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IN SILICO STUDY OF PHYSALIS ANGULATA COMPOUNDS AS POTENTIAL THERAPEUTICS FOR ECZEMATIC SKIN DISEASES

Yan Martin Witantra
Universitas Pertahanan Republik Indonesia
Email yanmartinwitantra@gmail.com

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Abstract

Eczema, a broad term encompassing a number of chronic inflammatory skin disorders, is typically characterized by symptoms such as redness (erythema), itching (pruritus), dryness, thickening of the skin due to repeated scratching (lichenification), and the possible appearance of fluid (exudation) or small blisters (vesicles). IL-4 and IL-13 activate the JAK-STAT pathway through the IL-4Rα and IL-13Rα1 receptors, which promotes STAT6 activation and the inflammatory response in atopic dermatitis, thus providing the basis for the use of upadacitinib as a selective JAK1 inhibitor that is effective in alleviating the symptoms of the disease. The aim of this study was to explore potential therapeutic pathways, with particular attention to compounds present in *Physalis angulata* , including the withanolide group such as withangulain B, physagulin C, and withanolide, which is one of 41 groups of compounds that have been identified in *Physalis angulata* . In addition, this study also evaluated the control drug upadacitinib, which is designed to target the IL-4Rα and IL-13Rα1 receptors, which play a key role in the type 2 (Th2) immune response. The study utilized several computational techniques, including data mining, biological activity analysis, ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) profiling, molecular mapping, and in silico studies. The results showed that the binding energies of the ligands (Physagulin C and Withangulatin B) with the IL-4Rα receptor were -12.6 kcal/mol and -12.7 kcal/mol, respectively. Similarly, Withanolide and Withagulatin B were identified as the top candidate compounds for the IL-13Rα1 receptor, with binding energies of -11.5 and -11.5 kcal/mol, respectively. The interactions above are the most beneficial for the development of eczematic disease therapy. The overall results of this study demonstrate great potential, indicating that the withanolide compounds, physagulin c, and withangulatin B derived from *Physalis angulata* offer an alternative pathway in targeting immune cells (Th2) through JAK-STAT activation and STAT6 translocation to the nucleus. Therefore, this study opens up opportunities for the development of innovative therapies in the treatment of eczematic diseases.

Keywords : eczematic, withangulain B, physagulin C, and withanolide, IL-4Rα receptor, IL-13Rα1 receptor, molecular docking

INTRODUCTION

Eczema is a general term encompassing a variety of chronic inflammatory skin conditions characterized by symptoms such as erythema (redness), pruritus (itching), dry skin, lichenification, and sometimes exudation or vesicles. One of the most common forms of eczema is atopic dermatitis, which often begins in childhood and can persist into adulthood (Rerknimitr et al., 2017). Eczema is caused by a complex interaction between genetic factors, impaired skin barrier function, immune system dysregulation, and environmental influences. A compromised skin barrier allows allergens and irritants to enter, which then trigger an inflammatory immune response, resulting in the characteristic symptoms of eczema, such as itching and skin inflammation (Rerknimitr et al., 2017). According to (Bieber, 2008), atopic dermatitis is a prototype of an eczematic disease involving significant immunological dysregulation and a genetic predisposition to impaired epidermal function and allergic sensitivity. Meanwhile, (Silverberg & Hanifin, 2013)the prevalence of eczema is increasing globally, with the disease burden significantly impacting patients' quality of life. Eczema, particularly atopic dermatitis (AD), is one of the most common chronic inflammatory skin diseases worldwide. Globally, the prevalence of AD is estimated at 10–20% in children and 1–3% in adults. (Nutten, 2015).Data from *Global Burden of Disease Study (GBD), 2021*states that more than 129 million people live with atopic dermatitis, with some reports estimating the number as high as 204 million cases, making it

one of the skin diseases with the highest burden of disability (DALY) (GBD , 2021; Karimkhani et al., 2017). The prevalence is higher in developed countries than in developing countries, which is influenced by lifestyle, allergen exposure, and other environmental factors.(Deckers et al., 2012) In Indonesia, data from *(RISKESDAS, 2010)*shows the prevalence of dermatitis in general is 6.8%, with quite large variations between provinces, with South Kalimantan reaching the highest figure at 11.3% and West Sulawesi the lowest at 2.57% (Ministry of Health of the Republic of Indonesia, 2010). More recent local studies, such as those conducted by by (Sainah et al., 2024)show a much higher figure, namely 60.79% in the Islamic boarding school population, especially among women of productive age. The South Sumatra Health Office also noted that of the total population of 7.3 million, approximately 35.25% suffer from dermatitis, indicating that this disease remains a significant public health problem in Indonesia. Indonesia is known as a mega-biodiversity country rich in natural resources, including medicinal plants that have the potential to be used in the development of new therapies. One native Indonesian plant with high pharmacological potential is the ground cherry (Physalis angulata L.), which has traditionally been used as an anti-inflammatory, anti-allergic, and antimicrobial agent (Fadhli et al., 2023). Plant parts such as the leaves and fruit contain active compounds such as withanolides, flavonoids, and steroids, which are believed to contribute to these pharmacological activities. The potential of biological resources such as ground cherry presents a significant opportunity for the development of alternative therapies for inflammatory skin diseases such as atopic dermatitis.

Given the high incidence of eczema, both globally and locally, new therapies are needed that are not only effective but also safe and accessible. Conventional medications such as topical corticosteroids and antihistamines often have long-term limitations, such as the risk of side effects, resistance, and are not suitable for all patients (Boguniewicz & Leung, 2010). Therefore, a new approach is needed through the selection and exploration of candidate active compounds from medicinal plants with anti-inflammatory and immunomodulatory effects to support safer and more sustainable eczema therapy. One modern approach to screening potential compounds from plants is through the molecular docking method. Molecular docking is a computer simulation used to predict the affinity and interaction between active compounds (ligands) and protein targets relevant to disease mechanisms, such as inflammatory enzymes like COX-2 or NF-κB. This method is efficient, cost-effective, and capable of identifying candidate bioactive compounds in silico before further biological testing (Meng et al., 2011). With this approach, compounds from plants such as ground cherry can be selected for their potential in suppressing the inflammatory mechanisms underlying eczema.

