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Original Research Article

Homology Modelling and Molecular Docking of Some Natural Compounds as Inhibitors of *Anopheles gambiae* Heat Shock Protein 70KDa and Bifunctional Glutamyl/prolyl-tRNA Synthetase

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ABSTRACT

Malaria has remained a global concern, primarily caused by *Plasmodium falciparum*, which is transmitted through the bite of female *Anopheline* mosquitoes. Although several insecticides have been developed to target the vector, resistance to currently available insecticides necessitate the development of novel, natural insecticides with little or no negative impact on the ecosystem towards the eradication of malaria. Natural product-derived compounds have shown promising effects in combating the disease-carrying vector. Homology modeling of the *Anopheles gambiae* (*A. gambiae*) heat shock protein 70KDa (*Ag*HSP70KDa) and bifunctional glutamyl/prolyl-tRNA synthetase (*Ag*EPRS) was carried out using the SWISSMODEL server, and the generated 3-dimensional (3D) structures were refined using the Chiron webserver for energy minimization. The structures were further validated using PROCHECK to verify and validate the 3D conformation. The top five compounds based on binding affinity, were then subjected to ADME-Tox profiling using SwissADME and ORISIS. The docking results reveal that compounds, particularly sesamin (-7.4 kcal/mol) exhibited a better binding affinity for *Ag*EPRS compared to the control, halofuginone, which showed a binding affinity of -6.4 kcal/mol. Additionally, sesamin showed superior affinity of -5.5 kcal/mol against *Ag*HSP70KDa when compared to the control geldanamycin, which had a binding affinity of -4.9 kcal/mol. However, violacein (control) demonstrated a stronger affinity of -5.6 kcal/mol for *Ag*HSP70KDa compared to sesamin. Violacein and sesamin form unique interactions with specific amino acids and engage with the active sites of *Ag*HSP70KDa and *Ag*EPRS through a range of bonds, including hydrogen bonds, Pi-Alkyl contacts, and Pi-Cation/Anion interactions. The research highlights the potential of natural compounds to act as potent inhibitors against *A. gambiae* proteins. Further biological validation of these compounds against *Ag*HSP70KDa and *Ag*EPRS is essential. This will ultimately contribute to the development of novel, target-specific insecticides against *A. gambiae*.

***Keywords*:** Insecticide resistance; Inhibitors, *Anopheles gambiae*, Molecular docking, Homology modelling; Malaria

Introduction

Malaria is a very devastating disease caused by Plasmodium falciparum, which is transmitted via the bite of a female *Anopheline mosquito*. Despite significant global efforts in malaria control and management, the disease continues to have a devastating impact. In 2022, the World Health Organisation (WHO) reported approximately 249 million cases and 608,000 deaths globally. Malaria incidence and mortality are particularly prevalent in sub-Saharan Africa, with Nigeria accounting for 26.8% of the global burden cases.[1] Various strategies, such as indoor residual spraying and the widespread use of insecticide-treated nets, have been deployed to control malaria vectors.

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However, the emergence and spread of resistance to insecticides have severely undermined these efforts.[2,3]

This growing resistance necessitates the exploration of alternative insecticidal to effectively target the mosquito vectors responsible for malaria transmission.[4,5]

Natural compounds have shown promise as alternative insecticides, with several exhibiting both insecticidal and larvicidal activity against *A. gambiae*, the primary vector of *P. falciparum*. Studies have identified compounds such as neral, geranial, mentha-2,8-dienol, carveol, piperitone, citronellal, citronellol, isopulegol, p-cymene, 1,8-cineole, ascaridodole,[6] caryophyllene, sesamin, and pellitorine[7] as having significant insecticidal effects against *A. gambiae*. These findings support the selection of natural compounds for further investigation in this study.

Among potential insecticidal target, *Ag*HSP70KDa and *Ag*EPRS have emerged as promising candidates.[8] While molecular docking have been conducted on heat shock proteins[9] and members of the aminoacyl-tRNA synthetase family,[10] no studies have yet focused on *Ag*HSP70KDa or *Ag*EPRS. Despite limited research on *Ag*EPRS, it has been observed to be up-regulated in *A. gambiae* in response to *E. coli* infection.[11] Moreover, certain aminoacyl-t-RNA synthetase have implicated in insecticide resistance.[10] Heat shock proteins, including *Ag*HSP70KDa,

are known to be induced upon exposure to high doses of insecticides and have been linked to stress tolerance mechanisms. *Ag*HSP70KDa, in particular, functions as a molecular chaperone involved in protein folding and the repair of proteins damaged by insecticide-induced stress.[12,13] Additionally, *Ag*HSP70KDa has been shown to be overexpressed in mosquitoes exposed to pyrethroids,[14] and plays a role in reducing stress induced apoptosis alongside its chaperone activity.[15] This study employed comparative homology modelling to predict the 3D structures of *Ag*HSP70KDa and *Ag*EPRS using SWISS-MODEL. Molecular docking and post-docking analyses were performed using PyRx and Discovery Studio 2021 to evaluate the binding affinities of natural compounds obtained from seven plant species.[41] The interactions between the targets proteins and the compounds were assessed to determine the most stable protein-ligand complexes. Additionally, the ADME and toxicity profile of the potential inhibitors were evaluated to predict their bioavailability and safety. While the findings of this study provide valuable insights into the potential of inhibitory effects of natural compounds on *Ag*HSP70KDa and *Ag*EPRS, further experimental validation is required. It is important to note that *in silico* approaches, while informative, may not fully predict the in vivo efficacy and safety of these compounds. Therefore, additional biological studies are required to confirm their effectiveness as insecticides and their specific interactions with the target proteins.

