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Research Article

IN SILICO APPROACH TO IDENTIFY POTENTIAL ANTI-PSORIATIC COMPOUNDS FROM *CURCUMA LONGA*

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ABSTRACT

Objectives: Psoriasis is a type of skin disease which is accompanied with over production of keratinocytes, itchiness, and scaly skin. In this study, an attempt was made to recognize naturally occurring phytocompounds from the plant *Curcuma longa* which can be helpful in treating psoriasis using molecular docking techniques.

Methods: The protein associated to the mechanism of psoriasis was obtained from the protein data bank database, along with retrieving the phytocompounds from *C. longa*. The phytocompounds were docked with the protein using PyRx docking. Further, analysis was done using Swiss-absorption, distribution, metabolism, and excretion (ADME), ADME toxicity (ADMET) LAB 2.0, and ProTox webservers to evaluate the credibility of the best docked compounds.

Results: Molecular docking study shows that two compounds, piperine and cyclocurcumin, have the potential to inhibit the protein interferon-gamma protein (IFN_{γ}), hindering the mechanism of psoriasis. Drug likeliness and ADMET properties also suggest that these two compounds exhibit potential drug like properties.

Conclusion: The present study suggests that piperine and cyclocurcumin have significant binding affinity and they could inhibit the protein IFN_{γ} and also helps to manage the therapeutic strategies against psoriasis.

Keywords: Psoriasis, Interferon-gamma protein, Keratinocytes, Inflammation, Molecular docking, *Curcuma longa*, Phytocompounds.

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INTRODUCTION

The skin being the largest human body organ, acts as the first protective layer against outside environmental defenses. Yet, one in every third person of earth suffers from one or other sort of skin-related disease [1]. The load of skin disease is significant with perspective of global health. Skin disorders were the fourth most common cause of non-fatal burden overall [2]. The skin is a remarkable organ. Skin illnesses are quite common because it is regularly harmed because it being the first protective layer of our body. More than 3000 skin conditions are recognized [3]. Skin diseases can range from mild acne, sun burn to more chronic cases such as eczema and psoriasis. The majority of chronic skin disorders, including atopic eczema, vitiligo, psoriasis, and leg ulcers, do not strike a life-threatening hazard right away. However, a condition that is visually deforming might have a substantial effect and result in significant anguish and suffering [4]. The papulosquamous skin condition termed as psoriasis is one of the most prevalent immune-mediated diseases. Dendritic cells, T-cells, and tumor necrosis factor all play major roles in its pathogenesis [5]. Psoriasis is a systemic inflammation skin condition with substantial hereditary predisposition and autoimmune pathologic elements. The figures vary by area but it is infecting roughly 2% globally. Despite the fact that, it has been attributed to a multitude of illnesses and can harm joints. It has been established that, in addition to the psoriatic skin, inflammation can harm other organ systems. As a result, it has been proposed that psoriasis is a condition that affects the entire body instead of merely the skin. When compared to the general population, psoriasis patients exhibited increasing levels of hyperlipidemia, hypertension, coronary artery disease, type 2 diabetes, and body mass index [6].

The hallmark of psoriasis is chronic inflammation that leads to aberrant differentiation and uncontrolled keratinocyte proliferation. The histology of the psoriatic plaque reveals an acanthosis that covers inflammatory infiltrates constituted of dermal dendritic cells, macrophages, T lymphocyte cells (T-cells), and neutrophils. Disruptions in the innate and adaptive cutaneous immune systems are what initiate and maintain psoriatic inflammation [7]. It is typical for innate immune system activation generated by endogenous danger signals and cytokines to coexist with autoinflammatory persistence in some patients and autoimmune reactions caused by T-cells in others. Due to the overlap and even potentiation of both pathways, psoriasis exhibits characteristics of an autoimmune illness on inflammatory background [8]. The keratinocyte-rich outermost layer of the skin is where the primary clinical signs of psoriasis are most visible. However, nonetheless, the development of the psoriatic plaque, which is not solely restricted to inflammation in the epidermal layer, is shaped by the interaction of keratinocytes with a wide range of cell types across the dermal layer of the skin. Psoriasis can be seen as having an initial phase that may be brought on by trauma, infection, or medication [9].