This study emphasizes the key role of interleukins IL-4 and IL-13 in activating the type 2 immune response that plays a role in chronic inflammatory conditions such as atopic dermatitis (Guttman-Yassky et al., 2018). These two cytokines bind to the IL-4Rα and IL-13Rα1 receptors, forming a type I and II receptor complex that triggers the activation of the JAK-STAT signaling pathway, specifically JAK1 and JAK3, which then phosphorylate and activate STAT6 (LaPorte et al., 2008; Nelms et al., 1999). Activated STAT6 will translocate to the cell nucleus to regulate gene expression that increases Th2 cell activity, IgE production, and inflammation. This pathway is the basis for the development of therapies such as upadacitinib, a selective JAK inhibitor that works by indirectly inhibiting signaling from IL-4 and IL-13 through JAK1 blockade, thus effectively relieving symptoms in moderate to severe atopic dermatitis.(Guttman-Yassky et al., 2021). Based on this, Indonesia's biological potential, particularly that of the ground cherry plant, deserves further study as a candidate for eczema therapy. The use of molecular docking methods provides a strong scientific basis for selecting and validating the interactions of active compounds with inflammatory targets. It is hoped that the results of this research will contribute to the development of safe, effective, and sustainable alternative treatments based on native Indonesian plants for eczema therapy.

METHOD

Data Mining

The compound data we used came from a literature study containing 43 compounds in *Physalis angulata* (Fadhli et al., 2023; Fitrianingsih et al., 2025; Indradi et al., 2025; Jonsen Subagio, 2024; Rengifo-Salgado & Vargas-Arana, 2013). We screened the existing compounds into four potential compounds for each receptor we determined. The potential compounds obtained include Physagulin C (CID 85155112), Withangulatin B (CID 16757497), and Withanolide (CID 53477765). The available receptors were obtained from the NCBI protein database. The proteins in this study include the cytokines IL-4Rα (PDB ID: 7VIF) and IL-13Rα1 (PDB ID: 7WF7).

Bioactivity Analysis of compounds

The activity of bioactive molecules was predicted using Way2Drug software, accessible at https://www.way2drug.com/passonline/ . The Simple Molecular Path Entry System (SMILES) chemical notation for

each compound was obtained from the PubChem database, matched to the PubChem ID for each substance. The data selected for analysis met specific criteria, with a requirement of Pa>0.7.

Absorption, distribution, metabolism, excretion, and toxicity (ADMET) analysis

ADMET encompasses absorption, distribution, metabolism, excretion, and toxicity parameters of compounds during the drug development process. ADMET profiles are generated in silico to anticipate the pharmacological and toxicological properties of potential drugs, particularly during the early stages of research. This computational model focuses on improving ADMET predictions, which is crucial for drug optimization and preventing late-stage setbacks. Leveraging this predictive model can avoid such failures, which can be time-consuming and costly. The capabilities of pkCSM-pharmacokinetics were utilized in this experiment. The web tool, found at https://biosig.lab.uq.edu.au/pkcsm/, offers an innovative approach to estimating and optimizing ADME/Tox properties of small molecules. This method utilizes graph-based signatures and experimental data.

Molecular Modeling

Computational techniques have long been used to predict 3D structures without experimental data. The application of the AlphaFold deep learning algorithm, a key biomedical tool, has revolutionized structural biology. AlphaFold 2 accepts protein sequences and template structures as input. Google Colab (https://colab.research.google.com/github/sokrypton/ColabFold/blob/v1.2.0/AlphaFold2.ipynb) is used to project 3D structures based on target sequences retrieved from the NCBI database.

Protein assessment

We used geometric and stereochemical standards to assess model quality. The PDBsum tool, accessible at http://www.ebi.ac.uk/pdbsum, was used to perform this evaluation. This tool plays a crucial role in validating PDB structures and focuses on stereochemical accuracy and predictive model accuracy. Calculation of Ramachandran plots, which examine the torsion angles Ø and Ψ within a protein's amino acid residues, is the basis for the assessment. The results are expressed as percentages and categorize areas as core, allowed, or disallowed. This provides a comprehensive measure of the quality of a protein structure.

Molecular docking

All ligands were prepared using software in *.sdf format* and receptors in *.pdbqt format* . The docking process was carried out using AutoDock 4. For the IL-4Rα receptor (PDB ID: 7VIF) with the ligand Physagulin C, the Vina search box dimensions include the X (22), Y (34), and Z (32) axes, with the center points at X (127), Y (132), and Z (144). In the IL-4Rα receptor (PDB ID: 7VIF) with the ligand Withangulatin B, the Vina search box dimensions include the X (24), Y (34), and Z (32) axes, with the center points at X (127), Y (132), and Z (144). Meanwhile, in the IL-13Rα1 (PDB ID: 7WF7) with the ligand Withangulatin B, the search box dimensions include X (35), Y (24), and Z (35), with the center points at X (134), Y (166), and Z (159). on IL-13Rα1 (PDB ID: 7WF7) with ligand Withanonlide the search box dimensions include X (35), Y (23), and Z (35), with centers at X (134), Y (166), and Z (159). The docking process between the ligand and all proteins was carried out using CbDock2 (http://clab.labshare.cn/cb-dock/), with binding energy selected based on the most negative energy. The docking results between proteins and compounds were visualized using Biovia Discovery Studio Visualizer.

