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Original Article

Molecular Docking and Pharmacokinetic Evaluation of Terpenoid Compounds from Ramie (*Boehmeria nivea* (L.) Gaudich.) Leaves as Potential Natural Agents for Inflammatory Bowel Disease

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ABSTRACT

Boehmeria nivea (L.) Gaudich (Ramie) is traditionally used in Indonesia as an anti-inflammatory agent, yet the molecular basis of its terpenoid activity against inflammatory bowel disease (IBD) remains poorly understood. This study aimed to characterize the pharmacokinetic properties and molecular interactions of five terpenoid compounds—Muscone, Navenone A, Jasmone, Sedanolide, and Curcumene—identified from Ramie leaves, against the IBD-related target protein CEACAM6 (PDB ID: 4Y8A) using an integrated in silico approach combining drug-likeness screening, ADMET prediction, and molecular docking. Tofacitinib, a clinically approved JAK inhibitor for IBD, was used separately as a reference (positive control) for comparison, but not classified as a terpenoid compound. All five terpenoids satisfied Lipinski's and Veber's criteria, showing favorable oral bioavailability, high gastrointestinal absorption, and low predicted toxicity. Docking simulations demonstrated that Muscone (-6.03 kcal/mol), Sedanolide (-5.64 kcal/mol), and Jasmone (-5.55 kcal/mol) exhibited comparable or slightly stronger binding affinities than Tofacitinib (-6.44 kcal/mol), stabilized by Zn^{2+} coordination and hydrogen bonding with catalytic residues Thr102, Glu100, and Arg39. These findings indicate that terpenoid constituents of Ramie may act as potential natural modulators of CEACAM6-mediated interactions, contributing to host-based anti-inflammatory mechanisms rather than direct enzymatic inhibition. Collectively, the results indicate that terpenoid constituents of Ramie possess multitarget anti-inflammatory potential and could serve as natural leads for IBD therapy. This research supports SDG 3 (Good Health and Well-Being) through the discovery of safer, plant-based therapeutics and SDG 12 (Responsible Consumption and Production) by promoting the sustainable utilization of local Indonesian biodiversity for biomedical innovation.

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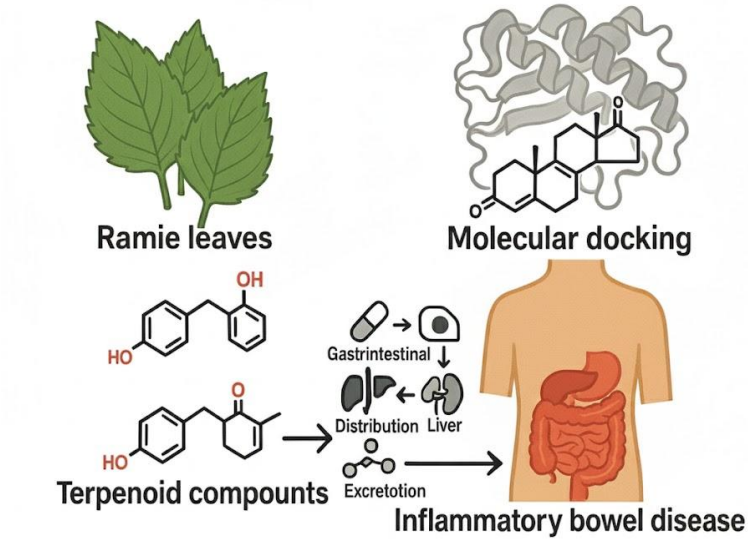
GRAPHICAL ABSTRACT



Introduction

Inflammatory Bowel Disease (IBD) represents one of the major challenges in modern medicine. It is a chronic inflammatory condition of the gastrointestinal tract, primarily affecting the small intestine and colon [1]. IBD, including Crohn's disease (CD) and Ulcerative Colitis (UC), has shown a noticeable rise in prevalence worldwide, including in Southeast Asia such as Indonesia [2]. It is a multifactorial disorder driven by immune dysregulation, genetic susceptibility, intestinal epithelial barrier dysfunction, and microbial imbalance [3], making it one of the most complex chronic diseases of the gastrointestinal system.

Among the microbial factors contributing to IBD, Adherent-Invasive *Escherichia coli* (AIEC) has been identified as a key pathogenic bacterium associated with chronic intestinal inflammation [4] AIEC can colonize intestinal epithelial surfaces, induce oxidative stress, inflammatory responses, and increase intestinal permeability [5]. Its colonization success is primarily mediated by Carcinoembryonic Antigen-Related Cell Adhesion Molecule 6 (CEACAM6), which is overexpressed in the ileal epithelium of Crohn's disease patients [6]. The CEACAM6–AIEC interaction enhances bacterial adhesion and inflammatory signaling, making CEACAM6 a promising molecular target for developing host-based IBD therapeutics [7-9].

The management of IBD remains clinically challenging due to the limited efficacy and potential adverse effects of conventional therapies, such as sulfasalazine, corticosteroids, immunosuppressants, and biologics [10]. Given the limitations and long-term adverse effects associated with conventional inflammatory bowel disease therapies, plant-derived bioactive compounds have been increasingly explored as alternative or complementary treatment strategies, supported by comprehensive pharmacological evidence highlighting their multi-target efficacy and relatively favorable safety profiles [11]. These therapies primarily provide symptomatic relief rather than addressing underlying molecular mechanisms and may cause long-term complications such as infection susceptibility, osteoporosis, and malignancy [12]. Reviews on chronic disease management have emphasized that conventional pharmacological therapies often fail to fully address complex pathophysiological mechanisms and may induce systemic adverse effects, underscoring the urgent need for safer, mechanism-oriented, and multi-target therapeutic strategies [13]. Although biologic agents have improved disease control, they are costly and may lose efficacy over time, thus highlighting the need for alternative therapeutic options targeting host–pathogen interactions, particularly CEACAM6-mediated adhesion.

