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Molecular Docking and ADMET Prediction of Bioactive Compounds from *Centella asiatica*, Coenzyme Q10, and Ethyl Ascorbic Acid Targeting PPAR Receptors as Potential Antioxidant Agents

Nur Khofifah[1], Dini Kesuma[2], Ni Luh Dewi Aryani[3*]

[1] Master's Degree Program Industrial Pharmacy, Faculty of Pharmacy, University of Surabaya, Surabaya, Indonesia.
[2] Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Surabaya, Surabaya, Indonesia.
[3] Department of Pharmaceutics, Faculty of Pharmacy, University of Surabaya, Surabaya, Indonesia.

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Corresponding Author:
Ni Luh Dewi Aryani
dewi_aryani@staff.ubaya.ac.id

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Abstract: Excessive ultraviolet exposure induces oxidative stress that accelerates skin aging, yet effective natural modulators of antioxidant pathways remain limited. This study investigated the potential of bioactive compounds from *Centella asiatica*, Coenzyme Q10, and ethyl ascorbic acid as PPAR receptor agonists associated with antioxidant regulation. An in silico approach was applied using molecular docking with Molegro Virtual Docker and ADME prediction analysis. Docking performance was evaluated using rerank scores and interaction analysis with key amino acid residues. Coenzyme Q10 and ethyl ascorbic acid isomers showed the most negative rerank scores (−62.08 and −55.65 kcal/mol), indicating strong receptor affinity. Asiaticoside and madecassoside formed extensive hydrogen and steric interactions with Arg284 and His280. ADME analysis revealed that ethyl ascorbic acid exhibited optimal balance between solubility, permeability, and safety. These findings suggest that ethyl ascorbic acid and Coenzyme Q10 are promising candidates for antioxidant therapy through PPAR activation. This study provides computational evidence supporting the development of natural antioxidant agents targeting oxidative stress–related skin damage.

Keywords: *Centella asiatica*; Coenzyme Q10; Ethyl ascorbic acid; Molecular docking; PPAR-γ

Introduction

Ultraviolet (UV) radiation is a universal environmental factor that significantly contributes to oxidative stress and premature skin aging worldwide. Chronic exposure to UVA and UVB radiation induces excessive production of reactive oxygen species (ROS), which damage cellular macromolecules such as proteins, lipids, and DNA, ultimately accelerating photoaging and increasing the risk of skin disorders (Pathak, 2022). The imbalance between ROS generation and antioxidant defense is recognized as a major mechanism underlying degenerative skin changes and inflammatory responses. This oxidative imbalance not only affects skin integrity but also disrupts cellular signaling pathways involved in tissue repair and regeneration, thereby intensifying long-term dermatological deterioration (Poljsak et al., 2013; Briganti et al., 2024).

The human body maintains redox homeostasis through endogenous antioxidant systems involving enzymes such as superoxide dismutase (SOD), catalase, and glutathione peroxidase. Regulation of these antioxidant defenses is closely linked to Peroxisome Proliferator-Activated Receptors (PPARs), a family of nuclear receptors that modulate gene expression related to lipid metabolism, inflammation, and oxidative stress. Activation of PPAR-α and PPAR-γ has been shown to

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enhance antioxidant enzyme expression and cellular protection mechanisms, positioning PPARs as important molecular targets in anti-aging and dermatological therapies. Through transcriptional regulation, PPAR signaling contributes to cellular adaptation against oxidative injury and supports maintenance of skin homeostasis (Muzio et al., 2021; Camps et al., 2012).

Although numerous natural antioxidants have been reported to protect against UV-induced oxidative damage, their molecular mechanisms of interaction with PPAR receptors remain insufficiently explored. Compounds such as coenzyme Q10, ethyl ascorbic acid, and bioactive triterpenoids from *Centella asiatica* demonstrate strong antioxidant and skin-protective properties. Coenzyme Q10 functions as a mitochondrial antioxidant and supports cellular energy production, while ethyl ascorbic acid offers enhanced stability and bioavailability compared to conventional vitamin C. Meanwhile, *Centella asiatica* contains triterpenoids known for anti-inflammatory and regenerative activities. However, comparative evaluation of their receptor-binding affinity and pharmacokinetic suitability as PPAR modulators has not been comprehensively investigated using integrated computational approaches, creating a gap in understanding their targeted molecular potential (Buranasudja et al., 2021; Golonka et al., 2022).

