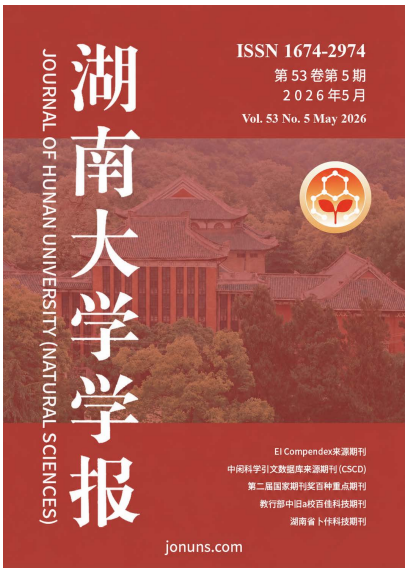

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GC-MS Analysis and Prediction of Anti-Inflammatory Effects of Lima Bean (*Phaseolus lunatus* L.) Chemical Constituents Using Computational Modeling

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Abstract: Malnutrition is associated with immune dysfunction and chronic inflammation, which may contribute to adverse health outcomes. This study aimed to explore bioactive compounds derived from lima beans (*Phaseolus lunatus* L.) with potential relevance to tumor necrosis factor-alpha (TNF-α)-mediated inflammation related to malnutrition using an integrated in silico approach. Bioactive compounds were identified by gas chromatography–mass spectrometry (GC–MS), followed by bioactivity prediction using PASS analysis. Selected compounds were further evaluated through molecular docking against TNF-α, along with in silico absorption, distribution, metabolism, excretion, and toxicity (ADME/toxicity) predictions. GC–MS analysis identified nineteen compounds in the lima bean extract. Based on PASS screening and docking analysis, five compounds were prioritized, including fatty acid ester derivatives and α-linolenic acid-related compounds. Among these, 9,12,15-octadecatrienoic acid, 2-phenyl-1,3-dioxan-5-yl ester exhibited the most favorable predicted binding profile toward TNF-α (ΔG = −6.8 kcal/mol), indicating a weak to moderate interaction typical of preliminary virtual screening. In silico ADME and toxicity predictions suggested generally favorable pharmacokinetic properties with low-to-moderate toxicity,

although these results remain predictive in nature. This study provides a hypothesis-generating computational framework linking lima bean-derived compounds to TNF-α-associated inflammatory pathways, supporting future experimental validation.

Keywords: Lima bean; Inflammation; Malnutrition; TNF-α; In silico analysis.

基于GC-MS分析和计算建模的利马豆（Phaseolus lunatus L.）化学成分抗炎作用预测

摘要：营养不良与免疫功能障碍和慢性炎症相关，这可能导致不良健康结局。本研究旨在采用综合性计算机模拟（in silico）方法，探讨利马豆（Phaseolus lunatus L.）来源的生物活性化合物及其与营养不良相关的肿瘤坏死因子-α（TNF-α）介导炎症的潜在关联。首先通过气相色谱-质谱联用技术（GC-MS）鉴定生物活性化合物，随后采用PASS分析进行生物活性预测。进一步对筛选出的化合物进行与TNF-α的分子对接分析，并开展计算机模拟的吸收、分布、代谢、排泄及毒性（ADME/毒性）预测。GC-MS分析在利马豆提取物中鉴定出19种化合物。基于PASS筛选和分子对接分析，优先筛选出5种化合物，包括脂肪酸酯衍生物和α-亚麻酸相关化合物。其中，9,12,15-十八碳三烯酸-2-苯基-1,3-二氧六环-5-基酯表现出对TNF-α最有利的预测结合特征（ΔG = -6.8 kcal/mol），提示其具有初步虚拟筛选中常见的弱至中等相互作用。计算机模拟的ADME和毒性预测表明，这些化合物总体上具有较为有利的药代动力学特征以及低至中等毒性，但这些结果仍属于预测性质。本研究建立了一个假设生成型计算框架，将利马豆来源化合物与TNF-α相关炎症通路联系起来，为后续实验验证提供支持。

关键词：利马豆；炎症；营养不良；TNF-α；计算机模拟分析。

1. Introduction

Malnutrition can begin during fetal development and extend throughout the first 1000 days of life. It remains a major public health challenge worldwide. Children under five who experience chronic malnutrition often exhibit impaired linear growth, resulting in stunting [1,2]. In Indonesia, stunting remains a critical nutritional problem, with a prevalence of 21.6% in 2022 and 21.5% in 2023. These values still exceed the World Health Organization threshold of 20% for a high public health concern [3–5]. Globally, malnutrition is estimated to contribute to approximately 45% of deaths among children under five, affecting more than 800 million undernourished individuals worldwide [6]. Beyond growth impairment, malnutrition is increasingly recognized as a condition closely associated with immune dysfunction and chronic inflammation.

Malnutrition induces profound alterations in immune regulation by suppressing immune cell activation and increasing susceptibility to infections. Deficiencies in both macronutrients and micronutrients impair immune responses, promote viral persistence, and facilitate inflammatory cell infiltration, thereby creating a pro-inflammatory milieu [7]. Acute and chronic malnutrition have been shown to disrupt intestinal barrier integrity, particularly in the colon, leading to bacterial translocation and systemic exposure to lipopolysaccharides (LPS) [8]. These effects are closely linked to gut microbiota dysbiosis, characterized by the expansion of Gammaproteobacteria and reduction of Bacteroidetes, resulting in increased fecal LPS activity. In parallel, malnutrition activates systemic stress responses involving the sympathetic nervous system, immune system, and hypothalamic–pituitary–adrenal axis, which collectively trigger the release of pro-inflammatory cytokines such as interleukin-6 (IL-6), interleukin-1β (IL-1β), and tumor necrosis factor-alpha (TNF-α) [9–11].

