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Research Article

COMPUTATIONAL MODELING AND ANALYSIS OF THEORETICAL STRUCTURE OF CORNEODESMOSIN RECEPTOR PROTEIN WITH EXISTING PHYTOCHEMICALS IN PSORIASIS

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ABSTRACT
Corneodesmosin is a protein in humans encoded by the Corneodesmosin (CDSN) gene on chromosome 6p21.3 and is localized to human epidermis and other cells like squamous epithelia reported for psoriasis, a common ch0ronic disfiguring skin disease. As no 3D structure reported in public database, 3D structure is modeled using in-silico modeling approach. The protein exhibits most favorable regions up to 87.1% with a minimum disallowed region of 3.2% and simulated under hydrophilic environment. Molecular interaction study is carried out with several traditional phytochemicals. The binding interactions analysis was carried out using Genetic algorithm. Several phytochemicals/plant extracts were reported to exhibit better interactions with in the protein binding sites.

Keywords: *Corneodesmosin, Homology Modeling, Phytochemical, Molecular Docking, Molecular Simulation*

INTRODUCTION
Psoriasis vulgaris is a chronic immune mediated skin disease which is caused due to an overactive immune system and attacks healthy skin cells. This is characterized by scaly patches, plaques which usually itchy. This triggers more healthy cells produced than normal and get pushed to the surface of the skin (Allen *et al*., 2001; Menter *et al*., 2008). Psoriasis lesions are not infectious and also not contagious. The most common form, plaque psoriasis, is commonly seen as red and white hues of scaly patches appearing on the top first layer of the epidermis (skin). Clinically, psoriasis most frequently affects the skin of the elbow, knees, scalp, lumbosacral areas, intergluteal cleft and glans penis (Orru *et al*., 2002). The most typical lesion is a well demarcated, pink to salmon colored plaque covered by loosely adherent scales that are characteristically silvery white in color (Duret *et al*., 1994). Psoriasis can be one cause of total body erythema and scaling known as erythroderma. Nail changes occur in 30% of cases of psoriasis and consist of yellow, brown discoloration (often linked to an oil slick), with pitting, dimpling, separation of the nail plate from the underlying bed (onycholysis), thickening and crumbling (Simon *et al*., 1997; Chang *et al*., 2006; Davis 2013). Corneodesmosin protein encoded by corneodesmosin (CDSN) gene is responsible for this disease as due to expression of many mutants' allelic variants and sometimes deletion of the gene from chromosome 6p21.3 (Michael *et al*., 2001).

MATERIALS AND METHODS
Sequence Analysis
To begin with, Corneodesmosin protein sequence was downloaded from the SwissProt database (accession number Q15517) (Magrane *et al*., 2011). With no reported crystal structure of Corneodesmosin protein till date, a BLASTP (Altschul *et al*., 1990) based search was carried out to identify suitable templates.

Homology Modeling
Manual based Approach
Pair wise alignment of the template and the query sequence were generated using Modeller9v13 (Eswar *et al*., 2006; Marti *et al*., 2000; Sali *et al*., 1993; Fisher *et al*., 2000) (Figure 2). A sequence alignment file was generated in PIR format for a query and template sequences using ClustalW2 online server (Larkin *et al*., 2007). Using Multiple Template Modeling protocol from module 100 structures was generated using

Python Scripts. Of these generated structures, the model with the least DOPE score (Discrete Optimized Protein Energy) was considered for energy minimization with 100 iterations using steepest descent in Swiss-Pdb Viewer (Guex *et al*., 1997). The template and the modeled structures were superimposed with each other (Figure 3). The DOPE score of the template was -30168.31250 and the modeled structure was 22989.41992.

Server based Approach

Due to the poor identity templates were considered for the former model we have considered an I-TASSER web server (Zhang *et al*., 2008; Roy *et al*., 2010).

Model Validation

The stereo chemical quality of the model was validated by RAMPAGE web server (Lovell *et al*., 2002).

