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A bioinformatic approach to establish P38α MAPK inhibitory mechanism of selected natural products in psoriasis

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In the present study, molecular docking studies of some selected natural products were carried out to identify the potential inhibitors and subsequently to suggest their mechanism of action in relation to P38α mitogen-activated protein kinases (P38α MAPK) enzyme. Psoriasis is an inflammatory disorder characterized by skin hyper-proliferation, differentiation in keratin expression, and increased production of pro-inflammatory cytokines. Increased expression of phosphorylated P38α MAPK in the cytoplasm and nucleus is observed in psoriatic lesions. Twelve natural antipsoriatic agents were included in the study and their molecular docking studies were carried out using AutoDock 4.2 simulator using a Lamarckian genetic algorithm. The crystal structure of P38α MAPK was retrieved from the protein data bank and three-dimensional chemical structures of natural ligands were prepared using ChemSketch 2015. Results indicated that all the natural ligands were fitted into the active site. Hypericin and Catechin (−9.00 and −8.05 kcal/mol, respectively) have shown good binding efficacy among other ligands. However, only Epicatechin interacted with residues in the enzyme required for enzyme inhibition. The study concludes that the Epicatechin effectively inhibited the enzyme and proved itself to be a type-$I^{1/2}$ inhibitor of the enzyme among other natural ligands and responsible for the treatment of psoriasis preclinically through this mechanism of action.

Keywords: Autoimmune disease, Docking study, Mitogen-activated protein kinase, Molecular interactions, Skin disorder

Psoriasis is an inflammatory disorder characterized by skin hyper-proliferation, differentiation in keratin expression, and increased production of pro-inflammatory cytokines[1]. Escalating instances of psoriasis across the world significantly impacted the social and mental well beings of humans. Psoriasis requires continuous assessment of treatment and management of the disease. 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. It has been postulated that P38α mitogen-activated protein kinases (p38α MAPK) enzyme is activated by external stimuli like ultraviolet light, irradiation, heat shock, high osmotic stress, pro-inflammatory cytokines, and certain mitogens[2,3]. P38α MAPK appears to be involved in many pathological conditions *viz.* rheumatoid arthritis, cardiovascular disorders, cancer and psoriasis[3,4]. Increased expressions of phosphorylated p38α MAPK in the cytoplasm and nucleus have been observed in the biopsy of psoriatic lesions. The kinase activity of p38α isoforms increases in psoriatic lesions when compared with the psoriatic lesion resolves[5]. These observations also endorse the role of p38αmitogen activated protein kinase in the pathogenesis of psoriasis induced by stress or other environmental factors. Therefore, p38α MAPK has become a striking target for the treatment of many autoimmune and inflammatory diseases. Several p38α MAPK inhibitors have been designed and tested clinically and preclinically in the pathophysiology of

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autoimmune and inflammatory diseases. The present study includes twelve natural ligands whose antipsoriatic mechanisms are not clear yet, but they have been described to have a prominent antipsoriatic property in preclinical studies. Therefore, this study was aimed to find some suitable P38α MAPK inhibitors and to establish their p38α MAPK inhibition mechanism for the treatment of inflammation and other cardinal symptoms of psoriasis. In the present study twelve natural, 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], which have shown antipsoriatic activity preclinically, were studied (Fig. S1). Interactions of all tested natural ligands with molecular targets were demonstrated by molecular docking study to elucidate their molecular mechanism of action to inhibit the inflammation and generation of cytokines and pathological mediators in psoriasis. Further, this communication is aimed to support the role of P38α MAPK in the pathophysiology of psoriasis and other skin diseases.