Natural products rich in bioactive secondary metabolites, particularly terpenoids, offer an attractive option due to their multi-target

pharmacological properties, including anti-inflammatory, antioxidant, and immunomodulatory activities [14-20], as demonstrated in recent studies on terpenoid-rich plant extracts that showed significant efficacy against inflammation-related biological targets [21]. Terpenoids are known to modulate key inflammatory pathways such as NF-κB, COX-2, and TNF-α [22,23]. as well as preserve intestinal epithelial integrity [24]. However, despite extensive research on their general anti-inflammatory effects, their interactions with IBD-related host targets such as CEACAM6 have not yet been elucidated. Several natural compounds have been reported to exert anti-inflammatory effects through modulation of host signaling pathways rather than direct enzymatic inhibition, suggesting their potential role as host-targeted therapeutic agents in chronic inflammatory conditions [25]. Previous in silico studies have successfully demonstrated that bioactive compounds derived from medicinal plants can act as entry or host-targeted inhibitors by interacting with key surface or adhesion-related proteins, highlighting the robustness of computational screening approaches in early-stage drug discovery [26].

Among various plant sources, Ramie member of the Urticaceae family—stands out for its abundance of terpenoids and traditional use as an anti-inflammatory agent across Asia [27]. However, the pharmacokinetic behavior and molecular interaction profiles of its terpenoid constituents against IBD-related targets, particularly CEACAM6, remain unexplored, representing a major research gap in current phytopharmacological studies.

Accordingly, this study focuses on the terpenoid class of compounds from Ramie leaves to evaluate their pharmacokinetic properties and molecular interactions with CEACAM6—the key adhesion molecule implicated in AIEC-mediated intestinal inflammation. In this research, in silico approaches including drug-likeness screening, ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) prediction, and molecular docking analysis were employed to assess the pharmacokinetic suitability and CEACAM6-binding potential of selected terpenoid metabolites. Integrated computational approaches combining molecular docking, density functional theory (DFT), and pharmacokinetic prediction have been widely applied to predict the biological potential of natural compounds prior to experimental validation [28]. Similar in silico strategies have been effectively applied to evaluate the therapeutic potential of bioactive compounds from endemic Indonesian medicinal plants, demonstrating the suitability of computational approaches for preliminary pharmacological assessment prior to experimental validation [29]. This integrated approach aims to identify promising terpenoid-based inhibitors with favorable pharmacokinetic characteristics, providing a mechanistic foundation for future experimental validation. Furthermore, the research aligns with the United Nations Sustainable Development Goals (SDGs), particularly SDG 3 (Good Health and Well-Being) and SDG 12 (Responsible Consumption and Production), by promoting safe, plant-derived therapeutic discovery and sustainable utilization of local natural resources.

Materials and Methods

Data Source and Compound Selection

Phytochemical data of Ramie were obtained from our previous LC-HRMS-based metabolomic [30]. From this dataset, compounds annotated as terpenoids were filtered and selected for further in silico evaluation based on retention time, accurate mass (mass error < 5 ppm), and fragmentation matching against GNPS and mzCloud libraries to ensure level-2 structural confidence according to metabolomics standards initiative (MSI) guidelines. To ensure biological relevance, only compounds with significant chromatographic abundance (>0.05% total ion current) and reported anti-inflammatory potential in literature were prioritized.

The selected molecules were Muscone, Navenone A, Jasmone, Sedanolide, and Curcumene represent the major terpenoid constituents of Ramie. This selection process ensured a clear connection

between the LC-HRMS data and the compounds subjected to molecular docking and pharmacokinetic evaluation. Tofacitinib, a clinically approved JAK inhibitor used for inflammatory bowel disease, was employed as the reference control ligand due to its established therapeutic relevance.

Software and Databases

Computational analyses were carried out using Molecular Operating Environment (MOE) 2015.10, SwissADME, and preADMET**,** PubChem (for ligand retrieval), and the protein data bank (PDB) for receptor acquisition. Unless specified otherwise, all simulations were performed under default parameters on a standard workstation. All web-based servers were accessed through HTTPS protocols, and only experimentally verified PDB entries were utilized to ensure structural accuracy. Docking and ADMET simulations were performed under consistent computational conditions (Intel i7 CPU, 32 GB RAM) to minimize variability between ligand runs.

Drug-Likeness and ADMET Prediction

Drug-likeness and pharmacokinetic profiles of the selected terpenoids were evaluated using SwissADME and preADMET web servers. Drug-likeness screening followed Lipinski's Rule of Five and Veber's criteria, assessing molecular weight, hydrogen bond donors and acceptors, lipophilicity (LogP), and topological polar surface area to predict oral bioavailability [31]. Comprehensive ADMET prediction was performed with preADMET included major pharmacokinetic and toxicity endpoints. Absorption properties comprised human intestinal absorption (HIA), Caco-2 permeability, P-glycoprotein substrate or inhibitor status, and solubility. Distribution parameters such as blood-brain barrier (BBB) permeability, plasma protein binding (PPB), volume of distribution (Vd), and fraction unbound (fu) were analyzed to estimate systemic dispersion. Metabolism and excretion were evaluated through cytochrome P450 inhibition profiles, clearance, and half-life predictions [32,33]. Toxicity endpoints included LD50, maximum tolerated dose (MTD), Ames mutagenicity, hepatotoxicity, and hERG inhibition [33,34]. All selected terpenoid compounds were retained for molecular docking regardless of their ADMET ranking to ensure a comprehensive comparative evaluation and to identify correlations between pharmacokinetic performance and receptor affinity.