Materials and Methods

The two proteins investigated in this study, *Ag*HSP70KDa and *Ag*EPRS, were identified in our previous research, which explored insecticide resistance mechanisms in *A. gambiae*.[8] For the first time, these proteins were linked to resistance against currently existing insecticides in *A. gambiae*, highlighting their potential as novel molecular targets for insecticidal intervention.

Homology Modelling

The protein IDs for *Ag*HSP70KDa and *Ag*EPRS (accession number A7UT42 and Q7PRA2, respectively) were retrieved from the UniProt Knowledgebase (UniProtKB)[16] and submitted to the SWISS-MODEL[17] server to generate the 3D structure for the proteins. SWISS-MODEL automatically searches for suitable templates and generates protein 3D structures using a list of generated templates. A total of 1,981 templates were retrieved and filtered using a heuristic algorithm to 50. The 50 templates were then automatically used to generate 10 models. The models were sorted based on their global model quality estimate (GMQE) values, with model with the highest GMQE selected for further analysis. GMQE values range between 0 and 1, where models with GMQE values closer to 1 are considered of high quality.

Structure Refinement and Validation

The obtained models were further refined using the Chiron web-base server.[18] Chiron is a server for protein energy minimization that utilizes discreet molecular dynamics to minimise steric clashes in proteins. Therefore, the models were individually uploaded to the Chiron server, and all parameters were set to default for the structure refinement. Afterward, the models were uploaded to the PROCHECK[19] server to check and validate the quality of the predicted 3D structure of the model. The Ramachandran plots and their statistics were obtained to assess the quality of the models in terms of the distribution of amino acids in different key regions. The 3D structure was further validated to determine how compatible the structure is with its own amino acids and other well-established structures.

Molecular Docking and Post-Screening Analyses

The chemical compounds and inhibitors used in this study were obtained from two previous studies that evaluated the insecticidal effect of different plant extracts against *A. gambiae*. For the first eleven chemical compounds in Table 1, essential oils from nine plants were extracted using hydrodistillation, and the chemical composition of the extracts was determined using GC-MS with the Agilent 6890 GC Plus automatic sampler system.[6] The remaining compounds were isolated from the bark of *Zanthoxylum heitzi*. The stem bark of *Zanthoxylum heitzi* was extracted using hexane, and the major chemical compounds were extracted by fractionation. Furthermore, the compounds were identified by NMR spectroscopy.[7] The compound CIDs were retrieved from the PubChem[20] database for further analysis. Molecular docking was performed using the virtual screening software PyRx.[21] The grid box dimension for *Ag*EPRS was set at 25 Å, 25 Å, 25 Å, and the grid box centre at (X = 4.014), (Y = -1.7731), (Z = 1.4202 Å), while the grid box dimension for *Ag*HSP70KDa was set at 25 Å, 25 Å, 25 Å, and the grid box centre at (X = -0.2219), (Y = -4.9567 Å), (Z = -3.1661 Å). Post-docking analyses were conducted using the Discovery Studio 2021 client.[22] Halofuginone[23] was used as a control for *Ag*EPRS due to its known ability to inhibit aminoacyl-tRNA synthetase, such as prolyl-tRNA synthetase, while violacein and geldanamycin were employed as controls for *Ag*HSP70KDa due to their efficacy in inhibiting HSP 90KDa.[24]

ADME-Tox and Toxicity Risk Assessment

The SMILES specification for the top 5 compounds with the best binding affinity was retrieved from the PubChem database, and ADME-Tox profiling was conducted using swissADME.[25] The estimated solubility (Log S (ESOL)), topological polar surface area (TPSA), and octanol/water partition coefficient (Log Po/w (iLOGP)) were considered as predictors. ESOL is an important factor since solubility is a major factor that influences absorption. The TPSA profile correlates strongly with absorption and the blood-brain barrier permeability.[26] The iLOGP is a crucial pharmacokinetic factor, important for evaluating the fate of chemicals in the environment.[27] The Lipinski, Veber, Egan, and Muegge rules were taken into consideration. Additionally, the compounds were assessed using ORISIS property explorer[28] to evaluate the toxicity risk associated with each compound. The mutagenic, tumorigenic, irritant, and reproductive effects of the compound were analysed.

Statistical Analysis

The binding affinities data's distribution was assessed for normality using the Shapiro-Wilk test. Principal component analysis (PCA) of the ligand properties was conducted to identify variability in the data and determine the ligand property with the most significant impact. The analysis was conducted for *Ag*EPRS and *Ag*HSP70KD using Excel's XLSTAT.[38]

Table 1: The fourteen chemical compound and the plant species they were obtained from.