Methods and Materials

The crystal structure of the molecular target (P38α MAPK, PDB id: 3lhj) engaged in the pathophysiology of psoriasis was retrieved from RCSB protein data bank[17]. The active site in the target was identified with the help of Biovia Discovery Studio 4.5. A macromolecule needs to be prepared prior to docking process. Preparation of the macromolecule involves the removal of water molecules and any unwanted hetero atoms because these may interfere with the docking process. After refining, the macromolecule was saved as .pdb execution file. After assigning hydrogen bonds and Gasteiger charges, the macromolecule was loaded and stored as macromolecules .pdbqt. The investigational ligands were designed using ChemSketch (ACD 2015). The optimization of energy minimization was carried out using MM2 force field and saved in .mol format and subsequently converted into .pdb format by Open Bable −2.3.2 software. Natural ligands were loaded and their torsions and rotatable bonds were assigned and the files were saved as ligand .pdbqt. To confirm the binding modes of selected compounds with receptor protein, molecular docking studies were carried out using AutoDock v 4.2.6 software. In this way, different conformers of the compounds were generated, and the docking was performed on the active site of molecular target. The best conformers were discussed with the lowest binding energy (−kcal/mol). The docking parameters were defined as coordinates of the center of binding site with x = 56, y = 58, z = 54 and binding radius = 0.375 Å and Coordinates of Central Grid Point of Maps were X= −3.261, Y = 12.341, and Z = 20.571. All AutoDock output files (.dlg) were analyzed through the analysis option provided in MGL Tools −1.5.6 rc3. Rigid docking was performed using Genetic Algorithms while keeping other docking parameters as default followed by the setting up of docking parameter files with the search parameter as genetic algorithm and docking parameter utilizing a Lamarckian genetic algorithm. Subsequently, ligand-protein interactions were visualized by Biovia Discovery studio 4.5.

Results and Discussion

P38α MAPKs are a class of mitogen-activated protein kinases (MAPKs) in which P38α has been implicated in several pathological conditions. The recent scientific findings suggested that P38α MAPK is expressed in psoriatic lesions in human beings. The p38α MAPK is a central signaling molecule in many pro-inflammatory pathways, regulating the cellular response to a multitude of external stimuli, including, heat, ultraviolet radiation, osmotic shock, and a variety of cytokines especially interleukin-1β and tumor necrosis factor α. Thus, the P38α MAPK inhibitors are postulated to have significant therapeutic potential for the treatment of autoimmune and inflammatory diseases. The present study revealed that all the selected natural ligands fitted into the active site and demonstrated appreciable binding affinity to the target (Fig. 1). Reported X-ray crystallographic analysis suggests that for the

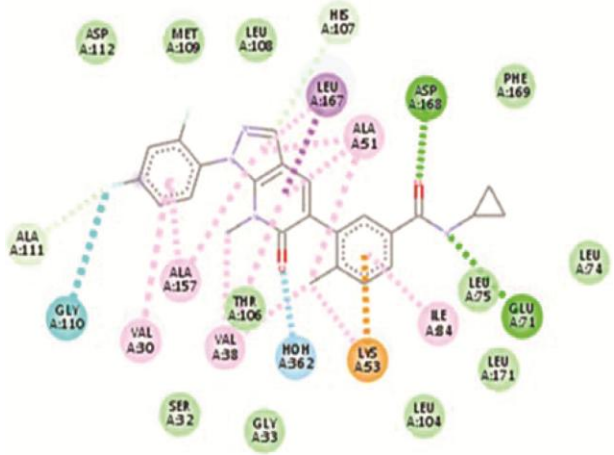

Fig. 1 — Active Site of p38α MAPK

inhibition of this enzyme, hydrogen bonds formed between amino acid residues Asp168, Glu71, Met109 with natural ligands are mandatory and Thr106 amino acids residue works like gatekeeper in the target and its involvement in the interaction with the ligands might not be compromised. The active site of this target enzyme comprises Val38, Ala51, Lys53, Leu74, Leu75, Ile84, Leu104, Thr106, His107, Leu108, Met109, Gly110, Ala111, Asp112, Ala157, Leu167, Asp168, Phe169, and Leu171 (Fig. 2). The best poses of most effective natural ligands and enzyme complexes, and the number of hydrogen bonds formed by both proteins with the drug and ligand binding pockets are shown in (Fig. 2A-F).The calculated binding energies, H-bond formations and corresponding H-bond distances and ligand-target interactions are elaborated in (Table 1). The data related to ligand binding to the target is presented in (Table 2). The 2D images of interactions between ligands and p38α MAPK are illustrated in supplementary data, (Fig. S2 A-L).

