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TO EVALUATE THE ANTI-PSORIATIC ACTIVITY OF SOME MEDICINAL PLANTS: AN IN-SILICO APPROACH

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ABSTRACT

Psoriasis is a common and chronic autoimmune skin disease that affect **2-3%** of population worldwide. Psoriasis not only affect skin but also other organ systems viz. gastro-intestinal tract, musculoskeletal system, and eye. It is illustrated by increased proliferative keratinocyte that multiply up to 10 times more rapidly than normal cells and causes dilation of cuticular capillaries. The current treatments available are topical, light therapy and systemic medications but the limitation is that these have side effects and is a long therapy. Many herbal plants are reported which can be used in the treatment of the Psoriasis. In this study we have selected the phytoconstituents and these were docked with the JAK protein. It was observed that Lupeol, Hypericin, Luteolin and Rigidin had good binding affinities with target molecule to inhibit the inflammatory mediators (IL-17, IL-23, IL-9, IL-28, IL-6, TNF-α etc.) activated due to activation of JAKs. The plants studied in the present work showed better affinity to bind with JAK, hence, we propose that the above mentioned phytoconstituents can be used for the treatment of psoriasis.

1. INTRODUCTION

The skin inflammation is a segment of the body immune reaction and exist as the oxidative trauma in any body parts. Among the variety of inflammatory diseases like eczema, fungal infection, bacterial infection, viral infection, parasitic infection, autoimmune disease and miscellaneous diseases. They are not life threatening, but threaten the beauty, which had a substantial impact on the life of patient. Among the different categories of above-mentioned diseases, psoriasis is a papulosquamous disorder which poses a great burden on patient life's (physically, psychologically and socially) and studies have shown that effect of this disease on quality of life is similar to comorbid disease like hypertension, diabetes, cancer arthritis

and depression. The exact etiology of psoriasis is still unknown but there is evidence for genetic predisposition. So, about psoriasis, its symptoms, treatment and preventive, alternatives of chemical drugs are important. The major remedies are topicals, light therapy and systemic medication. Topical is first line of treatment which include, emollients, moisturizers, tar anthralins, corticosteroids, vitamin A and vitamin D analogs. The over use of corticosteroids causes thinning of skin and excess use of vitamin D may cause skin irritation. In light therapy UV-A and UV-B or both lights are used to treat mild to moderate psoriasis by reducing the skin inflammation up to a certain limit. Systemic medication treats severe psoriasis which include, retinoids, methotrexate, cyclosporin and immunomodulators. Methotrexate act by supressing the immune system and reduce pain, itching and inflamed skin but upset stomach, loss of appetite, fatigue in patients. Cyclosporin work similar to methotrexate by supressing immune system, but cause kidney cancer, ulcer in stomach. These treatments have some limitations therefore, there is a requirement of safer and more effective agents is need of the time. Various medicinal systems like Ayurveda, Siddha, Korean, Chinese, Thai are used to treat psoriasis, vitiligo, dermatitis and leuco-derma. The most of the population uses complimentary medicine for two main reasons: firstly, the limitation /side effects of synthetic drugs; secondly the ability to act on multiple targets. So herbal plants can provide the new therapeutic approach to psoriasis treatment. Later they have substantial preventive activity against psoriasis. Traditional therapies improve psoriasis by decreasing the T-cells but in HIV patients the decrease in T-cell count worsen the psoriasis in other way. This point is sustained by certain researches in animal model, that psoriasis is elicited in mice lacking T-cell. Epidermal hyper proliferation, abnormal keratinocytes differentiation, angiogenesis with blood vessels dilation and over activation of Th-1 and Th-17 are associated with psoriasis. Active scaly lesions may activate phospholipaseA2, which lead to activation of Arachidonic acid pathway. Though PGE2 production result in dilating the blood vessels of the dermis which lead to leucocyte infiltration and stimulate keratinocyte cell growth. In recent time, WHO is also promoting the herbal drugs because of their therapeutic safety benefits. The aim of the study is to focus on *in-silico* studies on selected phytoconstituent having anti-inflammatory activity.

2. OBJECTIVES

1. To evaluate the binding affinity of phytoconstituents of various medicinal plants on pathological targets of psoriasis.

2. To evaluate binding affinity of Lupeol, Rigidins, Luteolin on selected molecular target with respect to tofacitinib.
3. Docking studies of phytoconstituents selected and target selected.
4. To evaluate ADMET and drug likeness property of plant phytoconstituents.

3. METHODOLOGY

3.1 Identification of molecular target

The crystal structure of the molecular target (JAK3, PDB id:6HZV) is selected by the intensive literature search which is responsible for the generation of various inflammatory mediators i.e...IL-6, IL-23, IL-29, IL-3, and IL-9 were retrieved from the RCSB protein data bank.