S/No	Plants	Compounds
1	*Cymbopogon citratus*	Neral, Geranial
2	*Cymbopogon giganteus*	Mentha-2,8-dienol, Carveol
3	*Cymbopogon schoenanthus*	Piperitone
4	*Eucalyptus citriodora*	Citronellal, Citronellol, Isopulegol
5	*Eucalyptus tereticornis*	p -Cymene, 1,8-Cineole
6	*Chenopodium ambrosioides*	Ascaridole
7	*Zanthoxylum heitzii*	Caryophyllene, Sesamin, Pellitorine

Results and Discussion

Homology Modelling and Model Analysis

*Ag*HSP70KDa had GMQE values, sequence identity, and sequence similarity of 0.86, 79.95%, and 0.55, while *Ag*EPRS had 0.36, 99.73%, and 0.62 (Table 2). The high GMQE value of *Ag*HSP70KDa shows that the model is of good quality. It indicates good structural reliability, aligning with previous studies on homologous proteins where GMQE values close to one were considered robust for drug design applications.[29] This suggest that *Ag*HSP70KDa could be a reliable target for further structural studies and therapeutic development. On the other hand, the lower GMQE value of *Ag*EPRS can be attributed to partial sequence coverage which has been shown to affect the accuracy of structural predictions;[17] Only 0.41 (41%) of the *Ag*EPRS was covered compared to *Ag*HSP70KDa, with a total coverage of 1.0 (100%). Further studies could address this by using multiple templates or utilizing other techniques to improve the coverage.

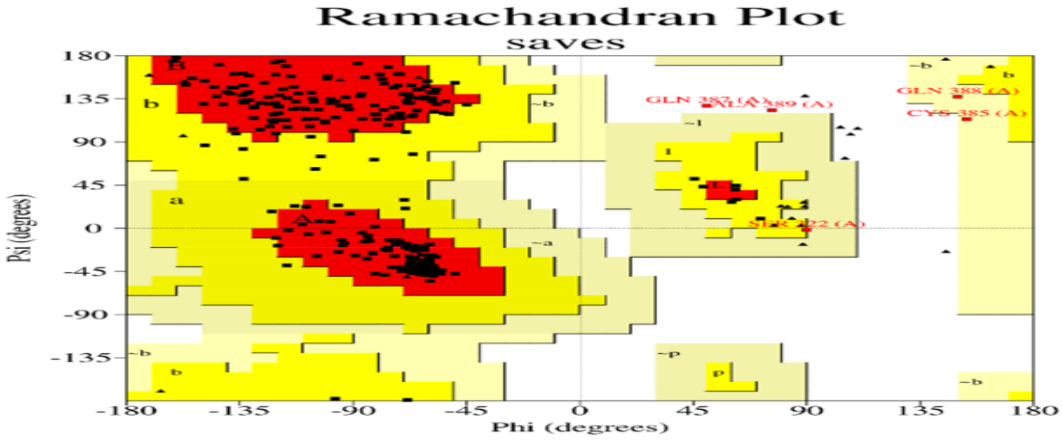
Structure Refinement and Validation

The 3D structure was refined using the Chiron web server to minimize steric clashes between proteins within the 3D structure of the generated models.[18] The Ramachandran plots for the 3D structures were obtained from PROCHEK. From the results obtained, 91.1% and 92.7% of the amino acid residues for *Ag*HSP70KDa and *Ag*EPRS, respectively, were in the preferred favoured region. Meanwhile, 7.5% and 6.2% were in the additionally allowed region, 0.8% and 0.9% were in the generously favoured region, and 0.6% and 0.2% were in the disallowed region (Figures 1A and 1B). The result obtained from the Ramachandran plot validation align with previous studies where over 90% of amino acid residues in the preferred region is considered ideal.[30] The validation of these structures increases their potential applications in drug design and development. Moreover, the low percentage of residues in the disallowed region indicates that steric clashes were effectively minimized.[31]

Molecular Docking and Binding Affinity Analysis

Tables 3A and 3B summarizes the molecular docking data for fourteen compounds, with geldanamycin and violacein serving as controls for *Ag*HSP70KDa, while halofuginone served as control for *Ag*EPRS. Molecular docking analysis was conducted to identify the optimal binding conformations of the target proteins with the selected inhibitors.[32] The results indicate that most compounds exhibited strong affinity for both *Ag*HSP70KDa and *Ag*EPRS, with affinities ranging from -7.4 kcal/mol to -2.9 kcal/mol (Tables 3A and 3B). The highest binding affinity was observed for sesamin with *Ag*EPRS and for violacein (control) with *Ag*HSP70KDa, yielding binding scores of -7.4 kcal/mol and -5.6 kcal/mol, respectively. These binding affinities highlight the potential of these compounds in modulating protein function. While violacein demonstrated superior binding to *Ag*HSP70KDa compared to other selected compounds, sesamin also dispalyed significant binding affinity, affirming its potency as reported by Moussavi.[7] For *Ag*EPRS, sesamin exhibited a stronger binding affinity than halofuginone (control), which had a binding affinity of -7.4 kcal/mol. Additionally, halofuginone, pellitorine, and carveol showed binding affinities of -6.4 kcal/mol, -5.2 kcal/mol, and -5.0 kcal/mol for *Ag*EPRS, while geldanamycin, caryophyllene, and ascaridole exhibited binding affinities of -4.9 kcal/mol, -4.0 kcal/mol, and -3.9 kcal/mol, respectively, for *Ag*HSP70KDa. Among the top five inhibitors, sesamin and caryophyllene demonstrated favourable to both proteins. Figures 2 and 3 illustrate the 2D and 3D representations of the interaction complex formed between *Ag*HSP70KDa and *Ag*EPRS with the top five compounds, highlighting the various interactions within these complexes. Other studies have reported that sesamin and violacein possess strong insecticidal activities, as inferred by their binding affinities.[33,34] The strong binding affinity of sesamin for *Ag*EPRS, even surpassing that of known inhibitor halofuginone, suggests that sesamin may offer a novel mode of action. Similarly, the high affinity of violacein for *Ag*HSP70KDa emphasises its potential as a heat shock protein inhibitor.

