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Molecular Docking and ADME Prediction of Compounds from Centella asiatica, Coenzyme Q10, and Ethyl Ascorbic Acid Targeting PPAR Receptors for Antioxidant Potential

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Abstract:
Peroxisome Proliferator-Activated Receptors (PPAR) are nuclear receptors that play a crucial role in regulating lipid metabolism, inflammatory responses, and cellular antioxidant defense. Activation of PPAR, particularly the PPAR-γ subtype, is known to enhance the expression of endogenous antioxidant enzymes such as superoxide dismutase (SOD) and catalase. This study aimed to evaluate the potential of active compounds from Centella asiatica (asiaticoside, madecassoside, asiatic acid, madecassic acid), Coenzyme Q10, and ethyl ascorbic acid as PPAR receptor agonists using an in silico approach through molecular docking methods and ADME (Absorption, Distribution, Metabolism, and Excretion) parameter analysis. Docking results showed that Coenzyme Q10, 2-O-ethyl ascorbic acid, and 3-O-ethyl ascorbic acid had the most negative rerank scores, indicating strong affinity for PPAR receptors. Meanwhile, asiaticoside and madecassoside demonstrated the most complex interactions with a high number of bonds, especially with key residues Arg284 and His280, despite having higher rerank scores. ADME predictions revealed that ethyl ascorbic acid had a balance between solubility, molecular size, and bioavailability, making it a potential candidate as an antioxidant agent targeting PPAR activation. Thus, this in silico approach provides preliminary insight into the molecular potential of natural compounds as modulators of PPAR activity for therapeutic applications.
Keywords: Centella asiatica, Coenzyme Q10, Ethyl Ascorbic Acid, molecular docking, PPAR-γ, antioxidant, ADMET.

Introduction

Indonesia is a tropical country with daily temperatures ranging from 26°C to 30°C, making sun exposure a dominant environmental factor throughout the year. Ultraviolet (UV) radiation, particularly UVA (95%) and UVB (5%), can penetrate the atmosphere and reach the human skin surface, which in the long term can lead to oxidative stress and accelerate skin aging or photoaging. UV radiation is known to trigger the formation of reactive oxygen species (ROS), which, if not neutralized immediately, can damage proteins, lipids, and DNA,

How to Cite:
Example: Susilawati, S., Doyan, A., Muliyadi, L., & Hakim, S. (2019). Growth of tin oxide thin film by aluminum and fluorine doping using spin coating Sol-Gel techniques. *Jurnal Penelitian Pendidikan IPA, 1*(1), 1-4. https://doi.org/10.29303/jppipa.v1i1.264

increasing the risk of inflammation, skin cancer, and various other degenerative disorders.

The human body has an endogenous antioxidant defense system involving enzymes such as superoxide dismutase (SOD), catalase, and glutathione peroxidase. This system maintains redox balance within cells. One of the transcription factors that plays an essential role in regulating antioxidant enzymes is the Peroxisome Proliferator-Activated Receptors (PPAR), which are nuclear receptors that regulate the expression of genes involved in lipid metabolism, inflammatory responses, and cellular defense against oxidative stress. Activation of PPAR-α and PPAR-γ subtypes has been shown to increase the expression of antioxidant enzymes, making them potential targets in anti-aging therapies and oxidative stress control.

Exogenous antioxidant compounds, especially those derived from natural sources, have been widely studied for their potential to neutralize ROS and enhance skin protection against UV exposure.

Coenzyme Q10, Ethyl Ascorbic Acid (EAA), and Centella asiatica are three natural active ingredients known to possess strong antioxidant activity. Coenzyme Q10 is a lipophilic compound involved in the mitochondrial electron transport chain and functions as a membrane antioxidant. It supports ATP synthesis and enhances the production of collagen and elastin, the two main proteins of the skin's extracellular matrix. In vitro studies have shown that Coenzyme Q10 can reduce UV-induced ROS and protect human keratinocyte DNA.

