Predicting the Potency of Bioactive Compounds in *Murraya paniculata* as an Antiaging Agent: Collagenase Inhibition by Molecular Docking and Antioxidant Activity Assessment

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Abstract. Depleting collagen in the skin due to the appearance of the collagenase enzyme is one of the causes of aging. The objective of this study was to predict the effectiveness of some bioactive compounds found in the leaves of *Murraya paniculata*, known as Kemuning in Indonesia, by molecular docking as a potential inhibitor for the collagenase enzyme by analyzing the Binding Energy and the potential interaction between ligan and macromolecule as well as an antioxidant investigation by DPPH method. According to several studies, more than a hundred small molecules are contained in *M. paniculata*, and all of the ligands will be tested in-silico using AutoDock computational software. In contrast, Pymol and Discovery Studio were used for visualization. The research phase begins with ligand and macromolecule preparation, followed by grid box determination and AutoDock, analyzing the docking score and visualizing the dock conformations. Of all the ligands tested, 50 compounds had the potential to inhibit the performance of the collagenase enzyme with a binding affinity lower than −7 kcal/mol compared to Gallic Acid and Ascorbic acid. Compound noracronycine has the best binding affinity by −9.35 kcal/mol, while the compound with the lowest value is germacrene d by −7.06 kcal/mol. However, Diphenylpicrylhydrazyl (DPPH) testing method used in this study revealed that the antioxidant capacity (IC_{50}) of the plant extracted with methanol was 2,360.73 ppm, which was significantly different from that of the positive control. Since the large number of compounds that play a role in inhibiting the development of the collagenase enzyme from this plant exist, there is an opportunity to be used as raw material for cosmetics and nutraceuticals.

Keywords: collagen · collagenase · *Murraya paniculata* · *in silico* · molecular docking · antioxidant

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1 Introduction

The chronologically of skin aging is influenced by external factors such as ultraviolet rays, pollution, and smoking, as well as internal factors, for instance, changes in elasticity and collagen depletion [1, 2]. Both elastin and collagen are the most common extracellular matrix components in the human dermis layer [3]. Collagen fiber produced by fibroblasts is degraded by the matrix metalloproteinase-1 (MMP-1) called Collagenase, which can generate skin changes such as wrinkles, pigmentation, and tensile strength. Collagen, one of the most abundant proteins in the skin, has been used as an adjuvant to wound healing therapy [4]. Collagen-based biomaterials have been employed for wound healing due to potential biocompatibility, low immunogenicity, attracting wound healing sensitive cells (macrophages, fibroblasts, neutrophils, platelets.), and high flexibility [5, 6]. The enzyme in charge of collagen breakdown in the skin continuously increases over time [7]. As a result, for the treatment of such skin problems, the invention of perspective and selective inhibitors for the enzyme is indispensable [8].

Collagen is made up of 19 different amino acids. Glycine, proline, arginine, lysine, and hydroxyproline (which are unique among proteins) are five of them [4, 9]. Collagen comes in 29 different kinds, but only types I, II, and III are present in the human body [4, 9]. Collagen, particularly type I and III, is generally derived from bovine, rodent, avian, porcine, human skin, placenta, and marine sources [4, 10]. However, animal collagen has some drawbacks, such as the potential for allergies and the ease of contamination by microbes. Additionally, in some groups, religious restrictions are linked with the utilization of bovine and porcine-derived material. Alternatively, novel sources of collagen from plants have been examined. Thring et al. (2009) observed anti-collagenase activity in several plants, of which the highest activity was seen in white tea, green tea, rose tincture, and lavender by 87%, 47%, 41%, and 31%, respectively, meanwhile studied of *Hypericum hircinum* proved that it could inhibit the activity of collagenase enzyme by 156 μg/ml of IC_{50} [11]. Additional resources, Funalenone in Aspergillus niger as another potential for anti-collagen activity, can inhibit type I collagenase by 170/μM of IC_{50} [8]. Moreover, a collagenase inhibition study demonstrated that Quercetin was one of the most potent flavonoids, with an IC_{50} value of 286 mM [13]. Plant extracts were also used in this study to inhibit the collagenase enzyme's activity. *M. paniculata* is initially evaluated by molecular docking, which is essential and widely used in contemporary drug discovery, followed by an experimental test. Numerous studies have examined the bioactive molecules found in *M. paniculata.* The chromatography method identified the group of alkaloids, phenols, triterpenoids, and coumarin extracted from leaves, branches, or flowers [14]. Yuehcukene, Nobiletin, 3-Methoxynobiletin, meranzin hydrate, murragatin, omphamurrayone, murralongin, isomurralonginol isovalerate, murrangatin, minumicrolin, mupanidin, coumurrayin, toddalenone, auraptene, toddasin, methyl 2,5-dihydroxycinnamate, murrayatin, t-caryophyllene, γ-element, β-element, perolidol, spathulenol, caryophyllene oxide, β-caryophyllene, and germacrene D are some compounds found in the leaves part [14–17]. Investigation of this plant's roots indicated the presence of murrayacarine, 3-formylindole, coumurrayin, murragleinin, omphamurin, murraol, (-)- murracarpin, (±)- murracarpin, mupanidin, mexoticin, and ferulyl esters