Psoriasis was previously defined by histopathology, but now due to greater understanding of functional genes and analysis of expressed genes, it can be defined as a disease. Extensive studies on this new defined disease pathology reveal some new findings. One such finding is that, there are a lot more chemokines expressed in skin lesions than what was previously thought to be and at least 16 different ligands are expressed firmly than others. Chemokines, whose expression is generally restricted to lymph nodes and formal lymphoid organs, are abruptly increased by psoriasis. Several other immune-regulating and pro-inflammatory gene products are also more often expressed, according to genomic study. Some of these inflammatory genes can be explained by the activation of a type 1 pathway, in which T helper 1 and T cytotoxic 1 T-cells release interferon-gamma protein (IFN_{γ}) on activation. Signal transducer and activator of transcription 1 is subsequently activated by released IFN_{γ}, increasing the transcription of

a wide number of immune-related genes. This IFN_{γ}-activated pathway can be used to explain why the psoriasis transcriptome is expressed more frequently. Importantly, the stimulation of IFN-regulated genes can be used to explain important cellular characteristics of psoriasis [10,11]. IL-23 has also been linked to enhanced expression using reverse transcriptase polymerase chain reaction genomic analysis as the primary inducer of IFN_{γ} production and type 1 T-cell polarity. IFN_{γ} may also originate from activated NK-T-cells [12,13].

Natural medications derived from plant sources are getting prominence due to a number of benefits, such as typically fewer side effects, improved patient tolerance, being relatively economical, and being acceptable due to a long history of use. Moreover, herbal treatments provide rational solutions to cure a range of disorders that are challenging to address and incurable using current medical approaches. These factors have led to the investigation of several plants as potential therapies for ailments affecting the skin, ranging from itching to skin cancer [14]. At present, the majority of traditional treatments can minimize psoriasis symptoms. However, the illness cannot be fully cured by any known medication. Research suggests that using herbal medicines and utilizing their antioxidative and immunoregulatory roles in the treatment may be one method to modify the response of the cells involved in the psoriasis course. They provide evidence for the efficacy of herbal based treatments for psoriasis and the beneficial function of phytochemicals in the management of this inflammatory illness [15,16]. *Aloe vera*, *Curcuma longa*, *Centella asiatica*, *Mahonia aquifolium*, and *Psorospermum febrifugum* have demonstrated the most promising results among the many plants that have been shown to have anti-psoriatic properties. [17]. Another research conducted on medicinal plants used by patients for psoriasis shows that the most popular medicinal plants for treating psoriasis include *A. vera*, *Trigonella arabica*, *Catharanthus roseus*, and *Anthemis cotula*. The study subjects used the leaves and fruits the most frequently. The most popular kind of preparation was paste [18]. *C. longa* from the *Zingiberaceae* family is a medicinal plant origin to the south west parts of the India. It is commonly known as turmeric to the local native. It has many therapeutic uses due to presence of many bioactive components. Turmeric can be employed as a medicine to cure an array of illnesses, including inflammations, microbial infections, diabetes, arthritis, muscular, biliary, anorexia, cough, diabetic wounds, hepatic abnormalities, and sinusitis [19,20]. Curcumin, a compound obtained from *C. longa*, has many anti-inflammatory properties with features related to the various receptors that curcumin binds to, this substance has demonstrated some notable effects on psoriasis [21]. There are several instances of its therapeutic success. One being that due to its antioxidative qualities, curcumin may reduce oxidative stress in psoriatic lesions [22]. It has recently been suggested for the treatment of psoriasis, where its effectiveness appears to derive from many mechanisms of action [23]. This study aims to find out further phytocompounds from the plant species *C. longa* which can be used to combat the spread of psoriasis with an *in silico* approach.