Among these mediators, TNF-α plays a central role in the pathophysiology of malnutrition-associated inflammation. Elevated TNF-α levels impair intestinal barrier function, increase epithelial permeability, and

inhibit nutrient absorption, thereby exacerbating metabolic disturbances and malabsorption [12,13]. TNF-α also promotes a hypermetabolic state and oxidative stress, accelerating muscle protein breakdown and adipose tissue loss, which contributes to wasting and growth failure. Previous studies have demonstrated that interventions targeting TNF-α signaling can improve inflammatory status, enhance nutrient utilization, and partially restore gut microbiota balance, highlighting TNF-α as a biologically relevant target in malnutrition-related inflammatory processes. Although multiple inflammatory mediators, including interleukin-6 (IL-6), interleukin-1β (IL-1β), and nuclear factor-κB (NF-κB), are implicated in malnutrition-associated inflammation, TNF-α was prioritized as the molecular docking target in this study for several reasons. TNF-α acts as a central upstream regulator of the inflammatory cascade, driving the activation of both NF-κB signaling and downstream cytokine production, including IL-6 and IL-1β [14,15]. Its well-established pathophysiological role in intestinal barrier disruption, metabolic dysregulation, and impaired nutrient absorption makes it a biologically relevant target in the context of malnutrition [12,13].

High-quality dietary protein sources are essential in the nutritional management of malnutrition, as they provide amino acids and bioactive components necessary for tissue repair, immune modulation, and growth [16]. Lima beans (*Phaseolus lunatus* L.) are recognized as nutritionally valuable legumes, with protein contents ranging from 14.24% to 38.57% and a favorable essential amino acid profile [17–19]. In addition to their nutritional value, lima beans contain diverse bioactive compounds, including polyphenols, fatty acid derivatives, peptides, and functional metabolites, which may contribute to anti-inflammatory effects [9,16,20]. However, the molecular basis underlying the potential of these compounds, particularly in relation to TNF-α modulation, remains insufficiently characterized. Therefore, this study aims to systematically profile bioactive compounds present in lima beans cultivated in Indonesia using gas chromatography–mass spectrometry (GC-MS) and to evaluate their predicted anti-inflammatory potential through integrated in silico analyses, including PASS prediction, molecular docking against TNF-α, and ADME/toxicity profiling. This computational approach provides mechanistic hypotheses regarding the inflammation-modulating potential of lima bean constituents in the context of malnutrition-associated inflammation.

2. Methods and Materials

2.1. Plant Materials

Lima beans (*Phaseolus lunatus* L.) were collected in November 2022 from plantations managed by local farmers in Air Dingin, West Sumatra Province, Indonesia. The plant material was taxonomically identified at the Botanical Laboratory, Department of Biology, Andalas University, West Sumatra, Indonesia. The identified samples were used for further extraction and analysis.

2.2. Extraction of Lima Bean Flour

Lima bean seeds were processed into powder prior to extraction. The powdered sample was extracted by maceration using ethanol as the solvent at room temperature for five days. Five liters of ethanol were used for maceration extraction. The resulting extract was filtered and subsequently concentrated under reduced pressure using a rotary evaporator to obtain a semi-dried crude ethanol extract.

2.3. Gas Chromatography–Mass Spectrometry (GC–MS) Analysis

Sample preparation was performed by dissolving the crude ethanol extract in a suitable solvent to a final volume of 1 mL. The solution was vortexed until homogeneous and centrifuged at 9500 rpm for 3 minutes. The supernatant was transferred into a GC vial for analysis. GC–MS analysis was conducted using a Thermo Scientific Trace 1310 Gas Chromatograph coupled with a Thermo Scientific ISQ LT Single Quadrupole Mass Spectrometer. Compound separation was achieved using an HP-5MS UI capillary column (30 m × 0.25 mm internal diameter × 0.25 μm film thickness). The injector temperature was maintained at 230°C with a split ratio of 50:1 and a split flow rate of 50 mL/min. Helium (99.99% purity) was used as the carrier gas at a constant flow rate of 1.00 mL/min. The MS transfer line temperature was set at 250°C, and the ion source temperature was maintained at 200°C. Mass spectra were acquired in scan mode over a mass range of 40–500 m/z. Additional parameters included a purge flow of 3 mL/min, a gas saver flow of 5 mL/min, and a gas saver time of 5 minutes. Compounds were identified by comparing retention times and mass spectra with those available in the NIST 14 mass spectral library.

2.4. In Silico PASS Online Prediction Analysis

The predicted biological activities of compounds identified by GC–MS were evaluated using the Prediction of Activity Spectra for Substances (PASS) online platform (https://www.way2drug.com/passonline/) [21]. PASS predicts potential biological activities based on the chemical structure of compounds, expressed as probability of activity (Pa) and probability of inactivity (Pi), with values ranging from 0.000 to 1.000. Compounds were considered to exhibit potential anti-inflammatory activity when $Pa > Pi$ and $Pa \geq 0.700$. This threshold was applied in accordance with established screening criteria [22] and reflects a level at which

PASS considers the probability of a compound being active to be substantially higher than inactive. A Pa ≥ 0.700 threshold has been widely adopted in natural product screening studies to reduce false positives while maintaining meaningful sensitivity [cite additional reference if available.