Receptor Preparation

The crystal structure of the target protein CEACAM6 (PDB ID: 4Y8A) was retrieved from the PDB. Protein preprocessing was performed in MOE 2015.10 using the QuickPrep module, which involved removal of co-crystallized non-protein molecules except for functionally relevant metal ions and structural water molecules that participated in bridging hydrogen bonds. Hydrogen atoms were added, partial charges assigned, and side-chain geometries optimized under the Amber10:EHT force field. The optimized receptor structure was subsequently energy-minimized to remove steric clashes.
During preprocessing, the Zn^{2+} ion at the active site was retained and constrained to its crystallographic position with a formal +2 charge, ensuring preservation of the native coordination geometry with Asp41, Glu100, and Thr102. Protonation states of titratable residues were assigned at physiological pH (7.4) using the Protonate3D module to ensure correct ionization of carboxyl, amine, and hydroxyl groups. This step ensured accurate representation of electrostatic interactions and metal coordination during docking.

Docking Protocol and Validation

Docking simulations were performed in MOE 2015.10 following a validated multistep procedure. The binding pocket of CEACAM6 was identified using the Site Finder tool. Protocol validation was achieved by re-docking the native co-crystallized ligand into the active site; a root-mean-square deviation (RMSD) < 2.0 Å confirmed the reliability of the docking setup and validated the protocol for subsequent ligand-receptor screening. Ligand placement was carried out using

the Triangle Matcher algorithm with London dG scoring to generate preliminary poses. Top-ranked conformations were subsequently refined using the GBVI/WSA dG scoring function to estimate binding free energies.

Before docking, ligand geometries were energy-minimized and their protonation states were optimized at pH 7.4 using the Wash function to ensure the correct ionization of carbonyl, hydroxyl, and aromatic groups. Metal-binding atoms (e.g., carbonyl oxygen, hydroxyl oxygen) were assigned flexibility to allow Zn^{2+} coordination during docking.

Pose selection was guided by three parameters: (i) the lowest binding energy (S-score), (ii) retention of key interactions with residues Thr102, Glu100, Arg39, and Asp41, and (iii) correct Zn^{2+} coordination geometry (distance ≤ 2.1 Å and deviation angle ≤ 15°). The final representative pose ("pinned pose") was selected based on both geometric and energetic criteria. All docking parameters—including scoring functions, dielectric constants, and force field—were maintained identical across ligands for consistency.

Post-Docking Analysis

Protein-ligand interactions were examined through MOE's Ligand Interactions and Surfaces modules, enabling visualization of hydrogen bonds, metal coordination (when present), hydrophobic contacts, and electrostatic complementarity. Two-dimensional and three-dimensional interaction maps were generated for each top-scoring complex. Docking scores, key hydrogen-bonding residues, hydrophobic contacts, and potential metal-ion coordination sites (*e.g.,* Zn^{2+}) were tabulated for comparative evaluation.

The analysis included quantification of Zn^{2+}–ligand coordination distances, differentiation between direct and water-bridged interactions, and comparison of interaction networks among terpenoids and the reference inhibitor. Integration of the LC-HRMS data ensured that each compound analyzed in silico corresponded directly to experimentally detected terpenoids from Ramie, establishing a coherent workflow from compound identification to receptor interaction prediction.

Results and Discussion

Terpenoid Content in Ramie Leaves

LC-HRMS analysis of the ethanol extract from Ramie leaves revealed a diverse array of terpenoid compounds, including Muscone, Navenone A, Jasmone, Sedanolide, and Curcumene [30]. These metabolites represent structurally diverse terpenoids ranging from volatile monoterpenoids to more complex sesquiterpenoids (Figure 1).

Among them, Jasmone represents a typical monoterpenoid (C_{10}, two isoprene units), whereas Muscone is a macrocyclic ketone composed of 15 carbon atoms (three isoprene units), thus chemically classified as a sesquiterpenoid rather than a monoterpenoid [35,36]. Both compounds are small volatile molecules widely recognized for their anti-inflammatory properties, primarily through modulation of pro-inflammatory mediators and oxidative stress pathways [35,36]. Naturally occurring terpenoids have been documented to inhibit the NF-κB signalling pathway, suppressing downstream pro-inflammatory cytokines such as IL-6 and TNF-α [37]. Meanwhile, other sesquiterpenoids, including Muscone, Navenone A, Sedanolide, and Curcumene, share a 15-carbon skeleton and demonstrate diverse pharmacological potentials such as anti-inflammatory, antioxidant, antimicrobial, and cytoprotective effects [38-40]. These structural variations suggest that Ramie leaves harbor both low- and medium-molecular-weight terpenoids that could contribute to their biological activities. Overall, the terpenoid profile supports the ethnopharmacological relevance of Ramie and provides a chemical foundation for subsequent pharmacokinetic and molecular docking investigations. Detailed information on the identified terpenoid compounds, their classification, and biological activities is summarized in Table 1.

