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In Silico Evaluation of Antioxidant Potential of *Adenostemma lavenia* Leaf Compounds Against IL-6 in Pulmonary Sepsis

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Abstract: This study aims to evaluate the antioxidant potential of bioactive compounds from Adenostemma lavenia in targeting interleukin-6 (IL-6) associated with pulmonary sepsis. Phytochemicals from Adenostemma lavenia leaves were identified using GC-MS, and ten bioactive compounds with potential antioxidant activity were selected. These compounds underwent further in silico evaluation, including drug-likeness screening, biological activity prediction, pharmacokinetic and toxicity analysis, and molecular docking against interleukin-6 (PDB ID: 8J6F). Among them, stigmasterol showed the highest docking score of –8.1 kcal/mol and a PASS prediction probability (Pa) of 0.867 for antioxidant activity. Half of them fully complied with drug-likeness criteria. Among these, D-Allose, 2,4-Di-tert-butylphenol, and Phytol demonstrated the highest predicted antioxidant activity. Toxicity evaluations revealed a generally safe profile, with minimal nephrotoxicity in two compounds. Notably, Phytol exhibited the closest similarity in binding residues to the native ligand of IL-6, suggesting a strong binding orientation and promising therapeutic value. The in silico findings highlight Phytol and other antioxidant-rich phytoconstituents of A. lavenia as promising agents targeting IL-6, supporting their potential use as adjunct therapies for oxidative stress-related conditions such as pulmonary sepsis. These results contribute to the scientific understanding of natural antioxidants in inflammation control and warrant further validation through in vitro and in vivo studies.
Keywords: Sepsis; oxidative stress; adenostemma lavenia; antioxidant; interleukin-6 (IL-6)

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INTRODUCTION

Sepsis is a severe and potentially fatal medical condition that results from a dysregulated immune response to infection, leading to widespread inflammation, tissue injury, and multiple organ dysfunction (Wiersinga & Van der Poll, 2022). It represents a major global health burden with high incidence and mortality rates, particularly in intensive care units. When the condition advances to include profound circulatory and cellular/metabolic dysfunction, it progresses into septic shock, which is associated with even higher mortality and poorer clinical outcomes (Guarino et al., 2023). The complexity of its pathogenesis and the lack of specific treatments make sepsis a pressing target for therapeutic innovation. A retrospective observational study of national sepsis data in Indonesia from 2013 to 2016 identified 14,076 cases. Of these, 58.3% resulted in death and 41.7% showed improvement. The average patient age was 49.4 years, with 31% diagnosed due to multifocal infections. The case fatality rate in intensive care units (ICUs) reached 69%.

One of the central pathological features of sepsis is the infiltration of host tissues by activated phagocytic immune cells. Among these, polymorphonuclear leukocytes (neutrophils) and monocytes/macrophages are the primary responders to septic stimuli. Upon activation, these cells initiate an oxidative burst by generating large quantities of reactive oxygen species (ROS)—including superoxide anions (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radicals (•OH)—as well as reactive nitrogen

species (RNS) such as nitric oxide (NO) and peroxynitrite ($ONOO^-$) (Cepinskas & Wilson, 2008; Cerretani et al., 2011; Sikora et al., 2023). While these reactive molecules are essential for microbial killing, their overproduction leads to significant oxidative stress, which exacerbates cellular and tissue damage. This uncontrolled oxidative response, driven primarily by innate immune mechanisms, plays a pivotal role in the early development and progression of sepsis, contributing to widespread inflammation and organ failure. Notably, although Adenostemma lavenia has been reported to possess anti-inflammatory and antioxidant properties, no scientific studies to date have specifically evaluated its effects on interleukin-6 (IL-6) in the context of sepsis. As such, mitigating oxidative stress has emerged as a promising therapeutic target in sepsis management.

Considering the complex pathophysiology of sepsis, which involves a broad range of dysregulated immune and oxidative mechanisms, there has been increasing scientific interest in the use of natural compounds with pleiotropic properties as alternative therapeutic strategies. Natural products are highly valued in drug discovery due to their structural diversity, evolutionary refinement for biological compatibility, capacity to modulate multiple molecular targets simultaneously, and relatively low toxicity profiles (Ho et al., 2018). Among the plants with promising medicinal properties is *Adenostemma lavenia*, locally known as Söfö-Söfö. Traditionally used in ethnomedicine, this plant is reported to exert a wide spectrum of bioactivities, including antioxidant, anti-inflammatory, antibacterial, anti-aging, and anti-melanogenic effects (Maeda et al., 2022; Nurlela et al., 2023). Its antioxidant potential, in particular, positions it as a suitable candidate for mitigating oxidative stress in sepsis, a condition where redox imbalance plays a pivotal role in disease progression.