A



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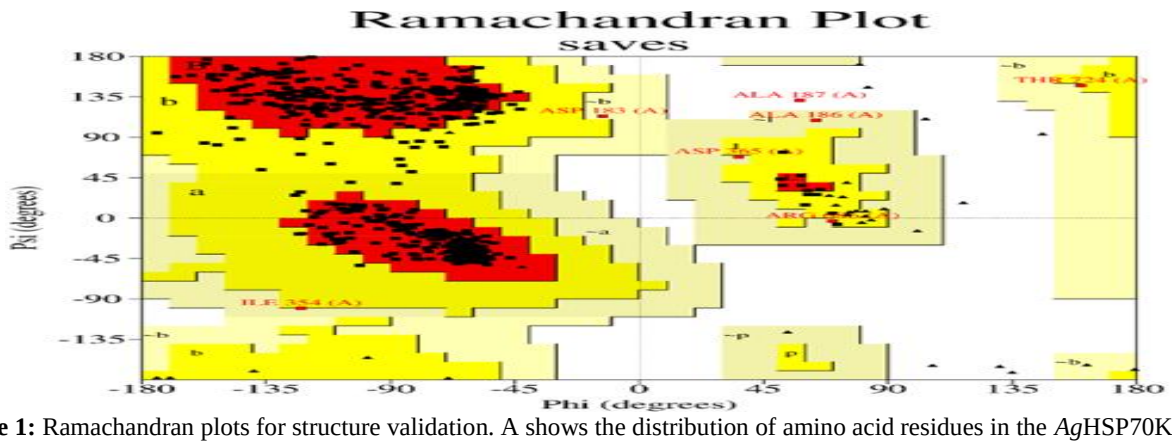

Figure 1: Ramachandran plots for structure validation. A shows the distribution of amino acid residues in the *Ag*HSP70KDa 3D structure, and B shows the distribution of amino acid residues in the 3D structure of *Ag*EPRS.

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Table 2: Ramachandran plot statistics

Regions	*Ag*HSP70KDa	*Ag*EPRS
Favored	91.1	92.7
Additionally allowed	7.5	6.2
Generously allowed	0.8	0.9
Disallowed	0.6	0.2

