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In silico study of andrographolide bioactive compound from *Andrographis paniculata* as a potential anti-photoaging agent

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ABSTRACT. Skin aging caused by UV radiation has become a growing concern among the Indonesian population. The effects of UV-induced skin aging can be mitigated by antioxidant compounds. Although synthetic antioxidants are commonly used to combat aging, their long-term use is discouraged due to potential systemic side effects and carcinogenic risks. Therefore, natural antioxidant compounds are needed as a safer alternative. *Andrographis paniculata*, known as Sambiloto, contains a natural antioxidant compound called andrographolide. This study aims to evaluate the potential of andrographolide by determining its binding affinity toward target protein receptors involved in the photoaging mechanism triggered by increased levels of Reactive Oxygen Species (ROS). Through in silico analysis, the potential of andrographolide was assessed using reverse docking techniques with databases such as PubChem, PharmMapper, SwissTargetPrediction, SuperPred, and PASS Online. Subsequent molecular docking was performed using PyRx 0.8 and PyMol software. The in silico data revealed interactions between the ligand compound and its receptors, including binding activity and binding positions based on hydrophobic interactions and hydrogen bonds, which were further analyzed. The results showed that andrographolide binds effectively to the IL-1, NF-κB, and IL-6 receptors with relatively low binding affinities of -7.5 (IL-1), -6.6 (NF-κB), and -6.5 (IL-6). Low binding affinity indicates stronger and more stable interactions between the ligand and receptor. Based on the results, andrographolide from *A. paniculata* exhibits promising potential as a candidate for anti-photoaging agents that can serve as an alternative to synthetic antioxidants.

Keywords: *Andrographis paniculata*; andrographolide; antioxidant; anti-photoaging; in silico

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INTRODUCTION

Skin is the body's outermost organ first seen by a person. One of the most visible changes in the skin is facial aging. Aging is a natural degenerative process characterized by signs like wrinkles, sagging skin, rough and dry skin texture, and dark spots or ephelis (Ginting *et al*., 2020). Skin aging is not just an issue for the elderly; young adults also experience it, also known as premature aging. Premature aging is usually seen when entering the thirties. According to a Jakpat survey conducted for ERHA Age Correcroe, approximately 76% of Indonesian women experience symptoms of premature aging (Tanjung *et al*., 2022). The high percentage of premature aging is further supported by research conducted by Green in Australia, which reported that among individuals aged 30 years, 72% of males and 42% of females exhibited signs of photoaging (Cahyani *et al*., 2022).

Skin aging can be overcome by giving antioxidants. An antioxidant is a compound that captures Reactive Oxygen Species (ROS) to inhibit ROS production. ROS plays a role in regulating the proliferation of epidermal keratinocytes and preserving cellular homeostasis. However, high amounts of ROS may trigger inflammatory responses and skin aging (Nakai & Tsuruta, 2021). According to Andarina & Djauhari (2017), free radical instability may lead to conditions such as photoaging. Antioxidants play a role in stabilizing free radicals through intramolecular hydrogen bonding and preventing further oxidation (Wardani *et al*., 2021). A standard method to prevent signs of aging is the application of chemical cosmetics that can indirectly affect human health by damaging the

immune, neurological, and respiratory systems through skin absorption (Istiningrum *et al*., 2016). According to Agustin *et al*. (2025), cosmetics contain various harmful substances such as retinoic acid, hydroquinone, mercury, and parabens when used in the long term. Research by Balwierz *et al*. (2023) showed that harmful ingredients used in cosmetics can cause systemic disorders and even cancer.

The use of chemical ingredients in cosmetics needs to be minimized. Antioxidants in plants can be natural alternatives to mitigate the effects of photoaging. An example is *Andrographis paniculata* (Sambiloto), which contains active compounds, including andrographolide, farnesol, flavonoids, and tannins. Andrographolide ($C_{20}H_{30}O_5$) is the primary active compound, with concentrations reaching up to 4% of the plant's dry weight (Martin, 2022). The pharmacological aspects of andrographolide are associated with its chemical profile and mechanism as an antioxidant in neutralizing free radicals. Free radicals are groups that have unpaired electrons in the outermost orbital and are highly reactive (unstable). Free radicals in the body can cause lipid peroxidation, damaging cell membranes and leading to cell death. This process is also linked to various diseases caused by oxidative stress. Under normal conditions, the body will form antioxidants to counteract free radicals, thereby maintaining a balance between free radicals and antioxidants (Sari *et al*., 2019).

