STM JOURNALS

International Journal of
Bioinformatics and
Computational Biology

Volume 1, Issue 2, 2023
DOI (Journal): 10.37628/IJBCB
July--December

https://journals.stmjournals.com/ijbcb/

Research IJBCB

A Computational Study to Elucidate the Phytochemicals as An Antagonist Against Pruritis in Psoriasis

Prateeksha Vijayakumar[1], Samiksha Bhor[2,*]

Abstract

Objective: *Psoriasis is a chronic, non-contagious, auto-immune skin disorder that causes inflammation, pain, and itching in the affected areas. The etiology of this condition is not entirely understood, and while there are treatments available to manage the symptoms, there is currently no cure. The Transient receptor potential cation channel, subfamily Vanillin, member 3 (TRPV3), present in keratinocytes, allegedly had a part in the development of psoriasis-related pain and itching. Specifically, this report's main goal was to identify a potential antagonist (an anti-pruritic medication) that could desensitize TRPV3, by blocking its activity and reducing these symptoms.* ***Methods:*** *An in-silico approach was carried out by docking the chosen twelve phytocompounds based on the recent pre-clinical studies, with the TRPV3 target using Auto dock 4.2 after optimizing the crystal structure of the protein and preparation of ligands. Bio via discovery studio was used to visualize the 3D and 2D interactions and draw a conclusion from the results obtained.* ***Results:*** *Almost all compounds showed good binding energy values, but Hypericin, Kaempferol, Quercetin, and Emodin showed stronger binding affinities and proved to be efficient antagonists against TRPV3.* ***Conclusion:*** *Further clinical studies and improvements are needed in the near future to confirm these natural compounds as useful antipruritic agents in the treatment of psoriasis.*

Keywords: Psoriasis vulgaris, Phytocompounds, Molecular docking, Autodocking, ADME analysis, pruritis, anti-psoriatic drug, Phytochemicals, Keratinocytes, TRPV3, Virtual screening, Pharmacokinetic profiling

INTRODUCTION

Psoriasis vulgaris, a non-contagious chronic inflammatory skin condition, accelerates the growth cycle of skin cells. It is characterized by patches with erythema, scaly lesions, and plaques that appear as a result of the accumulation of skin cells [1]. These patches can occur anywhere in the body but are most commonly seen in skin folds, elbows, palms, knees, soles of feet, scalp, and lower back. It can also affect the genital area and nails in the hands and toes. The plaques are unpleasant and itchy; they occasionally break open and bleed. This affects the skin and causes inflammation in some organs like gastrointestinal tract, Musculo skeletal system and eyes. It is an auto-immune disease, in which proinflammatory cytokines and certain other factors are excessively produced causing hyperproliferation and abnormal differentiation of the epidermal keratinocytes [1–3].

The International Federation of Psoriasis Association reports that this is a prevalent skin disorder, influencing 2-3% of world's population

***Author for Correspondence**
Samiksha Bhor
E-mail: samikshaB@bionome.in

[1]Student, Department of Life Sciences, Garden City University, 16th KM, Old Madras Road, Bangalore, Karnataka, India
[2]Bioinformatics Associate, Department of Bioinformatics, Bionome Benglore, Karnataka, India

Received Date: May 12, 2023
Accepted Date: July 25, 2023
Published Date: August 05, 2023

Citation: Prateeksha Vijayakumar, Samiksha Bhor. A Computational Study to Elucidate the Phytochemicals as An Antagonist Against Pruritis in Psoriasis. International Journal of Bioinformatics and Computational Biology. 2023; 1(2): 49–61p.

[4]. Psoriasis is caused due to several factors such as genetic and environmental, but the exact role of genetics is unclear [5, 8]. It may run in families, but can skip generations. The patches that occur tend to recover and reoccur throughout a person's life. The patients with psoriasis are often associated with obesity, diabetes mellitus, dyslipidaemia, cardiovascular diseases, inflammatory bowel diseases (IBD) and depression. This impacts their psychological and social well-being, thus decreasing the quality of their life. The pathogenesis of this skin condition and the cause of the overactive immune system is not yet completely known [6].

There are several types of Psoriasis, each with its signs and symptoms. Symptoms may often start at any age and can affect people of any skin colour. Each suffering from this ailment has a unique set of triggers. The symptoms of psoriasis are made worse by triggers like cold, dry weather, and stress as this condition affects the immune system [7–9]. The available treatments range from topical ointments to ultraviolet light therapy to drugs such as methotrexate. These treatments can only wipe out the symptoms but the complete cure is not yet known [10].

In the current context of designing drugs based on the structure, molecular docking proves itself to be an important component of computer-aided drug design [11, 12]. A key symptom of psoriasis that has a considerable impact on a person's social life is itching (pruritus). Modern studies have shown that certain TRP channels found in keratinocytes or synapses participate in the transmission of itchy impulses in prolonged dermatological disorders including psoriasis. The epidermal keratinocytes have high levels of the TRP family member TRPV3 [13–15]. Transient receptor potential cation channel subfamily vanillin member 3 (TRPV3) is a temperature-sensitive component of the TRP superfamily. Compared to those without the illness, psoriasis sufferers have significantly greater levels of TRPV3 expression [14, 16, 17]. Due to the paucity of TRPV3-specific antagonists, research on the channel's underlying molecular biology is advancing at a slower pace than that of other TRP channels. For the investigation of TRPV3 physiological functions, it is required to find TRPV3-specific antagonists [18–20]. Hence, TRPV3 is selected as the target as it is involved in almost all stages of Psoriasis. By making TRPV3 less sensitive to stimuli, the drug may be able to alleviate pain, itch, and inflammation in the skin.

Numerous therapies involve applying chemical substances as creams or taking them as pills. Although they help the patients, they also have certain negative consequences. Exploring the traditional and natural phytomedicine options available to treat this illness is necessary [21]. Here, in this study, 12 phytochemicals were chosen, which have exhibited anti-psoriatic activity in previous preclinical studies [22]. The chosen ligands are Apigenin, Capsaicin, Curcumin, Emodin, Genistein, Hypericin, Kaempferol, Naringin, Psoralen, Quercetin, Resveratrol, and Rutin. By using molecular docking studies their interactions with therapeutic targets were visualized, and their underlying mechanisms of action to suppress psoriasis pruritus were elucidated. This research will be useful in proving the involvement of TRPV3 in the pathophysiology of itch in psoriasis and other dermatological disorders.

METHODS

Retrieval of TRPV3 Protein Target

The Transient receptor potential cation channel Vanillin member 3 (TRPV3) gene, responsible for pruritus in Psoriasis, is also associated with various other skin diseases. Hence, this gene was selected to be the target molecule for this study. The RCSB Protein Data Bank (https://www.rcsb.org/structure/6DVZ) [23] was used to download the crystal molecular structure of TRPV3 (PDB Id: 6dvz), having 4.72 resolution power, a sequence length of 791, and four chains A, B, C, and D was downloaded in the PDB format (Figure 1).

