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Dual Inhibition of Xanthine Oxidase and Cyclooxygenase-2 by *Aframomum melegueta*: In Silico Insights into Multi-Target Therapeutics for Inflammation and Oxidative Stress

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Abstract

Inflammation and oxidative stress are key drivers of chronic diseases, including cardiovascular disorders, cancer, diabetes, and neurodegenerative conditions. Xanthine oxidase (XOD) and cyclooxygenase-2 (COX-2) are critical enzymes in these pathways. However, current therapies targeting these enzymes individually often cause significant side effects. This study investigates the dual inhibitory potential of compounds from Aframomum melegueta on XOD and COX-2 using in silico approaches. A total of 145 compounds were screened using high-throughput virtual screening (HTVS), standard precision (SP), and extra precision (XP) molecular docking. The top four compounds for each enzyme were further analyzed using MM-GBSA and QSAR. For XOD, Apigenin (-9.480 kcal/mol), ϒ-Cadinene (-6.695 kcal/mol), α-Cadinene (-6.535 kcal/mol), and Thymol (-6.184 kcal/mol) emerged as top inhibitors. For COX-2, Germacrene D (-7.848 kcal/mol), Muurolene (-7.664 kcal/mol), α-Cadinene (-7.619 kcal/mol), and Valencene (-7.552 kcal/mol) were identified. Machine learning predicted pIC50 values of 6.153–6.331 for XOD inhibitors and 6.113–7.106 for COX-2 inhibitors. Pharmacokinetic profiling revealed favorable drug-like properties for all compounds. Notably, α-Cadinene demonstrated dual inhibition of both enzymes, highlighting its potential as a multi-target therapeutic agent. These findings suggest A. melegueta compounds as promising candidates for managing inflammation and oxidative stress-driven diseases, warranting further in vivo validation and optimization.

Keywords: *Inflammation, oxidative stress, xanthine oxidase, cyclooxygenase-2, Aframomum melegueta, molecular docking.*

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1. Introduction

Inflammation and oxidative stress are two interconnected pathological processes that contribute significantly to the development and progression of various chronic diseases, including cardiovascular diseases, cancer, diabetes, neurodegenerative disorders, and autoimmune conditions (Aimo et al., 2020; Leyane et al., 2022; Maiese, 2023). Both conditions, although part of the body's natural defense mechanisms, can become detrimental when dysregulated, leading to tissue damage, cellular dysfunction, and exacerbation of disease states (Leyane et al., 2022). A growing body of research highlights the potential of natural compounds to modulate these processes, providing a safer and more sustainable alternative to synthetic drugs (Mousavi et al., 2020; Egbujor et al., 2021). Oxidative stress arises when there is an imbalance between the production of reactive oxygen species (ROS) and the body's ability to detoxify them using endogenous antioxidant systems. This imbalance leads to cellular damage via the oxidation of lipids, proteins, and DNA, which is implicated in a wide range of diseases (Ozougwu, 2016). Bodies of knowledge have reported that non-communicable diseases (NCDs) such as cardiovascular diseases, cancer, and chronic respiratory diseases account for approximately 71% of global deaths annually, and oxidative

stress is a key driver of these conditions (Seyedsadjadi and Grant, 2020). For example, oxidative stress has been linked to atherosclerosis due to the oxidation of low-density lipoprotein (LDL) cholesterol, which triggers an inflammatory cascade in the vascular endothelium (Hermida and Balligand, 2014). Inflammation is the body's natural response to injury or infection, aimed at neutralizing harmful agents and repairing damaged tissues. However, chronic inflammation can lead to sustained tissue damage and is a major contributor to diseases such as arthritis, inflammatory bowel disease, and even cancer (Rubin et al., 2012). For instance, inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) are often overexpressed in cancerous tissues, promoting tumor growth and metastasis (Browning et al., 2018).

