapeutic option in various inflammatory diseases. However, their adverse effects are serious and well known. Natural inhibitors of PDE4B receptor are advantageous since they are safer and exhibit specific activity on PDE4B. *Psoralea corylifolia* (Bakuchi), is reported to be useful in treatment of psoriasis, leukoderma and vitiligo. The goal of this study is to predict the mechanism of action of phytoconstituents of Bakuchi and to provide scientific justification for their anti-psoriatic potential. Molecular docking studies were conducted on the phytoconstituents of bakuchi seeds and apremilast. Docking score between the PDE4B receptor and these ligands was calculated. The phytoconstituents' Glide energy, binding free energy, hydrogen bond, and hydrophobic interactions with PDE4B were compared to those of the receptor-apremilast complex. The anti-inflammatory efficacy of the plant extract was tested using ELISA andmouse RAW 264.7 cell line. The phytoconstituents namely, neobavaisoflavone, bavachinin, and bavachalcone exhibited higher docking score, Glide energy, and binding free energy than the reference molecule, apremilast. Furthermore, the phytoconstituents' hydrogen bond and hydrophobic interactions with active site residues of PDE4B were robust. According to the findings, phytoconstituents in bakuchi seeds block active PDE4B sites. The phytoconstituents from *Psoralea corylifolia* seeds bind to PDE4B and function as strong PDE4B inhibitors. Bakuchi seed extract inhibited pro-inflammatory cytokines and stimulated anti-inflammatory cytokine in dose-dependent manner. The anti-psoriatic potential of *Psoralea corylifolia* is attributed to inhibition of PDE4B.

Keywords: PDE4B Inhibitor;Psoriasis; Molecular Docking; *Psoralea Corylifolia*; Bakuchi; Apremilast

Introduction

Psoriasis is an inflammatory disease, chronic in nature skin disease and affects patients' quality of life adversely. Recently psoriasis is being considered as a systemic disease of immune dysfunction. The pathogenesis and clinical features of psoriasis include several environmental and genetic risk factors, various immunological mechanisms, and pro-inflammatory cytokines. Currently prescribed drugs are associated with serious side effects, high rates of remission and resistance to drugs. The current treatment approaches have the limitations and there is a need of safer and effective natural anti-psoriatic agent [1,2]. Medicinal plants have been used to treat skin disorders. It is a common human activity

that lasted for centuries together [3]. Various plants from traditional Ayurveda, Siddha, Uighur, Thai, Korean, Chinese medicine are used for management of various skin ailments, psoriasis, vitiligo, dermatitis and leucoderma. A large population uses the complementary medicines for two reasons namely, the limitations of synthetic drugs and the ability of the natural compounds to act on multiple targets [4]. The plants can pave the way for new therapeutic approaches to psoriasis treatment since they have significant preventive activity against psoriasis [5]. However, lack of scientific data and documentation are needed before addressing the doctors and the patients about herbal anti-psoriatic medicines [3].

Molecular docking is a valuable method in visualizing binding of drug molecules with the target proteins and understanding their mode of action. Docking study involves neither animal experiments nor clinical trials [6]. At present computational models are used commonly in drug discovery related to synthetic drugs [7].

Researchers have employed molecular docking/ in silico technique for speculating the target of phytoconstituents and understanding their mechanism of action. Rosa HSD, et al. observed reduction in nociceptive response in mice pretreated with *Sida tuberculata* extract [8]. Molecular docking confirmed the interaction of kaempferol derivative and 20-hydroxyecdysone, the phytoconstituents, with μ- opioid receptors. *Angelica pubescens* roots contain the prenylated coumerin, oesthenol. Molecular simulation study by 9. Beak SC, et al. revealed that oesthenol is a potent, selective and reversible MAO A inhibitor [9]. In a docking analysis study, David TI, et al. studied an interaction between phytochemicals of *Cannabis sativa* and dihydrofolate reductase. The results confirmed the anti-malarial properties of *Cannabis* sativa [10]. D-galactouronic acid is isolated from *Momordia charantia*. Ghanta M, et al. studied the binding of soluble guanylate cylase and D-galactouronic acid in the catalytic domain of the enzyme and speculated its role in cardiovascular, neurodegenerative and Parkinson's disease [11]. In silico findings by Oleveira TLS, et al. suggested that hibalactone, bioactive from *Hydrocotyelle umbellata*, has anti-inflammatory activity. It interacts with cyclooxygenase-2 and 5-lipoxygenase enzymes [12]. Uddin MJ, et al. examined the antinociceptive, anxiolytic and sedative potential of *Anisomeles indica* with computer aided analysis [13]. Guaianolide, bioactive of *Cyathocline purpurea,* binds with COX-2 enzyme. Molecular docking confirmed its use for treatment of inflammatory diseases [14].

