RASĀYAN *J. Chem.*
Vol. 19 | No. 2 | 839-850| April-June | 2026
ISSN: 0974-1496 | e-ISSN: 0976-0083 | CODEN: RJCABP
http://www.rasayanjournal.com
http://www.rasayanjournal.co.in

IDENTIFICATION OF POTENTIAL ANTIOXIDANT COMPOUNDS FROM *Sonneratia caseolaris* AQUEOUS LEAF EXTRACTS THROUGH MOLECULAR DOCKING AND TOXICITY PREDICTION

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ABSTRACT

Sonneratia caseolaris, a mangrove species traditionally known for its antioxidant properties, requires molecular-level investigation to clarify its bioactivity mechanisms. This study evaluated the antioxidant potential of active compounds from *S. caseolaris* aqueous leaf extract using molecular docking and toxicity prediction against human protein targets related to oxidative stress. Docking results demonstrated that several phytochemical compounds exhibited strong binding affinities and stable interactions with target proteins, indicating their potential to modulate oxidative stress pathways. Comparative analysis showed binding performance comparable to standard antioxidant ligands. Toxicity prediction further revealed favourable safety profiles, with most compounds categorised as low-risk and pharmacologically acceptable candidates. These findings provide molecular evidence supporting the traditional medicinal use of *S. caseolaris* and identify specific compound–protein interactions underlying its antioxidant activity. The study bridges ethnomedicinal knowledge with computational drug discovery approaches and highlights mangrove-derived phytochemicals as promising antioxidant candidates for further experimental validation and future therapeutic development targeting oxidative stress–related diseases.

Keywords: Drug Discovery, *In Silico* Toxicity Prediction, Molecular Docking, Natural Antioxidants, Oxidative Stress, Phytochemical Compounds, *Sonneratia Caseolaris*.

RASĀYAN *J. Chem.*, Vol. 19, No. 2, 2026

INTRODUCTION

Oxidative stress is a major contributing factor to the development of chronic diseases, including cancer, diabetes, cardiovascular disorders, and neurodegenerative conditions, accounting for a substantial global health burden. As interest grows in natural antioxidants for safer therapeutic alternatives, mangrove plants have attracted significant scientific attention due to their ability to survive extreme coastal environments that stimulate the production of protective bioactive compounds. Among these species, *Sonneratia caseolaris* has long been utilised in traditional medicine for its antioxidant properties, attributed to diverse phytochemicals capable of neutralising reactive oxygen species.[1,2] These traditional uses are increasingly supported by scientific evidence suggesting that mangrove-derived compounds may serve as promising candidates for therapeutic development targeting oxidative damage.[3-5]

Despite growing interest, scientific validation of *S. caseolaris* at the molecular level remains limited. Previous studies have demonstrated significant antioxidant activity in various plant parts, including leaves, bark, and fruits.[6,7]

However, the precise molecular mechanisms-particularly how its phytochemical constituents interact with human protein targets involved in oxidative stress regulation-are still insufficiently understood.[8,9] This lack of mechanistic insight restricts the translation of ethnomedicinal knowledge into evidence-based drug development, as understanding ligand-protein interactions is essential for predicting biological efficacy and safety.[10]

http://doi.org/10.31788/RJC.2026.1929640

Recent advances in computational biology, especially molecular docking approaches, provide powerful tools to investigate these interactions efficiently. Studies have reported that compounds such as luteolin and ellagic acid from *S. caseolaris* exhibit strong binding affinities toward antioxidant-related protein targets, suggesting a molecular basis for their bioactivity.[4,11] Molecular simulations therefore offer critical insights into the mechanisms through which phytochemicals exert antioxidant effects and accelerate early-stage drug discovery.[12-14] This study aims to analyse the interactions between active compounds from aqueous leaf extracts of *S. caseolaris* and key human proteins associated with oxidative stress using molecular docking and toxicity prediction. By addressing the existing gap in molecular interaction data, this research seeks to validate the antioxidant potential of *S. caseolaris* and identify promising therapeutic candidates. Integrating traditional knowledge with modern computational techniques, this study contributes to advancing mangrove-based bioresources toward future pharmaceutical applications.