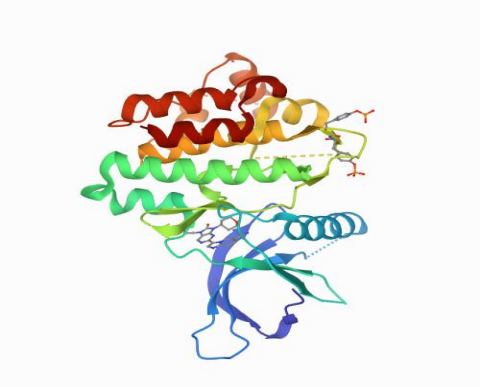


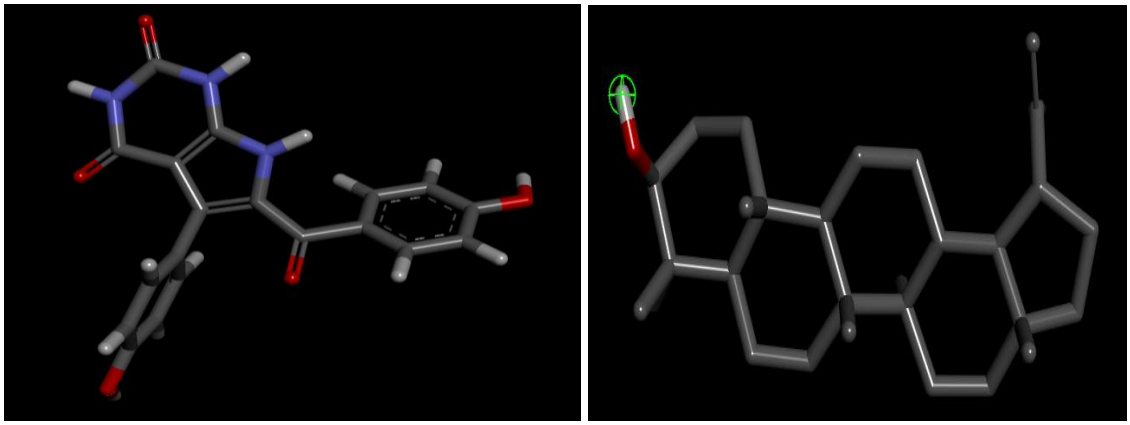
Figure 5: Structure of protein 6HZV.

3.2 Target optimization

Macromolecule was prepared, before the docking process using Autodock 4.2v software. The preparation method involved removal of water molecules and hetero atom. A specific chain was selected in the protein with which docking was done. The water molecules were deleted as they may interfere with the docking process. After filtering, the macromolecule was saved as a.pdb execution file. The macromolecule was loaded and stored as macromolecule.pdbqt and assigning the hydrogen bonds and Gasteiger charges.

3.3 Ligand preparation and optimization

The ligand was selected, designed using Marwin sketch and optimized for energy minimization using chimera 1.15. The ligand was loaded and the charges, torsions along with rotatable bonds were assigned and the file was saved as ligand.pdbqt format.

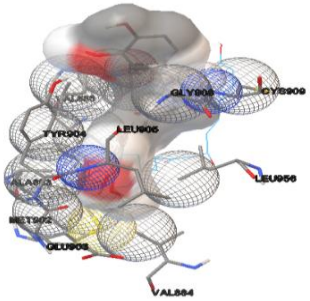


a **b**

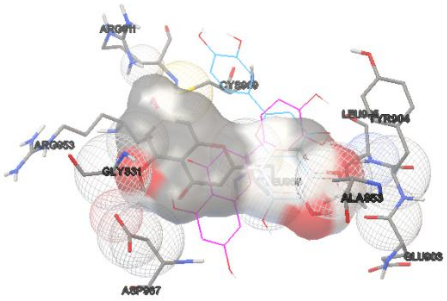
Figure 6: (a) Tofacitinib (b) Lupeol.

3.4 Prediction of active site

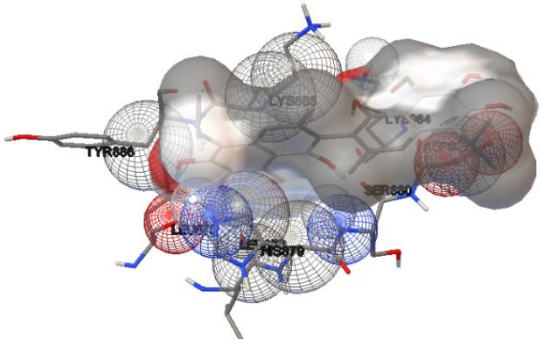
The prediction of active site for protein 6HZV was done using pymol software. The amino acids at the active site for Janus kinase (JAK3) were found to be: LEU905, CYS902, ASP912, LEU956, LEU828, ALA853, VAL836, VAL884, MET902, ASN954. After prediction of binding sites of protein, data was interpreted with the binding sites of standard drug (Tofacitinib).