2.5. Preparation of Protein and Ligand Structures

The crystal structure of tumor necrosis factor-alpha (TNF-α) (PDB ID: 2AZ5) along with its native ligand was retrieved from the Protein Data Bank (http://www.rcsb.org/pdb). Protein preparation involved the removal of water molecules and the addition of hydrogen atoms using Discovery Studio Visualizer. The structure was subsequently energy-minimized using Swiss-PDBViewer with the GROMOS96 force field and saved in PDB format.

Ligand structures corresponding to selected bioactive compounds were obtained from the ZINC database (https://zinc.docking.org) in SDF format and converted to PDBQT format using Open Babel software version 2.4.0.

2.6. Molecular Docking Analysis

Molecular docking was performed using AutoDock Vina version 1.1.2. A grid box of 20 Å × 20 Å × 20 Å was defined with center coordinates at x = −19.515, y = 74.840, and z = 33.894. The docking conformation with the lowest binding affinity was selected for further interaction analysis.

2.7. In Silico ADME Prediction

The absorption, distribution, metabolism, and excretion (ADME) properties of compounds predicted to exhibit anti-inflammatory activity were evaluated using the SwissADME online tool (http://www.swissadme.ch/) [23]. Predicted pharmacokinetic parameters were used to assess oral bioavailability and drug-likeness profiles for compound prioritization.

2.8. In Silico Toxicity Prediction

Toxicity prediction was performed using the ProTox 3.0 online platform (https://tox-new.charite.de/protox_II/, accessed January 25, 2025) [24]. Median lethal dose (LD_{50}) values were predicted and compounds were classified into six toxicity classes according to the Globally Harmonized System (GHS), ranging from Class I (extremely toxic) to Class VI (non-toxic).

3. Results

3.1. GC-MS Analysis of Lima Bean Extract

Gas chromatography–mass spectrometry (GC–MS) analysis of the lima bean flour extract led to the identification of 19 compounds with distinct molecular weights, retention times, and relative area percentages based on spectral matching with the National Institute of Standards and Technology (NIST) library (Table 1). The identified compounds represented a diverse chemical profile comprising fatty acids and their ester derivatives, sterols, alcohols and ether derivatives, aromatic compounds, as well as cholic and bile acid-related derivatives.

Sitosterol was the most abundant compound, accounting for 23.18% of the total relative area, followed by glycidyl palmitate (7.35%), 17-(1,5-dimethylhexyl)-derived compounds (5.50%), hexadecanoic acid ethyl ester (4.54%), and 9,12-octadecadienoic acid ethyl ester (3.10%). Several fatty acid esters, including methyl and ethyl esters of hexadecanoic and octadecanoic acids, were also detected. The complete list of identified compounds and their corresponding analytical parameters is presented in Table 1.

3.2. Prediction of Activity Spectra for Substances (PASS) Analysis

The Prediction of Activity Spectra for Substances (PASS) online platform was used to estimate the potential anti-inflammatory activity of compounds identified in the lima bean extract. A total of 19 compounds identified by GC–MS were subjected to PASS analysis. Anti-inflammatory potential was evaluated based on the criteria Pa > Pi and Pa ≥ 0.700. This threshold is consistent with commonly applied criteria in PASS-based studies to identify compounds with a relatively high probability of biological activity.

PASS prediction results indicated that several compounds met the predefined threshold for potential anti-inflammatory activity. These compounds included 10-octadecenoic acid, methyl ester (Pa = 0.882); 9,12,15-octadecatrienoic acid, 2-phenyl-1,3-dioxan-5-yl ester (Pa = 0.831); 9,12,15-octadecatrienoic acid, 2,3-dihydroxypropyl ester (Pa = 0.796); 9,12-octadecadienoic acid, ethyl ester (Pa = 0.764); and hexadecanoic acid, methyl ester (Pa = 0.758). All five compounds exceeded the Pa ≥ 0.700 threshold, with Pa values also exceeding their corresponding Pi values, confirming a higher probability of anti-inflammatory activity.

The distribution of Pa values for the analyzed compounds is presented in Figure 1. Based on the PASS screening results, compounds meeting the selection criteria were prioritized for subsequent molecular docking and in silico pharmacokinetic evaluation.