EXPERIMENTAL

Material and Methods

The previous study used *S. caseolaris* leaf collected from Ujung Pangkah, Gresik, East Java Province, Indonesia. The leaf was still attached to the branches with a dark green colour. All the leaves were washed with fresh water to remove epiphytes and salts, wiped with tissue, and air-dried for 7 days at 25 °C. The leaf samples were ground finely for the next extraction process. Water extraction was carried out using the maceration method, soaking the sample in the solvent by a ratio of 1:3 (w/v) for 3 x 24 hours. Every 24 hours, the extracts were filtered and re-macerated with new solvents. The macerated samples were filtered with Whatman paper no. 42 to separate the filtrate and residue. The re-macerated filtrates on the first, second, and third days were mixed before evaporating with a rotary evaporator (DLab rotary evaporator RG100-S, 40^0C). The active compounds of the samples were analysed using LC-HRMS (Thermo Scientific Diorex Ultimate 3000 RSLCnano, Japan).

Datamining of Active Compounds

Active compounds of this research were derived from LC-HRMS data from a previous study. Hereafter, the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) is used to obtain SMILES of each of the active compounds found in the sample extract.

Prediction of Active Compounds Activity

The active compounds were then analysed for their potential antioxidant activity using the WAY2DRUG PASS prediction (http://www.pharmaexpert.ru/passonline/predict.php) webserver to determine the potential as an antioxidant based on the PA value (Probability to Be Active). This value describes the potential of active compounds being tested.

Toxicity and Bioavailability Analysis

The active compounds with the best binding affinity were tested for toxicity predictions using an online toxicity test program at https://tox.charite.de/protox3/index.php?site=compound_input. Then, an active compound that showed a nontoxic result was tested for chemical absorption, distribution, metabolism, excretion, and toxicity (ADMET) using ADMET-Lab 2.0 accessed at (https://admetmesh.scbdd.com/service/evaluation/index).[15-17]

Prediction of Target Proteins and Gene Ontology Analysis

Protein targets were analysed using the SEA Search Server (https://sea.bkslab.org/).[18] and CTD (http://ctdbase.org/voc.go?type=chem).[19] Subsequently, a combined list was compiled using a Venn diagram, and gene ontology annotation was analysed using DAVID (https://david.ncifcrf.gov/tools.jsp).[20]

Graph Topological Network Analysis

The target protein list from both databases was subsequently compiled and input into the multiple protein menu of the STRING database (https://string-db.org/). In addition, additional settings included selecting the organism as Homo sapiens, setting the meaning of network edges to confidence, and setting the minimum required interaction score to 0.700 (high confidence). After updating the network

based on these additional settings, the visualization results were downloaded from the table/export menu in tab-separated values (TSV) format from the table/export menu. The downloaded (TSV) file was then imported into Cytoscape software v.3.9.0 for further analysis using the network analysis procedure in the tool's menu.

Mode of Actions Analysis

The mechanism of action of active compounds was analysed using CTD STITCH (http://ctdbase.org/voc.go?type=chem).[19] Visualisation was carried out using Cytoscape v.3.9.0 software.

Molecular Docking Analysis

The 3D protein structures of the target proteins were PPARG (PDB ID: 2YFE) and PTGS2 (PDB ID: 5IKT), obtained from the PDB database. Meanwhile, the 3D structures of the active compounds and control were acquired from the PubChem database (https://www.pubchem.ncbi.nlm.nih.gov). Subsequently, the proteins were prepared by removing water molecules, and the ligands were minimised in energy using OpenBabel in PyRx software v.0.9.8. Molecular docking was performed using Autodock Vina, which was integrated into PyRx v.0.9.8. AutoDock Vina employs an empirical scoring function to evaluate and rank the binding affinity between a ligand and a receptor during molecular docking. The scoring function aims to estimate the free energy of binding. AutoDock Vina's scoring method combines various energy terms, considering both the intermolecular interactions between the ligand and the receptor, as well as the intramolecular interactions within the ligand itself, as shown in formula-1.[20,21]

Score=w_vina_receptor×receptor_term+w_vina_ligand×ligand_term+w_vina_custom_bonds×custom_bonds+w_vina_custom_angle×custom_angle+w_vina_custom_torsion×custom_torsion+w_vina_custom_clash×custom_clash+w_vina_inter_clash×inter_clash+w_vina_intra_clash×intra_clashScore+w_vina_receptor×receptor_term+w_vina_ligand×ligand_term+w_vina_custom_bonds×custom_bonds+w_vina_custom_angle×custom_angle+w_vina_custom_torsion×custom_torsion+w_vina_custom_clash×custom_clash+w_vina_inter_clash×inter_clash+w_vina_intra_clash×intra_clash (1)

Molecular docking was carried out using the targeted docking method with an exhaustiveness parameter of 50. The grid box size (Table-1) was used as the search box for the binding pocket of the target proteins, obtained from PrankWeb (https://prankweb.cz/). The molecular docking results include binding energy and interactions between the compounds, which were visualised using BioVia Discovery Studio 2019 software.

