JSMARTech
Journal of Smart Bioprospecting and Technology **p-ISSN**: 2686-0805 **e-ISSN**: 2714-7894
October 2022, VOL 03 NO 02 **DOI**:https://doi.org/10.21776/ub.jsmartech.2022.003.02.73

Virtual Prediction of The Potency of Common Jasmine (*Jasminum officinale* L.) Bioactive Compounds as Anti-Aging Agents for Natural Sunscreen

Fathiyah Nurul Izzah[1], Dawama Nur Fadlilah[1], Yohanna Sisilia Grace Sirait[1], Nandagesta Aurelia Shafa Wagmi[1], Abdullah Abdullah[1], Turhadi Turhadi[1] and Fatchiyah Fatchiyah[1 2] *

[1]Department of Biology, Faculty of Mathematics and Natural Sciences, Brawijaya University, Malang, East Java, Indonesia, 65145
[2]Research Center of Smart Molecule of Natural Genetics Resource, Brawijaya University, Malang, East Java, Indonesia, 65145

Submission: 26 August 2022; **Revised**: 19 September 2022; **Accepted**: 30 October 2022

***Corresponding author**: Fatchiyah Fatchiyah; **e-mail**: fatchiya@ub.ac.id

ABSTRACT. *UV exposure causes protein denaturation in the skin, leading to wrinkles and photoaging. Matrix metalloproteinases (MMPs) are enzymes that degrade the matrix and are associated with destruction processes like skin aging. Tyrosinase is the rate-limiting enzyme in the melanin synthesis process. We predict that Jasminum officinale L. bioactive compounds can be used as inhibitors for MMP1, MMP3, and tyrosinase. This study aims to compare the potential of bioactive compounds in Jasminum officinale L. as an inhibitor for the MMP1, MMP3, and tyrosinase receptors to prevent anti-aging. Vanillin, hydroxytyrosol, salicylic acid, 3,4-dihydroxy benzoic acid, oleoside-11-methyl ester, ursolic acid, oleanolic acid, and jasminine were retrieved from PubChem database as ligands, to dock with MMP1, MMP3, and tyrosinase as receptors that were retrieved from RCSB PDB. ADMET analysis was performed using pKCSM. Target-based virtual screening was performed using AutoDock Vina in PyRx. Visualization and interactions of amino acid residues was performed using Biovia Discovery Studio 2021. The complex structure was analyzed by molecular dynamics using the CABS-Flex 2.0 website. The oleoside-11-methyl ester compound has the highest potential as an MMP1 inhibitor, the 3,4-dihydroxy benzoic acid compound has the potential to inhibit MMP3, and hydroxytyrosol has the potential to inhibit tyrosinase involved in skin aging because it has low toxicity, highest binding affinity, and low fluctuations based on RMSF values in molecular dynamics simulations. Thus, this study indicated that bioactive compounds in common jasmine (Jasminum officinale L.) can be used as a candidate for organic sunscreen.*

Keywords: *anti-aging, Jasminum officinale L., MMP1, MMP3, sunscreen, tyrosinase, UV*

INTRODUCTION

Skin is the outermost layer of the body as well as the largest organ in humans that acts as a physical and immunological barrier against environmental stressors such as external pathogens, toxins, chemical agents, and UV. One of the environmental effects that has the most potential to negatively impact human skin damage is ultraviolet (UV) light [1]. The most abundant protein found in the extracellular matrix of human skin connective tissue is collagen which functions as a connective tissue attachment. UV exposure causes protein denaturation in the skin, leading to wrinkles and photoaging. This process induces the formation of MMPs (matrix metalloproteinases), which are enzymes that degrade the matrix and are associated with destruction processes such as inflammation, tumor invasion, and skin aging. One of the MMPs is MMP1 or collagenase-1 which contributes to collagen degradation in the photoaging process of human skin and is secreted by dermal fibroblasts [2].

Stromelysin-1 protein (MMP3) belongs to the family of MMPs that are induced during development, inflammation, and wound repair. Stromelysin can degrade extracellular matrix proteins such as E-cadherin, laminin, and type IV collagen. [3]. Therefore, inhibitors of MMP enzymes may have potential against skin aging as they prevent the loss of skin elasticity [2]. Tyrosinase is the rate-limiting enzyme in the melanin synthesis process. Although melanin has an important role in protecting the skin from the toxic effects of UV light, its overproduction correlates with hyperpigmentation-related disorders. Brownish or blackish blotchy spots are a sign of skin pigmentation which is one of the major changes due to increased tyrosinase activity and melanin production associated with aging [4].

Sunscreens are produced as topical products that serve to protect the skin from damage by UV rays. Sunscreens are able to prevent the development of solar radiation-mediated skin conditions such as aging, wrinkle formation,

unwanted pigmentation, and collagen loss [5]. Vitamin C (L-ascorbic acid) is one of the important antioxidants that can penetrate the skin due to its small molecular weight. This compound is water-soluble and heat-labile and has been shown to have anti-aging effects by inducing the production of collagen-1 and 3 which are important enzymes in collagen formation and inhibiting MMP1 [6]. In addition, ascorbic acid can also inhibit tyrosinase at protein active sites [7]. Research related to natural ingredients in sunscreens is increasing to minimize skin irritation due to sunscreen use or referred to as green sunscreens [5].