The use of in silico techniques has become increasingly valuable in the field of drug discovery, relying on computational tools to simulate biological interactions. One widely used strategy within this framework is molecular docking, which enables researchers to predict the binding affinity of bioactive compounds to specific protein targets. In addition to docking, in silico methods offer insights into the pharmacokinetic profiles of compounds—such as their absorption, distribution, metabolism, excretion, and potential toxicity—as well as their physicochemical characteristics. This integrative approach facilitates early-stage screening and optimization of potential drug candidates (Chikhale et al., 2021).

This research utilized molecular docking techniques to explore the interaction between bioactive compounds and interleukin-6 (IL-6), a cytokine that plays a pivotal role in the inflammatory cascade of sepsis. IL-6 is widely recognized as a key early biomarker for sepsis and acute kidney injury (AKI), and its elevated levels have been strongly associated with disease severity and poor clinical outcomes. Several clinical studies have shown that high circulating IL-6 concentrations are predictive of septic shock and are correlated with increased mortality rates in affected patients (Martin et al., 2001). Therefore, targeting IL-6 may provide a promising approach for therapeutic intervention and early risk stratification in septic conditions.

This study contributes to clinical pharmacy and immunology by supporting the rationale for IL-6-targeted therapies through natural antioxidant agents. Moreover, it provides a preliminary foundation for the development of herbal-based adjunct treatments derived from Adenostemma lavenia, which may offer safer and more accessible alternatives in managing inflammation-driven diseases such as pulmonary sepsis.

Oxidative stress plays a critical role in the progression of pulmonary sepsis, with interleukin-6 (IL-6) acting as a key pro-inflammatory cytokine linked to inflammation

and tissue damage. Adenostemma lavenia, a traditional medicinal plant, contains phytochemicals with potential antioxidant activity that may help modulate IL-6 pathways.Therefore, this study aimed to evaluate the antioxidant potential of A. lavenia leaf compounds through an in silico approach. Molecular docking was used to assess their interaction with IL-6 and identify candidates for further investigation in oxidative stress-related conditions.

METHOD

Phytochemical Profiling and Molecular Docking Analysis

Gas Chromatography–Mass Spectrometry (GC–MS) profiling of *Adenostemma lavenia* leaf extract revealed several phytochemical constituents. These compounds were subsequently analyzed through molecular docking to evaluate their binding interactions with interleukin-6 (IL-6), a pro-inflammatory cytokine associated with oxidative stress and sepsis progression. The docking approach aimed to identify the potential antioxidant capacity of these compounds in modulating IL-6 activity, providing a foundation for further therapeutic exploration in pulmonary sepsis.

Prediction of Pharmacological Activities of *Adenostemma lavenia* Compounds

To determine the pharmacological viability of the phytochemicals derived from *Adenostemma lavenia* leaves, the drug-likeness properties were evaluated based on Lipinski's Rule of Five. According to this rule, oral bioavailability tends to decrease when a compound exhibits more than five hydrogen bond donors, over ten hydrogen bond acceptors, a molecular weight exceeding 500 Da, or a logP value greater than 5 (Lipinski et al., 2001). Additionally, the biological activities of both the test compounds and reference standard were predicted using the PASS (Prediction of Activity Spectra for Substances) online tool (Goel et al., 2011). Molecular structures in SMILES format were sourced from the PubChem database (https://pubchem.ncbi.nlm.nih.gov) and submitted to the PASS web platform (https://way2drug.com/PassOnline/) for analysis. The predictive potential for various pharmacological effects was assessed using Pa_max (probability of activity) scores, and compared against reference activities from the PASS training dataset to estimate each compound's functional likelihood.

Pharmacokinetic Profiling, Toxicity Assessment, and Molecular Docking of *Adenostemma lavenia* Compounds

Molecular docking analysis was carried out to predict and analyze the binding affinity of selected bioactive constituents toward the Interleukin-6 (IL-6) protein, a pro-inflammatory cytokine implicated in sepsis-related oxidative stress. The three-dimensional structure of IL-6 was obtained from the RCSB Protein Data Bank (PDB ID: 8J6F). Protein preparation steps included the removal of crystallographic water molecules using PyMOL, followed by ligand energy minimization via Open Babel embedded in the PyRx 0.0.8 docking environment.