RESULT

Bioactivity of *Physalis angulata* compounds

According to the results of the Prediction of Activity Spectra for Substances (PASS) server (Figure 1), it is shown that the compounds Physagulin C, Whitanolide, and whitangulatin B show the possibility of functioning as Antieczematic. However, data on the three compounds also indicate their function as antineoplastic, antifungal, immunosuppressant, and antiprotozoal inhibitors. All three compounds show significant biological activity, including antineoplastic and aneczematic effects.

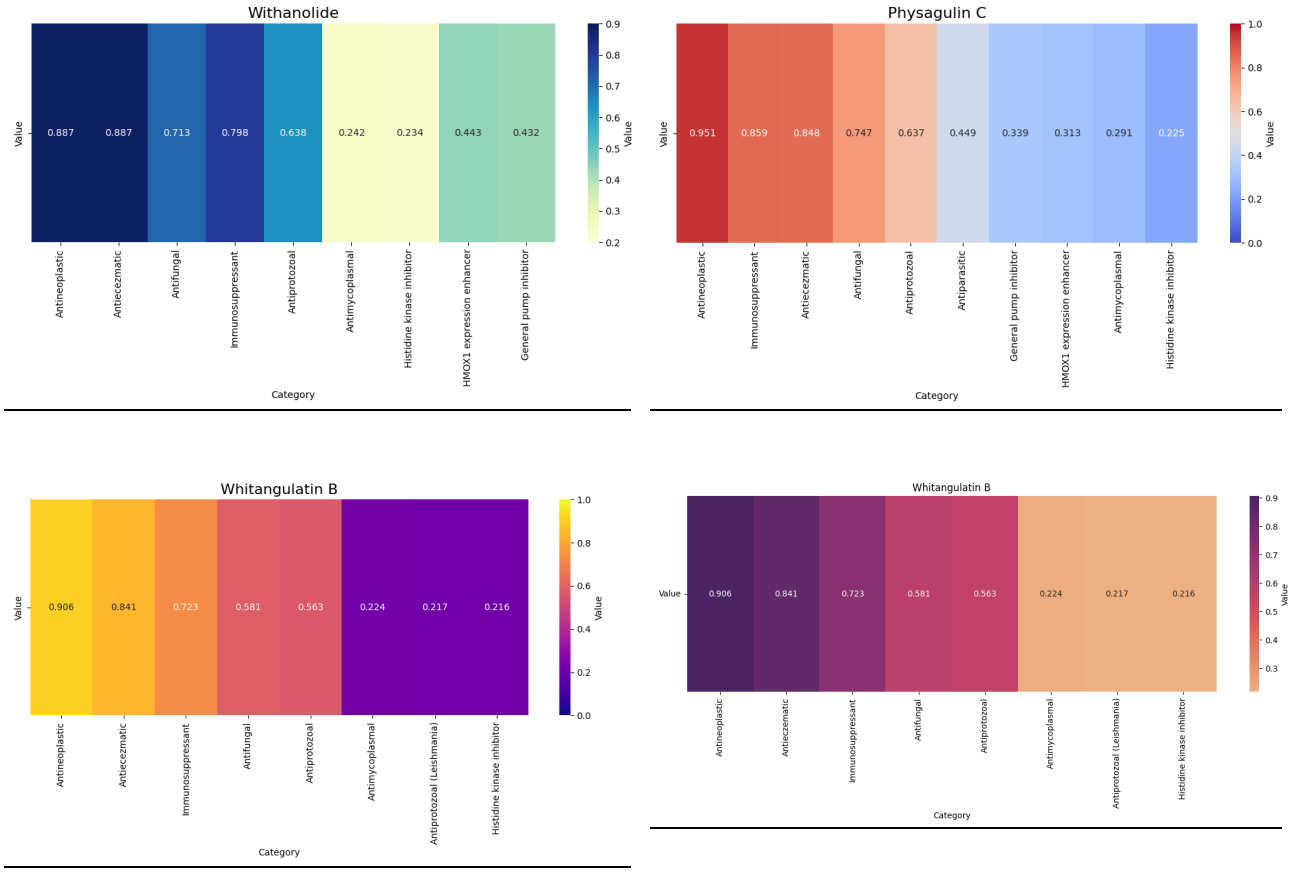


Figure 1. Prediction of Activity Spectra for Substances server results.

ADMET of *Physalis angulata*

As predicted by the pKCSM model (Table 1), categorizing substances based on Caco-2 permeability is crucial for evaluating their ability to be properly absorbed by the gut. Notably, all compounds exceeded the threshold of 0.90, indicating high Caco-2 permeability and likely significant absorption. In contrast, physalin F did not reach this threshold, indicating lower Caco-2 permeability and likely limited absorption. Compounds with an absorption rate of less than 30% through the human gut are considered poorly absorbed according to the pkCSM guidelines. Therefore, these compounds can be categorized accordingly. The absorption rate of withanolide (80.639%) and physalin (81.744%) is excellent. This indicates a significant ability for effective absorption in the human intestinal tract, an important feature in pharmaceutical applications. In addition, physalin F is considered highly absorbed because it shows an absorption rate of 100%. While withaphysalin A, with 98.421%, and withanolide A show an intestinal absorption rate of 100%. However, absorption based on glycoprotein P is physalin, a compound that can be absorbed in the presence of glycoprotein P 2 inhibitors, and physalin F interacts with glycoprotein P as a substrate. In contrast, withanolide does not interact with glycoprotein P.