In silico methods are often used to identify pharmacological agents, including andrographolide. This method facilitates drug discovery by predicting interactions between target proteins and ligands. Compared to in vitro and in vivo testing, in silico reduces time and cost. This research aims to predict the potential of andrographolide bioactive compounds as anti-photoaging candidates to replace synthetic antioxidants and determine target proteins that can bind to the active compound andrographolide. Therefore, research on "In silico Study of Andrographolide Bioactive Compound from *A. paniculata* as a Potential Anti-Photoaging Agent" is highly significant in providing valuable insights into the ability of andrographolide to bind to target protein receptors in the photoaging mechanism caused by elevated levels of ROS.

MATERIALS AND METHODS

The method used in this research is in silico analysis using a molecular docking approach. In silico has a role in modeling protein-target interactions through computer-based simulations. This process was conducted after researchers identified the writing subject and problem formulation. In silico studies using the molecular docking method are essential for identifying the target proteins, obtaining the 3D structure of the desired compound, and examining compound interactions using PyMol and Pyrx software. Additional analysis is required to validate the results obtained.

The data collection method of this research was obtained from databases including PubChem, PharmMapper, SwissTargetPrediction, SuperPred, and PASS Online web server. Molecular docking techniques were also utilized using PyRx and PyMol docking software. The steps of the molecular docking technique are as follows:

1. Obtaining the 3D structure of andrographolide using the PubChem database

Andrographolide compounds used in silico research in the form of Sybl data files (*.sdf) obtained from PubChem Database (https://pubchem.ncbi.nlm.nih.gov/) with CID 5318517.

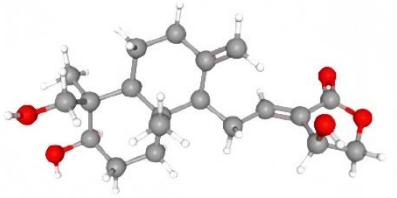

Fig. 1. 3D structure of andrographolide

2. Identifying the target proteins of the andrographolide compound

2.1 PharmMapper

The andrographolide compound with CID 5318517 was submitted to the PharmMapper webserver (http://www.lilab-ecust.cn/pharmmapper/check.html). The three-dimensional structure or

SMILES notation of this compound, CC12CCC(C(C(C1CCC(=C)C2CC=C3C(COC3=O)O)(C)CO)O was used to predict proteins that may interact with andrographolide. The output file from PharmMapper was downloaded in CSV format (*.csv). A results table generated with Job ID 231111092256 was also compiled and combined with the data gathered from the Swiss Target Prediction and SuperPred web servers.

2.2 SuperPred

The Andrographolide compound CID 5318517 was submitted to the SuperPred webserver (https://prediction.charite.de/) using its three-dimensional structure or SMILES (CC12CCC(C(C1CCC(=C)C2CC=C3C(COC3=O)O)(C)CO)O). The output obtained was compiled into a summary table and analyzed manually. Furthermore, the compilation results are used as target protein data whose interactions will be analyzed by molecular docking.

2.3 SwissTargetPrediction

The three-dimensional configuration or SMILES CC12CCC(C(C(C1CCC(=C)C2CC=C3C(COC3=O)O)(C)CO)O of Andrographolide compound CID 5318517 was submitted to the SwissTargetPrediction webserver (http://swisstargetprediction.ch/). After the file was downloaded in (*.csv) format, the results were entered into the compilation table and analyzed manually. The compilation results are then used as target protein data to analyze their interactions using molecular docking.

3. Target protein analysis using string-db

A protein target interaction network related to aging that interacts with the andrographolide compound was constructed using the String-db platform. This analysis was designed to visualize the protein network and analyze metabolic pathways, biological activities, and diseases associated with the predicted target proteins (Szklarczyk *et al*., 2020; Khoirunnisa *et al*., 2024). The construction was carried out by compiling all previously identified target proteins, which were then entered into the String-db website (https://string-db.org/) and selecting *Homo sapiens* in the "organisms" column. The interaction network result was subjected to KEGG pathway analysis to identify biological signaling pathways of aging or aging-related processes (Kanehisa *et al*., 2023).

4. Prediction of the biological activity of andrographolide using PASS online

To determine the biological activity of each compound to be used, the canonical SMILES string of the compound was entered into the PASS Online (Way2Drug) website. This process helps predict the biological activities relevant to the selected target. The compounds listed on the website display varying affinity ratio values. These values are represented by P1 and P2, which indicate the likelihood and strength of the biological activity against the selected target. Higher value has a greater potential effect on the biological target (Kartika, 2024).

5. Molecular docking

Molecular purification was carried out using the installed PyMOL application. This application controls protein selection, removes water molecules from the protein, and saves the protein part with no residues. Subsequently, the PyRx software conducted molecular docking on the isolated molecules to determine Binding affinity and RMSD (Root Mean Square Deviation). The RMS=D value indicating acceptable structural conformational alignment is under 5, with a value nearer to 0 signifying a better alignment. The conformation from the docking result matches the native ligand conformation obtained from crystallographic measurements. Once the c-process in PyRx was finished, the PyMOL application integrated the protein and docking outcomes from PyRx. Compounds with 3D structures of ligands (natural substances) were generated using the PubChem webserver (Syafar *et al.*, 2022).