This structure of the TRPV3 gene target was downloaded from Protein Data Bank (PDB) in .pdb format. This is the protein before optimizing for docking with its 4 chains.

Target Optimization

Before the docking process, the target must be prepared in order to reduce the complexity. Using Auto Dock Tools 4.2 (ADT) [24], water molecules and any undesired hetero atoms were also removed during preparation since they could obstruct the docking procedure. As the protein consists of four chains, the additional 3 subunits were removed and only chain A was included for docking. Macromolecule was stored as a 6dvz.pdb execution file after refinement. The polar hydrogen bonds and Kollman charges were assigned and the macromolecule was loaded and stored as 6dvz.pdbqt.

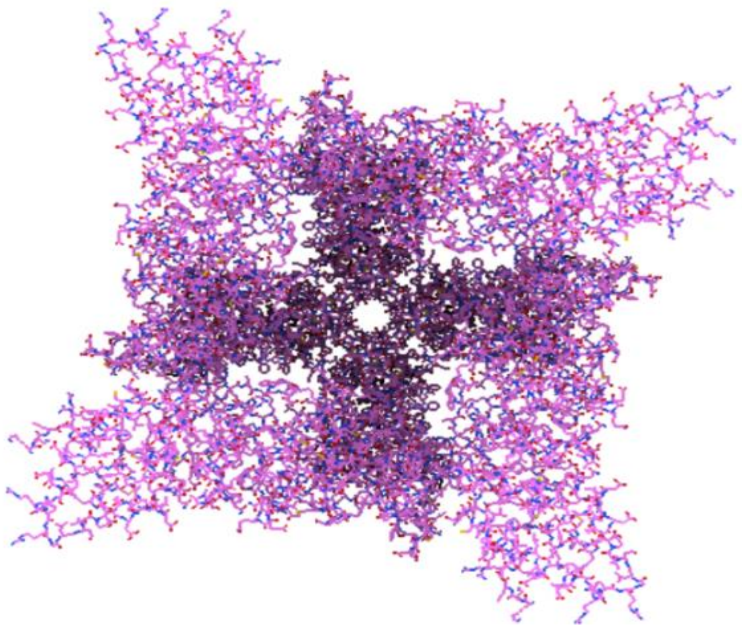

Figure 1. The downloaded TRPV3 protein in Auto Dock 4.2 before preparation.

Retrieval and Preparation of Ligand Molecules

The 12 phytocompounds that were included in this study were extracted in the 3D format structure (SDF) from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) [25]. Also, the canonical SMILES of each of these phytocompounds were obtained in order to evaluate their physicochemical properties. To convert the ligands to pdbqt format, Open Babel (https://sourceforge.net/projects/openbabel/) was used along with Auto Dock Vina (https://vina.scripps.edu/downloads/) [26, 27]. OpenBabel can convert more ligands from SDF format to PDBQT format simultaneously. Using the iterative loop command, all the ligands were converted into .pdbqt format (Figure 2) and were renamed as mol 1, 2, 3 till 12 in a separate folder.

ADME Analysis

To analyze the physicochemical properties, drug-likeliness properties, and pharmacokinetics of these phytochemicals, SWISS ADME (Absorption, Distribution, Metabolism, and Excretion) was used (http://www.swissadme.ch/) [28]. It sets criteria for drug similarity including the blood-brain barrier (BBB), Gastrointestinal absorption (GI), molar refractivity (MR), Synthetic accessibility (SA) score, hydrogen acceptors, and donors. The analysis was done by entering the collected SMILE formats of all 12 phytochemicals. The BIOLED-Egg was also obtained from Swiss ADME. According to the Lipinski Rule of 5, these important variables were established and chosen. When analysed, molecules 8 and 12 couldn't pass Lipinski's rule where they had 3 violations and were also out of range in the BOILED-Egg analysis, hence were not considered for further docking.

Molecular Docking

Both Computer-assisted drug design and structural molecular biology depend on molecular docking. It helps to determine the protein-ligand interaction, locate the potential site of interaction, and calculate binding affinity scores. Once the protein purification is done, the target and ligands were uploaded in the AD vina. Through energy minimization and optimization of grid dimensions, docking was performed between 10 ligands against the target, TRPV3. Several conformers were generated and the ones with the lowest binding energy (kcal/mol) among those produced were discussed. The binding energies were obtained in a CSV file. After the binding sites were analysed and modes were generated, the chosen conformers were then visualized in Biovia Discovery Studio, where both hydrophobic and 2D structures were looked at, and ligand-protein interactions were predicted.

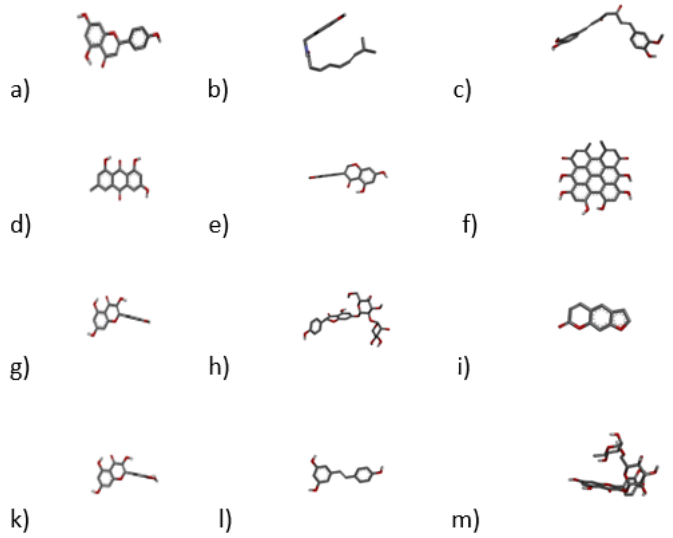

Figure 2. The 12 ligands that were included: a) Apigenin b) Capsaicin c) Curcumin d) Emodin e) Genistein f) Hypericin g) Kaempferol h) Naringin i) Psoralen j) Quercetin k) Resveratrol l) Rutin

RESULTS

Protein Retrieval and Preparation

The TRPV3 gene was downloaded from PDB in .pdb format. To increase the speed of docking and decrease the competitional load, the protein must always be purified before docking. Although they do not participate in the binding process during docking, water molecules and extra chains might affect the docking score and complicate the protein structure. As the TRPV3 structure is made of four subunits and only chain A is considered for docking, the additional three chains, water molecules, and any undesired hetero atoms present in the molecule were deleted using ADT. The protein was then prepared by adding polar hydrogen and Kollman charges. The prepared target was then saved in .pdbqt format (Figure 3).

