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(RESEARCH ARTICLE)

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The Identification of multi-target Inhibitors of *Wolbachia pipientis* and *Onchocerca volvulus* by molecular simulations

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Abstract

Background: Human Onchocerciasis, caused by the filarial nematode *Onchocerca volvulus* infection, is a neglected public health disease that affects millions of people in the endemic regions of sub-Saharan Africa and Latin America. It is also called river blindness because the Black flies that transmit infection breeds in rapidly flowing fresh water streams and rivers. The disease is second to trachoma as the leading cause of blindness due to infection in the developing world and only few drugs are commonly used to treat nematode infections, creating a dangerous environment for the emergence of drug resistance. The study aims to identify essential drug targets in *Onchocerca volvulus* and its endosymbiont (*Wolbachia pipientis)* and repurpose existing drugs with inhibitory activities against the drug targets.

Methods: Through molecular docking simulations, 2,015 approved drugs were screened against two critical protein targets: Glutamate Chloride ion gated channel and 30s ribosomal protein using Autodock-vina. Protein targets of frontrunner drugs were also evaluated using the Swiss target prediction server. The drugs' interactions with the target proteins were analyzed using Discovery Studio Visualizer. Molecular dynamics was executed using Schrödinger LLC Desmond software.

Results: The study identified Adapalene, Diosmin and Azelastine as promising multi-target drugs based on their binding affinities and potential to inhibit the *Onchocerca volvulus* and *Wolbachia pipientis* targets. Additionally, other compounds like Drospirenone, Alectinib, Dutsteride and finasteride showed significant potential and warrant further investigation.

Conclusion: The findings suggest that repurposing these drugs could provide an accessible and effective therapeutic option for onchocerciasis and broaden the range of treatment options. Further studies are recommended to validate the efficacy of these drugs against Onchocerciasis.

Keywords: Onchocerciasis; Molecular Docking; Binding Affinity and Molecular Dynamics

1. Introduction

Onchocerciasis is an eye and skin disease caused by the parasitic worm *Onchocerca volvulus*, which is transmitted by the bite of an infected black fly (1). Because the vectors that spread the parasite breeds and lives near fast-flowing water bodies, onchocerciasis is also known as river blindness. The vectors are species of the genus *Simulium* (black flies) in Africa, primarily *Simulium damnosum* complex. The immunological response to dead microfilariae, which includes inflammatory components, is responsible for the symptoms of the disease which range from itching, skin rash and

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blindness. The pathological re-evaluation of the disease has indicated that the blindness is caused by an inflammatory response of the human immune system to an antigen of *Wolbachia*, a bacterial endosymbiont of *Onchocerca volvulus*. The use of antibiotics targeting the obligate bacterial endosymbiont, *Wolbachia* of filarial parasites has been validated as an approach for controlling filarial infection in animals and humans (2). Only few drugs are commonly used to treat nematode infections, creating a dangerous environment for the emergence of drug resistance (3).There has been concern that *O. volvulus* resistance to ivermectin will emerge. Ivermectin resistance has become widespread in many parasitic nematodes of livestock (4). At present there are no alternative drugs for ivermectin for use in the *Onchocerca* mass drug administration programs that reduce microfilaria or kill adult worms, which can live up to 15 years in the human host. There still persist the suboptimal drug resistance in treatment of onchocerciasis in some communities in West Africa (5) and the adverse reactions post-ivermectin mass treatment in central Africa regions associated with high intensity of co-infection with O. volvulus/L. loa (6).

Drug repurposing entails the use of already existing drugs with known pharmacologic effects and testing them for new pharmacological action and effects (9). This concept has been performed in the search for therapeutic agents for onchocerciasis with emerging drug resistance. The field of Computer -Aided Drug Design (CADD) is expanding quickly with a lot success recently. Along with academics, a lot of pharmaceutical corporations use CADD to find medication leads (10). The rapid development in structural informatics, genomics and proteomics has greatly aided in the search for new drugs in the modern day (12). Molecular dynamics uses computer simulation to study the actual movement of atoms and molecules, molecular docking is utilized in CADD to anticipate the optimum interaction between molecules (11). With the benefit of reducing time and money of medication development, CADD is a crucial tool in drug repurposing, it provides a target approach to drug repurposing that enables quick screening of chemical libraries (12). The finding of a new medicine is huge task and the major components of modern drug discovery involve an *in silico*, chemical, and biological approach (13&14). The acceptance use and popularity of computer-aided techniques (CAT) in the drug research and development process are growing quickly (15). The present research investigates the multi-target inhibitors of *Onchocerca volvulus* and *Wolbachia pipientis*.

2. Materials and Methods

2.1. Materials

Personal Computer (Hp Elite book 9430m), African Natural Compounds Database PubChem (http://Pubchem.ncbi.nlm.nih.gov), Linux Operating System (Ubuntu desktop 18.04), Protein Data bank (www.pdb.com), Drugbank (www.drugbank.com), PyMol, Autodock tools 1.5.6, Autodock-vina 1.1.2 on Ubuntu operating system, Vina script, Vina get energy script, Discovery studio visualize, Swiss model-expasy and Swiss target prediction.

2.2. Methodology

2.2.1. Identification and Selection of targets

Bioinformatic mining of the TDR Target Database (http://tdrtargets.org/) and Protein Data Bank (PDB) were carried out to identify the essential proteins targets and 3D structures suitable for the study. The bioinformatic mining of the targets were based on the target essentiality, druggability, accessibility in PDB and the resolution. Further, literatures mining on the targets were done for proper understanding on their functions and possible selection of a novel target. These two proteins Glutamate Chloride ion gated channel (GluClx) and 30s Ribosomal protein (30sR) were identified respectively in *Onchocerca volvulus* and *Wolbachia pipientis.*

2.2.2. Preparation of receptors

The selected protein structures were prepared using Autodock Tools. The Targets structures were opened in chimera-1.10.1 (7) to visualize and remove the unwanted components and saved. The structures were further opened in Autodock tools version-1.5.6 (8), for addition of polar hydrogen and saved as pdbqt file. The Grid search spaces of the targets were also selected as appropriate. The protein targets that were not present in the PDB database were obtained through homology modeling in SWISS-MODEL of expasy (https://swissmodel.expasy.org/) using the FASTA amino acid sequences of the protein. Electrostaticgridboxesand3Daffinitymaps were generated around the active binding sites of each protein, with varying dimensions and centers as outlined in Table 1These configurations were then saved as configuration (.conf) files for docking simulations.

