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Analysis of the Bioactive Compounds from *Carica papaya* in the Management of Psoriasis using Computational Techniques

Misbaudeen Abdul-Hammed*, Ibrahim Olaide Adedotun, Tolulope Irapada Afolabi, Ubeydat Temitope Ismail, Praise Toluwalase Akande, Balqees Funmilayo Issa

Computational and Biophysical Chemistry Laboratory, Department of Pure and Applied Chemistry, Ladoke Akintola University of Technology, P.M.B. 4000, Ogbomoso, Nigeria

Abstract

Psoriasis is a persistent and mysterious autoimmune skin condition that affects 2-3% of the world's population. Currently, topical therapies, light therapy, and systemic drugs are the three main forms of treatment used to lessen inflammation and skin irritation/itching. However, all these treatments are only used to manage the disease each time it surfaces. Therefore, the main target of this work is to search for a safer and more effective remedy for psoriasis from the reservoir of phytochemicals present in Carica papaya via in silico studies due to its anti-psoriatic and anti-inflammatory properties. Reported phytochemicals isolated from Carica papaya were subjected to computational simulations using the PyRx docking tool and were docked against Janus Kinase 1 (JAK1) and Tumor necrosis factor α (TNFα) target receptors. The results obtained were visualized using PyMol, and Biovia 2019. Analysis of the results identified both Chlorogenic acid and Coumaroylquinic-acid with docking scores (-8.6 kcal/mol and -7.9 kcal/mol) respectively as potential inhibitors for the JAK1 receptor. The identified compounds also possessed excellent ADMET, drug-likeness, bioactivity, and activity spectra for substances (PASS) prediction properties. Their binding mode and the molecular interactions with the targets also affirmed their potency. In comparison with the standards (Methotrexate and Cyclosporine), Chlorogenic acid and Coumaroylquinic-acid have better ADMET properties, binding affinities, drug-likeness, PASS properties, bioactivities, oral bioavailability, binding mechanism, and interactions with the active site of the target receptor and are hereby recommended for further analysis towards the development of a new therapeutic agent for psoriasis treatment and management.

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Keywords: Psoriasis, *Carica Papaya*, Molecular docking, Anti-inflammatory, Skin disorder

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1. Introduction

Psoriasis is a chronic inflammatory noncontagious autoimmune skin condition that results in a rash with itchy, burning, and scaly patches [1]. This disease is common on the skin of the scalp, knees, elbows, lumbosacral regions, and trunks and may appear anywhere on the body's skin [2]. Psoriasis affects 2 to 3% of the world population of any age, skin color, and sex but is more prevalent in adults than children. The condition often starts to manifest around the age of 20. Psoriatic arthritis affects 10 to 15% of the population and about 7 mil-

*Corresponding author tel. no: +234 8069151819
Email address: mabdul-hammed@lautech.edu.ng (Misbaudeen Abdul-Hammed)

lion Americans (2%–3% of the population) suffer from psoriasis. Each year, between 150,000 and 260,000 new cases are diagnosed [3]. Some conditions such as obesity, high blood pressure, and diabetes tend to increase the risk of developing psoriasis [4], while several conditions are linked to psoriasis which includes cardiovascular disease, severe depression, and lymphoma [5, 6]. Chronic interactions between invading, activated immune cells and hyperproliferative keratinocytes cause it to occur, which depend heavily on the immune system. Psoriatic lesions have high levels of T cells, especially Th1 and Th17 [7], while dendritic cells that produce TNF and iNOS also heavily infiltrate psoriatic skin and polarize T cells to the Th1 and Th17 subtypes [8]. Psoriasis can be in minor patches or complete body coverage depending on the degree of severity and type. The degree of severity of psoriasis depends on environmental exposure and family history [9].

As the rate of occurrence of psoriasis is between 2 to 4% of the world's population, researchers are on the verge of seeking permanent treatments for the disease. The treatment presently available for psoriasis is only used to manage the disease, which are; Topical medications, these are often used to treat mild to moderate psoriasis. They include the use of topical corticosteroids, vitamin D analogs, anthralin, retinoids, and calcineurin inhibitors. The skin thins due to the abuse of corticosteroids. Anthralin and vitamin D analogs (Calcipotriene and Calcitriol) slow the development of skin cells, get rid of scales, and smooth the skin. Along with other therapies, these analogs relieve mild to severe psoriasis, but they also irritate the skin. Similar to topical retinoids, which may reduce inflammation but irritate skin and heighten sensitivity to sunlight. Additionally, oral retinoids increase the risk of birth abnormalities and are not advised for use by women who are pregnant or nursing. Tacrolimus and pimecrolimus are two calcineurin inhibitors that similarly lessen inflammation and plaque buildup, but they also come with a higher risk of skin cancer [10]. Phototherapy (ultraviolet light) which uses UV can lead to thinning of the skin on exposure. Although skin cell turnover is slowed by UV exposure, which also lessens scaling and irritation, also small quantities of sunshine each day may help with psoriasis, prolonged contact with the sun can exacerbate the condition and harm the skin [11]. Systemic treatments (retinoids, methotrexate, cyclosporine, acitretin, hydroxyurea, fumarates) are used to treat patients with severe psoriasis, but they come with serious side effects. Retinoids may result in hair loss and lip irritation. Methotrexate treats psoriasis by reducing the growth of skin cells and reducing inflammation, but it can also make you tired and upset your stomach.

Methotrexate can harm the liver over time and reduce the synthesis of platelets, red blood cells, and white blood cells. Cyclosporine has comparable immunosuppressive effects as methotrexate, but it should only be used temporarily due to the danger of infection, cancer, renal issues, and high blood pressure when taken at large dosages or ongoing treatment [12]. Each time the disease manifests, all of these therapies are solely employed to control it [13]. So, to effectively treat psoriasis, new and safer chemical agents are thus urgently needed.