Model Simulation

The selected modeled structure was further subjected to simulation process to mimic and analyze its behaviors in biological system. Simulation was carried out under the water solvent system using Visual Molecular Dynamics (VMD) (Humphrey *et al*., 1996) and NAnoscale Molecular Dynamics program (NAMD) (Phillips *et al*., 2005) at 5 nanoseconds with 373 Kelvin parameterization. The structure obtained after the simulation process is compared to the original model and root mean square deviation (RMSD) calculated using Superpose server (Maiti *et al*., 2004).

Active Site Prediction

The active site residues of the Corneodesmosin protein, is predicted using Cast-P sever (Computer Atlas of Surface Topology of Proteins) (Dundas *et al*., 2006)

Ligand Selection

Conversely phytochemical compounds needed for docking against Corneodesmosin protein, which is responsible for Psoriasis disease were obtained from Pubchem database and abundantly available in nature (Bolton *et al*., 2008). All these compounds are coming from natural resource and utilized in day to day life. Some of these compounds were reported to be anti cancer, anti-viral and anti-bacterial agents too (Table 1). All these selected compounds were taken into consideration for molecular interaction study against the Corneodesmosin proteins in the current study.

Table 1: Retreival of Phytochemical compounds from PubChem Database

Sr No.	Phytochemical Compound	Extracted From	Scientific Name
1	Benzaldehyde	Almond	Prunus dulcis [25]
2	Capsaicin	Chilly pepper	Capsicum annuum [26]
3	Carveol	Mint leaves	Mentha [27]
4	Curcumin	Turmeric	Curcuma longa [28]
5	Guaifenesin	Tulsi	Ocimum tenuiflorum [29]
6	Salanin	Neem	Azadirachta indica [30, 31]
7	Limonene	Lemon	Citrus limon [32]
8	Vat Olive Green B	Olive	Olea europaea [33]

Molecular Docking

The number of H-bond acceptors, H-bond donors, logP and Molecular weight were obtained using Molinspiration (Volkamer *et al*., 2012) (Table 5). Molecular docking was carried out using IGEM docking (Hsu *et al*., 2011) software tool and Auto Dock Tool from Scripts Vina Research Institute. Docking was used to predict both ligand orientation and binding affinity. The preferred orientation of Ligand to the receptor, when bound to each other to form a stable complex in three dimensional spaces is predicted. Auto Dock is a suite of automated docking tools. It is designed to predict how small molecules, such as substrates or drug candidates, bind to a receptor of known 3D structure. Auto Dock Vina (Trott *et*

al., 2010) is a new generation of docking software from the Molecular Graphics Lab. Results were analyzed by using AutoDock tools and Discovery Studio Visualiser3.5.Binding interactions were elucidated using Discovery Studio Visualiser3.5. Default parameters with generating 100 poses of the complexes were utilized.

RESULTS AND DISCUSSION

Result

The homology search resulted with poor identity and multiple templates were selected for model generation (Figure 1). Through the reported hits, 1Z5V, 3CB2, 3KRM (Aldaz *et al*., 2005; Rice *et al*., 2008; Chao *et al*., 2010) were selected as homologous templates and 3D crystallographic structures were downloaded from Protein Data Bank (www.rcsb.org) (Berman *et al*., 2000).

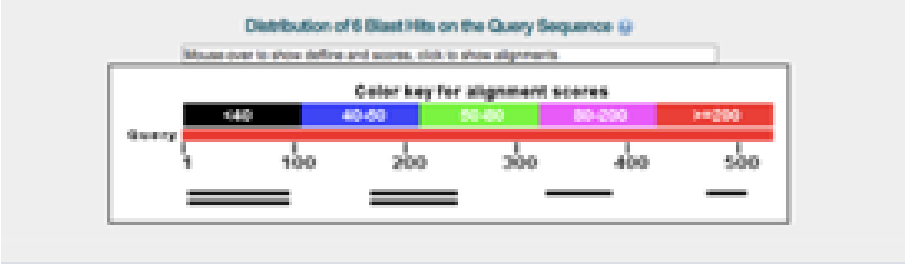

Figure 1: The Blastp analysis of corneodesmosin protein exhibiting the homologous sequences against a Protein database

3D Model

The predicted structure of Corneodesmosin Protein from modeller and I-Tasser were in good degree with no missing residual information in it (Figure 2A and 2B).