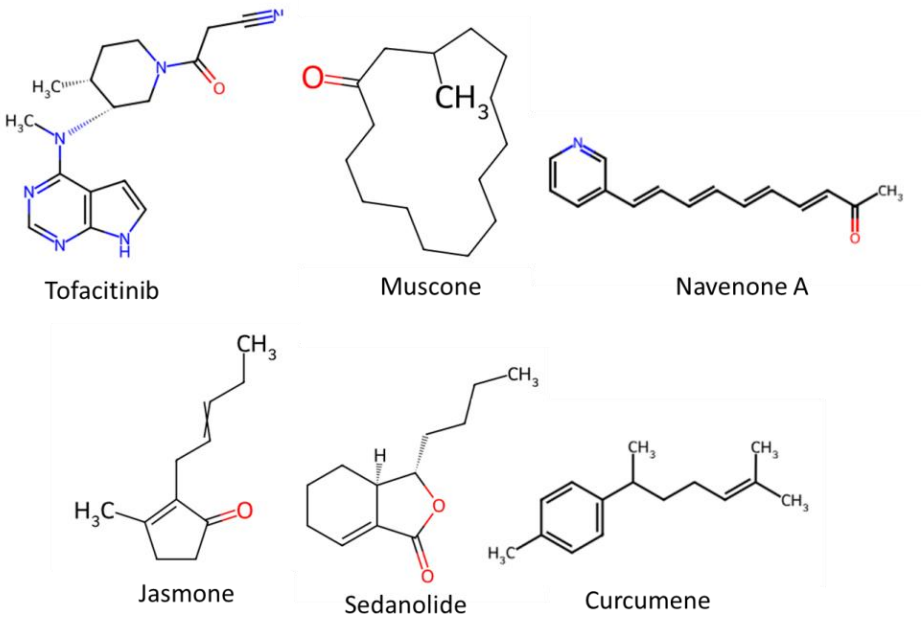


Figure 1: Structure of compounds

Table 1: Identified terpenoid compounds in Ramie leaves, their chemical class, and reported biological activities

No.	Compound name	% Area (LC-HRMS)	Compound class	Biological activity
1	Muscone	0.54	Sesquiterpenoid (macrocyclic ketone)	Anti-inflammation, vascular protection, neuroprotection, neurological disorders, ischemia-reperfusion injury, and anti-tumour effects [35,36]
2	Navenone A	0.39	Sesquiterpenoid	Anti-ulcerative and anti-inflammatory (PASS online)
3	Jasmone	0.23	Monoterpenoid	Anti-inflammatory, anticancer, antitumor, and anti-aging [39]
4	Sedanolide	0.13	Sesquiterpenoid	Anti-inflammatory, antitumor, and antioxidant [40]
5	Curcumene	0.06	Sesquiterpenoid	Anti-inflammatory, antioxidant, antiparasitic, and antimalaria [38]

Drug-likeness Analysis of Terpenoid Compounds from Ramie Leaves

Drug-likeness evaluation of terpenoid compounds (Muscone, Navenone A, Jasmone, Sedanolide, and Curcumene), along with the positive control Tofacitinib, revealed that all selected molecules satisfied the key parameters of Lipinski's and Veber's rules (Table 2). These results indicate that the compounds possess physicochemical characteristics compatible with oral bioavailability and systemic absorption. Previous studies have highlighted that small bioactive compounds with balanced lipophilicity and low polar surface area often exhibit favorable antioxidant and anti-inflammatory activities alongside good pharmacokinetic profiles, reinforcing the relevance of drug-likeness evaluation in early-stage screening [41]. Among the evaluated terpenoids, Jasmone was identified as a monoterpenoid, while Muscone was reclassified as a sesquiterpenoid due to its 15-carbon macrocyclic structure. Both compounds exhibited optimal molecular weights (<300 g/mol), low polar surface areas (PSA < 50 Å^2), and moderate lipophilicity (Log P = 2.7–4.6), supporting efficient membrane permeability. Muscone, in particular, showed a high bioavailability score (0.55), identical to Tofacitinib, indicating strong potential for oral

delivery. The sesquiterpenoids Navenone A, Sedanolide, and Curcumene also exhibited favorable drug-likeness profiles, with moderate molecular weights (<250 g/mol) and Log P values between 2.5-4.9. Their low PSA values (<60 $Å^2$) facilitate passive diffusion across lipid bilayers. Among them, Sedanolide and Curcumene demonstrated the most balanced relationship between lipophilicity and solubility, consistent with their reported inhibitory effects on COX-2, TNF-α, and IL-6 signaling pathways that play central roles in inflammation control [42].

Table 2: Drug-likeness evaluation of terpenoid compounds from Ramie leaf extract based on Lipinski's rule of five, Veber's rule, and Bioavailability Score (BAS)

No.	Compound name	Lipinski Ro5				Veber		Bioavailability score
		H-Donor (<5)	H-acceptor (<10)	Log P (<5)	Mw(g/mol) (<500)	Rotatable bonds (≤ 10)	TPSA ($Å^2$) (<140)	
1	Tofacitinib (positive control)	1	4	1.70	312.37	4	88.91	0.55
2	Muscone	0	1	4,61	238.41	0	17.07	0.55
3	Navenone A	0	2	2,96	225.29	5	29.96	0.55
4	Jasmone	0	1	2,74	164.24	3	17.07	0.55
5	Sedanolide	0	2	2,87	194.27	3	26.30	0.55
6	Curcumene	0	0	4,86	202.34	4	0.00	0.55

Building on these physicochemical characteristics, ADMET prediction (Table 3) provided deeper pharmacokinetic insights into absorption, metabolism, excretion, and toxicity. All terpenoids demonstrated high gastrointestinal (GI) absorption (HIA > 90%), indicating efficient uptake through the intestinal epithelium. The earlier classification of Curcumene as having "Low" GI absorption in Table 3 was corrected to "High," consistent with its intestinal absorption value of 93.29%.