The protein preparation was done by removing water molecules, heteroatoms and the 3 additional chains while the Kollman charges and polar hydrogens were added.

Ligand Preparation

Herbs are an excellent source of new drug development. There are numerous distinct varieties of medicinal plants in nature. Moreover, not all natural sources are inherently harmless. Thus, there is a dire need and potential for nontoxic therapy in recent times. For this study, 12 known phytocompounds (Table 1) were chosen based on their results in various pre-clinical studies. They were taken in 3D SDF format from PubChem and using AutoDock and Open Babel converted into pdbqt format. Their canonical SMILES were taken and subjected to ADME analysis to ascertain if the chosen ligands have properly defined physicochemical properties and structural features after which they can be marked as potential oral medication alternatives.

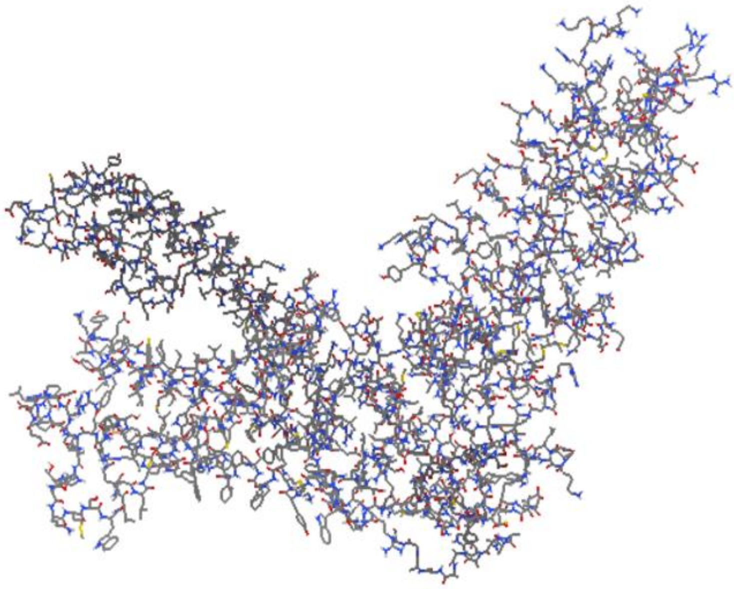

Figure 3. 6dvz - TRPV3 protein after purification using Auto Dock 4.2.

Table 1. The chosen phytocompounds, their molecular formula, and their canonical SMILES.

Ligands	**Molecular formula**	**Canonical SMILES**
Apigenin	C15H10O5	C1=CC(=CC=C1C2=CC(=O)C3=C(C=C(C=C3O2)O)O)O
Capsaicin	C18H27NO3	CC(C)C=CCCCCC(=O)NCC1=CC(=C(C=C1)O)OC
Curcumin	C21H20O6	COC1=C(C=CC(=C1)C=CC(=O)CC(=O)C=CC2=CC(=C(C=C2)O)OC)O
Emodin	C15H10O5	CC1=CC2=C(C(=C1)O)C(=O)C3=C(C2=O)C=C(C=C3O)O
Genistein	C15H10O5	C1=CC(=CC=C1C2=COC3=CC(=CC(=C3C2=O)O)O)O
Hypericin	C30H16O8	CC1=CC(=O)C2=C(C3=C(C=C(C4=C3C5=C2C1=C6C(=CC(=O)C7=C (C8=C(C=C(C4=C8C5=C67)O)O)O)C)O)O)O
Kaempferol	C15H10O6	C1=CC(=CC=C1C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O)O
Naringin	C27H32O14	CC1C(C(C(C(O1)OC2C(C(C(OC2OC3=CC(=C4C(=O)CC(OC4=C3)C5=CC=C (C=C5)O)O)CO)O)O)O)O)O
Psoralen	C11H6O3	C1=CC(=O)OC2=CC3=C(C=CO3)C=C21
Quercetin	C15H10O7	C1=CC(=C(C=C1C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O)O)O
Resveratrol	C14H12O3	C1=CC(=CC=C1C=CC2=CC(=CC(=C2)O)O)O
Rutin	C27H30O16	CC1C(C(C(C(O1)OCC2C(C(C(C(O2)OC3=C(OC4=CC(=CC(=C4C3=O)O)O) C5=CC(=C(C=C5)O)O)O)O)O)O)O)O

Lipinski's rule of 5

This rule states that every oral active medication must adhere to certain standards, including molecular mass (<=500 D), log P (<=5), hydrogen bond donor (<=5), hydrogen bond acceptor (<=10), and molar refractivity (40-130). It is regarded as the fundamental criterion for shortlisting. The candidate compound is eliminated from consideration as a potential source if any rule is broken. Hence, before docking, all 12 ligands were evaluated using this study (Tables 2-4).

When all the chosen ligands were analyzed with their canonical SMILES using Swiss ADME, every molecule except molecule numbers 6, 8 and 12 (Hypericin, Naringin and Rutin) couldn't pass the Lipinski Rule. There were 2 violations for molecule 6 and 3 violations for molecules 8, and 12 respectively. The Molecular Weight of a molecule should fall between 150 and 500 g/mol. From Table 2, it is evident that molecules 6,8, and, and 12 have molecular weights greater than 500 and the remaining ligands satisfy this parameter. The recommended topological polar surface area (TPSA) range is 20–130 and Molar refractivity (MR) values should be between 40 and 130. The TPSA and MR value of molecules 6,8, and 12 couldn't fulfill these parameters (Table 2).

Table 2. Molecular Weight (MW), Fraction CsP3, Topological Polar Surface Area (TPSA), and Molar Refractivity (MR) of ligands.

Ligands	**MW**	**Fraction CsP3**	**TPSA**	**MR**
Apigenin	270.34	0.00	90.90	73.99
Capsaicin	305.41	0.50	58.56	90.52
Curcumin	368.38	0.14	93.06	102.80
Emodin	270.24	0.07	94.83	70.78
Genistein	270.24	0.00	90.90	73.99
Hypericin	504.44	0.07	155.52	144.83
Kaempferol	286.24	0.00	111.13	76.01
Naringin	580.53	0.52	225.06	134.91
Psoralen	186.16	0.00	43.35	52.26
Quercetin	302.24	0.00	131.36	78.03
Resveratrol	228.24	0.00	60.69	67.88
Rutin	610.52	0.44	269.43	141.38

A drug's affinity for a lipid environment is measured by its lipophilicity (LogP), which must vary between -0.7 and +5.0. Less than five hydrogen donors and fewer than ten hydrogen acceptors are necessary. According to Table 3, all the molecules except 6, 8, and 12 meet the requirements (Table 3).

Table 3. Physicochemical properties and lipophilicity of phytocompounds.