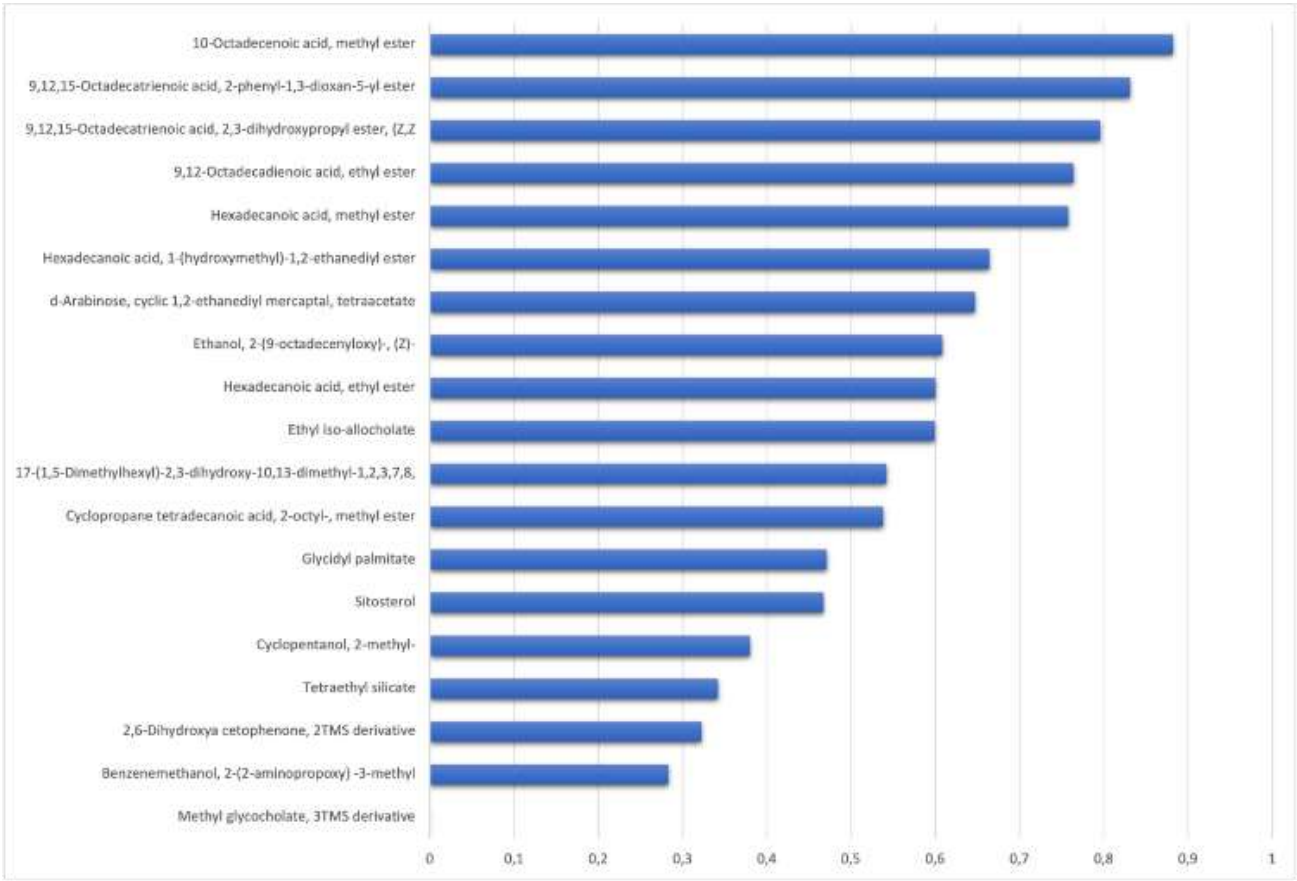


Figure 1. PASS Online Prediction of Anti-inflammatory Activity for Identified Lima Bean Compounds

3.3. Molecular Docking Analysis

Molecular docking analysis was conducted to evaluate the binding interactions between five selected bioactive compounds from lima bean extract and tumor necrosis factor-alpha (TNF-α). The docking results showed binding affinity values ranging from −5.0 to −6.8 kcal/mol, as summarized in Table 2. These values fall within the range typically observed in preliminary molecular docking studies.

The crystal structure of TNF-α complexed with the reference inhibitor SPD304 indicates that the binding site is located at the dimer interface and involves multiple contact residues, including Leu57, Tyr59, Ser60, Gln61, Tyr119, Leu120, Gly121, Gly122, and Tyr151 from chain A, as well as Leu57, Tyr59, Ser60, Tyr119, Leu120, Gly121, and Tyr151 from chain B [34]. Docking analysis demonstrated that the tested compounds interacted within this binding region.

Among the evaluated ligands, Compound B (9,12,15-octadecatrienoic acid, 2-phenyl-1,3-dioxan-5yl ester) exhibited the lowest predicted binding energy (−6.8 kcal/mol). Other compounds showed binding affinities between −5.0 and −5.8 kcal/mol. Hydrogen bond interactions with residues such as Tyr59 and Gly121 were observed for several ligands, while some compounds also displayed hydrophobic interactions within the TNF-α binding pocket. The predicted binding modes and interaction patterns of all tested compounds are illustrated in Figure 2.

Table 1. GC-MS Analysis Profile of Bioactive Compounds in Lima Bean Extract

Number compound	Pubchem ID	Name of the compound	Molecular Weight (g/mol)	Retention time (min)	Relative area (%)
1.	542489	d-Arabinose, cyclic 1,2-ethanediyl mercaptal, tetraacetate	394	4.16	0.24
2.	93285	Benzenemethanol, 2-(2-aminopropoxy)-3-methyl-	195	4.46	0.79
3.	32205	Cyclopentanol, 2-methyl-	100	7.08	1.26
4.	6517	Tetraethyl silicate	208	9.26	0.20
5.	91740707	2,6-Dihydroxyacetophenone, 2TMS derivative	296	9.43	0.20
6.	552099	Cyclopropanetetradecanoic acid, 2-octyl-, methyl ester	394	11.34	0.43
7.	6452096	Ethyl iso-allocholate	436	19.46	0.74
8.	5364713	Ethanol, 2-(9-octadecenyloxy)-, (Z)-	312	20.89	0.41
9.	8181	**Hexadecanoic acid, methyl ester**	270	21.76	1.39
10.	22214169	Methyl glycocholate, 3TMS derivative	695	22.26	0.96
11.	12366	Hexadecanoic acid, ethyl ester	284	22.41	4.54
12.	102024920	**10-Octadecenoic acid, methyl ester**	296	23.42	0.76
13.	5365672	**9,12-Octadecadienoic acid, ethyl ester**	308	23.98	3.10
14.	5367328	**9,12,15-Octadecatrienoic acid, 2,3-dihydroxypropyl ester, (Z,Z,Z)**	352	24.05	1.33
15.	99931	Hexadecanoic acid, 1-(hydroxymethyl)-1,2-ethanediyl ester	568	24.76	1.62
16.	347736	Glycidyl palmitate	312	25.15	7.35
17.	5367498	**9,12,15-Octadecatrienoic acid, 2-phenyl-1,3-dioxan-5-yl ester**	440	26.68	0.89
18.	541357	17-(1,5-Dimethylhexyl)-2,3-dihydroxy-10,13-dimethyl-1,2,3,7,8, ,10,11,12,13,14	617	32.13	5.50
19.	222284	Sitosterol	414	37.05	23.18