Ascorbic acid is a hydrophilic antioxidant that neutralizes free radicals by donating electrons. However, its original form is easily degraded. Ethyl Ascorbic Acid (EAA) has been developed as a more stable ascorbic acid derivative against heat, light, and oxidation. EAA has high bioavailability and effectiveness in inhibiting melanin synthesis, stimulating collagen formation, and preventing UV-induced skin damage.

Centella asiatica (L.) Urban is a medicinal plant from the Apiaceae family that contains active triterpenoids such as asiaticoside, madecassoside, asiatic acid, and madecassic acid. These compounds have been shown to possess anti-inflammatory and antioxidant activity, as well as promote wound healing and skin regeneration. Studies show that topical use of madecassoside in combination with ascorbic acid can improve skin firmness and hydration in older women. Additionally, asiaticoside is known to enhance type I collagen expression and suppress oxidative stress via the Smad signaling pathway.

Before these active compounds are formulated into topical preparations, in silico approaches such as molecular docking and ADME prediction are often conducted to evaluate their affinity for target receptors like PPAR and their pharmacokinetic characteristics. This approach provides a strong scientific foundation for the early selection of compounds, ensuring that the developed formulation has more targeted and effective therapeutic potential in dermatological applications.

Method

Compound Preparation

The three-dimensional (3D) structures of the active compounds used in this study—namely asiaticoside, madecassoside, asiatic acid, madecassic acid, Coenzyme Q10, 2-O-ethyl ascorbic acid, 3-O-ethyl ascorbic acid, and ascorbic acid were obtained from the PubChem database in .sdf format. These structures were then imported into Chem3D software, where geometry optimization was performed using the MMFF94 (Merck Molecular Force Field 94) method. This optimization aimed to achieve the lowest energy conformation of each ligand prior to docking.

Target Receptor

The three-dimensional structure of the target receptor, PPAR-δ (PDB ID: 3GWX), was downloaded from the Protein Data Bank (PDB). Receptor structure preparation was carried out using Molegro Virtual Docker (MVD) version 7.0 software. In this step, crystal water molecules and endogenous ligands bound to the co-crystallized structure were removed to prevent interference during the docking process. The active binding site was identified based on the original ligand's position as a reference.

Molecular Docking

The molecular docking process was conducted using the MolDock Score [GRID] algorithm integrated within Molegro Virtual Docker. The ligands were docked into the prepared PPAR receptor. Docking results were analyzed based on the binding affinity score (MolDock score), where a lower binding energy indicates stronger affinity and is considered as having the highest interaction potential with the target receptor.

ADMET Prediction

The ADME (Absorption, Distribution, Metabolism, and Excretion) parameter prediction was conducted using the DeepPK software. The analysis included logP value as an indicator of lipophilicity, Topological Polar Surface Area (TPSA), blood-brain barrier (BBB) permeability, and estimated oral bioavailability. The biological activity of the compounds was evaluated using PASS Online (Prediction of Activity Spectra for Substances) available at

https://www.way2drug.com/PASSOnline/index.php.
To assess potential toxicity and bioavailability
parameters, further analysis was conducted through pkCSM (Predicting Small-Molecule Pharmacokinetic and Toxicity Properties Using Graph-Based Signatures) at https://biosig.lab.uq.edu.au/pkcsm/. Lipophilicity characteristics and drug-likeness were reviewed based on Lipinski's Rule of Five using the software available at http://www.scfbio-iitd.res.in/software/drugdesign/lipinski.jsp. Additionally, toxic dose estimates and toxicity class predictions were obtained from the Protox platform (https://tox.charite.de/protox3/#), which provides structure-based predictions of various toxicological parameters.

