

SwissADME And Toxtree Analysis of Neem (*Azadirachta indica*) Leaf Active Compounds

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ABSTRACT

Neem (*Azadirachta indica*) leaves have been used as a traditional medicinal plant and possess notable pharmacological activities. The leaves contain active compounds that act as antihyperlipidemic, antioxidant, antibacterial, anticancer, and antiobesity agents. Safety profiling of these compounds requires comprehensive evaluation using established Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) parameters. This study aims to analyze the ADMET profiles of 70 active compounds from neem leaves utilizing the SwissADME and Toxtree methods. The research employed ChemDraw for 2D and 3D structure preparation, VegaZZ for structure optimization, SwissADME for ADME prediction, and Toxtree for toxicity prediction. Out of the 70 analyzed compounds, 51 met the Lipinski's Rule of Five and pharmacokinetic criteria, while 19 compounds failed to meet these criteria. Based on toxicity predictions, 43 compounds met the safety criteria, whereas 27 exhibited potential toxicity. Thymol, Eugenol, Isopulegol, Phenylacetic acid, and 2-Methoxy-4-vinylphenol demonstrate favorable ADME profiles and are devoid of carcinogenic and mutagenic properties.

Keywords: ADME; Neem Leaves; SwissADME; Toxicity; Toxtree

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INTRODUCTION

Mimba (*Azadirachta indica*) is a medicinal plant historically employed in traditional medicine and possesses diverse pharmacological activities. Its leaves, which are the most extensively investigated plant part, contain various bioactive compounds, such as flavonoids and phenolics, that exhibit antihyperlipidemic, antioxidant, antibacterial, anticancer, and antiobesity activities (1)(2). Despite these bioactive profiles, it is imperative to evaluate the absorption, distribution, metabolism, excretion, and toxicity (ADMET) of the active constituents within the neem leaves as a preliminary screening measure.

In silico absorption, distribution, metabolism, excretion, and toxicity (ADMET) analysis serves as an initial screening to identify compound viability and safety profiles that align with drug development parameters. This evaluation is conducted to predict pharmacokinetic and toxicity parameters, thereby yielding safe drug candidates (3). This study aims to analyze the ADME and toxicity profiles of active compounds in neem leaves using *SwissADME* and *Toxtree* for preliminary screening, and to predict compounds that adhere to the Lipinski Rule of Five for ADME profiles and exhibit low toxicity, specifically lacking mutagenic and carcinogenic properties.

METHODS

The study titled “*SwissADME* and *Toxtree* Analysis of Active Compounds in Neem Leaves (*Azadirachta indica*)” utilizes a computational experimental design conducted to analyze the ADME and toxicity profiles of the active constituents in neem leaves using *SwissADME* and *Toxtree*.

Instruments

The instrumentation utilized in this study comprises both hardware and software components. The hardware configuration consists of an Acer laptop (Device ID: DESKTOP-CBVPNL9) equipped with an Intel(R) Celeron(R) N4000 CPU @ 1.10 GHz and 4.00 GB of RAM. The software applications employed include *Windows* 10 Enterprise LTSC, *ChemDraw Ultra* version 22.0, *Chem3D Ultra* version 15.0, *VegaZZ* version 3.2.3.28, and *Toxtree* version 3.1.0.1851.

Materials

The materials utilized in this study consist of the 3D ligand structures of 70 active compounds from neem leaves (*Azadirachta indica*) retrieved from the following six journals:

Table 1. Seventy Active Compounds of Neem Leaves

No	Reference Source	Neem Leaf Compound
1	<i>Chemical Fingerprint of Azadirachta indica Unraveling the Bioactive Profil and Therapeutic Potential</i>	Azadirachtin, Nimbin, Nimbidinin, Carbazole, Quercetin, Kaempferol, Betulinic Acid, Chlorogenic Acid, Beta-sitosterol, Salannin, Hydroxymatairesinol, Azadirone, Luteolin, Terpeneol, Gedunin, Mahmoodin (4).
2	<i>Phytochemical Analysis, Antibacterial Activity, and GC-MS Characterization of Methanolic Extract of Azadirachta indica from Nuwakot, Nepal</i>	3E,5E,7E-6-methyl-8-(2,6,6-trimethyl-1-cyclohexenyl)-3,5,7-octatrien-2-one, dl- alpha-Tocopherol, Resorcinol, 2-p-mentha-1,8,-dien-3-yl-5-pentyl, Stigmasterol, 2H-1-Benzopyran-5-ol, 2- methyl-2-(4-methyl, gamma,-Sitosterol, 1,2-Benzenedicarboxylic acid, dioctyl ester, Octocrylene, Diethylhexylphthalate (5).
3	<i>Pharmacophoric Evaluation of Compounds Isolated from GC-MS Analytical Method of Aqueous Extract of Azadirachta indica (Neem)</i>	4-methylbenzaldehyde, 1-(2-hydroxy-5- methylphenyl) methylphenyl)ethan-1-one, 2,6-dimethoxyphenol, 2-methoxy-4-(prop-2-en -1-yl)phenol, (1S,2S)-1-ethenyl-1-methyl -4-propan-2-ylidene-2-prop- 1-en-2-ylcyclohexane, 4,4,7a-trimethyl-6, 7atetrahydro-4, 7-dihydro-5H-1-benzofuran-2-one, 1-ethenyl-1-methyl-2- (prop-1-en-2-yl)-4- (propan-2-ylidene) cyclohexane (6).
4	<i>Azadirachta indica leaf extract Phytochemical composition and antioxidant, antibacterial and antifungal activities</i>	Ascorbic acid, Catechin, Oleanolic Acid, Salicin, Beta carotene, Rutin, Curcumin, 8-hydroxyquinoline, Chrysin, Thymol (7).

5	<i>First Investigation of Phytochemical Screening, HPLC-MS Characterization, and Antibacterial Activity of Azadirachta indica A. Juss (Mim or Neem) Leaf Extract, Grown in the Republic of Chad.</i>	N, N-Dimethylaniline, Indole, Diethyl phthalate, Eugenol (2-Methoxy-4-(prop-2-en-1-yl) phenol), 2H-Benzocyclohepten-2-one, Isopulegol (5-methyl-2-(prop-1-en-2-yl) cyclohexan-1-ol), 2,3-Dihydro-benzofuran, Phenylacetic acid, 2-Methoxy-4-vinylphenol, Thiazole, 5-methyl-, Vanillin (4-Hydroxy-3-methoxy benzaldehyde), Carbofuran, 4-methyl-2,6-ditertiarybutylpheno, 2-Cyclohexen-1-one, 4-hydroxy-3,5,6-trimethyl-4-(3-oxo-1-butenyl), Hydromorphone, 4-(2,6,6-Trimethyl-2-cyclohexenyl)-3-buten-2-ol, 10-Bromo-7-hydroxy-11-iodolauren, Oxazepam, 1,2,4-Triazolo[4,3-a]pyridin-3(2H)-one, Aromadendrene, Hexamethylcyclotrisiloxane, 4,7-Dimethoxyisatin 1H-Indole-2,3-dione (8).
6	<i>Response Surface Methodology Based Extraction Optimization to Improve Pharmacological Properties and H NMR based Metabolite Profiling of Azadirachta indica</i>	Ferruginol, Meliatetraolenone, Odoratone, Nimonol, Nimbid acid, Epoxyazadiradione, Epicatechin (9).