METHODS

Protein selection

Three-dimensional structure of the protein IFN_{γ} (Interferon-gamma) receptor (protein data bank [PDB] ID: 1FG9) was retrieved from the RCSB PDB webserver (https://www.rcsb.org/) [24]. The obtained three-dimensional complex was weighed at 114.41 kilo Daltons and with a resolution of 2.90 Å. The structure consisted a total of 6905 atoms with chain a length of 134 amino acids. The pdb protein complex was purified; this was possible by the help of discovery studio visualizer 21.1. First, the pdf file of impurified protein was loaded onto the scene. The secondary chains were removed. Water molecules were also removed to stabilize the hydrogen bonds and nullify the atomic clashes. The next step was to remove any hetero atoms present which followed with the addition of polar hydrogens to balance charges. This new formed purified version of the protein was then saved for further docking studies.

Ramachandran plot

The Ramachandran plot is a representation of phi and psi torsional angles of the amino acids in a peptide. To analyse the Ramachandran plots, European Molecular Biology Laboratory-webbased, EBI's PDB server was employed (http://www.ebi.ac.uk/thornton-srv/databases/cgibin/pdbsum/GetPage.pl) was utilized [25]. An investigation of the Ramachandran plot was conducted using the PDB ID of impurified protein (1FG9), with outliers annotated by residue type, residue number, and chain, and displaying all the labels.

Ligand selection

For this study, a total of 190 unique phytocompounds were retrieved from the plant *C. longa*. The phytocompounds were first identified by the basic search guide of Indian medicinal Plants, Phytochemistry, and Therapeutics webserver (https://cb.imsc.res.in/imppat/) [26]. The unique phytocompounds were then retrieved from the PubChem database (https://pubchem.ncbi.nlm. nih.gov/) in three-dimensional spatial data file format [27].

Molecular docking

By simulating the interaction, using the molecular docking method, we could characterize how small compounds interact at the binding site of target proteins which help us better understand the underlying biological interactions between these molecules [28]. For the molecular docking study, PyRx, a virtual screening tool, was employed. The 190 phytocompounds retrieved from *C. longa* were then used for docking studies with the protein IFNY (PDB ID: 1FG9). The protein was loaded onto the scene and converted to a macromolecule for docking. The Open Babel extension of PyRx was utilized to load that the phytocompounds and their energy were minimized and converted to protein data bank, partial charge, and atom type file format file format for molecular docking. The grid was then set to maximum (Grid center – X:30.3203, Y:1.8292, and Z:10.9785. The grid was then set to maximum (Grid centre - X:30.3203, Y:1.8292, Z:10.9785 and Grid spacing - 0.3750 angstrom) after defining all the phytocompounds and the ligand. The docking was initiated and the interactions of the ligands with the target protein were evaluated based on their binding affinities. The top 10 ligands were then taken for further study based on their binding affinity and interaction. A binding affinity value of −7 and above was preferred as they are generally the compounds with better interaction with respect to the protein molecule. Visualization was carried out using the discovery studio visualizer 21.1.

Absorption, distribution, metabolism, and excretion (ADME) analysis

In pharmacokinetics and pharmacology, the term ADME describes how a drug is eliminated from the body. The efficacy and pharmacological activity of the chemical as a medication are influenced by the four criteria, which also have an impact on drug levels and the kinetics of drug exposure to tissues. Toxicity is occasionally taken into account also known as ADME and toxicity (ADMET) analysis. Drug likeliness and ADME analysis through Lipinski rule of 5 was done using Swiss-ADME (http://www.swissadme.ch/index.php/) [29] and ADMETLAB (https://admetmesh.scbdd.com/service/evaluation/) [30]. Toxicity studies were also carried out using the web server ProTox 2 (https://tox-new.charite.de/protox_II/index.php) [31]. Furthermore, Boiled-Egg analysis was also carried out using Swiss-ADME tool itself [32]. For ADME analysis, his study utilizes the Lipinski rule of 5. These rules are a set of conditions which dictates the drug likeliness of a molecule on a pharmacological level. These 5 rules include, molecular mass <500 Daltons, Log^{P} <4.15, H-bond donor <5, H-bond acceptor <10, and molar refractivity between 40<130.