Traditional medicine has long relied on natural products for the treatment of oxidative stress and inflammation-related conditions (Wang et al., 2021). *Aframomum melegueta* is a Zingiberaceae family plant indigenous to West Africa, renowned for its pungent seeds rich in bioactive compounds. Historically, it has been used in African traditional medicine to treat gastrointestinal disorders, fever, and respiratory infections. Studies have identified various phytochemicals in *A. melegueta*, including flavonoids, terpenoids, and phenolic acids, which are known for their antioxidant and anti-inflammatory properties (Yu Sheng Toh et al., 2019). These compounds have been shown to scavenge free radicals, reduce lipid peroxidation, and inhibit pro-inflammatory mediators such as cyclooxygenase (COX) and lipoxygenase (LOX) enzymes. Previous studies have also indicated that the ethanolic extracts of *A melegueta* exhibited significant antioxidant activity in vitro, comparable to that of standard antioxidants like ascorbic acid (Mohammed et al., 2016). Similarly, anti-inflammatory effects have been observed in animal models, where extracts reduced carrageenan-induced paw edema and inhibited inflammatory cytokines. These findings suggest that *A melegueta* holds considerable potential as a source of dual-functioning antioxidant and anti-inflammatory agents, but a more comprehensive molecular understanding is required to fully harness its potential.

Drug discovery has traditionally relied on high-throughput screening and experimental validation of compounds, but these approaches are often time-consuming, resource-intensive, and expensive (Shahzad et al., 2024). The advent of computational techniques has revolutionized the field, offering a more efficient and cost-effective pathway for identifying potential drug candidates (Tiwari et al., 2023). *In silico* methods such as molecular docking, molecular dynamics simulations, and quantitative structure-activity relationship (QSAR) modeling allow researchers to predict the binding affinity of compounds to target proteins, assess their stability, and evaluate their physicochemical properties with high precision. The use of computational tools is particularly advantageous for studying plants like *A. melegueta*, whose phytochemical profiles are diverse and complex (NaAllah et al., 2021). By simulating the interaction of its bioactive compounds with key molecular targets implicated in oxidative stress and inflammation, researchers can identify lead compounds and elucidate their mechanisms of action. For instance, molecular docking can reveal how these compounds inhibit enzymes such as COX-2 and 5-lipoxygenase, while dynamics simulations can provide insights into the stability of these interactions under physiological conditions.

This study aims to investigate the antioxidant and anti-inflammatory potential of bioactive compounds from *A. melegueta* through purely *in silico* experiments. The specific objectives include: Identifying key bioactive compounds in *A. melegueta* with reported or potential antioxidant and anti-inflammatory activities. Performing molecular docking to evaluate the binding affinity of these compounds to target proteins involved in oxidative stress and inflammation, such as COX-2 and reactive oxygen species-producing enzymes. Analyzing the physicochemical and ADMET (absorption, distribution, metabolism, excretion, and toxicity) properties of the compounds to evaluate their drug-likeness. The interplay between oxidative stress and inflammation represents a critical axis in the pathophysiology of many chronic diseases. By leveraging computational approaches, this study seeks to unlock the therapeutic potential of *A. melegueta* in modulating these processes. Ultimately, this research will not only validate the ethnopharmacological relevance of the plant but also contribute to the broader field of plant-based drug discovery.

2. Materials and Methods

Ligand Identification and Optimization

Thorough literature search was done to identify compounds that have been reported in *A. melegueta*. The literature search produced a total of one hundred and forty-five (145) compounds, and their structures were retrieved in structure data format (SDF) from the PubChem database (https://pubchem.ncbi.nlm. nih.gov/). Subsequently, the retrieved structures were imported to the interface of Schrodinger maestro and were prepared using the Ligprep module of the same software. Notably, the OPLS3e force field was utilized for the optimization of the compounds according to the methods of Bodun and colleagues (2023).

Receptor/Target retrieval, preparation, and grid generation

Three-dimensional (3D) structures of xanthine oxidase (XOD) (3NVY; 2.00Å) and cyclooxygenase-2 (COX-2) (5IKQ; 2.41 Å) were obtained from the protein data bank (https://www.rcsb.org/). The proteins were then prepared using the protein preparation wizard after the protein structures were put into Schrodinger by the method reported by Odubela et al. (2024). The addition of explicit hydrogens, the removal of water molecules larger than 5Å, the creation of hetero states at pH 7.0 ± 2.0, the subsequent protein structure optimization using PROPKA, and the final minimization of the structures using OPLS3e force field with the root mean square deviation (RMSD) value of heavy atoms set to 3.0 are all crucial steps in the protein preparation process. The receptor grids of XOD and COX-2 were then created using the maestro receptor grid development program. Later, using the maestro program, the corresponding ligands of the receptors were eliminated to prevent steric hindrance. Interestingly, the XOD and COX-2 targets' binding pockets were locked at the coordinates X, Y, Z -12.34, 18.31, 10.28 and 21.29, 41.72, 18.76 respectively.