Prior to ligand docking, validation of the docking protocol was performed through re-docking of the native ligand into the IL-6 binding site, ensuring reproducibility and reliability of the docking parameters. AutoDock Vina was employed to simulate ligand–protein interactions, with an exhaustiveness value of 8 applied to optimize conformational sampling. Each docking simulation generated up to nine poses per ligand, from which the most stable conformations were selected based on binding affinity scores. Docking simulations were carried out using a grid box centered on the IL-6 active site, with specific grid coordinates and box dimensions summarized in Table 1.

Visualization and post-docking interaction analyses were conducted using Discovery Studio Visualizer (BIOVIA, Dassault Systèmes), which facilitated the interpretation of binding poses and molecular interactions such as hydrogen bonding, hydrophobic interactions, and van der Waals forces (Agu et al., 2023).

Table 1. Coordinate Grid and Dimensions of IL-6 Protein for Molecular Docking

Protein	PDB ID	Coordinate Grid					
		Center			Dimension		
		X	Y	Z	X	Y	Z
IL6 Receptor	8J6F	160.0749	156.3506	131.6442	24.0865	18.8417	28.6142

RESULTS AND DISCUSSION

GC-MS Analysis of Söfö-Söfö (*Adenostemma lavenia*) Leaf Extract

Based on the GC-MS analysis of *Adenostemma lavenia* leaf extract, a total of ten major bioactive compounds were identified (Figure 1). The compound with the shortest retention time was 3,4-Anhydro-D-galactosan (9.735 minutes), reflecting its relatively high volatility and low molecular weight. Such physicochemical properties are often characteristic of small carbohydrate derivatives, which can act as reducing agents by donating electrons to neutralize free radicals. In contrast, 9,12,15-Octadecatrienoic acid exhibited the longest retention time (20.324 minutes), consistent with its larger molecular size and lower volatility. Long-chain unsaturated fatty acids of this type are known to contribute to antioxidant and anti-inflammatory activity through double-bond conjugation, which stabilizes radical intermediates and modulates inflammatory signaling pathways.

The remaining eight compounds displayed intermediate retention times (average 15.521 minutes), suggesting moderate volatility and structural diversity. This heterogeneity highlights the phytochemical complexity of A. lavenia, where the coexistence of volatile and non-volatile compounds may provide synergistic biological effects. For instance, small phenolic or sugar-derived compounds may act as direct radical scavengers, while fatty acids and terpenoids could function indirectly by enhancing membrane stability or regulating oxidative pathways.

Figure 1 illustrates the chromatogram profile, with distinct peaks at early retention times (around 9.7 minutes) corresponding to light and volatile molecules, and larger peaks at later retention times (15–20 minutes) reflecting heavier, less volatile bioactive constituents. Overall, the GC-MS findings suggest that A. lavenia contains a diverse range of phytochemicals with complementary physicochemical properties. This chemical diversity supports its potential role as a multi-target therapeutic agent, where different compound classes may jointly contribute to antioxidant and anti-inflammatory activity. Future studies should focus on fractionation and isolation of these compounds to determine which classes are most responsible for the observed bioactivities, particularly in the context of oxidative stress and inflammation-related diseases.

