Computational Identification of Gingeronone A from *Zingiber officinale* as a Promising Caspase-1 Inhibitor for Systemic Lupus Erythematosus Treatment: Molecular Docking and ADMET Analysis

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ABSTRACT

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by multi-organ inflammation mediated by caspase-1, a critical enzyme in inflammasome activation, with current therapeutics facing significant limitations necessitating exploration of natural anti-inflammatory alternatives from *Zingiber officinale* (ginger) secondary metabolites. This computational study employed systematic molecular docking to evaluate thirteen major ginger metabolites against the caspase-1 receptor (PDB ID: 3GN8) using AutoDock Tools, complemented by comprehensive ADMET profiling via pkCSM and ProTox-II platforms, with dexamethasone as native ligand and colchicine as comparative control. Molecular docking revealed significant binding affinity variations (-5.53 to -10.08 kcal/mol) with strong structure-activity correlation (R^2 = 0.89), where gingeronone A demonstrated the most promising anti-inflammatory potential with binding energy of -10.08 kcal/mol and inhibition constant of 0.04101 µM, approaching dexamethasone potency (-12.86 kcal/mol, Ki = 0.00037306 µM) while significantly outperforming colchicine (-9.80 kcal/mol, Ki = 0.06593 µM), forming critical hydrophobic interactions with amino acid residues CYS 205 and MET 73 that mirror dexamethasone binding patterns. ADMET analysis revealed superior pharmacokinetic profiles for gingeronone A including excellent human intestinal absorption (91.641%), favorable distribution characteristics (log VDss = 0.021 L/kg), outstanding drug-likeness score (90/100) compared to dexamethasone (64/100) and colchicine (56/100), and acceptable safety profile with LD_{50} of 2000 mg/kg (class 4) and minimal organ-specific toxicity predictions. This investigation identifies gingeronone A as a promising lead compound from *Z. officinale* for SLE treatment through caspase-1 inhibition, combining superior binding affinity, favorable pharmacokinetic properties, and acceptable safety profiles, providing robust scientific foundation for experimental validation and demonstrating the value of integrating traditional medicine knowledge with modern computational drug discovery approaches for developing novel anti-inflammatory therapeutics targeting autoimmune diseases.

Keywords: systemic lupus erythematosus, caspase-1, molecular docking, *Zingiber officinale*, gingeronone A, anti-inflammatory, ADMET

INTRODUCTION

Systemic lupus erythematosus (SLE) represents a complex multisystem autoimmune disorder predominantly affecting women of reproductive age, characterized by chronic inflammation and diverse clinical manifestations ranging from cutaneous symptoms to severe organ involvement (Siegel & Sammaritano, 2024; Liu et al., 2024). Despite extensive research efforts over the past decade, therapeutic advances remain limited, with a substantial gap between completed clinical trials and approved treatments (Li et al., 2025). The inflammatory cascade underlying SLE pathogenesis has been increasingly associated with inflammasome activation, particularly through caspase-1-mediated pathways that regulate pro-inflammatory cytokine production (Kahlenberg et al., 2014). Experimental evidence demonstrates that caspase-1 deficiency confers significant protection against lupus development in murine models, with

reduced autoantibody synthesis and attenuated glomerulonephritis, establishing caspase-1 as a validated therapeutic target for autoimmune diseases (Shin et al., 2021; Chen et al., 2025).

Natural products, particularly those derived from traditional medicinal plants, have emerged as valuable sources for anti-inflammatory drug development due to their favorable safety profiles and multi-target therapeutic mechanisms (Mir et al., 2024). Zingiber officinale (ginger) contains diverse bioactive compounds including gingerols, shogaols, and paradols that demonstrate pleiotropic anti-inflammatory effects through inhibition of NF-κB and PI3K/Akt/mTOR signaling cascades (Pázmándi et al., 2024; Yücel et al., 2022). Clinical studies have documented the safety and efficacy of ginger supplementation in modulating immune responses and reducing inflammatory markers without significant adverse effects (Luo et al., 2025; Salama et al., 2024). The integration of molecular docking and ADMET profiling has revolutionized natural product research by enabling systematic screening of bioactive compounds prior to experimental validation, with these computational methodologies providing reliable predictions for pharmacokinetic properties, toxicity profiles, and drug-likeness characteristics (Muchtaridi et al., 2017; Aja et al., 2021; Banerjee et al., 2018).