Table-1: Grid-box Analysis for Molecular Docking

Position	PPARG		PTGS2	
	Center	Dimensions	Center	Dimensions
X	15.3097	10	165.4386	20
Y	19.3481	17	185.8338	20
Z	45.6072	15	193.8492	20
Probability	0.748		0.827	

RESULTS AND DISCUSSION

Profile of Active Compounds

A total of 15 active compounds were obtained from the LC-HRMS analysis (Table-2). These active compounds were detected in *S. caesolaris* aqueous leaf extracts from a previous study. The active compounds were detected in all of the *S. caseolaris* aqueous leaf extracts with 97-99% similarity compared to the LC-HRMS data.

Table-2: Active Compounds of *S. caesolaris* Aqueous Leaf Extracts

No	Active Compound	CID	Canonical SMILES	Isomeric SMILES
1	Diisobutylphthalate	6782	CC(C)COC(=O)C1=CC=CC=C1C(=O)OCC(C)C	
2	2,2,6,6-Tetramethyl-1-	549976	CC1(CCCC(N1O)(C)C)C	

	piperidinol (TEMPO)			
3	Betaine	247	C[N+](C)(C)CC(=O)[O-]	
4	Hexamethylenetetramine	4101	C1N2CN3CN1CN(C2)C3	
5	Choline	305	C[N+](C)(C)CCO	
6	Bis(3,5,5-trimethylhexyl) phthalate	34277	CC(CCOC(=O)C1=CC=CC=C1C(=O)OCCC(C)CC(C)(C)C)CC(C)(C)C	
7	Caprolactam	7768	C1CCC(=O)NCC1	
8	2-[(2-chlorobenzyl)sulfanyl]-4,6-dimethylnicotinonitrile	691476	CC1=CC(=NC(=C1C#N)SCC2=CC=CC=C2Cl)C	
9	3,5-di-tert-Butyl-4-hydroxybenzaldehyde	73219	CC(C)(C)C1=CC(=CC(=C1O)C(C)(C)C)C=O	
10	Zearalenone	5281576	CC1CCCC(=O)CCCC=CC2=C(C(=CC(=C2)O)O)C(=O)O1	C[C@H]1CCCC(=O)CCC/C=C/C2=C(C(=CC(=C2)O)O)C(=O)O1
11	Tributyl phosphate	31357	CCCCOP(=O)(OCCCC)OCCCC	
12	Bis(4-ethylbenzylidene)sorbitol	66586233	CCC1=CC=C(C=C1)C=C(C(C(C(C(C(=CC2=CC=C(C=C2)CC)O)O)O)O)O)O	CCC1=CC=C(C=C1)C=C([C@@H]([C@H]([C@@H]([C@@H](C(=CC2=CC=C(C=C2)CC)O)O)O)O)O)O
13	Monobutyl phthalate	8575	CCCCOC(=O)C1=CC=CC=C1C(=O)O	
14	Bis(2-ethylhexyl) phthalate	8343	CCCCC(CC)COC(=O)C1=CC=CC=C1C(=O)OCC(CC)CCCC	
15	DL-Arginine	232	C(CC(C(=O)O)N)CN=C(N)N	

Bioactivity (Quantitative Structure-Activity Relationship)

The bioactive potential of compounds was analysed using the Way2Drug Pass Server, based on their structural formula. The Pa value (Probability to Be Active) represents a value that characterises the potential of a tested compound from *S. caesolaris* aqueous leaf extracts compared with a library of compounds proven as specific treatments, both computationally and in wet-lab experiments (PA>0.3) from PASS (Prediction of Activity Spectra for Substances) Server.[22] When the Pa value is more than 0.3 (Orange-Yellow), it indicates that the bioactivity is predicted to have considerable potential. However, when evaluated solely based on the PA value for antioxidant bioactivity, only 7 out of 15 active compounds showed significant potential (Fig.-1). These seven active compounds were then carried forward to the subsequent methodological steps. The significant advantages of QSAR are that it can be used not only for predicting the above functional peptides but also for other food-derived peptides. The result of a previous study by Bo *et al.*[23] showed that a total of 252 dipeptides were characterised as DPP-IV inhibitors using 16 physicochemical descriptors, followed by PCA, and then an MLR model to predict the biological activity of DPP-IV inhibitors.[24] Another QSAR modelling of DPP-IV inhibitors was conducted on 56 milk protein-derived peptides (2-5 amino acid residues).