P38α MAPK is a widely investigated enzyme due to its prominent role in many inflammatory processes. Activation of this enzyme leads to the generation of TNF-α and other cytokines proving it as a valid target for therapeutic intervention. The structure of P38α MAPK enzyme has been divided into three major parts which include (1) The gate area (Hydrophobic region-I) surrounded by Ala51, Lys53, Leu75, Leu167, and Thr106, (2) Front cleft (Hydrophobic region-II) composed of Val30, Ile108, Gly110, Ala111, Asp112 and Ala157, and (3) Back Cleft

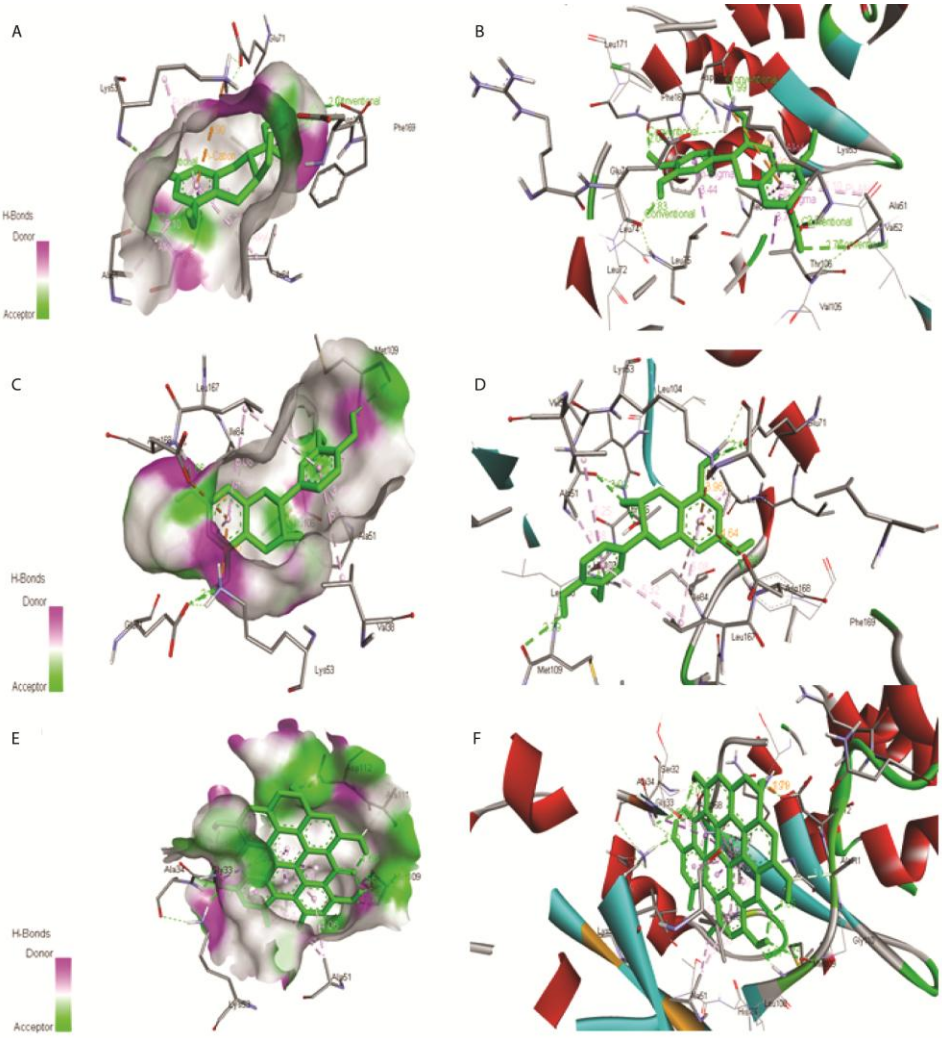

Fig. 2 — (A) Catechin interacted in the cavity of target enzyme *i.e*.P38α MAPK; (B) 3D image of interactions between Catechin and p38α MAPK; (C) Epicatechin interactedin the cavity of target enzyme *i.e*.P38α MAPK; (D) 3D image of interactions between Epicatechin and p38α MAPK; (E) Hypericin interactedin the cavity of targetenzyme *i.e*.P38α MAPK; and (F) 3D image of interactions between Hypericin and p38α MAPK