Ligands	**H donors**	**H acceptors**	**Lipophilicity**	**WlogP**
Apigenin	3	5	1.89	2.58
Capsaicin	2	3	3.15	3.64
Curcumin	2	6	3.27	3.15
Emodin	3	5	1.80	1.89
Genistein	3	5	1.91	2.58
Hypericin	6	8	3.10	5.76
Kaempferol	4	6	1.70	2.28
Naringin	8	14	2.38	-1.49
Psoralen	0	3	2.01	2.54
Quercetin	5	7	1.63	1.99
Resveratrol	3	3	1.71	2.76
Rutin	10	16	1.58	-1.69

The brain is protected from toxins in the blood by a specific mechanism called the blood-brain barrier (BBB), which is composed of brain microvascular endothelial cells (BMVEC). The process by which medication is absorbed from a pharmaceutical formulation into the bloodstream is referred to as GI absorption, which is a pharmacokinetic parameter. The efflux mechanism, which is supported by the permeability glycoprotein (PGP) substrate, helps remove chemicals from cells. Compounds can be synthesized efficiently if the SA score is less than 6. The amount of a chemical that can enter circulation and reach the intended site is known as its bioavailability, which is dependent on secretion and absorption. The Lipinski rule of five is met by the chemical if the bioavailability score is 0.55. According to Table 4, these parameters are also not fulfilled by molecules 6,8, and 12. All the molecules except them satisfy the needs (Table 4).

BOILED-Egg Analysis

As a precise predictive model, the Brain or Intestinal Estimated permeation technique (BOILED-Egg) is presented. It works by assessing the polarity and lipophilicity of biomolecules. This provides the intuitive evaluation of brain penetration (BBB) and passive gastrointestinal absorption capacities of the therapeutic molecule. The white section in the BOILED-Egg projects the high possibility that it will be passively absorbed by the gastrointestinal tract and the yolk or yellow section predicts the high probability of crossing the blood-brain barrier. There is no overlap between these two parts. Additionally, if P-gp is expected to actively efflux them, the spots are coloured blue (PGP+) and the spots are in red if they are projected to not be a P-gp substrate (PGP-). Here, as molecule 6 (Hypericin) is far from the shell, it neither will be absorbed nor be entered into the brain. Although it is projected that molecules 2, 9, and 11

(Capsaicin, Psoralen, and Resveratrol) will effectively cross the BBB, they are not absorbed by the gastrointestinal tract as they are in the yolk. Molecules 1,3,4,5,7 and 10 (Apigenin, Curcumin, Emodin, Genistein, Kaempferol, and Quercetin) are well-absorbed by the gastrointestinal tract but are not brain penetrant. Due to their location beyond the plot's coverage area, molecules 8 and 12 (Naringin and Rutin) are projected to be unabsorbed and BBB impermeable. Hence, all the molecules except 8, and 12 are considered for further docking against the TRPV3 protein (Figure 4).

Table 4. Pharmacokinetics and drug-likeliness from ADME analysis (BBB: Blood-brain barrier, PGP: Permeability glycoprotein, GI: Gastrointestinal, SA: Synthetic accessibility).

Ligands	BBB permeant	GI absorption	P-gp substrate	Bioavailability score	SA Score
Apigenin	No	High	No	0.55	2.96
Capsaicin	Yes	High	No	0.55	2.32
Curcumin	No	High	No	0.55	2.97
Emodin	No	High	No	0.55	2.57
Genistein	No	High	No	0.55	2.87
Hypericin	No	Low	No	0.17	3.89
Kaempferol	No	High	No	0.55	3.14
Naringin	No	Low	Yes	0.17	6.16
Psoralen	Yes	High	No	0.55	3.06
Quercetin	No	High	No	0.55	3.23
Resveratrol	Yes	High	No	0.55	2.02
Rutin	No	Low	Yes	0.17	6.52

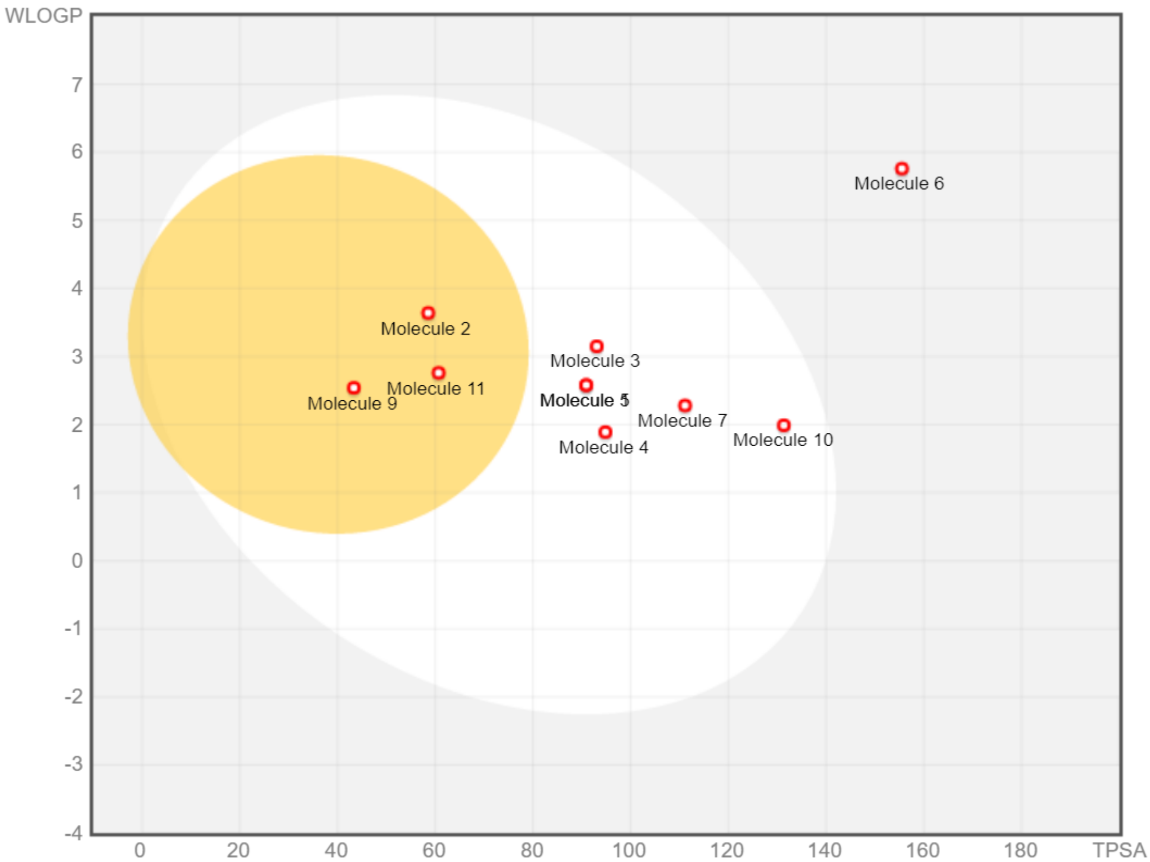

Figure 4. BOILED-Egg Analysis (Brain or Intestinal Estimated permeation method).