Table1. pKCSM results of Physagulin C, whitanolide, and whitangulatin B

Property	Model	Unit	Physagulin C	Withangulatin B	Withanolide
Abs	Water solubility	Numeric (log mol/L)	-5,093	-4,717	-5.127
Abs	Caco-2 permeability	Numeric (log Papp in 10-6 cm/s)	0.83	0.354	0.831
Abs	Intestinal absorption (human)	Numeric (% Absorbed)	100	79,242	99.2
Abs	Skin permeability	Numeric (log Kp)	-2.87	-2,754	-3,267
Abs	P-glycoprotein substrate	Categorical (Yes/No)	Yes	Yes	Yes
Abs	P-glycoprotein I inhibitor	Categorical (Yes/No)	Yes	No	Yes
Abs	P-glycoprotein II inhibitor	Categorical (Yes/No)	Yes	No	Yes
Dis	VDss (human)	Numeric (log L/kg)	0.029	-0.063	-0.048
Dis	Fraction unbound (human)	Numeric (Fu)	0.273	0.436	0.093
Dis	BBB permeability	Numeric (log BB)	-0.875	-1.02	-0.315
Dis	CNS permeability	Numeric (log PS)	-3.13	-3,292	-2,696
Met	CYP2D6 substrate	Categorical (Yes/No)	No	No	No
Met	CYP3A4 substrate	Categorical (Yes/No)	Yes	No	Yes
Met	CYP1A2 inhibitor	Categorical (Yes/No)	No	No	No
Met	CYP2C19 inhibitor	Categorical (Yes/No)	No	No	No

Met	CYP2C9 inhibitor	Categorical (Yes/No)	No	No	No
Met	CYP2D6 inhibitor	Categorical (Yes/No)	No	No	No
Met	CYP3A4 inhibitor	Categorical (Yes/No)	No	No	No
Exc	Total clearance	Numeric (log ml/min/kg)	0.254	0.444	0.347
Exc	Renal OCT2 substrate	Categorical (Yes/No)	No	No	No
Tox	Ames toxicity	Categorical (Yes/No)	Yes	No	No
Tox	Maximum tolerated dose (human)	Numeric (log mg/kg/day)	-0.813	-0.359	-0.867
Tox	hERG I inhibitor	Categorical (Yes/No)	No	No	No
Tox	hERG II inhibitor	Categorical (Yes/No)	No	No	No
Tox	Oral rat acute toxicity (LD50)	Numeric (mol/kg)	4,007	4,042	2,831
Tox	Oral rat chronic toxicity (LOAEL)	Numeric (log mg/kg_bw/day)	1,868	2,685	1,776
Tox	Hepatotoxicity	Categorical (Yes/No)	No	No	No
Tox	Skin sensitization	Categorical (Yes/No)	No	No	No
Tox	Skin T. pyriformis toxicity	Numeric (log ug/L)	0.285	0.285	0.305
Tox	Minow toxicity	Numeric (log mM)	4.16	5.108	1,178

BBB: blood-brain barrier, CNS: central nervous system. Abs: absorption, Met: metabolism, Dis: distribution, Exc: excretion, Tox: toxicity.

Molecular modeling and assessment

Molecular modeling in this study produced the results of the Ramachandran plot (Figure 2), and successfully generated models for both the cytokine receptors IL-4Rα (PDB ID: 7VIF) and IL-13Rα1 (PDB ID: 7WF7). The quality assessment of IL-4Rα (PDB ID: 7VIF), which consists of 1135 residues, revealed that 90.9% of the residues are in the favored and allowed regions, with the remaining 9.1% being in the disallowed regions. While the quality assessment for IL-13Rα1 (PDB ID: 7WF7, which consists of 1035 residues, revealed that 85.6% of the residues are in the favored and allowed region, with the remaining 14.4% being in the disallowed region. This finding indicates that the quality of IL-4Rα (PDB ID: 7VIF) is more promising, but does not rule out the potential for IL-13Rα1 (PDB ID: 7WF7 as well. So both are suitable for further analysis.

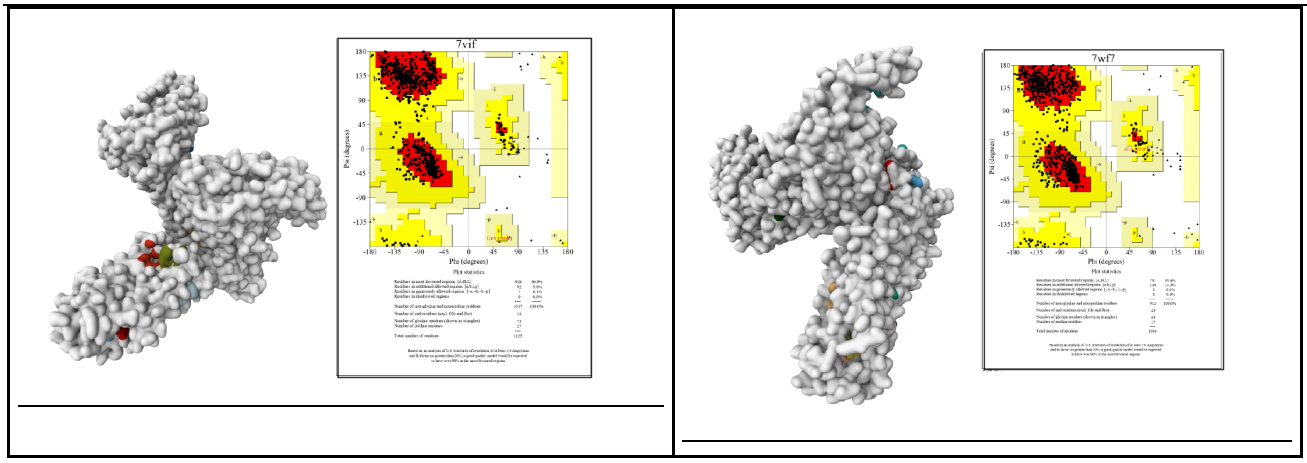
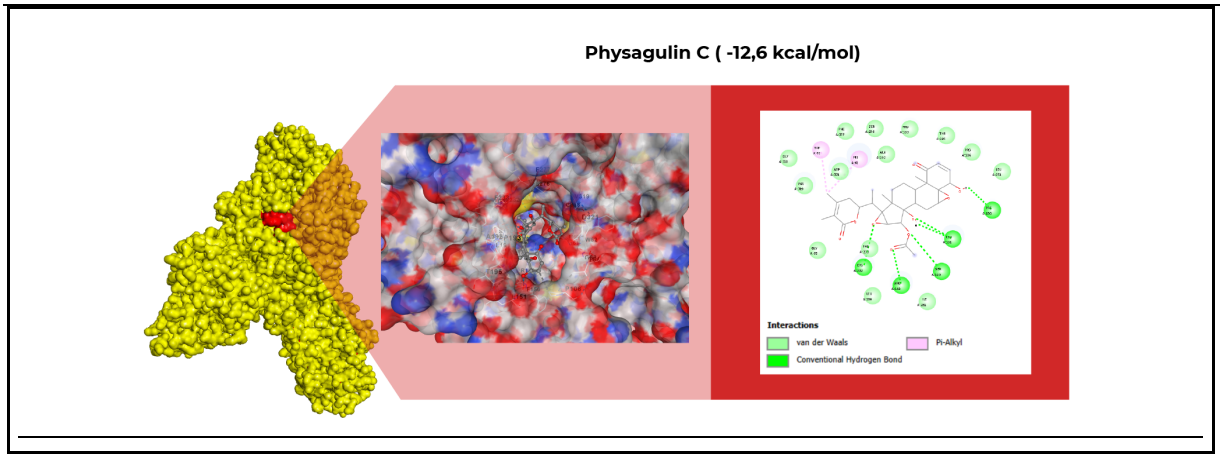