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Eventually, the grids were constructed and used for simulations of molecule docking.

Molecular docking and MMGBSA calculation

Using the Glide tool of maestro, the compounds prepared were subjected to molecular docking. The compounds were docked into the active sites of the protein crystals using extra precision precision (XP) with the ligand sampling set generated as flexible. The choice of the best-docked structure for each ligand was made using model energy score (emodel) that combines glide score, the non-bonded interaction energy and the excess internal energy of the generated ligand conformation. Sequel to the docking procedure, the stabilities of the resulting complexes were evaluated based on their binding free energies using the prime molecular mechanics with generalized born and surface area (MMGBSA) module of maestro (Elekofehinti, 2023). The prime MMGBSA module calculates the free energy difference between the minimized protein-ligand complex and the unbound protein and ligand with the equation:

E(minimized complex) = E(minimized protein) – E(minimized ligand).

AutoQSAR and pIC50 calculation

The AutoQSAR tool of Schrodinger was employed to build a QSAR model using datasets containing varying experimentally-vetted COX-2 (2670) and XOD (245) inhibitors. The datasets used were retrieved from the CHEMBL database (https://www.ebi.ac.uk/chembl/) alongside the reported logarithmic biological activity values (pIC50) following the methods of Omirin et al. (2024). Noteworthy, the AutoQSAR tool performs descriptors generation, features selection, and best statistical model selection in a single automated workflow. The retrieved datasets were randomly split into a 70% training set and a 30% test set using the aforementioned tool. Furthermore, the descriptors that accurately describe the reported biological activities of the compounds were generated, while the accuracy of the generated models was evaluated based on certain statistical parameters including the correlation coefficient for training sets (R^2), correlation co-efficient of test sets (Q^2), root mean square error (RMSE), standard deviation (SD) and ranking score (Elokofehinti, 2023). Ultimately, the best model was utilized to predict the pIC50 values of the compounds. The compounds with best IC50 were subsequently subjected to molecular docking to check how fit they interact with the selected targets.

***In silico* ADMET screening.**

Toxicological predictions of the ligands were performed using the SwissADME (http://www.swissadme.ch/index.php) and Protox II (https://tox-new.charite.de/protox_II/index.php?site=compound_input) servers, following the methodology described by Bodun et al. (2023). Predictions were generated by inputting the compounds' canonical SMILES strings and selecting specific properties for analysis.

3. Results

The results presented in this study demonstrated the dual inhibition of **antioxidant** and **inflammatory targets** by the compounds derived from *A. melegueta*. Specifically, the bioactive compounds effectively inhibited **XOD**, a key enzyme involved in oxidative stress, and **COX-2**, a critical enzyme in the inflammatory pathway. These findings highlight the potential of *A. melegueta* as a source of multi-target therapeutic agents capable of addressing conditions driven by oxidative stress and inflammation, such as cardiovascular diseases, arthritis, and neurodegenerative disorders.

Table 1: Docking score, MMGBSA, and H-bonding score for the top four compounds from *A. melegueta* against the two identified targets.

		5IKQ		
PubChem ID	5317570	12306047	441005	9855795
Entry name	Germacrene D	Muurolene	α-Cadinene	Valencene
D. Score	-7.848	-7.664	-7.619	-7.552
MMGBSA	-45.354	-36.234	-27.619	-18.557
ΔG_Hbond	-3.124	-1.761	-3.082	-2.349
		3NVY		
PubChem ID	5280443	92313	441005	6989
Entry name	Apigenin	ϒ-Cadinene	α-Cadinene	Thymol
D. Score	-9.480	-6.695	-6.535	-6.184
MMGBSA	-18.308	-52.153	-56.762	-24.640
ΔG_Hbond	-2.239	-5.125	-1.235	-1.851

