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COMPUTATIONAL EXPLORATION OF *ANNONA SENEGALENSIS* PHYTOCHEMICALS AS PROMISING ANTIVENIN AGENTS TARGETING SNAKE VENOM ENZYMES

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ABSTRACT

Snakebite envenomation poses a significant public health challenge, particularly in rural developing regions with limited access to effective antivenoms. Annona senegalensis, a plant revered in traditional medicine, is recognized for its potential antivenin properties. This study employs computational chemistry, utilizing tools such as AutoDock Vina, to investigate the phytochemicals of *A. senegalensis* for their ability to inhibit venom enzymes from Naja species. Twelve phytochemicals were screened using SwissADME for drug-likeness and Protox 3.0 for toxicity profiles. Molecular docking simulations identified three promising candidates; kaempferol (Lig4), caffeic acid (Lig6), and ellagic acid (Lig8) with superior binding affinities to key venom enzymes: Phospholipase A2 (Lig4: -7.1, Lig6: -7.1, Lig8: -7.4 kcal/mol), Metalloprotease (Lig4: -8.2, Lig6: -7.5, Lig8: -8.6 kcal/mol), and Serine Protease (Lig4: -8.5, Lig6: -6.9, Lig8: -6.9 kcal/mol), which drive venom-induced cytotoxicity and hemorrhage. These findings substantiate the traditional use of *A. senegalensis* in folk medicine and suggest its phytochemicals could serve as effective, accessible alternatives or complements to conventional antivenin therapies. Further *in-vivo* studies are recommended to validate these results and explore the therapeutic potential of *A. senegalensis* phytochemicals in snakebite management.

Keywords: *Annona senegalensis*, Antivenin, Molecular docking, Phytochemicals, Snake venom, Computational chemistry, Drug discovery, Traditional medicine

INTRODUCTION

Snakebite envenomation remains a significant public health challenge, particularly in rural regions of developing countries where access to conventional antivenom is often limited by cost, availability, and storage constraints (Gutiérrez *et al*., 2017; Pucca *et al*., 2019). Globally, snakebites result in an estimated 4.5–5.4 million cases annually, with 1.8–2.7 million leading to envenomation and up to 137,880 fatalities (Suhita, 2022). In Nigeria, species such as *Naja nigricollis* (black-necked spitting cobra), *Echis ocellatus* (carpet viper), and *Bitis arietans* (Puff adder) are major contributors to snakebite morbidity and mortality, primarily due to

their potent venom components, including Phospholipase A2 (PLA2), Metalloproteases (MMPs), and Serine Proteases (Ser-P) (Adeyi *et al*., 2024). These enzymes induce severe effects such as cytotoxicity, hemorrhage, and coagulopathy, necessitating urgent and effective interventions.

Conventional antivenom, derived from animal immunoglobulins, is the standard treatment for snakebite envenomation (Gamulin *et al*., 2023). However, its high cost, need for cold-chain storage, and potential for adverse reactions underscore the need for alternative or complementary therapies, particularly in resource-limited settings (Silva *et al*., 2021). Ethnomedicinal plants have long been used by traditional healers to manage snakebites, with many showing promising antivenin properties (Kumar *et al*., 2025). Among these, *Annona senegalensis* Pers. (Annonaceae), a shrub widely distributed across tropical Africa, has gained attention for its reputed efficacy against snake venom (Adzu *et al*., 2005). Known locally as "gwandardaajii" (Hausa) and "arere" (Yoruba), its leaves, bark, and roots are traditionally used to treat snakebites and other ailments, attributed to its rich phytochemical composition, including flavonoids, acetogenins, and phenolic compounds (Jada *et al*., 2014).

Previous studies have demonstrated that *A. senegalensis* extracts can inhibit venom-induced hemolytic, proteolytic, and phospholipase activities, reducing lethality in animal models (Sene *et al*. 2018). However, the specific phytochemicals responsible for these effects and their mechanisms of action remain underexplored. Advances in computational chemistry, particularly molecular docking, offer a powerful approach to identify and evaluate potential antivenin agents by simulating their interactions with venom enzymes (Ballante & Marshall, 2018). This study aims to screen the phytochemicals of *A. senegalensis* for their antivenin potential against *Naja* species venom, focusing on their ability to inhibit key enzymes (PLA2, MMPs, and Ser-P). By validating traditional claims through *in-silico* methods, we seek to provide a foundation for developing accessible and effective snakebite treatments.

MATERIALS AND METHODS

Materials

This study utilized computational tools and databases to investigate the antivenin potential of *Annona senegalensis* phytochemicals. Software included AutoDock Vina (Trott & Olson, 2009) for molecular docking, UCSF Chimera (Pettersen *et al*., 2004) for structure visualization, Spartan 14 for ligand optimization, ChemDraw Ultra 12 for structure design, and Biovia Discovery Studio 2021 Client for interaction analysis. SwissADME (http://www.swissadme.ch) and Protox 3.0 (https://tox.charite.de/protox3) were used for drug-likeness and toxicity profiling. High-resolution crystal structures of venom enzymes; Phospholipase A2 (PDB ID: 3NJU), Metalloprotease (PDB ID: 2W15), and Serine Protease (PDB ID: 3SBK) were retrieved from the RCSB Protein Data Bank (http://www.rcsb.org/pdb). Computations were performed on an HP Windows system with an Intel Core i7 processor.

Ligand Selection and Preparation

Twelve phytochemicals from *A. senegalensis* such as asimicin, squamocin, quercetin, kaempferol, chlorogenic acid, caffeic acid, gallic acid, ellagic acid, β-sitosterol, stigmasterol, triterpenoid, and steroidal were selected based on literature reports of their bioactivity (Jada *et al*., 2014; Yisa *et al*., 2010). Their 2D structures were

drawn using ChemDraw, converted to 3D using Spartan 14, and geometrically optimized via the AM1 semi-empirical method. Optimized structures were saved as mol2 files, with hydrogen atoms and Gasteiger charges added using AutoDock Tools, then converted to pdbqt format for docking (Pettersen *et al*., 2004).

Protein Preparation

Crystal structures of the target enzymes were downloaded from the Protein Data Bank. Non-essential components, including water molecules, ions, and co-crystallized ligands, were removed using UCSF Chimera version 1.19. The co-crystallized ligands were extracted, saved as Lig.mol files, and receptors were saved as rec.pdb files. Polar hydrogens and Gasteiger charges were added to both ligands and receptors using AutoDock Tools, and files were converted to pdbqt format.

Drug-Likeness and Toxicity Screening

The phytochemicals were screened for drug-likeness using SWISS ADME, applying Lipinski's Rule of Five (molecular weight ≤ 500 g/mol, MLogP ≤ 5, hydrogen bond donors ≤ 5, hydrogen bond acceptors ≤ 10, rotatable bonds ≤ 10) to evaluate oral bioavailability (Lipinski *et al*., 2001). Toxicity profiles, including LD_{50} values and toxicity classes, were predicted using Protox 3.0 to identify compounds with favorable safety profiles.