Plants that are constantly exposed to sunlight can produce special molecules that have protective activity and are able to resist damage due to UV radiation, such as alkaloids, phenolics, and carotenoids compounds, which are the main secondary metabolic compounds in plants [8]. One of the plants that contain antioxidant and photoprotective agents is common jasmine (*Jasminum officinale* L.). Common jasmine contains bioactive compounds such as flavonoids and phenolics that have potential as antioxidant and photoprotective [9]. Bioactive compounds in common jasmine can be assessed through *in silico* studies to predict their properties and see their potential as antioxidant and photoprotective agents. Molecular docking is a computational technique for conducting virtual screening on a large collection of compounds, ranking the results, and proposing structural hypotheses about how ligands can inhibit targets [10]. This study aims to determine the potential of bioactive compounds from common jasmine (*Jasminum officinale* L.) as an anti-aging agent for natural sunscreen candidates with *in silico* methods which are expected to be useful in the development of sunscreen products that are more effective and safer for the skin.

RESEARCH METHODS

Data mining

The bioactive compounds from common jasmine (*Jasminum officinale* L.) according to Al-Snafi (2018) [11] and ascorbic acid as control (CID: 54670067) were retrieved from PubChem database (https://pubchem.ncbi.nlm.nih.gov/) in SDF 3D structure. The protein receptors, collagenase-1 enzyme (MMP1) (PDB ID: 966C), stromelysin-1 (MMP3) (PDB ID: 1B3D) and tyrosinase (PDB ID: 2Y9X), were obtained from RCSB-PDB protein database (https://www.rcsb.org/) in PDB format. Receptors were prepared using Discovery Studio 2021 software to eliminate water molecules and native ligands from the protein. Ligands were then prepared to minimize the energy by using Open Babel in PyRx 0.8 software. The results were converted to PDB (.pdb) format.

ADMET Analysis

Canonical SMILES from common jasmine (*Jasminum officinale* L.) bioactive compounds were obtained from the PubChem database. ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) analysis was performed using pKCSM (https://biosig.lab.uq.edu.au/pkcsm/prediction) for bioactivity and physicochemical properties. The parameters used for screening were molecular weight, skin permeation, skin sensitization, and P-glycoprotein substrate.

Molecular Docking

Target-based virtual screening was performed using AutoDock Vina in PyRx 0.8 software to achieve the binding affinity value. Several key residues from MMP1 were GLU119, GLU209, GLU219, PRO238, and TYR240 [12]. Key residues from MMP3 were HIS201, HIS205, HIS211, LEU164, ALA165, and PHE210 [13]. Whereas key residues from tyrosinase were HIS61, ASN81, HIS 85, HIS94, HIS259, ASN260, HIS263, MET280, and HIS296 [14,15]. The grid box coordinations from every receptors were determined (Table 1). Visualization of the docking results in the form of 2D and 3D structures and interactions of amino acid residues was performed using Biovia Discovery Studio 2021 software, also colored and labeled. Binding affinity value results were compared with control.

Table 1. Specific active site grid of every receptor

Protein	Specific Active Sites Grid Coordination	
	Center	Dimension
MMP1	X: 4.3217 Y: -5.6617 Z : 31.9018	X: 20.667 Y: 22.8125 Z: 26.0439
MMP3	X: -2.6265 Y: 20.7686 Z: 26.6474	X: 17.5084 Y: 11.0059 Z: 19.2430
Tyrosinase	X: -11.5059 Y: -26.6089 Z: -40.4152	X: 21.0538 Y: 20.5545 Z: 17.0463

Molecular Dynamic

The complex structure was analyzed by molecular dynamics using the CABS-Flex 2.0 website (http://biocomp.chem.uw.edu.pl/CABSflex2). RMSF (Root Mean Square Fluctuation) analysis was performed to determine the flexibility or residue fluctuations during simulation between the ligand and the receptor. This analysis was carried out on the control and compounds with the highest binding affinity values for proteins with default

settings. The results of the analysis are presented in graphical form for each protein receptor.

RESULTS AND DISCUSSIONS

Screening of *Jasminum officinale* L. Bioactive Compounds

Compound data were obtained from literature studies of several research articles. The results of data mining are 60 bioactive compounds in the leaves and flowers of common jasmine. Canonical SMILES obtained from the PubChem database were used to obtain skin permeation (<-2.5), molecular weight (<500 g/mol), P-glycoprotein substrate (no), and skin sensitization (no) of common jasmine compounds from the pkCSM database. There are 47 out of a total of 60 compounds for which information is available in the database. Compounds that pass the screening results are polyphenols consisting of vanillin (CID 1183), hydroxytyrosol (CID 82755), salicylic acid (CID 338), and 3,4-dihydroxy benzoic acid (CID 72), as well as terpenoid compounds which include oleoside-11-methyl ester (CID 12313704), ursolic acid (CID 64945), oleanolic acid (CID 10494), and jasminine (CID 442551) (Table 2) [16].

A compound tends to have poor absorption or permeability if its molecular weight exceeds 500. The skin permeation parameter seen from the log Kp value <-2.5 has good skin permeability [17]. Materials that have good skin permeability can be used as a consideration for drug development. Another aspect of absorption is predicted through interactions with P-glycoprotein (Pgp), a transporter protein that plays several important roles during drug absorption, especially for pumping molecules out of the cell [18]. The required value from the P-gp pkCSM database is "no" which means that the compound cannot be removed from the cell because it is not a substrate for P-glycoprotein (Pgp) so that all of these compounds are well absorbed and can work on the skin. The skin sensitization parameter identifies the potential toxicity of a substance to cause allergic contact dermatitis. The compounds chosen for this molecular anchorage are those that do not cause toxic effects on the skin [19,20].