The need to manage psoriasis has usually been a lifelong one which used to result in a significant cost to mental well-being such as higher rates of depression and negative impact on individuals in a society. Social exclusion, discrimination, and stigmatization have always been associated. In the research and development of new drugs, phytochemicals are rapidly emerging as significant alternative medicinal and pharmacological agents. As opposed to synthetic medications, they have fewer or no adverse effects after administration, a unique mode of action, and a wide range of chemical constituents, all of which improve their therapeutic interaction with a variety of biological targets [14]. Phytochemicals derived from papayas such as flavonoids, terpenoids, tannins, and phenols have been found to have anti-psoriatic and antiinflammatory effects associated with psoriasis [15].

This study aims at investigating the anti-psoriatic and anti-inflammatory potential phytochemicals found in the Papaya plant against two psoriasis targeted enzymes; JAK1 (PDB ID: 6N7B) and TNFα (PDB ID: 2AZ5) through molecular docking coupled with ADMET studies, pharmacokinetic evaluation, drug likeliness among other analyses at a therapeutic dose as used previously in the study on enzyme inhibitors of SARS-COV2 main protease [16, 17] and human tyrosinase-related protein [18].

2. Materials and methods

2.1. Preparation of ligands

One hundred and three phytochemicals extracted from *Carica papaya* with their various classes of phytochemicals which are, 18 phenols, 5 amino acids, 2 carotenoids, 9 fatty acyls, 24 fatty acids, 24 flavonoids, 9 steroids, 4 terpenoids, and 3 Glycoside, 2 lactones and 3 organosulfur compounds were used in this investigation study.

Methotrexate and Cyclosporine are used as standard. PubChem database (https://pubchem.ncbi.nlm.nhi.gov) [19] was used to obtain the 2D/3D conformers of these ligands and the standard used. The 2D structure of these 103 ligands was converted to 3D using Spartan'14 software and the conformational search was also implemented using Spartan'14 as well with molecular mechanics in which the stable conformers were carefully chosen and optimized using density functional theory (DFT) with B3LYP function and 631+G(d) as a basis.

2.2. Preparation of the Target receptor

The Xray structure of tumor necrosis factor alpha (TNF alpha) (PDB ID: 2AZ5) and human Janus kinase JAK1 (PDB ID: 6N7B) (Fig 1) was downloaded from the protein data bank with a resolution of the retrieved structure given as 2.10Å and 1.81Å respectively in protein data bank (PDB) file format. The protein was prepared by removing the impurities including water molecules present using discovery studio software to escape interference. The binding pocket of the initial inhibitors present in 2AZ5 and 6N7B was used to determine the binding parameters as preferences.

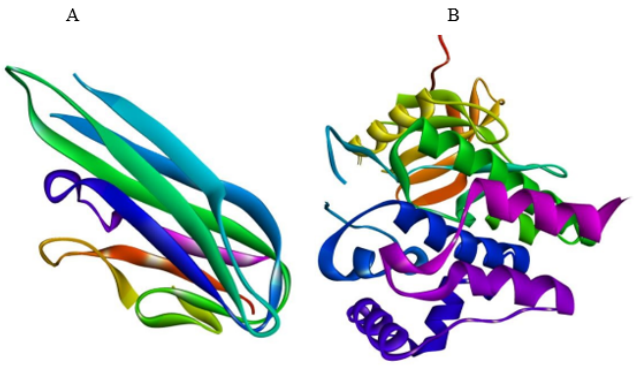


Figure 1. The Crystal Structure of (A) Tumor necrosis factor alpha (TNF-alpha) (PDB ID: 2AZ5) and (B) Human Janus kinase JAK1 (PDB ID: 6N7B)

2.3. Determination of receptors' active sites

Tumor necrosis factor alpha (TNF-alpha) (PDB ID: 2AZ5) and human Janus kinase JAK1 (PDB ID: 6N7B) binding pockets, ligand interactions, and all amino acids in the active site were established using CASTp (http://sts.bioe.uic.edu/castp-/index.html) and Biovia Discovery Studio [20]. Concerning the two receptor active sites complexed with their respective ligands, the obtained data were compared and validated against the previously published experimental data [21-23]

2.4. ADMET profiling and Drug likeness analysis

Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) of the docked ligands were evaluated using the ADMET SAR2 database (http://1mmd.ecust.edeu.cn/admetar2/) (www.admetexp.org) [24], which is a free web tool used in evaluating ADMET properties while drug-likeness (Lipinski rule of 5) were inspected using Molinspiration online tool (http://molinspiration.com/) [25].

2.5. Ligands oral bioavailability assessments

Oral bioavailability assessments of the ligands were achieved using the SwissADME web server (http://www.swissadme.ch/) [26].

2.6. Prediction of activity spectra for substances (PASS)

The biological activities of the ligands and the standard drugs used in this research study were carried out using a web server [27].

2.7. Molecular Docking Protocol

Molecular docking and scoring of optimized ligands and the standard drugs against tumor necrosis factor alpha (TNF-alpha) (PDB ID: 2AZ5) and human Janus kinase JAK1 (PDB ID: 6N7B) were obtained using PyRx software. The inhibition constants (Ki) in μM of the ligands and the standard method were obtained using their binding affinities (ΔG) in kcal/mol as shown in (equation 1), thus showing their potency against the target receptors (2AZ5 and 6N7B).

$$K_i = exp(\Delta G/RT) \quad (1)$$

Where R= Gas constant (1.987×10^3 kcal/mol); T=298.15K (absolute temperature); K_i= Inhibition constant and ΔG = Binding energy .