Molecular Docking

Molecular docking was performed using AutoDock Vina with exhaustiveness uniformly set to 8 for all docking simulations, with enzymes treated as rigid receptors and ligands as flexible. The docking protocol was validated by re-docking co-crystallized ligands to ensure superimposable conformations with their original structures as shown in Table 3 (De Oliveira *et al*., 2013). Grid box parameters for each enzyme were set as follows: PLA2 (3NJU: 8×20×10 Å, center: -5.791, -10.571, -1.962); MMP (2W15: 30×28×24 Å, center: 10.427, 12.857, 21.129); Ser-P (3SBK: 26×24×28 Å, center: 1.007, -33.636, -7.247). The Grid box sizes were adjusted for each enzyme based on structural analysis to ensure that the entire active site and all catalytic residues were fully encompassed. Each phytochemical was docked against the active sites of the three enzymes, and binding energies (kcal/mol) were calculated. Interactions were analyzed using UCSF Chimera and Biovia Discovery Studio to identify key hydrogen bonds, van der Waals forces, and pi-interactions.

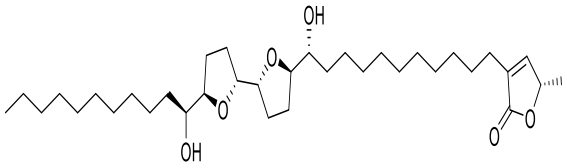
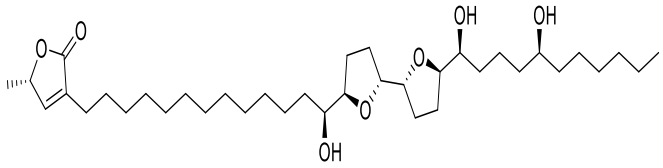
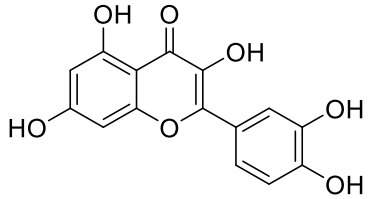
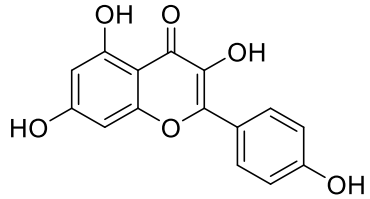
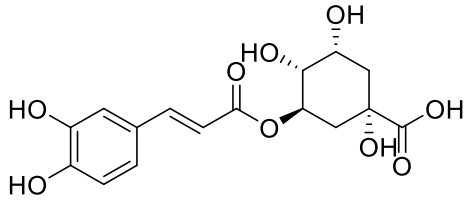
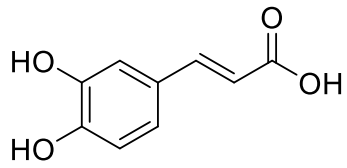
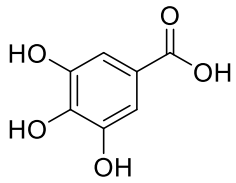
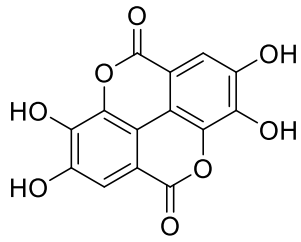
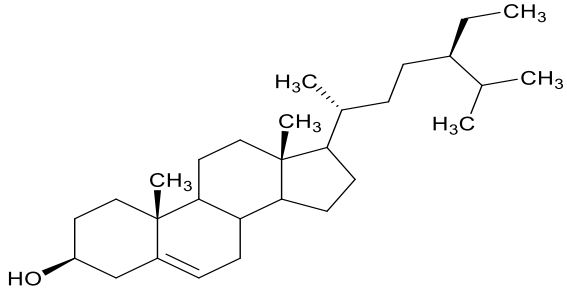
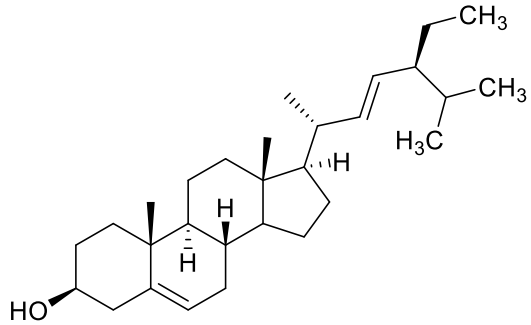
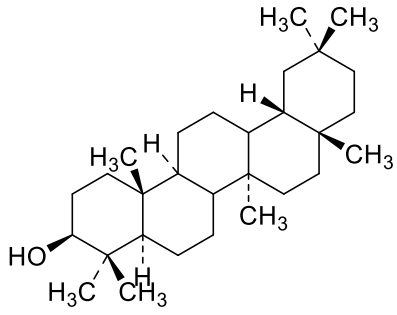
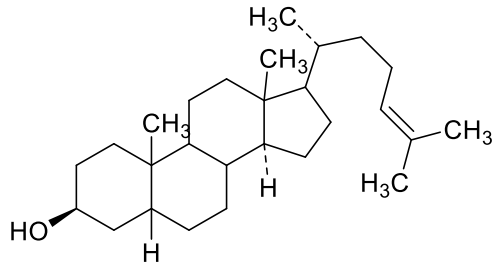
Post Dock Data Analysis

Compounds were ranked based on binding affinities compared to co-crystallized ligands (ANN for PLA2, WR2 for MMP, OG6 for Ser-P). Ligands with higher binding affinities and favorable interactions with critical residues were prioritized as potential antivenin candidates. Results were visualized in 2D and 3D to elucidate binding modes and interaction patterns.

RESULTS AND DISCUSSION

The chemical structures of the phytochemical constituents from Annona senegalensis are shown in Table 1.

Table 1: Chemical structure of the phytochemicals from *Annona senegalensis*

 Lig1	 Lig2
 Lig3	 Lig4
 Lig5	 Lig6
 Lig7	 Lig8
 Lig9	 Lig10
 Lig11	 Lig12

Chemical structures of phytochemicals from *Annona senegalesis*; lig1, lig2, lig3, lig4, lig5, lig6, lig7, lig8, lig9, lig10, lig11, lig12 are Asimicin, squamocin, quercetin, kaempferol, chlorogenic acid, caffeic acid, gallic acid, ellagic acid, β-sitosterol, Stigmasterol, triterpenoid and steroidal respectively.

The drug-likeness screening based on Lipinski's Rule of Five highlighted that Lig4 (kaempferol), Lig6 (caffeic acid), and Lig8 (ellagic acid) possess favorable physicochemical properties, with molecular weights, lipophilicity, and hydrogen bonding within acceptable ranges, suggesting good oral bioavailability (Lipinski *et al*., 2001). Toxicity predictions further supported their safety, with LD_{50} values indicating low to moderate toxicity (e.g., 3919 mg/kg for Lig4, 2980 mg/kg for Lig6, 2991 mg/kg for Lig8) as shown in Table 2, aligning with their potential as therapeutic agents. In contrast, other phytochemicals like asimicin (Lig1) and β-sitosterol (Lig9) were screened out due to high molecular weights or unfavorable lipophilicity, underscoring the selectivity of the computational approach.