Figure 2. Protein model and assessment of 7VIF (Left) and 7WF7 (Right)

Molecular docking analysis
IL-4Rα receptor (PDB ID: 7VIF)

As a control compound, Upadacitinib has a binding energy of -9.0 kcal/mol with 13 salt bridges, 18 hydrogen bonds, and 103 unbound bonds, according to the docking results. (Figure 3). Due to the natural differences in molecular interactions, a direct comparison of binding energies between protein-protein interactions in the control group and compound-protein interactions in the experimental group is not possible. However, the possibility of active compounds of Physalis angulata interacting with target proteins can be studied through docking studies. This offers an attractive alternative for drug development. Furthermore, compared to the extraction of natural compounds, modern antibody therapies, such as Upadacitinib, require more time and expense. The value obtained by withangulatin B of -12.7 kcal/mol (Figure 3) appears to be the best energy when assessing binding energy interactions. However, it is important to remember that unfavorable donor-donor interactions can lead to protein instability, ligand detachment from the protein, or even protein disintegration, compromising its function. Furthermore, physagulin C, which has a binding energy of -12.6 kcal/mol, is a potential candidate compound for the IL-4Rα cytokine receptor (PDB ID: 7VIF).



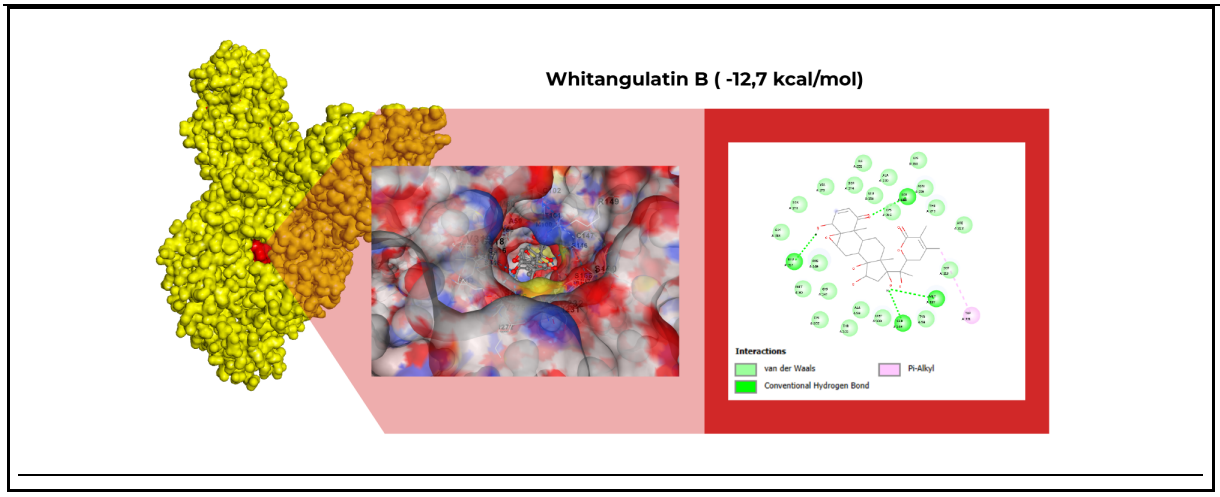
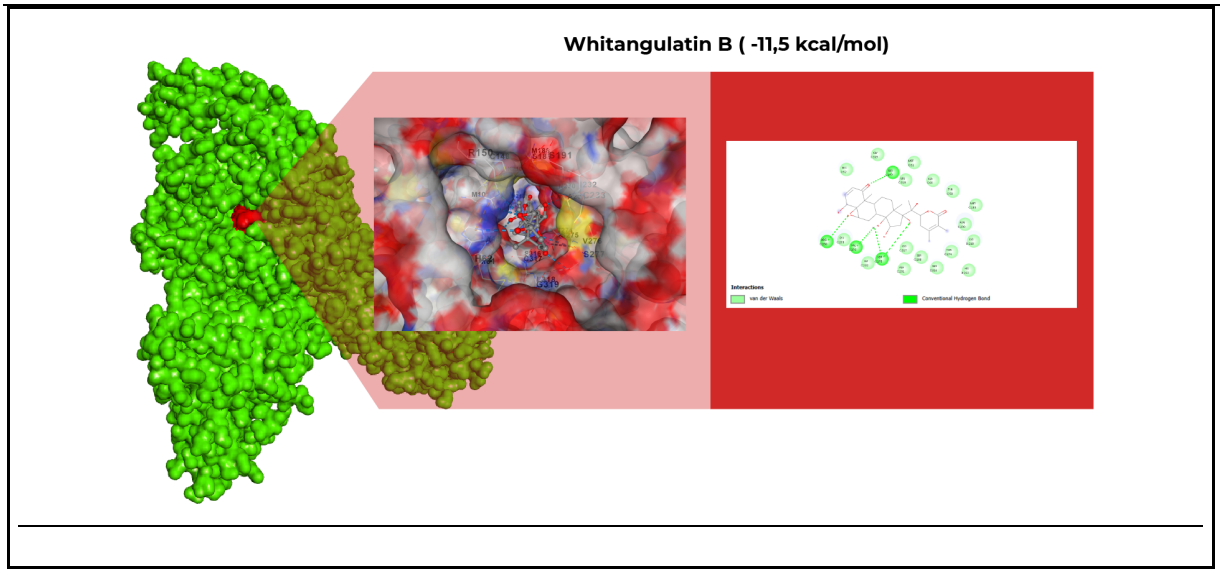