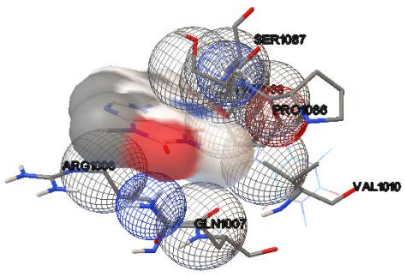
Curcumin



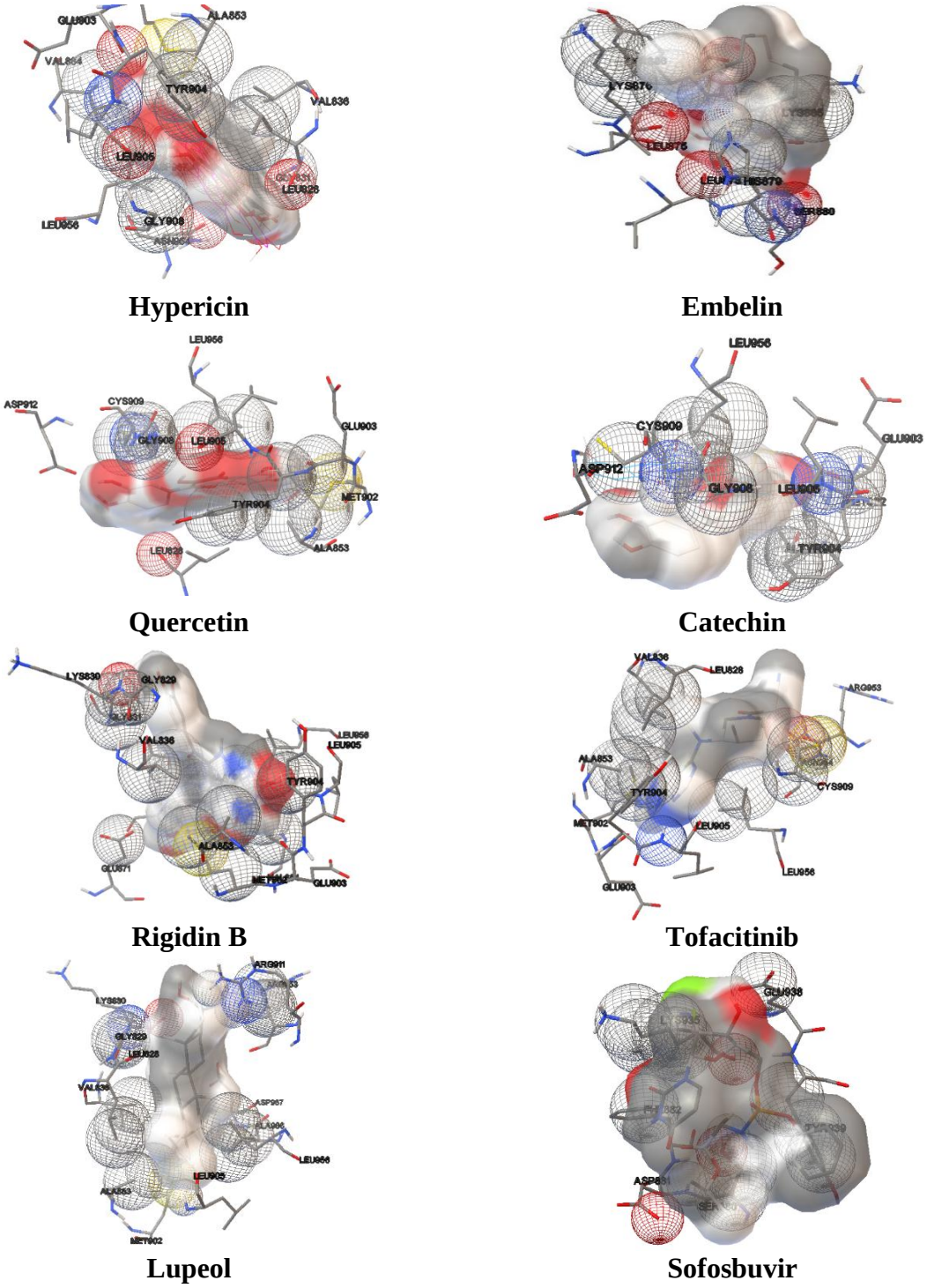
Luteolin



Gossypol



Caffiene



Figures 7: Binding modes of ligands with receptor protein target.