RESULTS

Ramachandran plot

The protein geometry obtained from Ramachandran plot (Table 1) provides insights for the residue as follows, visualization of protein folding (Fig. 1) regions from the Ramachandran plot shows how majority of residues falls under the most favored regions, and additional allowed regions of the graph.

Molecular docking

Molecular docking studies disclose that many of the phytocompounds of *C. longa* have good binding affinity toward the IFN_{γ} macromolecule. Out of the total 190 phytocompounds, 30 showed a binding affinity higher than seven which is considered a good score. From the list of phytocompounds with −7 and above binding affinity, the peak ten compounds were taken for further analysis (Table 2). The ten phytocompounds were first subjected to ADME analysis using the Swiss-ADME webserver, evaluating them by the Lipinski rule of 5 (Table 3).

Table 1: Protein geometry from Ramachandran plot

Placement of residues	Amount	Percentage
Residues placed in most favored regions (A, B, L)	580	74.6
Residues placed in additional allowed regions (a, b, l, p)	178	22.9
Residues placed in generously allowed regions (~a, ~b, ~l, ~p)	16	2.1
Residues placed in disallowed regions	4	0.5
Number of non-glycine and non-proline residues present	778	100.0
Number of end-residues (excl. Glycine and Proline) present	16	
Number of glycine residues present (shown as triangles)	32	
Number of proline residues present	36	
Total number of residues present	862	

Table 2: Top 10 phytocompounds from *Curcuma longa* having the highest binding affinity with IFN_{γ} (PDB ID: 1FG9)

S. No.	PubChem compound ID	Phytocompound name	Binding energy (Kcal/moL)
1.	CID_173183	Campesterol	−9.1
2.	CID_5280794	Stigmasterol	−8.5
3.	CID_14985	Vitamin E	−8.3
4.	CID_222284	Beta-sitosterol	−8.1
5.	CID_5997	Cholesterol	−8.1
6.	CID_638024	Piperine	−7.9
7.	CID_11586487	Beta-himachalene	−7.5
8.	CID_69879809	Cyclocurcumin	−7.5
9.	CID_101731	Beta-patchoulene	−7.4
10.	CID_11979920	Oleoresin curcumin	−7.3

IFN_{γ}: Interferon-gamma protein, PDB: Protein data bank

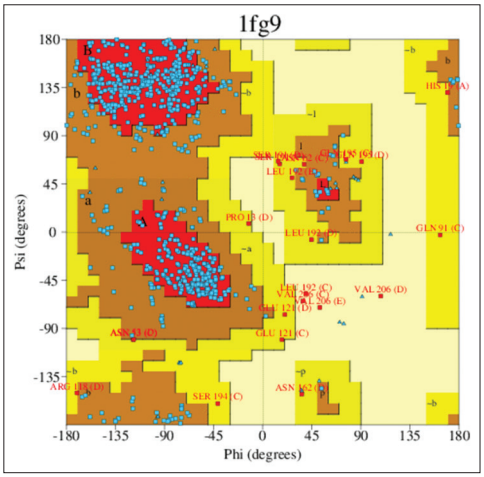

Fig. 1: Ramachandran plot analysis of 1FG9 showcasing how majority of the residues falls under the most preferred regions of protein folding

Drug likeliness and ADMET analysis

From Table 3, we can observe that only two phytocompounds piperine and cyclocurcumin follow all 5 rules of Lipinski. These two compounds were taken for further analysis for drug likeliness. Piperine and cyclocurcumin were also subjected to Boiled-Egg analysis, along with the other eight phytocompounds. Boiled-Egg analysis (Fig. 2) again revealed that these two compounds are the best out of the bunch as they fall under the preferred zones of the plot. Piperine falls under the yellow region of the plot indicating its ability to pass the blood brain barrier (BBB), while cyclocurcumin falls on the white region showcasing its human intestinal absorption (HIA) properties.

In addition, the water solubility (logS), HIA, carcinogenic effects, BBB, and glycoprotein substrate permeability of the two compounds were assessed using the standard scale using ADMETLAB 2.0 (Table 4).