Table 2. Screening results of compounds on *Jasminum officinale* L. with ADMET analysis

Part	Compound	MW	Skin Permeation	Skin Sensitisation	P-glycoprotein substrate
Leaves	Vanillin	152.15	-6.37	No	No
	Oleoside-11-methyl ester	454.695	-2.735	No	No
Flowers	Hydroxytyrosol	154.165	-2.893	No	No
	Ursolic acid	456.711	-2.735	No	No
	Salicylic acid	138.122	-2.723	No	No
	Jasminine	220.228	-3.63	No	No
	3,4-dihydroxy benzoic acid	154.121	-2.727	No	No
	Oleanolic acid	456.711	-2.735	No	No

Molecular Interactions

Oleoside-11-methyl ester as a ligand on the MMP1 receptor has the lowest binding affinity (-6.8 kcal/mol), on the MMP3 receptor, the lowest binding affinity value is obtained from the oleoside-11-methyl ester (-6.5 kcal/ mol), and for the tyrosinase receptor, the lowest affinity comes from oleanolic acid (-6.6 kcal/mol), as can be seen in Table 3. The lower the binding affinity value between a molecule, the less energy is required to allow interaction between the two [21].

Based on the docking results, it was found that most of the bonds resulting from the interaction of the ligand and the receptor were hydrogen bonds, van der waals interactions, and hydrophobic bonds. The binding of the selected ligand as a potential inhibitor to the target through the molecular docking method is based on two types of interactions, hydrogen bonds and hydrophobic bonds. The interaction of these two bonds makes a significant contribution in forming the bond between the ligand and the target, thus affecting the inhibitory potential of the ligand compound [22].

The distance between the ligand and the active residue in the receptor can affect the stability of the bond and the strength of the interaction between the two. If the distance is too close or too far, the bond can become unstable and can be easily released [23]. Based on the results of the interaction between the ligand and the receptor, the distance between the hydrogen bonds formed from the interaction of compounds in common jasmine and the receptor varies in the range of 1.8–3.8 Å, while in the control it is in the range of 2.2–3.6 Å, this indicates a strong residual bond.

Several important residues in the MMP1 protein are GLU209, GLU219, PRO238, and TYR240. The amino acid GLU219 is an important residue for catalysis and is also involved in

hydrogen bond interactions. The interaction between compounds on the substrate at the binding site is the basis for MMP1 inhibition [12]. The oleoside-11-methyl ester compound has a hydrogen bond with GLU219, so it has the highest potential as an inhibitor of MMP1.

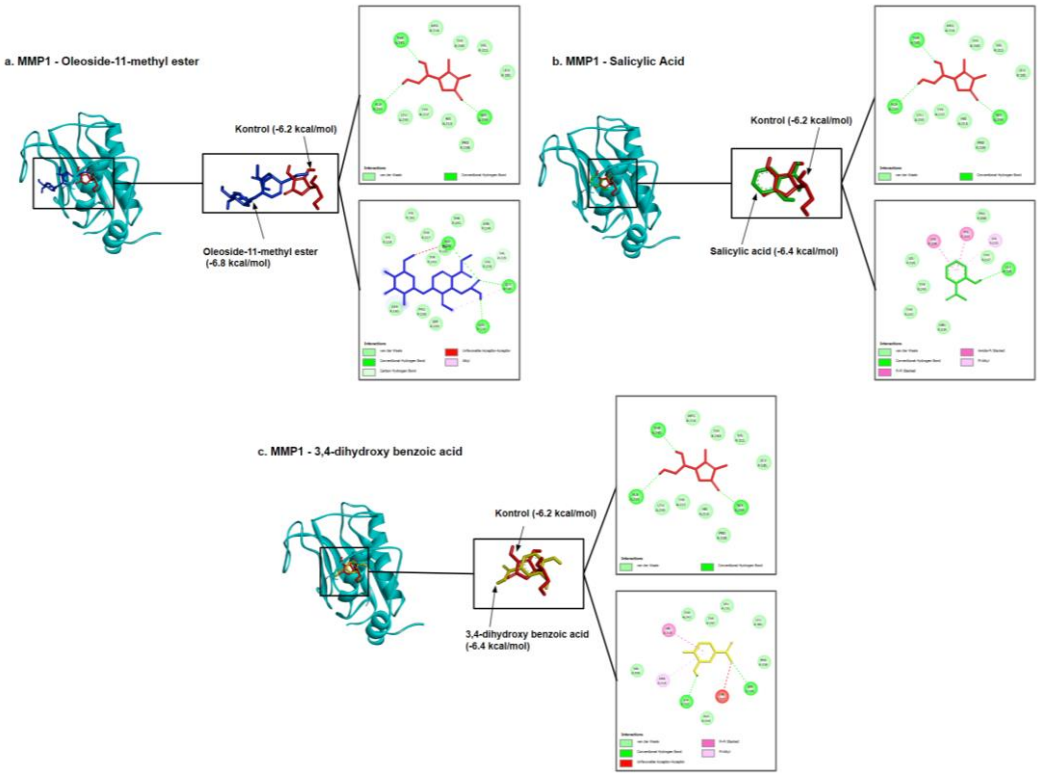


Figure 1. Visualization of 2D and 3D interactions of the MMP1 protein with compounds in common jasmine. A. Oleoside-11-methyl ester. B. Salicylic acid. C. 3,4-dihydroxy benzoic acid