3.5 Molecular docking analysis

To confirm the binding modes of compounds undertaken in the present study with receptor protein, molecular docking studies were carried out by AutoDock v 4.2.6 software and AutoDock Vina. In this way, the different poses of interaction of conformers of compounds were generated and force, blind docking was performed on molecular target and the best

conformer having lowest binding energy (-kcal/mol) was recorded. The blind docking was performed to find out the actual binding site of the psoriatic agent which pave the way to reveal the mode of action of selected ligands with protein. The conformers of ligand were automatically docked to targets, transient receptor protein channels. The docking parameters were defined coordinates of the center of binding sites selected were x=126, y=126, z=126 and binding radius with = 0.553 Å and coordinate of center grid point was X=11.012, Y=40.083, Z=6.859. The AutoDock output file(.dlg) was analyzed through the analysis option provided in AutoDock v4.2.6 and the conformation having the lowest binding energy was analyzed. The file of conformers was saved in.pdbqt format. Further, the interaction can also be seen in the Discovery studio and protein-ligand interaction profiler. This two-software helped in analyzing the number of hydrogen bonds, hydrophobic bonds interaction formed between protein and ligand with donor and acceptor atom (D-A) distance, donor angle, hydrogen acceptor, and donor angle.

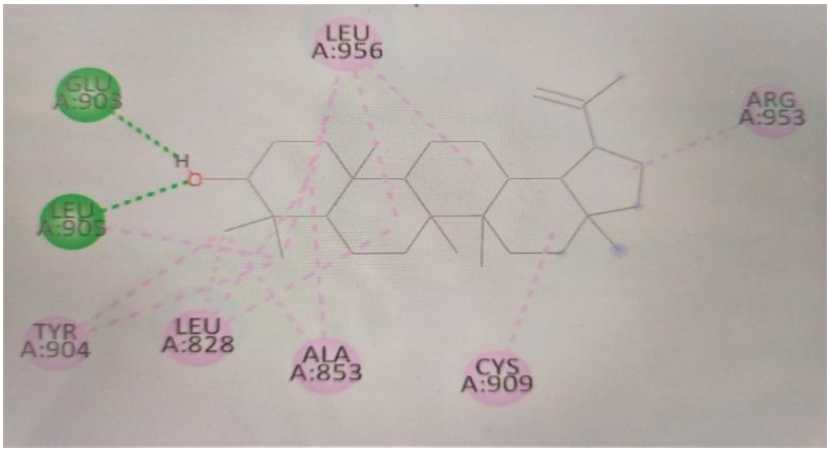


Figure 8: Interaction of lupeol with protein 6HZV in discovery studio.

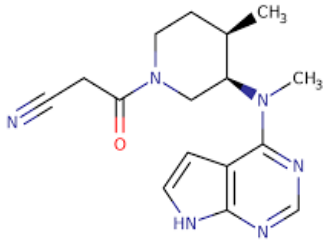
3.6 Phytochemical retrieval

The phytomolecules were gathered from pubchem and other evaluation like Lipinski rules of five (molecular weight, log P, HBA, HBD, and molar refractivity) of phytomolecule were evaluated by using SwissADME an online tool.

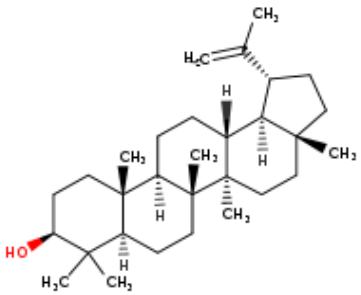
Table 2: Different parameters of phytomolecules having druglikeness.:

S. No	Phytomolecules	Molecular weight (g/mol)	LogP	Molar refractivity	H-bond acceptor	H-bond donor	Log S
1.	Tofacitinib	410.37	0.17	98.04	10	5	-2.85
2.	Luteolin	284.24	1.6	76.01	6	4	-3.71
3.	Lupeol	426.7	4.68	135.14	1	1	-8.64
4.	Rigidin E	363.32	0.55	98.90	5	5	-3.83