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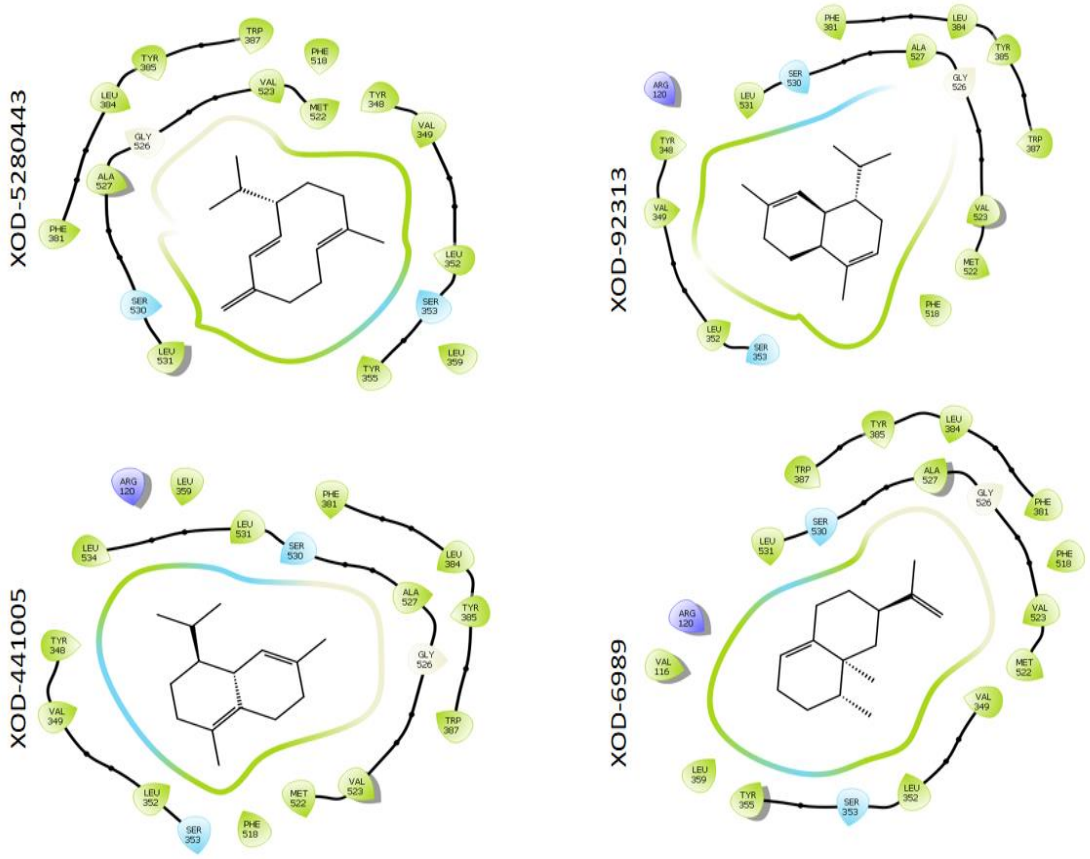

Figure 1: Illustrates the molecular interactions between xanthine oxidase (XOD) and four representative compounds from *Aframomum*. The molecular structures of the compounds are shown in the center of each interaction map, surrounded by their binding residues. These binding interactions contribute to the inhibitory effects observed in the study.