Table 2: Analysis of theoretical oral bioavailability of the phytochemicals from *Annona senegalesis* based on Lipinski rule of five and GI absorption

Compound ID	Lipinski rule of five								
	Mol.wt	**HbA**	**HbD**	**MLogP**	**Lipinski violations**	**GI**	**BA**	**LD_{50} (mg/kg)**	**Toxicity Class**
Lig1	578.86	6	2	4.26	1	Low	0.55	11210	6
Lig2	622.92	7	3	3.81	1	Low	0.55	11210	6
Lig3	302.24	7	5	-0.56	0	High	0.55	159	3
Lig4	286.24	6	4	-0.03	0	High	0.55	3919	5
Lig5	354.31	9	6	-1.05	1	Low	0.11	5000	5
Lig6	180.16	4	3	0.7	0	High	0.56	2980	5
Lig7	170.12	5	4	-0.16	0	High	0.56	2000	4
Lig8	302.19	8	4	0.14	0	High	0.55	2991	4
Lig9	414.71	1	1	6.73	1	Low	0.55	890	4
Lig10	412.69	1	1	6.62	1	Low	0.55	890	4
Lig11	414.71	1	1	6.88	1	Low	0.55	940	4
Lig12	386.65	1	1	6.34	1	Low	0.55	3450	5

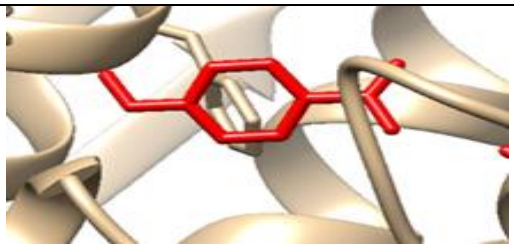
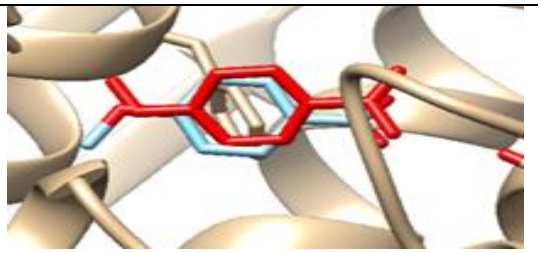
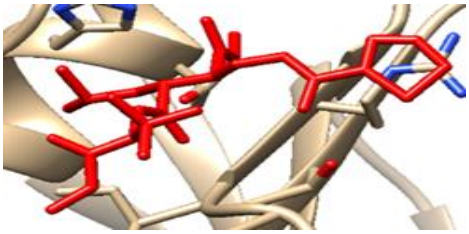
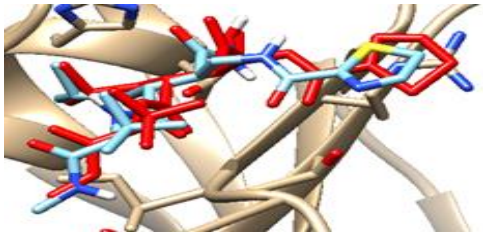
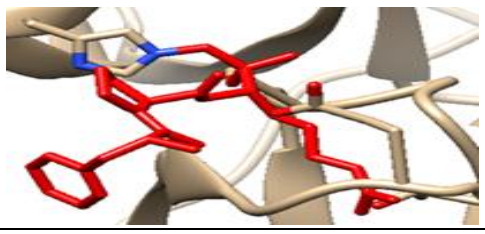
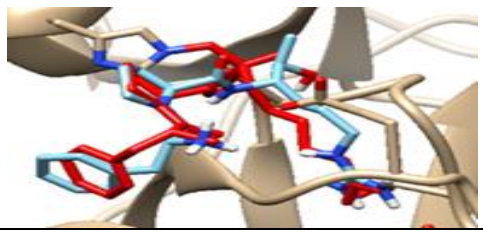
Mol.wt=Molecular weight in g/mol, HbA=Hydrogen bond acceptor, HbD=Hydrogen bond donor, GI=Gastrointestinal, [BA=Bioavailability; (probability of oral F > 10% based on polar surface area and Rule-of-Five criteria; Martin, 2005)], [(Mwt ≤ 500, MLogP ≤ 5, N or O ≤ 10 and NH or OH ≤ 5) Lipinski *et al*.,2001]

The virtual screening of *Annona senegalensis* phytochemicals revealed significant potential for their use as antivenin agents, supporting the plant's traditional application in snakebite management. The study focused on twelve phytochemicals, with three, kaempferol (Lig4), caffeic acid (Lig6), and ellagic acid (Lig8), emerging as promising candidates due to their superior binding affinities to venom enzymes Phospholipase A2 (PLA2), Metalloprotease (MMP), and Serine Protease (Ser-P). This enhanced binding may be attributed to their multiple hydroxyl groups and planar aromatic rings, which facilitate extensive hydrogen bonding and other stabilizing interactions with key active site residues. These enzymes are critical mediators of venom-induced cytotoxicity, hemorrhage, and coagulopathy, making their inhibition a key therapeutic strategy (Gutiérrez *et al*., 2017; Oliveira *et al*., 2022).

For PLA2 (PDB: 3NJU), Lig4, Lig6, and Lig8 exhibited binding energies of -7.1, -7.1, and -7.4 kcal/mol, respectively, surpassing the native ligand ANN (-6.0 kcal/mol) as shown in Table 4. These ligands formed robust interactions, including conventional hydrogen bonds with residues like ASP49, CYS45, and HIS48, and van der Waals interactions with TRP19 and TYR64 (Table 5 and Figure 1-3), which are essential for inhibiting PLA2's activity, thereby preventing the hydrolysis of phospholipids and subsequent generation of lysophospholipids and arachidonic acid, which are responsible for membrane disruption, inflammation, and myonecrosis (Gutiérrez *et al*., 2017). Notably, Lig8's stronger binding affinity suggests it may effectively stabilize the enzyme-ligand complex, potentially neutralizing PLA2's cytotoxic effects more efficiently than the native ligand.

In the case of MMP (PDB: 2W15), Lig4, Lig6, and Lig8 showed binding energies of -8.2, -7.5, and -8.6 kcal/mol, respectively, compared to WR2's -7.7 kcal/mol (native ligand) as shown in Table 4. Lig8 demonstrated the highest affinity, forming hydrogen bonds with ASN106 and pi-alkyl interactions with ILE108 as shown in Table 5 and Figure 4-6, which likely interfere with MMP's hydrolysis of basement membrane components like type IV collagen, a key factor in venom-induced tissue damage (Escalante *et al*., 2006). These interactions indicate that *A. senegalensis* phytochemicals could mitigate hemorrhage and microvascular damage, addressing a major clinical challenge in snakebite envenomation.

Table 3: The crystal structure of enzymes complexes and re-docked ligand super-imposed on the crystal structure for Validation

ENZYMES	Crystal structure complex (Enzyme and ligands)	Crystal structure complex with Re-docked ligand (validation)
3NJU		
2W15		
3SBK		

Cyano-blue colour molecule is the re-docked ligand and the red colour molecule is the co-crystallized ligand.