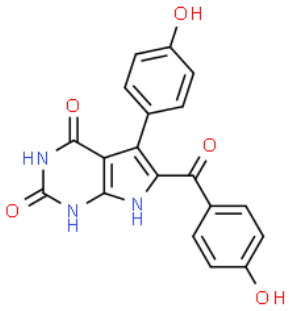
5.	Rigidin B	393.35	1.20	105.39	6	5	-4.98
6.	Curcumin	368.38	3.27	102.38	6	2	-3.94
7.	Catechin	290.27	1.47	74.33	6	5	-2.22
8.	Hypericin	504.44	3.10	144.83	8	6	-6.99
9.	Embelin	294.39	3.28	84.31	2	4	-4.41
10.	Gossypol	518	3.36	148.90	8	6	-7.40
11.	Caffeine	194.19	1.79	52.04	0	3	-1.48



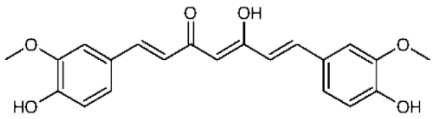
Tofacitinib



Lupeol



Rigidin



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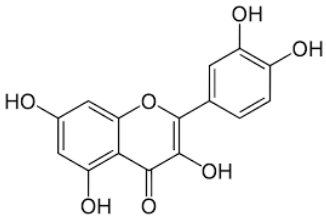
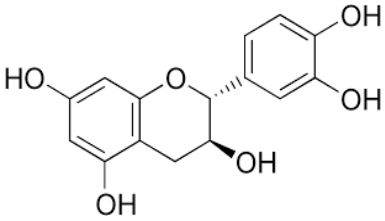
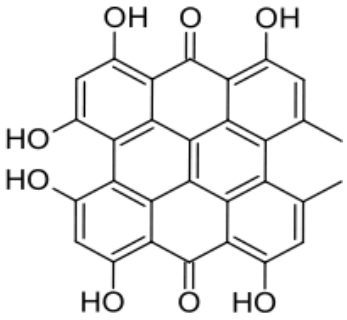


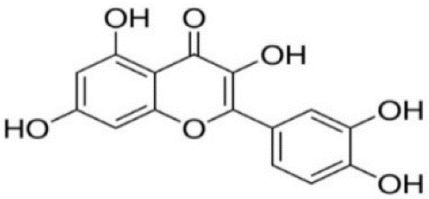
Luteolin



Catechin



Hypericin



Quercetin

Figure 9: Structures of Ligands.

4. RESULTS AND DISCUSSION

4.1 Molecular docking

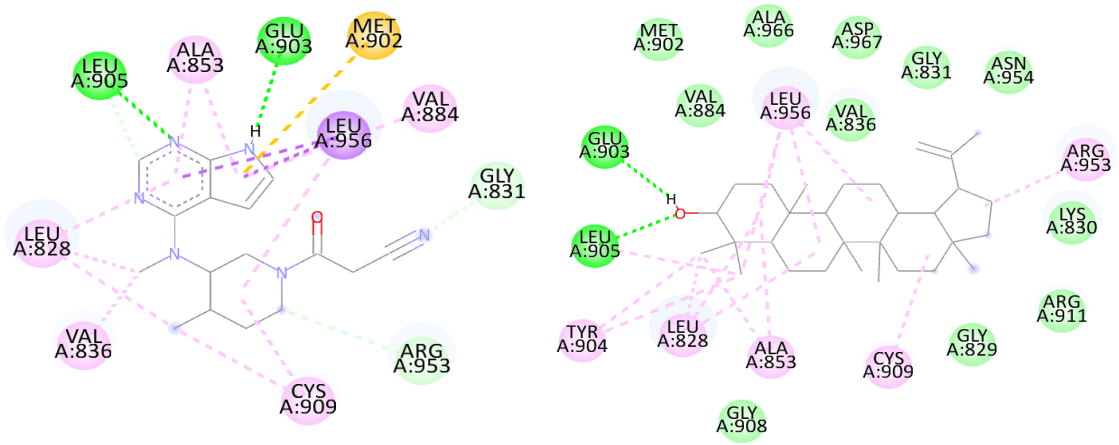
From table 2 it had been found that hypericin and gossypol violates the Lipnski rule of five, therefore these are not included in further study. The crystal structure of 6HZV contain four subunit chains but only chain A was used for molecular docking. In this molecular study, it has been found that Lupeol, Rigidin A, Rigidin E, **p**erfectly shows interaction with molecular protein by different affinities /conformation and create some conformational changes in JAK3 channel. These conformational changes subsequently cause desensitization of JAK3

and TRPV3 channel which are responsible for activation of inflammatory mediator IL-23, IL-6, IL-9, IL-5, IL-7. The interaction of Lupeol, Rigidin A, B and E with LEU905A have shown binding energy i. e, -9.12, -8.64, -8.54 kcal/mol as compared to tofacitinib (standard compound) which shows binding energy of -8.61 kcal/mol(fig.1). This clearly indicate that lupeol, rigidin A, B and E also have affinity comparable to standard with the target residue. In pymol, both lupeol and tofacitinib showed the formation of one hydrogen bond with target molecule, whereas with Discovery studio software Lupeol and the tofacitinib showed the formation of two H-bond (LEU905, GLU903) with interaction with target molecule. The nitrogen group in the tofacitinib is responsible for formation of H- bond with LEU905 residue of chain A of target molecule.