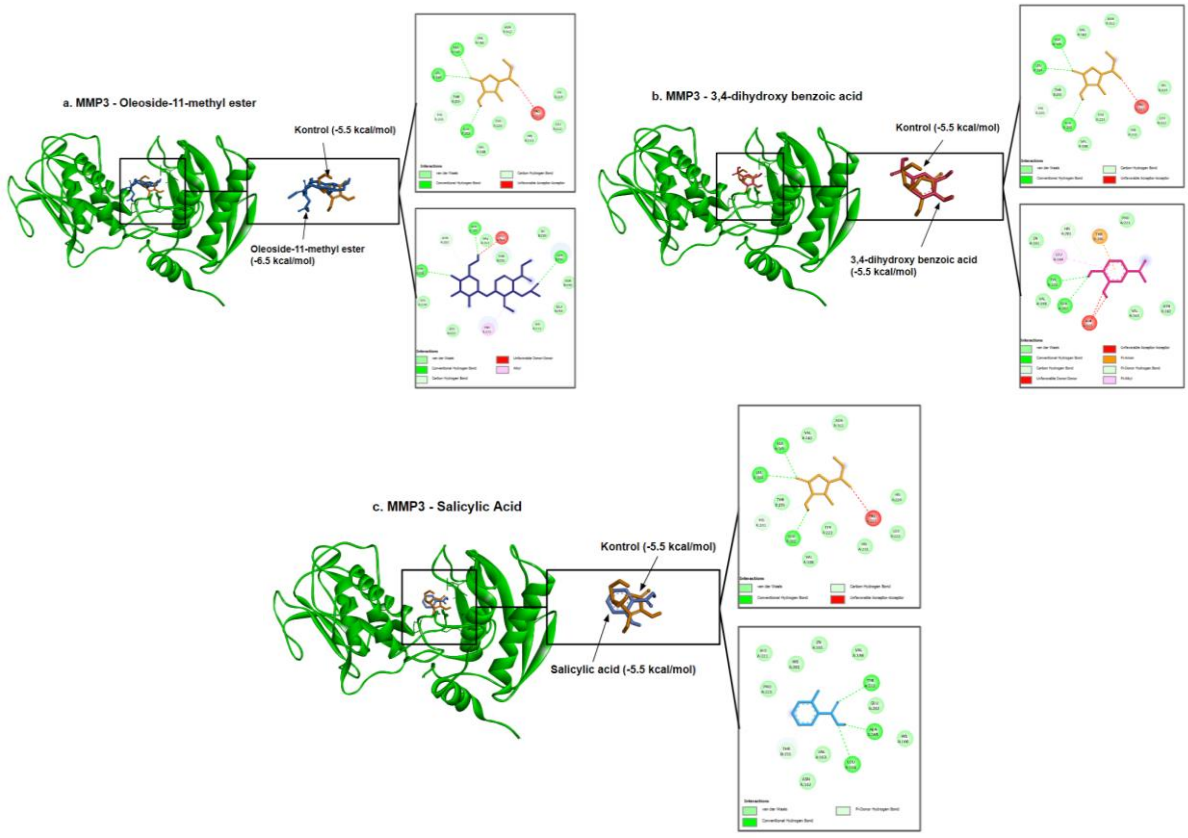


Figure 2. Visualization of 2D and 3D interactions of the MMP3 protein with compounds in common jasmine. A. Oleoside-11-methyl ester. B. Salicylic acid. C. 3,4-dihydroxy benzoic acid.