Molecular Docking and Visualisation

A notable, convenient tool called Auto Dock, is frequently employed in molecular docking to screen compounds against prospective targets. Here, Auto Dock 4.2 is used to dock the selected ligands against the TRPV3 protein. The crystal structure of the TRPV3 gene with four chains was taken as the target from PDB and optimized for the docking process. Recent studies provided more details on the TRPV3 channels' gating mechanism and proposed that site 4, which is crucial for channel opening containing the amino acids V458, Q483, L484, R487, M488, V490, L491, V537, Y540, and L551, is the site that causes target desensitization. As a result, in the current work, site 4 was picked in the channel of the target compound. The chosen ligands perfectly bound to the site's residues, with varying affinities, inducing a few structural alterations in the TRPV3 channel that consequently impacted channel performance and desensitized the TRPV3 channels that are most frequently expressed and responsible for itchy skin.

From this, several conformers were generated and the ideal mode with the least amount of binding energy was selected. Following the analysis of the binding sites and the generation of modes, the selected conformers were next viewed in Biovia Discovery Studio, where the ligand-protein interactions were anticipated. 2D and Hydrophobic structures were evaluated.

Table 5. Binding Affinities of ligands after docking them against TRPV3.

Ligands	**Binding Affinity (kcal/mol)**
Apigenin	-6.9
Capsaicin	-7.3
Curcumin	-7.0
Emodin	-7.5
Genistein	-7.2
Hypericin	-8.4
Kaempferol	-7.9
Psoralen	-6.6
Quercetin	-7.8
Resveratrol	-5.7

The molecules Hypericin (-8.4), Kaempferol (-7.9), Quercetin (-7.8), and Emodin (-7.5) interacted well against the active site and they have the lowest binding energies (Table 5). They were visualized in Biovia Discovery Studio with the best mode of several modes that were generated and their 3D and 2D interactions of Hypericin and Kaempferol were analysed (Figures 5 and 6).

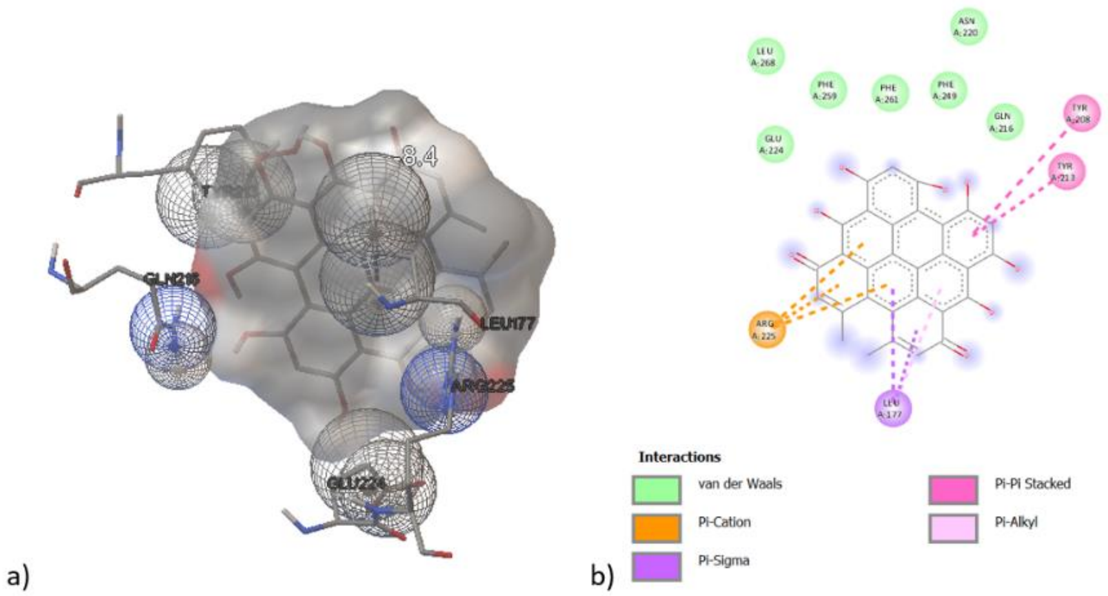

Figure 5. Interactions of Hypericin with TRPV3 a) 3D interaction b) 2D interaction diagram.

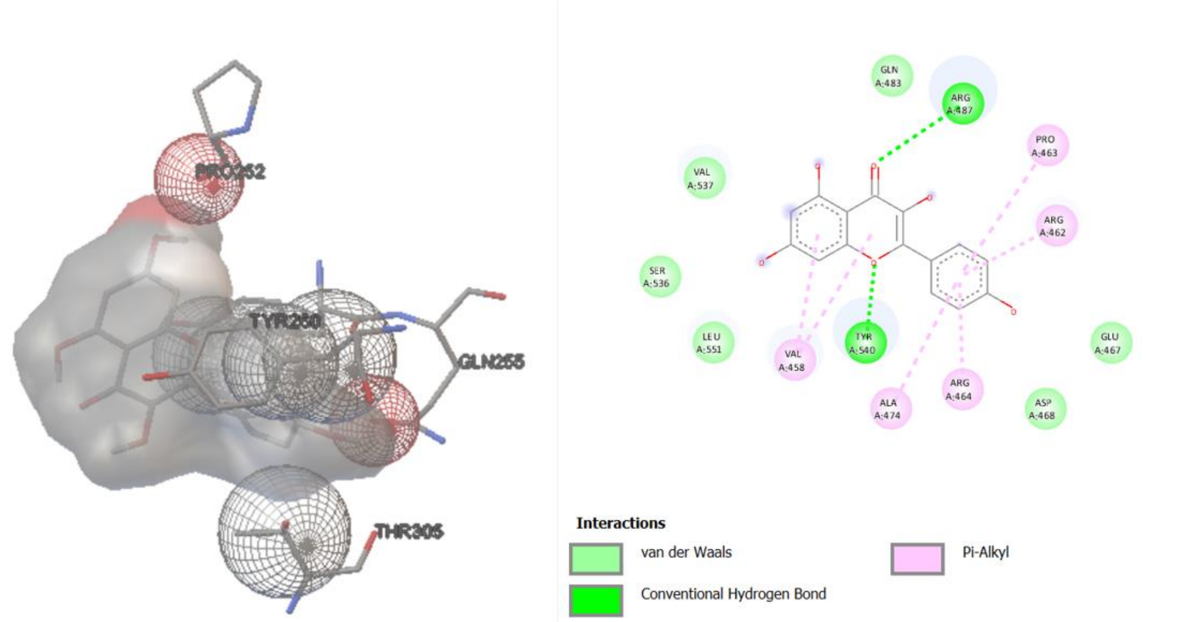

Figure 6. Visualization of Kaempferol interaction with TRPV3. Its 3D structure and 2D interaction diagram.

