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Molecular Docking Analysis of Psoriasis Specific Mediator IL-17 with Active Phytoconstituents from *Cocos nucifera, Carica papaya, Ichnocarpus frutescens*

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Abstract: Psoriasis is a chronic immune cell-mediated genetic skin disorder. It affects approximately 2% of the general population in Europe and the United States. In the past decade, biologics targeting tumor necrosis factor-α, interleukin (IL)-23, and IL-17 have been developed and approved for the treatment of psoriasis. The present study aimed to assess some biologically active compounds present in medicinal plants as potential anti-psoriatic agents using *in silico* methods. Docking studies were performed with Auto Dock Vina software, which simulates the molecular interaction of ligands and proteins. Protein with PDBID:5HI4 (Interleukin-17A) has been used for docking studies.03 ligands, Benzyl Isothiocyanate (BI) from *Carica papaya*, Caffeic acid (CA) from *Cocos nucifera*, and Oleanolic acid (OA) from *Ichnocarpus frutescens* respectively were used for molecular docking studies. Each docking study generated 09 poses for each ligand, with negative binding affinity values containing a unit of kilo-calorie per mol (kcal/mol). The pose with the highest negative binding affinity value was considered the best-docked pose at the provided binding site of the respective target. The results demonstrate the effectiveness of this screening strategy, which can lead to rapid drug discovery as anti-psoriatic drug therapy. The Docking results observed that Caffeic acid (CA) showed binding within the same pocket as the co-crystallized ligand does for the inhibition of Interleukin-17A (Protein PDBID: 5HI4). This result might prove to be a novel step in discovering a potent therapy for managing psoriasis**.**

Keywords: psoriasis; phytoconstituents; molecular docking analysis.

1. Introduction

An *in silico* molecular docking can forecast how a recommended ligand will bond to its macromolecular target while creating a stable complex. Docking has become crucial for illustrating the molecular interactions of natural substances with various receptors. Drugs, including natural phytochemicals that target the IL-17 pathway, are increasingly being explored to counter population-specific disease indicators [1-8].

Nowadays, the drug development process is incomplete without docking studies. Phytochemical agents acting on their molecular targets can be traced for managing diseases and disease-specific new therapies. Docking is a result of the ability of a protein (enzyme) and nucleic acid to interact with small molecules to form a supramolecular complex, which plays a significant role in the dynamics of the protein. This may synergize or inhibit biological function. Molecular docking also helps to find the behavior of small molecules in the binding

pockets of target proteins. Identification of the correct poses of ligand in the binding pocket of a protein and the affinity between ligand and the protein is done by molecular docking. 2-3% of the world's population suffers from the chronic and puzzling autoimmune skin disorder known as psoriasis. Immune dysregulation and chronic inflammatory skin conditions are the chief symptoms of psoriasis, which are clinically recognized erythematous plaques with non-uniform borders and silvery scales. It causes a major decline in the quality of life for patients by being linked to a number of serious diseases, such as depression, cardiometabolic syndrome, and psoriatic arthritis. In the early phases of psoriasis, lesions may appear because of recurrent episodes of auto-inflammation due to the burst release of neutrophils, cytokines, and interleukin-1 (IL-1) family, such as IL-1α, IL-1β, and IL-36. Currently, the three primary types of treatment used to reduce inflammation and skin irritation/itching are topical therapies, phototherapy, and systemic medications. These remedies are mainly used to control the disease condition, and its symptoms are especially limited to treating the disease topically. Many of those methods have a variety of adverse side effects on patients, including atrophy, organ toxicity, immunosuppression, infection, and carcinogenesis, which restricts the usage of these treatments over an extended period of time. Therefore, more research into psoriasis treatment options that are secure, efficient, and perhaps less expensive is required [9-19].

Numerous herbs have been used successfully in Ayurveda to treat psoriasis, however, a multimodal approach is required due to the disease's complex etiology. *Cocos nucifera*, *Carica papaya*, and *Ichnocarpus frutescens* have anti-psoriatic and anti-inflammatory capabilities-: the central goal of this research is to find a safer and more effective treatment for psoriasis using *in silico* studies to tap into the reservoir of phytochemicals found in these plants and investigating their involvement in the management of psoriatic symptoms as well as their immunomodulatory and anti-inflammatory impact on immune cell populations and cytokines involved for the emergence of psoriasis. This article includes detailed information about the correlating pathogenesis of this autoimmune disease in regards to the inflammation process and oxidative stress, with an *in silico* docking study to investigate molecular interactions between natural active compounds and immune system response. This information is provided to help readers better understand the role of naturally derived substances and present their potency in psoriasis treatment [20-21].