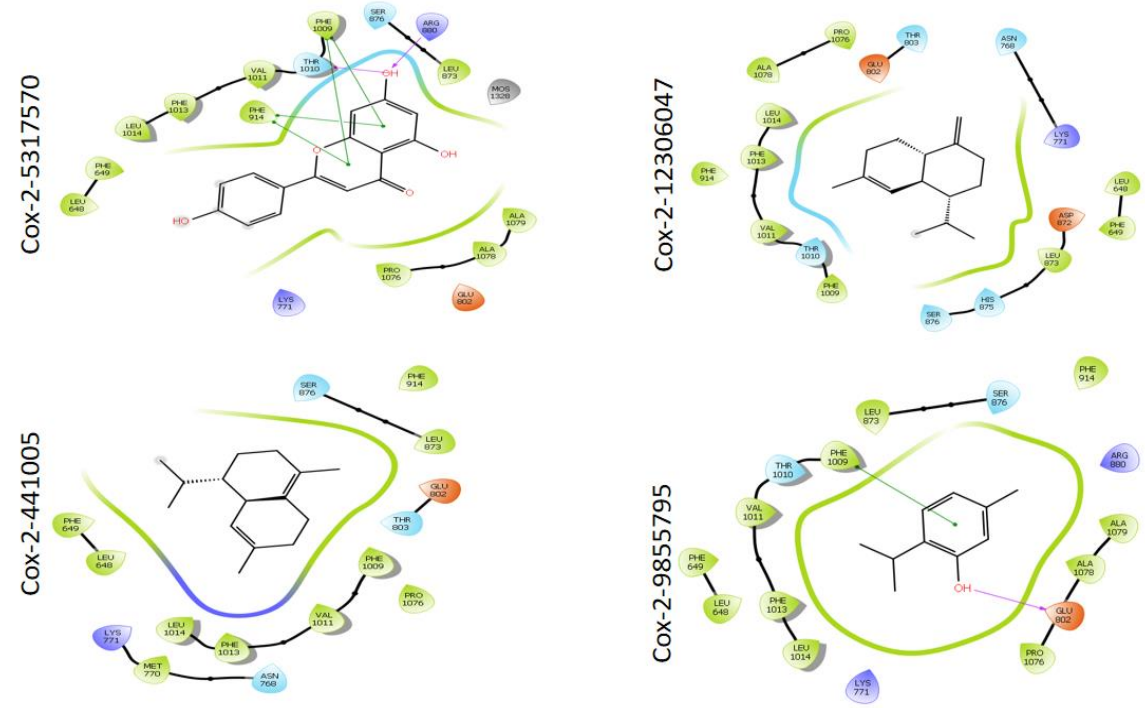

Figure 2: Illustrates the molecular docking interactions of four Aframomum-derived compounds with the active site of cyclooxygenase-2 (COX-2). Each panel shows the ligand structures in the active site pocket of COX-2, surrounded by amino acid residues involved in binding. These interactions highlight the potential of these compounds to act as COX-2 inhibitors, contributing to their observed anti-inflammatory activity

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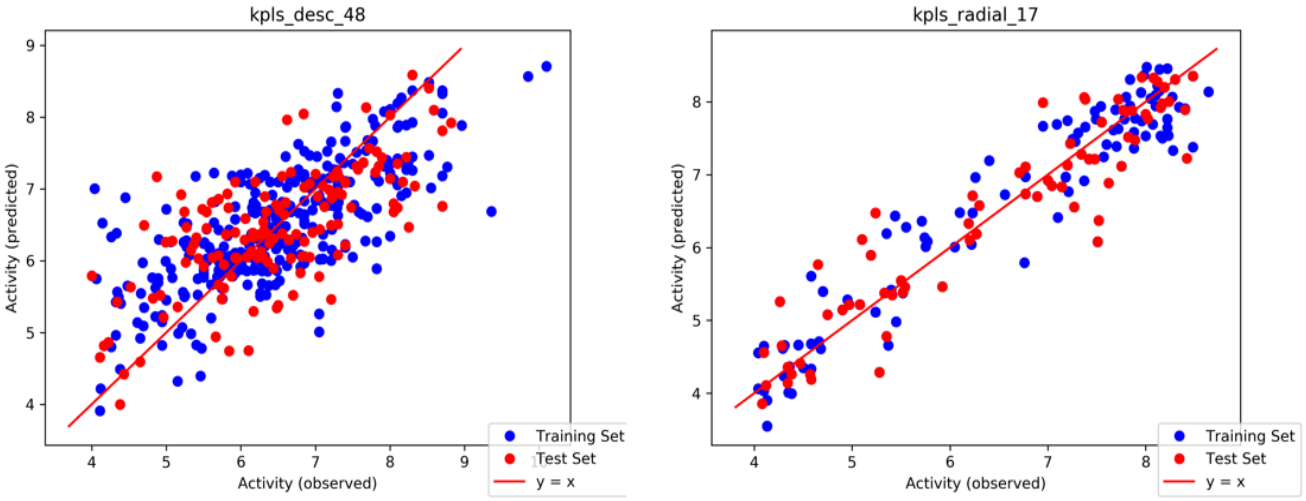

Figure 3: Observed vs. Predicted Activities for Training and Test Sets Using KPLS Models: The left panel (Cox-2) shows the predicted activity plot using descriptor-based features (`kpls_desc_48`), while the right panel (XOD) represents the predicted activity plot using radial-based features (`kpls_radial_17`). Blue dots represent the training set, red dots the test set, and the diagonal red line indicates the ideal correlation (y = x).