Toxicity and Bioavailability

Absorption, distribution, metabolism, excretion, and toxicity (ADMET) in drug candidates play a crucial role in the drug discovery process. The ADMET lab database (Table-2) is used to obtain Lipinski rule and

ADME/T predictions for a compound. The Protox III database15 is used to obtain Lipinski rule and toxicity predictions. Lipinski's rule of 5 (Table-3) helps distinguish drug-like and non-drug-like molecules. Lipinski can predict the likelihood of a compound's metabolic success or failure based on its similarity to the drug. The criteria for a compound that meets Lipinski's rule are those that have at least 2 of the 5 main properties. The Lipinski rule of 5 includes a molecular mass of less than 500 Daltons, high lipophilicity (expressed as LogP less than 5), having fewer than 5 hydrogen bond donors, having fewer than 10 hydrogen bond acceptors, and a molecular refractivity between 30 and 140.

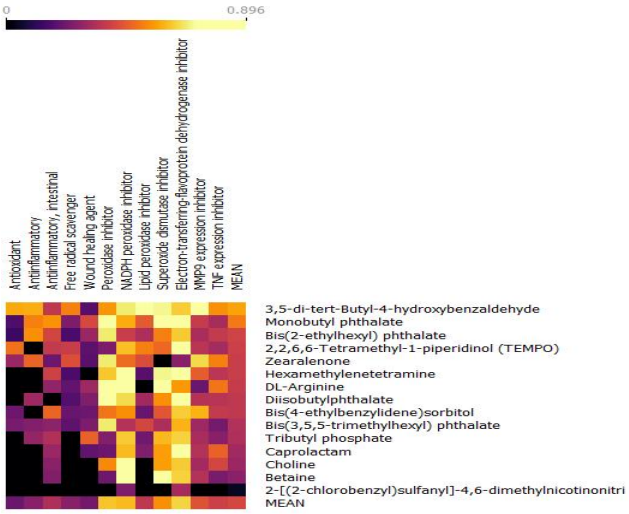

Fig.-1: Antioxidant Potential of Active Compounds of *S. caseolaris* Aqueous Leaf Extract

However, this drug-likeness does not indicate that the other five compounds lack drug potential, but rather that they require more energy or active transport mechanisms to localise within cells. Meanwhile, ADMET (absorption, distribution, metabolism, excretion, and toxicity) analysis shows that almost all compounds have good pharmacodynamics and pharmacokinetics. Furthermore, the toxicity of a compound can be grouped into 6 classes,[25] namely Class I fatal if swallowed ($LD_{50} \leq 5$), Class II fatal if swallowed ($5 < LD_{50} \leq 50$), Class III toxic if swallowed ($50 < LD_{50} \leq 300$), Class IV harmful if swallowed ($300 < LD_{50} \leq 2000$), Class V may be harmful if swallowed ($2000 < LD_{50} \leq 5000$), and Class VI non-toxic ($LD_{50} > 5000$). The results show that the toxicity of bioactive compounds is low except for several compounds that need to be watched out for as Drug-Induced Liver Injury (DILI), Maximum Recommended Daily Dose (FDAMDD), Carcinogenicity, and Immunotoxicity when in the form of a single compound. In addition, the average LD_{50} and toxicity class of 7 potential bioactive compounds ranged between class 5 and class 6, which are predicted to be interpreted as safe, except 4 compounds with toxicity class 3 and 4 that were eliminated (Fig.-2). Therefore, from the 7 most potent compounds, only 3 compounds with toxicity classes that are considered safe are continued to the docking process.

