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RESEARCH ARTICLE

In Silico Analysis of Metabolite Compounds from the Essential Oil of *Cinnamomum burmannii* Bark with COX-1 and COX-2 as Target Molecules

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Abstract

In silico approaches, including molecular docking, have emerged as powerful tools in predicting the interaction between natural compounds and molecular targets such as COX-1 and COX-2. These computational methods provide valuable insights into the binding affinity and selectivity of these compounds, making them indispensable in modern drug discovery. The interactions between metabolites from *C. burmanii* essential oil and COX-1 and COX-2 were investigated through *in silico* analysis. This analysis involves several stages, including *In Silico* Activity Analysis, Drug-likeness Test, Anti-inflammatory Agent Probability, and Molecular Docking. The study suggests that specific compounds could serve as anti-inflammatory adjuvants alongside conventional anti-inflammatory drugs (NSAIDs), potentially reducing dosages or minimizing the side effects associated with NSAID use. The *in silico* analysis results obtained by simulating the binding of metabolites with COX-1 and COX-2 target proteins using PyRx 0.8 software indicated that 12 out of 14 volatile oil metabolites might contribute to anti-inflammatory activity. However, the anti-inflammatory effects of cinnamon oil require further validation through *in vivo* testing.

Keywords: *In silico*, *Cinnamomum burmannii*, COX-1, COX-2, Anti-inflammatory

Introduction

Cinnamomum burmanii (Indonesian cinnamon) is a widely used spice with a rich history of medicinal applications, particularly for its anti-inflammatory, antioxidant, and antimicrobial properties. Essential oils derived from the bark of *C. burmanii* contain bioactive compounds such as cinnamaldehyde, eugenol, and coumarin, which contribute to its therapeutic effects [1]. Recent studies have highlighted the potential of these compounds in modulating inflammatory pathways, making them promising candidates for pain and inflammation management [2].

Inflammation is a biological response heavily mediated by enzymes such as cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). While COX-1 maintains normal physiological functions such as gastric protection, COX-2 is primarily induced during inflammation and leads to the production of pro-inflammatory prostaglandins responsible for pain and swelling [3]. Although both COX-1 and COX-2 enzymes are inhibited by non-steroidal anti-inflammatory medicines (NSAIDs), their non-selective activity frequently causes gastrointestinal adverse effects, especially from COX-1 inhibition [4]. Finding selective COX-2 inhibitors that have anti-inflammatory properties while reducing side effects has become more popular as a result [5].

Natural compounds, including essential oils, have been explored for their selective COX-2 inhibitory potential. C. burmanii essential oil has been identified as a potential source of such bioactive compounds due to its diverse chemical composition [6] . Molecular docking and other in silico techniques have become effective tools for forecasting how these natural chemicals would interact with molecular targets like COX-1 and COX-2 [7]. These computational methods offer valuable insights into the binding affinity and selectivity of compounds, making them indispensable in modern drug discovery.

This study aims to investigate the interactions between metabolites from *C. burmanii* essential oil and COX-1 and COX-2 through *in silico* analysis. The goal is to identify compounds that selectively inhibit COX-1 and COX-2, potentially offering a natural alternative for inflammation management with reduced side effects compared to conventional NSAIDs.

Materials and methods

In silico activity analysis

Sample preparation

Metabolites were retrieved from PubChem (https://pubchem.ncbi.nlm.nih.gov/) SMILES canonical data was collected and used for: Predicting drug-likeness, Screening compounds for anti-inflammatory potential and conducting molecular docking using control compounds.

Selection of metabolites

Metabolites were chosen based on their relative abundance in *C. burmanii* bark essential oil. Chemometric analysis identified the metabolites' potential role as anti-inflammatory agents.

Protein target preparation

Structure data format (.sdf) files for the metabolites were obtained from PubChem. Cyclooxygenase enzymes (COX-1 and COX-2) were retrieved from the Protein Data Bank (PDB) (https://www.rcsb.org/). Target proteins COX-1 and COX-2 from Homo sapiens. PDB provided detailed information on source organisms, experimental protein isolation, and visualization methods [8].