Table 4: The binding energies and binding interaction of phytochemicals from *Annona senegalesis* against Phospholipase A2, Metalloprotease and serine protease

Ligands	Binding Energies in Kcal/mol		
	Phospholipase A2 (3NJU)	Metalloproteinase (2W15)	Serine Protease (3SBK)
Lig0	-6.0	-7.7	-8.8
Lig1	-3.5	-5.5	-6.2
Lig2	-0.6	-4.8	-5.6
Lig3	-7.1	-8.5	-8.9
Lig4	-7.1	-8.2	-8.5
Lig5	-5.9	-7.1	-7.4
Lig6	-7.1	-7.5	-6.9
Lig7	-6.0	-6.6	-7.1
Lig8	-7.4	-8.6	-6.9
Lig9	-2.1	-6.4	-6.9
Lig10	-2.6	-7.1	-7.5
Lig11	10.7	-6.9	-8.6
Lig12	-0.9	-7.1	-7.5

Lig0= are the co-crystallized or native ligands for the enzymes, where ANN for Phospholipase A2, WR2 for Metalloproteinase and OG6 for Serine protease and

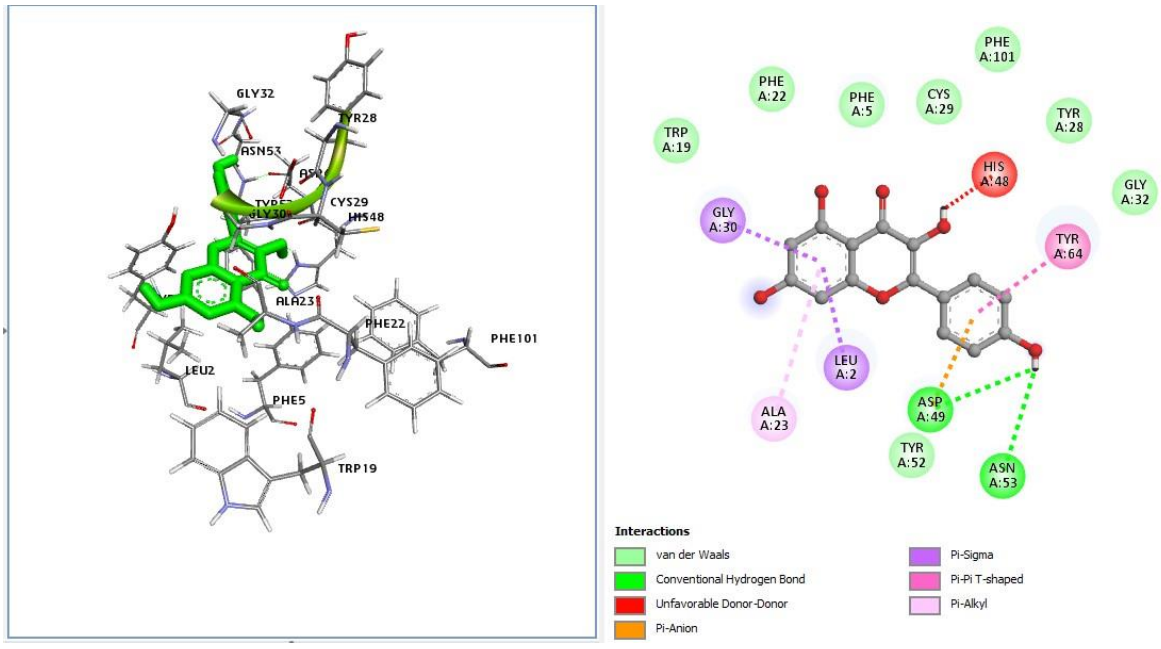


Figure 1: 3D and 2D Protein-ligand binding pose interaction of lig4 in relation to the active site of Phospholipase A2

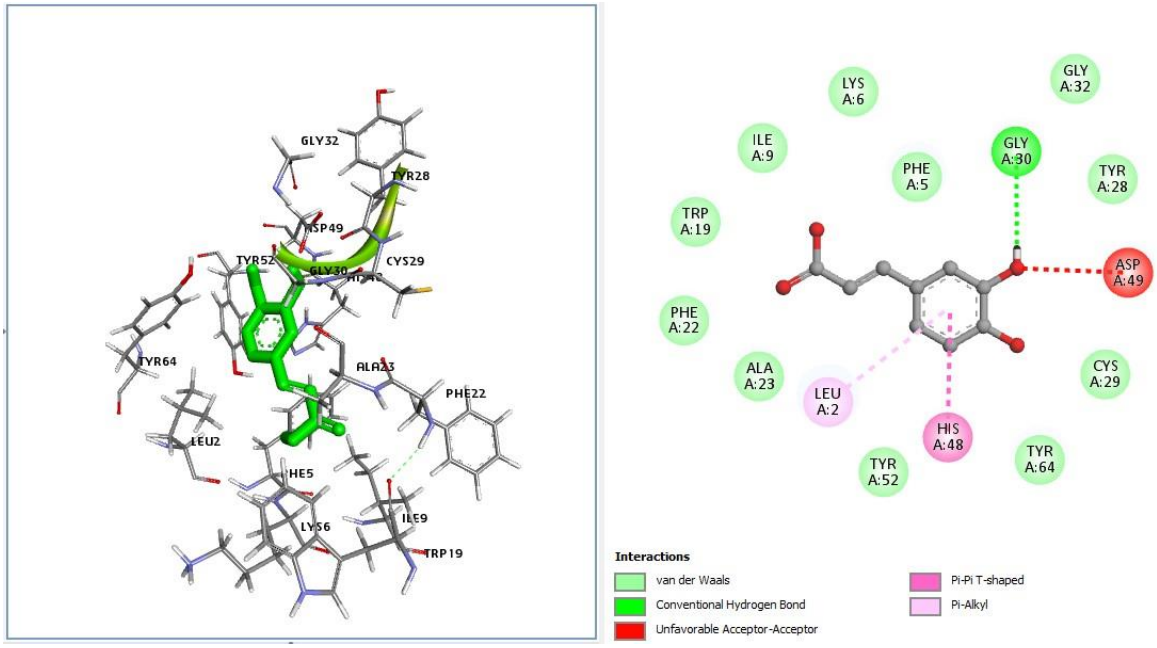


Figure 2: 3D and 2D Protein-ligand binding pose interaction of lig6 in relation to the active site of Phospholipase A2