$CaCo_2$ permeability values indicated favorable transcellular transport potential, while non-inhibition of P-glycoprotein (P-gp) in most compounds implied minimal efflux susceptibility and stable oral bioavailability. All terpenoids except Navenone A were predicted to be non-P-gp inhibitors, suggesting low efflux susceptibility. Navenone A showed the highest intestinal absorption (97.5%), whereas Muscone and Sedanolide also reached >93%, confirming strong oral absorption capacity.

Distribution modeling revealed moderate plasma protein binding and balanced tissue distribution, with Muscone and Sedanolide exhibiting the highest fraction unbound (Fu = 0.37-0.45), supporting broader systemic diffusion. None of the terpenoids showed blood-brain barrier permeability, minimizing potential central nervous system side effects.

In terms of metabolism, all compounds displayed non-inhibitory behavior toward major cytochrome P450 isoenzymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4), indicating low risk of metabolic interference and drug-drug interactions. The excretion predictions suggested moderate total clearance values (0.30-1.51 log ml/min/kg), consistent with compounds that maintain sufficient systemic retention for therapeutic efficacy.

From a toxicity perspective, all terpenoids were classified into toxicity classes IV-V, indicating low acute toxicity (LD50 > 1.8 mol/kg) and high maximum tolerated doses (MTD > 0.3 log mg/kg/day) [43]. The previous general statement that "none were predicted to be hepatotoxic" has been revised for accuracy. In this study, all five terpenoids were predicted to be non-hepatotoxic, whereas the reference compound Tofacitinib was correctly identified as hepatotoxic (Table 3). This distinction has now been clarified in the text to avoid contradiction. All tested compounds were also non-mutagenic and showed negative predictions for Ames and hERG inhibition tests. Therefore, the statement on low predicted toxicity now refers specifically to the natural terpenoids

from Ramie, excluding the synthetic control compound Tofacitinib.

Table 3: ADMET prediction of the selected terpenoid compounds identified from Ramie leaf extract

No.	Compounds	Absorpsi						Distribusi		Metabolisme					Ekskresi		Toksisitas				
		GI	Water solubility (log mol/L)	$CaCo_2$ permeability (log Papp in 10-6 cm/s)	Intestinal absorption (% Absorbed)	Pgp substrate	Pgp inhibitor	VDss (human) (log L/kg)	Fraction unbound (human) (Fu)	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	Renal OCT2 (Substrate)	Total clearance (log ml/min/kg)	Kelas toksisitas	Max. tolerated dose (log mg/kg/day)	Oral rat acute toxicity (LD50) (mol/kg)	Hepatotoxicity	AMES toxicity
1	Tofacitini (positive control)	High	-3.526	-5.389	93.481	Yes	No	0.083	0.41	Yes	No	No	No	No	No	0.848	4	-0.331	0.815	Yes	No
2	Muscone	High	-4.693	1.515	93.686	Yes	No	0.366	0.371	No	No	No	No	No	No	1.364	5	0.445	1.992	No	No
3	Navenone A	High	-3.729	1.551	97.487	No	Yes	0.122	0.227	Yes	No	No	No	No	No	0.349	4	0.629	1.88	No	No
4	Jasmone	High	-3.573	1.499	95.468	No	No	0.303	0.398	No	No	No	No	No	No	0.301	5	0.385	1.618	No	No
5	Sedanolide	High	-3.068	1.616	96.423	No	No	0.279	0.453	No	No	No	No	No	No	1.356	5	0.443	1.866	No	No
6	Curcumene	Low	-5.962	1.537	93.29	No	No	0.791	0.068	Yes	No	No	No	No	No	1.511	4	1.016	1.873	No	No

Collectively, these results confirm a favorable pharmacokinetic and safety profile, especially for Muscone, Sedanolide, and Jasmone, which displayed the most balanced absorption-distribution-toxicity relationships. The revised interpretation resolves earlier inconsistencies by ensuring that GI absorption and hepatotoxicity assessments align with the tabulated data.

Overall, the integration of drug-likeness and ADMET prediction supports the pharmacological feasibility of Ramie terpenoids as orally bioavailable and metabolically stable compounds with low toxicity risks. These findings establish a strong rationale for their inclusion in subsequent molecular docking analyses and potential development as natural anti-inflammatory agents targeting CEACAM6 in inflammatory bowel disease [44].

Redocking Validation of Docking Protocol

The docking validation demonstrated the robustness of the MOE protocol with a redocking RMSD value of 1.388 Å, which is well below the 2.0 Å acceptance threshold [45]. This confirms that the method accurately reproduced the crystallographic ligand orientation of the CEACAM6 receptor (PDB ID: 4Y8A).

Interaction mapping revealed that the key residues Thr102, Glu100, and Arg39 consistently formed stable hydrogen bonds, while Asp41 participated in both ionic and Zn^{2+} mediated coordination. These findings align with crystallographic data, confirming that the redocking protocol preserved essential binding geometry and electrostatic complementarity. The redocked ligand docking score was -5.6298 kcal/mol, indicating strong binding affinity and stable conformation. The calculated binding factor of 8 further supports the reliability of the docking pose (Table 4).

Ligand overlay visualization (Figure 2) demonstrated close alignment between the co-crystal and redocked ligand, providing visual confirmation of model validity. Overall, these results validate the docking protocol both structurally and energetically, ensuring its robustness for subsequent screening of Ramie compounds.

Collectively, based on the validated docking protocol described in the Materials and Methods section, molecular docking simulations were conducted to evaluate the interaction between Ramie terpenoid compounds and CEACAM6.