DISCUSSION

Skin cells multiply ten times more quickly than usual as a result of the skin disorder psoriasis. The most typical signs include patches of skin that are red, itchy, and covered with scales. Normally, the skin regenerates its cells within 10 to 30 days, however, in psoriasis patients, new skin cells begin to grow within 3 to 4 days. Silvery grey scales develop as the old cells are replaced by the new ones [29]. Hyperproliferation, aberrant keratinocyte multiplication, inflammation, and changes to the skin's immune system are all part of the pathophysiology of psoriasis. A malfunction in the immune system is what causes inflammation. Young adults are usually affected by psoriasis [30]. There is no known cause, although according to scientists, it could be caused by a multitude of factors. Even in extreme situations, psoriasis cannot be cured, but treatment can greatly lessen symptoms [31].

In this current study on Psoriasis, the aim is to find a possible antagonist against the TRPV3 target gene, which is found to be expressed in keratinocytes and is involved in generating pain and pruritis associated with the disease. Chromosome 17p13 contains the human TRPV3 gene close to TRPV1 with 18 exons [32]. Each of the four subunits that make up the TRP channel has six transmembrane segments (S1–S6) with an intracellular N- and C-terminus. TRPV3 includes six transmembrane segments, ankyrin repeats, coiled-coil domains at the amino terminus, a re-entrant pore loop, and a considerable amount of potential phosphorylation sites [33]. These are members of the family of widely dispersed nonselective cationic channel proteins, abundantly expressed in both the peripheral and central nervous systems. The first TRPs were discovered in a mutant Drosophila melanogaster with poor visual transmission [34]. Research suggests that TRPV3 channels are linked to the perception of discomfort and temperature and serve a significant part in maintaining the body's regular physiological activities. Moreover, TRPV3 channels are crucial for the development of skin and hair [35]. They are also involved in the development of the epidermal barrier, keratinocyte maturation, wound healing, and itching. Hair loss, inflammatory skin conditions, intense itching, and dermatitis can all occur from the overexpression of TRPV3 [36]. Reduced extracellular Ca^{+2} causes TTRPV3 sensitization, which may be the cause of some compounds' ability to suppress TRPV3 by blocking interactions with the ASP641 residue at the pore loop [37]. The inner pore region's two acidic residues E679 and E682 or the extracellular pore loop's ASP641 residue are crucial for TRPV3-mediated signalling. These residues react with Mg^{+2}, and TRPV3 desensitization is caused by this ion [38]. According to a study, the binding of 2-ABP (an agonist to TRPV3) at site 4 causes the channels to open and then desensitize. Better binding energies result from interactions between hydroxyl groups in the ligands and this channel, the ligands' increased hydrophobicity and propensity to donate electrons [39].

Natural substances have recently drawn a lot of attention during the search for innovative medicines and cutting-edge remedies as they are incredibly diversified, secure, and simple to obtain. Numerous scientific investigations demonstrated that certain chemicals of natural origin can lessen psoriasis through a variety of molecular processes linked to apoptosis, angiogenesis inhibition, and inflammation suppression [40, 41]. Researchers have also discovered that phytochemicals produced from flavonoids, terpenoids, tannins, and phenols have anti-psoriatic and anti-inflammatory actions related to psoriasis [42]. The phytocompounds Apigenin, Capsaicin, Curcumin, Emodin, Genistein, Hypericin, Kaempferol, Naringin, Psoralen, Quercetin, Resveratrol, and Rutin were chosen for this study. Because of their physiochemical, drug-like, ADMET, toxicological, and pharmacodynamic properties, these chemicals were helpful in the designing of therapeutic drugs.

Swiss ADME analysis was performed for the 12 phytochemicals that were taken for the study. The compounds were tested for their physicochemical properties, drug-likeliness, absorption into the bloodstream, and permeability to ensure safer consumption of the drug. Out of the 12 compounds analysed, only 10 were able to pass Lipinski’s rule of 5 with no violations except molecule 6 which has 2 violations. These 10 molecules were selected for further docking against the TRPV3 target.

ADT was used to dock the ligands by first selecting the active site residues at site 4 that were responsible for the desensitization of the TRPV3 channel. The screening was done with the 10 compounds chosen with the grid values center_x = 87.865, center_y = 116.684, center_z = 95.257 and size_x = 126, size_y = 126, size_z = 126 with energy_range = 4 and exhaustiveness value 8. Once the ligands interacted with different affinities, several conformers were generated which were then analysed. The molecule Hypericin was found to have the highest binding energy with -8.4 kcal/mol when compared to other molecules. Kaempferol, Quercetin, and emodin also showed higher binding affinities -7.9, -7.8, and -7.5 respectively. Other molecules also showed good binding affinities with the active site of the protein. Overall, Hypericin has shown the highest affinity towards the target site, but it should be noted that this molecule doesn’t fulfill most of the Lipinski rule and was neither absorbed nor brain permeant. So, the ligand Kaempferol is chosen to be the best antagonist against pruritis among the other ligands that were chosen for this study.

The final three phytochemicals (Kaempferol, Quercetin, and emodin) were chosen based on their potential for application in drug development. These three phytochemicals were taken from this *in silico* research using molecular docking and visualization. All the chosen ligands can be employed in pharmaceuticals and are amenable to *in vitro* testing. However, more extensive clinical and experimental studies are required to back up these findings.

CONCLUSION

Psoriasis, an auto-immune skin condition, remains untreatable given that the aetiology is unclear. Several medications suppress the effects of psoriasis or inhibit the activity of immune factors. There are certain downsides to current therapeutic chemicals and potential side effects. There is a dearth of effective, long-term therapeutic options for psoriasis. The constant development of novel, risk-free, and efficient psoriasis treatments is highly necessary. Extracts from plants and particular phytochemicals have garnered a lot of attention recently among the several active substances that have been investigated for the treatment of psoriasis. The phytocompounds involved in this study have been proven to be efficient against psoriasis in preclinical studies. To sum up the results obtained in this study, most of the molecules involved have a stronger binding affinity and the ability to occupy the binding site. These might have a detrimental effect by desensitizing the TRPV3 channel. As it is the main reason for causing the itch in psoriasis, these ligands can be employed as antagonists. This excellent binding mechanism and molecular interactions with the target receptor, make them suitable scaffolds for the improvement of psoriasis inhibitors. As this study completely relies on the available network database, further clinical research may be necessary to corroborate the findings that natural products may be a viable and beneficial choice for enhancing the clinical outcome of patients being treated.