Figure 3. Molecular docking results of physagulin C + 7VIF, and whitangulatin B + 7VIF.

IL-13Rα1 (PDB ID: 7WF7)

Whitangulatin B with a binding energy of -11.5 kcal/mol appears to be the most potent compound in its interaction with the IL-13Rα1 cytokine receptor (PDB ID: 7WF7) (Figure 4). Its specific interaction with proteins may contribute to this enhanced efficacy. This is demonstrated by the formation of three hydrogen bonds with residues VAL276, SER275, ARG150, and SER277. In addition, van der Waals interactions occur at several residues. The binding energy of withanolide with the IL-13Rα1 cytokine receptor (PDB ID: 7WF7) also shows a value of -11.5 kcal/mol. The specific interactions that occur are the formation of three hydrogen bonds with several residues, namely TYR59, SER275, and ILE232.



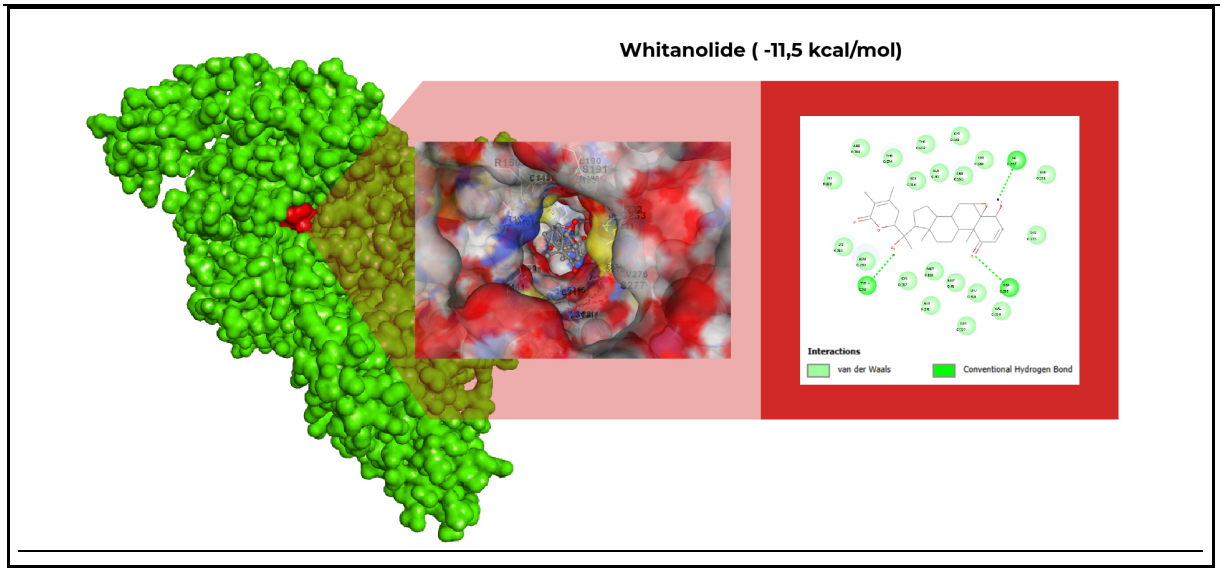


Figure 4. Molecular docking results of whitangulatin B + 7WV7, and whitanolide + 7WF7.