Drug-likeness test

Tool used

The Sanjeevini online tool (http://www.scfbio-iitd.res.in/sanjeeviny/sanjeevini.jsp) was employed for drug-likeness evaluation.

Lipinski's Rule of Five

Compounds were considered drug candidates if they met at least 2 criteria of Lipinski's Rule (http://www.scfbio-iitd.res.in/software/drugdesign/lipinski.jsp), which includes molecular mass: ≤ 500 Daltons, lipophilicity (LogP): ≤ 5, hydrogen bond donors: ≤ 5, hydrogen bond acceptors: ≤ 5, molar refractivity: 40 - 130 [9].

Anti-inflammatory agent probability

Tool used

PASS Online server (http://www.pharmaexpert.ru/passonline/) was used to predict anti-inflammatory potential.

Criteria for anti-inflammatory agents

The results of these checks are defined by the probabilities Pa (possibility of activity) and Pi (possibility of inactivity). The Pa and Pi values used as guidelines in determining anti-inflammatory opportunities are the Pa and Pi values of anti-inflammatory parameters. A test compound is said to be active for an activity if it has a Pi value < 0.3 and the Pa variation is categorized into 3 groups. A compound is categorized as having a high bioactivity opportunity if it has a Pa value > 0.7. If the Pa value of a compound is 0.3 < Pa < 0.7, it means that the compound is still in the active group that has a certain bioactivity. However, if a compound has a Pa value < 0.3, the compound is predicted to have a very low chance of being active in a bioactivity. Compounds with a medium activation probability (Pa) > 0.3 were considered positive candidates for anti-inflammatory activity. Pa > Pi as a Key Indicator: If a compound's Pa value is greater than its Pi value, it indicates that the compound is more likely to be active (in this case, anti-inflammatory) than inactive [10,19].

Molecular docking

Preparation of metabolite compounds

The metabolites from the essential oil of *C. burmanii* bark collected from 5 regions were sourced from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) in the structure data file (.sdf) format. PubChem is a well-established database containing information on metabolites, synthetic chemicals, and other substances [11]. The .sdf files were prepared for docking by loading them into the PyRx 08 software.

Receptor preparation

The receptors used were the cyclooxygenase enzymes COX-1 and COX-2, obtained from the Protein Data Bank (http://www.rcsb.org/). The PDB codes for the receptors were COX-1 (1EQG) and COX-2 (4PH9), both of which contain ibuprofen as the ligand, a widely known anti-inflammatory drug.

Docking method validation

The ibuprofen ligand produced by PyRx 08 was compared to the original ibuprofen ligand [2-(4-(2-methylpropyl)phenyl)] on the target proteins COX-1 (1EQG) and COX-2 (4PH9) in order to validate the docking approach. The root-mean-square deviation (RMSD) had to be less than 2 Å for the approach to be deemed legitimate [12,13].

Molecular docking

Molecular docking between the ligands and receptors was conducted using PyRx 08, focusing on the binding affinity values. This tool was used to screen metabolite compounds for their potential anti-inflammatory properties. The metabolites with the lowest binding affinity to COX-1 and COX-2 were selected, indicating higher predicted anti-inflammatory potential. Further docking of the selected compounds and trans-cinnamaldehyde, the dominant component of *C. burmanii* essential oil, was performed using Molegro Virtual Docker 5.5, with ibuprofen as the control. The docking results analyzed included the rerank score, RMSD, bond types (hydrogen bonds, electrostatic interactions, steric interactions), and receptor amino acids involved in the interactions.

Results and discussion

In this study, screening was conducted on 14 essential oil metabolites from the bark of *C. burmannii*, which have a relatively high content and are suggested by chemometric analysis to have potential anti-inflammatory properties. The results of the metabolite sample preparation of essential oils, available on PubChem (https://pubchem.ncbi. nlm.nih.gov/), can be seen in the **Table 1**.