[14–17]. On the other hand, molecules reported in the flower parts are murrayaculatine, yuehgesin-A, yuehgesin-B, and yuehgesin-C [14–17]. According to Afendy et al., other small molecules were also found in this plant, such as noracronycine, des-n-methylnoracronycine, des-n-methylacronycine, δ-selinene, cubebol, 14-hydroxy-9-epi-(e)-caryophyllene, copaene, meranzin, α-cadinol, zingiberenol, t-cadinol, cis-muurola-3, δ-cadinene, oplopanone, microminutin, α-ylangene, δ-cadinene, imperatorin, osthol, meranzin_hydrate, paniculidine B, suberosin epoxide, β-eudesmene, isomexoticin, anthragallol 2-methyl ether, β-cubebene, benzyl salicylate, auraptenol, 1-epi-cubenol, chloculol, β-eudesmol, cubenol, alpha-bergamotene, (2Z,6Z)-Farnesol, β-nootkatone, benzyl benzoate, β-sesquiphellandrene, γ-curcumin, phenylethyl_salicylate, mexoticin, β-element, (+)-γ-gurjunene, α-zingiberene, minumicrolin, omphalocarpin, germacrene, espatulenol, paniculidine C, (s)-β-bisabolene [18]. In-Silico study or Molecular modeling is an example of a computational-based technique that aims to figure out the interactions between macromolecules (target) and small-molecules (ligands) considered as activity during the drug discovery process which proposes to forecast chemical bound as well as binding affinity [19–21]. Though molecular docking is computationally expensive in the rapid drug development program, it is progressively being employed for screening massive compound databases to identify prospective medications [12].

An antioxidant is any substance that significantly delays or inhibits oxidation when present in low concentrations compared to the oxidizable substrate [22, 23]. Antioxidants are essential to prevent and repair cell damage in the body, mainly caused by free radical exposure. Various factors influence antioxidant effectiveness, including structural features, concentration, temperature, type of oxidation substrate, and physical state of the system [22]. When the proportion between reactive oxygen species (ROS) formation and detoxification promotes an improvement in ROS levels, oxidative stress takes place. The antioxidant testing method used in this study was 2,2-diphenyl-1-picrylhydrazyl (DPPH). DPPH radical is absorbed in 517 nm, and antioxidant properties can be derived in a second substrate-free system by measuring the decline in this absorbance [23].

The treatment made from natural ingredients can also effectively prevent the collagen in the human body from being depleted by suppressing the collagenase enzyme's activity. This study aimed to predict the effectiveness of some bioactive compounds found in *M. paniculata* leaves by molecular docking as potential inhibitors for the collagenase enzyme by analyzing the Binding Energy, the potential interaction between ligan and macromolecule, and antioxidant investigation by the DPPH method.