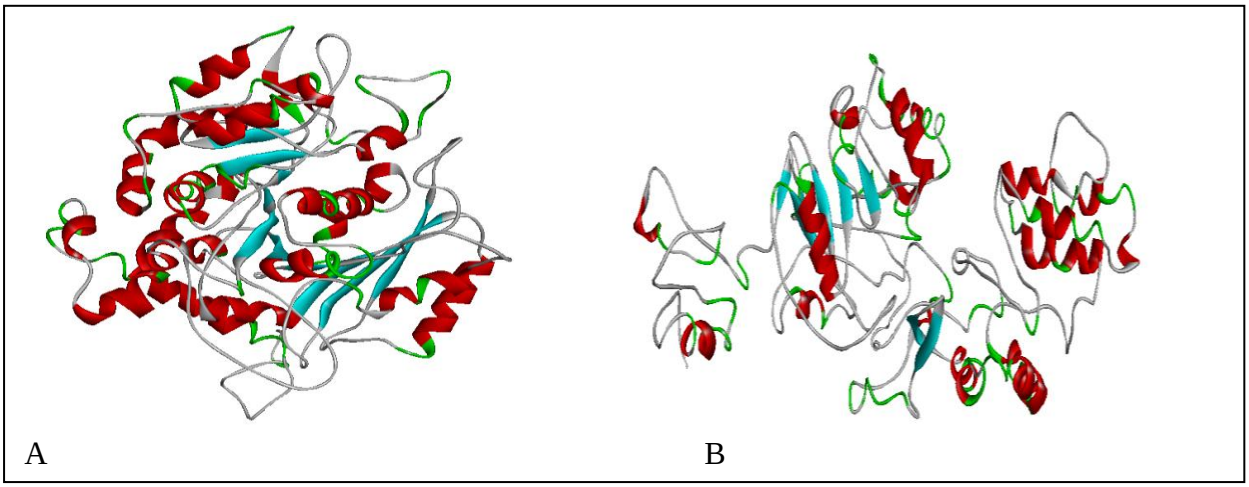

Figure 2: A - The modeled structure of Corneodesmosin protein from Modeller9v13 using Multiple Template Modeling Approach is having the best DOPE score -30168.31250 considered for further analysis. B- Corneodesmosin protein predicted using I-Tasser server

Table 2: Model validation using RAMPAGE Server

Model Predicted by	Number of residues in favored region	Number of residues in allowed region	Number of residues in outlier region
Modeller 9V3	459 (87.1%)	51 (9.7%)	17 (3.2%)
I-Tasser	347 (65.8%)	103 (19.5%)	77 (14.6%)