Table 1 Grid box parameters used in the molecular simulations

	GluClx		30SR	
Dimensions	**Centers**	**Sizes**	**Centers**	**Sizes**
X	-11.458	17	314.096	14
Y	38.613	16	275.545	14
Z	44.532	16	390.875	14

2.2.3. Preparation of ligands

The approved drugs and reference drugs were obtained in SDF-3D format from Drug Bank (www.drugbank.com). Using Auto Dock Tools, the ligands were prepared for molecular docking simulation. All rotatable bonds, Torsions, and Geistegers charges were assigned and saved as pdbqt files. The prepared ligands and receptors downloaded in SDF format were converted to pdbqt format using a script (prepared script) on the Ubuntu operating system.

2.3. Molecular docking

The AutodockVina1.1.2 was used for molecular docking simulations. The ligands were docked into the receptor to predict their free binding energies using AutodockVina with the aid of a virtual screening script. Four replicate simulations were done for each of the ligand and the binding affinities reported as mean and standard deviation. The ligands were ranked based on binding energies and frontrunners selected for molecular dynamics simulations.

2.4. Swiss target prediction

The Swiss target prediction was used to verify the protein class that the front-runner drugs could bind to and determine whether the protein target of interest falls within any of those classes.

2.5. Assessment of proteins-drugs interactions

The front-runner drugs were analyzed for protein interaction using a discovery video visualizer (https://www.3ds.com/products/biovia/discovery-studio/visualization) to study the amino acids responsible for the activity compared to the reference compounds.

2.6. Molecular Dynamics

Molecular dynamics (MD) simulations were performed for duration of 100 nanoseconds using the Desmond software suite developed by Schrödinger LLC (12). Prior to initiating the MD simulation, molecular docking was performed as a fundamental step to predict the static binding orientation of the ligand within the protein's active site (16). By applying Newton's classical equations of motion, MD simulations replicate atomic movements over time, offering insights into ligand-binding behavior under physiological conditions (17). The ligand-protein complex underwent preprocessing through Maestro's Protein Preparation Wizard, which involved optimization, energy minimization, and completion of missing residues when necessary. The system was then constructed using the System Builder tool. The TIP3P (Transferable Intermolecular Potential with 3 Points) water model was employed within an orthorhombic simulation box, maintaining a temperature of 300K, a pressure of 1 atm, and an OPLS_2005 force field (18). Counter ions and 0.15 M sodium chloride were added to ensure a neutral environment, mimicking physiological conditions. The system was equilibrated before the simulation, and trajectory data were recorded every 100 picoseconds for subsequent analysis. Visual representations of the molecular dynamics simulations were generated using Schrödinger's Maestro software (version 9.5). Interaction diagrams, extracted from Desmond modules within the Schrödinger suite, facilitated the assessment of simulation events and validation of MD reliability. The stability of the protein-ligand complex was evaluated by analyzing trajectory patterns and key parameters, including root mean square deviation (RMSD), root mean square fluctuation (RMSF) and protein-ligand interactions (PL).

2.7. Analysis after Molecular Dynamics simulation

After the MD simulation, the calculation of the RMSD for the protein and ligand, as well as analysis of the interactions exhibited by the ligand during the entire simulation duration, was done. RMSD measures the average change in displacement of selected atoms for a particular frame with respect to a reference frame.
The RMSD for frame x is:

$$\mathrm{RMSD}_X = \sqrt{\frac{1}{N}\sum_{i=1}^{N}\left(r'_j(t_x) - r_j(t_{ref})\right)^2}$$

where N is the number of atoms in the atom selection. t_{ref} is the reference time, and r′ is the position of the selected atoms in frame x. The procedure is repeated for every frame in the simulation trajectory.

3. Results

3.1. Molecular docking results against Glutamate Chloride ion gated channel (GluClx) and 30s ribosomal Protein (30sR)

The molecular docking against the target was executed using a total number of 2015 approved drugs. Ivermectin and Doxycycline were used as reference drug and a total number of 836 and 182 drugs respectively were obtained as frontrunners after the molecular docking simulation against target.

Table 2 The result summary for the molecular docking of drugs compounds against GluClx and 30sR target.

Target Organisms	Target protein/Receptor	Reference Drugs (Binding energies)	Number of identified frontrunners (approved drugs)
Onchocerca Volvulus	Glutamate Chloride gated ion channel	Ivermectin(-5.9Kcal/mol)	836
Wolbachia Pipientis	30s Ribosomal protein	Doxycycline(-8.3Kcal/mol)	182

3.2. Multi-targeting drugs

A total of 23 drugs were obtained as multi-targeting front-runner compounds after excel analysis of the frontrunners. The multi-targeting drugs in this study are the drugs that have better binding affinities than the least of the references in both Glutamate Chloride ion gated channel and 30s ribosomal proteins.

3.3. Target prediction of selected frontrunner drugs

The results of the target prediction of the reference drugs and selected frontrunner drugs are presented in Figure 1(a-f). The selected frontrunner drugs in Table 3 were based on Adverse Drug Reaction (ADR) and the ease of availability in Nigeria.