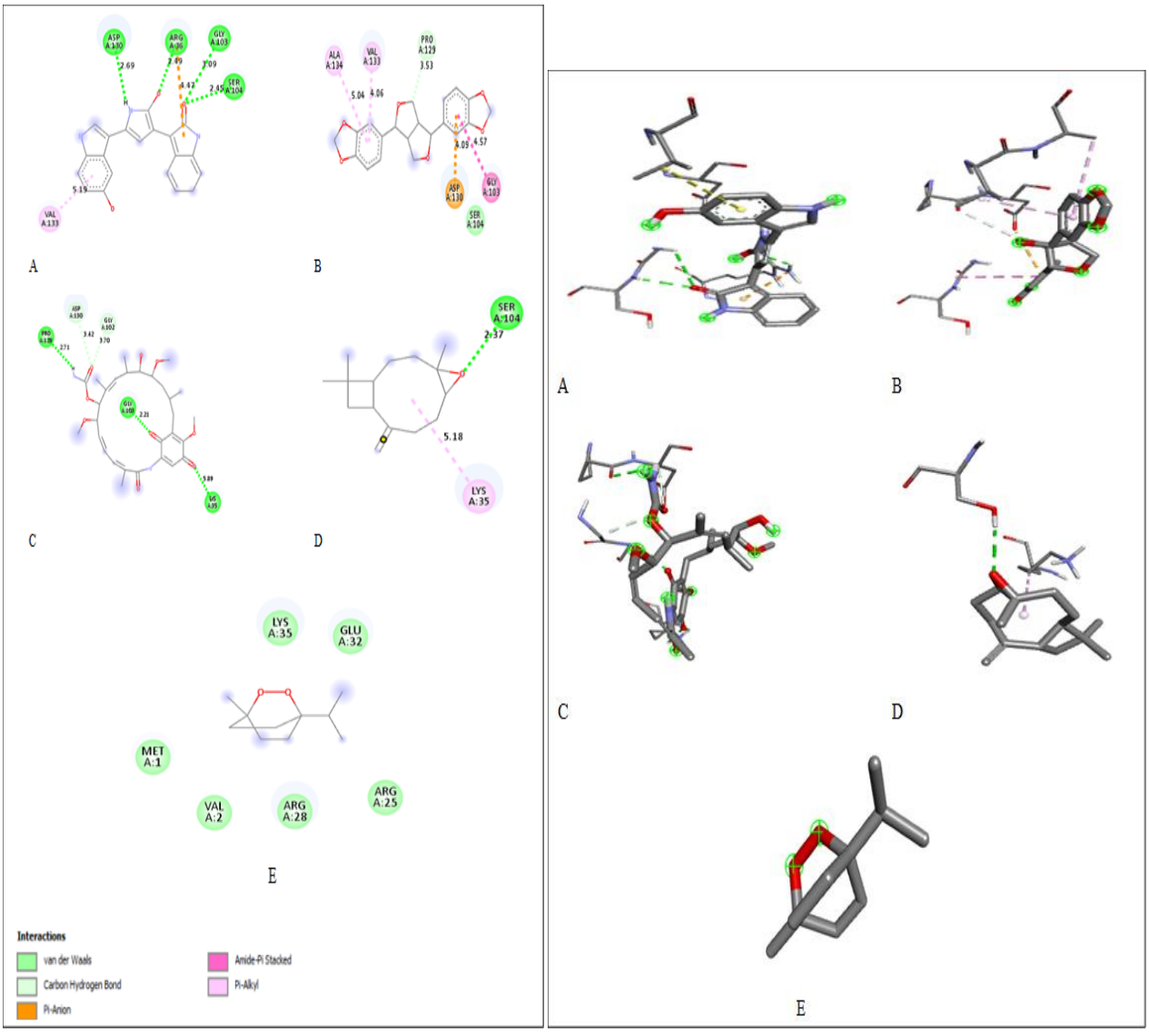

Figure 2: Docking interaction complex. I. 2D docked view complex of the top five compounds for *Ag*HSP70KDa. A; violacein, B; sesamin, C; geldanamycin, D; caryophyllene, E; ascaridole. II. 3D docked view complex of the top five compounds for *Ag*HSP70KDa. A; violacein, B; sesamin, C; geldanamycin, D; caryophyllene, E; ascaridole.

Table 3A: Binding affinity for *Ag*HSP70KDa inhibitors

Ligand	PubChem ID	Binding Affinity (kcal/mol)
Violacein	11053	-5.6
Sesamin	72307	-5.5
Geldanamycin	5288382	-4.9
Caryophyllene	1742210	-4.0

Ascaridole	10545	-3.9
p-Mentha-2,8-dienol	155626	-3.6
Pellitorine	5318516	-3.5
Geranial	638011	-3.4
Carveol	7438	-3.4
Isopulegol	24585	-3.3
p-Cymene	7463	-3.3
Citronellol	8842	-3.3
1,8-Cineole	2758	-3.2
Piperitone	6987	-3.2
Citronellal	7794	-3.0
Neral	643779	-2.9

Table 3B: Binding affinity for *Ag*EPRS inhibitors

Ligand	PubChem ID	Binding Affinity (kcal/mol)
Sesamin	72307	-7.4
Halofuginone	400772	-6.4
Caryophyllene	1742210	-5.2
Pellitorine	5318516	-5.2
Carveol	7438	-5.0
Ascaridole	10545	-4.8
Geranial	638011	-4.8
p-Mentha-2,8-dienol	155626	-4.7
Isopulegol	24585	-4.7
Neral	643779	-4.6
p-Cymene	7463	-4.5
Citronellol	8842	-4.5
Citronellal	7794	-4.4
Piperitone	6987	-4.3
1,8-Cineole	2758	-3.9

Interaction Analysis of Top Compounds

The top five compounds interacted with the amino acids in the active site of *Ag*HSP70KDa as follows: violacein formed conventional hydrogen bonds with ASP130, ARG36, GLY103, and SER104, pi-alkyl interactions with VAL133, and pi-cation interactions with ARG36. Sesamin establised van der Waals interactions with SER104, carbon-hydrogen bonds with PRO129, pi-anion interactions with ASP130, amide-pi-stacked interactions with GLY103, and pi-alkyl interactions with VAL133 and ALA134. Geldanamycin formed a conventional hydrogen bond with PRO129, GLY103, and LYS35, as well as a carbon-hydrogen bond with ASP130 and GLY102. Caryophyllene interacted through conventional hydrogen bonds with SER104 and an alkyl interaction with LYS35. Ascaridole formed only van der Waals interactions with VAL2, MET1, ARG28, ARG25, LYS35, and GLU32. In the case of *Ag*EPRS, the top compounds interacted with the amino acids in the active site as follows: sesamin formed conventional hydrogen bonds with LYS510, pi-alkyl interactions with ARG194, and pi-anion interactions with GLU485. Caryophyllene formed a pi-alkyl interaction with LYS510. Pellitorine formed conventional hydrogen bonds with GLU485 and LYS510 and alkyl/pi-Alkyl interactions with VAL511, PHE507, and ALA489. Carveol formed alkyl/pi-Alkyl interactions with ALA489, ARG194, and PHE507 (Figures 2I and 3I). The detailed interaction analysis reveals that violacein and sesamin formed multiple hydrogen bonds and pi-alkyl interactions, which are critical for stable binding in the active site.[35,36] Specifically, the pi-cation interaction between violacein and ARG36 in AgHSP70KDa is a strong electrostatic interaction, which may explain why it had a high binding score compared to the other compounds.