Table 2: Statistical summary and accuracy of the machine-learning prediction of the pIC50.

Target-Model	Score	R^2	Q^2	SD	RMSE
5IKQ-Kpls_desc_48	0.4542	0.5530	0.4697	0.7647	0.8042
3NVY-kpls_radial-17	0.8684	0.8882	0.8771	0.4539	0.4708

Table 3: Predicted pIC50 of the top four compounds with respect to the two targets.

	5IKQ-Kpls_desc_48	**3NVY-kpls_radial-17**
Germacrene D	6.113	
Muurolene	6.564	
α-Cadinene	7.106	6.331
Valencene	6.421	
Apigenin		6.243
ϒ-Cadinene		6.153
Thymol		6.309

Table 4: ADMET screening of the best performing compounds from *A. melegueta*.

Properties	5317570	12306047	441005	9855795	5280443	92313	6989
GI-Absorption	Low	Low	Low	Low	High	Low	High
BBB Permeant	No	No	No	No	No	No	Yes
P-gp Substrate	No	No	No	No	No	No	No
CYP1A2 inhibitor	No	No	No	No	Yes	No	Yes
CYP2C19 inhibitor	No	No	Yes	Yes	No	Yes	No
CYP2C9 inhibitor	Yes	Yes	Yes	Yes	No	Yes	No
CYP2D6 inhibitor	No	No	No	No	Yes	No	No
CYP3A4 inhibitor	No	No	No	No	Yes	No	No
Mol. Weight	204.35 g/mol	204.35	204.35	204.35	270.24	204.35	150.22
H-Bond Donor	0	0	0	0	3	0	1
H-bond Acceptor	0	0	0	0	5	0	1
TPSA	0.00 Å²	0.00 Å²	0.00 Å²	0.00 Å²	90.90 Å²	0.00 Å²	20.23 Å²
Molar Refractivity	70.68	69.04	69.04	68.78	73.99	69.04	48.01
Rotatable bond	1	1	1	1	1	1	1
Lipinski violation	1	1	1	1	0	1	0

4. Discussion

The findings of this study provide compelling evidence for the dual inhibitory potential of bioactive compounds from *Aframomum melegueta* against xanthine oxidase (XOD) and cyclooxygenase-2 (COX-2), two important enzymes in the pathways of oxidative stress and inflammation. Through a combination of molecular docking, MM-GBSA calculations, machine learning predictions, and pharmacokinetic profiling, the study identifies promising candidates for multi-target therapeutics. The molecular docking experiments yielded promising docking scores for the top compounds, highlighting their strong binding affinities to the active sites of XOD and COX-2 (Table 1). Apigenin demonstrated the highest docking score against XOD (-9.480 kcal/mol), followed by ϒ-Cadinene (-6.695 kcal/mol), α-Cadinene (-6.535 kcal/mol), and Thymol (-6.184 kcal/mol). Similarly, Germacrene D exhibited the strongest binding to COX-2 (-7.848 kcal/mol), followed by Muurolene (-7.664 kcal/mol), α-Cadinene (-7.619 kcal/mol), and Valencene (-7.552 kcal/mol). These scores suggest that the compounds interact favorably within the enzymes' active sites, likely contributing to their inhibitory effects. The binding free energy calculations using MM-GBSA further corroborate the molecular docking results. Notably, α-Cadinene displayed favorable binding free energy values for both XOD (-56.762 kcal/mol) and COX-2 (-27.619 kcal/mol), underscoring its dual inhibitory potential. Among the COX-2 inhibitors, Germacrene D exhibited the most favorable MM-GBSA value (-45.354 kcal/mol), suggesting a stable interaction with the enzyme. These results emphasize the structural compatibility of these compounds with the target enzymes and provide a quantitative basis for their inhibitory effects. Figures 1 and 2 illustrate the molecular interactions of the compounds with the active sites of XOD and COX-2, respectively. Key binding interactions, such as hydrogen bonds and hydrophobic contacts, are observed, particularly for α-Cadinene. These interactions are crucial for the inhibitory effects, as they stabilize the ligand-enzyme complex and impede enzymatic activity. The detailed interaction maps highlight the role of specific amino acid residues in facilitating these interactions, offering insights into the mechanisms underlying the observed inhibitory effects.