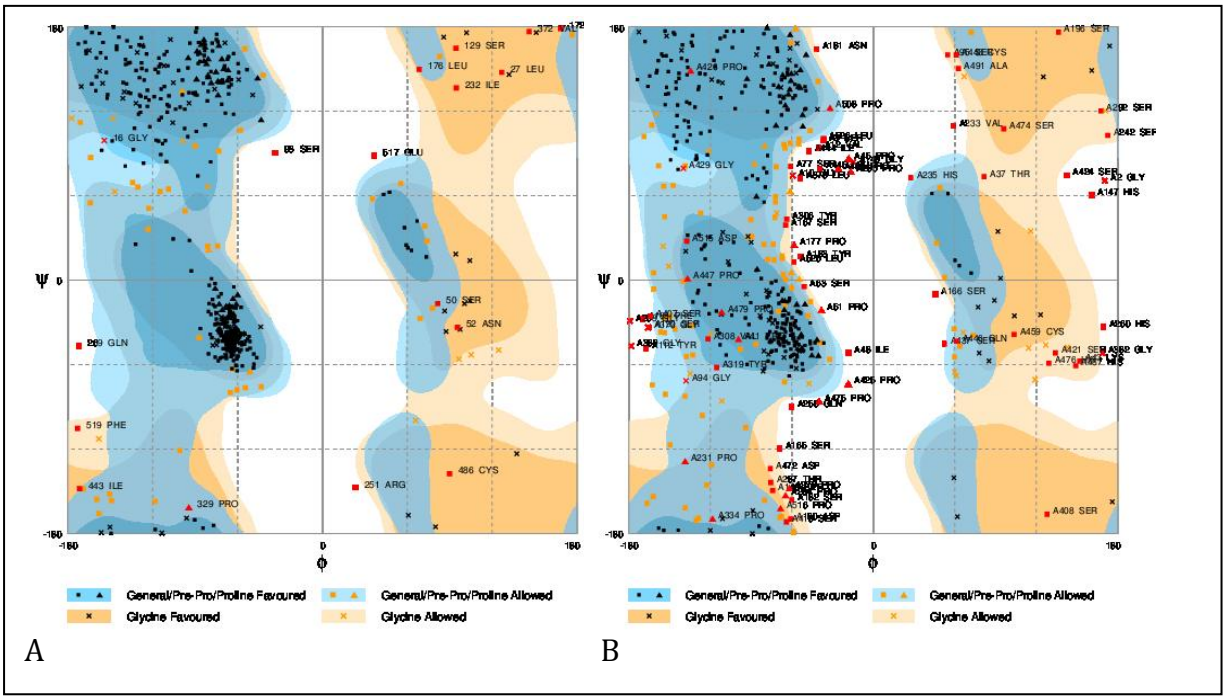

Figure 3: A- Ramachandran plot for model predicted using Modeller9v13. B- Ramachandran plot for model predicted using I-Tasser server

Molecular Simulation

The results obtained from the simulations process were good in agreement with a minimum deviation in all the selected features (Table 3) (Figure 4A and 4B).

Table 3: Simulation results for model predicted using Modeller9v13

Parameters	Alpha Carbon	Back Bone	Heavy	All
RMSD	0.02	0.02	0.02	0.02
Atoms	519	2075	3484	3484

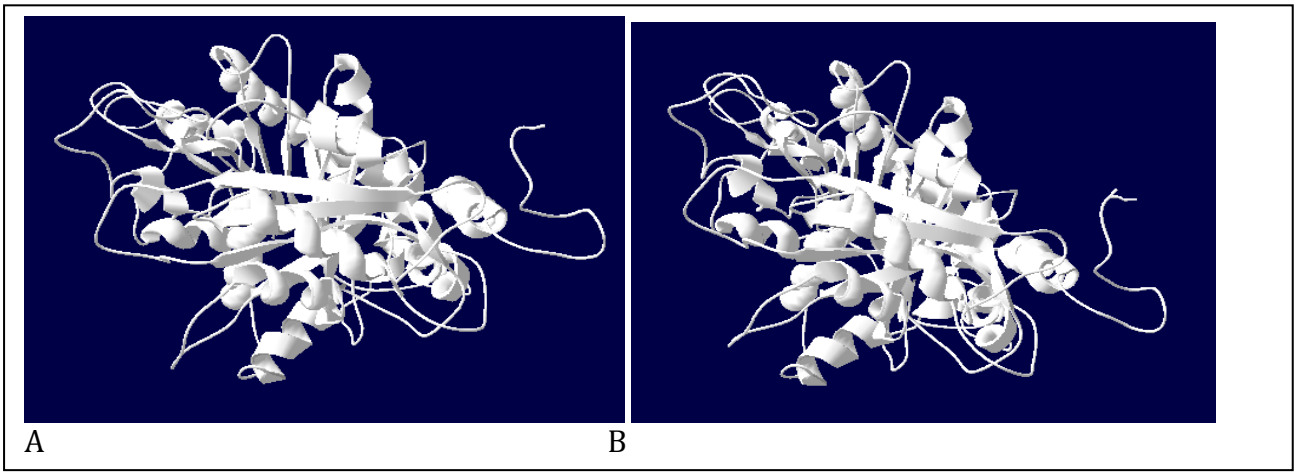

Figure 4: A- Non Simulated structure. B - Simulated structure, superim position and deviation calculated using Swiss-PDB viewer

Model Validation: The predicted model for Corneodesmosin protein was validated using Ramachandran plot using RAMPAGE online serve. The model predicted by Modeller9v13 revealed a more stable structure in comparison to I-Tasser (Table 2). Figure 3A shows a minimum number of amino acids lying in the outlier regions model predicted by Modeller9v13. Figure 3B shows a large number of amino acid residues lying in the outlier region model predicted by I-Tasser server.