ADME-Tox and Toxicity Risk Assessment

The top five inhibitors (including the control) were selected for the toxicity risk assessment and ADME analysis. Violacein, sesamin, geldanamycin, and caryophyllene were not associated with toxicity (Table 5). However, halofuginone presents a high mutagenic risk and a medium reproductive risk, while ascaridole is characterized by high tumorigenic and irritant risk. Pellitorine is associated with a high reproductive risk, and carveol poses a high irritant risk. These finding underscore the importance of selecting compounds with low toxicity profiles for further development as potential insecticides while maintaining good pharmacological profile[37]. This suggest that violacein, sesamin, geldanamycin, and caryophyllene can serve as potential insecticidal compounds for malaria control, as they exhibit no toxicity.

Among the four compounds with no toxicity activity, only violacein and sesamin adhered to the Lipinski, Veber, and Egan rules (Table 4), indicating favourable bioavailability.[25] In contrast, geldanamycin violates all three rules, while caryophyllene violates only the Lipinski

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rule. The log Kp value, which indicates skin permeation potential, reveals that all compounds exhibit low skin permeation potential and are moderately soluble, except for carveol and ascaridole, which are fully soluble. Notably, halofuginone and pellitorine, like violacein and sesamin, also comply with the three rules. Furthermore, these four compounds meet the Lipinski, Veber, and Egan criteria for drug likeness, demonstrating good bioavailability score (Table 4). These findings underscore the necessity of continuing research into the possible therapeutic uses of sesamin and violacein and show that they are viable candidates for pharmacological investigations.

Table 4: ADME analysis of the properties of selected compounds

Compd	MF	MW	Log Po/w (iLOGP)	Log S (ESOL)	TPSA (Å²)	Lipinski	Veber	Egan	Kp (skin permeation)	Synthetic accessibility
Violacein	C20H13N3O3	343.34	1.65	-4.13	101.47	0	0	0	-6.45	3.51
Sesamin	C20H18O6	354.35	3.46	-3.93	55.38	0	0	0	-6.56	4.12
Geldanamycin	C29H40N2O9	560.64	3.04	-4.24	163.48	2	3	1	-8.31	7.71
Caryophyllene	C15H24	204.35	0.00	-3.87	3.25	1	0	0	-4.44	
Ascaridole	C10H16O2	168.23	2.53	-2.23	18.46	0	0	0	-5.73	4.98
Halofuginone	C16H17BrClN3O3	414.68	2.54	-3.34	84.22	0	0	0	-7.84	3.37
Pellitorine	C14H25NO	223.35	3.61	3.40	29.10	0	0	0	-4.55	2.97
Carveol	C10H16O	152.23	2.50	-2.65	20.23	0	0	0	-4.98	3.25