Various researchers have discussed the influential role that natural compounds play in reducing oxidative stress, which in turn activates several signaling pathways that lead to the onset of this autoimmune disease, as well as the effects of plant-derived compounds, phytochemicals, and plant-based extracts on immune mediators and chemicals that cause inflammation and the progression of psoriasis [22].

1.1. Carica papaya seeds.

Carica papaya L (family Caricaceae) is a fast-growing, short-lived, single-stemmed, small tree, 2-10 m in height with straight, cylindrical, soft, hollow, grey trunk roughened by the presence of large leaf- and inflorescence scars [23]. The fruit contains black-colored seeds with multi-spectrum pharmacological activities like carminative, emmenagogue, abortifacient, vermifuge, and counter-irritant. A seed extract is used to treat bleeding piles and enlarged liver and spleen. A seed paste with glycerine is applied to cure ringworm and psoriasis [24].

1.2. Cocos nucifera water.

The scientific name of coconut is *Cocos nucifera*. Early Spanish explorers called it *Cocos*, which means "Monkey face" as the three indentations (eyes) on the hairy nut resemble the head and face of a monkey, and *nucifera* means nut-bearing. It has been proven that scientists worldwide have worked on *Cocos nucifera* and revealed too many pharmacological activities such as antimicrobial, anti-inflammatory, antiparasitic, antidiabetic, antineoplastic, insecticidal, and leishmanicidal activities [25]. These activities are accurate results of the active phytoconstituents present in plants like flavonoids, phenols, tannins, glycosides, alkaloids, steroids, triterpenes, phlobatannins and anthraquinones [26-27].

1.3. Ichnocarpus frutescens.

Commonly known as 'black creeper'. The plant *Ichnocarpus frutescens* belongs to the family Apocynaceae. It is a large, evergreen, woody climbing plant sprawling to 10 meters in maximum length and 6 centimeters in diameter. In ancient cultures, naturopathy has been used in the treatment of diabetes, demulcent, skin troubles, fevers, nephrolithiasis, seminal weakness, liver disorders, etc.[28]. It is rich in photochemical parameters like flavonoids, carbohydrates, phenolic acid, triterpene, steroids, natural rubber, proteins, oils, hydrocarbons, polyphenols, etc. The plant's leaves stem, and roots show enormous pharmacological activity such as antidiabeteic, hepatoprotective, antioxidant, antitumor, wound healing, analgesic, and antipyretic [29].

1.4 Molecular docking studies.

Molecular docking aims to predict the ligand-receptor complex structure using computation methods. This is performed through two interrelated steps: first, by sampling conformations of the ligand in the protein's active site-: and then ranking these conformations via a scoring function. Ideally, sampling algorithms should be able to reproduce the experimental binding mode, and the scoring function should rank highest among all generated conformations [30]. With six degrees of translational and rotational freedom and confirmational degrees of freedom of both the ligand and protein, the two molecules have many possible binding modes. Generating all the possible conformations is a costly affair. Docking software has widely used various sample algorithms such as matching algorithms, genetic algorithms, incremental constructions, MCSS, LUDI for *de novo* designs, molecular docking, etc. [31-32].

2. Materials and Methods

2.1. Database and tools.

For carrying out the study, National Center for Biotechnology Information's (NCBI.) website and Protein Data Bank's (PDB) website were used as receptor sources. Chemdraw Ultra 7.0 [33] was used to design and optimize the geometry of the derivatives.

2.1.1 3D structure of protein.

Protein with PDB ID: 5HI4 (Interleukin-17A) has been used for docking studies.

2.1.2 3D structure of ligand molecules.

03 ligands, i.e., Benzyl Isothiocyanate (BA), Caffeic acid (CA), and Oleanolic acid (OA) were used for molecular docking studies.