The 14 compounds listed in **Table 2** can be used for further prediction, specifically the probability of functioning as anti-inflammatory agents, through the PASS Online server, with the results presented in **Table 3**.

Molecular docking simulations were conducted to evaluate the binding interactions between the metabolites in the essential oil of *C. burmannii* bark and target proteins COX-1 and COX-2 using PyRx 0.8 software. The findings of the molecular docking screening for metabolites with anti-inflammatory potential utilizing the COX-1 target protein (PDB ID: 1EQG) [12] are presented in **Table 4** and **Figure 1**. Similarly, the results for the COX-2 target protein (PDB ID: 4PH9) [13] using PyRx 0.8 software are shown in **Table 5** and **Figure 2**.

The results of the specific molecular docking of 3 metabolites with the COX-1 target protein (1EQG) can be seen in **Table 6**. Validation using the native ligand ibuprofen (2-[4-(2-methylpropyl) phenyl]) with the COX-1 target protein showed an RMSD of 1.26235 Å, a Rerank score of –81.38370 kcal/mol, hydrogen bonds with amino acids Tyr 355, Arg 120, and 2 electrostatic interactions with Arg 120.

From **Table 7**, it can be concluded that the Rerank Scores suggest that γ-Muurolene, trans-Cinnamaldehyde, and α-Terpineol are predicted to have anti-inflammatory properties, although their effectiveness is still lower than the control compound (ibuprofen) . Therefore, these 3 compounds could potentially serve as anti-inflammatory adjuvants alongside conventional anti-inflammatory drugs (NSAIDs) to reduce dosages or minimize the side effects associated with NSAID use.

Table 1 The results of the sample preparation of essential oil metabolites from the bark of *C. burmannii* on PubChem.

Metabolite compounds	PubChem ID	Molecular weight (g/mol)	SMILE canonical
α-Pinene	440968	136.23	CC1=CCC2CC1C2(C)C
D-Limonene	440917	136.23	CC1=CCC(CC1)C(=C)C
Eucalyptol	2758	154.25	CC1(C2CCC(O1)(CC2)C)C
Linalool	6549	154.25	CC(=CCCC(C)(C=C)O)C
Benzenepropanal	7707	134.17	C1=CC=C(C=C1)CCC=O
α-Terpineol	443162	154.25	CC1=CCC(CC1)C(C)(C)O
Trans-Cinnamaldehyde	637511	132.16	C1=CC=C(C=C1)C=CC=O
Bornyl Acetate	6448	196.29	CC(=O)OC1CC2CCC1(C2(C)C)C
Copaene	12303902	204.35	CC1=CCC2C3C1C2(CCC3C(C)C)C
trans-α-Bergamotene	86608	204.35	CC1=CCC2CC1C2(C)CCC=C(C)C
Caryophyllene	5281515	204.35	CC1=CCCC(=C)C2CC(C2CC1)(C)C
γ-Muurolene	12313020	204.35	CC1=CC2C(CC1)C(=C)CCC2C(C)C
α-Muurolene	12306047	204.35	CC1=CC2C(CC1)C(=CCC2C(C)C)C
Caryophyllene Oxide	1742210	220.35	CC1(CC2C1CCC3(C(O3)CCC2=C)C)C

Table 2 The results of the drug-likeness analysis on the Sanjeevini server.