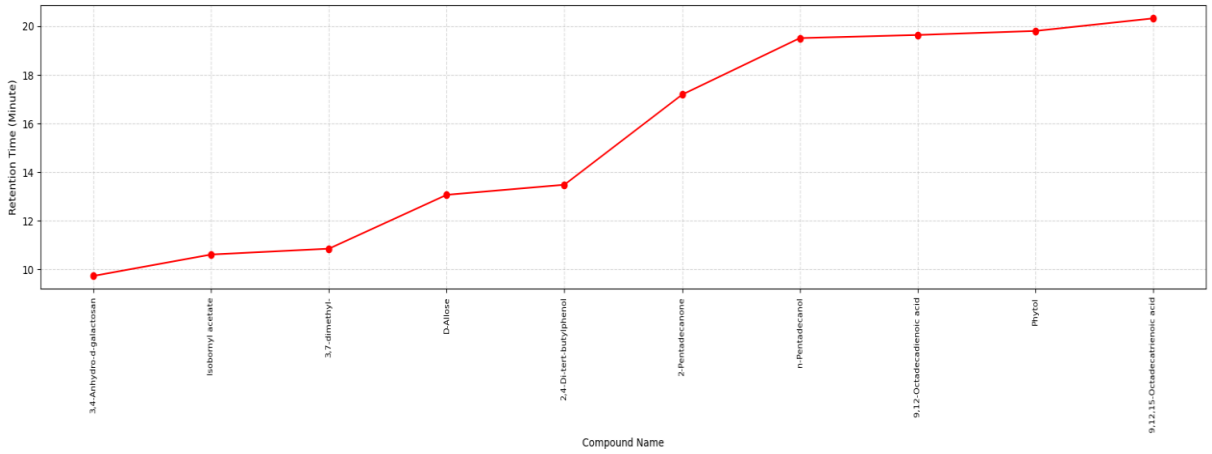

Figure 1. Retention time of Söfö- Söfö leaf (*Adenostemma lavenia*)

In Silico Evaluation of *Adenostemma lavenia*

Drug-Likeness Evaluation

Based on Lipinski's Rule of Five (RO5), five compounds—3,4-Anhydro-D-galactosan, Isobornyl acetate, 3,7-dimethyl-, D-Allose, and 2,4-Di-tert-butylphenol—were found to have zero violations, indicating full compliance with the Lipinski criteria for drug-likeness. In contrast, the other five compounds—2-Pentadecanone, n-Pentadecanol, 9,12-Octadecadienoic acid, Phytol, and 9,12,15-Octadecatrienoic acid—each presented one violation. Despite this, they remain within the acceptable range, since a single violation generally does not significantly compromise oral bioavailability.

According to the Lipinski's Rule of Five, a compound intended for oral administration is predicted to exhibit good drug-likeness if it does not violate more than one of the following parameters: molecular weight ≤ 500 Da, logP ≤ 5, hydrogen bond donors ≤ 5, and hydrogen bond acceptors ≤ 10. Compounds that fail more than one threshold usually show reduced absorption or permeation (Protti et al., 2021; Chen et al., 2020). This framework remains a cornerstone in early-stage drug discovery because it provides a rapid and cost-effective method for identifying viable candidates while filtering out molecules with poor pharmacokinetic potential.

The compliance of 3,4-Anhydro-D-galactosan, D-Allose, and 2,4-Di-tert-butylphenol with RO5 can be explained by their relatively small molecular sizes and balanced polarity. In particular, 2,4-Di-tert-butylphenol, a phenolic derivative, benefits from a hydroxyl group capable of hydrogen donation, which not only satisfies Lipinski's criteria but also underlies its predicted antioxidant potential. Conversely, borderline compounds such as Phytol and 9,12,15-Octadecatrienoic acid violate RO5 due to their long hydrophobic chains and higher molecular weights. These characteristics may reduce solubility and absorption, but at the same time, the extended conjugated double bonds present in unsaturated fatty acids can enhance radical stabilization, contributing to antioxidant activity despite lower drug-likeness compliance.

Figure 2 presents the RO5 evaluation, showing that approximately half of the compounds fully comply with drug-likeness criteria, while the remaining half display minor deviations primarily linked to lipophilicity or molecular size. This balance between polar and non-polar molecules reflects the phytochemical diversity of the extract.

Taken together, these findings indicate that *A. lavenia* provides a dual spectrum of bioactive molecules: RO5-compliant compounds with high absorption potential and borderline lipophilic compounds that may contribute through complementary

mechanisms. Future research should experimentally assess these pharmacokinetic predictions, for instance by using in vitro intestinal permeability assays, to validate the oral bioavailability of these promising candidates.