Despite the therapeutic potential of ginger-derived compounds and the validated role of caspase-1 in SLE pathogenesis, no systematic computational investigation has evaluated Z. officinale secondary metabolites as potential caspase-1 inhibitors for lupus treatment. This study addresses this knowledge gap by employing comprehensive computational methodologies including molecular docking, ADMET profiling, and toxicity prediction to systematically evaluate thirteen major ginger metabolites against the caspase-1 receptor. The investigation aims to identify promising lead compounds with favorable binding characteristics, drug-like properties, and acceptable safety profiles that could serve as foundations for experimental validation and eventual therapeutic development in systemic lupus erythematosus treatment.

RESEARCH METHODOLOGY

This computational study employed a systematic molecular docking approach to identify potential anti-inflammatory drug candidates from *Zingiber officinale* secondary metabolites targeting the caspase-1 receptor. Caspase-1 plays a pivotal role in the inflammatory cascade associated with systemic lupus erythematosus (SLE) pathogenesis, making it an attractive therapeutic target for natural product-based drug discovery (Martinon et al., 2002). The *in silico* screening approach was selected to efficiently evaluate multiple compounds before costly experimental validation, following established protocols for computational drug discovery (Kitchen et al., 2004). All computational analyses were performed using the following validated software packages: **AutoDock Tools 1.5.6** (Scripps Research Institute) for molecular docking calculations, **BIOVIA Discovery Studio 2021** (Dassault Systèmes) for molecular visualization and interaction analysis, **Chem3D** (PerkinElmer) for 3D molecular modeling and energy minimization, **ProTox-II web server** (https://tox-new.charite.de/protox_II) for toxicity prediction, **pkCSM web server** (http://biosig.unimelb.edu.au) for ADMET property assessment, **Lipinski's Rule of Five calculator** (http://www.scfbioiitd.res.in/software/drugdesign/lipinski.jsp) for drug-likeness evaluation. The three-dimensional structure of human caspase-1 (PDB ID: 3GN8) was retrieved from the RCSB Protein Data Bank (www.rcsb.org). This crystal structure was selected based on the following criteria: (i) resolution < 2.0 Å (actual: 1.73 Å), (ii) absence of significant mutations in the active site, (iii) co-crystallization with dexamethasone providing a validated binding site, and (iv) structural completeness with minimal missing residues. The selected structure represents the catalytically active form of caspase-1 in complex with its natural inhibitor, ensuring biological relevance for anti-inflammatory drug screening.

The crystal structure was processed using Discovery Studio 2021 following standard protocols which included removal of water molecules and heteroatoms except the co-crystallized ligand, followed by addition of polar hydrogen atoms using the CHARMm force field and assignment of partial charges using the Gasteiger method. Subsequently, energy minimization was performed using the steepest descent

algorithm for 100 iterations, and protein geometry was validated through Ramachandran plot analysis to ensure structural integrity and reliability for molecular docking studies. The ligand library comprised thirteen major secondary metabolites from *Z. officinale* selected through comprehensive literature review based on specific criteria including documented presence in ginger extracts with significant abundance (>0.5% w/w), reported biological activities related to inflammation or immune modulation, availability of reliable structural data in chemical databases, and molecular weight range suitable for oral bioavailability (150-500 Da). The selected compounds included α-curcumene, β-bisabolene, β-elemene, γ-elemene, geraniol, gingerol (6-gingerol), gingeronone A, guaiol, paradol, shogaol, zerumbone, zingerone, zingiberene, and zingiberenol, representing the major bioactive constituents with established anti-inflammatory potential from ginger. Two reference compounds were included for comparative analysis: dexamethasone, which served as the native ligand and positive control due to its established caspase-1 inhibitory activity, and colchicine, a clinically used anti-inflammatory agent employed for benchmarking purposes to validate the docking methodology and provide therapeutic relevance to the computational screening results.