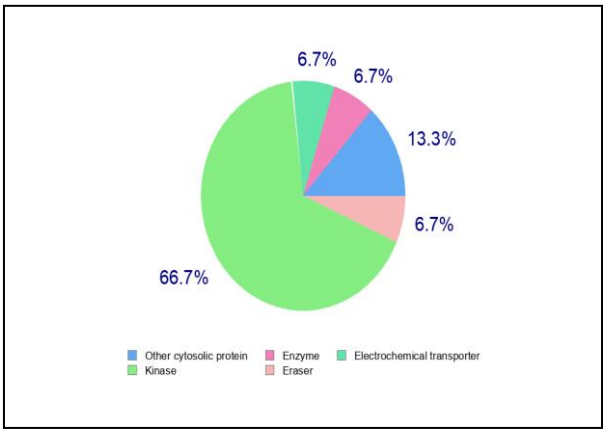


Figure 1a Doxycycline target prediction

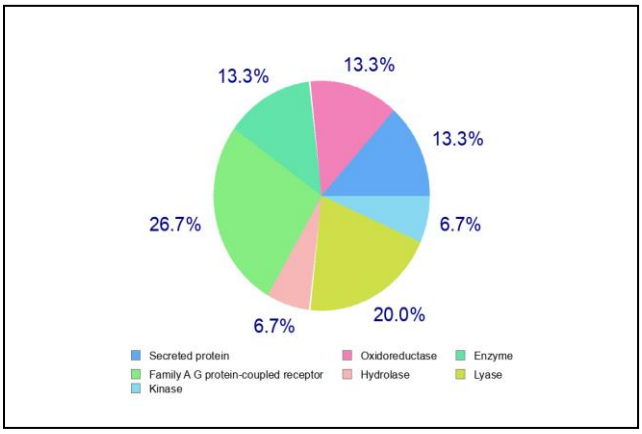


Figure 1b Diosmin target prediction

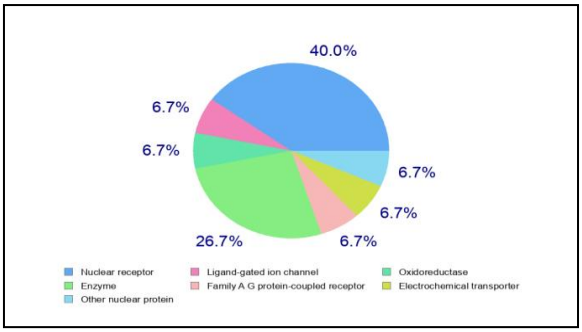


Figure 1c Adapalene target prediction

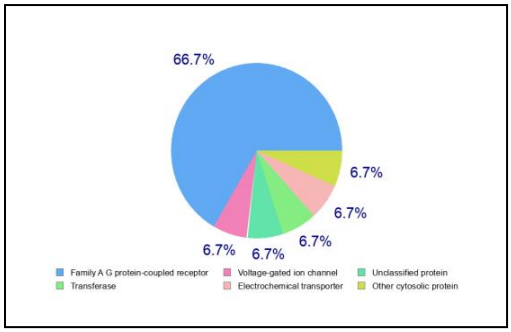


Figure 1d Azelastine target prediction

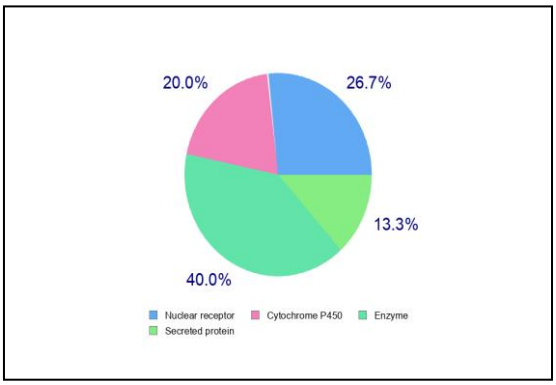


Figure 1e Drospirenone target prediction

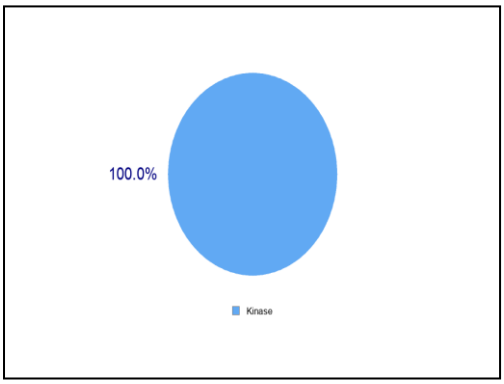


Figure 1f Alectinib target prediction.

Table 3 Target prediction of selected frontrunner drugs

Drug Compound	**Predicted Target/Binding energies**			
	Glutamate Chloride ion gated channel (Channel Protein)(percentage) /Binding energy (Kcal/ mol)		**30s Ribosomal protein (Structural protein) (percentage)/Binding energy (Kcal/ mol)**	
Ivermectin	-	-5.9	-	-
Doxycycline	-	-	13.3	-8.9
Adapalene	6.7	-6.8	-	-9.4
Diosmin	-	-7.1	-	-9.2
Azelastine	6.7	-6.0	6.7	-9.3
Drospirenone	-	-7.4	-	-9.5
Alectinib	-	-6.3	-	-9.0

3.4. 2D interaction assessment of selected frontrunner drugs

The 2D interaction assessments of the reference drugs and some selected drugs shown in table 2 are presented in figures 2(a-e).The 2D interaction assessment was done for the selected multi-target drugs against the Glutamate Chloride ion gated channel and 30s ribosomal protein according to their predicted targets in table 3 above.