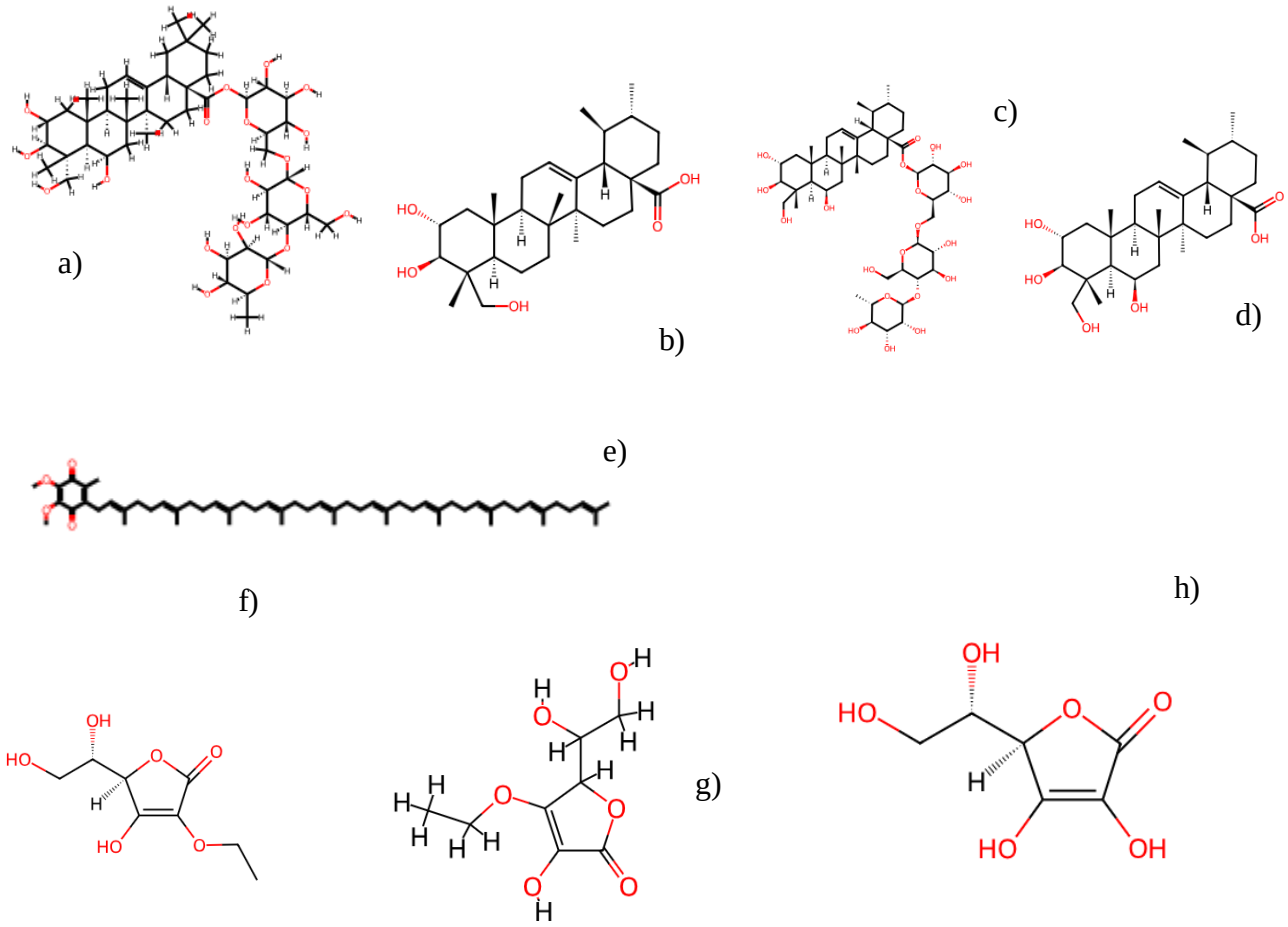

Figure 1. Chemical structur a) asiaticoside, b) asiatic acid, c) madecasosida, d) madesic acid, e) coenzyme Q10, f) 2-O-ethyl ascorbic acid, g) 2-O-ethyl ascorbic acid, h) ascorbic acid

Result and Discussion

To evaluate the validity and accuracy of the molecular docking process, Root Mean Square Deviation (RMSD) analysis was performed between the docked ligands and the original ligand in the crystal complex of the receptor. RMSD values provide insight into how much deviation occurs in ligand positioning compared to the reference ligand in the active site. The smaller the RMSD value (generally <2 Å), the more valid the docking result is considered. The RMSD values for each ligand against the target receptor are presented in Table 1.