Molecular docking (predicting ligand or natural compound interactions) Molecular docking predicts the interactions between a ligand or natural compound and target proteins or receptors using PyRx and PyMOL, with a predefined grid box and an exhaustiveness value of 8 (Mirza *et al*., 2021). The data analysis refers to Khalil (2023), where autoDock Vina integrated in PyRx was used for molecular docking analysis. In this analysis, the blind docking technique was used to find the best

conformation on all target protein sequences. Then, the interpretation is done by comparing the bond scores, bond locations, and interactions between the ligand and the receptor that form the complex bond. Lower binding affinity scores indicate better binding interaction. The predicted binding sites and ligand-receptor interactions were visualized using PyMol to provide a clearer understanding of the molecular interactions.

RESULTS AND DISCUSSION

Target proteins capable of binding to the active compound andrographolide

This study obtained candidate target proteins for the andrographolide compound (CID 5318517) from the PharmMapper, SwissTargetPrediction, and SuperPred web servers. A total of 298 proteins were identified using the PharmMapper webserver (Job ID: 231111092256), 100 proteins from the SwissTargetPrediction web server, and 119 proteins from the SuperPred webserver. So, there are 517 target protein candidates for andrographolide compounds. These candidate target proteins were then used to predict protein-protein interactions within the human body using the String-db web server. The interaction network result is presented in Figure 2 below.

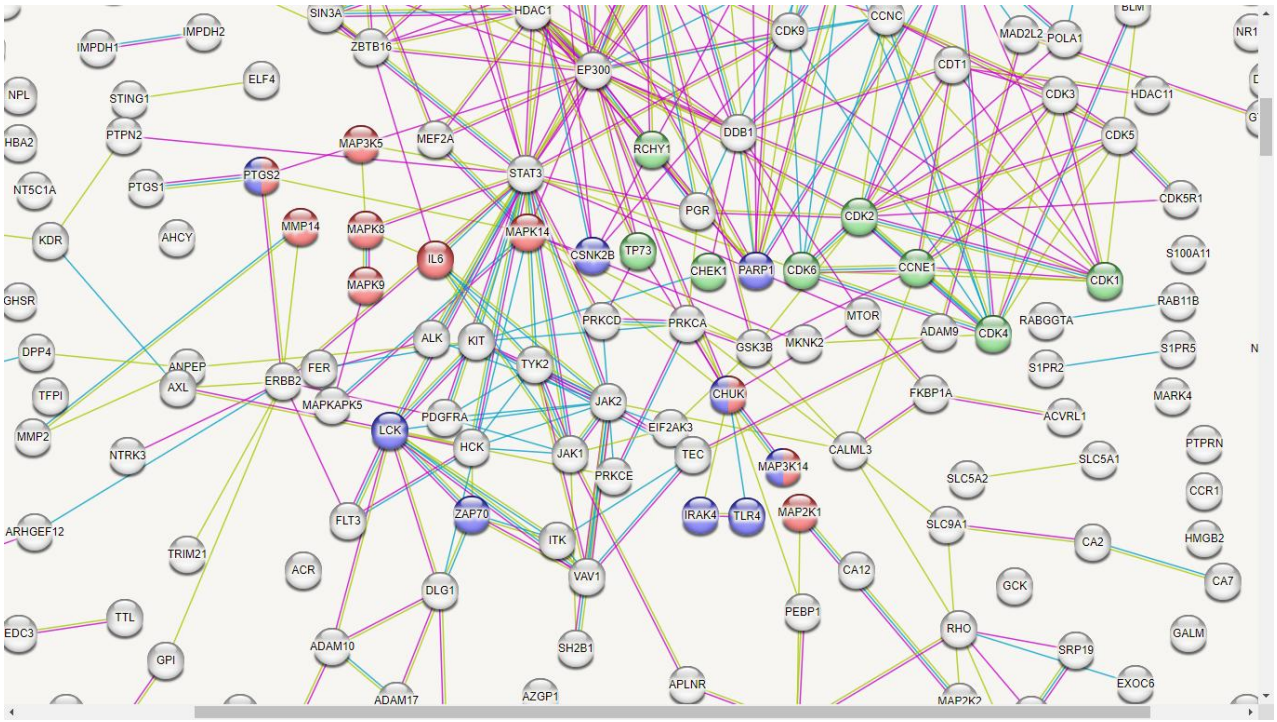

Fig. 2. Interaction of andrographolide target proteins (Red: p53 pathway, Blue: TNF pathway, Green: NF-κB pathway)