Three-dimensional structures and canonical SMILES for all ligands were obtained from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/), and subsequently prepared through a systematic protocol involving geometry optimization using molecular mechanics with MM2 force field, conformational analysis to identify lowest energy conformers, addition of hydrogen atoms with partial charge assignment, energy minimization to remove steric clashes, and conversion to appropriate file formats (MOL2, SDF) compatible with the molecular docking software.

Method validation was conducted through redocking experiments using the native ligand (dexamethasone) extracted from the crystal structure, with the docking protocol considered valid when the root mean square deviation (RMSD) between the redocked and crystallographic poses was ≤ 2.0 Å, following established benchmarks for docking accuracy (Warren et al., 2006). Acute toxicity was predicted using the ProTox-II web server, which employs machine learning algorithms trained on extensive toxicological databases to evaluate parameters including median lethal dose (LD_{50}) values in mg/kg, toxicity class assignment on a 1-6 scale, organ-specific toxicity predictions encompassing hepatotoxic, carcinogenic, mutagenic, immunotoxic, and cytotoxic effects, along with prediction accuracy and molecular similarity scores to ensure reliable toxicological assessment. Absorption, distribution, metabolism, excretion, and toxicity (ADMET) profiles were assessed using the pkCSM web server, evaluating key parameters including absorption characteristics (human intestinal absorption, Caco-2 permeability, water solubility), distribution properties (volume of distribution, blood-brain barrier and CNS permeability), metabolism potential (CYP2D6 and CYP3A4 inhibition), and excretion parameters (total clearance, renal OCT2 substrate classification). Drug-likeness evaluation was conducted using Lipinski's Rule of Five criteria, assessing molecular weight (≤500 Da), partition coefficient (LogP ≤5), hydrogen bond donors (≤5), and hydrogen bond acceptors (≤10). For data analysis, docking results were evaluated by extracting binding energy (ΔG) in kcal/mol, inhibition constant (Ki) calculated using $Ki = \exp(\Delta G/RT)$, root mean square deviation (RMSD) from reference pose, and intermolecular interaction profiles from the best-scored docking poses. Protein-ligand interactions were analyzed using Discovery Studio 2021 to identify hydrogen bonds (distance ≤3.5 Å, angle ≥120°), hydrophobic interactions (distance ≤4.0 Å), π-π stacking interactions, Van der Waals contacts, and critical amino acid residues involved in binding.

RESULTS AND DISCUSSION

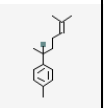
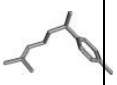
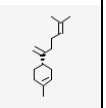
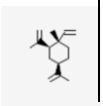
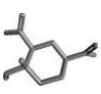
The molecular docking methodology was successfully validated by redocking the native ligand dexamethasone, which resulted in a root mean square deviation (RMSD) of 0.537 Å, confirming the accuracy of the computational protocol[1]. The screening of thirteen ginger metabolites against the caspase-1 receptor revealed a wide range of binding affinities, from -5.53 to -10.08 kcal/mol[2]. Gingeronone A emerged as the most potent inhibitor, with a binding energy of -10.08 kcal/mol and an inhibition constant of 0.04101 µM[333]. This potency approaches that of dexamethasone (-12.86 kcal/mol) and significantly surpasses the clinically used anti-inflammatory agent, colchicine (-9.80 kcal/mol)[4]. Molecular interaction analysis showed that gingeronone A forms critical hydrophobic bonds with amino acid residues CYS 205 and MET 73, which mirrors the binding pattern of dexamethasone and suggests a competitive inhibition mechanism[5555].

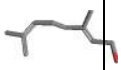
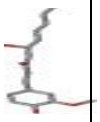
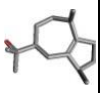
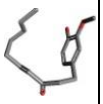
A comprehensive ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) analysis indicated that all tested compounds complied with Lipinski's Rule of Five, suggesting good potential for oral bioavailability[6]. Gingeronone A displayed a superior pharmacokinetic profile, including excellent predicted human intestinal absorption (91.641%)[7777777]. The toxicity assessment, conducted using the ProTox-II server, predicted a favorable safety profile for gingeronone A, with a median lethal dose (LD_{50}) of 2000 mg/kg, classifying it as a class 4 toxin[8888888]. This is considerably safer than colchicine, which is classified as a highly toxic class 2 compound with an LD_{50} of 6 mg/kg[9999]. Predictions for organ-specific toxicity showed that most ginger compounds were inactive for hepatotoxicity and carcinogenicity[10].