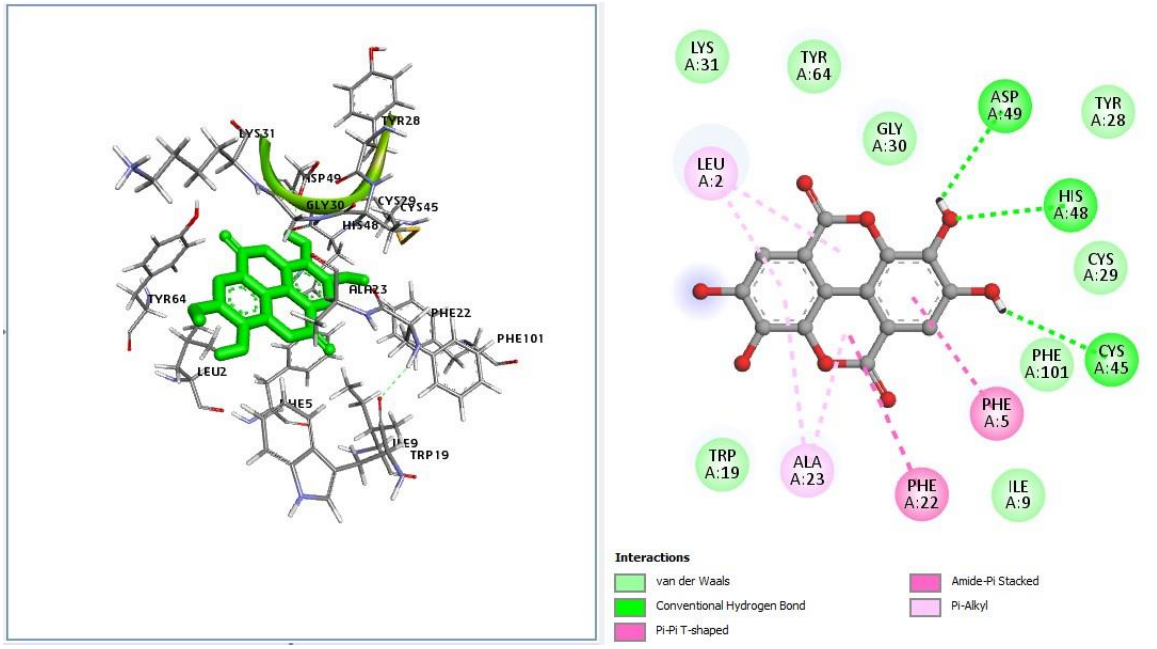


Figure 3: 3D and 2D Protein-ligand binding pose interaction of lig8 in relation to the active site of Phospholipase A2

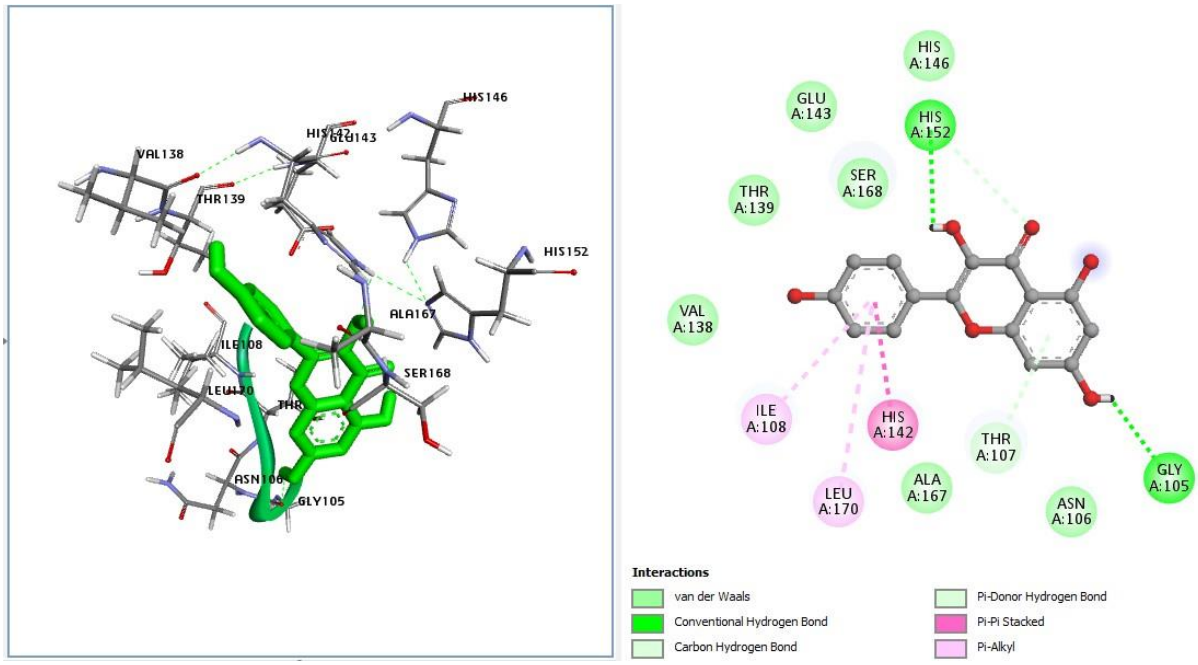


Figure 4: 3D and 2D Protein-ligand binding pose interaction of lig4 in relation to the active site of Metalloprotease

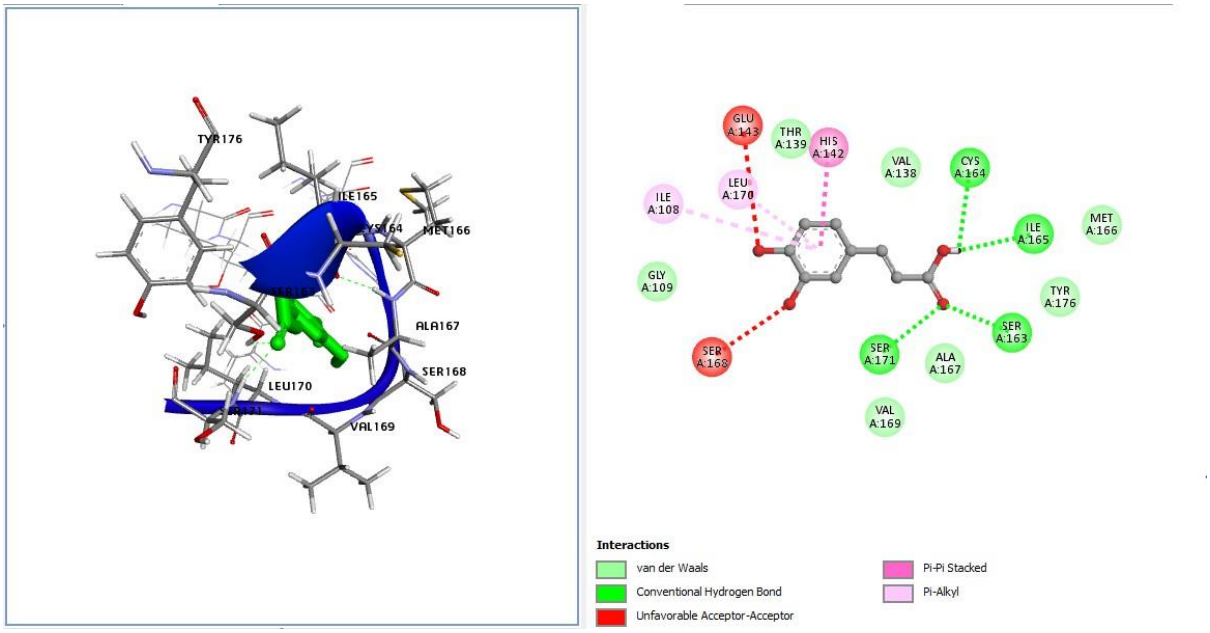


Figure 5: 3D and 2D Protein-ligand binding pose interaction of lig6 in relation to the active site of Metalloprotease