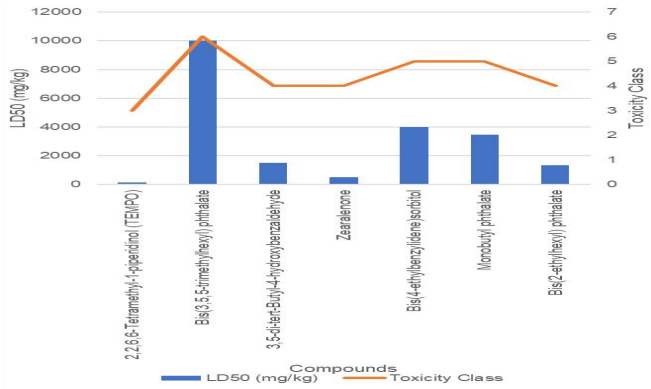

Fig.-2: Toxicity Analysis of Active Compounds of *S. caseolaris* Aqueous Leaf Extract

Prediction of Target Protein and Gene Ontology

The results of the protein target prediction for each compound obtained from the SEA Target and CTD databases are shown. The analysis using a Venn diagram revealed that 75 proteins identified can be targeted by active compounds from *S. caseolaris* aqueous leaf extracts in both databases (Fig.-3). These 75 proteins are as follows: GABRB1, PRTN3, CAPN1, KIF11, CAPNS1, PTGS1, PTGS2, GABBR2, ERN1, CACNA1A, CACNB1, ESR2, PTK2B, CBR1, PDGFRA, FLT4, RELA, MAP3K7, MAP2K1, MAP2K6, CYP1A2, CYP2C19, PPARA, CNR2, CHRM2, CHRM4, CHRM5, STS, CYP2C9, NR4A1, CNR1, PPARG, CYP2D6, AKR1C1, AKR1C2, AKR1C3, RARB, BCHE, MIF, STAT1, CDC25B, CES1, CES2, S1PR3, FAAH, GRM6, PRKCA, PRKCH, CAPN2, ALOX5, NAAA, MDH2, PTGES, ADORA3, S1PR5, CHRNA4, CHRNB4, THRA, THRB, LTB4R, FABP4, PLA2G4A, PLA2G2A, CTSH, ABCB1, PRNP, P2RY12, CACNA1D, PADI3, AKR1B10, CTRB1, LPAR5, FKBP1A, ACE2, and CPA1. These proteins were subsequently processed in the next analytical method, which is Gene Ontology (GO) annotation. The results of the GO annotation showed that there were 12 biological processes (BP) and 5 pathways supporting the antioxidant mechanism. Among the targeted proteins from active compounds in *S. caesolaris* aqueous leaf extracts, 37 out of 75 were involved in BP and pathways relevant to antioxidant activity (Fig.-4).

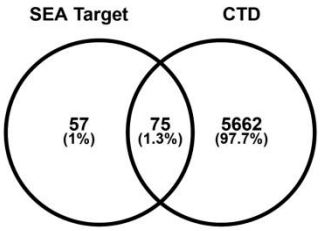

Fig.-3: Protein Target Cross-Analysis of *S. caseolaris* Aqueous Leaf Compounds Using SEA and CTD

Gene Ontology (GO) enrichment analysis of potential targets was performed using the Metascape database, and the functions were enriched under the conditions of p-value < 0.01 and enrichment factor > 1.5. GO results on the Kartikaningsih *et al.*[26] research showed the top 20 most significant functions. The point size represents the number of genes with the same function. The more significant point is that the more genes there are. The results showed that the potential antioxidant compounds affected numerous biological functions involving biological processes, cellular components, and molecular functions, such as the regulation of ageing, the active regulation of programmed cell death, the regulation of reactive oxygen metabolism, the regulation of neuronal apoptosis, positive regulation of the cell cycle, and regulation of the collagen metabolism process. The oxidation process, by participating in the process of antioxidant reaction, will have an impact on slowing the occurrence and development of ageing and hypoxia.