Active site Residues Prediction

A numerous hydrophobic centres were identified on the Corneodesmosin protein, which is predicted using Cast-P sever (Computer Atlas of Surface Topology of Proteins) with a probe radius of 1.4 Armstrong. Out of these numerous cavities, the cavity with largest area of 3045.3 and a volume of 4343.7 units Armstrong is selected as a cavity site to target the phytochemical interactions (Figure 5) (Table 4).

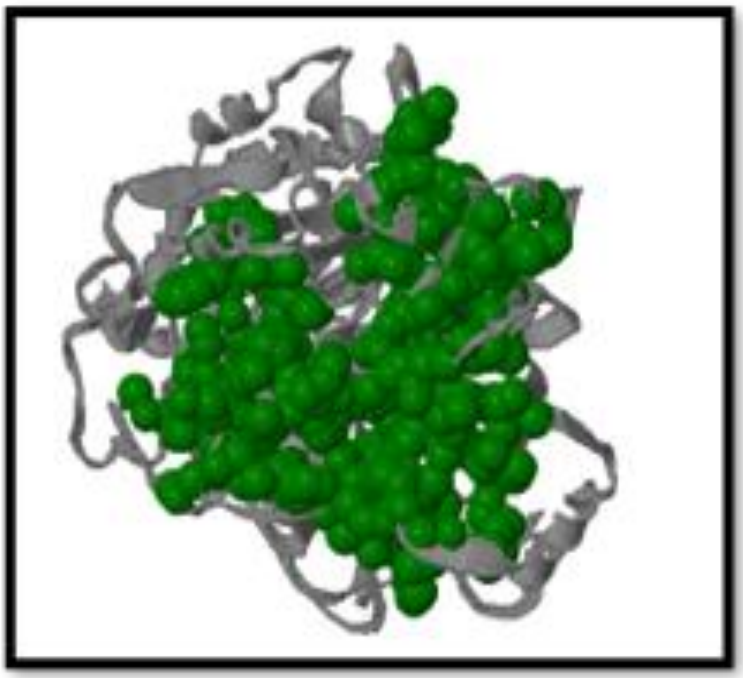

Figure 5: The active site pocket of Corneodesmosin modeled protein using the Cast p server

Table 4: Active site residues

Residues	Position	Residues	Position	Residues	Position	Residues	Position	Residues	Position
ARG	11	ARG	82	SER	262	LYS	331	SER	417
HIS	15	SER	83	VAL	268	SER	333	ALA	418
LEU	20	SER	89	GLN	269	VAL	336	SER	419
THR	49	ALA	103	PRO	271	ALA	340	GLN	420
LEU	56	PHE	106	CYS	273	PRO	344	SER	421
PHE	65	LYS	107	SER	274	GLU	347	PRO	422
SER	66	THR	110	ASN	275	TYR	350	LYS	442
GLY	70	LEU	176	GLY	276	VAL	372	ILE	443
SER	71	SER	207	LYS	281	GLY	409	ILE	444
SER	72	SER	210	ASN	328	TYR	412	GLN	446
GLY	75	SER	212	PRO	329	HIS	413		
SER	77	ASN	214	VAL	330	CYS	415		

Table 5: Physiochemical properties of selected phytochemical compounds

Phytochemical Compounds	LogP	Molecular weight	H Bond acceptor	H Bond donor
Benz aldehyde	1.5	106.1219	1	0
Capsaicin	3.6	305.411	3	2
Carveol	2.1	152.233	1	1
Curcumin	3.2	368.3799	6	2
Guaifenesin	1.4	198.2157	4	2
Salanin	3.9	596.7077	9	0
Limonene	3.4	136.23	0	0
Vat Olive Green B	6.5	449.4557	4	1