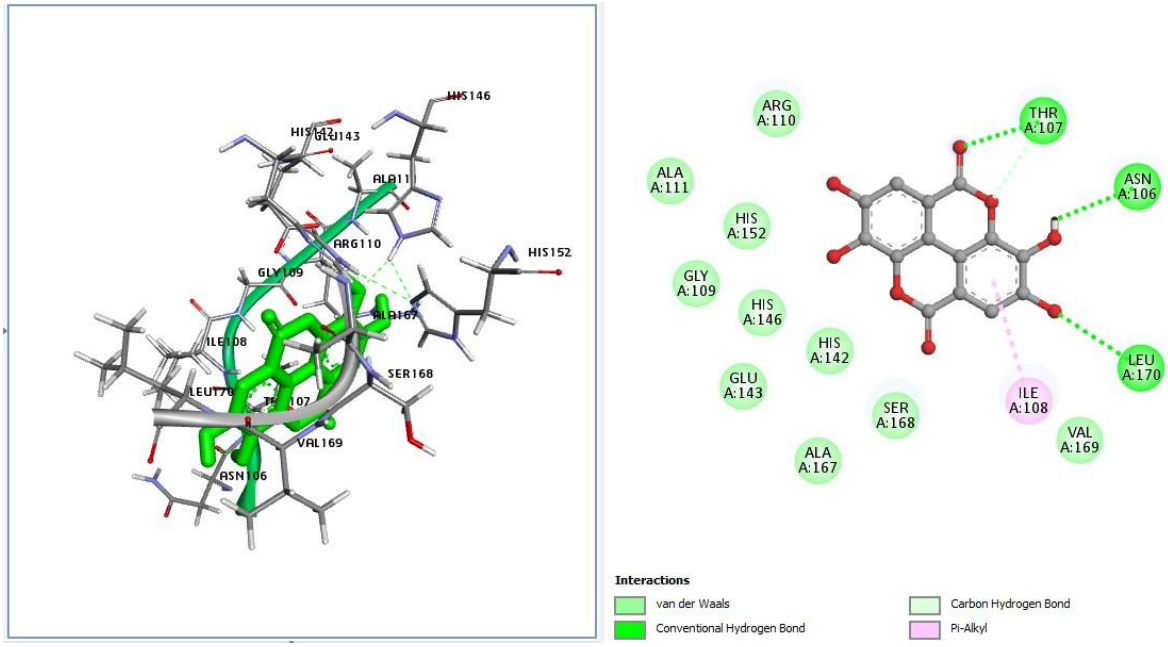


Figure 6: 3D and 2D Protein-ligand binding pose interaction of lig8 in relation to the active site of Metalloprotease

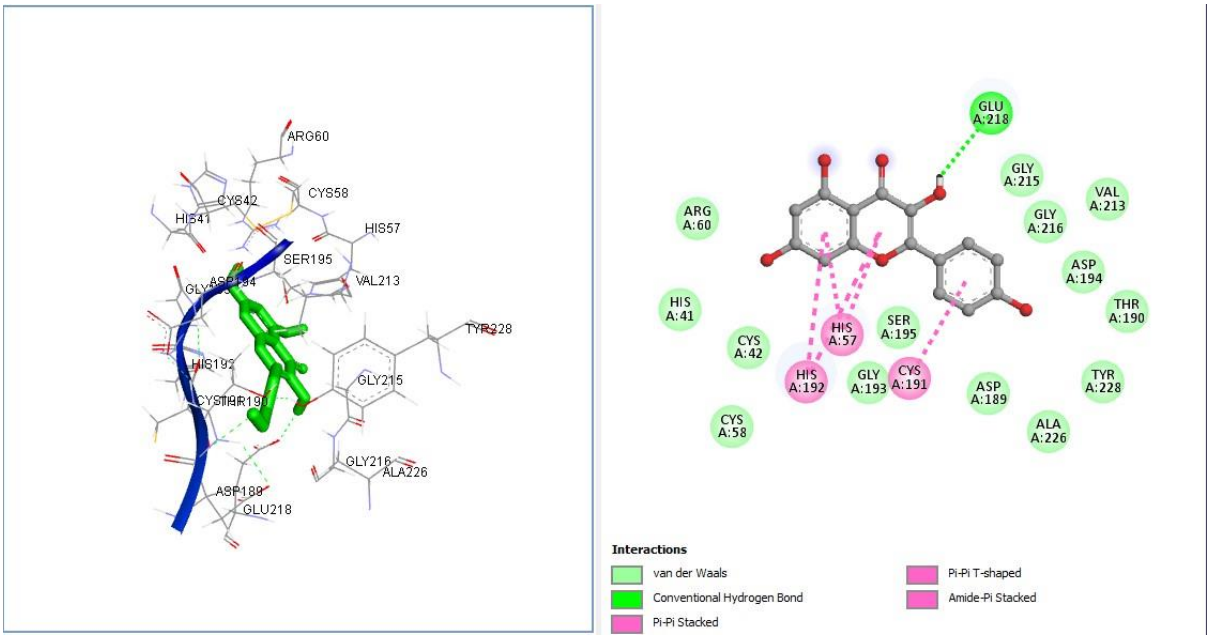


Figure 7: 3D and 2D Protein-ligand binding pose interaction of lig4 in relation to the active site of Serine protease

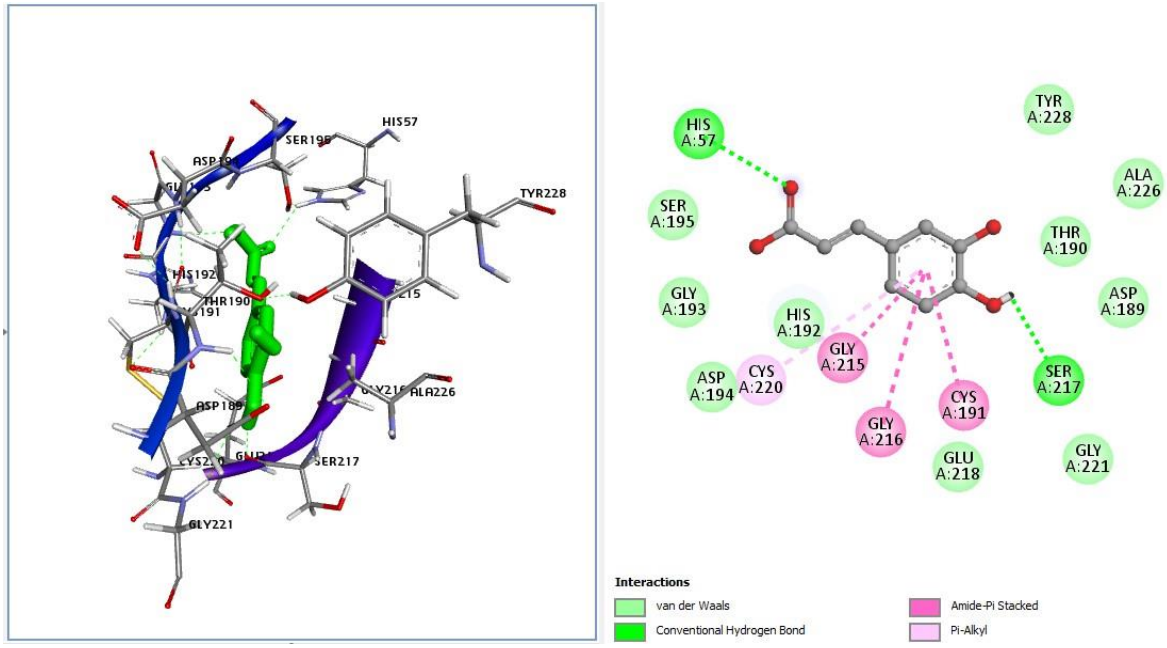


Figure 8: 3D and 2D Protein-ligand binding pose interaction of lig6 in relation to the active site of Serine Protease