Experimental Procedures

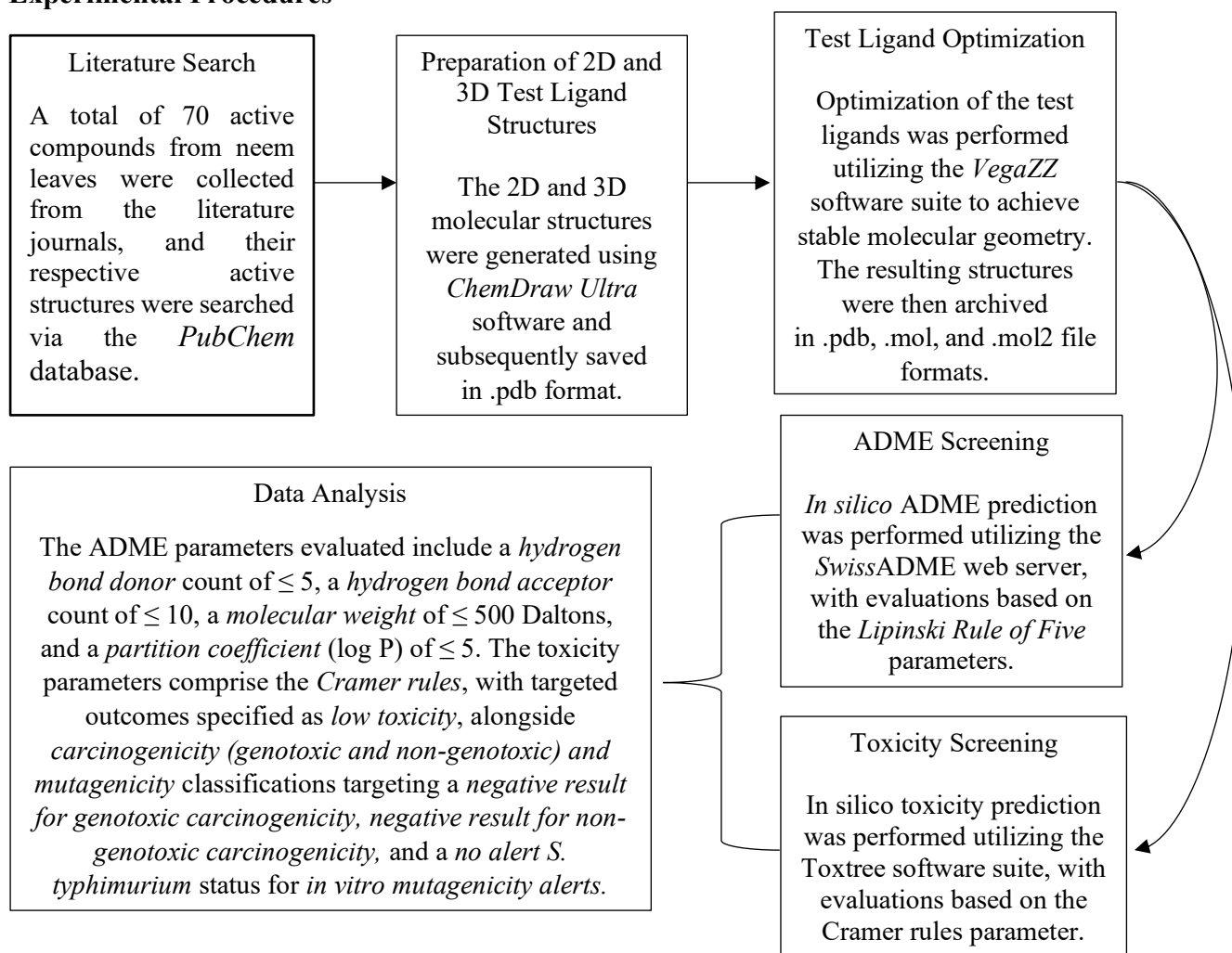


Figure 1. Research Protocol Workflow

Literature Search

Seventy active constituents of neem leaves (*Azadirachta indica*) were gathered from published literature, followed by a targeted retrieval of their molecular structures from the *PubChem* database.