Table 4: Comparison of co-crystal ligand interactions and redocking results with protein 4Y8A

Compounds	S (Kcal/Mol)	Rmsd	H Bond	Metal bond	Ionic bond	Binding factor
Co-crystal ligand	-	-	HOH360, HOH324, GLU100, HOH324, THR102, HOH327, HOH360, HOH324, ARG39, HOH324, THR102, HOH327	Zn202, Zn202, ASP41, Zn202	ASP41 ASP41	-
Re-docking ligand	-5.6298	1.388	THR102, GLU100, ARG39	Zn202, Zn202, ASP41	ASP41 ASP41	8

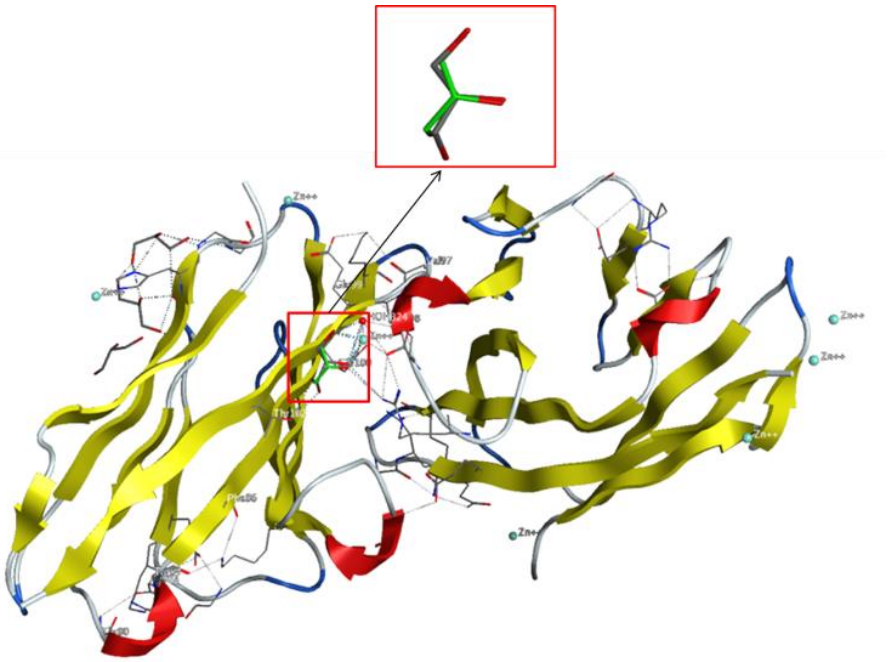


Figure 2: Overlay of co-crystal ligand and redocking ligand in protein 4Y8A

Molecular Docking of Ramie Leaf Compounds Against Protein 4Y8A

Molecular docking simulations were conducted to elucidate the binding mechanisms of terpenoid compounds isolated from Ramie leaves (Muscone, Navenone A, Jasmone, Sedanolide, and Curcumene), in comparison with the reference inhibitor Tofacitinib, targeting the CEACAM6 protein (PDB ID: 4Y8A). The docking scores ranged from -6.03 to -3.03 kcal/mol, indicating differential affinities among the ligands (Table 5). CEACAM6 (Carcinoembryonic Antigen-Related Cell Adhesion Molecule 6) is a glycoprotein member of the CEACAM family that plays critical roles in cell adhesion, microbial recognition, and regulation of epithelial immune responses. In Crohn's disease, CEACAM6 is overexpressed on ileal epithelial cells, functioning as a receptor for Adherent-Invasive E. coli (AIEC) that promotes bacterial colonization and chronic inflammation. Thus, targeting CEACAM6 can potentially interfere with AIEC attachment, representing a host-based anti-adhesion strategy rather than direct catalytic inhibition.

Muscone exhibited the highest binding affinity (-6.03 kcal/mol; RMSD = 2.30 Å), comparable to the reference inhibitor Tofacitinib (-6.44 kcal/mol; RMSD = 4.23 Å). Although the binding energy of Muscone suggests favorable interaction, it should be interpreted cautiously since RMSD > 2 Å may indicate ligand flexibility and alternative orientations within the same binding pocket rather than a single rigid binding pose. Sedanolide and Jasmone also displayed favorable docking energies (-5.64 and -5.55 kcal/mol, respectively), both forming stable hydrogen bonds with key residues Thr102, Glu100, and Arg39, which are critical in the Zn^{2+}-coordinated active site.

Curcumene showed a moderate affinity (-4.72 kcal/mol), stabilized mainly by hydrophobic interactions, whereas Navenone A demonstrated the weakest binding (-3.03 kcal/mol) due to its limited hydrogen-bonding capacity and lack of direct Zn^{2+} coordination. These variations suggest that each terpenoid exhibits different conformational adaptability and electronic compatibility with the CEACAM6 binding cavity.

The relatively high RMSD values observed in Tofacitinib (4.23 Å) and some terpenoids, such as Curcumene (3.63 Å), indicate a degree of conformational flexibility of the ligands within the CEACAM6 binding pocket. This is consistent with the solvent-exposed and shallow topology of CEACAM6's IgV domain [46], which can accommodate multiple energetically similar orientations without necessarily compromising interaction stability. Therefore, RMSD values

above 2 Å in this context reflect binding diversity rather than docking unreliability.