3. Results and Discussion

3.1. Structural and active site analysis of prostate cancer target receptors

3.1.1. Tumor necrosis factor alpha (TNF alpha)

The Xray crystallographic structure of tumor necrosis factor alpha (TNF alpha) (PDB ID: 2AZ5) (Fig. 1) contains 148 amino acid residues complexed with an inhibitor (6,7 dimethyl-3-[(methyl-{2[methyl-({1-[3(trifluoromethyl)phenyl]-1-hindol3yl}methyl)-amino] ethyl}amino)methyl]-4-chrome-4-one). The resolution of the protease as revealed by Xray diffraction was 2.10 Å, crystal dimension is a = 165.25 Å, b = 165.25 Å, and c = 63.72 Å with angles α (900), β (900), and γ (120) respectively. R values (free, work, and observed) are 0.278, 0.220, and 0.2127 respectively. TNFα plays a crucial role in the exacerbation of inflammation in psoriasis. Its main function is to control the immune system's cells. TNF is an endogenous pyrogen that can cause fever, apoptotic cell death, inflammation, cachexia, and cancer while also inhibiting virus replication and triggering IL1 and IL6producing cells in response to sepsis. Several human disorders, including Alzheimer's disease, cancer, severe depression, psoriasis, and inflammatory bowel disease have been linked to dysregulation of TNF production [28-31]. Amino acid residue at the active site is as follows Leu57, Tyr59, Ser60, Gln61, Tyr119, Leu120, Gly122, Tyr151 [21].

3.1.2. Human Janus kinase JAK1

The X-ray crystallographic structure of Human Janus Kinase JAK1 (PDB ID: 6N7B) (Fig.1) contains 302 amino acid residues complexed with N[3(5chloro2methoxyphenyl)-1methyl1Hpyrazol4yl]1Hpyrazolo[4,3c]pyridine7carboxamide. The resolution of the protease as revealed by X-ray diffraction was 1.81Å, crystal dimension is a = 170.28 Å, b = 42.78 Å, and c = 44.98 Å with angles α (900), β (900), and γ (900) respectively. Rvalues (free, work, and observed) are 0.264, 0.220, and 0.222 respectively. Through interactions with signal transducers and transcriptional activators, the Janus kinase (JAK) family, which consists of four receptor associated protein tyrosine kinases (JAK1, JAK2, JAK3, and TYK2), is involved in the interferon and cytokine signaling process [32]. Seven JAK homology domains make up the JAK kinases (120130 kDa) [33]. The catalytically active region of the protein that is in charge of its physiological action is known as the C-terminal kinase module (JH1) and it has been demonstrated that the catalytically inactive JH2 domain controls the JH1 domain's activity [34]. Two Src homology 2 (SH2) domains (JH3 and JH4) are located at the N-terminus, followed by the FERM domain (JH5–JH7). The ATP binding site, which is located in the JH1 domain, has been targeted by several small molecule inhibitors. Amino acid residue at the active site is as follows Leu881, Gly887, Glu883, Gly884, Gly887, Lys908, Glu957, Leu959, Gly962, Glu966, Arg1007, Asn1008, Leu1010, Gly1020, Asp1021 [21, 22].

Table 1. ADMET profiling of the selected Hit compounds and standard drug

Ligands	Absorption and Distribution				Metabolism					Extn.	Toxicity					
	BBB	HIA	LogS	Caco-2	2C19	1A2	3A4	2C9	2D6	B	AM	AOT	EI	EC	HI	C
L-1	0.96	0.99	-1.85	0.79	-	-	-	-	+	+	-	III	+	+	-	-
L-2	-0.44	0.98	-0.56	0.55	-	-	-	-	-	+	-	III	+	-	-	-
L-3	0.97	0.97	-2.42	0.93	-	-	-	-	-	+	-	III	+	+	-	-
L-4	0.9	0.98	-2.58	0.53	-	-	-	-	-	-	-	III	+	-	-	-
L-5	-0.99	0.99	-1.61	0.93	-	-	-	-	-	+	-	III	+	+	-	-
L-6	-0.44	0.96	-1.69	0.5	-	-	-	-	-	-	-	IV	+	-	-	-
L-7	-0.76	0.98	-1.35	0.92	-	-	-	-	-	+	-	III	+	+	-	-
L-8	-0.73	0.97	-0.22	0.85	-	-	-	-	-	+	-	III	+	+	-	-
L-9	-0.24	0.91	-2.48	-0.92	-	-	-	-	-	-	-	III	-	-	-	-
L-10	0.98	0.96	-1.75	0.62	-	-	-	-	-	-	-	III	+	-	-	-
L-11	-0.3	0.9	-2.46	-0.92	-	-	-	-	-	-	-	III	-	-	-	-
L-12	-0.39	0.99	-3.74	-0.95	-	-	-	-	-	+	-	III	+	-	-	-
L-13	-0.31	0.77	0.45	-0.84	-	-	-	-	-	+	-	III	+	-	-	-
L-14	-0.44	0.77	0.28	-0.96	-	-	-	-	-	+	-	III	+	-	-	-
L-15	0.97	0.84	-3.5	0.71	-	+	-	-	-	+	-	IV	+	+	-	-
L-16	0.99	0.84	-0.14	0.83	-	+	-	-	-	-	-	III	+	+	-	-
L-17	0.56	0.91	-4.04	0.9	-	+	-	-	-	+	-	IV	+	+	-	-
L-18	0.96	0.91	-4.04	0.71	-	+	-	-	-	+	-	IV	+	+	-	-
L-19	0.97	0.84	-3.5	0.71	-	+	-	-	-	+	-	IV	+	+	-	-
L-20	0.99	0.84	-0.14	0.83	-	+	-	-	-	+	-	III	+	+	-	-
L-21	0.97	0.84	-3.5	0.86	-	+	-	-	-	+	-	IV	+	+	-	-
L-22	0.97	0.84	-3.5	0.77	-	+	-	-	-	+	-	IV	+	+	-	-
L-23	0.97	0.84	-3.5	0.59	-	+	-	-	-	+	-	IV	+	+	-	-
L-24	0.97	0.84	-2.02	0.86	-	+	-	-	-	+	-	III	+	+	-	-
L-25	0.98	0.92	-3.67	0.68	-	-	-	-	-	-	-	III	+	+	-	-
L-26	0.95	0.89	-2.75	-0.7	-	-	-	-	-	-	-	III	-	-	-	-
L-27	0.94	0.89	-2.59	-0.66	-	-	-	-	-	-	-	III	-	-	-	-
SD-1	-0.99	0.9	-3.06	-0.86	-	-	-	-	-	-	-	III	-	-	-	-
SD-2	0.91	0.93	-1.76	-0.85	-	-	-	-	-	-	+	III	-	-	-	-