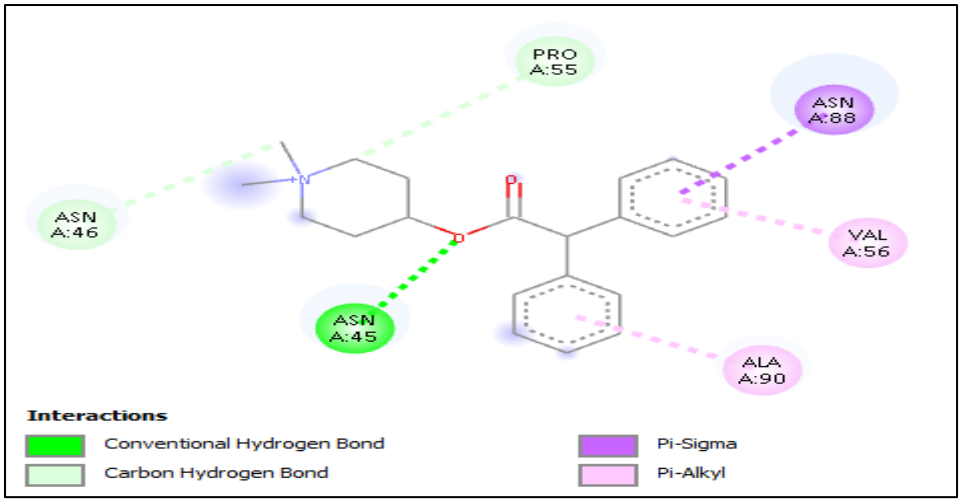


Figure 2a Ivermectin+GluClx complex 2D interaction assessment

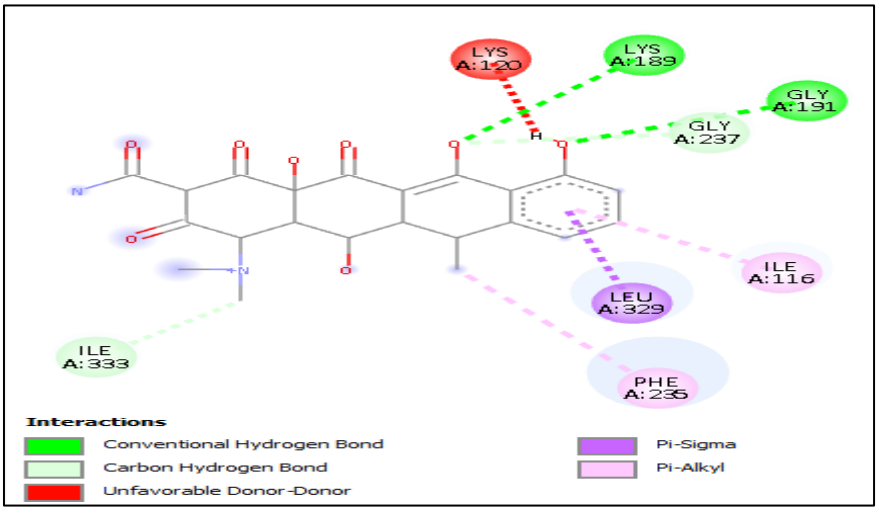


Figure 2b Doxycycline+30sR complex 2D interaction assessment

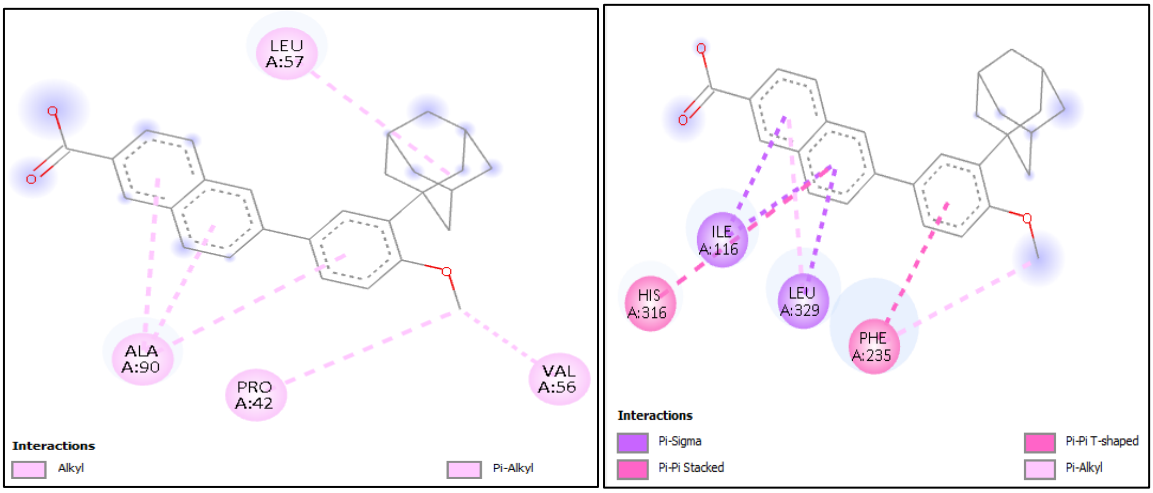


Figure 2c Adapalene+GluClx and Adapalene+30sR complexes 2D Interaction Assessment

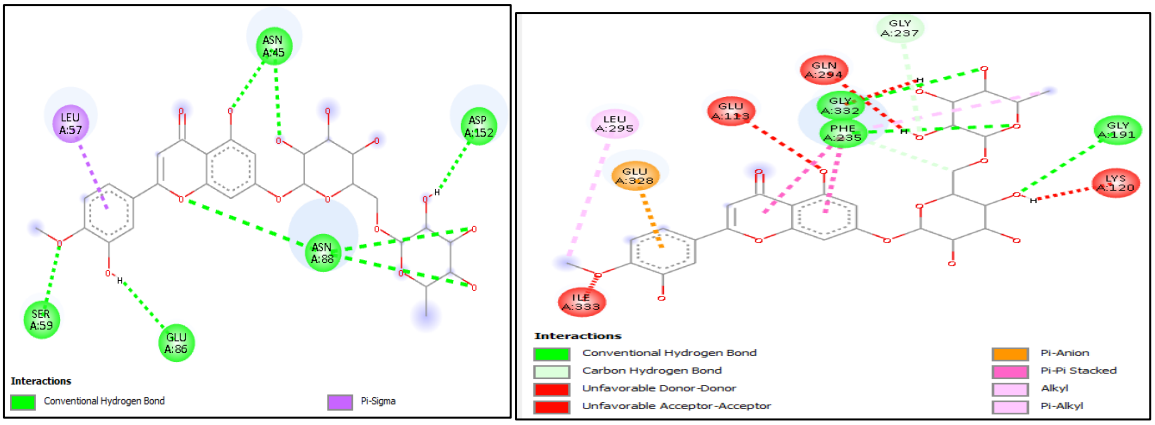


Figure 2d Diosmin-GluClx and Diosmin-30sR complexes 2D interaction assessment

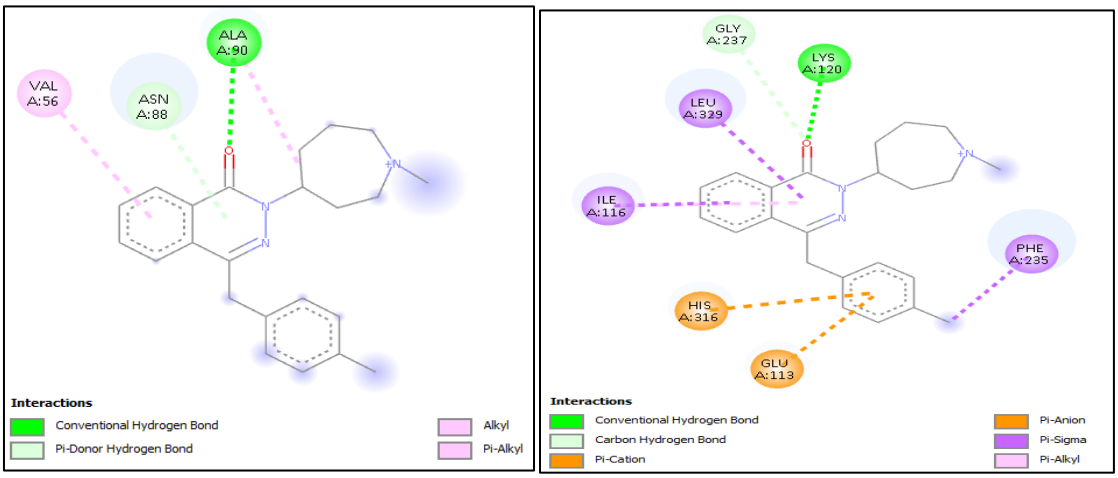
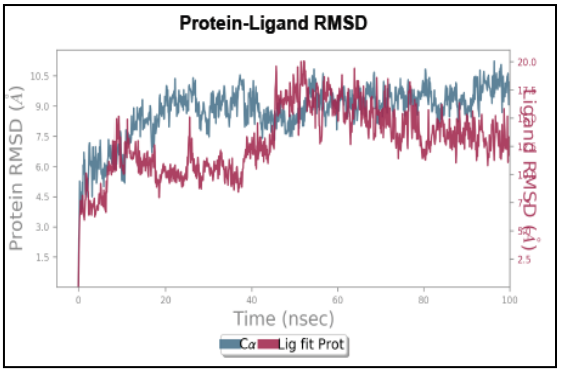


Figure 2e Azelastine-GluClx and Azelastine-30sR complexes 2D interaction assessment

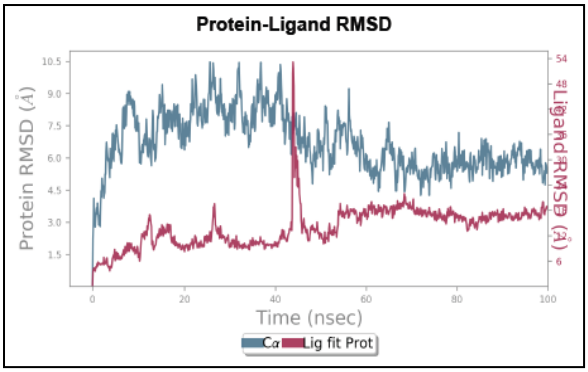
3.5. Molecular dynamics simulation

The MD simulation is viewed as an essential computational tool for exploring the dynamic interactions within ligand–protein complexes. It provides several benefits compared to molecular docking, primarily by overcoming the limitations posed by the rigid structure of proteins in traditional docking approaches. In MD simulations, the protein–ligand complex exhibits dynamic behavior, allowing for conformational changes of ligands within the active site of the protein. This phenomenon also mimics the scenario of a biological system, where the stability of the protein–ligand complex is evaluated in the simulated water boundary.