Preparation of 2D and 3D Test Ligand Structures

Two-dimensional (2D) molecular structures of the 70 test ligands were constructed utilizing *ChemDraw Ultra* version 22.0. These structures were subsequently converted into three-dimensional (3D) models using *Chem3D Ultra* version 22.0 and archived in the Protein Data Bank (.pdb) file format. The 3D structures were further optimized using *VegaZZ* software by selecting *Calculate*, navigating to *ammp*, clicking *Minimization*, and saving the refined configurations in .pdb format (10).

Test Ligand Optimization

The 3D structures of the target compounds were opened using *VegaZZ* software, where hydrogen atoms were added by navigating to *Calculate* → *Charge & Pot*, selecting *Charges* → *Gasteiger*. The molecular charges were subsequently corrected by assigning partial charges using the *AutoDock force field*. Energy minimization was performed for 3,000 steps to achieve stable low-energy conformations by navigating to *Calculate* → *ammp*, clicking *Minimization*, setting the minimum steps to 3,000, tolerance to 1,000, and enabling the 'trust' parameter (√). The resulting optimized structures were archived in .pdb, .mol, and .mol2 formats (10).

In Silico ADME Screening

In silico pharmacokinetic screening was conducted via the *SwissADME* web server (<http://www.swissadme.ch>). The 2D molecular structures of the neem (*Azadirachta indica*) active constituents were imported into the molecular sketcher interface. The sketched structures were then transferred into the *SMILES* input list configured with one molecule per line alongside optional space-separated names by clicking the double-arrow button. Once the compound library array was ready, calculations were initiated by executing the 'Run' command (10).

In Silico Toxicity Screening

Toxicity profiles were predicted using the *Toxtree* software suite. The 2D molecular structure files of the target derivative compounds were loaded via *File* → *Open*. The specific evaluation metrics were selected by navigating to the Method menu, choosing the desired parameters, and executing the Estimate command. Calculated toxicity classifications were then generated in the Classification Area, while specific structural pathway details were reviewed using *Method* → *View Decision Tree*. The evaluation parameters comprised the *carcinogenicity* (*genotoxic and non-genotoxic*) and *mutagenicity rules based on ISS, the Cramer rules, and the in vitro mutagenicity (Ames test) alert by ISS* (10).

Data Analysis

The filtering of ADME predictions utilized *Lipinski's Rule of Five* to assess the *drug-likeness*, biological viability, and physicochemical properties of the chemical constituents. The evaluating parameters strict thresholds included a hydrogen bond donor count of ≤ 5 , a hydrogen bond acceptor count of ≤ 10 , a molecular weight of ≤ 500 Daltons, and a partition coefficient ($\log P$) of ≤ 5 (11). Toxicity evaluation prioritized profiles exhibiting *low toxicity* according to the *Cramer rules*, alongside *carcinogenicity* (*genotoxic and non-genotoxic*) and *mutagenicity* classifications targeting a *negative result for genotoxic carcinogenicity, negative result for non-genotoxic carcinogenicity*, and a *no alert S. typhimurium* status for *in vitro mutagenicity alerts*, establishing a functional group-dependent safety classification (12).

RESULTS

Preparation of 2D and 3D Test Ligand Structures

The Simplified Molecular Input Line Entry (SMILES) strings of the active constituents from neem leaves (*Azadirachta indica*) were retrieved from the *PubChem* database. Subsequently, two-dimensional (2D) structures were constructed using *ChemDraw Ultra* version 22.0, while three-dimensional (3D) structures were generated utilizing *ChemDraw 3D Ultra* version 22.0 and archived in the Protein Data Bank (.pdb) file format.

Test Ligand Optimization

The generated 3D test ligands were subsequently optimized using the *VegaZZ* software suite. This optimization process was performed to energetically stabilize the compounds, thereby refining and improving upon the baseline structural configurations.