BBB= Blood Brain Barrier, HIA=Human Intestinal Absorption, AS =Aqueous Solubility. Extn. = Excretion; B=Biodegradation (+/-) Biodegradable (+), Non-biodegradable (-). AM =Ames mutagenesis (+/-); AOT= Acute Oral Toxicity(+/-) Acute toxic (+), Non acute-toxic (-); hI = Human either-a-go-go inhibition (+/-), C=Carcinogenicity (+/-) Carcinogenic (+), Non-carcinogenic (-). L1 = 2,6Dimethoxyphenol, L2 = Gentisyl Alcohol, L3 = Cinnamic acid, L4 = Sinapinic acid, L5 = Salicylic Acid, L6 = Caffeic Acid, L7=phydroxybenzoic acid, L8=pcoumaric acid, L9=Coumaroylquinic acid, L10=Chlorogenic Acid, L11=transLinalool oxide, L12 = PHydroxyl Benzoic, L1 = Citric acid , L14 = Malic acid, L15= nHexadecanoic acid, L16= Butanoic acid, L17=Linoleic acid, L18=Oleic acid, L19=Palmitic acid, L20=nButyric acidl, L21=nOctanoic acid, L22=Myristic acid L23=Stearic acid, L24=nHexanoic acid, L25=cisvaccenic, L26=Dehydrocarpaine I, L27=Dehydrocarpaine II, SD1=methotrexate, SD2=Cyclosporine

3.2. ADMET (pharmacokinetics) analysis of the selected compounds

Adsorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) profiling of ligands is a crucial step in the early stages of the drug discovery process for expediting the conversion of hits and lead compounds into approved candidates for therapeutic development. A high-quality drug candidate is highlighted by drugs' efficacies against therapeutic targets in conjunction with good ADMET profiling at a therapeutic dose [35, 36]. As part of the drug ADMET profile, a drug must possess good human intestinal absorption (HIA), solubility (Log S) which ranges between 1 and 5, should be a non-inhibitor of cytochrome P450 enzymes, and should be non-Ames toxic (AM), non-carcinogenic(C), non-inhibitor of HERG(HI), and no or low level of toxicity [37]. All the 103 compounds isolated from *Carica papaya* understudies were screened using ADMET SAR2 webserver, 27 passed the analysis, the result was shown in Table 1 and they were subjected to further analysis.

Notably, all the selected Hit compounds and the standard (STD) have excellent chances of being absorbed in the human intestine (HIA), some of the selected Hit compounds and STD2 can penetrate the blood brain barrier (BBB+), although only drugs that are specifically targeted for the central nervous sys-

Table 2. Drug Likeness properties of the best hits and two standard drugs (SD)

Compounds	Heavy Atoms (HA)	Molecular Weight (MW)	RO5 Violations	Hydrogen Bond Donor (HBD)	Hydrogen Bond Acceptor (HBA)	miLogP
L1	10	138.12	0	2	3	1.37
L2	12	164.16	0	2	3	1.43
L3	24	338.31	0	5	8	0.04
L4	11	146.15	0	0	2	2.01
L5	11	154.16	0	1	3	1.34
L6	10	140.14	0	3	3	0.71
L7	11	148.16	0	1	2	1.91
L8	16	224.21	0	2	5	1.26
L9	10	138.12	0	2	3	1.87
L10	12	170.25	0	1	2	1.94
L11	25	354.31	1	6	9	0.45
L12	16	222.28	0	2	3	3.83
L13	13	192.12	0	4	7	1.98
L14	9	134.09	0	3	5	1.57
L15	18	256.43	1	1	2	7.06
L16	6	88.11	0	1	2	1.00
L17	20	280.45	1	1	2	6.86
L18	20	282.47	1	1	2	7.58
L19	18	256.43	1	1	2	7.06
L20	6	88.11	0	1	2	1.00
L21	10	144.21	0	1	2	3.02
L22	16	228.38	1	1	2	6.05
L23	20	284.48	1	1	2	8.07
L24	8	116.16	0	1	2	2.01
L25	27	396.73	1	0	2	9.36
L26	34	476.70	1	1	6	6.60
L27	34	474.69	1	0	6	6.79
SD1	33	454.45	2	7	13	1.97
SD2	85	1202.63	2	5	23	3.61

L1 = 2,6Dimethoxyphenol, L2 = Gentisyl Alcohol, L3 = Cinnamic acid, L4 = Sinapinic acid, L5 = Salicylic Acid, L6 = Caffeic Acid, L7= phydroxybenzoic acid, L8=pcoumaric acid, L9=Coumaroylquinic acid, L10=Chlorogenic Acid, L11=transLinalool oxide, L12 = PHydroxyl Benzoic, L13 = Citric acid , L14 = Malic acid, L15= nHexadecanoic acid, L16= Butanoic acid, L17=Linoleic acid, L18=Oleic acid, L19=Palmitic acid, L20=nButyric acidl, L21=nOctanoic acid, L22=Myristic acid L23=Stearic acid, L24=nHexanoic acid, L25=cisvaccenic, L26=Dehydrocarpaine I, L27=Dehydrocarpaine II, SD1=methotrexate, SD2=Cyclosporine