Toxicity study

Toxicity prediction was carried out using the web tool ProTox-2. The lethal dosage and the toxicity classes were predicted with the webserver. While both the compounds showed toxicity class of 4, cyclocurcumin shows much greater lethal dose 50 value (LD_{50}) value, suggesting it might be safer than piperine (Table 5).

Molecular visualization

Visualization of molecular interaction between the two ligands piperine and cyclocurcumin with the protein IFN_{γ} (PDB ID: 1FG9) was done using the Biovia discovery studio visualizer 21.1 software. After the compounds were docked using PyRx, the docked ligands were saved in the PDB file format. This PDB file format was then open, along with the protein in its purified form. Various 2D and 3D interaction between the phytocompounds and the protein was analyzed.

Piperine

Piperine forms multiple bonds with the protein 1FG9. It includes carbon hydrogen bonding with the residue methionine A77 and Pi-Pi bond with the residue tyrosine A4. It also forms alkyl and Pi-alkyl bonds with the residues phenylalanine (PHE) A15 and leucine (LEU) A11 (Fig. 3).

Cyclocurcumin

Interaction between the protein 1FG9 and cyclocurcumin results in formation of many Van der Waals forces. Along with this, it also forms conventional Pi-sigma bonds with the residues LEU A11 and PHE A15. Alkyl and Pi-alkyl bonds are also observed in interaction with the residues amino acid isoleucine A49 and amino acid valine A50 (Fig. 4).

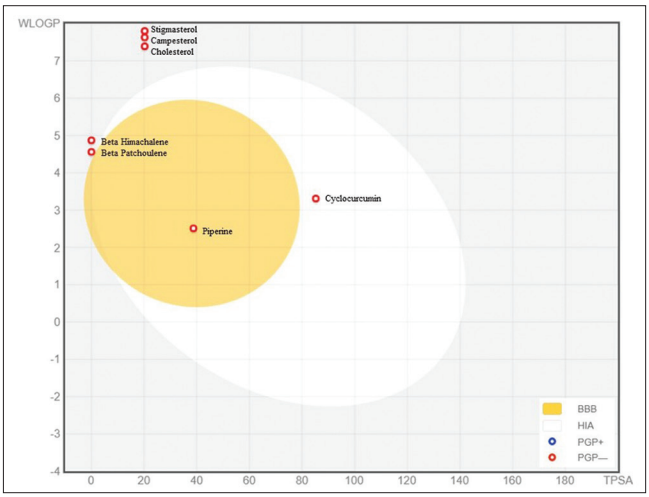

Fig. 2: Boiled-Egg analysis of the top 10 docked compounds of Curcuma longa with protein 1FG9. (Note: 3 compounds are out of range)*

Table 3: ADME analysis based on Lipinski rule of 5 for the top 10 phytocompounds

S. No.	Phytocompound name	Molecular weight	Hydrogen bond acceptors	Hydrogen bond donors	Molar refractivity	Log^P
1.	Campesterol	400.68	1	1	128.42	7.63
2.	Stigmasterol	412.69	1	1	132.75	7.80
3.	Vitamin E	430.71	2	1	139.27	8.84
4.	Beta-sitosterol	414.71	1	1	133.23	8.02
5.	Cholesterol	386.65	1	1	123.61	7.39
6.	Piperine	285.34	3	0	85.47	2.51
7.	Beta-himachalene	204.35	0	0	68.78	4.87
8.	Cyclocurcumin	368.38	6	2	100.78	3.31
9.	Beta-patchoulene	204.35	0	0	66.88	4.56
10.	Oleoresin curcumin	1015.06	15	6	288.93	9.43

ADME: Absorption, distribution, metabolism, and excretion

Table 4: ADME analysis using ADMETLAB 2.0

S. No.	Ligand name	logS	HIA	Carcinogenicity	BBB	Pgb-sub	Skin sensitization
1.	Campesterol	−7.006	0.004	0.067	0.854	0.001	0
2.	Stigmasterol	−6.978	0.005	0.054	0.691	0.001	0
3.	Vitamin E	−6.5	0.003	0.024	0.813	0	2
4.	Beta-sitosterol	−7.052	0.004	0.047	0.84	0.001	0
5.	Cholesterol	−6.984	0.003	0.069	0.833	0.001	0
6.	Piperine	−4.11	0.002	0.804	0.381	0.002	4
7.	Beta-himachalene	−6.341	0.004	0.056	0.096	0	0
8.	Cyclocurcumin	−4.222	0.038	0.677	0.083	0.006	9
9.	Beta-patchoulene	−5.444	0.005	0.420	0.341	0	0
10.	Oleoresin curcumin	−3.921	0.06	0.706	0.103	0.014	8