A comprehensive analysis of the 517 target proteins was conducted using STRING-DB to identify those with potential involvement in the aging mechanism, as supported by literature studies. The pathways examined included the p53 pathway (red line), TNF pathway (blue line), and NF-κB pathway (green line). The p53 pathway is a major tumor-suppressive pathway that prevents the spread of abnormal cells by regulating DNA repair, cell cycle progression, cell death, or senescence (Lahalle *et al*., 2021). Tumor Necrosis Factor (TNF) is a type II transmembrane protein expressed on the plasma membrane as a trimer. Recruitment of kinase complexes leads to the activation of NF-κB and MAPK signaling pathways, followed by the expression of pro-inflammatory cytokines such as interleukin-6 and -8 (IL-6, IL-8), as well as pro-survival proteins such as c-IAP2 and the caspase-8 inhibitor cellular FLICE inhibitory protein (cFLIP) (Webster, 2020). The NF-κB pathway is induced by TNF-α, IL-1, and other stimuli through an IKKβ-dependent cascade. Activation of this cascade results in the phosphorylation of IκBα, leading to its degradation by the proteasome. It forms the NF-κB complex and allows it to move to the nucleus (Khongthong *et al*., 2019). Hereafter, target proteins

identified from the three web servers that showed potential roles in aging-related processes or similar mechanisms were compiled and presented in Table 1. Three receptors were selected for this study: Interleukin-1 receptor-associated kinase 4 (IRAK4), Inhibitor of nuclear factor kappa B kinase alpha subunit (IKKα), and Interleukin-6 (IL-6). These receptors were chosen based on their known roles in the anti-photoaging mechanism.

Table 1. Target proteins that play a role in the aging mechanism

No	Protein	Webserver			Pathway
		PM	SP	STP	
1	Interleukin-1 receptor-associated kinase 4 (IL-1)	-	-	v	NF-κB signaling pathway
2	Inhibitor of nuclear factor kappa B kinase alpha subunit	-	v	-	
3	Interleukin-6 (IL-6)	-	-	v	TNF signaling Pathway

Notes: PM=PharmMapper; SuP=SuperPred; STP=SwissTargetPrediction

Andrographolide (AD) exhibits a mechanism like that of protocatechuic aldehyde (PA) in protecting human dermal fibroblast (HDF) cells from inflammatory responses, reactive oxygen species (ROS) formation, and various skin lesions that lead to skin photoaging. According to Ding *et al*. (2020), the accumulation of reactive oxygen species (ROS) in the skin is one cellular circumstance after sun exposure. This oxidative stress is due to the induction of cellular changes, including guanine modification (8-hydro-2-deoxy-guanine), single-chain DNA damage, pyrimidine base oxidation, membrane protein carbonylation, lipid peroxidation, and apoptosis of epidermal keratinocytes (sunburn cells). Damaged keratinocytes release pro-inflammatory cytokines (IL-1, IL-6, TNF-α) and activate dermal fibroblast growth factor receptors (EGFR, TNF-α, PAF, prostaglandins, and insulin). The transcription factor NF-κB is also activated by UV radiation, stimulating the transcription of inflammatory cytokines that attract neutrophils. Neutrophils express a matrix metalloproteinase (metalloproteinase-8) that degrades extracellular matrix proteins simultaneously. The target receptors selected from multiple databases used in this study (IL-1, IL-6, and NF-κB) are involved in the ROS accumulation mechanism in the skin. This mechanism is illustrated in the following Figure 3.

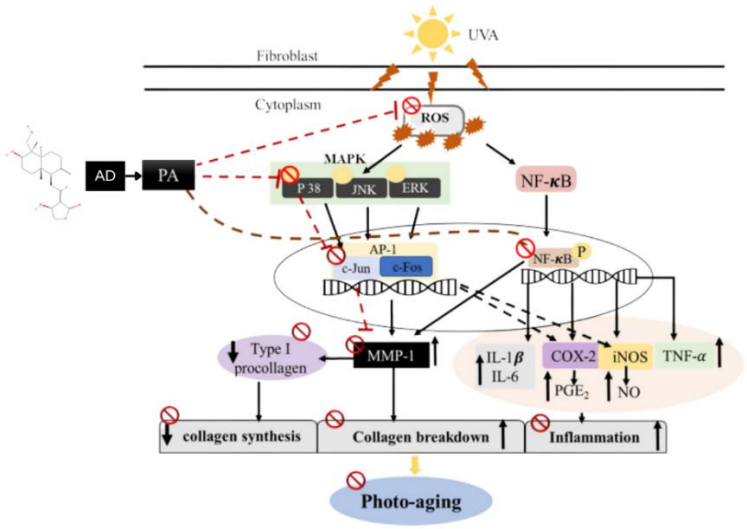

Fig. 3. Anti photo-aging mechanism (Ding *et al*., 2020 modification)