ADME Prediction Results

Table 2. In Silico ADME Profiles of 70 Active Constituents from Neem Leaves

Parameter	Screening Criteria	Number of Compounds
molecular weight	≤ 500 g/mol	63
H-bond acceptors	≤ 10	69
H-bond donors	≤ 5	68
Log P	≤ 5	57
GI Absorption	Soluble	53
BBB Permeant	High	38
P-GP Substrate	No	52
CYP1A2 Inhibitor	No	55
CYP2C19 Inhibitor	No	58
CYP2C9 Inhibitor	No	47
CYP2D6 Inhibitor	No	67
Bioavailability score	≥ 0.55	64

Toxicity Prediction Results

Table 3. In Silico Toxicity Profiles of 70 Active Constituents from Neem Leaves

Parameter	Screening Criteria	Number of Compounds
Cramer Rules	Low (Class I)	20
	Intermediate (Class II)	2
	High (Class III)	48
Carcinogenicity and Mutagenicity	Structural alert for genotoxic carcinogenicity	26
	Structural Alert for nongenotoxic	4
	Negative for genotoxic carcinogenicity	44
in vitro mutagenicity	Negative for nongenotoxic carcinogenicity	66
	Structural alert for <i>S. typhimurium</i>	23
	mutagenicity	
	No alert for <i>S. typhimurium</i> mutagenicity	47

DISCUSSION

Preparation of 2D and 3D Test Ligand Structures

The molecular structures of the active constituents from neem leaves (*Azadirachta indica*) were retrieved from the *PubChem* database. Two-dimensional (2D) structural formulation was carried out using *ChemDraw Ultra* version 22.0, while three-dimensional (3D) spatial profiling was achieved using *ChemDraw 3D Ultra* version 22.0. The *ChemDraw* computational suite serves as a high-fidelity visualization tool, providing strict geometric accuracy during structural sketching (13). Given that 2D structural drafting dictates the baseline configuration for 3D generation, absolute structural precision is vital as errors directly propagate into the downstream 3D spatial conformation. Subsequently, the 2D sketches were converted into 3D models using *Chem3D* to yield accurate conformations and assess their drug-likeness potential; the resulting files were archived in the Protein Data Bank (.pdb) format (14).

Test Ligand Optimization

A total of 70 active compounds from neem leaves (*Azadirachta indica*) were processed as 3D starting structures. Every test ligand was subjected to geometric refinement using the *VegaZZ* software suite. Geometric optimization aims to minimize the total potential energy of the molecular systems, thereby establishing stable 3D low-energy conformations (15). Successful optimization was verified by structural changes toward stable thermodynamic states during the energy minimization protocol. Achieving stable conformations is vital to eliminate structural strain components within the molecular scaffolds (16).

In Silico ADME Profiling

Computational pharmacokinetic screening was carried out via the *SwissADME* web server across the 70 active constituents of neem leaves, utilizing *Lipinski's Rule of Five* parameters as summary values Table 2, *Molecular Weight* compounds displaying a molecular mass ≤ 500 Da. Align with previous findings (15), which suggest that low molecular weight accelerates structural penetration across biological barriers and improves human oral absorption. *Hydrogen Bond Dynamics* the *hydrogen bond donor* (HBD) and *hydrogen bond acceptor* (HBA) counts of the primary compounds conformed to *Lipinski's* boundaries ≤ 5 donors and ≤ 10 acceptors. This trend establishes an ideal balance between aqueous solubility and lipid membrane permeation. Conversely, molecules that violated these thresholds carried complex glycoside decorations rich in polar hydroxyl ($-\text{OH}$) moieties. *Lipophilicity* ($\log P$) lipophilic parameters strictly adhered to *Lipinski's* constraint ≤ 5 . According to literature models (17). Compounds exceeding this lipophilic ceiling carry an elevated risk of poor ADME attributes.