2 Materials and Method

2.1 Molecular Docking

The docking process was launched on a computer with an Intel Core (MT) i7-10700F 2.9 GHz processor and 32 GB of RAM. Each ligand's 3D conformer obtained from the National Library of Medicine (pubchem.ncbi.nih.gov) was arranged by Open Babel. In contrast, the collagenase protein's structure was retrieved from Protein Data Bank (www.rcsb.org) with PDB ID 5O7E was prepared using Autodock Tools. The water molecules

of crystalline protein were removed, the protein as a receptor was then separated from its natural ligand, and both were saved in PDB format. After that, the macromolecule and the ligand should be converted to the extension of PDB format, PDBQT [21] file but previously, by default adding hydrogen atom. Choosing the polar form and computing the Gasteiger charge must also be done. Since docking ligands to the whole surface of a protein typically computationally requires much time, the location of the binding site should be identified before [24]. The position of the binding site may be identified using Autodock Tools, and the adjustment for the number of points in the xyz dimension was 24 × 26 × 22 with center grid boxes in x, y, and z are 12.688, 1.755, and 15.720 respectively. Moreover, the gap between grid points measured 0.375 A. Converting ligan in PDB format to PDBQT and energy minimalization were carried by Open Babel. Autodock Wizard was utilized to execute the docking procedure using the Lamarckian Genetic algorithm with up to tenfold trials. Both Open Babel and Autodock Wizard are embedded in PyRx. Moreover, the docking data were visualized using PyMol 2.5.1 and Biovia Discovery Studio 2021, and the type of bond generated between the chemical and amino acids was analyzed.

2.2 Extraction Process and Antioxidant Activity

Materials used in this research include Methanol pro Analysis, L-ascorbic acid, Ethanol, DPPH (2,2-diphenyl-1-picrylhydrazyl), Gallic Acid, Quercetin, and Ascorbic acid were purchased from Sigma-Aldrich. About 100 g of *M. paniculata* plant material leaves originating from West Bali National Park were washed, dried, and extracted for 18 h with 2,000 ml of ethanol using the maceration technique. The extract was then concentrated in order to produce a viscous extract. A total of 100 μl of thick extract and 400 ml of 0.1 mM DPPH solution were added to a microplate. DPPH was incubated with extract in 5-range concentrations (31.25–500 μg/ml). The solution was homogenized with a shaker for three minutes, then incubated for thirty minutes, and the absorbance was measured at a wavelength of 517 nm using a microplate reader. L-ascorbic acid was the standard solution used in this analysis. The obtained absorbance value was utilized in the equation for calculating the free radical activity:

$$\%\ inhibition = \frac{Absorbance\ of\ control - absorbance\ of\ sample}{absorbance\ of\ control} \times 100$$

3 Results

3.1 Molecular Docking

The 5O7E receptor has only chain A and one reference ligand, ~{N}-(4-ethanoylphenyl)-2-sulfanyl-ethanamide (9NB), allowing the docking site to be easily determined. RMSD (Root Mean Square Deviation) was used to measure the accuracy between the atom coordinates and has frequently been employed in reproducing a known binding pose. In this study, RMSD generated by redocking reference ligan 9NB was 0.48 Å, conforms

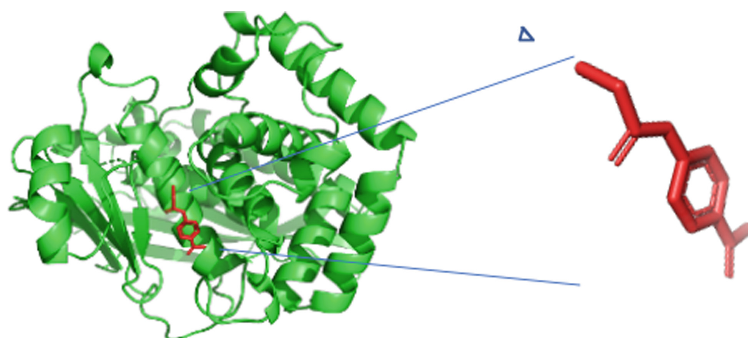

Fig. 1. A three-dimensional representation of reference ligan ~{N}-(4-ethanoylphenyl)-2-sulfanyl-ethanamide (9NB) in Crystal structure of Peptidase domain of Collagenase H (PDB ID: 5O7E)