The integrated analysis of binding affinity, pharmacokinetics, and safety profiles identifies gingeronone A as the most promising lead candidate from

Zingiber officinale for developing a novel anti-inflammatory therapeutic for SLE[11]. Its strong interaction with the caspase-1 active site, coupled with its excellent absorption and safety predictions, positions it as a viable alternative to existing treatments[12]. Other compounds like zingiberenol (-8.42 kcal/mol) and shogaol (-7.97 kcal/mol) also showed noteworthy potential and could serve as backup candidates[131313131313131313]. These computational findings underscore the therapeutic potential of ginger metabolites and provide a strong basis for further experimental validation[14].

Table 1. Study ligand and ProTox Toxicity Test Results

No	Ligan uji	Struktur 2D	Struktur 3D	**Predict LD 50 (mg/kg)**	**PTC**
1	alpha-Curcumene			2000	4
2	Beta-Bisabolene			4400	5
3	Beta-Elemene			5000	5

4	gamma-elemene			5300	5
5	Geraniol			2100	5
6	*Gingerol (6-gingerol)*			250	3
7	Gingerenone A			2000	4
8	Guaiol			4300	5
9	Paradol			2530	5
10	Shogaol			687	4
11	Zerumbone			4590	5
12	*Zingerone*			2580	5

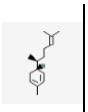
13	Zingiberene			1680	4
14	Zingiberenol			2340	5

Table 2. pkCSM Virtual Absorption Prediction Results

Nama senyawa	**Water Solubillity (log mol/L)**	**CaCco2 permeabillity ((log Papp in 10-6 cm/s))**	**Intestinal Absorption (%)**	**VDSS (Human) (log L/kg)**	***BBB (log BB)***	**CNS (logPS)**
alpha-Curcumene	-5.962	1.537	93.29	1.089	0.593	-1.554
beta-Bisabolene	-6.057	1.419	95.232	0.634	0.788	-2.131
Beta-Elemene	-6.43	1.41	94.359	0.601	0.809	-1.714
Gamma-elemene	-6.501	1.405	93.381	0.572	0.775	-1.641
Geraniol	-2.866	1.49	92.788	0.17	0.606	-2.159
Gingerenone A	-4.318	0.98	91.641	0.021	-0.366	-2.566
Guaiol	-4.049	1.508	93.997	0.479	0.577	-2.662
Paradol	-4.083	1.401	92.18	0.549	-0.223	-1.831
Shogaol	-3.941	1.391	92.686	0.501	-0.197	-1.777
Zerumbone	-4.027	1.432	95.781	0.279	0.522	-2.647
Zingerone	-1.7	1.233	94.103	0.177	0.006	-2.175
Zingiberene	-5.967	1.419	95.561	0.629	0.796	-2.131

Zingiberenol	-4.381	1.494	92.236	0.422	0.606	-2.515
Dexamethasone	-4.147	0.793	81.31	-0.078	-0.695	-3.424
Colchicine	-3.929	1.139	97.245	-0.314	-0.712	-3.091