Gastrointestinal (GI) Absorption the compound library showed varied GI absorption rates (ranging from high to low), implying potential bioabsorption barriers in the digestive tract for certain structures. This depressed GI absorption is driven by the complex architecture of neem's limonoid and triterpenoid scaffolds, which present high molecular weights combined with a dense network of oxygenated and hydroxyl functional groups (17). *Blood-Brain Barrier (BBB) Permeation* a predominant "No" status was observed for BBB permeation, indicating that the compounds do not cross into the central nervous system. This significantly minimizes unintended central pharmacological interactions and mitigates potential neurotoxicity risks (18). *P-glycoprotein (P-gp) Substrate* compounds returning a "No" classification indicate they are not actively effluxed by the P-gp active transporter, thereby favoring favorable intestinal retention and systemic tissue distribution (19).

CYP1A2 a widespread "No" status shows negligible affinity toward this enzyme, suggesting a low probability of clinical drug-drug interactions and contributing to a more stable pharmacokinetic lifespan. CYP2C19 the lack of inhibitory action "No" means the compounds

do not interfere with this metabolic pathway, lowering the risk of metabolic disruptions when co-administered with other therapeutic agents (20). CYP2C9 returning a "No" status suggests that these compounds lack the weak acid affinities toward hydrogen-acceptor pockets typical of NSAID-like frameworks, which are processed during the hepatic oxidation of endogenous and xenobiotic compounds. CYP2D6 & CYP3A4 the absence of inhibition "No" across the majority of the compound library ensures a more predictable metabolic clearance pattern, offering a strong advantage for modern drug development by maintaining low metabolic interaction risks (21).

In Silico Toxicity Screening

Computational toxicology profiling of the 70 neem constituents was evaluated via the Toxtree suite using the Cramer rules system as summary benchmarks Table 3, *Cramer Rule Classification* compounds categorized with a "Low" (*Class I*) safety profile possess simple, non-reactive structural configurations that suggest high baseline safety margins (22). In contrast, those assigned to the "High" (*Class III*) tier present structural alerts indicating elevated safety risks (23). This aligns with established toxicology data (22), where Class III designations are driven by reactive functional groups within the molecular scaffold.

Carcinogenicity and Mutagenicity the presence of structural alerts indirectly points to potential carcinogenicity and tissue damage mediated through non-genotoxic mechanisms (12). Alternatively, a "Negative for genotoxic carcinogenicity" outcome indicates that the molecules do not cause DNA damage or genetic alterations that trigger oncogenesis (24). Concurrently, a "Negative for non-genotoxic carcinogenicity" status confirms a low risk of tumor induction via secondary biochemical pathways (25). *In Vitro Mutagenicity (Ames Test Alert)* molecules that triggered structural alerts in this category highlight specific functional groups capable of inducing genetic mutations (25). Conversely, a "No alert for *S. typhimurium* mutagenicity" result indicates a low probability of causing point mutations or nucleic acid damage, highlighting their safety for development as anti-obesity drug candidates (26).

CONCLUSION

In silico analysis using SwissADME and Toxtree of the 70 active constituents from neem leaves revealed that 51 compounds conformed to Lipinski's parameters. For the toxicity profiles, 20 compounds were categorized as 'Low' (*Class I*) according to the *Cramer rules*, 43 compounds exhibited *non-carcinogenic and non-mutagenic properties*, and 43 compounds showed *no structural alerts for in vitro mutagenicity*. Based on these screening outcomes, thymol, eugenol, isopulegol, phenylacetic acid, and 2-methoxy-4-vinylphenol demonstrated favorable ADME profiles that strictly adhere to Lipinski's Rule of Five, while displaying low toxicity along with a complete absence of carcinogenic and mutagenic properties.

Acknowledgments: The authors gratefully acknowledge the Directorate of Research, Technology, and Community Service (DRTPM), the Ministry of Education, Culture, Research, and Technology of the Republic of Indonesia, and the Institute for Research and Community Service (LPPM) of Universitas Duta Bangsa Surakarta for financially supporting this research through the Fiscal Year 2026 funding, under Contract Numbers: 042/LL6/AL.04.03/PL-BARU/2026 and 049/UDB.LPPM/A.34-HK/II/2026.

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