comprised Met78, Val83, Ile141, and His148 and sub-divided into Linker region composed of Glu71, Leu74, Leu75, Ile84, Asp168, Leu171, Phe169 and α-c helix pocket composed of Arg67, Arg70, Glu71[18]. In the present study all the ligands were found to be fitted into the active site and have essentially occupied the gate area (hydrophobic region-I) irrespective to their chemical structures. The inhibitors interactions at the ATP binding site are further categorized into four sub-categories (1) Type-I inhibitors occupy Hinge region and make hydrogen bonds with Met109, Gly110. Ala157 residue also involves in the interaction with inhibitors, (2) Type-$I^{1/2}$ inhibitors involve in making the hydrogen bonds with Glu71, Asp168, including Met109 and occupy Hinge region in the active pocket, (3) Type-II inhibitors also occupy the Hinge region and make hydrogen bonding with Glu71, Asp168, Met109, and Gly110. Ala157 was also found in interaction with inhibitors, and (4) Type-III inhibitors (Hinge region in the active site) form H-bonds with Glu71, Asp168 and Arg70 residues[17]. Vali *et al.* 2005 examined the efficacy of topical application of caffeine in the treatment of psoriasis vulgaris affected patients *via* randomized, double blind, placebo controlled study[6]. Kalyan Kumar *et al.* 2011 reported the role of TNF-α in pathogenesis of psoriasis and beneficial effect of Embelin on production of TNF-α through lipopolysaccharide induced tumor necrosis factor-α production in mice model and *in vitro* human

Table 1 — Interactions between natural ligands and P38α MAPK

Ligand	Binding energy (Kcal/mol)	H-bond with amino acid	H-bond distance (Å)	Amino acids involved in the interactions
Caffeine	−4.86	Nil	-	Lys53, Glu71, Leu75, Ile84, Leu104, Thr106, Leu167, Asp168, Phe169, Leu171
Capsaicin	−5.59	Asp168	1.72	Ala34, Val38, Ala51, Lys53, Glu71, Leu75, Ile84, Leu104, Thr106, His107, Leu108, Met109, Ala111, Asp112, Ala157, Leu167, Asp168
Catechin	−8.05	Ala51, Lys53, Glu71, Asp168, Phe169	2.74, 2.29, 1.99, 2.04, 1.83	Ala34, Val38, Ala51, Val52, Lys53, Glu71, Leu72, Leu74, Leu75, Ile84, Leu104, Val105, Thr106, His107, Leu167, Asp168, Phe169, Gly170, Leu171
Curcumin	−5.82	Lys53, Met109, Asp112, Ser154	2.13, 2.04, 2.84, 2.24	Ser32, Gly33, Ala34, Ala51, Lys53, Glu71, Ile84, Thr106, His107, Leu108, Met109, Gly110, Ala111, Asp112, Ser154, Asn155, Ala157, Leu167, Asp168
DMF	−4.24	Nil	-	Lys53, Glu71, Leu75, Ile84, Leu104, Thr106, Leu167, Asp168, Phe169, Leu171
Embelin	−5.45	His107, Met109	1.653, 2.093	Ala34, Val38, Ala51, Lys53, Glu71, Leu74, Leu75, Thr106, His107, Leu108, Met109, Leu167, Asp168, Phe169, Leu171
Epicatechin	−7.98	Ala51, Glu71, Thr106, His107, Met109, Asp168	3.03, 2.11, 2.11, 1.81, 2.79, 1.66	Val30, Val38, Ala51, Lys53, Glu71, Leu75, Ile84, Leu104, Thr106, His107, Leu108, Met109, Ala157, Leu167, Asp168, Phe169, Leu171
Gossypol	−6.69	His107	1.85	Val30, Ser32, Gly33, Ala34, Tyr35, Val38, Ala51, Lys53, Ile84, Thr106, His107, Leu108, Met109, Asp112, Lys152, Ser154, Ala157, Leu167, Asp168
Hypericin	−9.00	Ala34, Lys53, Met109, Asp168	2.51 1.70, 2.42, 1.79	Ser32, Gly33, Ala34, Val38, Ala51, Lys53, Ile84, Thr106, His107, Leu108, Met109, Gly110, Ala111, Asp112, Ser154, Leu167, Asp168
Luteolin	−7.77	His107, Met109, Asp168	2.00, 2.38, 2.04	Val30, Ala34, Val38, Ala51, Lys53, Glu71, Leu75, Ile84, Leu104, Thr106, His107, Leu108, Met109, Ala157, Leu167, Asp168
MEF	−5.14	His80, Gly85, Lys165	2.10, 1.84, 1.84	Met78, Lys79, His80, Glu81, Val83, Ile84, Gly85, Leu87, Thr106, His107, Lys165
Quercetin	−7.50	Met109, His107, Asp168, Ala51	2.63, 2.46, 1.71, 2.13, 2.29	Val30, Ala34, Val38, Ala51, Val52, Lys53, Glu71, Leu75, Ile84, Leu104, Val105, Thr106, His107, Leu108, Met109, Ala157, Leu167, Asp168, Phe169, Leu171