Docking Analysis

These generated *in-silico* models helps us to understand the interaction behaviour between known protein receptor and ligand or unknown protein receptor and ligand. The docked results obtained from IGEMDOCK and Autodock both were in good agreement. The protein-ligand docked complex shows occurrence of phytochemical under the cavity with a good binding interactions following amino acid are actively participated in bond formation with phytochemicals. (LYS107, THR49, ALA418, HIS413, ALA418, SER419, ALA418). On the basis of Binding energy and pharmacological interactions one can conclude the optimum result. Listed phytochemicals has successfully placed them in to the cavity of receptor protein. Whereas, Benzaldehyde (Figure 6), Salanin (Neem) (Figure 11), and Vat olive green B (Figure 13) has been actively formed a hydrogen-bond with the active site residues. Among these 03 optimum complexes Salanin with (-146 and -9.2 kj/mol) binding energy and Vat Olive green B (-126.3 and -11.2) binding energy using iGEMDOCK and Autodock Vina highlights more stable complexes (Table 6).

Table 6: Analysis of docking score from iGEMDOCK and Auto Dock

Sr no	Name of the Lead	iGEM DOCK score	AutoDock score	Binding Interaction residues	Active site residue
1	Benzaldehyde	-59.1	-5.2	ALA19, ARG251, LYS291, ALA418, SER352, SER352, SER198, SER288, TYR296	ALA418
2	Capsaicin	-95.05	-8.7	THR57	---
3	Carveol (Mint)	-73	-6.3	LYS291	---
4	Curcumin	-101	-8.6	SER164,GLY2,SER4:OG	---
5	Guaifenesin	-83.2	-6.3	SER410	
6	Salanin (neem)	-146	-9.2	THR49	THR49
7	Limonene	-65.9	-6.1	---	---
8	Vat olive green B	-126.3	-11.2	LYS107, THR49	LYS107, THR49

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In future Corneodesmosin protein can be act as a optimum target in the treatment of psoriatic disease, whereas more number of phytochemicals should be consider to screen the significant chemical compounds which may act as a optimum inhibitor to this receptor protein.

Binding Interactions

Structural View of Binding Analysis of Phytochemical compounds:

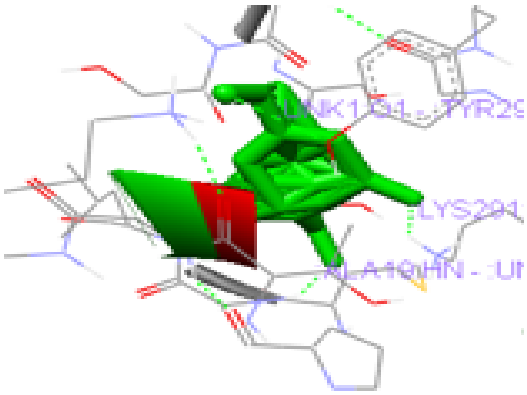

Figure 6: Benzaldehyde interaction

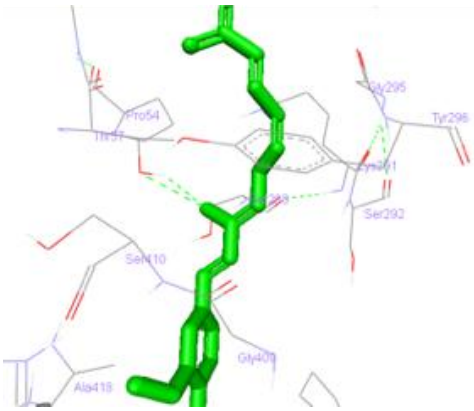

Figure 7: Capsaicin interaction

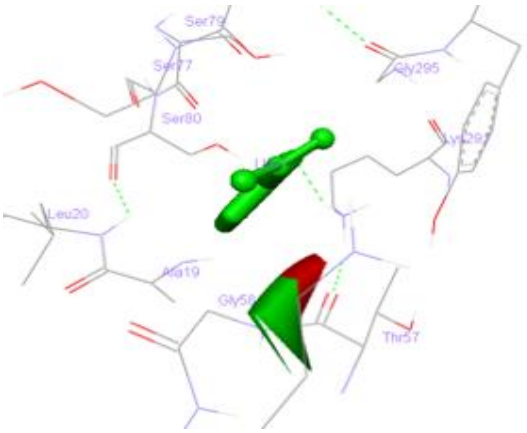

Figure 8: Carveol interaction

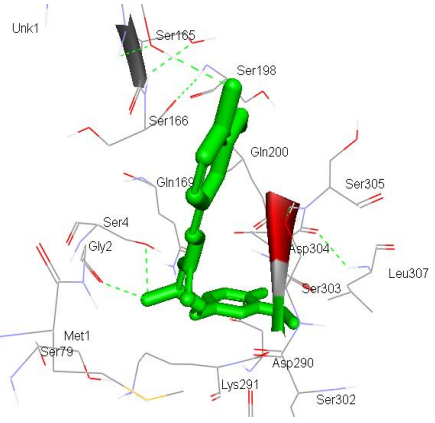

Figure 9: Curcumin interaction

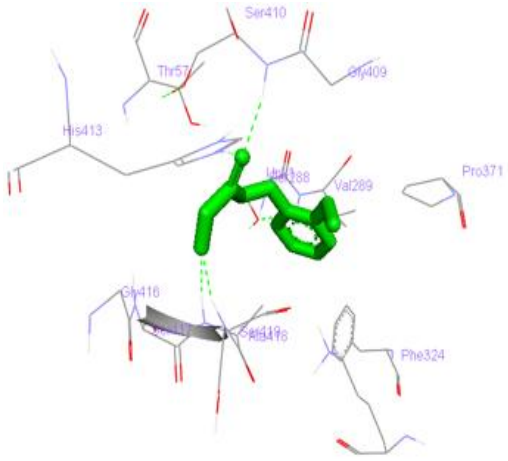

Figure 10: Guaifenesin interaction

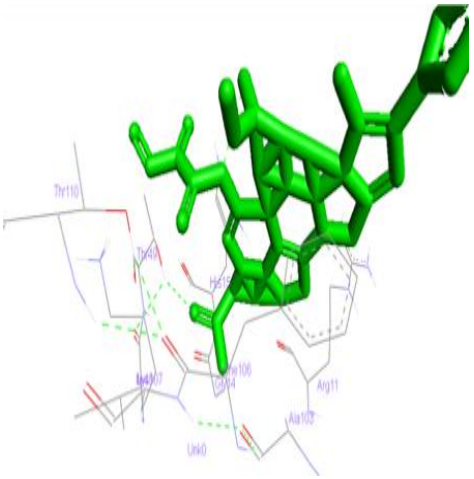

Figure 11: Salanin interaction

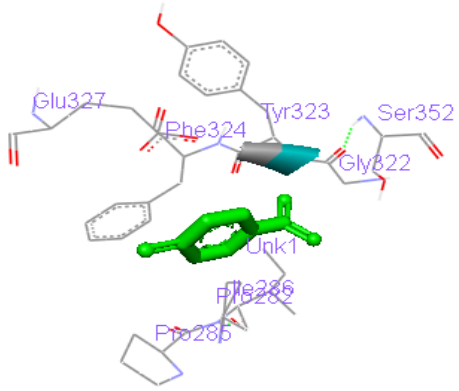

Figure 12: Limonene interaction

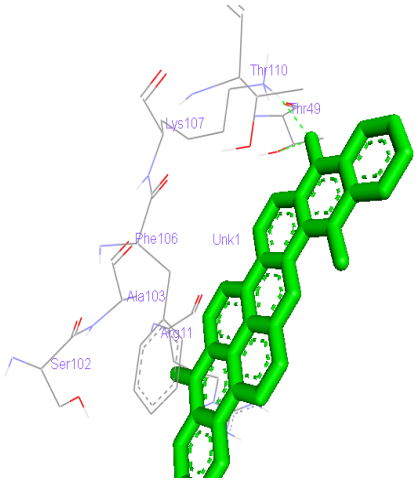

Figure 13: Vat olive green B interaction

Conclusion

The present work states that the listed phytochemicals showed a positive path of interaction with the receptor protein and reported stable complexes too. Since past the approach of application and use of phytochemical compounds that exist in the natural habitat in the treatment of Psoriasis, These computational analysis and trail methodology studies, it seems to be justified to conclude that selected Phytochemical Compounds may be a good option in treatment of psoriasis. Further studies and synthesis of novel compounds considering these findings can expect similar response rates and cure the Psoriasis.

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