Alalaiwe A, et al. calculated stratum corneum lipid docking of five compounds derived from *Psoralea corylifolia* and correlated their percutaneous absorption with the chemical structure [15]. Du G, et al. studied the binding of (S) and (R) isomers of bavachinin with peroxisome proliferator activated receptor-γ (PPAR-γ) by docking. Further, it was confirmed by fluorescence resonance energy transfer-based competitive binding assay [16]. Methanol fraction of *Psoralea corylifolia* and its bioactive, bakuchiol, reduced biofilm production and virulence by regulating quorum-sensing in pathogenic microbes. Husain FM, et al. demonstrated formation of stable complex between bakuchiol and the binding cites of LasR and RhIr by various hydrophobic interactions with results of molecular docking [17]. The fungus *Magnoparthe grisea* was inhibited by isobavachalcone. Liu X, et al. attributed the antifungal activity of isobavachalcone to its binding ability with chitinase, the fungal enzyme, as revealed in molecular docking [18]. Zhang T, et al. developed fluorescence polarization assay for evaluation of estrogenic activity of flavonoids using molecular docking. The results revealed that the flavonoids show estrogenic activity if the hydroxyl and the prenyl group are present and intact [19]. Liu X, et al. attributed the use of psoralidin in breast and endometrial cancer to its binding ability with ERα and mimicking the actions of E_2 [20]. Sun DX, et al. confirmed inhibition of human carboxylestrase by neobavaisoflavone, corylifolinin, coryfolin, corylin in noncompetitive manner and by bavachinin in competitive manner with molecular simulation [21]. Inhibition of acetylcholinestrase by psoralin was reported by Somani G, et al. Hydrogen bonding and π-π interactions, were observed in between psoralin and acetylcholinestrase during molecular docking [22]. Zarmouh NO, et al. examined molecular docking of bavachinin and bavanin with MAO-B and speculated that the methoxy group at C7 of bavachinin was responsible for strong, selective and reversible binding of bavachinin with MAO- B and its therapeutic efficacy in Parkinson's disease [23]. Srinivasan S identified a new phenyl derivative of pyranocoumerin in petroleum ether extract of *Psoralea corylifolia*. In silico studies revealed its affinity towards trichothecene 3-0-acetyltransferase and explained its antifungal activity [24].

Researchers have explored antibacterial, antifungal, antiparkinsonain, anticancer activity of *Psoralea corylifolia* using virtual screening. However, the plant's anti-psoriatic potential was not explored. The present work was aimed at investigation of mechanism of anti-psoriatic action of *Psoralea corylifolia* (bakuchi) through molecular docking.

Phosphodiesterase-4 (PDE4) is a non-receptor intracellular enzyme and occurs in immune cells (monocyte /macrophages, granulocytes), epithelium, vascular endothelium, smooth muscles, brain and chondrocytes. It degrades cAMP and regulates keratinocytes inflammation and epithelial integrity [25,26]. Apremilast, an oral PDE4 inhibitor, is less emetic and possesses a wide therapeutic window. However, it lacks in selectivity among the PDE4 isotypes [27]. Apremilast is useful in psoriasis treatment [28-30] since it inhibits PDE4,

enhances cAMP levels which in turn regulates many genes and proteins and reduces pro-inflammatory responses in different cells.