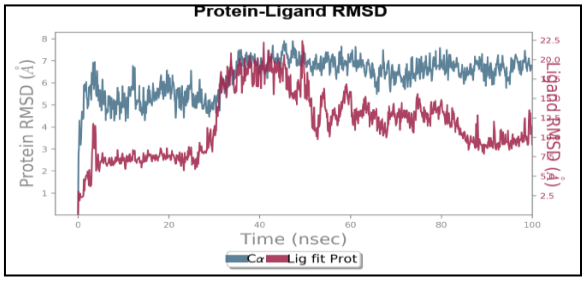
The molecular dynamics simulation results are presented in figures 12 to 14, as shown below. The molecular dynamics was executed for the reference drugs (ivermectin & doxycycline) and for the selected frontrunners (Adapalene, Diosmin and Azelastine) against the two targets (GluClx and 30sR). The figure 3a represents the Root Mean Square Deviation (RMSD), which measures the average change in displacement of a selection of atoms for a particular frame concerning a reference frame. The figure 3b represents the Root Mean Square Fluctuation (RMSF) for the protein, which is useful for characterizing local changes along the protein chain. While figure 3c represents the protein-ligand contact during the simulation.



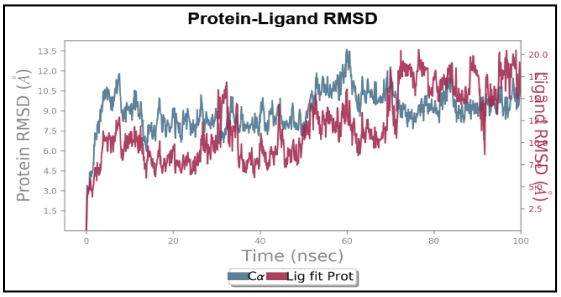
Complex A1 Ivermectin+GluClx



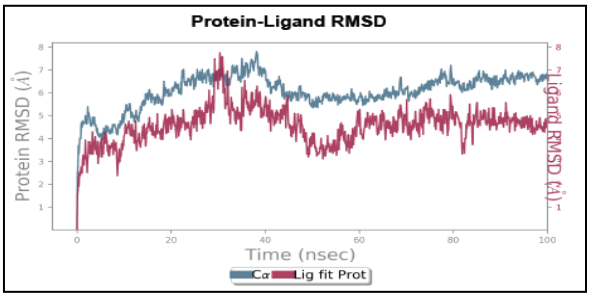
Complex A2 Adapelene+GluClx



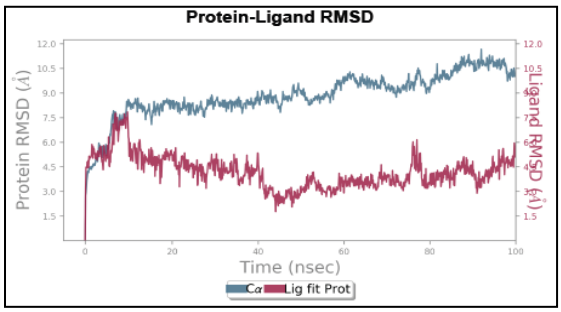
Complex A3 Diosmin+GluClx



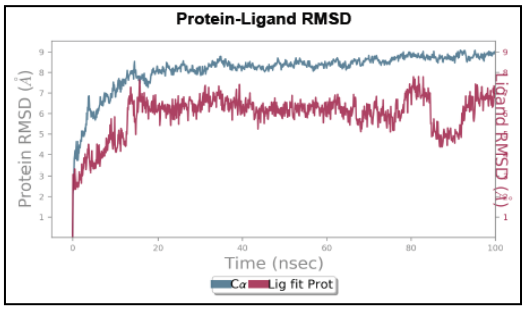
Complex A4 Azelastine+GluClx



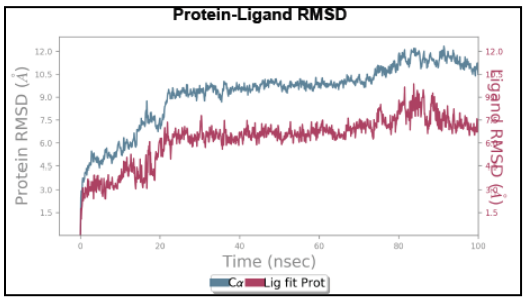
Complex B1 Doxycycline+30sR



Complex B2 Adapalene+30sR

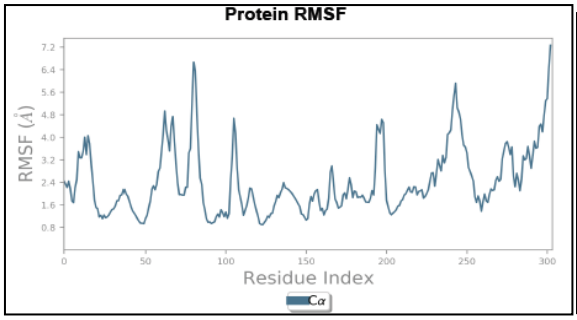


Complex B3 Diosmin-30sR

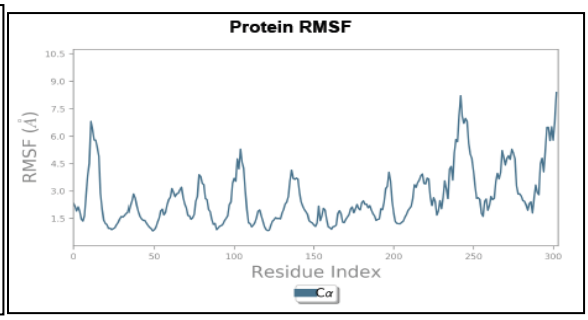


Complex B4 Azelastine+30sR

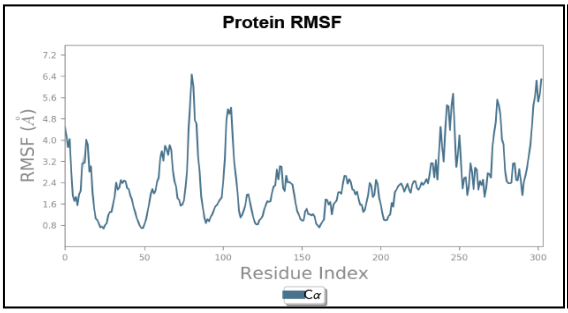
Figure 3a The Root Mean Square Deviations (RMSDs) of the two reference drugs and the selected frontrunners against the two proteins (GluClx and 30sR). The Root Mean Square Deviation (RMSD) measures the average change in displacement of a selection of atoms for a particular frame with respect to a reference frame.