4. In Silico Prediction of ADME Properties and Toxicity Profiles

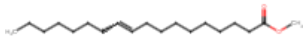
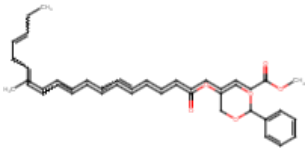
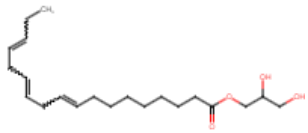
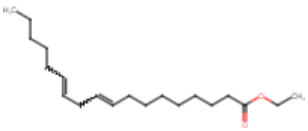
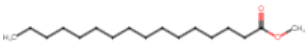
The in silico absorption, distribution, metabolism, and excretion (ADME) properties of five selected compounds were predicted using the SwissADME online platform. The predicted ADME parameters are summarized in Table 3.

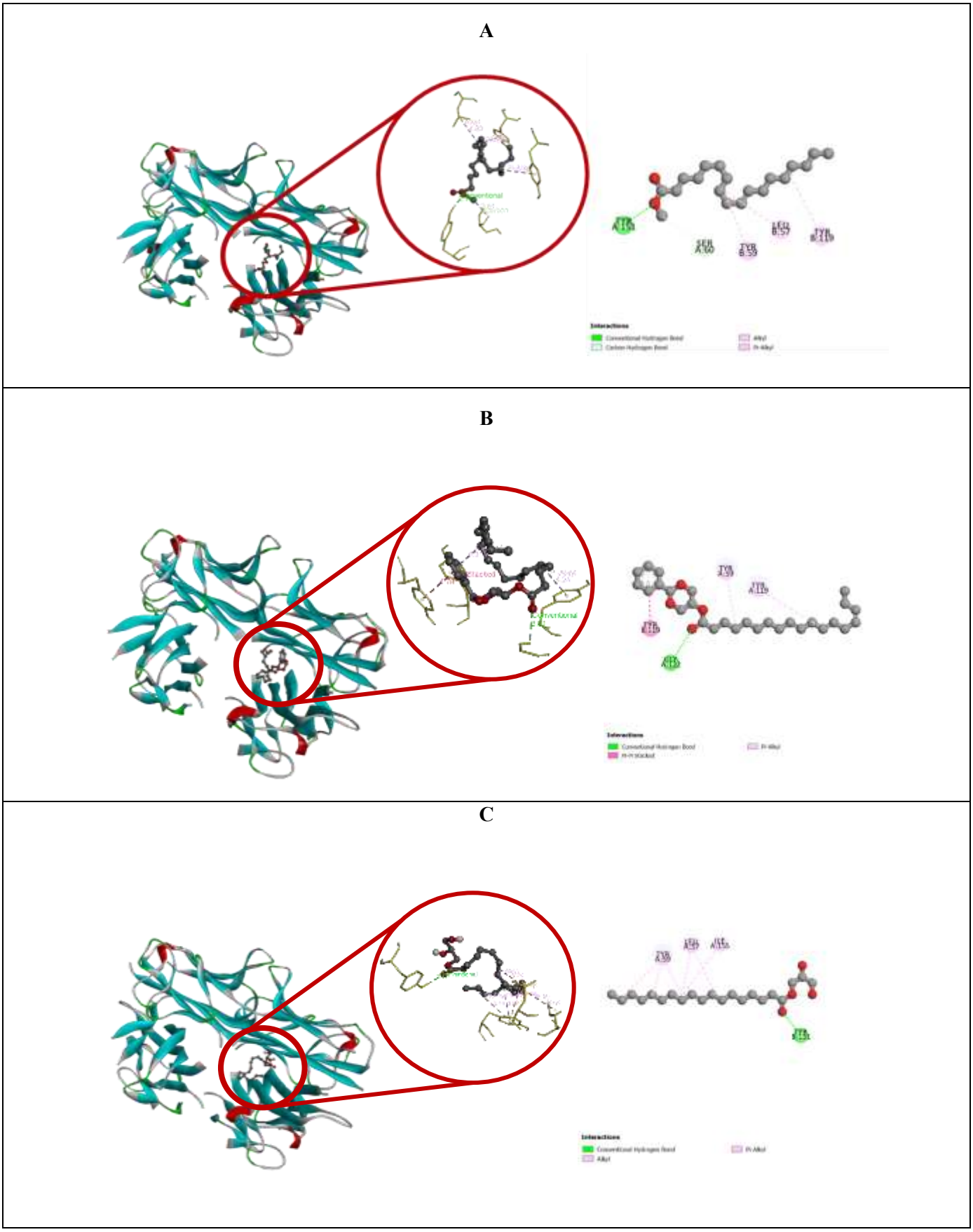
All five compounds exhibited high predicted intestinal absorption, with values ranging from 90.683% to 92.632%. The predicted skin permeability (log Kp) values for all compounds were negative, indicating limited transdermal permeability. Distribution-related parameters showed variable predicted volume of distribution (VDss) values, while predicted blood–brain barrier (BBB) and central nervous system (CNS) permeability values varied among compounds.