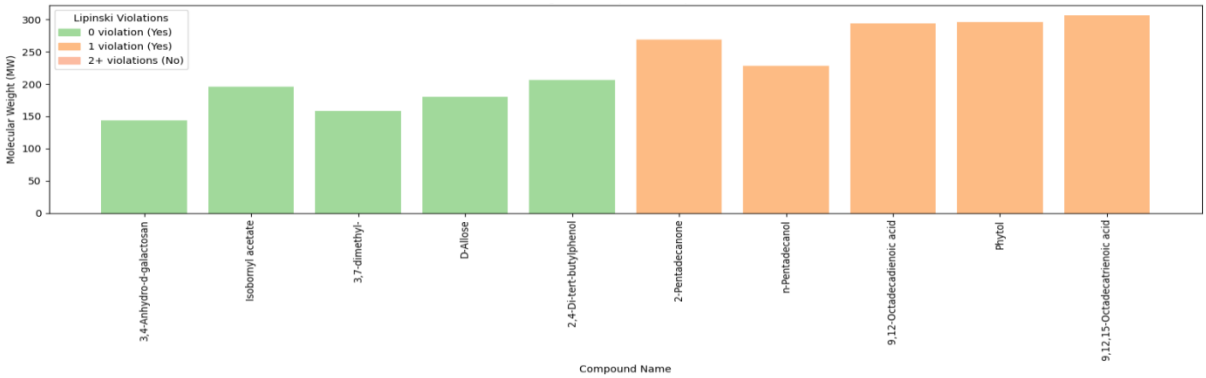

Figure 2. Lipinski's rule of five Söfö-Söfö leaf (*Adenostemma lavenia*)

Predicted Biological Activity

The PASS (Prediction of Activity Spectra for Substances) analysis indicated that four compounds—D-Allose (Pa = 0.778), 2,4-Di-tert-butylphenol (Pa = 0.525), Phytol (Pa = 0.470), and 3,4-Anhydro-D-galactosan (Pa = 0.440)—exhibited the highest predicted antioxidant activities. Among these, D-Allose showed the strongest probability of activity, suggesting a high potential to act as an effective free radical scavenger. In contrast, the remaining compounds yielded lower Pa values (<0.4), suggesting a relatively weaker antioxidant contribution. These results highlight the diverse antioxidant potential within the *A. lavenia* extract, where only a subset of compounds demonstrate strong predictions of biological activity.

The PASS platform operates using a large-scale pharmacophore-matching algorithm built on over 3,000 known biological activities. Predictions are expressed as Pa (probability to be active) values, where compounds with Pa > 0.5 are considered likely to demonstrate measurable activity in vitro, while those below this threshold are less promising (Shady et al., 2022). Thus, the prediction for D-Allose (Pa = 0.778) strongly supports its potential for further experimental validation, while 2,4-Di-tert-butylphenol and Phytol, though slightly above or near the threshold, may act as moderate antioxidants.

Importantly, the predicted activities can be explained by molecular structures. D-Allose, a rare aldohexose sugar, contains multiple hydroxyl groups that can donate hydrogen atoms to neutralize reactive oxygen species, a property consistent with its high Pa score. Similarly, 2,4-Di-tert-butylphenol possesses a phenolic hydroxyl group, a well-established structural motif for antioxidant action, where electron donation stabilizes free radicals via resonance. Phytol, an acyclic diterpene alcohol, contains a long unsaturated chain that provides multiple double bonds, enabling radical stabilization through conjugation. In contrast, the lower Pa values of saturated fatty acids and long-chain alcohols (e.g., n-Pentadecanol, 2-Pentadecanone) reflect their lack of conjugated systems and reduced electron-donating capacity, explaining their weaker predicted antioxidant potential.

Figure 3 illustrates the PASS predictions of antioxidant activity, highlighting D-Allose as the strongest candidate, followed by phenolic and terpenoid derivatives. This figure underscores the structure–activity relationship, where molecules containing hydroxyl or conjugated systems demonstrate superior antioxidant potential compared to saturated lipophilic compounds.

Taken together, the PASS results reinforce the importance of hydroxylated and conjugated structural motifs in determining antioxidant activity. These predictions provide a mechanistic basis for selecting promising lead compounds for experimental validation. Future studies should include in vitro antioxidant assays (e.g., DPPH, ABTS, FRAP) to confirm these activities and assess their relevance to oxidative stress-related diseases such as sepsis, where antioxidant therapy could play a critical therapeutic role.