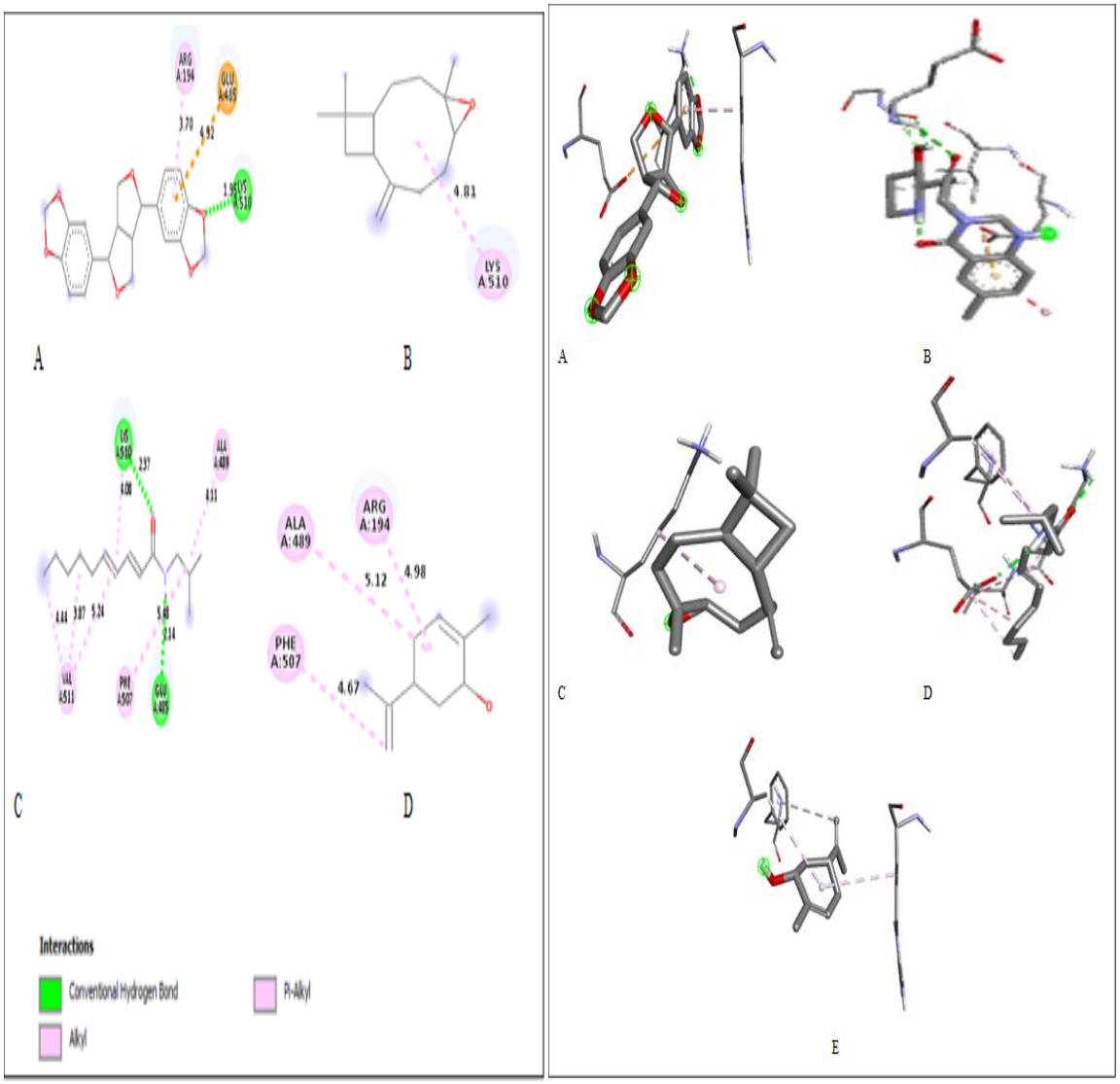

Figure 3: Docking interaction complex. I. 2D docked view complex of the top five compounds for *Ag*EPRS. A; sesamin, B; caryophyllene, C; pellitorine, D; carveol. II. 3D docked view complex of the top five compounds for *Ag*EPRS. A; sesamin, B; Halofuginone C; caryophyllene, D; pellitorine, E; carveol.

Table 5: Toxicity risk assessment of compound

Compounds	Mutagenic	Tumorigenic	Irritant	Reproductive
Violacein	No	No	No	No
Sesamin	No	No	No	No
Geldanamycin	No	No	No	No
Caryophyllene	No	No	No	No
Ascaridole	No	High	High	No
Halofuginone	High	No	No	Medium
Pellitorine	No	No	No	High
Carveol	No	No	High	No

Principal Component Analysis

Principal component analysis (PCA) is a statistical tool that determines linear combinations of variables that explain certain percentages of a collection of variables' variation.[39] By presenting the observations and variables as points on maps, PCA also illustrates the pattern of similarity between them. To assess the relationship between binding affinity, solubility (Log S), Log Po/w (iLOGP) and TPSA (Å²), PCA was performed for both *Ag*EPRS and *Ag*HSP70KD.[38,40] The first two components account for over 95% of the total variability (Figure 4A, Table 6), with F1 accounting for 56.023% and F2 accounting for 39.236%. The first component is strongly influenced by binding affinity, followed by solubility, Log Po/w and TSPA and the second by all the component with binding affinity having a negative binding. There is an inverse relationship between binding affinity (loading = 0.929) and TSPA (loading = -0.838). From the analysis, binding affinity and TPSA, solubility and Log Po/w are significant factors to consider in compounds selection. The biplot reveals that binding affinity is negatively correlated with the TSPA and slightly negatively correlated with Log Po/w. However, there is a strong correlation between binding affinity and solubility (due to small angle size).[40] Sesamin binds more strongly to AgEPRS followed by halofuginone while pellitorine has the least interaction (Figure 4A).

For AgHSP70KDa, the first two components captured a substantial 87.05% of the total variance. Binding affinity has a strong positive correlation (loading of 0.890), indicating its impact on variability, and TPSA showed a strong negative correlation within F1 (Table 6). The biplot shows that binding affinity has a modest negative correlation with TSPA and Log Po/w. Nevertheless, because of the small angle size, there is a substantial link between binding affinity and Log S. According to Figure 5B, geldanamycin has the strongest binding to AgHSP70KDa, followed by violacein and sesamin, whereas ascaridole has the least interaction. From the eigenvalues, F1 is strongly influenced by binding affinity, with TPSA having a strong negative effect. This suggests that as binding affinity increases, TPSA decreases (Figures 4B).

The PCA result indicate that binding affinity is a significant factor influencing both proteins and their bioactivity. Thus, these findings emphasize the need to consider these factors in the selection of compounds for targeted therapy.