Acknowledgement

I hereby express my gratitude to the Department of Bioinformatics, BioNome, Bengaluru, for its provision of computing resources and assistance with scientific study. I thank Ms. Samiksha Bhor for her assistance throughout the project.

Abbreviations

ADME – Absorption, Distribution, Metabolism, and Excretion
ADT – Auto Dock Tools
BBB – Blood-Brain Barrier
BOILED - Egg - The Brain or Intestinal Estimated permeation method
IL – Interleukin
IBD – Inflammatory Bowel Disease
MR – Molar Refractivity
PDB – Protein Data Bank
P-gp Substrate - Permeability glycoprotein substrate
SA – Synthetic Accessibility
TNF – Tumour Necrosis Factor
TRPV3 – Transient Receptor Potential Cation channel, subfamily Vanillin, member 3
TPSA - Topological Polar Surface Area

REFERENCES

1. Agrawal, Anurag & Kulkarni, Giriraj & Lakshmayya,. (2020). Molecular docking study to elucidate the anti-pruritic mechanism of selected natural ligands by desensitizing TRPV3 ion channel in Psoriasis: An *in silico* approach. Indian journal of biochemistry & biophysics. 57. 578-583.
2. Gong, Ke & Guo, Wen & Du, Kaiqing & Wang, Fang & Li, Mengli & Guo, Jianhui. (2022). Mechanism of Huoluo Xiaoling Dan in the Treatment of Psoriasis Based on Network Pharmacology and Molecular Docking. Evidence-Based Complementary and Alternative Medicine. 2022. 10.1155/2022/7053613.
3. Agrawal, Anurag & Awasthi, Rajendra & Kulkarni, Giriraj & Lakshmayya,. (2022). A bioinformatics approach to establish P38α MAPK inhibitory mechanism of selected natural products in psoriasis. Indian Journal of Biochemistry & Biophysics. 59. 165-171.
4. Gupta, Sonali & Tewatia, Parul & Misri, Jyoti & Singh, Rajni. (2017). Molecular Modeling of Cloned Bacillus subtilis Keratinase and Its Insinuation in Psoriasis Treatment Using Docking Studies. Indian Journal of Microbiology. 57. 10.1007/s12088-017-0677-x.
5. Ibezim, Akachukwu & Onah, Emmanuel & Dim, Ebubechukwu & Ntie-Kang, Fidele. (2021). A computational multi-targeting approach for drug repositioning for psoriasis treatment. BMC Complementary and Alternative Medicine. 21. 10.1186/s12906-021-03359-2.
6. Singh, Omveer & Rahman, Mahbubur & Yashika, & Kaur, Manveen & Anurag,. (2023). A REVIEW ON PSORIASIS. NeuroQuantology. 20. 5786-5793|. 10.48047/NQ.2022.20.16.NQ880588.
7. Paramalingam, Dinika & Li, Bowen & Reynolds, Nick & Zuliani, Paolo. (2023). Computational Modelling of Immune Interaction and Epidermal Homeostasis in Psoriasis. 10.1101/2023.02.23.529657.
8. Torres, Tiago & Filipe, Paulo & Brandão, Francisco & Figueiredo, Américo & Soares, António & Basto, Artur & Rebelo, Clarisse & Correia, Osvaldo & Ferreira, Paulo & Brasileiro, Ana & Mendes-Bastos, Pedro & Paiva-Lopes, Maria & Pinto, Gabriela & Severo, Milton & Mendonça, Denisa & Oliveira, Pedro & Selores, Manuela & Massa, Antonio & Pereira, Marta & Venereology, On.

(2023). Epidemiology of Psoriasis in Portugal: A Population-Based Study. Acta Médica Portuguesa. 10.20344/amp.19048.

9. Ahmad, Mohammad Zaki & Mohammed, Abdul & Algahtani, Mohammed & Mishra, Awanish & Ahmad, Javed. (2022). Nanoscale Topical Pharmacotherapy in Management of Psoriasis: Contemporary Research and Scope. Journal of Functional Biomaterials. 14. 19. 10.3390/jfb14010019.
10. Honma, Masaru & Hayashi, Kei. (2021). Psoriasis: Recent progress in molecular-targeted therapies. The Journal of Dermatology. 48. 10.1111/1346-8138.15727.
11. Sethi, Aaftaab & Joshi, Khushboo & Sasikala, K. & Alvala, Mallika. (2019). Molecular Docking in Modern Drug Discovery: Principles and Recent Applications.
12. Zothantluanga, James & Chetia, Dr. Dipak. (2022). A beginner's guide to molecular docking. 1. 37-40. 10.58920/sciphy01020037.
13. Um, Ji & Kim, Han & Kim, Jin & Park, Jin & Lee, So & Chung, Bo & Park, Chun & Kim, Hye One. (2022). TRPV3 and Itch: The Role of TRPV3 in Chronic Pruritus according to Clinical and Experimental Evidence. International Journal of Molecular Sciences. 23. 14962. 10.3390/ijms232314962.
14. Su, Wuyue & Qiao, Xue & Wang, Wumei & He, Shengnan & Liang, Ke & Hong, Xuechuan. (2023). TRPV3: Structure, Diseases, and Modulators. Molecules. 28. 774. 10.3390/molecules28020774.
15. Shen, Y.-J & Zhang, X.-R & Wu, Y. & Wang, K.-W & Liu, Z.-M & Jin, H.-W & Zhang, L.-R & Zhang, L.-H. (2018). Identification of novel selective TRPV3 antagonists based on virtual screening, molecular docking and bioassay. Yaoxue Xuebao. 53. 966-975. 10.16438/j.0513-4870.2018-0047.
16. Martin, Lisa & Fraillon, Emma & Chevalier, Fabien & Fromy, Bérengère. (2022). Hot on the Trail of Skin Inflammation: Focus on TRPV1/TRPV3 Channels in Psoriasis. 10.5772/intechopen.103792.
17. Tripathy, Chandra & Bhattacharya, Deepak. (2022). Psoriasis Vrs Cassia Fistula: In-Silico Study. Saudi Journal of Medicine. 7. 10.36348/sjm.2022.v07i03.005.
18. Meng, Ciara. (2020). Novel insights into the TRPV3-mediated itch in atopic dermatitis. The Journal of allergy and clinical immunology.
19. Fan, Junping & Hu, Linghan & Yue, Zongwei & Liao, Daohong & Guo, Fusheng & Ke, Han & Jiang, Daohua & Yang, Yong & Lei, Xiaoguang. (2022). Structural basis of TRPV3 inhibition by an antagonist. Nature Chemical Biology. 19. 1-10. 10.1038/s41589-022-01166-5.
20. Liu, Qiang & Wang, Jin & Wei, Xin & Hu, Juan & Conghui, Ping & Gao, Yue & Xie, Chang & Wang, Peiyu & Cao, Peng & Cao, Zhengyu & Yu, Ye & Li, Dongdong & Yao, Jing. (2021). Therapeutic inhibition of keratinocyte TRPV3 sensory channel by local anesthetic dyclonine. eLife. 10. 10.7554/eLife.68128.
21. Kombate, Bignoate & Kossi, Metowogo. (2023). Pharmacological mechanisms of medicinal plant extracts in the treatment of dermatological diseases: *in vitro, in vivo* studies and clinical trials. Journal of Dermatology & Cosmetology. 7. 1-7. 10.15406/jdc.2023.07.00224.
22. Nowak-Perlak, Martyna & Szpadel, Krzysztof & Jabłońska, Izabella & Pizon, Monika & Woźniak, Marta. (2022). Promising Strategies in Plant-Derived Treatments of Psoriasis-Update of *In Vitro*, *In Vivo*, and Clinical Trials Studies. Molecules. 10.3390/molecules27030591.
23. BEHZADI, Payam & Gajdács, Márió. (2021). Worldwide Protein Data Bank (wwPDB): A virtual treasure for research in biotechnology. European Journal of Microbiology and Immunology. 11. 10.1556/1886.2021.00020.
24. Helgren, Travis & Hagen, Timothy. (2017). Demonstration of AutoDock as an Educational Tool for Drug Discovery. Journal of Chemical Education. 94. 10.1021/acs.jchemed.6b00555.
25. Kim, Sunghwan & Chen, Jie & Cheng, Tiejun & Gindulyte, Asta & He, Jia & He, Siqian & Li, Qingliang & Shoemaker, Benjamin & Thiessen, Paul & Yu, Bo & Zaslavsky, Leonid & Zhang, Jian & Bolton, Evan. (2022). PubChem 2023 update. Nucleic acids research. 51. 10.1093/nar/gkac956.