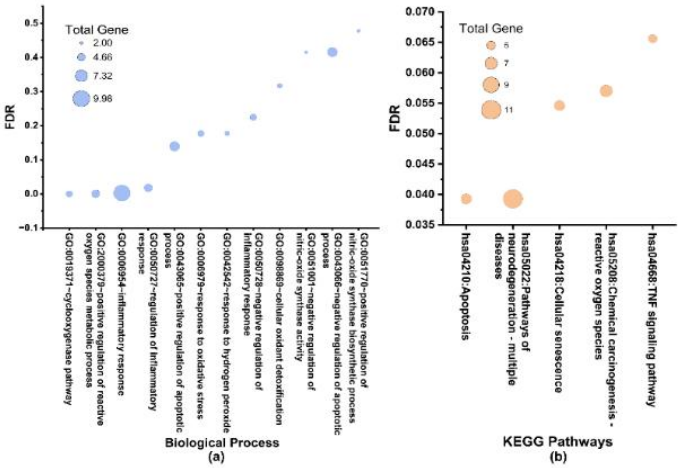

Fig.-4: Gene Ontology Annotation Analysis: (a) BP and (b) KEGG Pathways

Graph Topological Network

Graph topological analysis was performed using the STRING server. Network analysis employed several variables that indicated the relationships between each target protein and each other, or Protein-Protein Interaction (PPI). These variables include Stress, Degree, Betweenness Centrality, and Closeness Centrality. The degree centrality variable represents the number of interactions between one node and other nodes, where a high value can indicate that the protein had many interactions with different nodes and may be a key protein or a regulatory influencer. The betweenness centrality variable compares the shortest path used by a node in the entire pathway and can be interpreted as having a dominant function. Meanwhile, closeness centrality represents the shortest distance to access a node in the pathway, where a high value can indicate ease of access and becoming a central regulator for other proteins. The analysis results showed that PTGS2 and PPARG were the proteins with the most dominant roles compared to the other 73 proteins, especially based on the centrality parameter (Fig.-5). Additionally, both proteins were identified to have roles in several biological processes supporting the antioxidant mechanism, including GO:0019371~cyclooxygenase pathway; GO:2000379~positive regulation of reactive oxygen species metabolic process; GO:0006954~inflammatory response; GO:0050727~regulation of inflammatory response; GO:0043065~positive regulation of apoptotic process; GO:0006979~response to oxidative stress; GO:0042542~response to hydrogen peroxide; GO:0050728~negative regulation of inflammatory response; and GO:0098869~cellular oxidant detoxification.

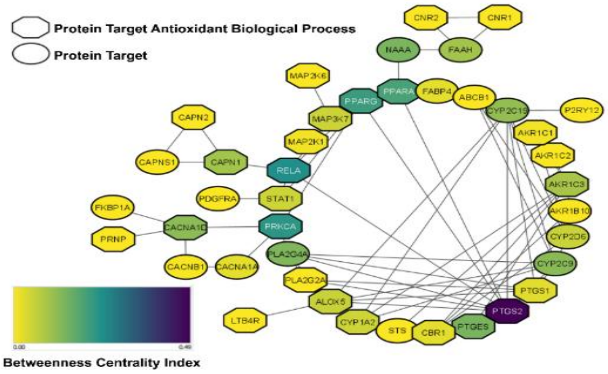

Fig.-5: STRING-Based Topological Network Analysis of Antioxidant-Related Protein Targets in *S. caseolaris* Aqueous Leaf Extract (Purple Indicates Higher Protein Significance)

Mode of Action

The mode of action analysis of each compound and protein was obtained from the CTD and STITCH databases (Fig.-6). The results indicated that several active compounds exhibit activities that support the antioxidant mechanism by activating PPARG as an anti-inflammatory protein[27] and inhibiting PTGS2/COX-2, which was a pro-inflammatory protein.[28] We excluded 2,2,6,6-Tetramethyl-1-piperidinol (TEMPO); 3,5-di-tert-Butyl-4-hydroxybenzaldehyde; Zearalenone; and Bis(2-ethylhexyl) phthalate due to their moderate-to-high toxic potential and fatalities if ingested. The Monobutyl phthalate can bind and activate PPARG,[29,30,] allowing PPARG to inhibit PTGS2.[31] Furthermore, the Bis(3,5,5-trimethylhexyl) phthalate can inhibit PTGS.[32] While the compound Bis(4-ethylbenzylidene)-sorbitol has not been widely known for its potential mode of action.

Molecular Docking

The selected protein markers as targets were the two with the most potential bioactivity predictions and topological graph or PPI analysis, namely, PPARG and PTGS2 (Table-3). Molecular docking was performed with the six most potent active compounds along with two positive control ligands for their respective target proteins: Amorfrutin 1 (PPARG)[33] and Tolfenamic Acid (PTGS2).[34] Amorfrutin 1 is a promising natural candidate for preventing or treating conditions where metabolic dysfunction, inflammation, and oxidative stress are intertwined, such as type 2 diabetes and its complications. At the same time, Tolfenamic Acid is a repurposing candidate for diseases characterised by massive oxidative

stress and neuroinflammation, such as Alzheimer's disease, where its dual NSAID and Nrf2-activating properties could be uniquely beneficial.