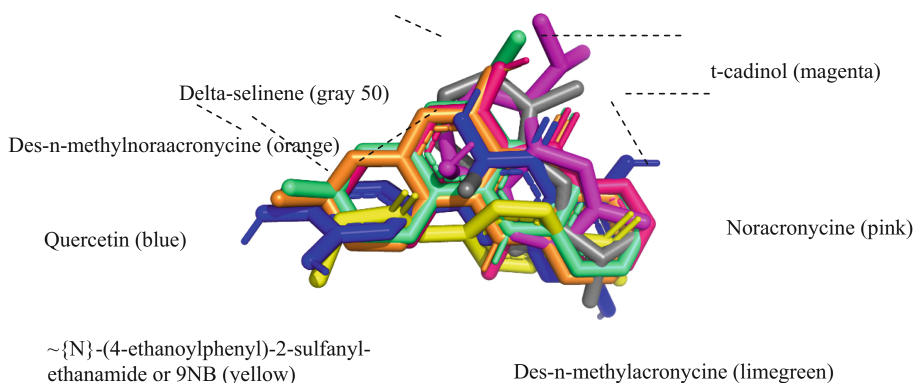

Fig. 2. Superimposition of reference ligan with best 5 docking score of *M. paniculata*'s substances and the best control positive

to the rule that the smaller the RMSD ligand (less than 2 Å), the better because it was getting closer to the initial pose and used as a standard in order to make the correct prediction of the bound structure [8]. In the crystal structure of the Peptidase domain of collagenase H (PDB ID: 5O7E), the location of the binding pocket reference ligand 9NB was visualized in Fig. 1. By utilizing Pymol tools, the reference ligan was superimposed and then aligned with five compounds with the best docking score in *M. paniculata* and the positive control, Quercetin. An illustration of the superimposed can be seen in Fig. 2.

Focusing on the reference ligand's original location and determining the grid box's position, as previously mentioned, docking was carried out with the consecutive outcomes achieved from the best, as shown in Table 1. To investigate the interactions between a receptor and its ligand Discovery Studio Visualizer was utilized. In this study, hydrogen bond, hydrophobic, and electrostatic were the three most common types of interactions found in complexes between macromolecules and ligands. Table 2 provides the type of Amino acid residue and the interactions that occur.

Table 1. The top 50 compounds in *M. paniculata* leave extract based on docking score

Compound	Docking score (kcal/mol)	**Compound**	Docking score (kcal/mol)
Noracronycine	−9.35	Suberosin epoxide	−7.72
Des-n-methylnoracronycine	−8.82	Alpha bergamotene	−7.72
Des-n-methylacronycine	−8.81	Beta eudesmene	−7.71
t-cadinol	−8.74	(2Z,6Z)-Farnesol	−7.71
Delta selinene	−8.54	Beta nootkatol	−7.7
Zingiberenol	−8.41	Oplopanone	−7.70
Cubebol	−8.35	Beta-cubebene	−7.69
14-hydroxy-9-epi-(e)-caryophyllene	−8.30	Anthragallol 2 methyl Ether	−7.66
Alpha cadinol	−8.29	Cubenol	−7.65
Meranzin	−8.28	1-epi-cubenol	−7.58
Copaene	−8.23	Benzyl_salicylate	−7.56
Quercetin**	−8.18	Omphalocarpin	−7.51
Auraptenol	−8.10	Chloculol	−7.50
Gamma-cadinene	−7.99	Beta elemene	−7.49
Cis-muurola-3	−7.99	Gamma curcumene	−7.43
Osthol	−7.98	9nb*	−7.35
Imperatorin	−7.96	Alpha zingiberene	−7.32
Phenylethyl salicylate	−7.93	(+)-Gamma gurjunene	−7.27
Paniculidine b	−7.89	Benzyl benzoate	−7.25
Paniculidine c	−7.87	Mexoticin	−7.24
Alpha-ylangene	−7.86	(S) beta bisabolene	−7.18
Microminutin	−7.86	Minumicrolin	−7.11
Meranzin hydrate	−7.84	Espatulenol	−7.06
Delta cadinene	−7.82	Germacrene d	−7.06
Beta eudesmol	−7.81	Ascorbic acid**	−4.60
Beta sesquiphellandrene	−7.76	Gallic acid**	−4.00
Isomexoticin	−7.75		

* reference ligan ** positive control

List the amino acid residues that are involved in the ligand-receptor interaction relationship shown in Table 2. Only compounds with a higher docking score than Quercetin are listed (Fig. 3).