All compounds were predicted to be substrates of cytochrome P450 3A4 (CYP3A4). The predicted total clearance values ranged from 1.861 to 2.188 log mL/min/kg. None of the compounds were predicted to be substrates of the renal organic cation transporter 2 (OCT2).

Toxicity prediction using the ProTox platform indicated that the predicted median lethal dose (LD_{50}) values ranged from 3,000 to 39,800 mg/kg (Table 4). Based on the Globally Harmonized System (GHS) classification, the compounds were categorized into toxicity Classes V and VI. Among the analyzed compounds, 9,12-octadecadienoic acid, ethyl ester was predicted to exhibit carcinogenic potential, while the remaining compounds were predicted to be inactive in this category.

Table 2. Binding Affinity Analysis of Lima Bean Anti-inflammatory Compounds with TNF-α

Compound	Information	2D Chemical Structure	Docking Score (kcal/mol)	Amino acids involved in hydrogen bonding
10-Octadecenoic acid, methyl ester	MF= C19H36O2 H-bond Donor= 0 H-bond Acceptor= 2		-5.3	Ser60 (2.11 Å) Tyr151 (3.64 Å)
9,12,15-Octadecatrienoic acid, 2-phenyl-1,3-dioxan-5-yl ester	MF= C28H40O4 H-bond Donor= 0 H-bond Acceptor= 4		-6.8	Gly122 (3.01 Å)
9,12,15-Octadecatrienoic acid, 2,3-dihydroxypropyl ester, (Z,Z,Z)	MF= C21H36O4 H-bond Donor= 2 H-bond Acceptor= 4		-5.7	Tyr151 (2.17 Å)
9,12-Octadecadienoic acid, ethyl ester	MF= C20H36O2 H-bond Donor= 0 H-bond Acceptor= 2		-5.8	Tyr151 (2.15 Å)
Hexadecanoic acid, methyl ester	MF= C17H34O2 H-bond Donor= 0 H-bond Acceptor= 2		-5.0	-


A
B
C

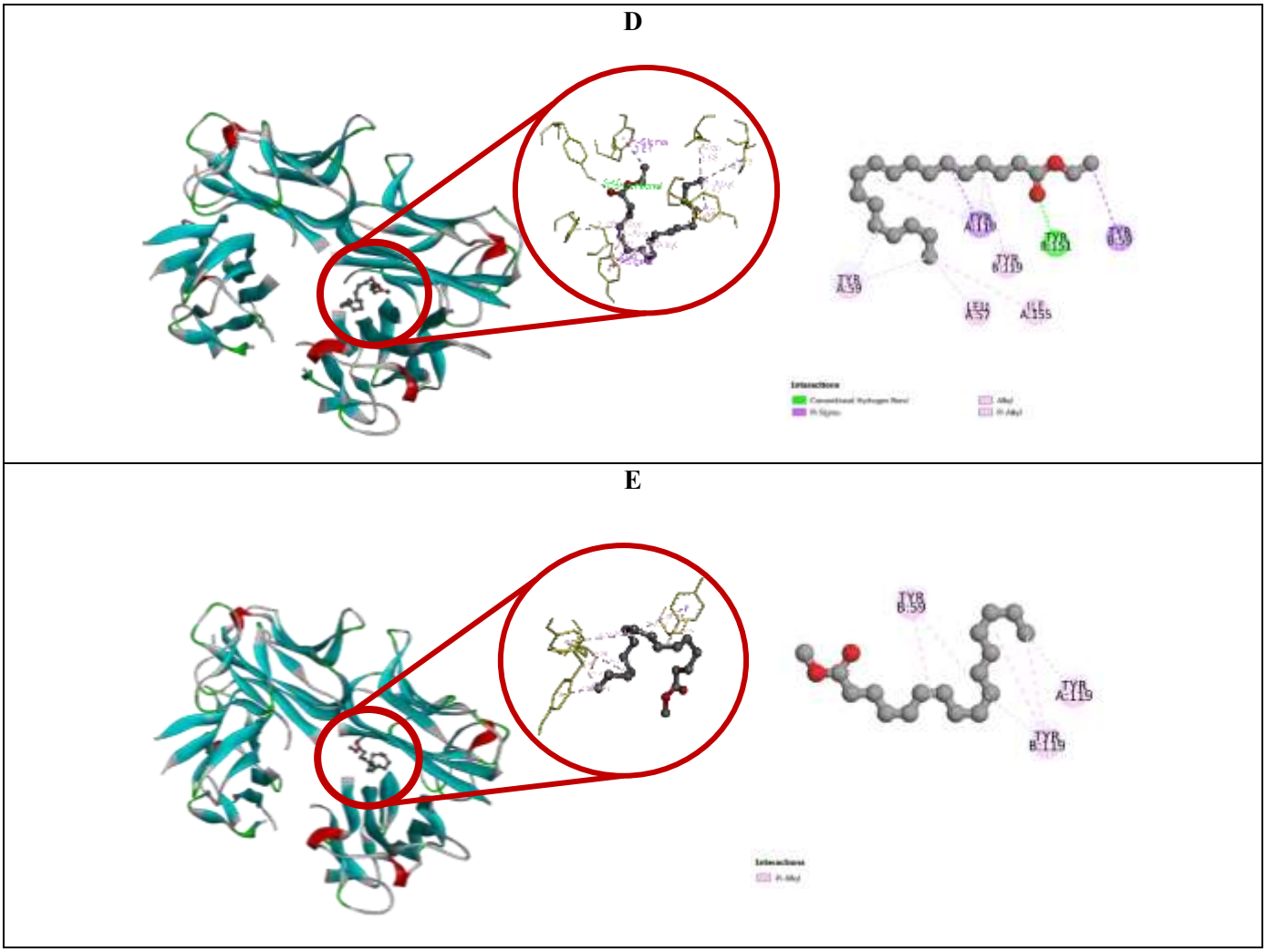


Figure 2. Predicted binding modes of selected lima bean-derived compounds within the TNF-α binding site.