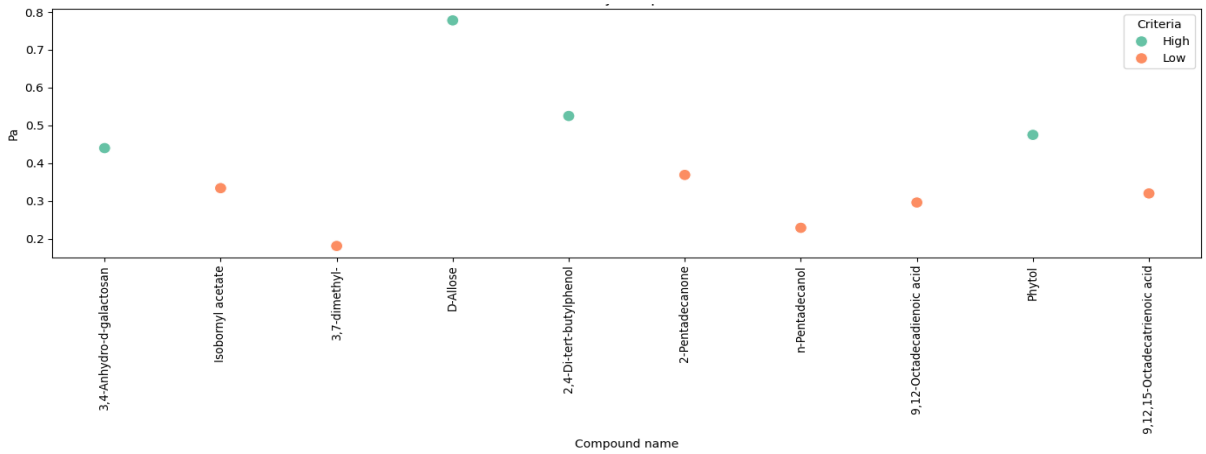

Figure 3. Predicted biological activity profile of Söfö-Söfö (*Adenostemma lavenia*) leaf extract

ADMET Analysis (Absorption, Distribution, Metabolism, Excretion, and Toxicity)

Figure 4 presents the predicted ADMET profile of the ten major compounds identified in *Adenostemma lavenia* leaf extract. The analysis specifically focused on three key toxicity parameters—hepatotoxicity, nephrotoxicity, and respiratory toxicity. Overall, the results indicated that all compounds exhibited low toxicity risks, suggesting a favorable safety margin for further pharmacological exploration. Notably, two compounds, 3,4-Anhydro-D-galactosan and D-Allose, showed a slightly higher probability of nephrotoxicity compared to the others, though their predicted values remained within a tolerable threshold.

The relatively low overall toxicity underscores the potential of *A. lavenia* compounds as safe therapeutic agents. However, the nephrotoxicity signal detected for 3,4-Anhydro-D-galactosan and D-Allose warrants closer scrutiny. Structurally, both compounds contain reactive hydroxyl groups, which may contribute to renal burden through oxidative stress or interference with tubular reabsorption mechanisms. Such structural features could explain their elevated nephrotoxicity scores compared to more lipophilic molecules like phytol or fatty acid derivatives, which are generally metabolized via alternative detoxification pathways.

From a theoretical standpoint, nephrotoxicity represents one of the most critical adverse effects during drug development, as it leads to impaired kidney function and increased clinical risks. Predictive ADMET platforms thus play a central role in early-stage drug discovery by flagging compounds with potential organ-specific toxicity before advancing to in vivo or clinical stages (Perazella, 2009).

In conclusion, while the overall toxicity profile of *A. lavenia* compounds appears favorable, further in vivo nephrotoxicity assessments are recommended, particularly for sugar-derivative compounds like 3,4-Anhydro-D-galactosan and D-Allose. Such studies will be crucial for validating the computational predictions and ensuring renal safety in future therapeutic applications.

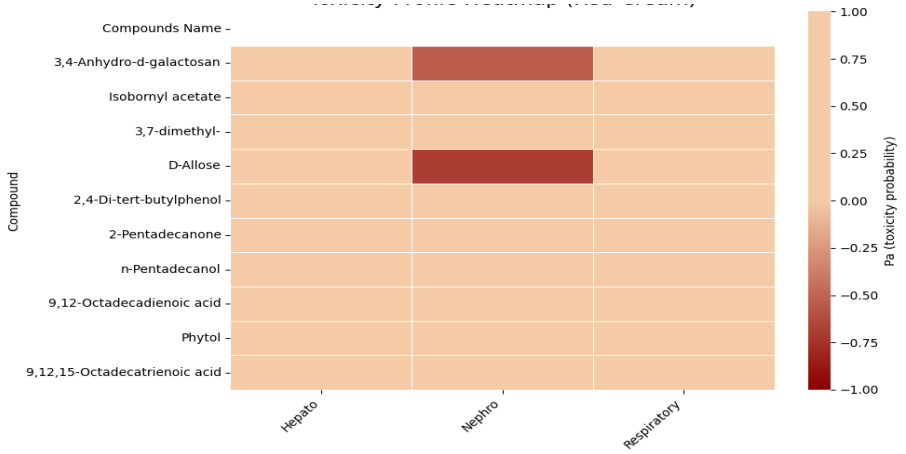

Figure 4. Biological activity of Söfö- Söfö Leaf (*Adenostemma lavenia*)

Molecular Docking and Visualization of Interactions with IL-6 Receptor

Figure 5 illustrates the binding affinity values obtained from molecular docking simulations of the ten compounds against the IL-6 receptor. Among these, phytol demonstrated one of the most favorable docking scores, suggesting a strong and stable interaction with the receptor. This finding is notable given the structural features of phytol, such as its long hydrophobic chain, which may facilitate insertion into the binding pocket and enhance van der Waals interactions with surrounding residues.