ADME: Absorption, distribution, metabolism, and excretion, HIA: Human intestinal absorption, BBB: Blood-brain barrier

Table 5: Toxicity prediction using ProTox 2 server

S. No.	Ligand name	LD_{50} (mg/kg)	Tox class	Average similarity (%)
1.	Piperine	330	4	100
2.	Cyclocurcumin	1500	4	52.11

LD_{50}: Lethal dose 50 value

DISCUSSION

Psoriasis, although an autoimmune disease whose cure is yet to be found, can be managed to a great extent if treated in the early years of its outbreak [33]. Psoriasis's onset represents a threat that lasts a lifetime. Although the recent advancement of biologic medicines has improved systemic treatment and expanded understanding of psoriasis as a systemic illness with high comorbidity rates, none of the available psoriasis treatment options offer a cure for the patient. A modification to our understanding of T-cell-mediated illness may also result from the efficacy of diverse recombinant proteins. At present, there are many conventional synthetically derived medicines, both available by prescription and over-the-counter methods. These medications usually focus on reducing inflammation. Minimizing inflammation results in the reduction of any itching and soothes the skin. This property of reducing inflammation is very crucial for any type of drug development for psoriasis. This is the same reason *A. vera* is very popular among herbal medications to treat psoriasis. Overproduction of skin cells that form scales is an attribute of this autoimmune disease. The most commonly used compound for psoriasis medication is salicylic acid, this compound helps in shedding dead skin and softening it. Hence, it helps in decreasing rashes and itching [34,35]. The introduction of naturally occurring compounds for the treatment is highly revered. Hence, many studies aim to find ways to treat the mechanism of psoriasis by finding compounds that are naturally occurring. For this study, we tried to find antipsoriatic compounds from the plant *C. longa*, which is a naturally occurring medicinal plant.

As the protein, IFNY is an essential factor for the induction of psoriasis altercation; many studies are aimed around deviating the mechanism relates to either IFNY or its subsequent proteins. Aside from IFNY,

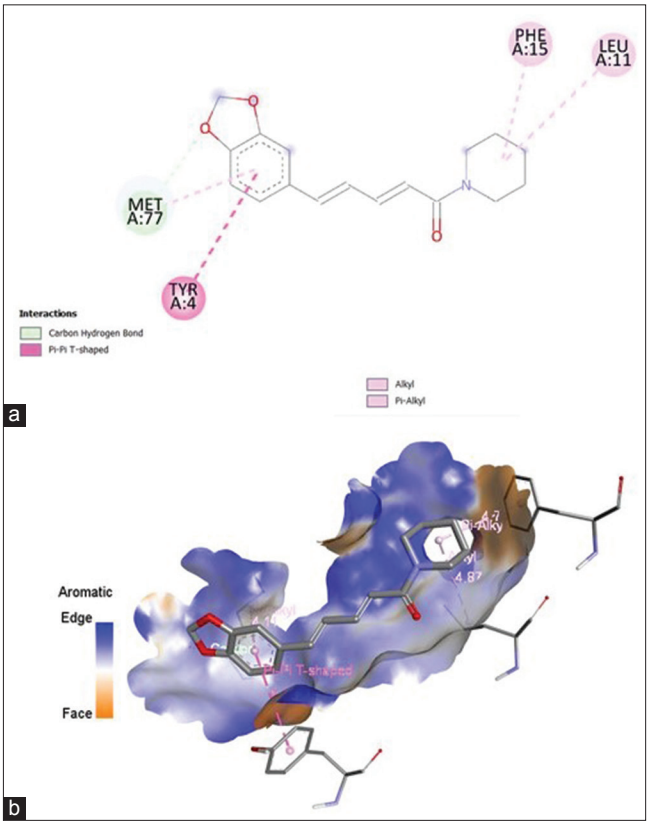

Fig. 3: Interaction between piperine and 1FG9 (a) 2D structure and (b) 3D structure in aromatic edges and faces