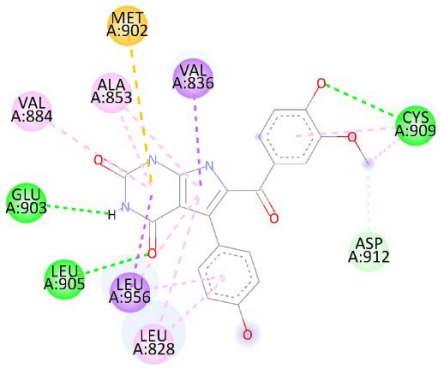
The other molecules which follow Lipinski rule and have good binding affinity with target molecule are luteolin, embelin, caffeine, curcumin, catechin, ganciclovir and penciclovir (fig .7). These show effective binding energy of -7.75, -5.2, -5.36, -5.4, -5.36, -3.76 and -4.73 kcal/mol respectively, and fulfill the prerequisite of hydrogen bond formation with JAK3 and TRPV3 channel.

The interaction shows that embelin formed H-bond with LYS 855(3.36 Å) and quercetin do not form any hydrogen bond with TRPV3 and JAK3.

With the docking result we can predict that the Lupeol, Rigidin A, B, E and Luteolin are the phytoconstituents which have better interaction with the target molecule and hence can inhibit JAK3 as compared to the tofacitinib.



a b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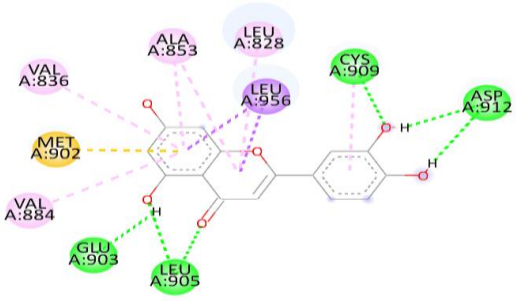
LEU A:828