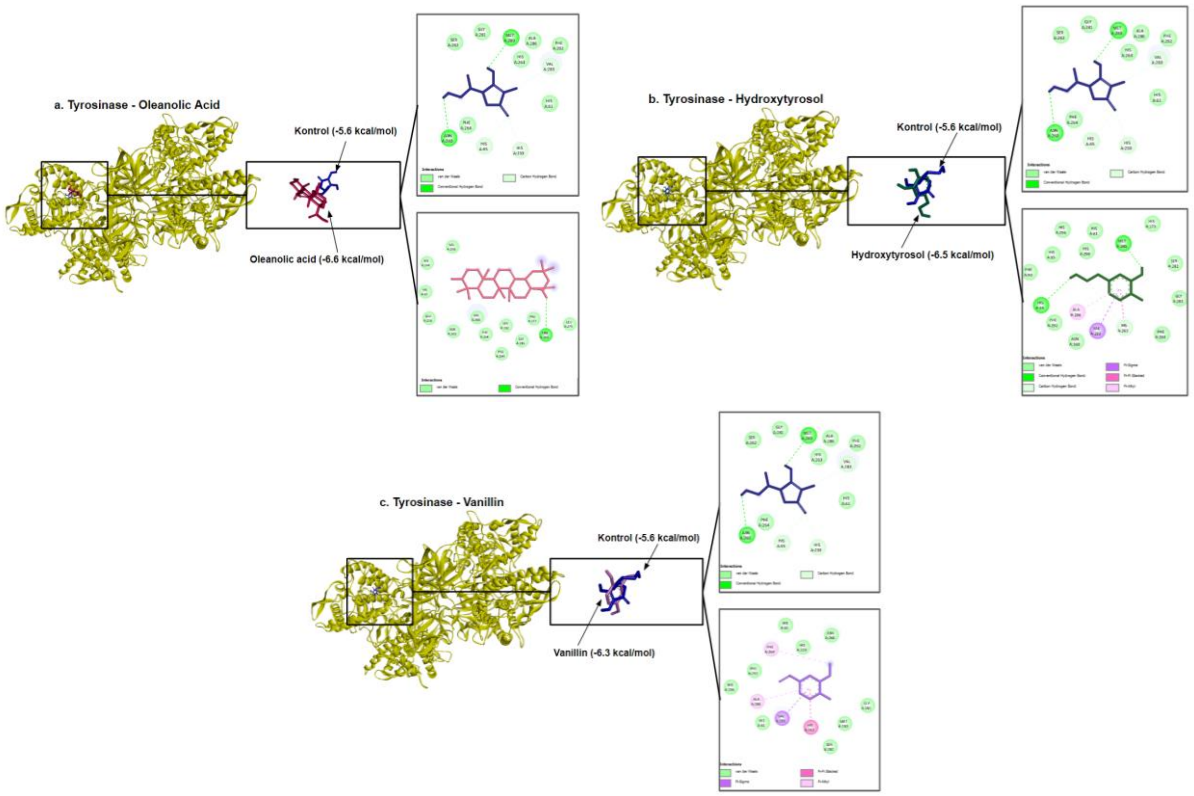


Figure 3. Visualization of 2D and 3D interactions of protein tyrosinase with compounds in common jasmine. A. Oleanolic acid. B. Hydroxytyrosol. C. Vanillin.

The inhibitor compound for MMP3 must conform to the S1' MMP3 pocket, bind to VAL198 and LEU164, have a flexible or semi-flexible structure and have hydrophobic interactions with the side chain residues S1-S2. The inhibitor also interacts with ASN162, VAL163, LEU164, ALA165 and LEU222 on the S2' hydrophobic pocket [13]. 3,4-dihydroxy benzoic acid has a hydrophobic bond with LEU164, so it can be concluded that this compound has a good relationship with MMP3.

Proteins with tyrosinase inhibitory activity have high hydrophobic and aromatic amino acids. This reaction can absorb ultraviolet light and form π-π interactions with Cu^{2+} in tyrosinase. Conjugation with Cu^{2+} can interfere with oxidative tyrosinase so that it can inhibit melanin synthesis [15]. The hydroxytyrosol and vanillin compounds have a π-π bond on the HIS263 residue which is located at the catalytic site [14]. Therefore, these two compounds have the potential to inhibit tyrosinase in the formation of melanin.

Molecular Dynamics

Molecular dynamics simulation is performed using RMSF (root mean square fluctuation). The fluctuation of each atom during simulation is shown through RMSF [24]. The residues calculated and averaged during the simulation are used to determine the region that is more flexible to changes in protein conformation [25]. The RMSF calculation involved 156 amino acid residues in MMP1 protein, 168 amino acids in MMP3 protein, and 523 amino acids in tyrosinase protein, along with three candidate compounds that have been selected based on the highest binding affinity value and ascorbic acid as a control. The ligands selected for MMP1 and MMP3 were oleoside-11-methyl ester, 3,4-dihydroxy benzoic acid, and salicylic acid, while for the tyrosinase receptor, the ligands used were oleanolic acid, hydroxytyrosol, and vanillin.

The results of the RMSF analysis between the ligands and MMP1 show that the three ligands have almost the same RMSF value as the control by showing a graph that follows most of the fluctuations given by the control. However, there are several points that show obvious differences in fluctuations. At residue positions 120-126, 168, and 228-234, ascorbic acid as the control has higher fluctuations than the three ligands. This suggests that the treatment can have a stabilizing effect on MMP1 in the region, potentially changing the dynamics of protein conformation. Whereas at residue positions 128 and 175 all three ligands had higher fluctuations, indicating that the treatment could cause flexibility in this specific region of MMP1 [26].

Table 3. Binding affinity and residue interactions of each compound with the receptor protein

No	Ligand	Hydrogen Bonds	Hydrophobic Bonds	Van der Waals interactions	*Binding Affinity* (kcal/mol)
MMP1					
1	Ascorbic acid (Control)	**ALA234, SER239, THR241**		**LEU181, ARG 214, VAL 215, HIS218, LEU235, TYR237, PRO238, TYR240**	-6.2
2	Oleoside-11-methyl ester	**LEU181**, ALA182, **HIS218**, GLU219		HIS183, **ARG214**, HIS228, **TYR237**, **TYR240**, **THR241**, ZN265	-6.8
3	3,4-dihydroxy benzoic acid	**LEU235**, **SER239**	**ARG214**, **HIS218**	**LEU181**, **VAL215**, ALA234, **PRO238**, **TYR240**, **THR241**, VAL246	-6.4
4	Salicylic acid	**LEU235**	**VAL215**, **HIS218**, **SER239**	**LEU181**, **ARG214**, **TYR237**, **TYR240**, **THR241**	-6.4
MMP3					
1	Ascorbic acid (Control)	**LEU164, ALA165, HIS201, GLU202**		**ASN162, VAL163, VAL198, HIS211, LEU222, TYR223, HIS224, THR255, ZN301**	-5.5
2	Oleoside-11-methyl ester	**ASN162**, **ALA165**, **TYR223**, GLN2366	PRO221	**VAL163**, **HIS211**, **LEU222**, **HIS224**, ILE239, ASN240, GLU254, **THR255**	-6.5
3	3,4-dihydroxy benzoic acid	**HIS201**, **GLU202**, **TYR223**	**LEU164**	**ASN162**, **VAL163**, **VAL198**, PRO221, **ZN301**	-5.5
4	*Salicylic acid*	**LEU164**, **ALA165**, **TYR223**, **THR255**		**ASN162**, **VAL163**, HIS166, **VAL198**, **HIS201**, **GLU202**, **HIS211**, PRO221, **ZN301**	-5.5
Tyrosinase					
1	Ascorbic acid (Control)	**HIS85, HIS259, ASN260, MET280, VAL283**		**HIS61, HIS263, PHE264, GLY281, SER282, ALA286, PHE292**	-5.6
2	*Oleanolic acid*	ARG268		**HIS85**, HIS244, VAL248, GLU256, **ASN260**, **PHE264**, LEU275, PRO277, **GLY281**, **SER282**, **VAL283**, PRO284	-6.6
3	Hydroxytyrosol	HIS94, **HIS263**, **MET280**	**HIS263**, **VAL283**, **ALA286**	**HIS61**, **HIS85**, PHE90, **HIS259**, **ASN260**, **PHE264**, HIS279, **GLY281**, **SER282**, **PHE292**, HIS296	-6.5
4	Vanillin		**HIS263**, **PHE264**, **VAL283**, **ALA286**	**HIS61**, **HIS85**, PHE90, **HIS259**, **ASN260**, **PHE264**, HIS279, **GLY281**, **SER282**, **PHE292**, HIS296	-6.3