Table 6: Eigenvalues for Principal Component Analysis

	***Ag*EPRS**				***Ag*HSP70KDa**			
	F1	F2	F3	F4	F1	F2	F3	F4
Eigenvalue	2.241	1.569	0.185	0.005	2.402	1.080	0.408	0.110
Variability (%)	56.023	39.236	4.622	0.118	60.043	27.005	10.194	2.757
Cumulative %	56.023	95.259	99.882	100.000	60.043	87.049	97.243	100.000

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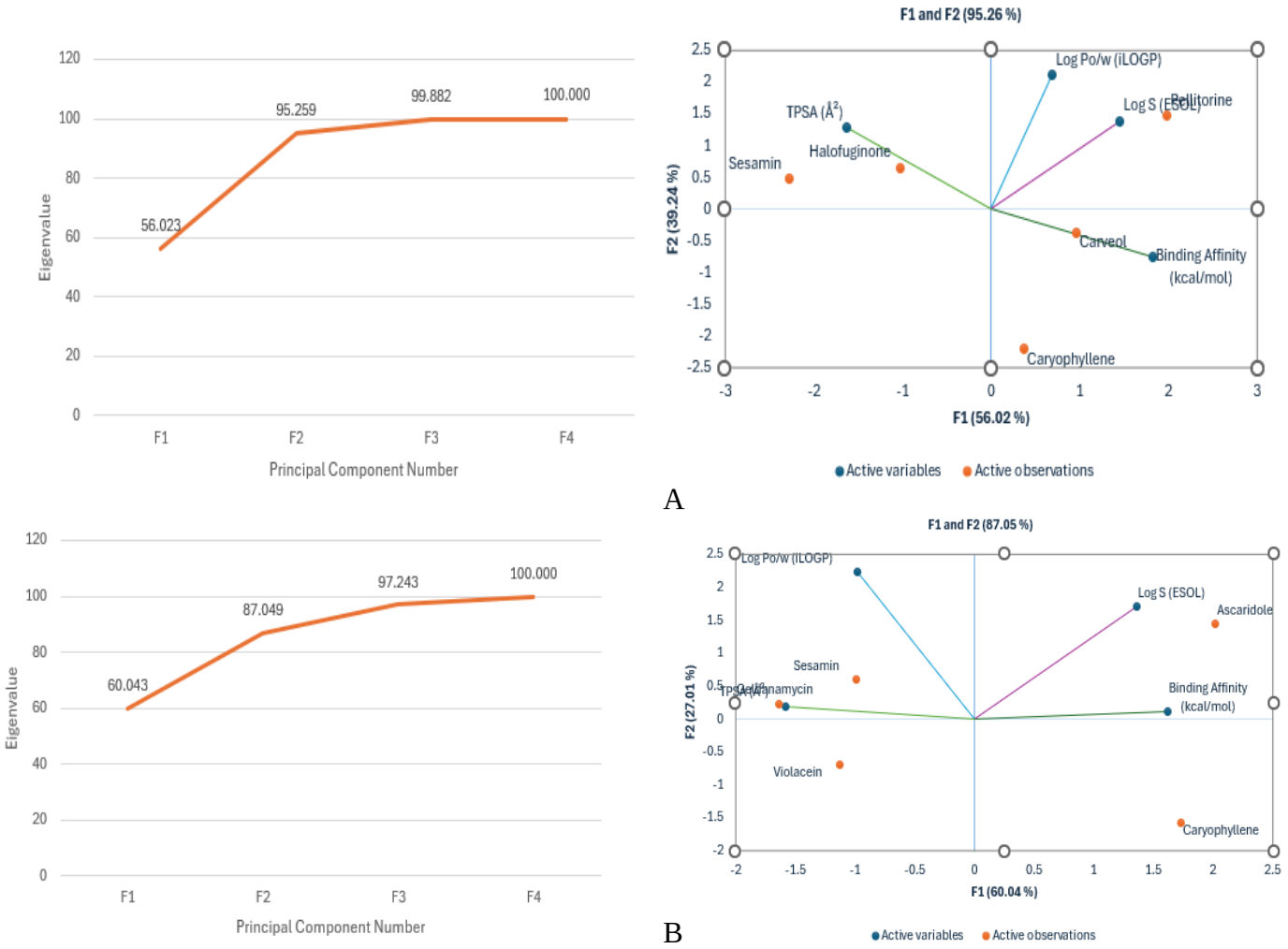

Figure 4. A: Scree plots for the eigenvalue and variability against the principal component F1-F4 and Biplot for correlation and observations for compound interaction with *Ag*EPRS. **B**: Scree plots for the eigenvalue and variability against the principal component F1-F4 and Biplot for correlation and observations for compound interaction with *Ag*HSP70KDa.

Conclusion

Our recent study identified *Ag*HSP70KDa and *Ag*EPRS as promising insecticidal targets against *A. gambiae*. These proteins offer potential avenues for developing new insecticides. This research underscores the potential of natural compounds derived from various plant species in modulating the activity of these targets. Among the compounds studied, sesamin emerged as a particularly promising candidate due to its favorable binding characteristics, lack of toxicity, and good bioavailability. The PCA results indicate that binding affinity is a significant factor in influencing both protein and their bioactivity. This underscores the significance of considering binding affinity, solubility and TPSA in the selection of compounds for targeted therapy. Additionally, further experimental studies are necessary to validate the efficacy of these target proteins and the inhibitory effects of sesamin and other high-affinity compounds. It is also noteworthy that their overall biological effectiveness needs to be investigated against these proteins.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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