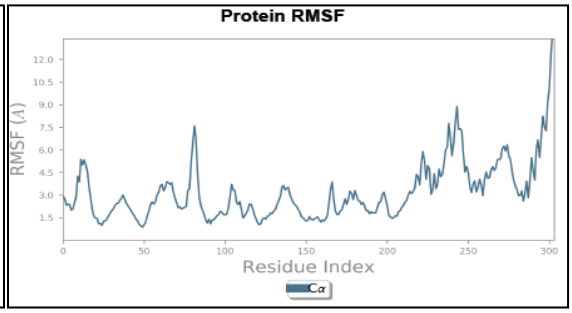
Complex A1 Ivermectin+GluClx



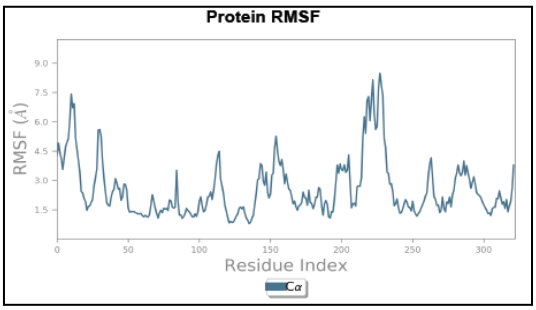
Complex A2 Adapelene+GluClx



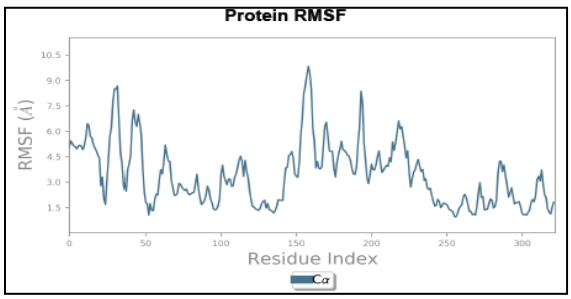
Complex A3 Diosmin+GluClx



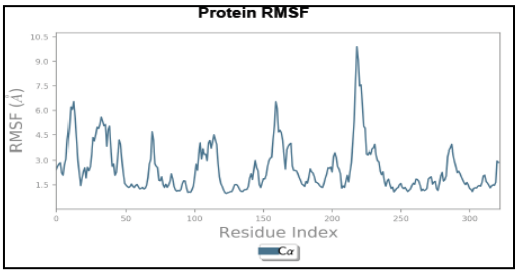
Complex A4 Azelastine+GluClx



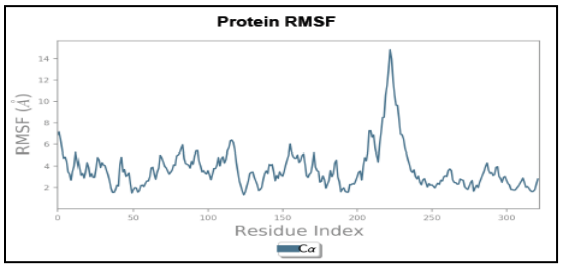
Complex B1 Doxycycline+30sR



Complex B2 Adapalene+30sR

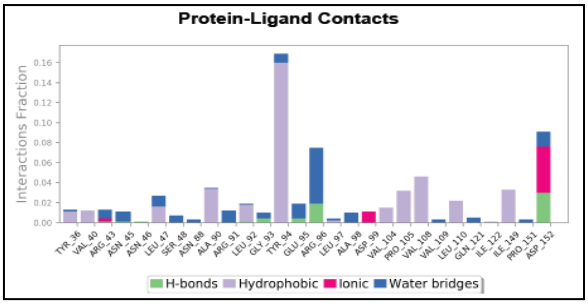


Complex B3 Diosmin-30sR

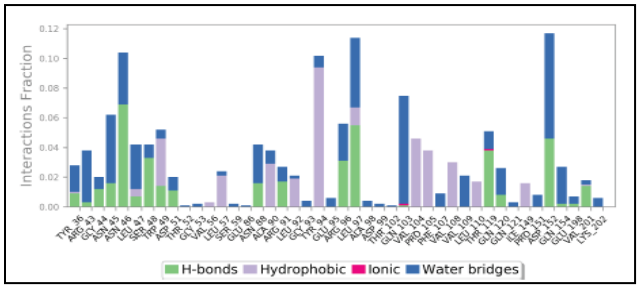


Complex B4 Azelastine+30sR

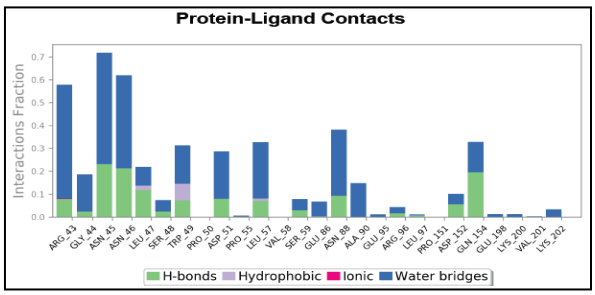
Figure 3b The Root Mean Square Fluctuations (RMSFs) of the two reference drugs and the selected frontrunners against the two proteins (GluClx and 30sR). The Root Mean Square Fluctuation (RMSF) is useful for characterizing local changes along the protein chain.