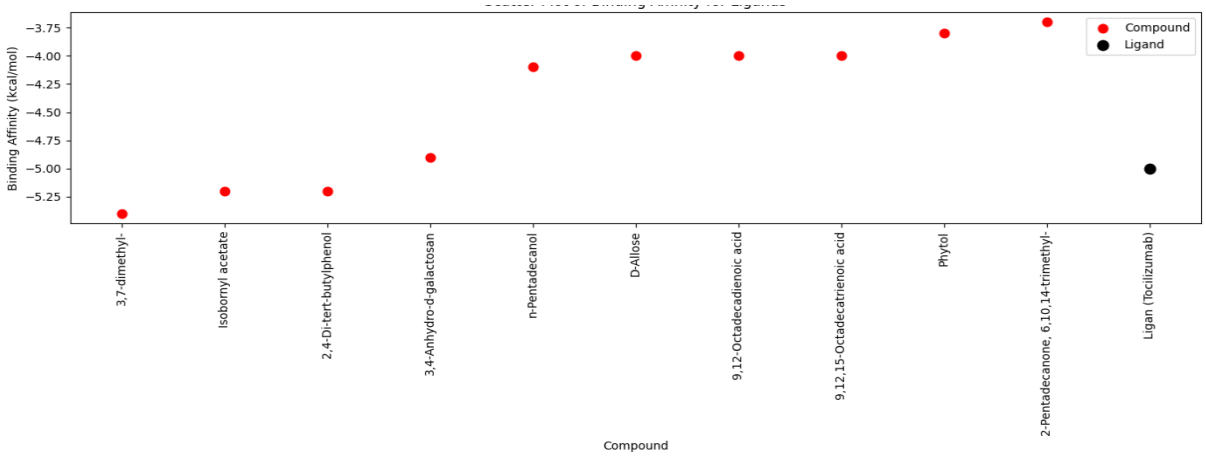

Figure 5. Binding affinity of Söfö- Söfö Leaf (*Adenostemma lavenia*)

Further visualization of protein–ligand interactions is provided in Figure 6, where the 2D interaction diagram highlights the amino acid residues involved in binding. Phytol exhibited a high degree of overlap with the reference ligand, sharing eight out of nine interacting residues, including GLU302, GLN215, GLY301, GLN300, GLU296, PRO216, GLN295, and TRP244. The only differing residue was LEU251, which was absent from phytol's interaction profile. This close similarity suggests that phytol can mimic the native ligand's binding conformation, potentially stabilizing the IL-6 receptor and modulating its role in inflammatory signaling pathways.

These results are important because IL-6 is a key cytokine in the pathogenesis of sepsis and related oxidative stress conditions. Compounds capable of effectively binding to the IL-6 receptor may interfere with its signaling cascade, thereby exerting anti-inflammatory or antioxidant effects. The ability of phytol to reproduce most of the key interactions observed in the native ligand highlights its promise as a candidate for

further evaluation. In conclusion, molecular docking identified phytol as the compound with the most favorable interaction profile with IL-6 receptor residues. Future studies should focus on molecular dynamics simulations to validate the stability of these interactions over time and in vitro assays to confirm its functional impact on IL-6-mediated inflammatory responses.