Skin aging is a complex process caused by external and internal factors. Skin aging due to internal factors is overlooked as unpreventable, while aging caused by external factors such as harmful environments can still be prevented. The primary cause of skin aging is photo-oxidative damage induced by ultraviolet (UV) radiation, commonly called photoaging. Most UV-induced skin damage occurs due to excess ROS that induce a complex molecular cascade pathway that can activate

inflammation to accelerate physiological aging and determine dermal or epidermal degeneration. ROS and reactive nitrogen species (RNS) can damage essential cellular components (DNA, proteins, lipids) and also affect the regulation of signaling molecules, such as MAPK (Mitogen-Activated Protein Kinase), inflammatory cytokines such as nuclear factor-kβ (NF-κB) and activator protein-1 (AP-1). UV radiation can stimulate the activation of enzymatic systems such as lipoxygenase (LOX) and cyclooxygenase (COX), which catalyze the formation of additional inflammatory mediators. Skin exposed to UV radiation has been reported to trigger the development of skin cancer (Scapgnini *et al*., 2014).

In silico simulation results

The biological activity prediction of andrographolide as an anti-photoaging agent was conducted using PASS Online (Prediction of Activity Spectra for Substances). The results are presented in Table 2.

Table 2. Potential of andrographolide compounds as anti-photo-aging according to PASS online

Pa	Pi	Activity
0.967	0.001	Transcription factor NF kappa β stimulant
0.845	0.005	Antiinflammatory
0.628	0.013	Dermatologic

The biological activities of andrographolide related to anti-photoaging, as predicted bypass Online, include Transcription Factor NF-kappa B stimulant (Pa 0.967), Anti-inflammatory (Pa 0.845), and Dermatologic (Pa 0.628). Probability active (Pa) indicates that some compounds can be active in various biological activities, whereas the Probability inactive (Pi) is used to look at the inactive compound in biological activity. The value of Pa> 0.3 means that dry lab or in silico is proven to be applied in various activities, while Pa> 0.7 means some compounds have been demonstrated in wet lab to be shown in multiple activities. Based on this explanation, Transcription factor NF kappa β stimulant and Anti-inflammatory activities have been proven in silico and wet labs. Dermatologic activity is only proven in silico, and all three are unlikely to be inactive in biological activity. According to Azmi *et al*. (2021), the Pa>0.7 value indicates that the compound will likely show biological activity in both in vivo and in vitro experiments. Riyadi *et al*. (2021) also stated that the compound will show biological activity in an experiment.

The next step following the potential prediction using PASS Online is molecular docking. The first step in molecular docking is to get the FASTA sequence of the target protein using the National Center for Biotechnology Information (NCBI) database. This sequence is then used to create a 3D structural protein model. Protein preparation is carried out to remove water molecules (H_2O) and native ligands, leaving only amino acids for the next docking step. This step is essential to ensure no unblocked binding site for the test compound inside the protein's binding pocket. The 3D configurations of proteins were visualized using PyMOL, and their surface models are shown in Figure 4.

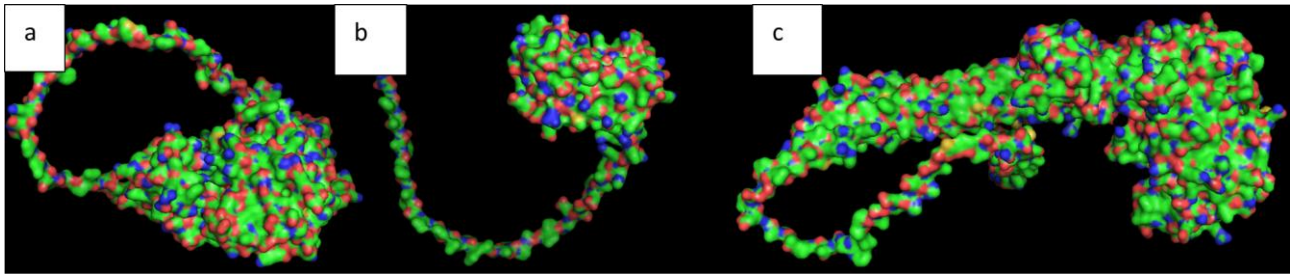

Fig. 4. 3D structure visualization of proteins (surface) of IL-1 (a) IL-6 (b) NF-κB (c)

The colors in the visualization results represent specific atoms: red for oxygen atoms, light green for chlorine atoms, and dark blue for nitrogen atoms (Ramadhan, 2021). The visualization results also indicate that NF-κB has the most complex structure, while IL-1 has the simplest structure. The protein structure that was prepared using PyMol software before was then observed by the docking process using PyRx software. The docking process begins with minimizing the energy of the andrographolide ligand, which produces the output shown in Figure 5.