STAT 1 protein and its requisite genes are also well studied to oppose the mechanism of this autoimmune disease. In our following study, we try to incorporate a molecular docking method from which a subsequent compound is discovered which has the ability to treat

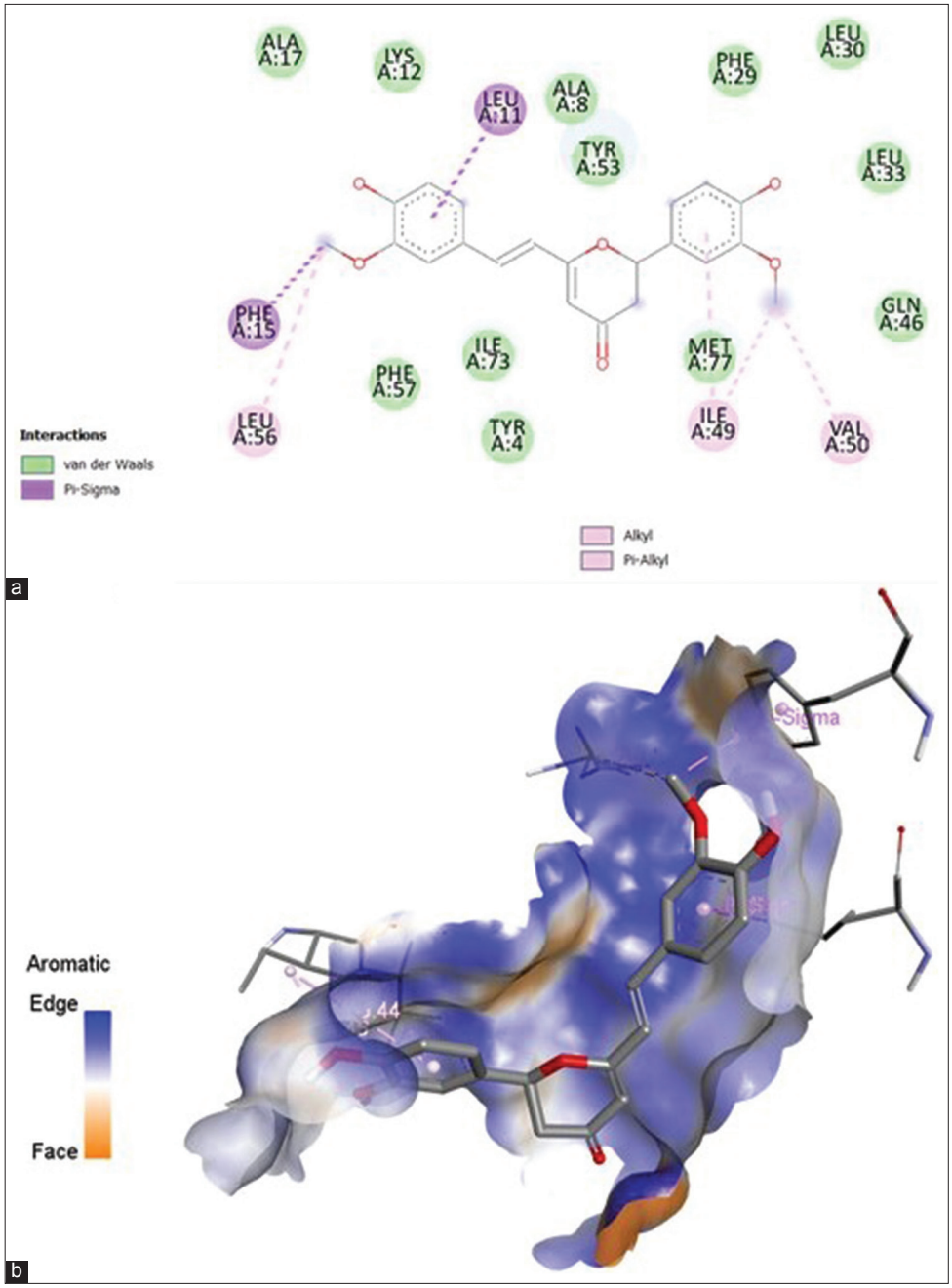

Fig. 4: Interaction between cyclocurcumin and 1FG9 (a) 2D structure and (b) 3D structure in aromatic faces and edges