Recent advances in computational drug discovery enable rapid screening of bioactive compounds through molecular docking and absorption, distribution, metabolism, excretion, and toxicity (ADMET) prediction, providing early insight into receptor interactions and pharmacokinetic behavior. These in silico techniques allow efficient identification of promising compounds before experimental validation, thereby accelerating the development of targeted therapeutic agents. Nevertheless, limited studies have simultaneously examined natural antioxidant compounds targeting PPAR receptors in the context of dermatological oxidative stress. Therefore, this study aims to evaluate the binding affinity and ADMET characteristics of active compounds from *Centella asiatica*, Coenzyme Q10, and ethyl ascorbic acid as potential PPAR agonists. This research is urgent for supporting the development of targeted antioxidant therapies and innovative dermatological formulations based on molecular evidence, contributing to more effective strategies for preventing oxidative skin damage (Sobhon et al., 2023; Thomsen & Christensen, 2006).

Method

Research Design, Time, and Location

This study employed a quantitative in silico computational research design using molecular docking and ADMET prediction approaches. The research was conducted from January to June 2025 at the Computational Chemistry Laboratory, University of Surabaya, using licensed molecular modeling software and validated online pharmacokinetic prediction platforms.

Population and Sample

The research population consisted of natural antioxidant compounds reported to interact with oxidative stress pathways. The sample included eight selected ligands: asiaticoside, madecassoside, asiatic acid, madecassic acid, coenzyme Q10, 2-O-ethyl ascorbic acid, 3-O-ethyl ascorbic acid, and ascorbic acid. The molecular structures of these compounds are presented in Figure 1. The target protein was the three-dimensional structure of Peroxisome Proliferator-Activated Receptor delta (PPAR-δ) obtained from the Protein Data Bank (PDB ID: 3GWX).

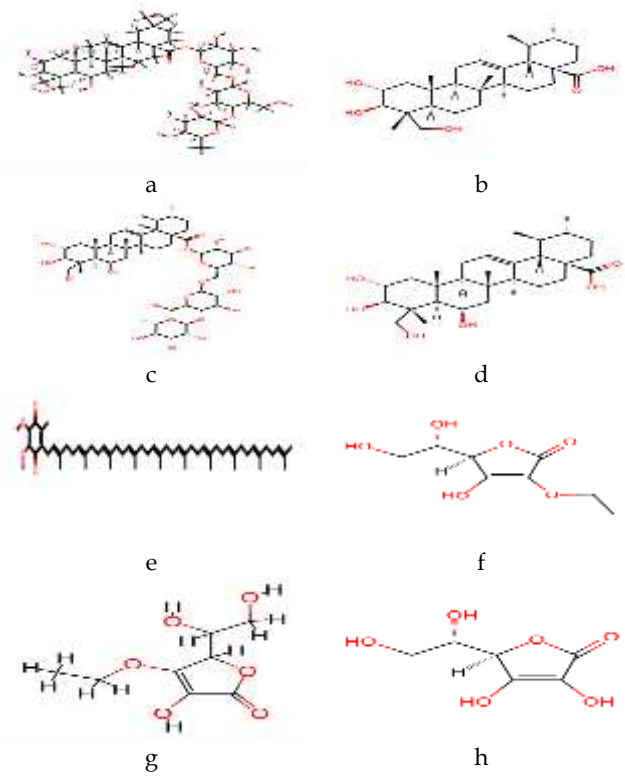

Figure 1. Chemical structure a) asiaticoside, b) asiatic acid, c) madecasosida, d) madesic acid, e) coenzyme Q10, f) 2-O-ethyl ascorbic acid, g) 2-O-ethyl ascorbic acid, h) ascorbic acid

Research Methods

This study integrated ligand preparation, receptor preparation, molecular docking simulation, and ADMET prediction. Molecular docking was performed to evaluate ligand–receptor binding affinity and interaction stability, while ADMET analysis was used to predict pharmacokinetic and toxicity profiles (Morris et al., 2009).