26. O'Boyle, Noel & Banck, Michael & James, Craig & Morley, Chris & Vandermeersch, Tim & Hutchison, Geoffrey. (2011). Open Babel: An Open Chemical Toolbox. Journal of cheminformatics. 3. 33. 10.1186/1758-2946-3-33.
27. Shidi, Tang & Chen, Ruiqi & Lin, Mengru & Lin, Qingde & Zhu, Yanxiang & Ding, Ji & Hu, Haifeng & Ling, Ming & Wu, Jiansheng. (2022). Accelerating AutoDock Vina with GPUs. Molecules. 27. 3041. 10.3390/molecules27093041.
28. Daina, Antoine & Michielin, Olivier & Zoete, Vincent. (2017). SwissADME: A free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Scientific Reports. 7. 42717. 10.1038/srep42717.
29. Gordon, Kenneth & Feldman, Steven & Koo, John & Menter, Alan & Rolstad, Tara & Krueger, Gerald. (2005). Definitions of Measures of Effect Duration for Psoriasis Treatments. Archives of dermatology. 141. 82-4. 10.1001/archderm.141.1.82.
30. Augustin, Matthias & Langenbruch, A. & Naatz, Mandy & Reich, K. & Körber, Andreas & Maaßen, D. & Mrowietz, U. & Thaçi, D. & Kiedrowski, R. & Radtke, Marc. (2018). Definition of psoriasis severity in routine clinical care: current guidelines fail to capture the complexity of long-term psoriasis management. British Journal of Dermatology. 179. 10.1111/bjd.17128.
31. Boehncke, Wolf-Henning. (2018). Systemic Inflammation and Cardiovascular Comorbidity in Psoriasis Patients: Causes and Consequences. Frontiers in Immunology. 9. 579. 10.3389/fimmu.2018.00579.
32. Nilius, Bernd & Biro, Tamás & Owsianik, Grzegorz. (2013). TRPV3: Time to decipher a poorly understood family member!. The Journal of physiology. 592. 10.1113/jphysiol.2013.255968.
33. Shi, Di-Jing & Ye, Sheng & Cao, Xu & Zhang, Rongguang & Wang, Kewei. (2013). Crystal Structure of the N-Terminal Ankyrin Repeat Domain of TRPV3 Reveals Unique Conformation of Finger 3 Loop Critical for Channel Function. Protein & cell. 4. 10.1007/s13238-013-3091-0.
34. Yang, Pu & Feng, Jing & Luo, Jialie & Mack, Madison & Hu, Hongzhen. (2017). A Critical Role for TRP Channels in the Skin. 10.4324/9781315152837-6.
35. Koivisto, Ari-Pekka & Belvisi, Maria & Gaudet, Rachelle & Szallasi, Arpad. (2021). Advances in TRP channel drug discovery: from target validation to clinical studies. Nature Reviews Drug Discovery. 21. 1-19. 10.1038/s41573-021-00268-4.
36. Nilius, Bernd & Owsianik, Grzegorz. (2011). The transient receptor potential family of ion channels. Genome biology. 12. 218. 10.1186/gb-2011-12-3-218.
37. Kim, Sung & Patapoutian, Ardem & Grandl, Jörg. (2013). Single Residues in the Outer Pore of TRPV1 and TRPV3 Have Temperature-Dependent Conformations. PloS one. 8. e59593. 10.1371/journal.pone.0059593.
38. Fatima, Mahar & Slade, Hannah & Horwitz, Lorraine & Shi, Angela & Liu, Jingyi & McKinstry, Delaney & Villani, Troy & Xu, Haoxing & Duan, Bo. (2022). Abnormal Somatosensory Behaviors Associated With a Gain-of-Function Mutation in TRPV3 Channels. Frontiers in Molecular Neuroscience. 14. 10.3389/fnmol.2021.790435.
39. kumar singh, Appu & McGoldrick, Luke & Sobolevsky, Alexander. (2018). Structure and Gating Mechanism of the Transient Receptor Potential Channel TRPV3. Nature Structural & Molecular Biology. 25. 10.1038/s41594-018-0108-7.
40. Svendsen, Mathias & Jeyabalan, Janithika & Andersen, Klaus & Andersen, Flemming & Johannessen, Helle. (2016). Worldwide Utilization of Topical Remedies in Treatment of Psoriasis: A Systematic Review. The Journal of dermatological treatment. 28. 1-36. 10.1080/09546634.2016.1254331.
41. Farahnik, Benjamin & Sharma, Divya & Alban, Joseph & Sivamani, Raja. (2017). Topical Botanical Agents for the Treatment of Psoriasis: A Systematic Review. American Journal of Clinical Dermatology. 18. 10.1007/s40257-017-0266-0.
42. Pandey, Ashish & Shukla, Alok & Dubey, Ramesh & Pratap, Ravi. (2021). A review on the important phytochemicals and their role in psoriasis. Journal of Applied and Natural Science. 13. 880-896. 10.31018/jans.v13i3.2717.