Compound	MW	HBD	HBA	Log P	MR
α-Pinene	136.23	0	0	2.998	43.751
D-Limonene	136.23	0	0	3.308	45.911
Eucalyptol	154.25	0	1	2.744	45.526
Linalool	154.25	1	1	2.669	49.485
Benzenepropanal	134.17	0	1	1.818	40.826
α-Terpineol	154.25	1	1	2.503	47.395
Trans-Cinnamaldehyde	132.16	0	1	1.898	41.539
Bornyl Acetate	196.29	0	2	2.764	54.782
Copaene	204.35	0	0	4.270	64.512
Trans-α-Bergamotene	204.35	0	0	4.725	66.742
Caryophyllene	204.35	0	0	4.725	66.742
γ-Muurolene	204.35	0	0	4.581	66.672
α-Muurolene	204.35	0	0	4.581	66.672
Caryophyllene Oxide	220.35	0	1	3.936	66.263

Note: MW = Molecular weight, HBD = Hydrogen bond donors, HBA = Hydrogen bond acceptors, Log P = Logarithmic partition coefficient, MR = Molar refractivity.

Table 3 The prediction results for the probability of anti-inflammatory agents on PASS Online.

Metabolite compounds	Probabillity ativation (Pa)	Probabillity Inactive (Pi)	Antiinflamatory Prediction
α-Pinene	0.4	0.06	+
D-Limonene	0.6	0.02	+
Eucalyptol	0.3	0.04	-
Linalool	0.5	0.04	+
Benzenepropanal	0.3	0.03	-
α-Terpineol	0.6	0.02	+
Trans-Cinnamaldehyde	0.5	0.03	+
Bornyl Acetate	0.5	0.03	+
Copaene	0.4	0.06	+
trans-α-Bergamotene	0.6	0.02	+
Caryophyllene	0.7	0.01	+
γ-Muurolene	0.6	0.02	+

Table 4 Results of metabolite screening predicted to have anti-inflammatory properties using molecular docking techniques (Target Protein COX-1: 1EQG) with PyRx 0.8 Software.

Metabolite compounds	PubChem ID	Target proteins	Binding affinity (kcal/mol)
α-Terpineol	443162	COX-1	–6.9
γ-Muurolene	12313020	COX-1	–6.8
Caryophyllene	5281515	COX-1	–6.4
Copaene	12303902	COX-1	–6.4
Caryophyllene oxide	1742210	COX-1	–6.2
α-Muurolene	12306047	COX-1	–6.2
Trans-Cinnamaldehyde	637511	COX-1	–5.9
α-Pinene	440968	COX-1	–5.9
D-Limonene	440917	COX-1	–5.9
Trans-α-Bergamotene	86608	COX-1	–5.9
Linalool	6549	COX-1	–5.6
Bornyl acetate	6448	COX-1	–5.5

Table 5 Results of metabolite screening predicted to have anti-inflammatory properties using molecular docking techniques (Target Protein COX-2: 4PH9) with PyRx 0.8 Software.

Metabolite compounds	PubChem ID	Target proteins	Binding affinity (kcal/mol)
γ-Muurolene	12313020	COX-2	–7.4
Copaene	12303902	COX-2	–6.8
Trans-α-Bergamotene	86608	COX-2	–6.8
Caryophyllene	5281515	COX-2	–6.6
α- Muurolene	12306047	COX-2	–6.6
Caryophyllene oxide	1742210	COX-2	–6.5
α-Terpineol	443162	COX-2	–6.0
D-Limonene	440917	COX-2	–5.9
Trans-Cinnamaldehyde	637511	COX-2	–5.9
α-Pinene	440968	COX-2	–5.6
Bornyl acetate	6448	COX-2	–5.6
Linalool	6549	COX-2	–5.5