Traditionally *Psoralea corylifolia* is useful in treating many diseases, including gynecological bleeding, vitiligo and psoriasis [31]. Its mode of action however is not understood. It contains bavachinin, bavachin, neobavaisoflavone, corylin, corylifol A, 8-prenyldaidzin, isobavachalcone, corylifol B, bakuchiol, 3-hydroxy-Δ^1 --bakuchiol, 2-hydroxy-Δ^3 -bakuchiol, 12,13-diolbakuchiol, psoralen, isopsoralen and corylifol C [31]. In the present study, apremilast and PDE4 binding was compared with binding behavior of *Psoralea corylifolia* through molecular docking. Further, the inflammatory background of the plant was determined by estimating the anti-inflammatory and pro-inflammatory cytokines through ELISA test.

Materials and Methods

Molecular Docking of the phytoconstituents and apremilast was performed using Glide, Version 5.8, (Schrödinger, LLC, New York, NY 2014-2) of Maestro 9.3 (Schrödinger, LLC, New York, NY, 2014-2). Mouse specific ELISA kits were purchased from Ray Biotech USA.

Preparation of Ligand

Molecular modelling begins with ligand preparation. The phytoconstituents such as neobavaisoflavone, bavachinin, bavachalcone, corylifolin, bakuchiol are present in *Psoralea corylifolia* seeds. The structure of ligands namely, apremilast and the phytoconstituents was retrieved from PubChem database [32]. Initially the chemical structures of apremilast and the phytoconstituents were drawn in Maestro module followed by geometrical refining with LigPrep module, version 2.5, 2010. LigPrep is important since it predicts chiralities accurately and converts 2D structures of ligands to 3D structures. The ligand preparation includes creating various structures, correcting, verifying and optimizing ligand structure. Finally, the downloaded ligands were generated as low energy ring conformations and were converted to 3D MOL format using suitable software. Hydrogen atoms and energy were minimized using Maestro application. The phytoconstituents were converted to maestro.maegz extension format.

Modeling of Protein

Protein preparation was accomplished with protein preparation wizard of Maestro software. Protein data bank was referred to obtain 3D X-ray crystal structures of Human Phosphodiesterase 4 B enzyme (PDB ID:1XMU) PDE4B with roflumilast [33]. The ligand (roflumilast) was separated from the enzyme-ligand complex and the enzyme structure was used in docking study. The enzyme structure was refined for missing hydrogen and proper bond orders, displaying polar hydrogens and removing water molecules. Using sample orientation, the hydrogen bonds were optimized. Eventually, the enzyme structure was reduced to a default value of 0.30 for RMSD (Root Mean Square Deviation).

Generation of Receptor Grid

The receptor grid for 1XMU was generated using Glide application (Glide, version 5.8, Schrödinger, LLC, and New York-2) of Maestro 9.3 (Schrödinger, LLC, New York, NY, 2014-2). Site Map tool was employed for identifying the active/binding sites in 1XMU. Generation of receptor grid was followed by docking of the ligands to 1XMU (target protein) using Glide version 5.8 docking protocol in Extra precision mode (XP). Glide (G) Score was determined as follows.

G Score = a*VdW + b*Coul + Lipo + H bond + Metal + BuryP + RotB + Site

Where a=0.065 and b=0.130

Evaluation of Molecular Docking

Flexible docking was performed on predefined receptor grid. OPLS_2005 force field was used for ligand- protein interaction study. The limits for defining interactions between ligands and proteins were not established. The structure output format was set to pose viewer file in order to display the resulting output of docking. The ligands were evaluated on the basis of G Score.

Validation of Anti-inflammatory Activity

National Centre for Cell Science, Pune, India provided RAW 264.7, a mouse macrophage cell line. Dulbecco's Modified Eagle Medium (DMEM), containing 10% heat-inactivated Fetal Bovine Serum (FBS), 100 µg/ml streptomycin, and 50 units/ml of penicillin was used for growth of cell line. The cells were sub-cultured every two days and incubated at 37°C in the presence of 5% CO2. The extract of bakuchi seeds (prepared by microwave assisted extraction, 6 min) was diluted to produce E1 (1mg/ml concentration of extract) and E2 (0.5mg/ml concentration of extract).