DISCUSSION

Bioactivity of *Physalis angulata* compounds

Eczema, particularly atopic dermatitis, is a type of skin inflammation that is heavily influenced by the T-helper 2 (Th2) immune response. Two key components involved in this pathogenesis are interleukin-4 (IL-4) and interleukin-13 (IL-13). These two cytokines are IL-4Rα (PDB ID: 7VIF) and IL-13Rα1 (PDB ID: 7WF7), which subsequently activate the JAK/STAT6 pathway, inhibit pro-inflammatory gene expression, and cause skin barrier damage and pruritus. (Guttman-Yassky et al., 2018).It is known that Physalis angulata, a herbal medicine that contains a lot of steroidal withanolides and glycosides, has strong immunomodulatory and anti-inflammatory properties. Withanolides and glycosides have strong immunomodulatory and anti-inflammatory properties. Using molecular docking, in silico studies have shown that active substances from Physalis angulata, such as physalin B and withanolide, have high affinity to interact with IL-4Rα and IL-13Rα1 in situ, with binding affinity comparable to or better than commercial antagonists such as dupilumab. This interaction is believed to inhibit the binding of IL-4 and IL-13 to their receptors, thereby inhibiting JAK1/STAT6 activity and reducing the expression of pro-inflammatory cytokines such as CCL17 (TARC) and IL-31 which are important in the pathophysiology of atopic dermatitis. Some of its downstream effects include reduced eosinophil and Th2 infiltration and increased loricrin and filaggrin expression which are crucial in reducing the skin barrier. (Boguniewicz & Leung, 2010).Therefore, Physalis angulata has the potential as a phytochemical agent in the treatment of eczema, especially by reducing the interaction between IL-4 and IL-13 and their receptors through competitive or allosteric mechanisms directly related to the crystal structure of 7VIF and 7WF7.

ADMET of *Physalis angulata*

The volume of distribution (VDss) was categorized as low if < 0.71 L/kg (log VDss < -0.15) and high if > 2.81 L/kg (log VDss > 0.45). Based on this criterion, all three compounds – *Physagulin C* (log VDss = 0.029), *Withangulatin B* (-0.063), and *Withanolide* (-0.048) – were in the middle distribution range, indicating that their distribution in body tissues was neither too restricted nor too extensive. For blood-brain barrier (BBB) permeability, a logBB value > 0.3 indicates the compound can easily cross the BBB, while a value < -1 indicates poor distribution to the brain. In this case, *Withangulatin B* (-1.02) is close to the lower limit, indicating very limited brain distribution, *Physagulin C* also shows low permeability (-0.875), while *Withanolide* (-0.315) shows moderate permeability to the BBB. Permeability to the central nervous system (CNS) was assessed using logPS, where logPS > -2 indicates the ability to penetrate the CNS and < -3 means inability. *Physagulin C* (-3.13) and *Withangulatin B* (-3.292) were categorized as unable to penetrate the CNS, while *Withanolide* (-2.696) was in the category of still being able to penetrate the CNS. All three compounds showed good results in human intestinal absorption, with high predictive values: *Physagulin C* (100%), *Withanolide* (99.2%), and *Withangulatin B* (79.242%). Caco-2 permeability, which supports oral absorption, was also quite good: *Physagulin C* (0.83), *Withanolide* (0.831), and *Withangulatin B* (0.354). All compounds are also categorized as P-glycoprotein substrates, which can affect tissue distribution and oral bioavailability. Interestingly, only *Physagulin C* and *Withanolide* were predicted to be inhibitors of P-gp I and

II, while *Withangulatin B* was not. This suggests that both compounds have the potential to inhibit active transport by P-gp, which could influence drug interactions. In the context of cytochrome P450 metabolism, only *Physagulin C* and *Withanolide* are predicted to be CYP3A4 substrates, meaning they will be metabolized by this major isoform. None of the three compounds act as inhibitors or substrates of other CYP isoforms such as CYP1A2, CYP2D6, CYP2C9, and CYP2C19. This indicates a relatively safe drug interaction profile in the context of metabolism, with a low risk of inhibition.

Predicted total clearance values were quite low for all three compounds: *Physagulin C* (0.254 log ml/min/kg), *Withangulatin B* (0.444), and *Withanolide* (0.347). This indicates that all three compounds have moderate elimination rates, with potentially neither too short nor too long half-lives. None of the compounds are substrates of the renal transporter OCT2, so renal elimination is likely not dominant. Toxicity evaluation of the three compounds – *Physagulin C* , *Withangulatin B* , and *Withanolide* – showed variations in their safety profiles. Based on the Ames test, only *Physagulin C* showed a positive result, indicating mutagenic potential, while *Withangulatin B* and *Withanolide* showed no indication of mutagenicity. In terms of acute toxicity, the oral LD50 value in rats showed that *Withanolide* (2.831 mol/kg) had a higher acute toxic potential than *Physagulin C* (4.007 mol/kg) and *Withangulatin B* (4.042 mol/kg), indicating that the latter two compounds tend to be safer. Meanwhile, the higher LOAEL (Lowest Observed Adverse Effect Level) value of *Withangulatin B* (2.685 log mg/kg/day) indicates that this compound is better tolerated in chronic exposure than *Physagulin C* (1.868) and *Withanolide* (1.776).

In terms of hepatotoxicity and skin sensitization, the three compounds were predicted not to cause toxic effects on the liver or allergic skin reactions, indicating good safety potential for systemic and topical use. For toxicity to aquatic organisms, all compounds showed low toxicity to *Tetrahymena pyriformis* , with log values around 0.285–0.305. However, a striking difference was seen in toxicity to minnow fish, where *Withanolide* showed the lowest log value (1.178), indicating a higher level of aquatic toxicity, while *Physagulin C* (4.16) and *Withangulatin B* (5.108) showed much lower toxicity to aquatic organisms.

Molecular modeling and assessment

Rapid advances in computational methods for protein modeling have made significant contributions to structure-based drug development and understanding of molecular interactions. One widely used software tool in this analysis is BIOVIA Discovery Studio Visualizer, which since its introduction in 2002 has become an essential tool for predicting and visualizing three-dimensional (3D) protein structures with high accuracy. This software utilizes *computational chemistry* and *molecular modeling- based approaches* , enabling researchers to analyze ligand-protein interactions in detail, facilitating a more efficient and targeted drug discovery process. In this study, IL-13Rα1 (PDB ID: 7WF7) and IL-4Rα receptor (PDB ID: 7VIF) proteins were selected as targets for *molecular docking studies* using BIOVIA Discovery Studio Visualizer. Based on the structure quality assessment through *Ramachandran plot analysis* , both protein models showed good characteristics, where most of the residues were located in the favored region *and* allowed *region* . The IL-13Rα1 protein exhibits a dominant residue distribution in the favored region, indicating adequate modeling quality for further analysis. Similarly, the IL-4Rα receptor displays high structural quality with the majority of residues falling within the allowed region, indicating model stability and accurate structure prediction. This validation ensures that both proteins have viable structures for ligand-protein interaction simulations, thus allowing for further *molecular docking* and *molecular dynamics simulations* to explore the potential of active compounds from Physalis angulata as potent inhibitors of both cytokine receptors.