The similarity of interactions is marked with bold letters (bold)

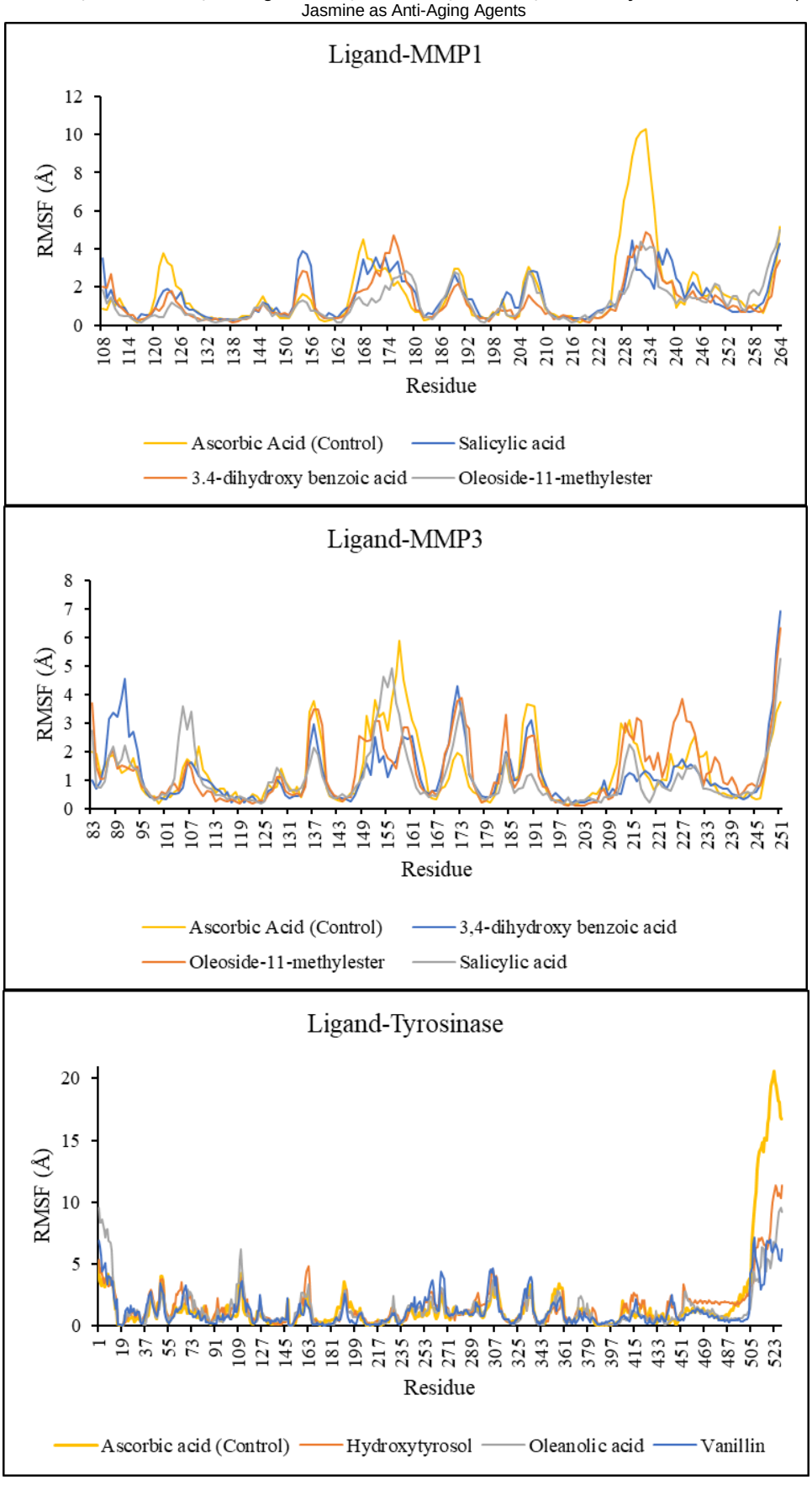


Figure 4. Molecular dynamics results of compounds with controls determined by RMSF (Å) values. A. Ligand - MMP1. B. Ligand - MMP3. C. Ligand - Tyrosinase.