2.1.3 Docking experiment.

PDB files of the 3D structure of ligands and protein structures were processed for the docking studies. Docking studies were performed with AutoDock Vina software [34-36], simulating the molecular interaction of ligands and proteins. Each docking study generated 09 poses for each ligand, with negative binding affinity values containing a unit of kilo-calorie per mol (kcal/mol). The pose with the highest negative binding affinity value was considered the best docked- pose at the provided binding site of the respective target.

2.2. Molecule designing and optimization.

The chemical structures were drawn using ChemDraw Ultra 7.0, and energy minimization of derivatives was achieved with Chem3D Pro of Chem Office suit for taking the energy of each molecule up to its lowest energy state (highest stability). The 3D structure of 5HI4 (CID: 36462) was retrieved from the Pub Chem compound database at NCBI.[37]

2.3 Docking studies.

Molecular docking is based on the "key and lock" hypothesis and is believed to find the best-fit orientation of ligands and proteins. Various phytochemicals isolated from *Cocos nucifera*, *Carica papaya* seeds, *Ichnocarpus frutescen* extracts were selected for molecular docking study. Target protein 5HI4 (interleukin-17A) [38-41] was docked with selected phytochemical compounds using AutoDock Vina software, and binding energies were calculated [42-44]. The ligand and the target protein were prepared following the standard ligand and protein preparation procedure, and the prepared files for the protein and ligands were submitted to AutoDock vina. Each ligand's binding energy and contacts were obtained, and the docked complexes were analyzed using Discovery Studio 3.1 visualizer interactions with ARG100, PRO59 & GLU60 (Figure 1). Caffeic acid (CA) interacted with a binding affinity of -5.8 kcal/mol and showed H-bond interactions with TYR44, TYR43, SER118 & SER41 (Figure 2). Oleanolic Acid (OA) interacted with a binding affinity of -7.6 kcal/mol and showed no hydrogen bonding. (Figure 3).

3. Results and Discussion

3.1. Docking results.

The possible molecular interaction between Interleukin-17A (PDB ID: 5HI4) & 03 ligands, i.e., Benzyl Isothiocyanate (BI), Caffeic acid (CA), and Oleanolic acid (OA), was clearly depicted in Table 1. Benzyl Isothiocyanate (BI) interacted with a binding affinity of -4.3 kcal/mol (best pose) and showed H-bond interactions with ARG100, PRO59 & GLU60 (Figure. 1).

Table 1. Molecular interaction studies of 03 ligands, i.e., Benzyl Isothiocyanate (BI), Caffeic acid (CA), and Oleanolic acid (OA) with Protein PDBID:5HI4 (Interleukin IL-17A).

Ligand	**No. of pose**	**Binding affinity(kcal/mol)**		**Number of Hydrogen bond interactions**
BenzylIsothiocyanate(BI)	9	-4.3	Bestpose	2

Ligand	No. of pose	Binding affinity(kcal/mol)		Number of Hydrogen bond interactions
		-4.2		
		-4.1		
		-4.1		
		-4.1		
		-4		
		-4		
		-3.9		
		-3.9		
Caffeicacid(CA)	9	**-5.8**	Bestpose	**3**
		-5.2		
		-4.9		
		-4.9		
		-4.8		
		-4.6		
		-4.6		
		-4.5		
Oleanolicacid(OA)	9	-7.6	Bestpose	Zero
		-7.5		
		-7.4		
		-7.2		
		-7		
		-6.8		
		-6.8		
		-6.8		
		-6.8		