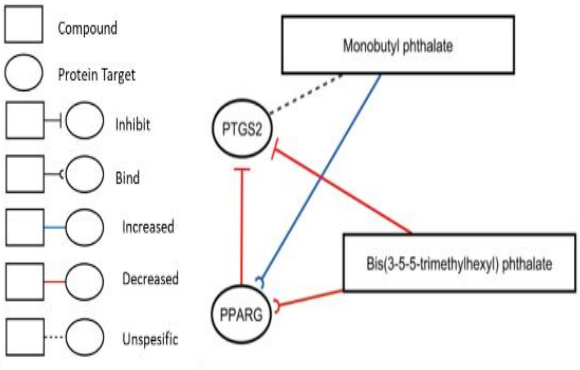

Fig.-6: Mechanism of Action of Active Compounds on Key Antioxidant-Related Proteins

The analysis results indicated that active compounds from *S. caesolaris* aqueous leaf extracts with PPARG and PTGS2 did not perform better than the control drug. However, Bis(3,5,5-trimethylhexyl) phthalate to PPARG and Monobutyl phthalate to PTGS2 showed binding energies equivalent to the threshold for a stable bond, which is -7.00 kcal/mol.[21] Meanwhile, the more negative the binding affinity value, the lower the free energy required for the ligand to bind with the target protein based on the scoring calculation.

Table-3: Binding Affinity of *S. caseolaris* Aqueous Leaf Extract Ligands with Protein Markers

Protein	Ligand	Binding Affinity (kcal/mol)
PPARG	Amorfrutin 1 (control)	-7.9
	Bis(3,5,5-trimethylhexyl) phthalate	-7.0
	Monobutyl phthalate	-5.6
PTGS2	Tolfenamic Acid (control)	-8.7
	Monobutyl phthalate	-7.0
	Bis(3,5,5-trimethylhexyl) phthalate	-3.3

Furthermore, the most dominant bonds formed between both PPARG and PTGS2 with active compounds from *S. caesolaris* aqueous leaf extracts or ligands were Van der Waals and hydrophobic bonds. The bold font residues in the compound column were the control amino acid residues retained in the compound samples. In contrast, the italic font residues indicated the changes in the types of bonds formed (Table-4). The analysis of amino acid residue interactions aligns with the binding affinity analysis, where Bis(3,5,5-trimethylhexyl)-phthalate emerges as the best ligand for PPARG (Fig.-6) and Monobutyl phthalate for PTGS2 (Fig.-7) because they effectively maintain bonds with active site residues, especially hydrogen bonds. The binding energy value will increase or become more positive due to the reduction of H-bonds and hydrophobic bonds, because they turn into weaker Van der Waals bonds. This is because each formation of one hydrogen bond can significantly reduce the binding energy value, and vice versa, when the hydrogen bond is reduced, it will increase the bond energy value.

Table-4: Amino Acid Interactions in Protein Binding with *S. caseolaris* Active Compounds

Protein	Ligand	Interaction				
		Van der Waals	Hydrogen Conventional	Hydrogen Carbon	Hydrophobic	Other
PPARG	Amorfrutin 1 (control)	A: ILE326 A: SER289 A: PHE287 A: GLU259 A: MET348 A: ILE249	A: GLY284 A: SER342		A: ILE341 A: GLY284 A: CYS285 A: LEU353 A: MET364 A: LEU330 A: ARG288	

					A: LEU255 A: ARG280 A: ILE281 A: PHE363	
	Bis(3,5,5-trimethylhexyl) phthalate	A: LEU333 A: LEU340 A: SER342 A: ILE249 A: MET348 A: ILE281 A: ARG280 A: GLY284 A: MET364 A: TYR327 A: SER289		A: ILE341	A: ILE341 A: ALA292 A: ARG288 A: ILE326 A: CYS285 A: LEU330 A: ILE262 A: VAL339	
	Monobutyl phthalate	A: GLY284 A: MET348 A: PHE363 A: MET364 A: VAL339 A: LEU330 A: LEU340 A: LEU333 A: SER342	A: CYS285		A: ILE281 A: CYS285 A: LEU353 A: ARG288 A: ILE341	A: CYS285
PTGS2	Tolfenamic Acid (control)	A: SER530 A: TYR348 A: ARG120 A: TYR355 A: SER353 A: MET522 A: GLY526 A: LEU384 A: TRP387 A: PHE381	A: TYR385		A: VAL349 A: LEU531 A: VAL116 A: LEU352 A: ALA527 A: VAL523	
	Monobutyl phthalate	A: SER353 A: LEU531 A: VAL116 A: TYR348 A: PHE381 A: TRP387 A: MET522 A: GLY526	A: TYR385 A: SER530	A: SER530	A: VAL349 A: LEU359 A: LEU352 A: VAL523 A: ALA527 A: TYR355	
	Bis(3,5,5-trimethylhexyl) phthalate	A: TYR348 A: VAL344 A: PHE205 A: THR206 A: PHE209 A: TRP387 A: PHE381 A: ALA527 A: GLY526 A: SER353 A: TYR355 A: ARG120 A: MET113	A: SER530	A: TYR385	A: LEU352 A: MET522 A: VAL523 A: VAL349 A: LEU531 A: LEU534 A: VAL116 A: LEU359 A: PHE518	A: SER530