tem must penetrate the blood brain barrier; oral drug may not always require to achieve this [38]. and all the Hit compounds and STD have excellent aqueous solubility (LogS) values, falling within the recommended range of (-1 to -5). This shows that the selected Hit compounds and the standard have good absorption and distribution potential. The metabolic activities of the selected Hit compounds were assessed using Microsomal Enzyme (Cytochrome P450 inhibitors) which catalysed reactions involved in the metabolic activities of the drug. As observed in Table 1, L1, L15 to L24 are non-inhibitors of all the CYP450 inhibitors. Moreover, critical observation of the results obtained in the Table 1 revealed that all the selected Hits are non-carcinogenic, Furthermore, the potential of a drug molecule to cause mutation in DNA is revealed by Ames toxicity value and could be a major reason for excluding a drug molecule along the discovery process, as shown in Table 1, all the selected hit compounds are non-AMES toxic. Similarly, the majority of the Hit compounds possess type III acute oral toxicity (LD50) values (slightly toxic) which could easily be converted to type IV (non-toxic) during hit lead optimization. L6, L15, L17, L18, L19, L21, L22, and L23 possess type IV which makes it nontoxic while SD1 possesses type II which means it is highly toxic. Interaction of drug candidates with human ether a-go-go (hERG) is one of the important factors to consider in selecting a good drug candidate. A good drug candidate is expected to be a non-inhibitor of hERG, because hERG inhibition may lead to blockage of the potassium ion channel of the myocardium, which will affect the heart, causing chronic health challenges, and that may lead to death [39]. As observed in Table 1, all selected Hits and STDs are non-hERG in-

Table 3. The docking scoring, binding affinities, and inhibition constant (K_i) of the interaction of passed ligands and the standard drug with human Janus kinase JAK1 (PDB ID: 6N7B)

Compounds	Binding Affinity (ΔG), kcal/mol	Inhibition constant (K_i), μM
Dehydrocarpaine-II	-10.5±0.0	0.02
Chlorogenic-acid	-8.6±0.0	0.50
Dehydrocarpaine-I	-7.9±0.0	1.60
Coumaroylquinic-acid	-7.9±0.0	1.60
Cis-vaccenic	-6.9±0.0	8.8
Sinapinic-acid	-6.5±0.0	18.8
Caffeic-acid	-6.6±0.0	15.9
Pcoumaric-acid	-6.3±0.0	24.2
Phydroxyl-Benzoic-Acid	-6.4±0.0	20.4
Cinnamic-acid	-6.1±0.0	33.9
Linoleic acid	-5.8±0.0	56.2
Oleic-acid	-5.7±0.0	66.5
Translinalool-oxide	-5.6±0.0	85.7
Stearic acid	-5.6±0.0	78.8
Citric-acid	-5.5±0.0	101.4
Myristic-acid	-5.4±0.0	110.4
Gentisyl Alcohol	-5.4±0.0	110.4
Palmitic-acid	-5.3±0.0	130.7
nHexadecanoic-acid	-5.2±0.0	168.3
2,6-Dimethoxyphenol	-5.2±0.0	168.3
Octanoic-acid	-5.1±0.0	183.1
Hexanoic-acid	-4.5±0.0	504.0
Malic-acid	-4.4±0.0	596.6
nButyric-acid	-3.9±0.0	1387.0
Butanoic-acid	-3.9±0.0	1387.0
Methotrexate	**-8.9±0.0**	**0.36**
Cyclosporine	**-8.0±0.0**	**1.62**

Table 4. The docking scoring, binding affinities, and inhibition constant (K_i) of the interaction of passed ligands and the standard drug with tumor necrosis factor alpha (TNF alpha) (PDB ID: 2AZ5)

Compounds	Binding Affinity (ΔG), kcal/mol	Inhibition constant (K_i), μM
Dehydrocarpaine-II	-7.6±0.0	2.7
Dehydrocarpaine-I	-7.5±0.0	3.2
Chlorogenic-acid	-6.2±0.0	28.7
Coumaroylquinic-acid	-5.5±0.0	93.3
Cinnamic-acid	-5.0±0.0	215.0
Sinapinic-acid	-4.9±0.0	256.9
Pcoumaric-acid	-4.9±0.0	256.9
Cis-vaccenic	-4.9±0.0	256.9
Caffeic-acid	-4.8±0.0	304.1
Phydroxyl_Benzoic-acid	-4.8±0.0	304.1
TransLinalool_oxide	-4.8±0.0	304.1
Linoleic acid	-4.5±0.0	504.7
Stearic acid	-4.4±0.0	597.1
Oleic-acid	-4.4±0.0	649.0
nHexadecanoic-acid	-4.4±0.0	649.0
Palmitic-acid	-4.2±0.0	836.8
nOctanoic-acid	-4.2±0.0	836.8
Myristic-acid	-4.2±0.0	836.8
Citric-acid	-4.1±0.0	990.5
Gentisyl Alcohol	-4.0±0.0	1172.6
2,6-Dimethoxyphenol	-3.8±0.0	1643.2
NHexanoic-acid	-3.7±0.0	1945.2
Malic-acid	-3.3±0.0	3819.8
nButyric- acid	-3.2±0.0	4521.9
Butanoic-acid	-3.2±0.0	4521.9
Methotrexate	**-6.4±0.0**	**23.3**
Cyclosporine	**-4.3±0.0**	**770.9**

hibitors. Summarily, all the selected Hit compounds and STDs show excellent ADMET properties and are better drug candidates against the target receptors.

3.3. Drug-likeness analysis of the selected ligands

As proffer by Lipinski 2004, orally active drugs must obey the rule of five

(RO5) which are, Molecular weight (MW) ≤ 500, octanol-water partition coefficient (Log P) ≤ 5, hydrogen bond donor (HBD) ≤ 5, and Hydrogen bond acceptor ≤ 10 and no more than one violation is allowed [40]. Drug-likeness of the selected phytochemicals with standard drugs was carried out to make a model that can successfully predict whether a molecule is druglike or not [20]. Out of 27 ligands isolated from *Carica papaya* that passed ADMET screening, all of them obeyed the Lipinski RO5 with violations of 1 and 0 except the two standard drugs having a violation of 2. These properties were estimated by an online server called molinspiration (http://www.molinspiration.com/) [41], and are shown in Table 2.