psoriasis by utilizing the phytocompounds of the plant C. longa. These phytocompounds are meant to stop the production of excess keratinocytes by IFNY. For this instance, phytocompounds were docked with the protein IFNY (PDB ID: 1FG9). Two compounds, piperine and cyclocurcumin, demonstrated very good results based on the interaction energies with the protein IFNY. Cyclocurcumin also being the derivative of the compound curcumin. Both the phytocompounds showed similar binding energies on PyRx docking. Lipinski's rule of 5 dictates the trajectory of drug development of any compound and both the phytocompounds were found to be agreeing with all 5 of Lipinski's rules. Visualization of molecular docking also showed very viable interactions in terms of stability. ADME analysis and Boiled-Egg analysis also support the usage of both phytocompounds as possible drugs. Toxicity studies reveal that both the phytocompounds fall under the tox class 4, but piperine shows very little LD_{50}. Cyclocurcumin shows almost 5X lethal dosage required value to that of piperine which is a very useful quantification showing it is less toxic.

The previous studies show that these types of naturally occurring phytocompounds can be developed to ensure a complete sustainable non-synthetic way of treating psoriasis. These types of studies are profoundly thought to be effective as more common types of skin diseases such as itching, inflammation, and acne are treated with ease using just the naturally occurring plant ingredients. Developing a drug either synthetic or non-synthetic takes very furbished research and identifying a compatible compound through an *in silico* approach aids in the initial steps. The results from this study show how although piperine and cyclocurcumin maybe the best possible compounds, they can still be toxic to the human body on an individual scale. The skin sensitization results of these compounds also show how developing a topical treatment for psoriasis may result in skin irritations. This study provides a foundation for identifying additional compounds that, when used together with piperine and cyclocurcumin, can counteract the toxic effects. This combination has the potential to serve as an effective drug in certain cases. Furthermore, we can look into different immune pathways of psoriasis to

develop drugs which can act selectively and can yield better results than focusing on the IFN_{γ} protein and STAT genes. Compounds can be identified which block selective receptors for psoriasis pathways on different body parts hence making them more potent. If a compound is to be found with very less skin irritation ability, they can generally be used for development of topical ointments rather than conventional digestives.

Based on all the results, both piperine and cyclocurcumin are very much viable options to be developed as possible drugs for treating psoriasis. Further, strong research is needed to yield the best possible qualitative and quantitative measures for these phytocompounds as sustained treatment drugs for psoriasis.

CONCLUSION

The objective of this study was to identify phytocompounds from Curcuma longa that can potentially inhibit the adverse effects of psoriasis. Psoriasis is an autoimmune disease that can be characterised by the activation of many pathways. It is accompanied by expressions such as skin sensitization, itchiness, scaly skin and inflammation. This study focuses on inflammatory gene expression in psoriasis, which activates the type 1 pathway resulting in the release of interferon-gamma protein (IFNY). IFNY was targeted with natural phytocompounds as it is a key protein that further expresses the cellular characteristics of psoriasis. This study concludes that phytocompounds from Curcuma longa were predicted to suppress the IFNY protein, preventing further expression of any pathways leading to the cellular characteristics of psoriasis. These phytocompounds have the highest binding affinity to IFNY and high inhibitory efficacy. With good drug like properties, toxicity predictions and safe ADMET profiles, these phytocompounds can be utilized to develop potential inhibitors for psoriasis disease with minimal side effects.

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AUTHORS' CONTRIBUTIONS

All authors contributed equally to the manuscript.

CONFLICTS OF INTEREST

Nil.

AUTHORS FUNDING

Nil.

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