Research Stages

Compound Preparation

Three-dimensional (3D) structures of all ligands were retrieved from the PubChem database in Structure Data File (.sdf) format to ensure standardized molecular representations. The selected compounds included asiaticoside, madecassoside, asiatic acid, madecassic acid, Coenzyme Q10, 2-O-ethyl ascorbic acid, 3-O-ethyl ascorbic acid, and ascorbic acid. Each structure was imported into Chem3D software for geometry optimization using the Merck Molecular Force Field (MMFF94). This force field is widely used for small organic molecules because it provides reliable estimations of molecular energy and geometry. Energy minimization was performed iteratively until a stable lowest-energy conformation was achieved. This step was essential to eliminate steric strain and unrealistic bond angles, ensuring that the ligands adopted biologically relevant conformations prior to docking simulations (Trott & Olson, 2010).

Target Receptor Preparation

The three-dimensional crystal structure of Peroxisome Proliferator-Activated Receptor delta (PPAR-δ) with PDB ID 3GWX was obtained from the Protein Data Bank (PDB). Receptor preparation was conducted using Molegro Virtual Docker (MVD) version 7.0 to ensure proper docking conditions. All crystallographic water molecules, ions, and co-crystallized ligands were removed to prevent interference with ligand binding simulations. Hydrogen atoms were added to stabilize the protein structure, and partial charges were assigned according to the software's default parameters (Saputro et al., 2024). The active binding cavity was identified automatically and verified based on the position of the native ligand in the crystal structure. Proper receptor preparation is critical to maintain structural integrity and ensure accurate prediction of ligand–receptor interactions (Thomsen & Christensen, 2006).

Molecular Docking Simulation

Molecular docking simulations were performed using the MolDock Score [GRID] algorithm integrated in Molegro Virtual Docker. This algorithm applies a guided differential evolution search strategy to explore optimal ligand conformations within the receptor binding pocket. Each ligand was docked into the identified active site using standardized docking parameters, including multiple simulation runs to ensure reproducibility (Elkhattabi, 2023; Errington et al., 2025). The docking process generated several binding poses ranked according to MolDock scores, which represent estimated binding energies. Lower (more negative) MolDock scores indicate stronger predicted binding affinity and greater interaction stability (Thomsen & Christensen, 2006). Interaction analysis was conducted to identify hydrogen bonds, steric interactions, and key amino acid residues involved in ligand binding. The best docking pose for each compound was selected based on the lowest energy score and favorable interaction patterns (Saputro et al., 2024; Damale et al., 2019).

ADMET Prediction

Pharmacokinetic and toxicity properties of the selected compounds were evaluated using multiple computational prediction platforms. DeepPK software was used to estimate absorption and distribution parameters, including lipophilicity (logP) and topological polar surface area (TPSA), which influence membrane permeability. PASS Online was applied to predict the probability of biological activity spectra of the compounds. pkCSM was utilized to assess absorption, distribution, metabolism, excretion, and toxicity (ADMET) profiles using graph-based signatures (Pires et al., 2011). Drug-likeness was evaluated according to Lipinski's Rule of Five, which considers molecular weight, hydrogen bond donors and acceptors, and lipophilicity as indicators of oral bioavailability (Gheidari et al., 2024). Additionally, toxicity class predictions and lethal dose estimations were obtained using the Protox platform. The combined ADMET analysis provided a comprehensive evaluation of the pharmacokinetic suitability and safety profile of each compound (Karakoti et al., 2022).

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 (Chang et al., 2023).

Result and Discussion

Docking Validation Based on RMSD Analysis

Validation of the docking protocol is a critical step to confirm that the computational method can accurately

reproduce ligand binding within the receptor active site. Root Mean Square Deviation (RMSD) analysis was used to compare the re-docked native ligand with its crystallographic position. RMSD values below 2 Å are widely accepted as indicators of reliable docking performance and accurate ligand orientation. This validation ensures that the docking parameters are suitable for screening the tested compounds (Najmi et al., 2023).

The RMSD values of native ligand Eicosapentaenoic Acid (EPA1) on PDB ID: 3GWX were 1,7308 ± 0,1914. The RMSD values were below 2 Å, confirming that the docking protocol was valid and reproducible. Similar RMSD thresholds have been reported in previous docking validation studies, where values under 2 Å indicate accurate prediction of ligand binding poses (Syamsul et al., 2022; Amiri et al., 2025). Therefore, the validated docking system was considered appropriate for further molecular interaction analysis.