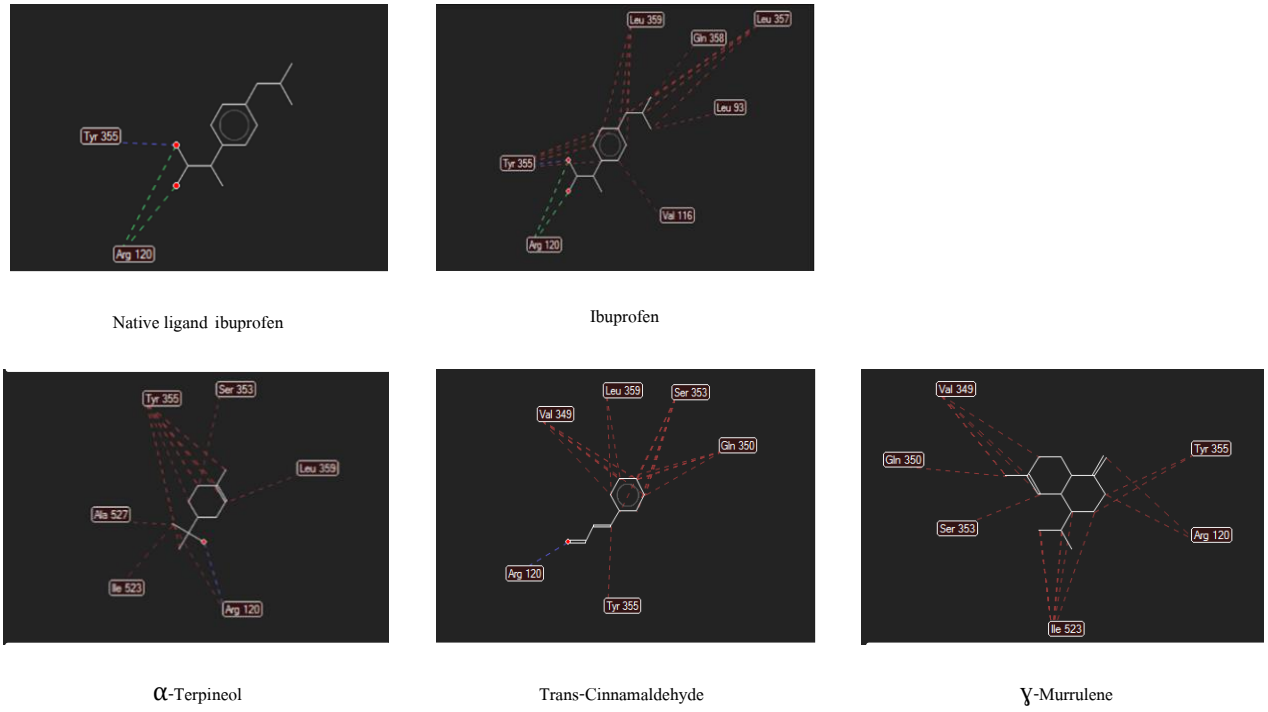


Figure 1 Results of specific molecular docking of 3 selected metabolite compounds with COX-1 Enzyme (1EQG).