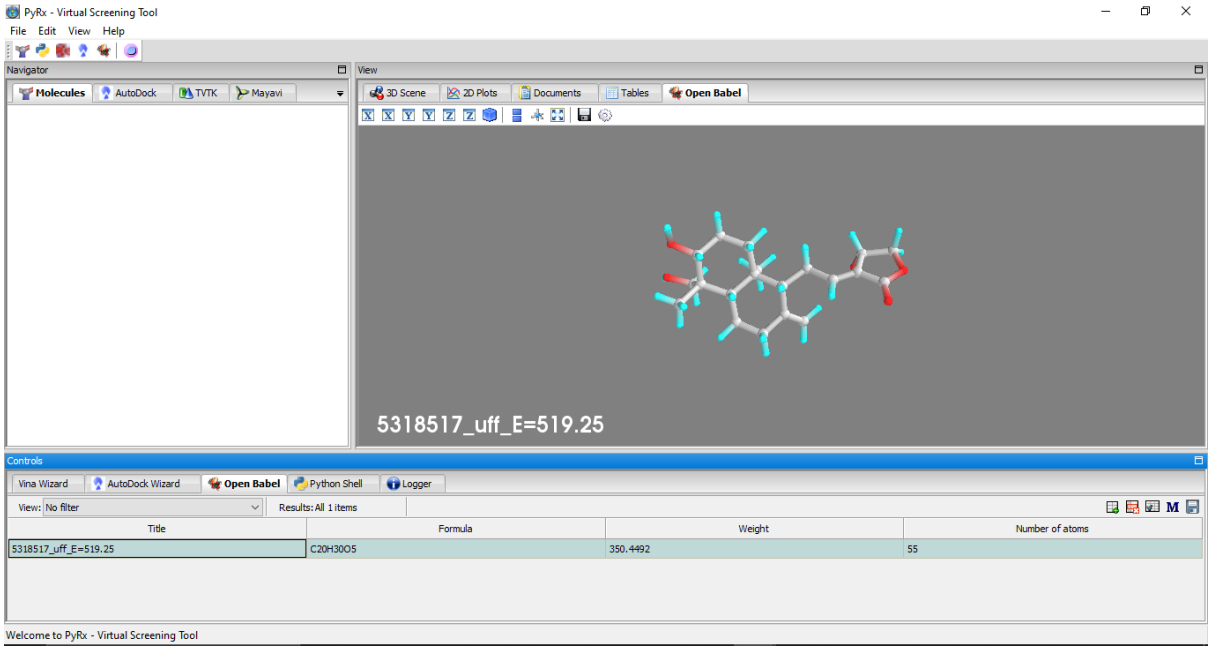

Fig.5. Docking process of andrographolide ligand using PyRx software

Result of minimizing andrographolide compound

General molecular docking in the PyRx application was carried out according to the method described by Amanda (2021). The ligand and target macromolecular protein structures, previously prepared using the PyMol application, were downloaded in PDB format and then imported into the Vina Wizard module of PyRx 0.8. The process was initiated by clicking "forward," after which the scoring results were awaited and subsequently saved. The general molecular docking results yielded binding affinity values, as presented in Table 3.

Based on the molecular docking results using PyRx 0.8 presented in Table 3, it can be observed that the andrographolide compound is capable of interacting with the proteins Interleukin-1 receptor-associated kinase 4 (IL-1), Inhibitor of nuclear factor kappa B kinase alpha subunit (NF-κB), and Interleukin-6 (IL-6), as indicated by their lowest binding affinity values of –7.5, –6.6, and –6.5, respectively. The target protein with the highest potential to bind with the ligand is IL-1, due to its lowest binding affinity value. This finding aligns with Saputri *et al*. (2016), who stated that binding affinity is a measure of a drug's ability to bind to its receptor. A lower binding affinity value indicates a stronger affinity between the receptor and ligand. Conversely, a higher binding affinity value indicates weaker interaction between the receptor and the ligand.

Table 3. The binding affinity of the target protein

Macromolecule	Binding affinity (kcal/mol)	rmsd/ub	rmsd/lb
NF-κB	-6.6	0	0
	-6.4	19.358	15.662
	-6.4	18.662	15.368
	-6.3	45.727	42.302
	-6.2	63.187	60.167
	-6.2	20.579	17.176

	-6.2	21.195	19.577
	-6.1	61.004	57.682
	-6	56.013	54.022
IL-1	-7.5	0	0
	-7.5	32.037	26.426
	-7.4	4.541	2.642
	-7.3	26.886	25.001
	-7.2	7.022	3.863
	-6.9	16.255	11.082
	-6.7	26.885	25.415
	-6.7	14.683	9.454
	-6.6	32.424	27.8
IL-6	-6.5	0	0
	-5.9	15.813	12.484
	-5.8	8.657	4.082
	-5.7	6.876	3.972
	-5.7	30.649	27.693
	-5.7	14.452	12.209
	-5.6	19.601	14.465
	-5.5	14.535	13.009
	-5.5	20.045	15.427