The results of RMSF analysis between the ligands and MMP3 showed many fluctuations with different heights between the three ligands and the control. There were 10 residue positions where peaks occurred with the highest value ligand. The effect of these differences in fluctuations can be attributed to variations in the ligand's structural properties, binding affinity, or

specific interactions with protein active sites or allosteric regions. Such interactions can modulate the flexibility and stability of the protein, potentially affecting its function [27]. The results of the RMSF analysis between the ligands and tyrosinase showed a relatively uniform fluctuation pattern between the control and Oleanolic acid, Hydroxytyrosol, and Vanillin, indicating that the ligands interact with tyrosinase in the same way. The atoms with the highest peaks indicate that they are highly active, thus involved in protein conformational changes [25]. The interaction is good if the RMSF value is in the range of 1-3 Å. Peak values higher than this value may indicate a high degree of fluctuation and significant conformational changes [28]. The ligand that has the best interaction with MMP1 is oleoside-11-methyl ester, on MMP3 is salicylic acid, while on tyrosinase is hydroxytyrosol.

CONCLUSION

Bioactive compounds such as vanillin, hydroxytyrosol, salicylic acid, and 3,4-dihydroxy benzoic acid, oleoside-11-methyl ester, ursolic acid, oleanolic acid, and jasminine in common jasmine (*Jasminum officinale* L.) can be used as a candidate for organic sunscreen based on ADMET analysis. The oleoside-11-methyl ester compound has the highest potential as an MMP1 inhibitor, the 3,4-dihydroxy benzoic acid compound has the potential to inhibit MMP3, and hydroxytyrosol has the potential to inhibit tyrosinase, which are involved in skin aging because they have low toxicity, the highest binding affinity, and the lowest fluctuations based on RMSF values in molecular dynamics simulations.

ACKNOWLEDGMENT

We would like to express our gratitude to all our bioinformatics lecturers and laboratory assistants who have helped and supported us in completing this research.

REFERENCES

[1] Mohania D, Chandel S, Kumar P, et al. Ultraviolet Radiations: Skin Defense-Damage Mechanism. *Adv Exp Med Biol*, **2017** 996:71-87.

[2] Azmi, N., Hashim, P., Hashim, D. M., Halimoon, N., & Majid, N. M. N. Anti–Elastase, Anti–Tyrosinase and Matrix Metalloproteinase–1 Inhibitory Activity of Earthworm Extracts as Potential New Anti–Aging Agent. *Asian Pac J Trop Biomed*, **2014** 4: 348-352.

[3] Mirastschijski, U., Lupše, B., Maedler, K., Sarma, B., Radtke, A., Belge, G., & Ågren, M. S. Matrix Metalloproteinase-3 is Key Effector of TNF-α-Induced Collagen Degradation in Skin. *Int J Mol Sci*, **2019** 20(20): 5234.

[4] Pintus, F., Floris, S., Fais, A., Era, B., Porcedda, C., Tuberoso, C. I. G., & Caddeo, C. *Euphorbia characias* Extract: Inhibition of Skin Aging-Related. *Plants*, **2022** 11(1849): 1-11.

[5] Cefali, L. C., Ataide, J. A., Moriel, P., Foglio, M. A., & Mazzola, P. G. Plant-Based Active Photoprotectants for Sunscreens. *Int J Cosmet Sci*, **2016** 38(4): 346-353.

[6] Ganceviciene, R., Liakou, A. I., Theodoridis, A., Makrantonaki, E., & Zouboulis, C. C. Skin anti-aging strategies. *Dermatoendocrinol*, **2012** 4(3), 308-319.

[7] Deniz, S. S. F., Khan, M. T. H, Orhan, G., Gurkas, E., Orhan, I. E, Oztekin, N. S, & Ak, F. *In silico* approach to inhibition of tyrosinase by ascorbic acid using molecular docking simulations. *Curr Top Med Chem*, **2014** 14(12): 1469-1472.

[8] Torres-Contreras, A. M., Garcia-Baeza, A., Vidal-Limon, H.R., Balderas-Renteria, I., Ramírez-Cabrera, M. A., & Ramirez-Estrada, K. Plant Secondary Metabolites against Skin Photodamage: Mexican Plants, a Potential Source of UV-Radiation Protectant Molecules. *Plants (Basel, Switzerland)*, **2022** 2: 220.

[9] Jayalandri, N. L. G. L., Nangoy, E., Posangi, J., & Bara, R. A. Uji Efektivitas Ekstrak Melati (*Jasminum sambac*) Pada Penyembuhan Luka Insisi Kelinci (*Oryctolagus cuniculus*). *J eBm*, **2016** 4(1).

[10] Pagadala, N. S., K. Syed., & J. Tuszynski. Software for Molecular Docking: A Review. *Biophys Rev*, **2017** 9(2): 91–102.

[11] Al-Snafi, A. E. Pharmacology and Medicinal Properties of *Jasminum officinale* L.. *IAJPS*, **2018** 5(4): 2191-2197.

[12] Priya, S. V., Pradiba, D., Aarthy, M., Singh, S. K., Achary, A., & Vasanthi, M. *In-silico* Strategies for identification of potent inhibitor for MMP-1 to prevent metastasis of breast cancer. *J Biomol Struct Dyn*, **2021** 39(18): 7274-7293.