Molecular docking analysis

Molecular docking results showed that the active compound from Physalis angulata has good binding affinity to the IL-4Rα receptor (PDB ID: 7VIF), which is one of the main targets in the inflammatory pathway of atopic dermatitis. Withangulatin B showed the lowest binding energy of −12.7 kcal/mol, followed by Physagulin C at −12.6 kcal/mol. The more negative binding energy value indicates the higher stability of the ligand-receptor complex and indicates the potential for better biological activity against inflammatory protein targets.(Meng et al., 2011). The interaction between Withangulatin B and IL-4Rα involves the formation of hydrogen bonds and hydrophobic interactions at the active residues of the receptor, which play a role in increasing the stability of the protein-ligand complex. This interaction is thought to inhibit the activation of the IL-4/IL-13 pathway that mediates the Th2 type immune response in atopic dermatitis (Guttman-Yassky et al., 2018). In addition, Physagulin C also shows a stable interaction pattern with IL-4Rα, making it a potential candidate for natural-based anti-inflammatory compounds.
As a comparison, upadacitinib was used as a positive control because it is known to work as a selective JAK1 inhibitor that is able to inhibit IL-4 and IL-13 signal transduction indirectly through the JAK-STAT pathway. Although the mechanism of action of natural compounds and synthetic drugs is different, the docking results show that compounds

from Physalis angulata have the potential for competitive affinity for inflammatory targets of atopic dermatitis (Guttman-Yassky et al., 2021). At the IL-13Rα1 receptor (PDB ID: 7WF7), Withangulatin B and Withanolide showed the same binding energy, which was −11.5 kcal/mol. This value indicates that both compounds have stable interaction capabilities with the IL-13Rα1 receptor, which is known to play an important role in activating the type 2 immune response in atopic dermatitis.(LaPorte et al., 2008).

Withangulatin B forms several hydrogen bonds with amino acid residues such as VAL276, SER275, ARG150, and SER277. These interactions contribute to the stability of the protein-ligand complex and can increase the binding affinity of the compound to the target receptor. Furthermore, van der Waals interactions are also found at several residues around the active site of the protein, which also strengthen the stability of the molecular complex. Meanwhile, Withanolide showed hydrogen interactions with residues TYR59, SER275, and ILE232. The formation of hydrogen bonds is known to play an important role in maintaining the conformation of the protein-ligand complex during the docking process and can increase the effectiveness of target receptor inhibition. (Lionta et al., 2014).Based on these results, Withangulatin B and Withanolide are thought to be able to inhibit the activation of the IL-13Rα1/JAK/STAT6 pathway which contributes to the chronic inflammatory process in eczematic diseases. Overall, the molecular docking results indicate that the active compounds from Physalis angulata have potential as natural-based therapeutic candidates for eczematic diseases through inhibition of the IL-4Rα and IL-13Rα1 receptors involved in the Th2 immune response.

Strengths and limitations

This study provides a comprehensive approach to exploring the potential of active compounds from Physalis angulata as therapeutic candidates for eczema through an in silico approach. The integration of data mining, bioactivity analysis, ADMET prediction, molecular modeling, and molecular docking enabled the identification of potential compounds that can target the IL-4/IL-13 inflammatory pathway in atopic dermatitis. This computational approach offers the advantage of time and cost efficiency in the early stages of drug discovery.(Meng et al., 2011). However, this study still has limitations because all analyses were conducted in silico, thus not being able to accurately depict biological activity in biological systems. Therefore, further validation through in vitro, in vivo, and clinical trials is needed to confirm the effectiveness, safety, and mechanism of action of the active compounds from Physalis angulata in the treatment of eczematous diseases. Furthermore, molecular docking simulations cannot fully depict the dynamics of complex protein-ligand interactions under physiological conditions in the human body.(Lionta et al., 2014)

CONCLUSION

Eczematic diseases, especially atopic dermatitis, are chronic inflammatory skin diseases closely related to dysregulation of the Th2 type immune response through the IL-4 and IL-13 pathways mediated by the IL-4Rα and IL-13Rα1 receptors. In an effort to find potential therapeutic candidates, this study explored active compounds from Physalis angulata, especially the withanolide group such as Physagulin C, Withangulatin B, and Withanolide, using an in silico approach that included bioactivity analysis, ADMET profiles, molecular modeling, and molecular docking. The results showed that these compounds have potential anti-inflammatory and immunomodulatory activities with good binding affinity to the IL-4Rα and IL-13Rα1 receptors. Withangulatin B and Physagulin C showed the most stable interaction with IL-4Rα, while Withangulatin B and Withanolide showed good interaction with IL-13Rα1, thus potentially inhibiting the activation of the JAK-STAT pathway which plays a role in the pathogenesis of eczematic disease. In addition, the ADMET prediction results showed a fairly good pharmacokinetic profile with a high absorption rate and relatively low toxicity. The diversity of structures and biological activities of withanolide compounds from Physalis angulata show great potential as a source of natural-based drug candidates for the therapy of eczematic disease. However, further research is needed through in vitro, in vivo, and clinical trials to ensure their effectiveness, safety, and therapeutic potential in more depth.

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