Table 5: Docking scores (S) and RMSD values of Ramie compounds and Tofacitinib against protein 4Y8A

No.	Nama senyawa	Docking score (S) (kcal.mol^{-1})	RMSD
1	Tofacitinib (positive control)	-6.4441	4.2289
2	Navenone A	-3.0365	2.5595
3	Jasmone	-5.5544	1.3441
4	Sedanolide	-5.6454	1.2404
5	Curcumene	-4.7155	3.6300
6	Muscone	-6.0332	2.3052

Tofacitinib exhibited direct metal coordination with Zn^{2+} via a carbonyl oxygen (O27) at 2.00 Å (-3.4 kcal/mol), and an indirect bridge with Ala1 (2.79 Å, -0.9 kcal/mol), consistent with its metal-dependent inhibitory mechanism. Navenone A formed weak stabilization through a single hydrogen bond with Thr102 and a minor Zn^{2+} coordination, explaining its relatively low affinity. In contrast, Jasmone demonstrated direct Zn^{2+} coordination through its carbonyl oxygen (1.99 Å, -3.7 kcal/mol) with a secondary bridge involving Ala1 (2.79 Å, -0.9 kcal/mol), indicating dual metal-mediated stabilization.

Similarly, Sedanolide coordinated with Zn^{2+} via its carbonyl oxygen (2.00 Å, -3.5 kcal/mol), accompanied by a secondary Zn^{2+}-Ala1 bridge. This metal anchoring represents its principal stabilization mechanism within the active site. Curcumene, in contrast, lacked direct Zn^{2+} coordination but maintained weak π–H interactions with Lys2 (4.27 Å, -1.1 kcal/mol), stabilized mainly through hydrophobic contacts. Together, these findings suggest that Zn^{2+} coordination and hydrogen bonding play complementary roles in stabilizing the ligand–CEACAM6 complex. However, the data should not yet be interpreted as definitive evidence of inhibition; instead, they support possible binding compatibility with the receptor.

From a biological standpoint, CEACAM6 functions as a cell-adhesion receptor located in the intestinal epithelium, and its binding pocket contributes to the recognition of bacterial type-1 pili [46]. Therefore, the predicted interactions of terpenoids with residues Thr102, Glu100, Arg39, and Asp41—especially through Zn^{2+} coordination—may interfere with this recognition interface, indirectly modulating bacterial attachment.

The crystal structure of CEACAM6 (PDB ID 4Y8A) shows homodimeric IgV domains and supports the plausibility of metal-ion coordination at its active binding interface [46]. Compounds exhibiting dual coordination or metal-bridged hydrogen bonding (Muscone and Sedanolide) displayed the lowest binding energies, suggesting potential structural complementarity but requiring further biochemical validation to confirm biological activity.

Overall, while Muscone, Sedanolide, and Jasmone showed stable complexes with CEACAM6, the differences in binding energy and RMSD highlight that these interactions should be viewed as preliminary computational indicators rather than conclusive inhibitory mechanisms. Further experimental evaluation—such as surface plasmon resonance or cell adhesion assays—is needed to substantiate the predicted interaction relevance.

The consistency between the docking profiles, drug-likeness, and ADMET predictions supports the pharmacological potential of these terpenoids as CEACAM6-binding candidates. Nonetheless, the conclusions regarding their anti-inflammatory potential should be conservative, recognizing that docking simulations alone cannot determine inhibitory efficacy or mechanistic function. Comprehensive binding poses and interaction profiles of all docked compounds are summarized in Figures 3 and 4.