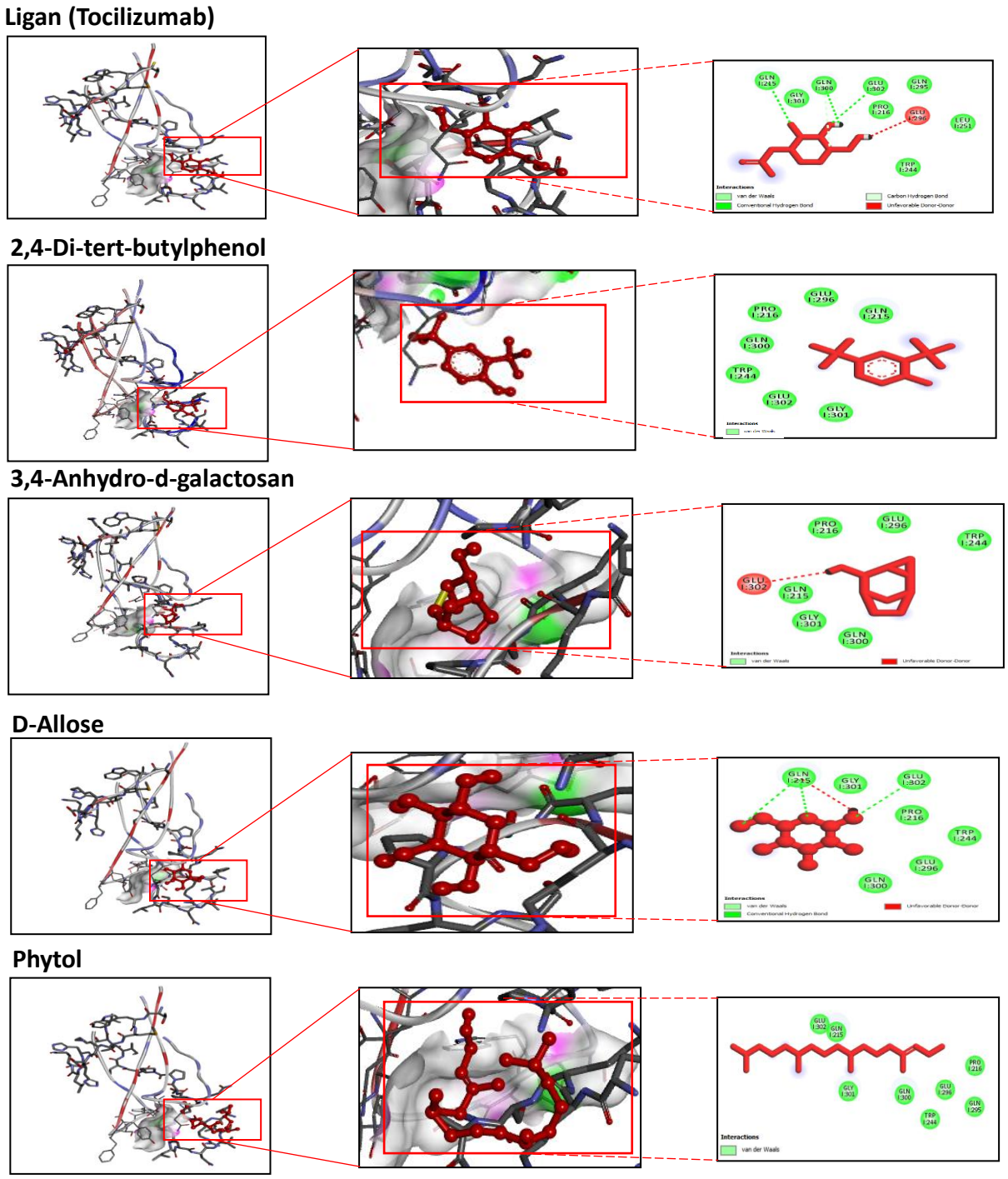

Figure 6. 2D interaction diagram of phytol with IL-6 receptor compared with the reference ligand

CONCLUSION

Based on the research results, it can be concluded that Ten bioactive compounds were identified through GC-MS analysis and further assessed for drug-likeness, antioxidant potential, toxicity, and IL-6 binding affinity. Five compounds met all Lipinski's criteria, and three compounds—D-Allose, 2,4-Di-tert-butylphenol, and

Phytol—showed strong predicted antioxidant activity. All compounds exhibited low toxicity, with minor nephrotoxicity concerns for two. Molecular docking revealed that Phytol had the highest amino acid residue similarity with the native ligand, suggesting favorable binding behavior. These findings contribute to the early-stage discovery of natural antioxidant candidates targeting IL-6, supporting the integration of A. lavenia into herbal drug development pipelines. Moreover, the study demonstrates the value of in silico screening in accelerating candidate selection for anti-inflammatory therapies in clinical pharmacy and sepsis research.

RECOMMENDATION

Further in vitro and in vivo studies are recommended to validate the antioxidant potential, safety profile, and pharmacological efficacy of the most promising compounds—particularly Phytol, D-Allose, and 2,4-Di-tert-butylphenol—as potential therapeutic agents.

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