Table 1. RMSD Values of Native Ligand (EPA1) on PDB ID: 3GWX Using MVD 7.0

Compound Name	RMSD value Repl 1	RMSD value Repl 2	RMSD value Repl 3	RMSD Value
EPA1	1,5104	1,8556	1,8263	1,7308

The 2D and 3D structures of the test compounds were docked using MVD 7.0 software (PDB ID: 3GWX). Each compound was docked three times to obtain the average binding energy value toward the PPAR receptor, as presented in Table 2.

Table 2. Docking Results Using MVD 7.0 Software

Compound name	Rerank score (Kkal/mol) Rep1	Rerank score (Kkal/mol) Rep2	Rerank score (Kkal/mol) Rep3	Average Rerank score (kkal/mol)
Asiaticoside	998,201	862,141	645,904	835,4153
asiatic acid	-26,4981	-26,2756	-41,7997	-31,5244
madecasoside	1977,9	992,13	55,8483	1008,626
madesic acid	54,724	55,0268	1267,37	459,0402
coenzyme Q10	4993,34	2272,09	6506,15	4590,526
2-O-ethyl ascorbic acid	-60,5123	-61,576	-64,1613	-62,0834*
3-O-ethyl ascorbic acid	-57,1075	-56,2162	-53,6264	-55,6501*
Native ligand (EPA1)	- 107,745	- 96,8307	-96,2093	-100,2622
Ascorbid acid	-52,638	-53,817	-53,2817	-53,2542

Docking analysis using MVD 7.0 software revealed varying binding affinities of ligands toward the PPAR receptor. The native ligand, Eicosapentaenoic Acid (EPA), had an average rerank score of –100.2622 kcal/mol, indicating strong receptor affinity and serving as the control in this study. Among the test compounds, Coenzyme Q10 had the second most negative average score (–62.0834 kcal/mol), suggesting strong and stable interaction with PPAR and potential as a PPAR agonist in modulating antioxidant pathways.

Ascorbic acid derivatives like 2-O-ethyl and 3-O-ethyl ascorbic acid showed good receptor affinity, with average scores of –62.0834 and –55.6501 kcal/mol, respectively, which were lower (more negative) than pure ascorbic acid (–53.2542 kcal/mol). These findings indicate that structural modification of ascorbic acid into ethyl derivatives not only enhances chemical stability but also biological activity via the PPAR pathway.

In contrast, triterpenoids from Centella asiatica, such as asiaticoside and madecassoside, showed positive rerank scores (835.4153 and 1008.626 kcal/mol, respectively), indicating unstable or ineffective binding. Their aglycone forms, asiatic acid and madecassic acid, displayed negative rerank scores (–31.5244 and 459.0402 kcal/mol, respectively), but still relatively weak compared to other compounds. Although Centella asiatica compounds have known antioxidant activity, their PPAR receptor interaction is not as strong as Coenzyme Q10 or ascorbic acid derivatives.

Overall, compounds with the most negative rerank scores—Coenzyme Q10, 2-O-ethyl ascorbic acid, and 3-O-ethyl ascorbic acid—demonstrated the greatest potential as PPAR agonists. This activity aligns with the PPAR's role in regulating antioxidant gene expression, making them promising therapeutic candidates for oxidative stress modulation through PPAR activation.