Mouse specific antibodies against TNF- α, IL-1α, IL-10 were applied (100 µl/well) as a thin layer on the inner walls of ELISA plates (24 well) and incubated at 4°C for overnight. The plates were then treated with test samples E1 and E2 (200µl/well), lipopolysaccharide (LPS) (1µg/ml) or without LPS (normal) and incubated for 24 hr. The RAW 264.7 cells were seeded at a density of 2×10^4 cells per well and incubated at 25°C for 2 hr. After incubation, ELISA plates were washed 5 times with wash solution, consisting of Phosphate Buffer Saline (PBS) and Tween-20 (0.05%v/v) and each well was filled with 100 µl of detecting solution, (specific against each antibody and streptavidin horse-

radish peroxidase). The plates were sealed and incubated for 1 hr at 25° C followed by 5 times washing with wash buffer. Then the media was discarded, and each well was filled with 100 µl of Tetramethylbenzidine (TMB) solution and the plates were incubated, without sealing, for 30 min in dark at 25°C. Finally, 50 µl of 2N sulfuric acid was added to each well. The supernatant from each well was used to measure the pro- and anti-inflammatory cytokines at 450 and 570 nm. For each cytokine, the concentrations from three wells, were determined and expressed as pg/ml.

Results and Discussion

Molecular modeling is used commonly for forecasting the reaction of the ligand molecule with protein receptor molecule for last few years. The technique is particularly useful in identifying and optimizing "drug lead" from drug databases. Drug lead indicates a molecule which binds at one or more binding site/s of the receptor/ target molecule. Molecular docking is advantageous since it is accurate, comparatively cheap, fast and requires less manpower. It filters hundreds and thousands of molecules from the virtual database/s and determines ligand-protein binding with computational parameters [34].

Literature search reveals the use of computational docking for study of synthetic drug molecules and biotechnological products. Significantly less research has been done on application of in silico techniques for study of phytopharmaceuticals. The objective of our study is to check whether the phytoconstituents of *Psoralea corylifolia* can be potential ligands with pharmacological activity as PDE4 inhibitors. We used inverse docking to predict the target protein for the phytoconstituents (ligand). Our central idea was the phytoconstituent shows anti-psoriatic action through binding with a target protein (PDE4B) and acting as antagonist of the protein. To achieve this, the results of molecular interactions between phytoconstituents and PDE4B ligand binding domain were analysed and the binding affinity was determined using Glide. We compared the binding affinity of apremilast, a known PDE4B inhibitor, with that of the phytoconstituents, potential PDE4B inhibitors.

A study indicated that PDE4 inhibitors bind with target protein through histidine, two tryptophan residues, tyrosine residue and Zn^{2+} ion. The subtypes of PDE4 (PDE4 A-D) differ in positions of tryptophan, histidine, and tyrosine residues. Rolipram has high-affinity towards PDE4A and binds with tyrosine residues 432 and 602, as well as histidine 588. No interaction was detected between tryptophan and rolipram. The inhibitor also binds with phenylalanine 613 and 645 of PDE4 [35].

Another study suggested that the hydrophobic stack against Phe372 hydrophobic stack against Phe372, the hydrophobic interactions with Ile336, Phe340, and Phe372 and the hydrogen bond with Gln369 contribute to basic affinity of PDE inhibitors for PDEs [36]. PDEs' active site is an open space, consisting of Zn^{2+} ion, an open region and an inhibitor pocket. The latter includes hydrophobic clamp and two subpockets namely, Q1 and Q2. Rolipram binds with PDE through hydrophobic clamp. Hydrogen bonds are formed between roflumilast and Gln369 as well as Val365. Q2 subpocket is occupied by roflumilast [36].