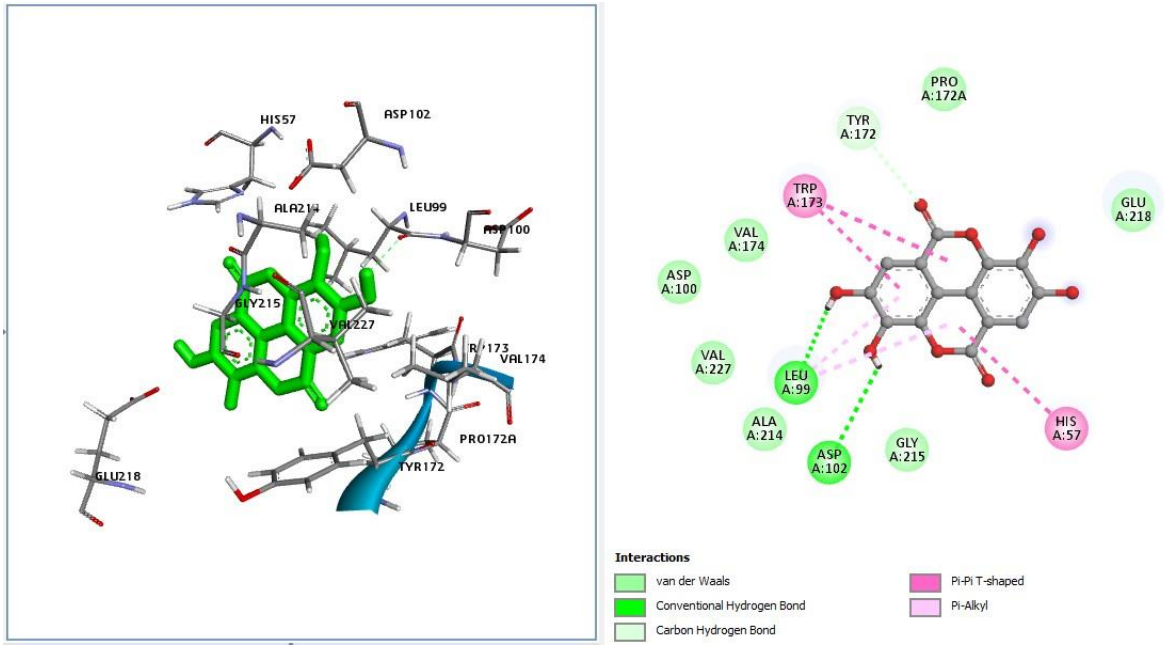


Figure 9: 3D and 2D Protein-ligand binding pose interaction of lig8 in relation to the active site of Serine Protease

For Ser-P (PDB: 3SBK), Lig4 achieved a binding energy of -8.5 kcal/mol, closely approaching the native ligand OG6's -8.8 kcal/mol, while Lig6 and Lig8 recorded -6.9 kcal/mol each as shown in Table5. Lig4's interactions, including hydrogen bonds with GLU218 and pi-pi stacking with HIS192 as shown in fig 7-9, suggest its potential to disrupt Ser-P's haemotoxic effects, such as coagulopathy and fibrinolysis (Kini, 2006).

Although Lig6 and Lig8 showed lower affinities, their interactions with residues like HIS57 and SER217 indicate complementary roles in stabilizing the enzyme-ligand complex.

Table 5: Binding Energies and interactions bond types of the best performing Phytochemical compounds (Lig4, Lig6, Lig8) and respective co-crystallized ligand

PDB ID	Ligands	Binding affinity (Kcal/mol)	Residues involved in bond interactions
3NJU	ANN	-6.0	Hydrogen Bond: GLY30, TYR64 Hydrophobic: PHE5, ILE9, LYS6, LEU2, TRP19, ALA23, ASP49, CYS29, HIS48, PHE22, TYR28
	Lig4	-7.1	Hydrogen Bond:ASP49, ASN53 Hydrophobic: ASP49, GLY30, LEU2, TYR64, ALA23, CYS29, GLY32, PHE5, PHE22, PHE101, TYR19, TYR19
	Lig6	-7.1	Hydrogen Bond: GLY30 Hydrophobic: HIS48, ALA23, ASP49, CYS29, GLY32, ILE9, PHE5, PHE22, TYR19, TYR28, TYR52, TYR64
	Lig8	-7.4	Hydrogen Bond: ASP49, CYS45, HIS48. Hydrophobic: ALA23, PHE22, PHE5, ALA23, LEU2, CYS29, GLY30, ILE9, LYS31, PHE101, TRP19, TYR28, TYR64
2W15	WR2	-7.7	Hydrogen Bond: ASN106, SER168, GLY109, GLU143, ILE108, LEU170, THR107 Hydrophobic: ARG110, ALA167, GLY105, HIS142, HIS146, HIS152, SER71, THR139, VAL169
	Lig4	-8.2	Hydrogen Bond: HIS152, GLY105, HIS152, THR107 Hydrophobic: HIS142, ILE108, LEU170, ALA167, ASN106, GLU143, GLY105, HIS146, SER168, THR106, THR139, VAL138
	Lig6	-7.5	Hydrogen Bond: CYS164, ILE165, SER163, SER171 Hydrophobic: HIS142, ILE108, LEU170, ALA167, GLY109, MET166, THR139, THR176, VAL138, VAL169
	Lig8	-8.6	Hydrogen Bond: THR107, ASN106, LEU170, THR107 Hydrophobic: ILE108, ALA111, ALA167, ARG110, GLY109, GLU143, HIS142, HIS146, HIS152, SER168, VAL169
3SBK	OG6	-8.8	Hydrogen Bond: ALA214, GLY215, ALA214, ASP189, CYS220, GLU218, GLY193, GLY216,

		GLY218, SER195, SER217, THR190 Hydrophobic: GLY215, GLY216, VAL227, ALA226, ASP194, CYS191, GLY221, HIS57, HIS192, TRP173, TYR172, TYR228, VAL174
Lig4	-8.5	Hydrogen Bond: GLU218 Hydrophobic: HIS192, HIS57, CYS191, HIS192, ALA226, ARG60, ASP189, ASP194, CYS42, CY58, GLY193, GLY215, GLY216, SER195, HIS41, THR190, TYR228, VAL213
Lig6	-6.9	Hydrogen Bond: HIS57, SER217 Hydrophobic: CYS191, GLY215, GLY216, HIS192, SER217 Pi-Alkyl: CYS220, ALA226, ASP189, ASP194, GLU218, GLY193, GLY221, HIS192, SER195, THR190, THR228
Lig8	-6.9	Hydrogen Bond: TYR172, ASP102, LEU99 Hydrophobic: HIS57, TRP173, LEU99, ALA214, ASP100, GLU218, GLY218, PRO172 VAL174, VAL214

ANN, WR2 and OG6 are the co-crystallized ligands for the respective enzyme

These findings align with previous studies demonstrating *A. senegalensis*'s antivenin properties. For instance, Sene *et al*., (2018) reported that its extract reduced *N. nigricollis* venom lethality, likely due to flavonoids and phenolic compounds like those identified in this study. The current study advances this knowledge by pinpointing specific phytochemicals and their molecular interactions, offering a mechanistic basis for their efficacy. Compared to conventional antivenoms, which require complex production and storage (Adeyi *et al*., 2023), these phytochemicals could provide a cost-effective, accessible alternative, particularly for rural communities where snakebites are prevalent.