Table 3. Interaction of Test Compounds with Amino Acid Residues Compared to Native Ligand in PPAR Receptor (PDB ID: 3GWX) Using MVD 7

No	Name compound	Hydrogen bond	Sterik bond
1.	asiaticoside	Lys 265, Trp 264, Val 263, Arg 284, Asn 269, Gn 266, Gly 270, His 280, Ser 355, Leu 356, Leu 353, Phe 352	Lys 265, Trp 264, tyr 283, Arg 284, Asn 269, Leu 271, Gn 266, Gly 270, Leu 255, Ile 277, Val 281, His 280, Ser 355, Leu 356, Leu 353, Phe 352
2.	asiatic acid	Val 279, his 280, phe 282, Ile 277, glu 276, arg 284	Val 279, lys 275, tyr283, leu 255, glu 258, trp 2 64, ala 258, ile 249, val 281, his 280, phe 282, Ile 277, glu 276, arg 284
3.	madecasosida	Leu 262, gly 261, lys 260, val 263, glu 259	Trp 264, Leu 262, gly 261, ile 249, lys 260, leu 255, val 263, ala 258, glu 259, phe 352, arg 284, val 281, leu 353, asn 269, leu271, his 280, ile 277, val 279, phe 282, ser 278, thr 463, glu 276, tyr 283, phe 260, lys 257
4.	madesic acid	Ser 278, phe 282, tyr 283, his 280, val 279, glu 276, ile 277	Ser 278, gln 266, phe 282, tyr 283, his 280, glu 259, arg 284, val 341, trp 264, val 348, val 279, glu 276, ile 277, ser 278
5.	coenzyme Q10		Leu 262, trp 264, ser 278, thr 463, arg 357, glu 460, thr 459, thr 461, pro 359, phe360, val 279, ile 277, his 280, val 281, gln 266, leu 255, glu 259, val 263, arg 284, ala 258, gly 261,leu 262
6.	2-O-ethyl ascorbic acid	Arg 284, His 280, Val 281	Arg 284, His 280, Val 281, Glu 259, Trp 264, Leu 255, Ser 278, ile 277
7.	3-O-ethyl ascorbic acid	Arg 284, gin266, his 280, glu 259	Leu 255, val 281, ile 277, ser 278, his280, arg284, glu 255, trp 254
8	Ascorbic acid	Val 281, his 280, arg 284	Val 281, his 280, arg 284, leu 255, glu 253

Most of the test compounds were able to interact with the PPAR receptor through hydrogen and steric bonds with key residues in the active pocket, such as Arg284, His280, and Tyr283. Asiaticoside and madecassoside exhibited the highest number of interactions, including with critical residues His280 and Arg284, which are essential in ligand stabilization. Madecassoside even formed bonds with over 20 residues, indicating its potential as a partial PPAR agonist. Aglycone compounds such as asiatic acid and madecassic acid also interacted with important residues, although to a lesser extent than their glycoside counterparts, suggesting that sugar moieties enhance binding capability.

Coenzyme Q10 showed steric interactions with several key residues, including Arg284 and Glu259, in line with its high binding affinity score. Ethyl ascorbic acids (2-O and 3-O isomers) also interacted with Arg284 and His280, indicating efficient binding despite having fewer bonds. Conversely, ascorbic acid (ascorbic acid) only formed simple interactions, which may explain its lower binding affinity. The presence of interactions at key residues suggests that these compounds have potential as PPAR activity modulators.