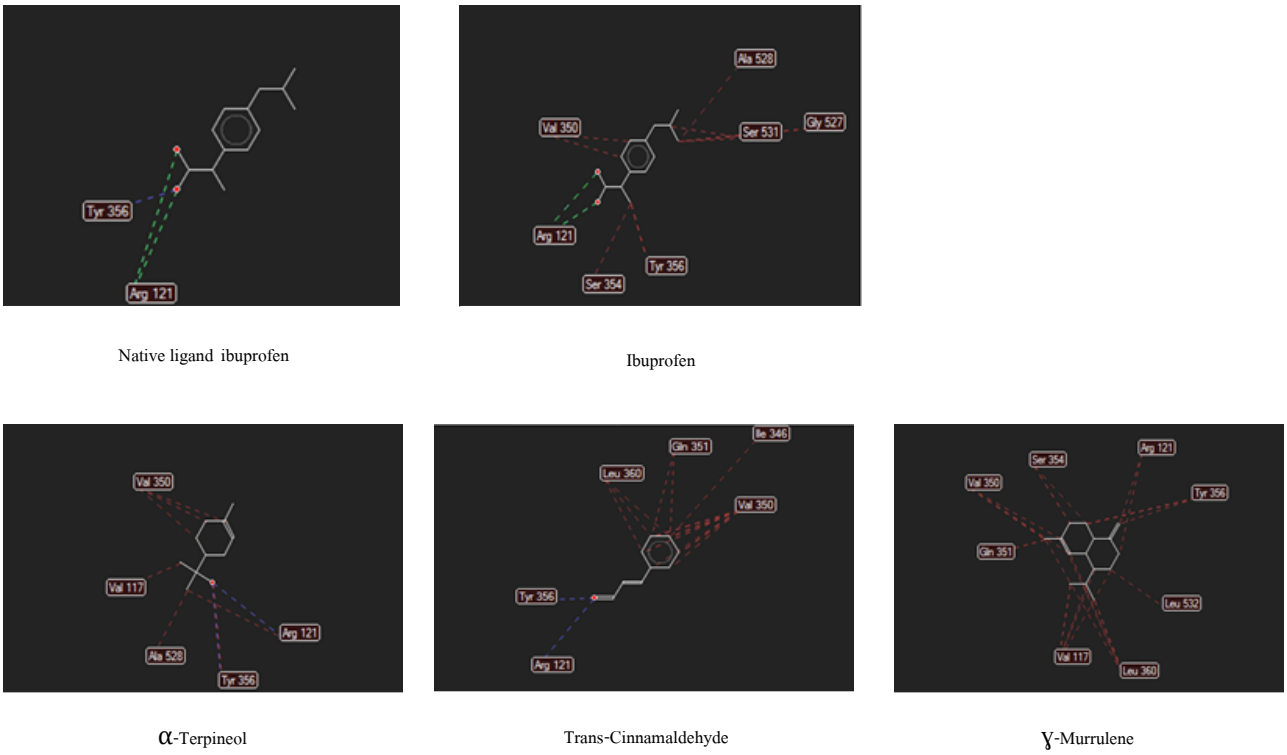


Figure 2 Results of molecular docking of 3 selected metabolite compounds with COX-2 (4PH9).

Table 6 Results of specific molecular docking of 3 metabolite compounds with COX-1 target protein (1EQG).

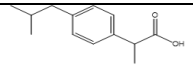
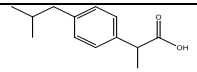
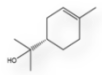
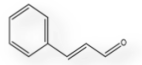
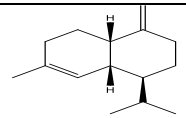
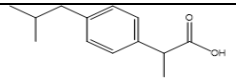
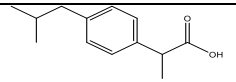
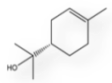
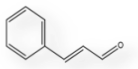
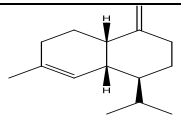
Compound name	2D Structure	Rerank score	RMSD	Hydrogen bond	Electrostatic interactions	Steric interactions
Native Ligand Ibuprofen	 2-[4-(2-methylpropyl)phenyl] propanoic acid	1) –82.0501 2) –80.2243 3) –81.8767 Average –81.38370 ± 1.00781	1.18584 1.18940 1.41182 Average 1.26235 ± 0.12945	3 bond with Try 355, 2 dengan Arg 120	2 interaction with Arg 120	-
Ibuprofen	 2-[4-(2-methylpropyl)phenyl] propanoic acid	1) –80.9704 2) –82.3334 3) –80.4241 Average –81.24263 ± 0.98333	8.14495 8.20340 8.73232 Average 8.36022 ± 0.32357	3 bond with Try 355, 2 dengan Arg 120	2 interaction with Arg 120	15 bond with Tyr 355, Leu 359, Gln 358, Leu 357 Leu 93, Val 116
α-Terpineol	 2-[(1S)-4-methylcyclohex-3-en-1-yl]propan-2-ol	1) –60.0217 2) –60.0624 3) –59.9281 Average –60.00407 ± 0.06886	7.18158 7.58395 7.16914 Average 7.31156 ± 0.23598	1 bond with Arg 120	-	11 bond with Ile 523, Ala 527, Tyr 355, Ser 353 Leu 359
Trans-Cinnamal-dehyde	 (E)-3-phenylprop-2-enal	1) –59.7091 2) –59.6834 3) –59.6730 Average –59.6885 ± 0.01858	7.73425 7.73730 7.73631 Average 7.73595 ± 0.00156	1 Bond with Arg 120	-	14 bond with Val 349, Leu 359 Ser 353, Gin 350 Tyr 355
ɣ-Murrulene	 (1S,4aS,8aR)-7-methyl-4-methylidene-1-propan-2-yl-2,3,4a,5,6,8a-hexahydro-1H-naphthalene	1) –72.0711 2) –72.0627 3) –72.0680 Average 72.06727 ± 0.00425	4.87238 4.87311 4.87265 Average 4.87271 ± 0.00037	-	-	14 bond with Ile 523, Ser 153 Gln 350, Val 349 Tyr 355, Arg 120