In silico docking studies were performed and the most favourable binding mode of plant actives against 1XMU protein was determined. The amino acid sequence of Human Phosphodiesterase 4 B was retrieved from PDB with PDB ID 1XMU. The structure was predicted by Mastero software and optimized using OPLS_2005 force field so that 1XMU possesses minimum energy. The structure of 1XMU, after preparation of protein is depicted in (Figure 1a). Active sites of 1XMU were identified (Figure 1b) using Mastero. Tripuraneni NS, et al. predicted the active sites of 1XMU as Tyr233, His234, Asp392, Asn395, Gln443, Phe414 and 446 [37]. In the present study, a grid was prepared around the active sites. Schrodinger's Glide docking tool was used to dock the ligands to 1XMU protein.

Sr. No.	Ligand	Molecular weight (g/mole)	Docking score	Binding energy (Glide G Score)
1	Apremilast	460.5	-8.008	-8.008
2	Neobavaisoflavone	322.36	-8.828	-8.838
3	Bavachinin	338.403	-8.531	-8.531
4	Bavachalcone	324.376	-8.116	-8.158
5	Corylifolin	188.7	-7.67	-7.67
6	Bakuchiol	256.389	-7.046	-7.046

Table 1: Glide Docking Score of Protein 1XMU- Ligand Association.

Psoralea corylifolia phytoconstituents, with five different organic nuclei such as flavonone (bavachinin), isoflavone (neobavaisoflavone), chalcone (bavachalcone), meroterpene (bakuchiol), phenol (corylifolin), are used for the analysis [31]. The ligands are small flexible molecules, and therefore extensive conformational sampling is not needed. The calculations for ligand docking were made in Glide mode with extra precision (XP). Docking results of the phytoconstituents and apremilast, a known inhibitor of 1XMU, are listed in (Table 1).

Docking score for apremilast was -8.008 kcal $mole^{-1}$. Apremilast, establishes one hydrogen bond with Gln443 (bond distance 2.10Å) and π-π stacking with Phe446 (Figure 2a and 2b). Docking studies against PDE4B revealed that all phytoconstituents form hydrogen bonds with PDE4B. Most active phytoconstituent, neobavaisoflavone, with the binding energy of -8.838 kcal/mol, has formed hydrogen bond interactions with Thr345 and Gln443 (bond distances 2.03 Å and 1.83 Å respectively). Moreover, this compound exhibited π-π interaction with benzene ring of Phe446 (Figure 3a and 3b). Bavachinin has formed hydrogen bond with Thr345 (bond distance 2.07Å) and ionic interaction with Zn^{2+} ion. The phytochemical depicted π-π interaction with Phe446 and T-stacking interaction with Phe414 (Figure 4a and 4b). Bavachalcone has formed vital π-π interaction with Phe 446 and two hydrogen bonds with Gln443 and His278 (bond distances 2.65Å and 2.22Å respectively). It is interesting to note that its ketone group has formed ionic interaction with both Zn^{2+} and Mg^{2+} (Figure 5a and 5b). Corylifolin showed hydrogen bonding with Thr345 (bond distance 1.87Å) and T-stacking interaction with Phe414 and π-π stacking interaction with Phe446 (Figure 6a and 6b). Bakuchiol indicated hydrogen bond interaction with Asn395 (bond distance 2.06Å) and π-π interaction with Phe446 (Figure 7a and 7b). The phytoconstituents fitted adequately into the hydrophobic pocket of PDE4B and have formed hydrophobic interactions with different amino acids. The understanding of these interactions between PDE4B and phytoconstituents is essential to predict their mechanism of action. Nunes IKDC, et al. [38] reported π-π stacking between Phe residue of PDE4B and sulphonamides. We observed π-π interaction between Phe residue of PDE4B and the phytoconstituents.