However, limitations of this *in-silico* study include the reliance on static docking models, which may not fully capture the dynamic behavior of ligand-enzyme interactions. Additionally, while the selected phytochemicals show promise, their efficacy and safety require validation through *in-vitro* and *in-vivo* experiments. Future research should focus on molecular dynamics simulations to explore complex stability and clinical trials to confirm therapeutic potential, ensuring alignment with traditional uses and modern pharmacological standards.

This study provides preliminary computational evidence for the antivenin potential of Annona senegalensis phytochemicals, validating its traditional use in snakebite treatment through computational analysis. Among the twelve compounds screened, kaempferol (Lig4), caffeic acid (Lig6), and ellagic acid (Lig8) demonstrated superior binding affinities to venom enzymes Phospholipase A2, Metalloprotease, and Serine Protease, while other compounds, such as Lig11 with PLA2 (3NJU), showed weak or no binding, indicating selective inhibitory potential. The enhanced interactions of the top candidates appear to stem from key structural features, including multiple hydroxyl groups and planar aromatic rings, which facilitate

hydrogen bonding and other stabilizing interactions with critical active site residues. These phytochemicals also exhibited favorable drug-likeness and low toxicity profiles, positioning them as promising candidates for developing accessible antivenin therapies. By bridging ethnomedicine and modern computational chemistry, this work underscores the value of natural products in addressing global health challenges like snakebite envenomation. Further experimental validation is essential to translate these findings into practical treatments, offering hope for improved snakebite management in resource-limited settings.

References

Adeyi, A.O., Ajisebiola, B.S., Sanni, A.A. *et al*. Kaempferol mitigates reproductive dysfunctions induced by Naja nigricollis venom through antioxidant system and anti-inflammatory response in male rats. *Sci Rep* 14, 3933 (2024). https://doi.org/10.1038/s41598-024-54523-w

Adzu B, Abubakar MS, Izebe KS, Akumka DD and Gamaniel KS (2005). Effect of *Annona senegalensis* root bark extracts on *Naja nigricotlis* nigricotlis venom in rats. *Journal of Ethnopharmacology* 96: 507–513.

Ballante, F., & Marshall, G. R. (2016). An automated strategy for binding-pose selection and docking assessment in structure-based drug design. *Journal of Chemical Information and Modeling*, *56*(1), 54-72.

De Oliveira, M. E., Cenzi, G., Nunes, R. R., Andrighetti, C. R., De Sousa Valadao, D. M., Dos Reis, C., Simoes, C. M. O., Nunes, R. J., Júnior, M. C., Taranto, A. G., Sanchez, B. A. M., Viana, G. H. R., & De Pilla Varotti, F. (2013). Antimalarial activity of 4-metoxychalcones: docking studies as falcipain/plasmepsin inhibitors, ADMET and lipophilic efficiency analysis to identify a putative oral lead candidate. *Molecules* (Basel, Switzerland), 18(12), 15276–15287. https://doi.org/10.3390/MOLECULES181215276

Escalante, T., Shannon, J., Moura-da-Silva, A. M., Gutiérrez, J. M., & Fox, J. W. (2006). Novel insights into capillary vessel basement membrane damage by snake venom hemorrhagic metalloproteinases: a biochemical and immunohistochemical study. *Archives of biochemistry and biophysics*, *455*(2), 144-153.

Gamulin, E., Mateljak Lukačević, S., Halassy, B., & Kurtović, T. (2023). Snake Antivenoms-Toward Better Understanding of the Administration Route. *Toxins*, 15(6), 398. https://doi.org/10.3390/toxins15060398

Gutiérrez, J. M., Calvete, J. J., Habib, A. G., Harrison, R. A., Williams, D. J., & Warrell, D. A. (2017). Snakebite envenoming. *Nature reviews Disease primers*, *3*(1), 1-21.

Jada M, Usman W and Adamu Y (2014). *In vitro* Antimicrobial effect of Crude Tannins Isolated from the Leaf of *Annona senegalensis*. *Int. J Biochem Res Rev* 4(6):615623.

Kini, R. M. (2006). Serine proteases affecting blood coagulation and fibrinolysis from snake venoms. *Pathophysiology of haemostasis and thrombosis*, *34*(4-5), 200-204.

Kumar A, Banjara RA, Aneshwari RK, Khan J and Bernarde PS (2025) A comprehensive review on recent advances in the use of ethnomedicinal plants and their metabolites in snake bite treatment. *Front. Pharmacol.* 16:1548929. doi: 10.3389/fphar.2025.1548929

Lipinski, C. A. (2001). Avoiding investment in doomed drugs. *Curr Drug Discov*, 1, 17–19.

Martin, Y. C. (2005). A bioavailability score. *Journal of Medicinal Chemistry*, 48(9), 3164–3170. https://doi.org/10.1021/JM0492002

Oliveira, A. L., Viegas, M. F., da Silva, S. L., Soares, A. M., Ramos, M. J., & Fernandes, P. A. (2022). The chemistry of snake venom and its medicinal potential. *Nature Reviews Chemistry*, *6*(7), 451-469.

Pettersen, E. F., Goddard, T. D., Huang, C. C., Couch, G. S., Greenblatt, D. M., Meng, E. C., & Ferrin, T. E. (2004). UCSF Chimera - A visualization system for exploratory research and analysis. *Journal of Computational Chemistry*, 25(13), 1605–1612. https://doi.org/10.1002/jcc.20084

Pucca, M. B., Cerni, F. A., Janke, R., Bermúdez-Méndez, E., Ledsgaard, L., Barbosa, J. E., & Laustsen, A. H. (2019). History of envenoming therapy and current perspectives. *Frontiers in immunology*, *10*, 1598.

Sene, M., F. S. Barboza, A. Ndong, A. Sarr, A. Wele, E. Bassene, and G. Y. SY. 2018. "Phospholipase A2 Inhibition and Antiinflammatory Activity of F4

Fraction of Total Ethereal Leaf Extract of *Annona Senegalensis* Pers. (Annonaceae)." *European Journal of Medicinal Plants* 26(2):1–9. doi:10.9734/EJMP/2018/45788.

Silva, G. M. D., Berto, D. H., Lima, C. A. D., Waitman, K. D. B., Lima, C. F. G. D., Prezoto, B. C., ... & Andrade, S. A. (2021). Synergistic effect of serine protease inhibitors and a bothropic antivenom in reducing local hemorrhage and coagulopathy caused by Bothrops jararaca venom. *Toxicon*, *199*, 87-93.

Suhita, R., Begum, I., Rashid, M., Chandran, V. P., Shastri, S. A., Kantamneni, R., Rajan, A. K., & Thunga, G. (2022). Systematic review and meta-analysis of global prevalence of neurotoxic and hemotoxic snakebite envenomation. *Eastern Mediterranean health journal*, 28(12), 909–916. https://doi.org/10.26719/emhj.22.090

Trott, O., & Olson, A. J. (2010). AutoDock Vina: Improving the speed and accuracy of docking with a new scoring function, efficient optimization and multithreading. *Journal of Computational Chemistry*, 455–461. https://doi.org/10.1002/jcc.21334

Yisa, J., Egila, J. N., & Darlinton, A. O. (2010). Chemical composition of Annona senegalensis from Nupe land, Nigeria. *African Journal of Biotechnology*, *9*(26), 4106-4109.