In addition to binding affinity, the accuracy of the docking predictions was further evaluated using the Root Mean Square Deviation (RMSD) values. As shown in Table 3, all target proteins have zero RMSD values at the lowest binding affinity values, both lower bound (RMSD/lb) and upper bound (RMSD/ub. This RMSD value is used to determine whether the bond prediction is successful. According to Ischak *et al*. (2023), RMSD/lb represents the minimum error in predicting the ligand atom positions, while RMSD/ub reflects the difference in atomic distances between two conformations. The RMSD value is generally considered good if it is less than 2 A. Higher RMSD values indicate a more low-grade prediction of ligand-protein interactions.

The molecular docking results obtained using PyRx were further visualized with the PyMol application to observe the three-dimensional interactions between the ligand and the target proteins. The visualization results are presented in Figure 6. In this figure, it can be observed that the ligand, which has a hexagonal three-dimensional structure colored green, gray, and red, can bind to each of the target proteins: Interleukin-1 receptor-associated kinase 4 (IL-1), Inhibitor of nuclear factor kappa B kinase alpha subunit (NF-κB), and Interleukin-6 (IL-6). This binding is indicated by yellow connecting dots between the ligand and the respective target proteins, which are displayed in a ribbon-like structure.

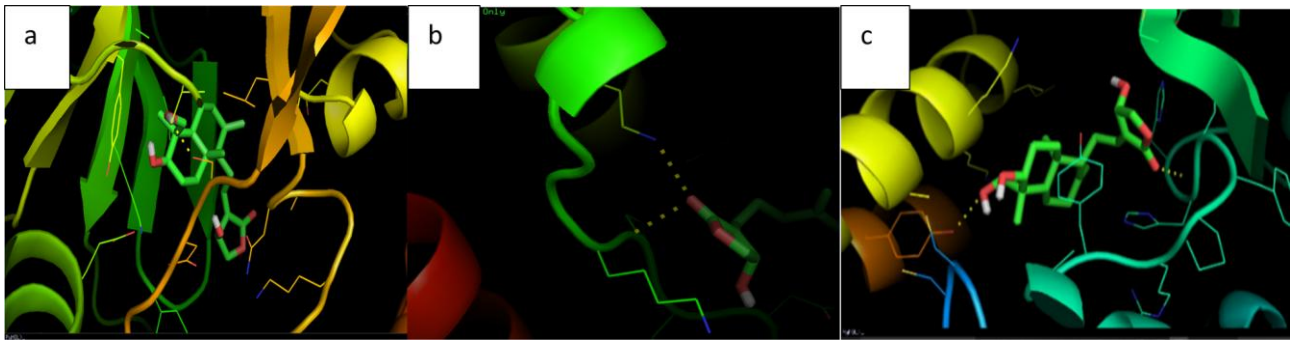

Fig.6. 3D Visualization of ligand-protein interaction of IL-1 (a) IL-6 (b) NF-κB (c) targets

A further analysis was conducted using the Ramachandran Plot to assess the structure and quality of the protein by examining the distribution of non-glycine residues in the “Disallowed Area” and the most favored regions (MFR). The results obtained are presented in Figure 7