3.4. Molecular docking analysis

Molecular docking procedures can be used to recognize the interaction between a small ligand and a target molecule and to determine if they could behave in combination as the binding site of two or more constituent molecules with a given structure. A potential active drug is expected to have inhibitory values from 0.1 and 1.0μM and it should not be greater than 10nM. The inhibition constant was calculated using Ki = exp [ΔG/RT]. Where Ki = Inhibition constant, ΔG = Binding energy, R = Gas constant (1.937×103kcal/mol); T=298.15K (absolute temperature) [42]. Figure 1 shows the structure of tumor necrosis factor alpha (TNF alpha) (PDB ID: 2AZ5) and human Janus kinase JAK1 (PDB ID: 6N7B) that was used as the target proteins for this research. The 27 ligands that passed both ADMET and druglikeness parameters were docked separately with the

Table 5. Oral bioavailability Analysis of the selected compounds and the standard drug

Ligands	M.F	M.W	TPSA	#R.B	Xlog P3	ESOL logs	B.S.	Frac. CSP3	#Pain alert	S.A
C1	C28H46N2O4	474.68	77.32Å²	0	5.66	-6.35	0.55	0.86	0	7.34
C2	C16H18O9	354.31	164.75Å²	5	-0.42	-1.62	0.11	0.38	1	4.16
C3	C28H48N2O4	476.69	76.99Å²	0	5.97	-6.56	0.55	0.89	0	7.45
C4	C16H18O8	338.31	144.52Å²	5	-0.07	-1.75	0.56	0.38	0	4.07
SD1	C20H22N8O5	454.44	210.54Å²	10	-1.85	-1.19	0.11	0.25	0	3.58
SD2	C62H111N11O12	1202.61	278.80Å²	15	2.92	-8.15	0.17	0.79	0	10.00

M. F = Molecular formular, M.W = Molecular weight, #RB = Rotatable bond, B.S = Bioavailability score, S.A = Synthetic accessibility C1=Dehydrocarpaine_II, C2=Chlorogenic_acid , C3=Dehydrocarpaine_I , C4=Coumaroylquinic_acid, SD1=methotrexate , SD2=Cyclosporine

Table 6. Bioactivity Properties of the selected Ligands and standard drug with human Janus kinase JAK1 (PDB ID: 6N7B)

Bioactivity	C1	C2	C3	C4	SD1	SD2
AutoDock Vina docking score (kcal/mol)	-10.5	-8.6	-7.9	-7.9	-8.9	-8.0
Ki (μM)	0.02	0.50	1.60	1.60	0.36	1.62
miLog P	6.60	1.94	6.79	1.87	-1.97	3.6f1
Ligand efficiency (LE)/kcal/mol/heavy atom)	0.31	0.72	0.23	0.79	0.27	0.09
LE scale	0.30	0.58	0.30	0.61	0.31	0.03
Fit quality (FQ)	1.04	1.25	0.78	1.30	0.88	2.96
Ligand efficiency dependent lipophilicity (LELP)	21.37	2.71	29.22	2.37	-7.30	38.36

C1=Dehydrocarpaine-II, C2=Chlorogenic-acid, C3=Dehydrocarpaine-I , C4=Coumaroylquinic-acid , SD1=methotrexate, SD2=Cyclosporine

Table 7. Bioactivity Properties of the selected Ligands and standard drug with tumor necrosis factor alpha (TNF alpha) (PDB ID: 2AZ5)

Bioactivity	C1	C2	SD1	SD2
AutoDock Vina docking score (kcal/mol)	-7.6	-7.5	-6.4	-4.3
Ki (μM)	2.70	3.20	23.30	770.9
miLog P	6.60	6.79	-1.97	3.61
Ligand efficiency (LE) /kcal/mol/heavy atom)	0.22	0.22	0.19	0.05
LEscale	0.30	0.30	0.31	0.03
Fit quality (FQ)	0.75	0.74	0.63	1.59
Ligand efficiency dependent lipophilicity (LELP)	30.338	29.92	-10.16	71.36

C1=Dehydrocarpaine_II, C2=Dehydrocarpaine_I, SD1=methotrexate, SD2=Cyclosporine

Table 8. PASS prediction of the passed ligands and standards

COMPOUNDS	P_a	P_i	ACTIVITY
Chlorogenic-acid	0.52	0.02	Antipsoriatic
	0.6	0.03	Antiinflammatory
	0.7	0.02	Immunosuppressant
Coumaroylquinic-acid	0.51	0.02	Antipsoriatic
	0.71	0.02	Immunosuppressant
	0.65	0.02	Antiinflammatory
Methotrexate	0.23	0.11	Antipsoriatic
Cyclosporine	0.86	0	Immunosuppressant
	0.42	0.19	Antieczematic
	0.27	0.09	Antipsoriatic
	0.28	0.18	Antiinflammatory

receptors, (PDB ID: 2AZ5) and (PDB ID: 6N7B), the major cytokines (TNFα) exacerbated in psoriasis, and inflammatory pathways particularly JAK1 which are responsible for the initiation, progression, and exacerbating the disease's development. The docking results of the passed ligands with both good ADMET and drug-likeness profiles were reported in Table 3 and 4. Dehydrocarpaine-II had -10.5kcal/mol, Chlorogenic-acid had -8.6kcal/mol, Dehydrocarpaine-I and Coumaroylquinic-acid had -7.9kcal/mol, cis-vaccenic had 6.9kcal/mol while Methotrexate and Cyclosporine had -8.9kcal/mol and -8.0kcal/mol binding energy values with the target protein (PDB ID: 6N7B). Dehydrocarpaine-II and Dehydrocarpaine-I had -7.6kcal/mol and -7.5kcal/mol while Methotrexate and Cyclosporine had -6.4kcal/mol and -4.3kcal/mol binding energy values with the second target protein (PDB ID: 2AZ5). This show that Dehydrocarpaine-II, Chlorogenic-acid, and Dehydrocarpaine-I have higher binding affinity than the two standard drugs, Methotrexate and Cyclosporine.