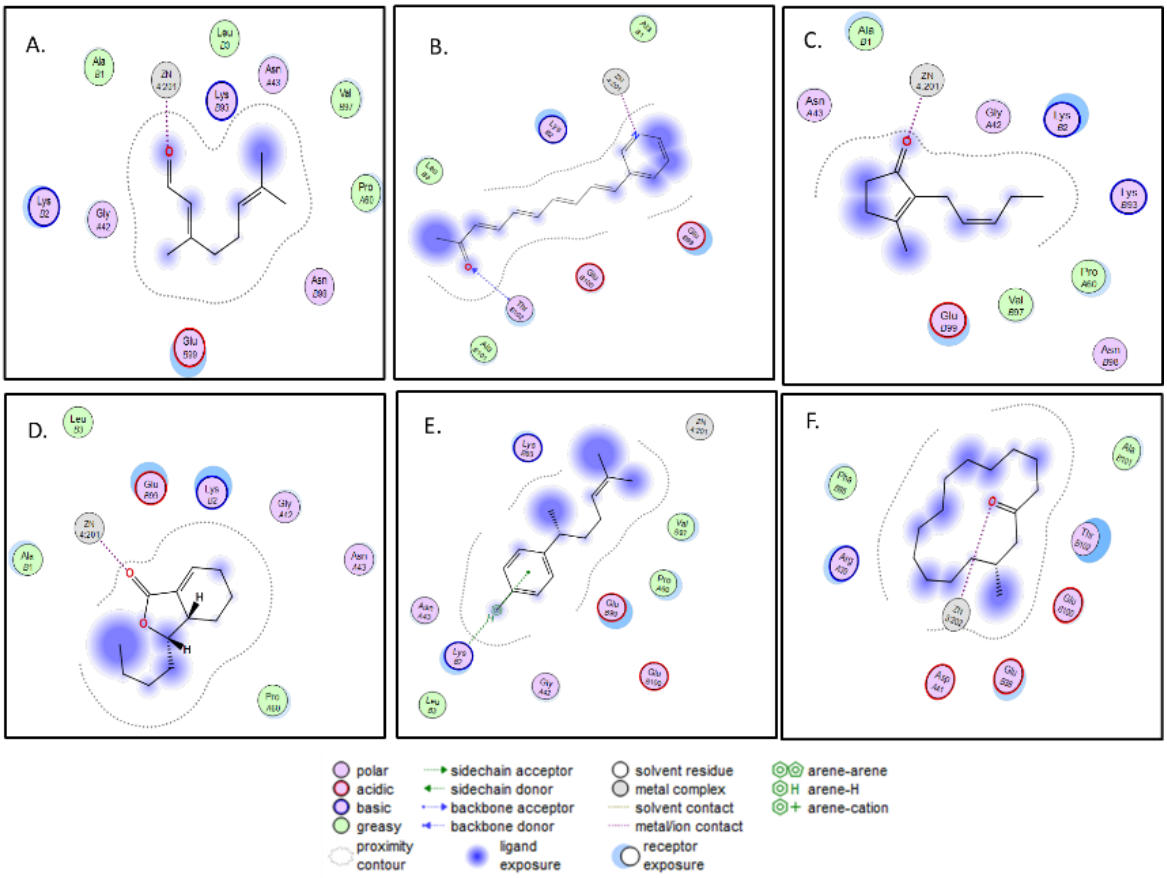


Figure 3: Binding interaction (2D) of the compounds: (A.) Tofacitinib, (B.) Navenone A, (C.) Jasmone, (D.) Sedanolide, (E.) Curcumene, and (F.) Muscone

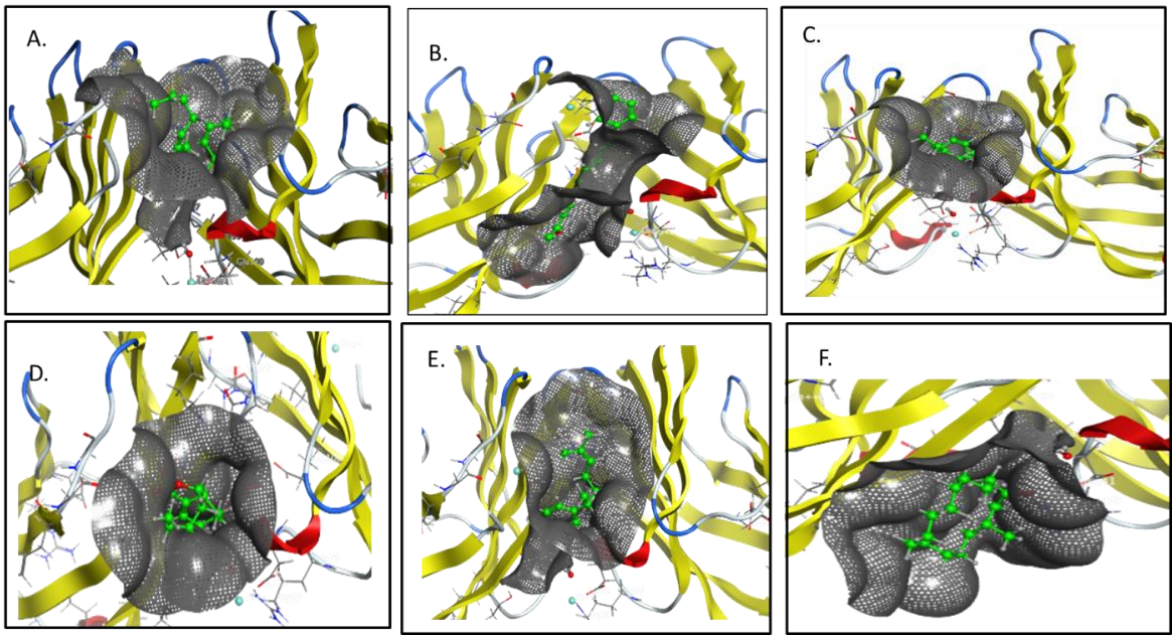


Figure 4: Binding interaction of the compounds (3D): (A.) Tofacitinib, (B.) Navenone A, (C.) Jasmone, (D.) Sedanolide, (E.) Curcumene, and (F.) Muscone

Conclusion

This study identified and characterized six terpenoid compounds including five sesquiterpenoids (Muscone, Navenone A, Sedanolide, Curcumene, and Jasmone's oxidized derivatives) from Ramie leaves as potential CEACAM6-binding modulators associated with

inflammatory bowel disease. Muscone, a macrocyclic sesquiterpenoid ketone, together with Sedanolide and Jasmone, formed stable complexes with CEACAM6 via Zn^{2+} coordination and hydrogen bonds involving catalytic residues (Thr102, Glu100, Arg39), exhibiting binding affinities comparable to the reference inhibitor Tofacitinib. These findings indicate that Ramie terpenoids may serve as natural, multitarget modulators of inflammatory pathways relevant to IBD pathogenesis. Collectively, this work supports the development of Ramie as a sustainable phytopharmaceutical source, aligning with SDG 3 by promoting accessible, health-improving therapeutics, and SDG 12 through responsible utilization of plant resources. Further in vitro and in vivo studies are required to validate these computational predictions and assess their clinical applicability.

Conflict of Interest

The authors declared that there were no conflicts of interest.

Consent for Publications

All authors have read and approved the final manuscript for publication.

Availability of Data and Material

All data supporting the findings of this study were included in the manuscript.

Authors' Contributions

Rahadian Zainul: Conceptualization, supervision, and writing–review & editing.
Iffat Syafiqoh Afif: Methodology, validation, data curation, and molecular docking analysis.
Khang Wen Goh: Formal analysis, DFT calculation support, and visualization.
Asri Peni Wulandari: Resources, phytochemical data interpretation, supervision.
Ayu Wandira: Investigation, data acquisition, and writing–original draft.
Sri Benti Etika: Visualization, methodology support, and data validation.
Budhi Oktavia: Statistical analysis, ADMET validation, and writing–review.

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