Table 2 — Data related to Ligand binding

	Parameters						
Ligand	Inhibitory constant (μM)	Intermolecular energy (kcal/mol)	Total internal energy (kcal/mol)	Torsional energy (kcal/mol)	Electrostatic energy (kcal/mol)	Unbound energy (kcal/mol)	Vdw desolvation energy (kcal/mol)
Caffeine	274.3	−4.86	0.00	0.00	0.08	0.00	−4.94
Capsaicin	79.95	−8.57	−1.02	2.98	−0.26	−1.02	−8.31
Catechin	1.26	−9.84	−0.45	1.79	−0.11	−0.45	−9.73
Curcumin	54.62	−8.80	−1.61	2.98	−0.18	−1.61	−8.62
DMF	782.74	−5.43	− 0.18	1.19	−0.07	−0.18	−5.36
Embelin	100.39	−9.03	−1.48	3.58	−0.09	−1.48	−8.95
Epicatechin	1.4	−9.77	−0.78	1.79	−0.26	−0.78	−9.51
Gossypol	12.75	−9.37	−2.19	2.68	−0.22	−2.19	−9.15
Hypericin	251.02	−11.09	−2.48	2.09	−0.93	−2.48	−10.16
Luteolin	2.03	−9.26	−1.24	1.49	−0.20	−1.24	−9.06
MEF	171	−6.63	−0.15	1.49	−1.11	−0.15	−5.52
Quercetin	3.17	−9.29	−1.55	1.79	−0.25	−1.55	−9.05

keratinocytes[9]. In the study carried out by Kamuhabwa *et al.* 1999, Hypericin was applied in the form of ointment with Solketal® or in polyethylene glycol on hairless mice for 4 h. For induction of psoriasis like features irradiation was done with 500 watt halogen lamp. This study further elaborated that no quantifiable photosensitization occurred when Hypericin was added into PEG ointment or 10 mg/kg Hypericin was administered *i.p*[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 release of three mediators involved in the inflammatory process like IL-6, IL-8 and VEGF in concentration dependent manner. They also reported that this flavanoid also reduced TNF-α induced mRNA expression of two genes, ONFKB1 and RELA, and gene expression of RELA is increased in skin having psoriasis. Also Luteolin effectively reduced the keratinocytes proliferation which is a salient feature of psoriasis, but not in primary keratinocytes[13]. Harries *et al.* 2005 showed that the efficacy of fumaric acid esters (FAEs) used in 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]. Waranuch *et al.* (2013) reviewed the role of green tea which contains Catechins, Epicatechin and other ingredients on the skin[19]. Arora *et al.* 2015 reported the efficacies of some herbal extracts on imiquimod induced psoriasis like dermatitis. They elucidated the beneficial role of four medicinal plants *i.e*. *Tinospora cardifolia*, *Curcuma longa*, *Celastrus paniculatum* and *aloe vera* against psoriasis induced by imiquimod. When extracts of these mentioned plants were given orally or topically in combination down regulated the over expressed cytokines. Therefore, results suggested that these medicinal plants might play a role to develop new strategies for treatment of psoriasis[20]. 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 most potent antiproliferative agent. Therefore, this study concluded that gossypol as either recemic mixture or the individual atropisomers has potential to treat psoriasis[21]. Vijayalakshmi *et al.* 2014 evaluated the antipsoriatic activity of traditionally used plant *Cassia tora* L. In this study leaves of this plant were used to prepared 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 property at the dose of 400 mg/kg using ultraviolet B rays photo-dermatitis in rat model. Ethanolic extract

and isolated flavanoids exhibited significant ($P< 0.01$) reduction of epidermal thickness when compared to standard. Study concluded that isolated herbal molecules from Cassia tora possessed the antipsoriatic property[22]. Sun *et al.* 2013 determined the antipsoriatic potential of curcumin; a key ingredient of turmeric had been reported to possess various medicinal properties. In this study, they determined the inhibitory potency of curcumin against imiquimod induced psoriasis like inflammation in mice which was developed on the basis of IL-23/ IL-17A axis. They reported that IMQ induced inflammation in mice ears was significantly inhibited after curcumin treatment. Also, expressions of IL-17A, IL-17F, IL-22, IL-1β, IL-6 and TNF-α cytokines were decreased. This effect was as similar as that of Clobestol. This study revealed that curcumin was a potent inhibitor of IL-23/IL-17A so that inflammation could be treated in this study[23].