c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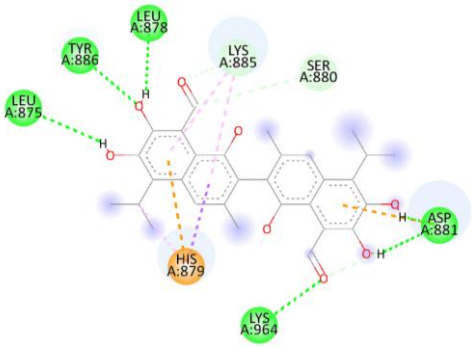
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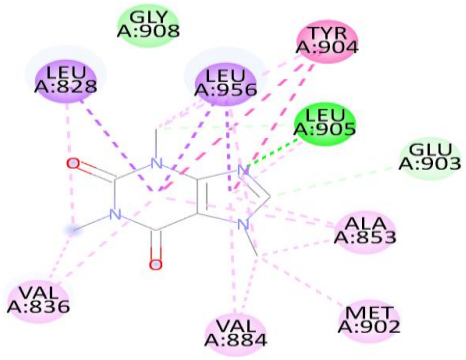
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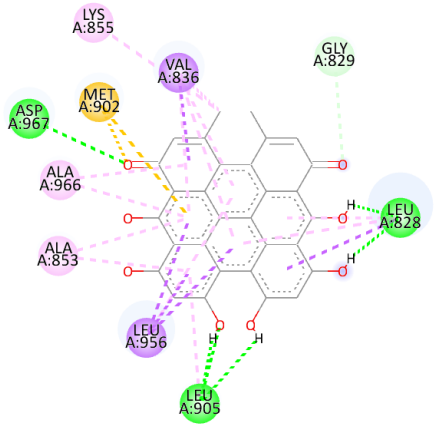
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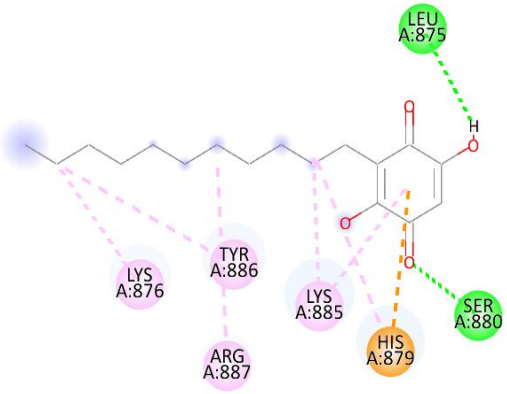
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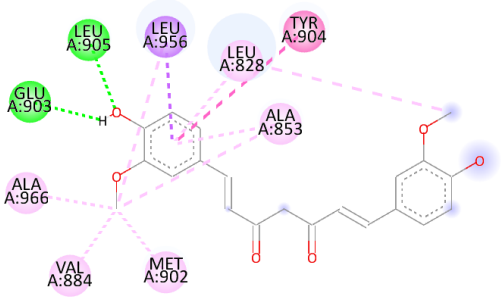
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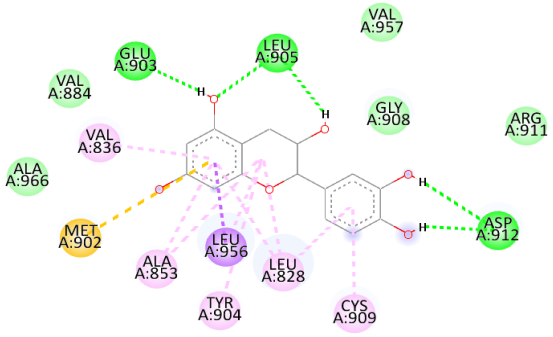
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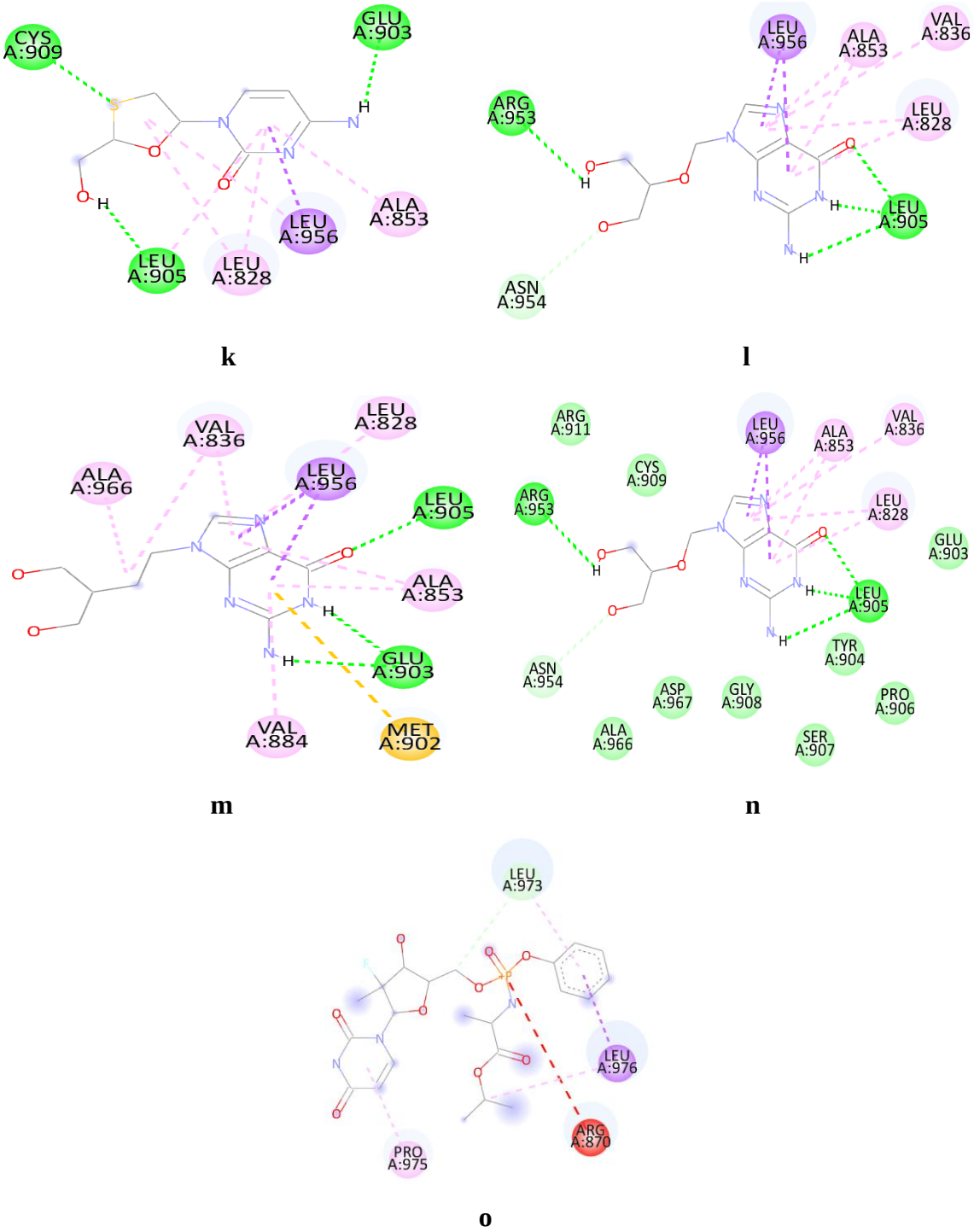