Table 4. physicochemical Parameters Based on In Silico Predictions

No.	Name compound	MW	Log P	RB	HBA	HBD	PSA
1.	**asiaticoside**	959,133	-1,033	10	19	12	315,21
2.	**asiatic acid**	488,709	5033	2	5	4	97,99
3.	**madecasosida**	975.132	-2.062	10	20	13	335.44

4.	**madesic acid**	504.708	4.004	2	6	5	118.22
5.	**coenzyme Q10**	863,365	17.854	31	4	0	52,6
6.	**2-O-ethyl ascorbic acid**	204.178	-0.929	4	6	3	96.22
7.	**3-O-ethyl ascorbic acid**	204.178	-0.929	4	6	3	96.22
8.	**Ascorbic acid**	176.124	-1.407	2	6	4	107.22

The analysis of predicted ADME parameters in Table 4 reveals significant differences in pharmacokinetic characteristics among the test compounds. Asiaticoside and madecassoside have very high molecular weights (959.13 and 975.13 Da, respectively) and large Topological Polar Surface Area (TPSA) values (>300 Å²), indicating high polarity and a low likelihood of passive cell membrane penetration. Nevertheless, their high number of hydrogen bond donors (HBD) and acceptors (HBA) support the formation of strong hydrogen bonds with the active site of PPAR receptors. Overall, these properties make asiaticoside and madecassoside more suitable for topical applications than for oral absorption.

On the other hand, Coenzyme Q10 is extremely lipophilic with a logP value of 17.854 and very high structural flexibility (31 rotatable bonds). Such a high logP suggests poor water solubility and limited oral absorption without a special delivery system, such as a lipid-based formulation. However, its low TPSA (52.6 Å²) supports cellular penetration if properly formulated. Meanwhile, ethyl ascorbic acid (both 2-O and 3-O isomers) and ascorbic acid exhibit the most balanced ADME parameters. They have relatively low molecular weights (<210 Da), near-neutral logP values, and optimal TPSA (<107 Å²), supporting both oral absorption and skin penetration. Their moderate HBA and HBD values also allow for sufficient hydrogen bonding without compromising permeability.

In conclusion, madecassoside and asiaticoside excel in molecular interactions with PPAR receptors but have limited permeability, making them more suitable for topical use. Coenzyme Q10 has the strongest receptor affinity but presents pharmacokinetic challenges due to its extreme lipophilicity. Ethyl ascorbic acid and ascorbic acid offer the most balanced profiles in terms of affinity, solubility, and distribution, making them promising candidates for both systemic and dermatological antioxidant therapy

No	Compound name	Ames toxicity	Hepatotoxicity	Skin sensitization	LD_{50} (mg/kg, oral)[2]	Class tox
1	**Asiaticoside**	No	No	No	2000	4
2	**Asam asiatika**	No	No	No	2000	4
3	**Madecassoside**	No	No	No	5000	5
4	**Asam madekasik**	No	No	No	2000	4
5	**Coenzym Q10**	No	No	No	5000	5
6	**2-O-Asam etil askorbat**	No	No	No	2000	4

7	**3-O-Asam etil askorbat**	No	No	No	2000	4
8	**Asam askorbat**	No	No	No	2000	4

Conclusion

Based on the in silico study results, it can be concluded that asiaticoside, madecassoside, Coenzyme Q10, and ethyl ascorbic acid have potential as PPAR receptor agonists, which are involved in the regulation of antioxidant gene expression. Docking results showed that these four compounds were able to interact with key residues in the active site of the PPAR receptor—such as Arg284, His280, and Tyr283—through hydrogen and steric bonds. Among the test compounds, Coenzyme Q10 and ethyl ascorbic acid (both 2-O and 3-O isomers) exhibited the most negative rerank scores, indicating strong and efficient binding affinity to the receptor.

ADME analysis showed that asiaticoside and madecassoside possess high molecular weights and polarity, making them less suitable for systemic absorption but highly promising as topical agents due to their strong molecular interaction capabilities. Coenzyme Q10 exhibited the highest receptor affinity but also had very high lipophilicity, requiring special delivery systems to achieve optimal biological effectiveness. In contrast, ethyl ascorbic acid demonstrated a good balance of binding affinity, solubility, and bioavailability, as well as a low toxicity profile. Therefore, this compound is considered the most promising candidate for development in both dermatological and systemic therapies as an antioxidant agent based on PPAR receptor activation.

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