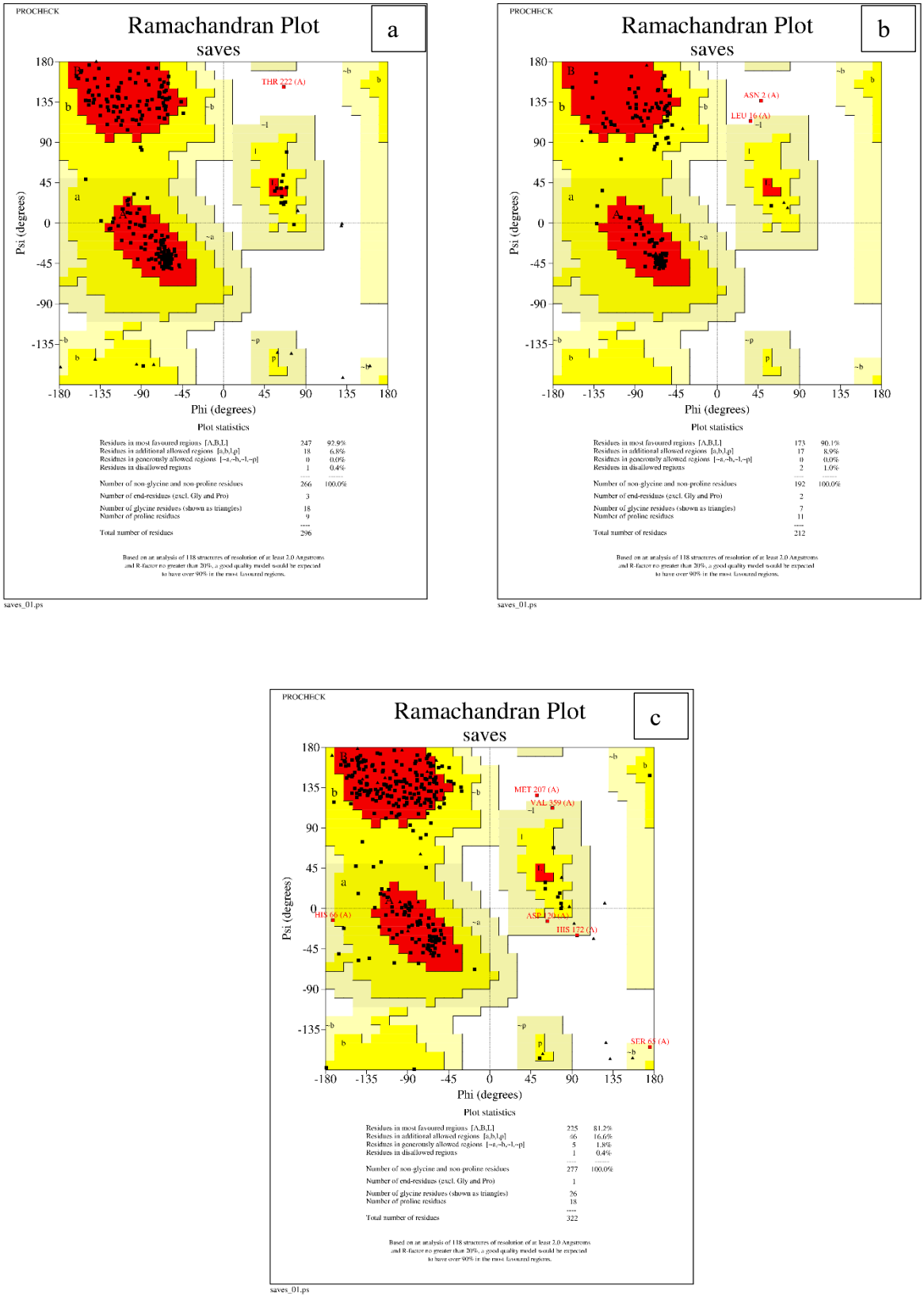

Fig. 7. Ramachandran plot analysis results for IL-1 (a) IL-6 (b) NF-κB (c)

An analysis of the Ramachandran plot was performed to assess the structural integrity of the target proteins. As shown in Figure 7, the proportions of residues in the Most Favored Regions (MFR) for IL-1, IL-6, and NF-κB were 92.9%, 90.1%, and 81.2%. On the other hand, the percentage of residues in the Disallowed Area was 0.4% for both IL-1 and NF-κB, while for IL-6, it was 1.0%. These findings mean that IL-1 and IL-6 have good MFR values, while for the Disallowed Area values, all three have good values. According to Gaffar *et al*. (2016), the protein structure standard is good if the number of residue plots in Most Favored Regions is more than 90% and the Disallowed Area is less than 20%.

The molecular docking results are further supported by data from previous studies, which have shown that the compound andrographolide can reduce TNF-α levels. TNF-α is a marker of inflammation, such as IL-8 and fibrinogen. Inflammation is a physiological phenomenon that happens due to prolonged oxidative stress. TNF-α and other markers of inflammation can be found in higher amounts when a person is aging (Sutanto *et al*., 2021). A study conducted by Mussard *et al*. (2020) on human dermal fibroblasts (HDFa) proved that andrographolide (5µg/mL) can decrease TNF-α expression in inflammatory conditions. Compounds from *A. paniculata* also regulate TNF-α protein. For example, andrographolide sodium bisulfate reduced higher TNF-α levels in mouse skin associated with UV exposure. In HaCaT cells, andrographolide sodium bisulfate downregulated p65 protein expression and decreased TNF-α production.

CONCLUSION

In silico analysis identified Interleukin-1 receptor-associated kinase 4, Inhibitor of nuclear factor kappa B kinase alpha subunit, and Interleukin-6 as target proteins for andrographolide, the active compound in Andrographis paniculata leaf. Molecular docking simulations showed a good binding affinity between andrographolide and the target proteins, with the lowest binding affinity recorded in interaction andrographolide and IL-1 (-7.5 kcal/mol). Based on its ability to reduce inflammatory responses and its stable binding interactions with target protein receptors in the photoaging mechanism, the bioactive compound andrographolide present in Andrographis paniculata is predicted to have the potential to inhibit the photoaging process.

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