3.5. Oral bioavailability Analysis of the selected ligands and standard

The compounds with good ADMET and drug-likeness profiles were docked with the choice target receptor. And the compounds that interact with the amino acid residue in the active site pocket were subjected to oral bioavailability analysis obtained through the SwissADME web tool (http://www.swissadme.ch/) [26]. The bioavailability radar of the compounds and the standard is presented in Figure 2, showing the pink area of the

Table 9. Receptor amino acids forming Hydrogen bond and other Electrostatic/ Hydrophobic interaction with passed ligands

Compounds	Binding Affinity (ΔG), kcal/mol	6N7B Receptor amino acids forming Hbond ligands	Electrostatic/Hydrophobic Interactions involved	Inhibition constant (K_i), μM
Chlorogenic_acid	-8.6±0.0	Phe282, Leu959, Asn1008, Arg1007,	Val889, Leu1010, Asp1021, Lys908	0.50
Coumaroylquinic-acid	-7.9±0.0	Lys908, Asp1021, Gly887, Asp1003, Arg1007, Glu925	Gly1023	1.60
Methotrexate	-8.9±0.0	His918, Gly887, Phe886, Asp1021, Gly1020	Ala906, Leu1010, Met956, Gly1023, Arg1007, Asn1008, Val889	0.36
Cyclosporine	-8.0±0.0	Asp880, Glu883, Arg879, Pro960	His918, Asn1008, Leu1010, Ala906, Val889, Gly882, Asp1021, Asp921, Phe958, Leu959, Arg1007, Leu881, Glu966, Lys970, Asp1003, 886	1.62

radar for the optimum zone for each of the properties (POLAR, FLEX, LIPO, SIZE, INSOLU, and INSATU). The recommended ranges for the properties as revealed in Table 4 are -0.7 and +5.0 for lipophilicity (XLOGP3), 500g/mol for Molecular weight (MW), 20-130 $Å^2$ for Total Polar Surface Area (TPSA), ≤6 for Solubility (LogS), 0.25-1.0 for Fraction of carbon in the Sp^3 hybridization (INSATU), and ≤9 for Rotatable bond for an effective drug candidate [38]. The molecular weight (<500), as well as the Solubility of water (Esol logs) for the selected compounds, were analyzed in the acceptable range with an exception for SD2 (1202.61 g/mol). The partition coefficient (Xlog P3), a very crucial parameter ranges for all the compounds from -0.07 to 5.66 with an exception for C3 (5.97). The saturation; a fraction of carbons in the sp3 hybridization range from 0.25 to 0.86 and both SD1 and SD2 has rotatable bonds of more than 9 while C2, C4, SD1, and SD2 failed the polarity with TPSA value of 164.75Å², 144.52Å², 210.54Å², and 278.80Å² respectively. C2 and C4 can still be orally bioavailable because they are not too flexible while the two standards are predicted not to be orally bioavailable, because too flexible and too polar [26]. The passed ligands are further subjected to other analyses.

3.6. Bioactivity test of the selected ligands and standard drug

Table 3 reveals the bioactivity properties of the selected ligands and standards showing the Ligand Efficiency (LE) with a recommended range of ≥0.3, Fit Quality (FQ) with a recommended range of ≥0.8, and Ligand efficiency dependent lipophilicity (LELP) with a recommended range of -10 to 10 [43], which was calculated using Eqn, 2-5. All the selected ligands were reported in Table 6 and 7, only C2 and C4 in Table 6 has an excellent bioactivity profile with all their values within the recommended range and are subjected to further analysis.

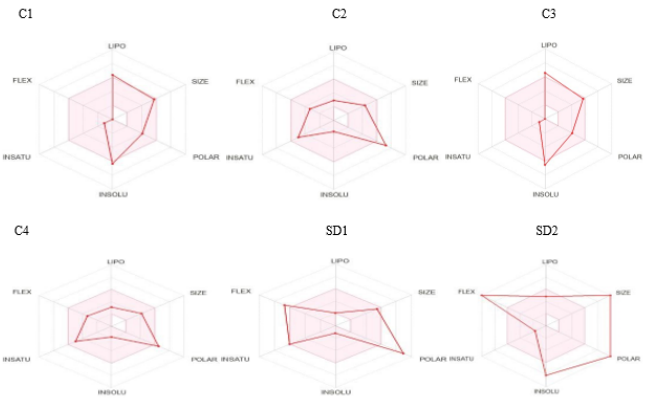


Figure 2. The bioavailability radar for the selected hit compounds and Standards (C1) Dehydrocarpaine-II; (C2) Chlorogenic-acid; (C3) Dehydrocarpaine-I; (C4) Coumaroylquinic-acid; (SD1) methotrexate; and (SD2) Cyclosporine

$$\text{Ligand Efficiency (LE)} = -(B.E) \div \text{Heavy atoms (H.A)} \quad (2)$$