Glide score values, Van der Waals energy values, and Coulomb energy values of the plant actives varied considerably which was attributed to different chemical structures (Table 2). The best fitting ligand in the active site of the target macromolecule can be predicted on the basis of Glide score and it is summed up as: Glide score of phytoconstituents varied from −7.046 to −11.201. It was interesting to note that Glide score of neobavaisoflavone, bavachinin and bavachalcone was less than apremilast. Halpin [39] has reported that the conformational status of glutamine, which is present in the catalytic region of PDE4, is important in identification of inhibitor. Our results indicated that the phytoconstituents showed interactions with different amino acid residues. Apremilast, neobavaisoflavone and bavachalcone formed hydrogen bond with glutamine. In addition, bavachinin and bavachalcone revealed electrostatic interaction with Zn and Mg ions. It was suggested that the bavachinin-receptor complexes were more stable than apremilast-receptor complex.

Ligand	Glide G Score	Glide energy	Van der Waals Energy	Coulombic Energy
Apremilast	-8.008	-55.306	-50.357	-4.949
Neobavaisoflavone	-8.838	-36.846	-27.833	-9.014
Bavachinin	-8.531	-41.688	-36.222	-5.466
Bavachalcone	-8.158	-32.485	-29.495	-2.99
Corylifolin	-7.67	-44.908	-37.269	-7.639
Bakuchiol	-7.046	-30.017	-28.367	-1.65

Table 2: Glide Parameters.

Coulomb's energy and Van der Waals energy, representing the non-bonded interaction energies, are negative. It indicated net attractive interaction. The Coulomb energy term increased in the order: bakuchiol > bavachalcone > apremilast >bavachinin > corylifolin > neobavaisoflavone. Van der Waals energy value was the lowest for apremilast whereas Coulomb energy value was highest for apremilast. Coulomb energy value, for the phytoconstituents, in ascending order is corylifolin < bavachinin < bavachalcone < bakuchiol < neobavaisoflavone. A direct relationship in between Coulomb's energy, Van der Walls energy and the lipophilic contact points of the ligands was observed by Subramanian, et al. [25]. Our results indicated that Coulombic energy and Van der Waals energy of neobavaisoflavone, corylifolin and bavachinin were higher than that of apremilast indicating better binding interaction of these phytoconstituents with PDE4B than apremilast.

Validation of Anti-inflammatory Activity

Results indicated that bakuchi extract possesses significant inhibitory activity.

Inhibition of TNF-α: RAW264.7 cells, which are treated with LPS (positive control) depicted significantly higher TNF-α levels than the cells which aren't treated with LPS (negative control). *Psoralea corylifolia* seed extracts E1 and E2, at concentrations 0.5 mg/ml and 1mg/ml, inhibited TNF-α, in RAW264.7 cells, in dose-dependent manner (Figure 1).

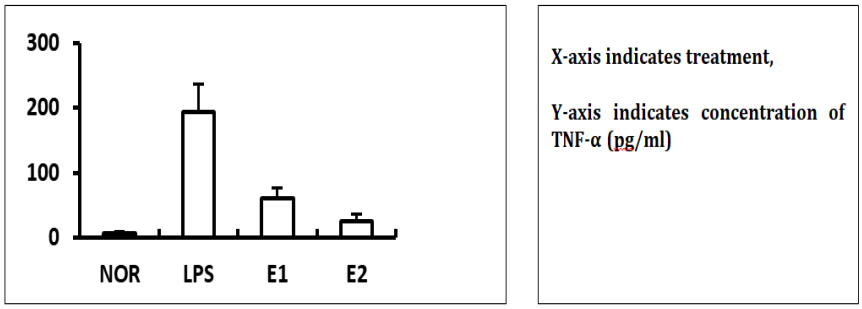

Figure 1: Inhibition of TNF-**α**.

Interlukin-1β: Results indicated that treatment with extracts E1 and E2 lowered IL-1β levels RAW264.7 cells when compared to LPS (positive control) (Figure 2).