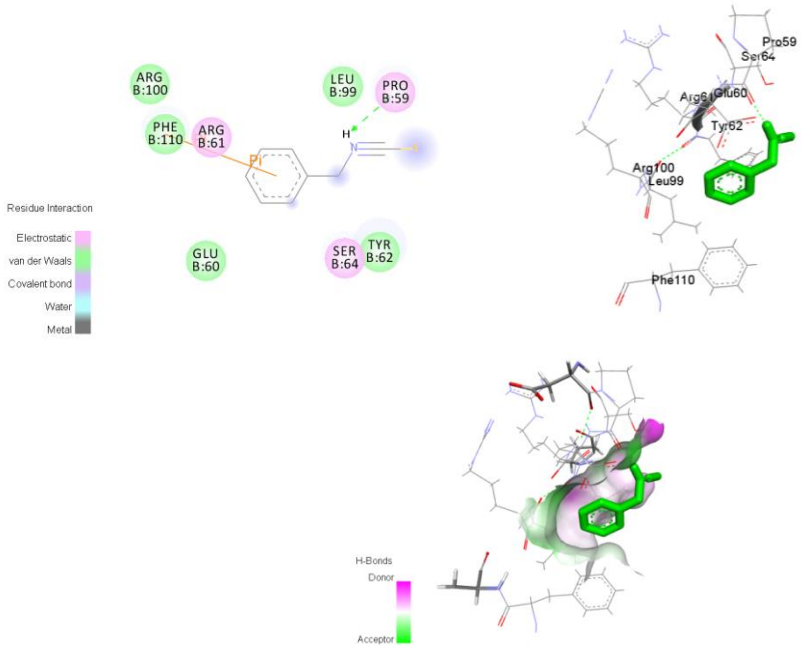

Figure 1. Docked images of Benzylisothiocyanate with protein 5HI4 with residues.

3.1.1. Binding site analysis.

The experimental analysis of the binding site shows that ARG100, PRO59 & GLU60, TYR44, TYR43, SER118 & SER41 could be the catalytic site residue present in the structure of Protein PDB ID: 5HI4 receptor.

3.1.2. Docking Studies of 3 ligands with Interleukin-17A.

All three ligands interacted in different fashions, i.e., binding sites were different for all ligands with binding affinity ranging between -4.3 to -7.6 kcal/mol (Table:1). Benzyl Isothiocyanate(BI) interacted with a binding affinity of -4.3 kcal/mol (best pose); and showed H-bond interactions with ARG100, PRO59 & GLU60 (Figure 1). Caffeic acid (CA) interacted with a binding affinity of -5.8 kcal/mol and showed H-bond interactions with TYR44, TYR43, SER118 & SER41 (Figure 2). Oleanolic Acid (OA) interacted with a binding affinity of -7.6 kcal/mol and showed no hydrogen bonding. (Figure 3).

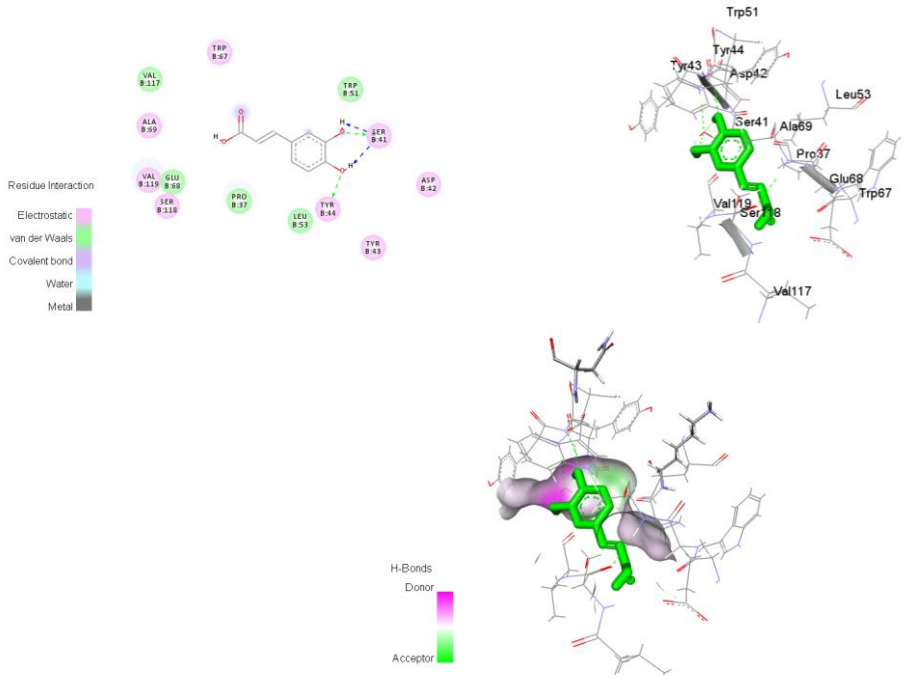

Figure 2 Docked images of Caffeic Acid (CA) with protein 5HI4 with residues.