Figure 10: 2-D structure of phytoconstituents with the active sites. (a) Tofacitinib (b) Lupeol (c) Rigidin B (d) Luteolin (e) Gossypol f) Caffeine g) Hypericin h) Embelin i) Curcumin j) Catechin k) Lamivudine l) Ganciclovir m) Penciclovir n) Ganciclovir o) Sofosbuvir.

Table 3: Interaction of phytoconstituent with amino acid of active sites using Autodock 4.2v.

Drug	protein	Binding energy
Tofacitinib	6HZV	-8.61(LEU905)
Lupeol	6HZV	-9.12(LEU905, GLU903)
Rigidin A	6HZV	-6.4(LEU905; ASP967; TYR904; LEY828)
Rigidin B	6HZV	-8.64(LEU905; ASP967; TYR904; ASN954; MET902)
Caffeine	6HZV	-5.36 (LEU905)
curcumin	6HZV	-(LEU905, GLU903)
Catechin	6HZV	-6.99(LEU905, CYS 909, ASP912)
Hypericin	6HZV	-12.15(LEU905, ASP967, LEU828)
Embolin	6HZV	-5.2(TYR886; SER880; LEU875)
Quercetin	6HZV	-7.71(LEU905, CYS 909, ASP 912, GLU 903)
RigidinE	6HZV	-8.54(LEU905; ASP967; TYR904; LEY828)
Luteolin	6HZV	-7.75(LEU905; GLU903)
Penciclovir	6HZV	-4.73(LEU905; GLU903)
Lamivudine	6HZV	-5.11(LUE905; GLU903; TYR904)
Ganciclovir	6HZV	-3.75(LEU905; GLU903; MET914)

4.2 ADMET Properties

The study of absorption, distribution, metabolism, excretion, and toxicity of molecules play an important role to make it safe and efficacious. The ADMET of molecule/phytomolecule can be analysed by using an online tool called ADMETSAR and pkCSM. The result obtained by this software are reported in table 4. ADME properties serve to aim firstly, the design stage of new compound to reduce the risk of last stage attrition and second, to optimize the screening by scanning at the most promising compound. In absorption, molecule with an absorbance of greater than 30% considered to be good, while permeability of compound greater than 2.5 considered to low or poor. The drug which acts on CNS need to cross blood brain barrier to reach to molecular target, molecule with logBB>0.3 readily cross the blood barrier while molecule have logBB<-1 are poorly distributed in brain. The drug clearance is measured by proportion constant CLot and occur primarily as a combination of hepatic clearance. The predicted total clearance of a compound given in log(ml/min/kg). Drug-induced liver toxicity is major concern with drug development, molecule is predicted to cause liver toxicity, if it had at least one pathological disfunction of normal liver. Maximum tolerated dose should be less than 0.477 log (mg/kg/day) for recommended starting dose in clinical phase I. Chronic studies aim to identify the lowest dose of a compound that results in an observed adverse effect. For a given compound, the predicted log Lowest Observed Adverse Effect (LOAEL) in log (mg/kg _ bw/day) will be generated.

Table 4: ADMET of the Phytoconstituents.

As it has been reported that hepatotoxicity is a major concern in the development of new drugs and almost all the synthetic drugs cause liver toxicity. But from the above mentioned ADMET studies of the phytoconstituents it has been illustrated that most of the natural constituents do not have liver toxicity. It is clearly mentioned in the ADMET results that Toficitinib is hepatotoxic in nature but the phytoconstituents such as Lupeol, Quercetin, Luteolin, Curcumin has no toxic effect on liver.

5. CONCLUSION

This study aimed at evaluation of binding of selected phytoconstituents to JAK3 in a sequence to find out the possible use in the treatment of psoriasis. It can be concluded that phytoconstituents such as Lupeol, Curcumin, Luteolin and Rigidin A, B and E can be the potential therapeutic agent which can be used in the management of psoriasis by inhibiting the JAK3 pathway. These phytoconstituents have anti-inflammatory activity and therefore, can be the next generation immunosuppressant for the treatment of psoriasis.

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7. Conflict of Interest

The Authors declared no conflict of interests.

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