Table 7 Results of specific molecular docking of 3 metabolite compounds with COX-2 target protein (4PH9).

Compound name	2D Structure	Rerank score	RMSD	Hydrogen bond	Electrostatic interactions	Steric interactions
Native Ligand Ibuprofen	 2-[4-(2-methylpropyl)phenyl] propanoic acid	1) –78.5474 2) –78.6864 3) –76.6223 Average –77.95203 ± 1.15368	0.568205 0.682736 0.531957 Average 0.59430 ± 0.07870	1 bond with Tyr 356 2 bond with Arg 121	2 bond with Arg 121	-
Ibuprofen	 2-[4-(2-methylpropyl)phenyl] propanoic acid	1) –80.3256 2) –79.6909 3) –82.5077 Average –80.8414 ± 1.47754	5.90367 1.38703 5.96873 Average 4.41981 ± 2.62666	2 bond with Arg 121	2 bond with Arg 121	8 interaction with Val 350, Ala 528 Ser 531, Gly 527 Ser 354, Tyr 356
α-Terpineol	 2-[(1S)-4-methylcyclohex-3-en-1-yl]propan-2-ol	1) –58.8908 2) –58.8858 3) –58.8803 Average –58.88563 ± 0.00525	5.24059 5.24315 5.24590 Average 5.24321 ± 0.00265	2 bond with Arg 121 Tyr 356	-	7 bond with Arg 121, Tyr356, Ala 528, Val 117, Val 350
Trans-Cinnamal-dehyde	 (E)-3-phenylprop-2-enal	1) –59.6735 2) –59.9385 3) –59.5923 Average –59.73477 ± 0.18105	6.87610 7.47409 6.87256 Average 7.07425 ± 0.34628	2 bond with Arg 121 Tyr 356	-	12 bond with 6873Leu 360, Gln 351 Ile 346, Val 350
ɣ-Murrulene	 (1S,4aS,8aR)-7-methyl-4-methylidene-1-propan-2-yl-2,3,4a,5,6,8a-hexahydro-1H-naphthalene	1) –74.7544 2) –74.7005 3) –74.7220 Average –74.72563 ± 0.02713	7.10789 7.10582 7.10550 Average 7.10640 0.00130	-		19 bond with Leu 360, Leu 532 Tyr 356, Arg 121 Ser 354, Gln 351, Val 350, Val 117

After being identified as drug-like molecules, the 14 essential oil compounds from *C. burmannii* were analyzed for their probability as anti-inflammatory agents using the PASS Online server (http://www.pharmaexpert.ru/ passonline/). With an average accuracy of more than 95%, PASS Online forecasts almost 4,000 biological activities, including as pharmacological activities, metabolic enzyme and transporter interactions, mechanisms of action, toxicity, side effects, and influences on gene expression [14]. Using their structural formulas or SMILES strings, this server assesses the biological activity of query compounds *in silico* [15].

This study used medium evidence predictions, where compounds with a Pa value > 0.3 were categorized as good candidates for anti-inflammatory agents [10]. Among the 14 compounds, 2—eucalyptol and benzenepropanal—had Pa values equal to 0.3 and were therefore not considered strong candidates for anti-inflammatory activity compared to other compounds.