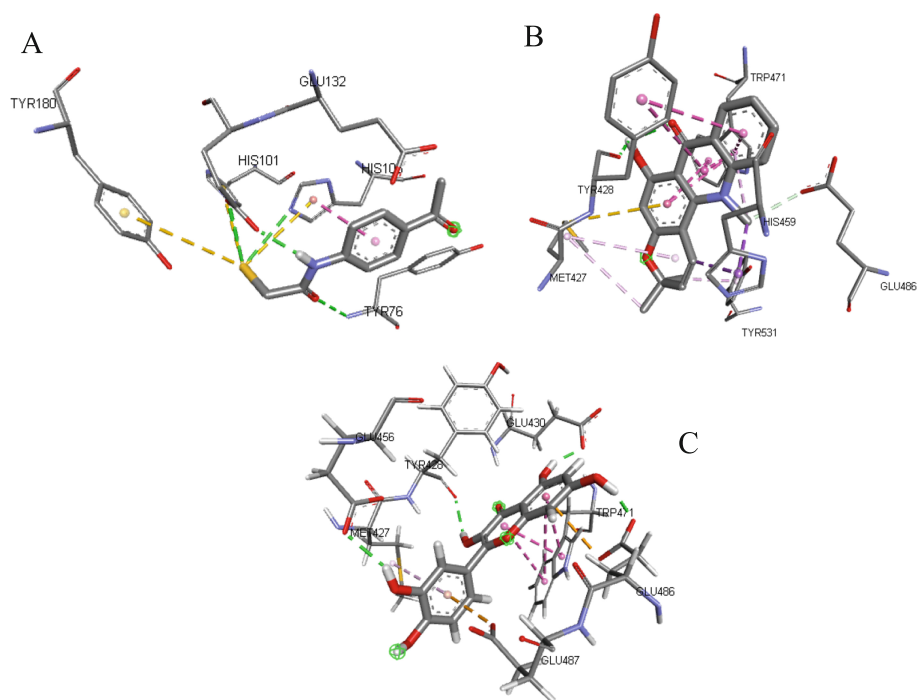

Fig. 3. Schematic representation of ligan and Active amino acid residue. A. Reference ligan B. Noracronycine C. Quercetin

Table 2. Active amino acid residues that play a role in ligand and receptor interactions

Compound	Amino acid residu
Noracronycine	TYR 428[a], GLU 486[a], HIS 459[b], TRP 471[b], TYR 428[b], MET 427[b], TRY 531[b]
Des-n-methylnoracronycine	TYR 428[a], HIS 459[a], HIS 459[b], TRP 471[b], TYR 428[b], MET 427[b], TYR 531[b], GLU 486[c]
Des-n-methylacronycine	GLU 430[a], TYR 428[a], HIS 459[a], TRP 471[b], TYR 428[b], HIS 459[b], MET 427[b], ILE 429[b], TYR 531[b], GLU 486[c]
t-cadinol	TYR 428[a] MET 427[b], TYR 428[b], HIS 459[b], TRP 471[b], TYR 531[b]
Delta selinene	MET 427[b], TYR 428[b], HIS 459[b], TRP 471[b]
Zingiberenol	HIS 455[a], GLU 487[a], MET 427[b], HIS 459[b], TRP 471[b]
Cubebol	TYR 428[a], MET 427[a], TYR 428[b], HIS 459[b], TRP 471[b]
14-hydroxy-9-epi-(e)-caryophyllene	TYR 428[a], GLU 456[a], TRP471[b], HIS 459[b], PRO 431[b], TYR 531[b]

(*continued*)

Table 2. (*continued*)

Compound	Amino acid residu
Alpha cadinol	GLU 487[a], TYR 428[b], HIS 459[b], TRP 471[b],
Meranzin	TYR 428[a], ILE 429[a], TRP 471[b], MET 427[b], PRO 431[b], HIS 459[b]
Copaene	MET 427[b], TYR 428[b], HIS 459[b], TRP 471[b], TYR 531[b]
Quercetin**	GLU 456[a], TYR 428[a], GLU 430[a], GLU 486[a], TRP 471[b], MET 427[b], GLU 486[c], GLU 487[c]
9nb	TYR 76[a], GLU 132[a], HIS 101[a], HIS 105[a], HIS 105[b]
Auraptenol	GLU 430[a], TYR 428[a], ILE 429[a], TRP 471[b], PRO 431[b], GLU 486[c]