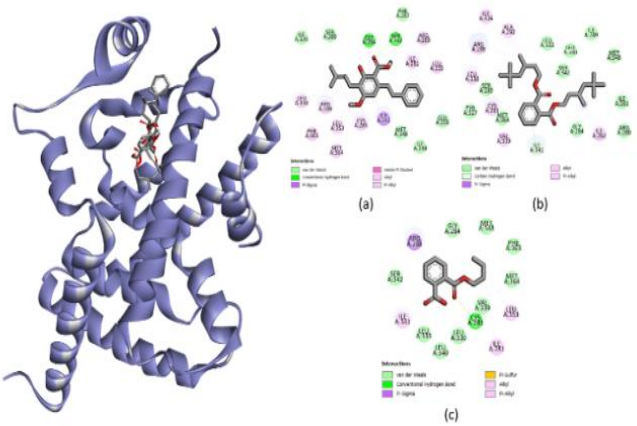

Fig.-7: PPARG Docking Visualisation with (a) Amorfrutin 1 (control), (b) Bis(3,5,5-trimethylhexyl) Phthalate, and (c) Monobutyl Phthalate; 3D Structures (left) and Ligand–Protein Interactions (right)

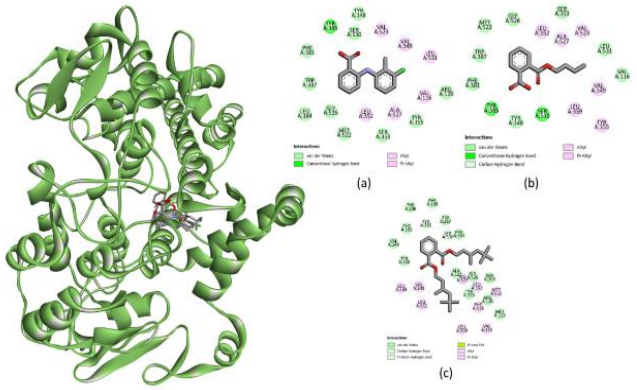

Fig.-8: PTGS2 Docking Visualisation with (a) Tolfenamic Acid (control), (b) Monobutyl Phthalate, and (c) bis(3,5,5-trimethylhexyl) Phthalate; left: 3D Complexes, Right: Ligand–Protein Interactions

CONCLUSION

The results of the bioactivity and gene ontology analysis indicated that active compounds of *S. caesolaris* aqueous leaf extracts had the potential to support antioxidant mechanisms. Furthermore, Monobutyl phthalate and Bis(3,5,5-trimethylhexyl)-phthalate also possessed the best drug-likeness and bioavailability, making them promising drug candidates. The primary mechanism of action of the active compounds from *S. caesolaris* aqueous leaf extracts in supporting antioxidant pathways involved the activation of PPARG and the inhibition of PTGS2. However, further testing needs to be done, especially in the wet lab, to validate the results of the *in-silico* study.

ACKNOWLEDGMENTS

This study was funded by a research grant *Penelitian Doktor Lektor Kepala* 2024 from *Badan Penelitian dan Pengabdian kepada Masyarakat* (BPPM), Faculty of Fisheries and Marine Science (FFMS), Universitas Brawijaya, Malang, Indonesia (ID No. 3717/UN10.F06/KS/2024).

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

The present work is related to *SDG-3: Good Health and Well-being*. All the authors contributed significantly to this manuscript, participated in reviewing/editing and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

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Cite this article as: H. Kartikaningsih *et al.*, *Rasayan J. Chem.*, 19(2), 839-850(2026), https://doi.org/10.317 88/RJC.2026.1929640.

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