Specific molecular docking with the anti-inflammatory control compound ibuprofen was performed on 2 compounds with the lowest binding energy affinity from the screening results, namely α-Terpineol and γ-Muurolene, as well as the compound with the highest concentration, trans-cinnamaldehyde, to predict the orientation and binding affinity using Molegro Virtual Docker. This study used ibuprofen as the control compound [12,13].

The Rerank Score represents the compound's binding energy to the receptor. The activity is indicated by a lower binding energy value, as it reflects a more stable bond, thereby predicting greater activity [16]. The docking results for α-Terpineol, γ-Muurolene, and trans-Cinnamaldehyde suggest that they have the potential to inhibit the inflammatory response through COX-1 inhibition, consistent with previous studies [17]. The Rerank Score values show that α-Terpineol, trans-Cinnamaldehyde, and γ-Muurolene have higher binding energies compared to the ibuprofen control compound, indicating that their potential anti-inflammatory activity through interaction with the COX-1 target protein is lower than that of ibuprofen.

In COX-1, the compound Ibuprofen, serving as the control, exhibits an average rerank score of –81.38 kcal/mol, with an RMSD of approximately 1.26 Å. The detected interactions include hydrogen bonds with Try 355 and Arg 120, along with electrostatic interactions involving Arg 120. Conversely, the compounds α-Terpineol and trans-Cinnamaldehyde present lower rerank scores of –60.00 and –59.69 kcal/mol, respectively. These 2 compounds demonstrate fewer interactions with the COX-1 target, yet they do exhibit hydrogen bonding and electrostatic interactions with Arg 120. These results suggest that while these substances might not be as effective in reducing inflammation compared to ibuprofen, they could potentially serve as adjuvants to reduce NSAID dosages [18].

For the COX-2 target, the compound ibuprofen shows an average rerank score of –77.95 kcal/mol and a low RMSD (0.59 Å). Detected interactions include 1 hydrogen bond with Tyr 356 and 2 hydrogen bonds with Arg 121, supporting the strong anti-inflammatory effects of ibuprofen. Other compounds, such as γ-Muurolene and trans-cinnamaldehyde, exhibit lower rerank scores (around –74 to –59 kcal/mol), with hydrogen and electrostatic interactions detected at Arg 121 and Tyr 356, but fewer interactions compared to ibuprofen. These fewer interactions indicate that while these compounds may have anti-inflammatory properties, their effectiveness might be lower than ibuprofen [5]. Thus, it is necessary to conduct preclinical and clinical trials.

Conclusions

The results of *in silico* analysis by simulating the binding of metabolites with COX-1 and COX-2 target proteins on PyRx 0.8 software (https://www.rcsb.org/) on 14 volatile oil metabolites showed that there were 12 compounds thought to contribute to the activity of anti-inflammatory. These metabolites are α-Terpineol, α-Pinene, α-Muurulene, ɣ-Muurulene, trans-α-Bergamotene, transCinnamaldehyde, Caryophyllene oxide, Caryophylene, D-Limonene, Bornyl acetate, Copaene, and Linalool. The lowest binding affinity value with COX-1 target protein is α -Terpineol, which is –6.9 kcal/mol. The lowest binding affinity value with COX-2 target protein is ɣ-Muurulene which is –7. 4. Specific molecular docking with Molegro Virtual Docker software against α-Terpineol and ɣ-Muurulene and trans-Cinnamaldehyde with ibuprofen as control

compounds to strengthen the prediction that these 3 compounds have potential as anti-inflammatory.

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Declaration of Generative AI in Scientific Writing

The authors declare that no generative AI tools were used in the writing or preparation of this manuscript.

CRediT Author Statement

BB, MHE, and VNH conducted data collection. ARK, BPP, and MA drafted the manuscript. AP, ENU, and IBM performed data analysis. HP, RZA, and WT conducted the concept research. All authors have read and approved the final manuscript.

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