Binding Affinity of Test Compounds Toward PPAR Receptor

Following docking validation, the binding affinities of the tested compounds toward the PPAR receptor were evaluated. Each ligand was docked three times to minimize computational variability and obtain reliable average rerank scores (Touny et al., 2025). Binding energy values (rerank scores) provide an estimation of ligand–receptor interaction strength, where more negative values indicate stronger predicted affinity (Rhahmadini et al., 2025).

The rerank scores of all compounds are presented in Table 1. The rerank score values indicate variations in binding affinity between each compound and the receptor. The compound with the most negative binding energy was 2-O-ethyl ascorbic acid (−62.0834 ± 1.877), followed by 3-O-ethyl ascorbic acid (−55.6501 ± 1.808) and ascorbic acid (−53.254 ± 0.590), indicating relatively strong binding affinities. Meanwhile, the native ligand (EPA1) showed a value of −100.262 ± 6.488, serving as a reference with the highest binding affinity.

In contrast, some compounds, such as asiatic acid (−31.5244 ± 8.899), exhibited weaker binding affinity. The high positive values observed for asiaticoside (868.749 ± 26.767), madecassoside (1008.626 ± 62.676), madesic acid (458.374 ± 5.771), and coenzyme Q10 (4590.527 ± 367.954) indicated less stable or unfavorable interactions with the receptor.

Table 1. The Rerank Scores of All Compounds

Compound name	Rerank score (kkal/mol)
Asiaticoside	868,749 ± 26,767
asiatic acid	-31,5244 ± 8,899
Madecasoside	1008,626 ± 62,676
madesic acid	458,374 ± 5,771
coenzyme Q10	4590,527 ± 367,954
2-O-ethyl ascorbic acid	-62,0834* ± 1,877
3-O-ethyl ascorbic acid	-55,6501* ± 1,808
Native ligand (EPA1)	-100,262 ± 6,488
Ascorbid acid	-53,254 ± 0.590

The interaction of test Compounds with amino acid Residues compared to the native ligand in PPAR Receptor (PDB ID: 3GWX) is presented in Table 2. This showed compounds that share similar amino acid residues with the native ligand exhibit better binding potential. 2-O-ethyl ascorbic acid, 3-O-ethyl ascorbic acid, and ascorbic acid shared key residues such as Arg 284, His 280, and Val 281, indicating good binding affinity. Asiatic acid and madesic acid showed more limited similarities, while asiaticoside, madecassoside, and coenzyme Q10 had fewer similarities with reference compound. In general, the greater the similarity of interacting residues with the native ligand, the better the potential interaction and biological activity (Azmal et al., 2024; Broccatelli & Brown, 2014).

Table 2. Interaction of Test Compounds with Amino Acid Residues Compared to the Reference Compound in the PPAR receptor (PDB ID: 3GWX)

Name compound	Hydrogen bond	Sterik bond
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
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
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
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
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

Name compound	Hydrogen bond	Sterik bond
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
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
Ascorbic acid	Val 281, his 280, arg 284	Val 281, his 280, arg 284, leu 255, glu 253

Physicochemical and ADME Properties

Evaluation of physicochemical parameters is important to predict compound absorption and bioavailability. Properties such as molecular weight, lipophilicity, hydrogen bonding capacity, and topological polar surface area influence membrane permeability and pharmacokinetic behavior. Balanced ADME characteristics are essential for therapeutic development.

The predicted physicochemical properties are presented in Table 3.

Table 3. Physicochemical Parameters Based on In Silico Predictions

Name compound	MW	Log P	RB	HBA	HBD	PSA
asiaticoside	959.133	-1,033	10	19	12	315.21
asiatic acid	488.709	5033	2	5	4	97.99
madecasosida	975.132	-2.062	10	20	13	335.44
madesic acid	504.708	4.004	2	6	5	118.22
coenzyme Q10	863,365	17.854	31	4	0	52.6
2-O-ethyl ascorbic acid	204.178	-0.929	4	6	3	96.22
3-O-ethyl ascorbic acid	204.178	-0.929	4	6	3	96.22
Ascorbic acid	176.124	-1.407	2	6	4	107.22

The analysis of predicted ADME parameters in Table 3 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.