[13] Zeng, W., Shen, C., Mo, S., Ni, C., Lin, Y., Fang, Y., Yang H., Luo, G., Xiao, L., Zhan, R., & Yan, P. The Effective Treatment of Purpurin on Inflammation and Adjuvant-Induced Arthritis. *Molecules*, **2023** 28(1): 366.

[14] da Silva, A. P., Silva, N. D. F., Andrade, E. H. A., Gratieri, T., Setzer, W. N., Maia, J. G. S., & da Silva, J. K. R. Tyrosinase inhibitory activity, molecular docking studies and antioxidant potential of chemotypes of *Lippia origanoides* (Verbenaceae) essential oils. *PloS one*, **2017** 12(5): e0175598.

[15] Song, Y., Chen, S., Li, L., Zeng, Y., & Hu, X. The hypopigmentation mechanism of tyrosinase inhibitory peptides derived from food proteins: An overview. *Molecules*, **2022** 27(9): 2710.

[16] Krihariyani, D., Sasongkowati, R., & Haryanto, E. Studi *in silico* Sifat Farmakokinetik, Toksisitas, dan Aktivitas Imunomodulator Brazilein Kayu Secang Terhadap Enzim 3-Chymotrypsin-Like Cysteine Protease Coronavirus. *J Med Lab S*, **2020**, 1(1):76-90.

[17] Wahyuningsih, D., Purnomo, Y., & Tilaqza, A. *In Silico* Study of Pulutan (*Urena lobata*) Leaf

Extract as Anti Inflammation and Their ADME Prediction. *J Trop Pharm Chem* **2022**, 6(1): 30-37.

[18] Firdausy, A. F., Muti'ah, R., & Rahmawati, E. K. Predicting Pharmacokinetic Profiles of Sunflower's (*Helianthus annuus* L.) Active Compounds Using *in silico* Approach. *J Islam Med*, **2020**, 4(1): 1-7.

[19] Strickland, J., Daniel, A. B., Aguila, C., Ahir, S., Bancos, S., Craig, E., Germolec, D., Ghosh, C., Hudson, N. L., Jacobs, A., Lehmann, D. M., Matheson, J., Reinke, E. N., Sadrieh, N., Vukmanovic, S., & Kleinstreuer, N. Skin Sensitization Testing Needs and Data Uses by U.S. Regulatory and Research Agencies. *Arch. Toxicol.* **2019**, 93(2): 273–291.

[20] Bitew, M., Deslegn, T., Demissie, T. B., Belayneh, A., Endale, M., & Eswaramoorthy, R. Pharmacokinetics and Drug-Likeness of Antidiabetic Flavonoids: Molecular Docking and DFT Study. *PLOS ONE*, **2021**, 1-22.

[21] Agustin, A. T., Safitri, A., & Fatchiyah, F. An *in Silico* Approach Reveals the Potential Function of Cyanidin-3-o-glucoside of Red Rice in Inhibiting the Advanced Glycation End Products (AGES) Receptor (RAGE) Signaling Pathway. *Acta Inform Med*, **2020** 28(3): 170–179.

[22] Azam, S. S & Abbas, S. W. Molecular Docking Studies for the Identification of Novel Melatoninergic Inhibitors for Acetylserotonin-O-Methyltransferase Using Different Docking Routines. *Theor Biol Med Model*, **2013** 10:63.

[23] Naufa, F., Mutiah, L., & Indrawijaya, Y. Y. A. Studi in Silico Potensi Senyawa Katekin Teh Hijau (*Camellia sinensis*) sebagai Antivirus SARS CoV-2 terhadap Spike Glycoprotein (6LZG) dan Main Protease (5R7Y). *J Food Pharm Sci*, **2022** 10(1): 584-596.

[24] Peele, K. A., Durthi, C. P., Srihansa, T., Krupanidhi, S., Ayyagari, V. S., Babu, D. J., Indira, M., Reddy, A. R., & Venkateswarulu, T. C. 2020. Molecular docking and dynamic simulations for antiviral compounds against SARS-CoV-2: A computational study. *Inform Med Unlocked*, **2020** 19: 100345.

[25] Cai, Z., Zhang, G., Tang, B., Liu, Y., Fu, X., & Zhang, X. Promising anti-influenza properties of active constituent of *Withania somnifera* ayurvedic herb in targeting neuraminidase of H1N1 influenza: computational study. *Cell Biochem Biophys*, **2015** 72: 727-739.

[26] Wang, Y., Zheng, Q-C., Kong, C-P., Tian, Y., Zhan, J., Zhang, J-L., & Zhang, H-X. Heparin makes differences: A Molecular Dynamics Simulation Study on the Human βII-tryptase monomer. *Mol Biosyst*, **2015** 11: 252–261.

[27] Chu, X., Liu, F., Maxwell, B. A., Wang, Y., Suo, Z., Wang, H., Han, W., & Wang, J. 2014. Dynamic Conformational Change Regulates the Protein-DNA Recognition: An Investigation on Binding of A Y-Family Polymerase to its Target DNA. *PLOS Comput Biol*, **2014**.

[28] Kumar, N., Sood, D., Tomar, R., & Chandra, R. Antimicrobial Peptide Designing and Optimization Employing Large-Scale Flexibility Analysis of Protein-Peptide Fragments. *ACS omega*, **2019** 4(25): 21370-21380.