4. Discussion

The GC–MS profiling of lima bean flour extract revealed a chemical composition dominated by fatty acid derivatives and sterol compounds, with sitosterol identified as the most abundant constituent. Sitosterol is a well-documented phytosterol commonly found in plant-based foods and has been associated with multiple biological activities, including modulation of lipid metabolism and inflammatory signaling pathways [25,26]. Its predominance in the extract suggests that phytosterols may represent an important component of the bioactive profile of lima beans.

In addition to sterols, several fatty acid esters, such as hexadecanoic acid ethyl ester and 9,12-octadecadienoic acid ethyl ester, were detected in appreciable proportions. Fatty acid derivatives have been widely reported to influence inflammatory responses and oxidative stress through diverse molecular mechanisms [27,28]. Unsaturated fatty acid esters, in particular, are known to modulate inflammatory mediator production and immune-related signaling pathways [29]. The detection of glycidyl palmitate and other esterified lipid compounds further reflects the chemical diversity of the extract and is consistent with previous reports describing their occurrence in plant-derived matrices and their association with antimicrobial and anti-inflammatory activities [30-32].

Variations in compound composition and relative abundance compared with previous studies on lima beans may be attributed to differences in cultivar type, geographical origin, environmental growing conditions, and extraction procedures. Such variability underscores the importance of region-specific chemical profiling when evaluating the functional and biological potential of plant-based food sources [33]. Although many of the identified compounds, such as fatty acid esters and phytosterols, have been widely reported in plant-derived extracts, the novelty of this study lies in the integration of region-specific chemical profiling with a multi-step in silico approach to establish a systematic link between lima bean-derived compounds and TNF-α-mediated inflammatory pathways in the context of malnutrition. Collectively, the GC–MS results provide a chemical basis for subsequent in silico analyses aimed at

exploring inflammation-related molecular interactions of selected lima bean-derived compounds.

PASS analysis was applied as an initial in silico screening approach to prioritize compounds with potential anti-inflammatory relevance. Several fatty acid esters and lipid-derived compounds exhibited Pa values exceeding the predefined threshold (Pa ≥ 0.700), indicating a higher probability of association with anti-inflammatory activity. However, PASS predictions are probabilistic and structure-based and therefore should be interpreted as hypothesis-generating rather than confirmatory evidence [34,35].

Table 3. Predicted ADME parameters of selected lima bean-derived compounds

ADME	Parameters	10-Octadecenoic acid, methyl ester	9,12,15-Octadecatrienoic acid, 2-phenyl-1,3-dioxan-5-yl ester	9,12,15-Octadecatrienoic acid, 2,3-dihydroxypropyl ester	9,12-Octadecadienoic acid, ethyl ester	Hexadecanoic acid, methyl ester
Absorption	Intestinal absorption (%)	90.683	92.632	91.753	91.753	92.335
	Skin permeability (log Kp)	-2.768	-2.701	-2.834	-2.834	-2.595
Distribution	VDss (human) (log L/kg)	0.102	0.184	-0.356	-0.356	0.334
	BBB permeability (log BB)	0.103	-0.211	-0.83	-0.83	0.749
	CNS permeability (log PS)	-1.886	-1.334	-3.207	-3.207	-1.678
Metabolism	CYP3A4 substrate (Yes/No)	Yes	Yes	Yes	Yes	Yes
Excretion	Total Clearance (log mL/min/kg)	2.01	1.92	2.188	2.188	1.861
	Renal OCT2 substrate (Yes/No)	No	No	No	No	No

Note: Log Kp refers to the logarithm of the skin permeability coefficient; BBB stands for Blood-Brain Barrier; CNS denotes Central Nervous System; Log PS is the logarithm of the permeability-surface area product; CYP3A4 refers to the Cytochrome P450 3A4 enzyme; and OCT2 stands for Organic Cation Transporter 2.

Notably, many of the compounds prioritized through PASS screening are structurally related to unsaturated fatty acids, including derivatives of α-linolenic acid and linoleic acid. Previous studies have demonstrated that omega-3 and omega-6 fatty acid derivatives can modulate key inflammatory signaling pathways, such as nuclear factor-κB (NF-κB), mitogen-activated protein kinase (MAPK), and cyclooxygenase (COX)-mediated processes. These pathways are critically involved in the regulation of pro-inflammatory mediators, including nitric oxide, prostaglandins, and tumor necrosis factor-α (TNF-α) [36-38]. Nevertheless, the biological activities discussed here are derived from independent experimental studies on related compounds and were not directly assessed in the present study. Based on these screening results, selected compounds were further evaluated using molecular docking to investigate their structural interaction patterns with TNF-α. The predicted binding affinities ranged from −5.0 to −6.8 kcal/mol, which fall within the range typically reported as weak to moderate interactions in virtual screening studies [39,40]. These values

suggest a potential ability of the compounds to occupy the TNF-α binding interface. However, they should be interpreted as preliminary indications rather than evidence of strong binding or biological inhibition. This level of binding affinity is commonly reported in early-stage computational screening and primarily serves to prioritize compounds for further experimental validation.