Ethyl ascorbic acid derivatives demonstrated the most balanced ADME characteristics among the tested compounds, indicating favorable pharmacokinetic behavior. These compounds exhibited optimal molecular weight, polarity, and hydrogen bonding capacity, which are essential parameters for membrane permeability and oral bioavailability. Balanced solubility and permeability are critical factors in determining drug-likeness and biological effectiveness.

Previous pharmacokinetic studies have shown that stabilized derivatives of vitamin C possess improved chemical stability and enhanced transdermal and systemic delivery compared to native ascorbic acid. Research by Pullar et al. (2017) reported that vitamin C derivatives improve bioavailability and antioxidant performance due to increased molecular stability and cellular uptake. Similarly, demonstrated that modified vitamin C compounds exhibit enhanced penetration properties, supporting their pharmaceutical and cosmetic applications (Makrantonaki & Zouboulis, 2007).

In contrast, large glycosidic compounds such as asiaticoside and madecassoside showed high molecular weight and elevated polar surface area, which may limit passive diffusion across biological membranes. Previous studies on Centella asiatica phytochemicals indicate that these glycosides are more suitable for topical formulations due to restricted systemic permeability but strong local antioxidant and anti-inflammatory activity (Gray et al., 2018; Aszrin et al., 2024). These findings are consistent with the current ADMET prediction results.

The results revealed that madecassoside and asiaticoside were highly effective in their 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.

Toxicity Prediction

Safety evaluation represents an essential stage in early drug discovery to minimize potential adverse effects before experimental validation. Computational toxicity prediction provides an efficient approach to screen mutagenicity, hepatotoxicity, and skin sensitization risks. All tested compounds were assessed using in silico toxicity platforms to estimate their safety profiles. The predicted toxicity profiles are summarized in Table 4.

The computational results indicate that none of the evaluated compounds exhibit predicted mutagenic or hepatotoxic effects. This outcome is consistent with experimental toxicological studies reporting the safety of natural antioxidant compounds. For instance, safety evaluations of Centella asiatica extracts have demonstrated low toxicity and good tolerability in biological systems (Johnson et al., 2023; Orhan, 2012). Likewise, Coenzyme Q10 has been widely documented as a safe antioxidant with minimal adverse effects in clinical applications (Hidaka et al., 2008). Vitamin C and its derivatives are also recognized for their high safety margin and low toxicity in pharmacological use (Pullar et al., 2017).

These findings collectively support the continued development of the studied compounds as potential antioxidant agents targeting PPAR receptors.

Table 4. Predicted Toxicity Profiles of Test Compounds

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

Conclusion

The in silico study results demonstrated that asiaticoside, madecassoside, Coenzyme Q10, and ethyl ascorbic acid exhibit potential as PPAR receptor agonists associated with antioxidant gene regulation. Molecular docking analysis confirmed that these compounds interact with key active-site residues of the PPAR receptor, including Arg284, His280, and Tyr283. Coenzyme Q10 and ethyl ascorbic acid isomers showed the strongest binding affinity, while ADME predictions indicated that ethyl ascorbic acid presents the most balanced pharmacokinetic profile in terms of solubility, bioavailability, and safety. From a broader scientific perspective, these findings support the exploration of natural antioxidant compounds as modulators of PPAR signaling pathways in dermatological and oxidative stress–related therapies. The identification of ethyl ascorbic acid as a promising candidate may contribute to the development of targeted antioxidant formulations with improved therapeutic efficacy and safer pharmacological profiles. Molecular docking and ADMET predictions cannot fully capture the complexity of biological interactions in living systems, including receptor dynamics, metabolism, and cellular responses. Therefore, future research should focus on in vitro and in vivo experimental studies to validate receptor activation, antioxidant activity, and safety profiles. Further investigation into formulation strategies, drug delivery systems, and long-term pharmacokinetic behavior is also necessary to optimize the clinical application of these compounds.

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Author Contributions

Conceptualization, D.K. and N.L.D.A; methodology, N.K., D.K. and N.L.D.A; conduct of the experiment, N.K; writing—original draft preparation, N.K., D.K. and N.L.D.A.; writing—review and editing, N.K., D.K. and N.L.D.A.; supervision, D.K. and N.L.D.A.

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Conflicts of Interest

The authors declare no conflict of interest.

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