The molecular docking analysis in this study suggested that although most of the natural ligands interacted with Hinge region (residues 106-110), but could not form mandatory hydrogen bonds, except Epicatechin, to fulfil the requirement of absolute inhibition of enzyme. Epicatechin form H-bond with Met109 in the Hinge region and with Glu71 and Asp168 in the linker region of the enzyme therefore proves itself to be type-$I^{1/2}$ inhibitor. The established H-bond with Ala51, Thr106 and His107 had better binding score (−7.98 kcal/mol) among other ligands except Catechin (−0.07 kcal/mol) and Hypericin (−1.02 kcal/mol) in binding energy. However, both (Catechin and Hypericin) could not formed required hydrogen bonds with residues *i.e.* Glu71, Met109 and Asp168 for the enzyme inhibition. The molecular docking approach in this study discloses that the flavonoids *i.e.* Catechin, Epicatechin, Quercetin, and Luteolin demonstrates better binding affinity to the enzyme (−8.05, −7.98, −7.50 and −7.77 kcal/mol, respectively). Only Epicatechin was found to be responsible for complete enzyme inhibition by forming H-bond with Ala51, Glu71, Thr106, His107, Met109 Asp168, having an H-bond distances of 3.03, 2.11, 2.11, 1.81, 2.79, and 1.66, respectively, (in Å). Luteolin and Quercetin have quite similar interactions with amino acids *viz.* His107, Met109, and Asp168 and have very less difference in the binding energies. Hypericin has shown maximum binding affinity (−9.00 kcal/mol) among other natural ligands to the enzyme and fitted into the active site but could not afford prerequisite H-bond interactions and formed H-bonds with Ala34, Lys53, Met109 and Asp168 residues. Gossypol found to be docked into the active pocket and had binding energy of −6.69 kcal/ mol. However, this can construct an H-bond only with His107 in the active pocket of P38α MAP kinase enzyme. Formic acid esters have been used widely for the treatment of psoriatic patients, but their mechanism of action was not elucidated to date. In this study both the esters *i.e.* Monoethyl Fumerate (MEF) and Dimethyl Fumerate (DMF) were included and an attempt was made to identify their mode of action through the docking study. Both the esters were fitted into the active site but could not inhibit the kinase enzyme. This can be because DMF not formed required hydrogen bonds to p38α MAPK enzyme whereas MEF formed hydrogen bonds with His80, Gly85 and Lys165 with a binding energy of −4.24 kcal/ mol and −5.14, respectively. Curcumin also has active site, but it cannot make hydrogen bonds with inhibitory amino acids in enzymes rather than formed H-bond with Lys53, Met109, Asp112 and Ser154 in the active pocket with a moderate binding score of −5.82 kcal/mol. Capsaicin included in the present study is an active component of Chili pepper which formed hydrogen bonding with inhibitory amino acid, Asp168 in the enzyme with binding energy −5.59 kcal/mol. Caffeine also has quite similar interaction with the target with a lesser binding affinity (−4.86 kcal/mol). However, Caffeine could not interact with the enzyme through the H-bond. Embelin also interacts with amino acids in the active site but the binding score is very less compared to those of flavonoids and Hypericin. Embelin interacted with His107 and Met109 (binding energy −5.45 kcal/mol). The inhibitory constant and vander Waals H-bond desolvation energy are the prominent parameters that influence the inhibitory potential of compounds. In this report, Catechin and Epicatechin intriguingly exhibited the least inhibitory constant *i.e.* 1.4 and 1.26 μM, respectively, and better vander Waals desolvation energy −9.51 and −9.73 kcal/mol, respectively. Hypericin exhibited maximum vander Waals H-bond desolvation energy (−10.16 kcal/mol) rather than that of other natural compounds in the current study. Also, Agrawal *et al.* 2020 did a similar kind of *in silico* study using the natural products in case of psoriasis disease. They proved that Hypericin exhibited the maximum binding affinity and better interactions among other natural products and was capable to desensitize the TRPV-3 channel responsible for itching and pain in psoriasis[24].

Conclusion

In the present report, molecular docking study pertaining to p38α MAPK and natural ligands established antipsoriatic activity of Epicatechin by making suitable hydrogen bonds with amino acids necessary for kinase enzyme inhibition. Hypericin and Catechin by exhibiting appreciable binding affinities towards p38α MAPK. Although more research work would be required for the future use of these natural compounds for the treatment of psoriasis.

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Conflict of interest

All authors declare no conflict of interest.

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