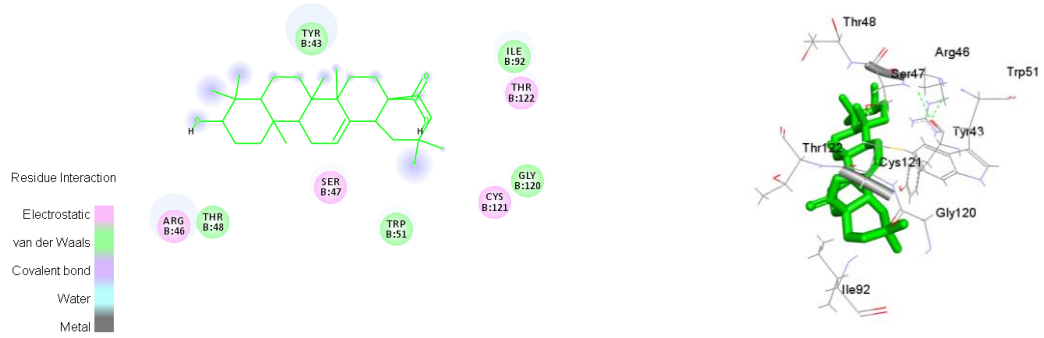

Figure 3 Docked images of Oleanolic Acid (OA) with protein 5HI4 with residues.

3.1.3. Comparison of docking results.

On comparing the binding pocket, it was observed that Caffeic acid showed the binding within the same pocket as the co-crystallized ligand does for the inhibition of Interleukin-17A (Protein PDB ID: 5HI4) (Figure 4). The docking analysis showed that it is nicely docked with protein in the catalytic domain so that it can be used with an anti-psoriatic profile.

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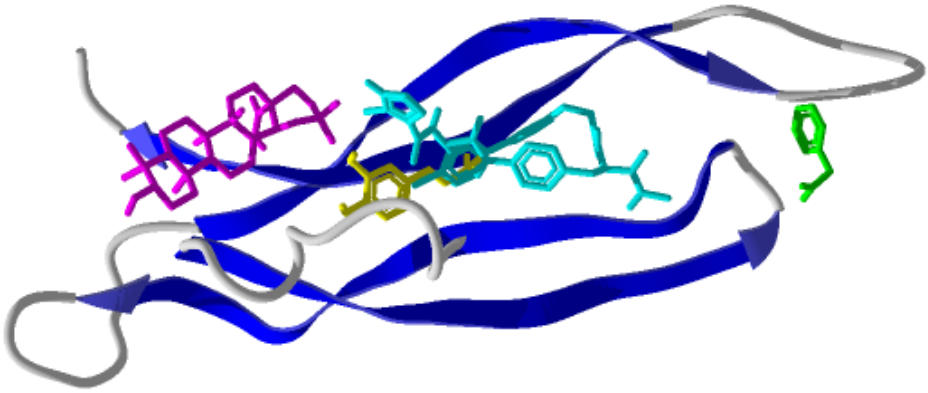

Figure 4. Binding pocket-Cyan color (Co-crystallized ligand), Yellow color (Caffeic acid), Green color (Benzyl isothiocyanate), and Violet color (Oleanolic acid). Caffeic acid was docked in the same binding pocket as the Co-crystalised ligand.

4. Conclusions

Docking analysis of 03 extracted compounds, i.e., Benzyl Isothiocyanate(BI), Caffeic acid (CA), and Oleanolic acid(OA), was performed and analyzed with interleukin -7 (PDB ID : 5HI4), which is a potential key link for the management of psoriasis. It was observed that one of the extracted compounds, Caffeic acid (CA) from *Cocos nucifera*, is found to dock in the same pocket as the co-crystallized ligand. Hence, it may be concluded that caffeic acid (coconut water) may play a potential role in managing and treating psoriasis. However, a deep and exhaustive clinical and biochemical study is required to prove and support the findings of this research work. Further, these findings might prove beneficial for designing the formulation for anti-psoriatic activity.

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Conflicts of Interest

The authors declare no conflict of interest.

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