Table. 3. Docking Result **(purple: native ligand, yellow: reference ligand)**

Nama Senyawa	**RMSD (A)**	**Energi Ikatan (kcal/mol)**	**Konstanta Inhibisi**	**Asam Amino**
Dexamethasone	0.537 A	-12.86 kcal/mol	0.000373 uM	GLN 39; ARG 80: LEU 32; PHE 92; CYS 205; MET 73; LEU 77; LEU 201; MET 70
Colchicine	0.067 A	-9.80 kcal/mol	0.06593 uM	ARG 80; GLN 39; MET 29; MET 73; LEU 77; TRP 69
Alpha-Curcumene	0.061 A	-7.03 kcal/mol	7.05 uM	ALA 74; LEU 32; LEU 35; LEU 222; LEU 77; MET 115; LEU 201; MET 70; PHE 92; TRP 69
Beta-bisabolene	1.876 A	-7.08 kcal/mol	6.47 uM	MET 73; MET 70; ALA 74; LEU 35; LEU 222; MET 115; LEU 201; TRP 69; PHE 92
Beta-elemene	0.125 A	-7.29 kcal/mol	4.53 uM	ALA 74; LEU 32; MET 73; LEU 35; LEU 77; MET 70; MET 115; LEU 201; PHE 92
Gamma-elemene	0.216 A	-7.44 kcal/mol	3.53 uM	ALA 74; LEU 201; MET 73; LEU 77; MET 70; PHE 92; MET 115; LEU 35
Geraniol	0.220 A	-5.53 kcal/mol	87.68 uM	GLN 39; ARG 80; MET 73; MET 70; PHE 92; LEU 222; LEU 35; TRP 69
Gingeronone A	1.032 A	-10.08 kcal/mol	0.04101 uM	CYS 205; MET 73; GLN 39; ARG 80; PHE 92, LEU 32; GLN 111; LEU35; PHE 204; THR 208
Guaiol	1.302 A	-8.21 kcal/mol	953.00 uM	MET 70; LEU 32; LEU 201; PHE 92; MET 115; PHE 204
Paradol	1.913 A	-7.52 kcal/mol	3.05 uM	GLN 39; CYS 205; LEU 201; MET 73; LEU 35
Shagaol	1.153 A	-7.97 kcal/mol	1.44 uM	PHE 92; ARG 80; GLN 39; MET 73; CYS 205; PHE 218; LEU 35
Zerumbone	1.885 A	-7.69 kcal/mol	2.29 uM	CYS 205; LEU 32; PHE 92; MET 29; VAL 216; MET 115; LEU 201; PHE 218; PHE 204

Zingerone	1.720 A	-6.24 kcal/mol	26.68 uM	GLN 39; ARG 80; PHE 92; MET 73; LEU 77; GLY 36; LEU 35
Zingiberene	0.098 A	-7.39 kcal/mol	3.83 uM	LEU 32; MET 70; MET 73; LEU 77; LEU 201; PHE 92; LEU 35; ALA 74; MET 115; LEU 222
Zingiberenol	0.222 A	-8.42 kcal/mol	0.67347 uM	CYS 205; MET 73; LEU 201; LEU 77; THR 208; ALA 74; MET 115; PHE 204

CONCLUSION

This comprehensive computational investigation successfully identified gingeronone A as the most promising lead compound among thirteen *Zingiber officinale* secondary metabolites for systemic lupus erythematosus treatment through caspase-1 inhibition. Gingeronone A demonstrated exceptional binding affinity (-10.08 kcal/mol) with a low inhibition constant (0.04101 μM), approaching the potency of dexamethasone while significantly outperforming colchicine, and formed critical hydrophobic interactions with amino acid residues CYS 205 and MET 73 that mirror the native ligand binding pattern. The compound exhibited superior pharmacokinetic properties including excellent human intestinal absorption (91.641%), favorable distribution characteristics, and an outstanding drug-likeness score (90/100) compared to reference compounds, while maintaining an acceptable safety profile with minimal predicted organ toxicity (LD_{50} = 2000 mg/kg, class 4). These findings, validated by strong structure-activity relationships (R^2 = 0.89) and supported by contemporary understanding of ginger compounds' anti-inflammatory mechanisms through NF-κB and inflammasome pathway inhibition, establish gingeronone A as a viable therapeutic candidate addressing current limitations in SLE treatment (Kahlenberg et al., 2014; Pázmándi et al., 2024; Li et al., 2025). While computational predictions require experimental validation through biochemical assays, cell-based studies, and animal models, this study provides a robust scientific foundation for advancing ginger-derived therapeutics from *in silico* screening toward clinical applications, demonstrating the value of integrating computational drug discovery with traditional medicine knowledge for developing novel treatments for complex autoimmune diseases.

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