Type of Interaction: a. Hydrogen bond, b. Hydrophobic, c. Electrostatic

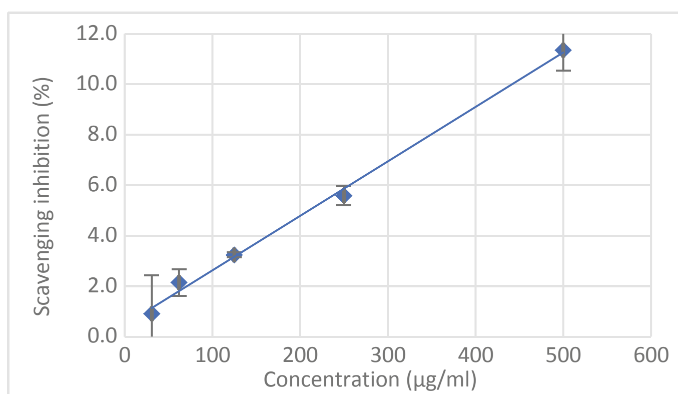

Fig. 4. DPPH scavenging activity of *M. paniculata* crude extract. DPPH was incubated with extract in 5 range concentration (31.25–500 µg/ml)

Table 3. IC_{50} of *M. paniculata* and three positive controls

Material	IC_{50} (ppm)
***M. paniculata* crude extract**	2360.73
Gallic acid	6.29
Ascorbic acid	16.55
Quersetin	16.75

3.2 Antioxidant Activity

The outcomes of the DPPH assay for *M. paniculata* plants and three positive controls are shown in Table 3. In contrast, the influence of concentration on scavenging inhibition of the plant can be found in Fig. 4.

4 Discussion

According to the study, several compounds found in *M. paniculata* had higher binding scores than positive control and reference ligands. Fifty compounds with a higher docking value than the positive control compounds, ascorbic acid and gallic acid. Eleven of the fifty compounds scored better than Quercetin (-8.18 kcal/mol), and 41 of the 50 compounds had a better docking score than the reference ligand. This demonstrates that *M. paniculata* has the potential to inhibit the collagenase enzyme based on in-silico screening, but this must be confirmed further by Molecular Dynamic and cellular mechanisms. The docking of small molecules and macromolecules (5O7E) involved three interactions: hydrogen, hydrophobic, and electrostatic bonds, whereas the reference ligand contained only two types: hydrogen and hydrophobic bonds. TYR 428, GLU 486, HIS 459, TRP 471, and MET 427 were examples of amino acid residues that appear most frequently in compounds containing these bonds. Hydrogen bonds play a significant role in the function, and interaction specificity of biomolecules [25], particularly interactions involving HIS and TRP, which contribute significantly to protein structure [26]. On the other hand, hydrophobic interactions are crucial to folding proteins. This is essential for maintaining the stability and biological activity of amino acids, as it allows the protein to reduce its surface area and decrease its unfavorable interactions with water. Electrostatic interaction is also quite crucial as it plays a role in maintaining binding stability and kinetics [27]. As can be seen in Table 3, the antioxidant analysis IC_{50} was significantly different from the positive control, 2360.73. This can be affected by the type of source of material and type of solvent used, in the extraction method, resulting in improper extraction of some essential compounds. Many reviews described a direct relationship between collagenase enzyme inhibition and antioxidant activity. Thring (2009) study revealed that anti-collagenase inhibitory activity had a strong correlation with total phenolic content means compounds with higher total phenolic content showed better anti-collagenase and antioxidant activity [3]. Hydrogen donors in phenolic content have an efficient antioxidant activity. Flavonoids are secondary metabolites reported to have antioxidant activity, the capacity of which depends on the number and position of free OH groups. Based on the plant's crude extract investigation, total phenolic content (TPC) and Total flavonoids were 112.76 ± 2.17 mg Gallic acid equivalent/g extract and 51.86 ± 2.61 mg Quercetin equivalent/g extract, respectively. Nevertheless, based on molecular docking *M. paniculata* contains many compounds that inhibit the formation of the collagenase enzyme, and it has the potential to be used as a raw material for cosmetics and nutraceuticals. Further research should focus on the in-vitro assay by a cellular mechanism.

5 Conclusion

Our findings indicate that several compounds in *M. paniculata* leaf extract can inhibit the collagenase enzyme based on molecular docking results and also have potential as anti-aging after testing for antioxidant activity. Therefore, there is an opportunity to be used as raw material for cosmetics and nutraceuticals.

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