Table 4. Predicted toxicity profiles of selected lima bean-derived compounds

Compound	Predicted LD50, mg/kg[a]	Predicted Toxicity Class[a]	Predicted Toxicity
10-Octadecenoic acid, methyl ester	3000	5	Inactive
9,12,15-Octadecatrienoic acid, 2-phenyl-1,3-dioxan-5-yl ester	3520	5	Inactive
9,12,15-Octadecatrienoic acid, 2,3-dihydroxypropyl ester	39800	6	Inactive
9,12-Octadecadienoic acid, ethyl ester	20000	6	Carcinogenicity
Hexadecanoic acid, methyl ester	5000	5	Inactive

Among the evaluated ligands, Compound B, an α-linolenic acid derivative containing a 2-phenyl-1,3-dioxan-5-yl moiety, exhibited the most favorable predicted binding energy. The presence of multiple hydrogen bond acceptors likely facilitates interactions with residues such as Tyr59 and Gly121, which have been reported to contribute to ligand stabilization at the TNF-α dimer interface [41-43]. Additionally, the aromatic ring within this compound supports potential stabilization through π–π stacking or hydrophobic interactions that enhance binding stability [44, 45]. Despite these observations, molecular docking represents a static and simplified model that does not account for protein flexibility, solvent effects, or dynamic conformational changes, and therefore cannot confirm functional inhibition [46].

In silico ADME and toxicity predictions were conducted to provide preliminary insights into the pharmacokinetic and safety-related characteristics of the selected compounds. The consistently high predicted intestinal absorption values suggest favorable oral absorption potential, although these predictions are model-based and indicative rather than definitive [47]. Negative skin permeability values indicate limited transdermal penetration [48], while relatively low predicted BBB and CNS permeability for several compounds suggests a reduced likelihood of central nervous system exposure, which may be advantageous for compounds targeting peripheral inflammatory processes [49].

All five compounds were predicted to be substrates of CYP3A4, the most abundantly expressed cytochrome P450 isoform responsible for the metabolism of approximately 50% of clinically used drugs [50]. This prediction carries two principal pharmacokinetic implications. First, if these compounds are co-administered with other CYP3A4 substrates or inhibitors (e.g., certain antibiotics, antifungals, or statins), competitive inhibition or induction of this enzyme may result in altered plasma concentrations, potentially reducing efficacy or increasing the risk of adverse effects. Second, as lipid-derived natural compounds, their first-pass hepatic metabolism via CYP3A4 may substantially reduce oral bioavailability compared to what intestinal absorption values suggest. These considerations highlight the need for in vitro metabolic stability assays (e.g., human liver microsome studies) in future experimental validation stages.

Predicted clearance values indicate moderate elimination rates, although these findings should be interpreted cautiously due to the inherent limitations of in silico pharmacokinetic modelling [51]. Toxicity prediction further suggested that most compounds fall within low-to-very-low acute toxicity categories (GHS Classes V and VI), based on predicted LD_{50} values [52]. It is important to note that 9,12-octadecadienoic acid, ethyl ester is a simple ethyl ester derivative of linoleic acid, a naturally occurring omega-6 polyunsaturated fatty acid widely present in plant-based foods and generally regarded as safe. The carcinogenicity prediction generated by ProTox-3.0 is based on structural similarity models, which may not fully account for the metabolic fate, bioavailability, or dose-response characteristics of naturally occurring lipid compounds. Furthermore, no experimental in vitro or in vivo evidence currently supports carcinogenic activity for this class of compounds in the peer-reviewed literature. Nevertheless, in accordance with the precautionary principle, this computational flag warrants further experimental clarification particularly through Ames test or in vitro mutagenicity assays before this compound is considered for any applied nutraceutical development.It should be interpreted with caution, as in silico toxicity predictions may not fully reflect in vivo biological effects and require further experimental validation. [53]. The integrated GC–MS profiling and in silico analyses presented in this study provide a hypothesis-generating framework for understanding the potential inflammation-related relevance of lima bean-derived compounds. These findings support the prioritization of selected compounds for further experimental validation using

biochemical, cellular, or in vivo models to confirm their functional roles in modulating TNF-α-mediated inflammatory pathways.

5. Conclusion

This study combined GC–MS profiling and in silico analyses to explore the inflammation-related potential of bioactive compounds in lima bean (*Phaseolus lunatus* L.) flour. Five compounds were prioritized based on PASS screening, molecular docking against tumor necrosis factor-alpha (TNF-α), and ADME/toxicity predictions, with the α-linolenic acid derivative containing a 2-phenyl-1,3-dioxan-5-yl moiety showing the most favorable predicted binding affinity. These findings provide a hypothesis-generating framework linking lima bean-derived compounds to TNF-α-associated inflammatory pathways. Further experimental validation is required to confirm the biological relevance of these computational predictions.

Declarations

Author Contributions

Conceptualization, R.M., B.A., P.S., and A.T.; methodology, R.M. and B.A.; software, B.A. and P.S.; validation, R.M., A.T., and B.A.; formal analysis, R.M.; data curation, P.S.; writing—original draft preparation, R.M., B.A., P.S., and A.T.; writing—review and editing, R.M., B.A., P.S., and A.T.; visualization, B.A.; supervision, R.M.; project administration, P.S.; funding acquisition, A.T. All authors have read and agreed to the published version of the manuscript.

Data Availability Statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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Conflicts of Interest

The authors declare that they have no conflicts of interest regarding the publication of this manuscript.

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