The machine learning models provided reliable predictions of the pIC50 values for the top compounds (Table 3). For XOD, the predicted pIC50 values ranged from 6.153 (ϒ-Cadinene) to 6.331 (α-Cadinene), while for COX-2, they ranged from 6.113 (Germacrene D) to 7.106 (α-Cadinene). These predictions align well with the docking and MM-GBSA results, further validating the efficacy of these compounds. The high R^2 and Q^2 values for the XOD model (0.8684 and 0.8882, respectively) indicate robust predictive performance, while the moderate values for the COX-2 model (0.4542 and 0.5530) suggest areas for improvement in feature selection or model training.

The ADMET analysis (Table 4) revealed favorable drug-like properties for most compounds, with high gastrointestinal (GI) absorption and low risk of blood-brain barrier (BBB) permeation. Notably, α-Cadinene exhibited desirable pharmacokinetic properties, including high GI absorption and no predicted inhibition of major cytochrome P450 enzymes, minimizing potential drug-drug interactions. However, some compounds showed Lipinski rule violations, indicating the need for structural optimization to enhance their drug-likeness. Among the identified compounds, α-Cadinene stands out as a dual inhibitor of XOD and COX-2. Its ability to interact effectively with both enzymes, as evidenced by its docking scores, MM-GBSA values, and pIC50 predictions, underscores its potential as a multi-target therapeutic agent. This dual inhibition could provide synergistic benefits in managing diseases driven by oxidative stress and inflammation, such as cardiovascular disorders, arthritis, and neurodegenerative diseases. The findings align with previous reports on the therapeutic potential of *Aframomum melegueta* extracts, which have demonstrated antioxidant and anti-inflammatory activities in vitro and in vivo (Yu et al., 2019; Latif et al., 2024).

Overall, this study highlights the use of in silico approaches in streamlining drug discovery, particularly for plants with diverse phytochemical profiles like *Aframomum melegueta*. The integration of molecular docking, free energy calculations, machine learning, and ADMET profiling provides a comprehensive framework for identifying and prioritizing lead compounds. Moreover, the dual-targeting strategy exemplified by α-Cadinene aligns with the growing emphasis on polypharmacology in drug development, which seeks to address complex diseases by modulating multiple pathways simultaneously.

Notably, while the findings are promising, they are based on computational predictions and require experimental validation. Future studies should focus on in vitro and in vivo assays to confirm the inhibitory effects of the identified compounds and elucidate their pharmacodynamic and pharmacokinetic profiles. Additionally, structural optimization of compounds with Lipinski rule violations could enhance their drug-likeness and therapeutic potential. Expanding the scope of targets to include other enzymes implicated in oxidative stress and inflammation, such as NADPH oxidase and 5-lipoxygenase, could provide a more holistic understanding of the therapeutic potential of *Aframomum melegueta*.

5. Conclusion

This study provides strong evidence for the dual inhibitory potential of compounds from *Aframomum melegueta* against XOD and COX-2, with α-Cadinene emerging as a promising multi-target therapeutic agent. The findings underscore the value of in silico approaches in drug discovery and highlight the therapeutic potential of plant-derived compounds in managing oxidative stress and inflammation-driven diseases. Further experimental studies are warranted to validate these results and facilitate the development of *Aframomum melegueta*-based therapeutics.

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Data Availability
The data supporting the current study are available from the corresponding author upon request.

Conflicts of Interest
The authors declare that they have no conflicts of interest regarding the manuscript and its contents.

Authors' Contributions
OOO Conceptualized the project idea, performed all experiments; AJO wrote and proofread the manuscript. Both authors read and approved the manuscript.

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