$$\text{L.E scale} = 0.873e - 0.026 \times \text{H.A} - 0.064 \quad (3)$$

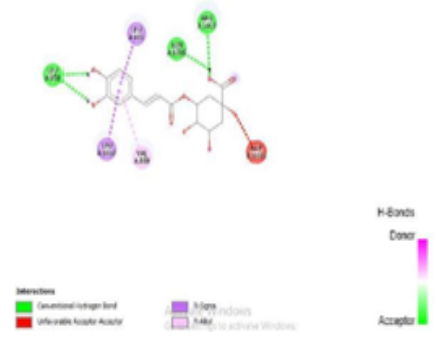
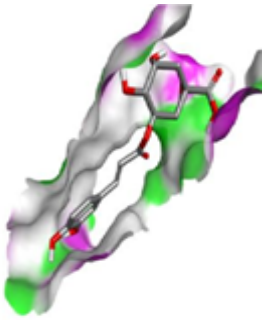
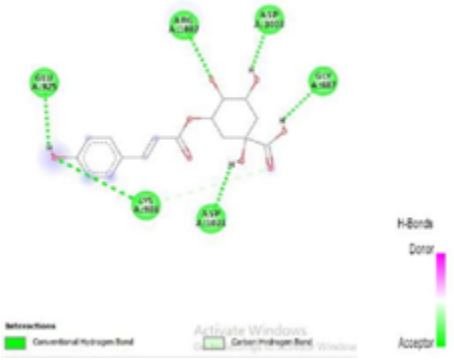
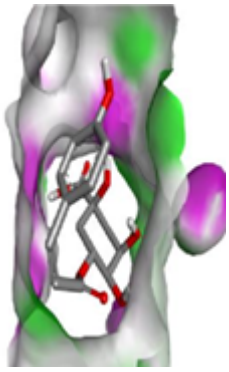
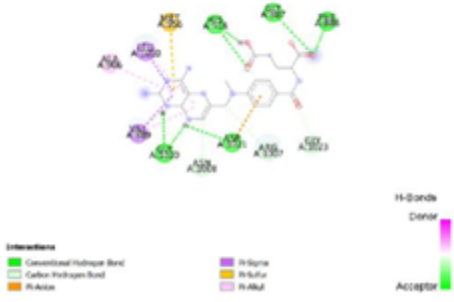
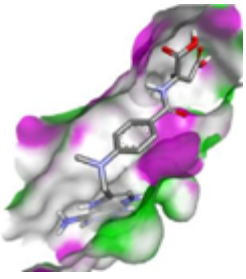
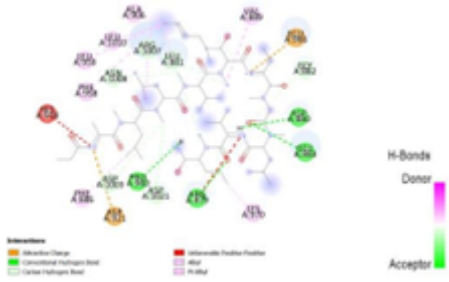
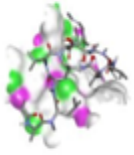
$$\text{FQ} = \text{LE} \div \text{LEscale} \quad (4)$$

$$\text{LELP} = \text{LogP} \div \text{LE} \quad (5)$$

3.7. Prediction of Activity Spectra for Substances (PASS) Biological Activity Prediction of the Selected Compounds and Standard

A computer-based program for an online web server PASS software [27] was used for the prediction of the biological activity of the selected compounds**.** As shown in Table 8 the

Table 10. Binding mode and binding interaction for passed ligands

Ligands	Binding interaction	Binding mode
Chlorogenic_acid		
Coumaroylquinic acid		
Methotrexate		
Cyclosporine		

value of the probability to be active must be greater than the probability to be inactive. This works in hand with the activity spectrum concerning the high probability to be active (Pa) to the probability to be inactive (Pa > Pi). All the ligands in Table 8 show excellent biological activity against psoriasis, Chlorogenic-acid, and Coumaroylquinic-acid displayed Anti-psoriatic activity, Anti-inflammatory, and Immunosuppressant activity. They both can be further explored in the development of novel drugs for the management, prevention, and curing of psoriasis.

3.8. Binding Mode and Molecular Interactions of the Best Hit Compound and the Standard

In the lead optimization stage of drug development, the molecular interactions and binding mode involved in the binding of ligands to the target receptors' active site are of utmost importance. It aids in improving the potency and efficacy of the selected hit compounds. Notably, all analyses performed so far on the phytochemicals from *Carica papaya*, Chlorogenic-acid, and Coumaroylquinic-acid showed outstanding results owing to their excellent binding affinities and inhibition constant, excellent ADMET properties, drug-likeness properties, bioactive, orally bioavailable analysis and Pass analysis. The binding modes of Chlorogenic-acid and Coumaroylquinic-acid suggest that these compounds neatly fit at the active site of JAK1 where Lys908, Arg1007, Asn1008, Leu959, Gly887, Asp1003, and Asp1021 particularly stabilize these compounds through conventional H-bonding. Hydrophobic/electrostatic interactions are also reported to participate and for 6N7B_Chlorogenic-acid, the hydrophobic interactions include Val889, Leu1010, Asp1021, and Lys908 while for 6N7B_Coumaroylquinic-acid we have Gly1023. Similarly, the standard drugs (Methotrexate and Cyclosporine) formed a conventional hydrogen bond with His918, Gly887, Phe886, Asp1021, Gly1020, and Asp880, Glu883, Arg879, Pro960. Hydrophobic/electrostatic interactions with Ala906, Leu1010, Met956, Gly1023, Arg1007, Asn1008, Val889 and His918, Phe958, Asn1008, Leu959, Leu1010, Arg1007, Ala906, Leu881, Val889, Glu966, Gly882, Lys970, Asp1021, Asp1003, Asp921, Phe886. As expected, Arg1007 and some other important amino acid residues are common to Chlorogenic-acid, Coumaroylquinic-acid, and the standard drugs (Methotrexate and Cyclosporine) showing that they shared similar binding pockets and interactions with the active site of human Janus kinase JAK1. The molecular interaction and binding mode are displayed in the tables below.

4. Conclusion

The anti-psoriatic potential of Carica papaya was explored via in silico studies. The structure-based screening was employed by using molecular docking simulation, ADMET profiling, Lipinski Rule of 5 (RO5), and other analysis for the target fishing of phytochemicals isolated from papaya against 2 possible targets of psoriasis. Major cytokines, tumor necrosis factorα (TNF-α) exacerbated in psoriasis and inflammatory pathways particularly Janus Kinase 1 (JAK 1). This computational analysis reflects that papaya can serve as excellent anti-psoriatic and anti-inflammatory agents by targeting human anti-inflammatory molecular targets (JAK 1). The results obtained revealed Chlorogenic acid (- 8.6 kcal/mol) and Coumaroylquinic acid (- 7.9 kcal/mol) as probable inhibitors of Janus Kinase 1 (JAK 1) compare to the two standard Methotrexate (- 8.9 kcal/mol) and Cyclosporine (- 8.0 kcal/mol) due to their excellent binding energies, ADMET profile, drug-likeness, oral bioavailability properties, PASS properties, Bioactivity, outstanding binding mode and molecular interactions with the target receptor and can serve as promising chemical scaffolds for the development and improvement of inhibitors to treat psoriasis.

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