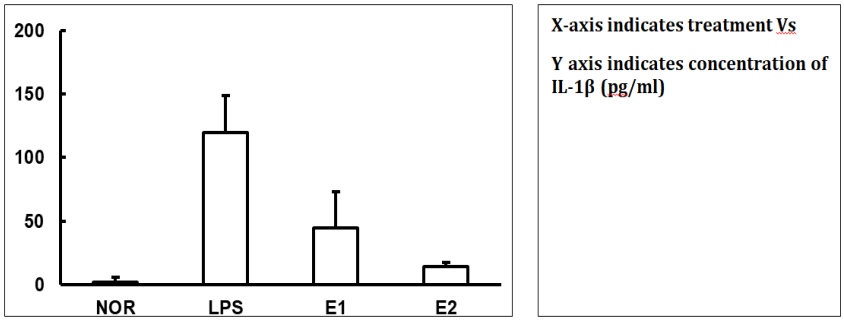

Figure 2: Inhibition of Interleukin-1**β**.

Interlukin-10: IL-10 is a natural anti-inflammatory cytokine. Bakuchi seed extracts E1 and E2 are effective in stimulating the production of IL-10 in RAW264.7 cells (Figure 3).

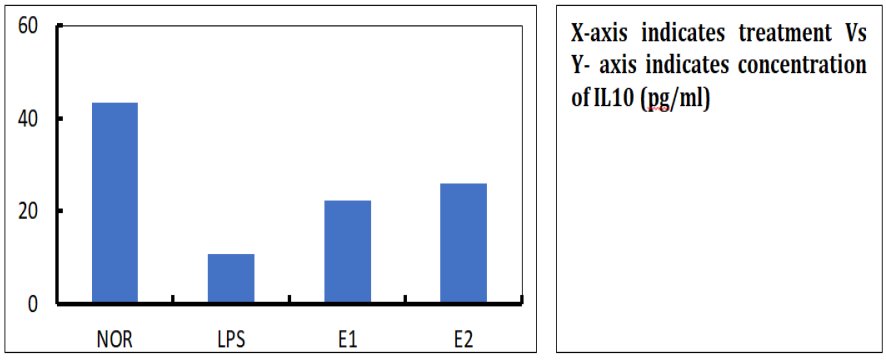

Figure 3: Stimulation of IL-10.

cAMP is a key secondary messenger [25,40] that is expressed in all cells and is intimately involved in a wide variety of normal cellular responses. Intracellular cAMP concentrations are mediated by adenylyl cyclase (AC) and phosphodiesterases (PDE). PDEs are responsible for degrading cAMP, of which the PDE-4 isoenzyme is the most prominent in immune cells, such as lymphocytes, granulocytes and monocytes/ macrophages. When intracellular cAMP concentrations are low, cAMP is activated by G-protein coupled receptor ligands. Upon activation of cAMP, protein kinase A (PKA) activates cAMP response element-binding protein (CREB). Activation of CREB leads to generation and secretion of inflammatory cytokines, including IFN-γ, TNF-α, IL-2, IL-12, IL-23, and stimulation of the anti-inflammatory cytokines such as IL-10. Bakuchi phytoconstituents inhibit PDE4B and are responsible for elevating cAMP levels. As a result, cAMP is not activated by G-protein coupled receptor ligands leading to inactivation of both PKA and CREB. Hence, it suppresses inflammatory cytokines, namely, TNF-α, IL-1, and stimulates IL-10, the anti-inflammatory cytokine.

Conclusion

Study has revealed that cAMP is mainly hydrolyzed by PDE4B, a subclass of PDE4 enzyme. Inhibition and/or depletion of PDE4B produce anti-inflammatory effect on multiple organs with minimum adverse effects. Screening of novel PDE4 B inhibitors is crucial since psoriasis is an inflammatory disorder of skin. The study demonstrated the affinity between PDE4B and the phytoconstituents of *Psoralea corylifolia* through hydrogen bonds, π-π stack, T-stack and hydrophobic interactions. Molecular docking results reveal inhibition and expression of PDE4B by the phytoconstituents and support the use of *Psoralea corylifolia* in treatment of psoriasis. However, further studies are essential to confirm these results. These results demonstrate that one of the anti-inflammatory mechanisms of the phytoconstituents can be attributed to their ability to inhibit PDE4B.

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Conflict of Interest

The authors declare that they have no conflicts of interest regarding this article.

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