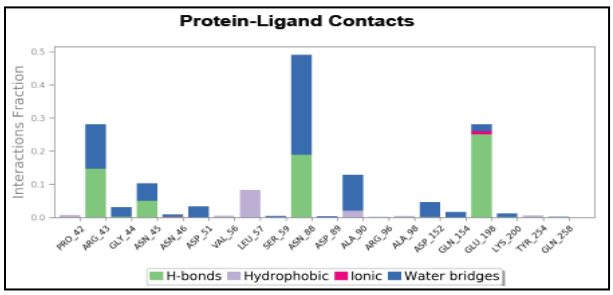
Complex A1 Ivermectin+GluClx



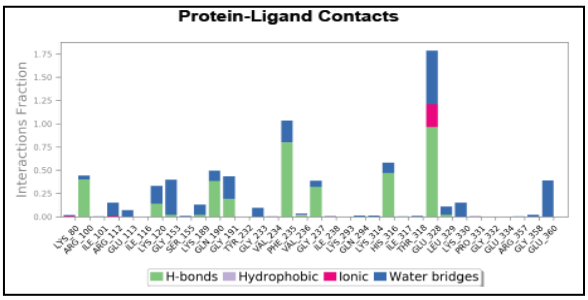
Complex A2 Adapelene+GluClx



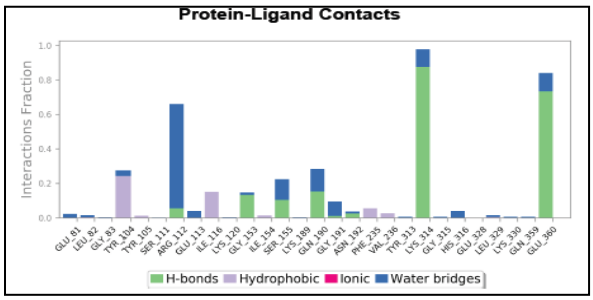
Complex A3 Diosmin+GluClx



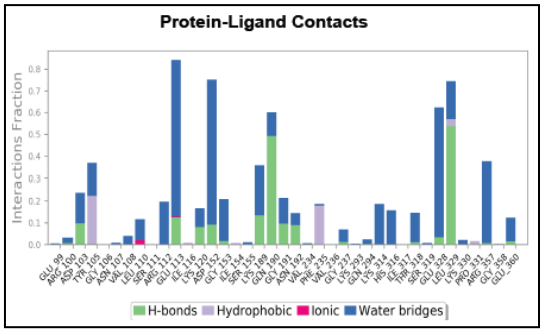
Complex A4 Azelastine+GluClx



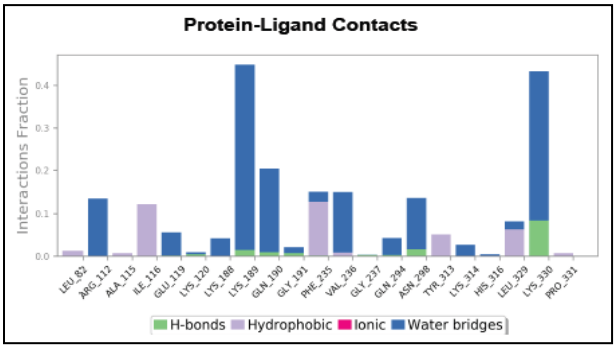
Complex B1 Doxycycline+30sR



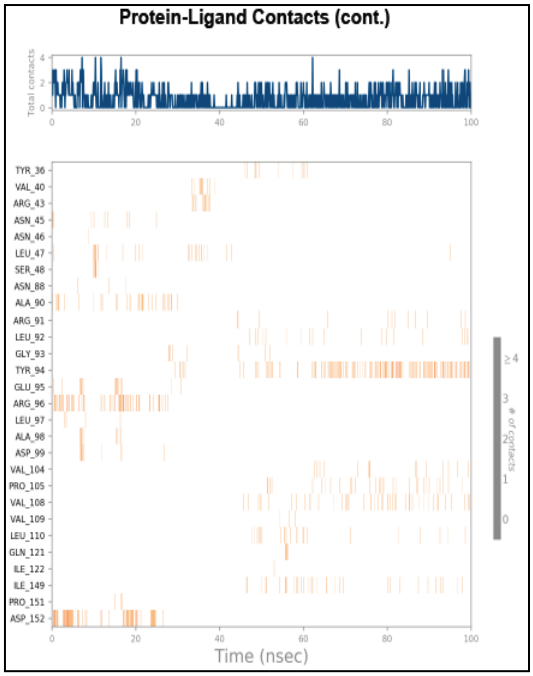
Complex B2 Adapalene+30sR



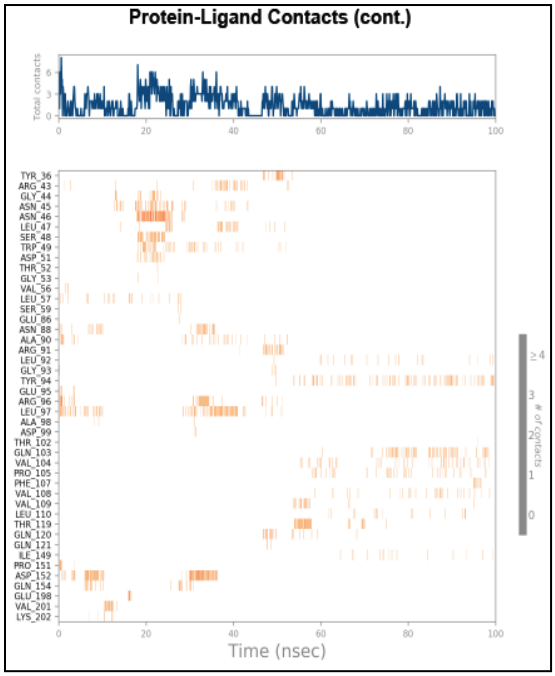
Complex B3 Diosmin-30sR



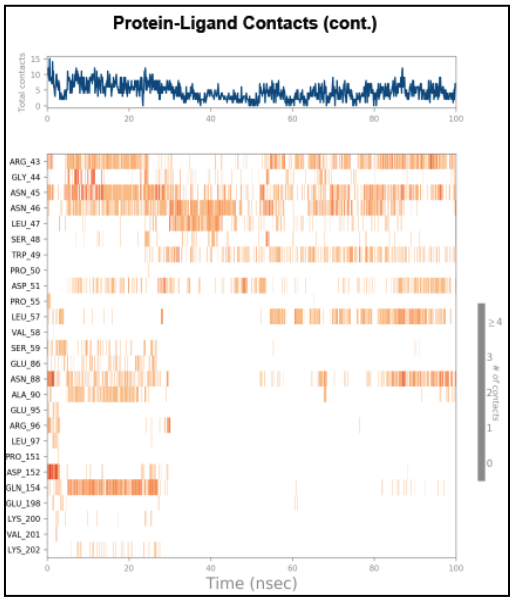
Complex B4 Azelastine+30sR



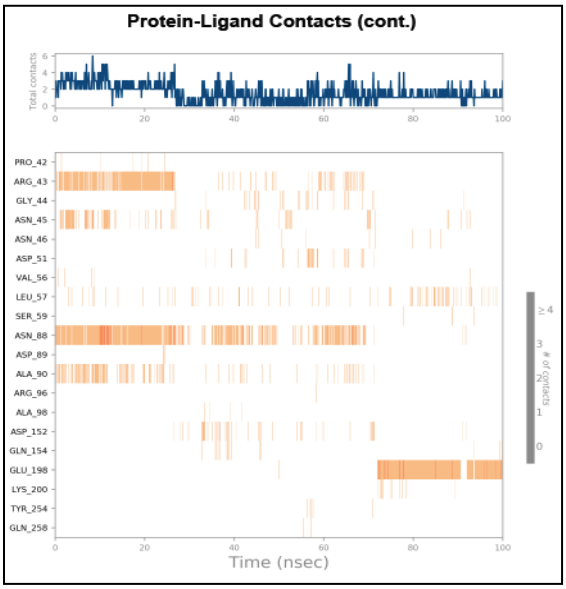
Complex A1 Ivermectin+GluClx



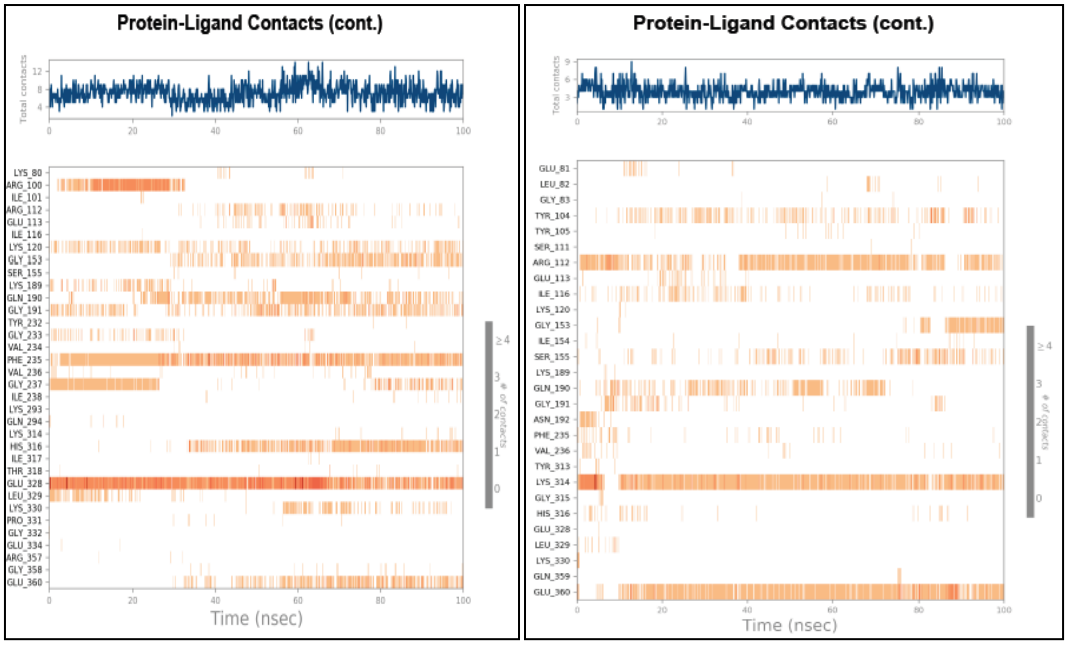
Complex A2 Adapelene+GluClx



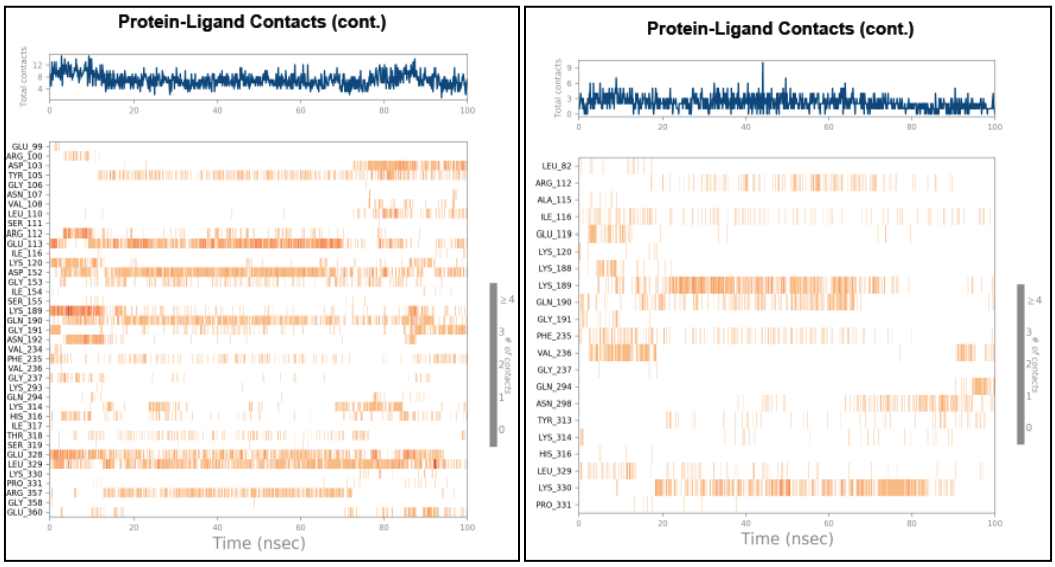
Complex A3 Diosmin+GluClx



Complex A4 Azelastine+GluClx



Complex B1 Doxycycline+30sR **Complex B2** Adapalene+30sR



Complex B3 Diosmin-30sR **Complex B4** Azelastine+30sR

Figure 3c The Protein-Ligand contacts of the two reference drugs and the selected frontrunners against the two proteins (GluClx and 30sR). It is a timeline representation of the interactions and contacts (H-bonds, Hydrophobic, Ionic, Water bridges) between the ligand (drugs) and the target protein as seen in the bar charts. On the second charts, the top panel shows the total number of specific contacts the targets make with the drugs over the course of the trajectory. The bottom panel shows which residues interact with the drugs in each trajectory frame. Some residues make more than one specific contact with the drugs, which is represented by a darker shade of orange, according to the scale to the right of the plot

4. Discussion

The results of the molecular docking simulation against the selected targets are presented in Tables 2. The results, which are expressed in binding affinity (kcal/mol), showed that 836 and 182 drug compounds have higher binding energy

than their reference drugs, ivermectin and doxycycline, respectively. Binding affinity refers to the strength of the interaction between a drug, often called a ligand, and its target molecule, typically a protein involved in a specific disease-related process or mechanism. Scientists use this value to determine the drug's affinity for the target's binding site, indicating the likelihood and stability of the drug's attachment. The 'lock and key' analogy is useful for understanding drug-target interactions: the lock symbolizes the target protein, which has a binding site where the drug molecule can attach, while the key represents the drug molecule itself. Just as a key that fits perfectly into a lock unlocks it, binding affinity reflects the strength of the drug's interaction with its target. A key that fits well exhibits higher binding affinity, leading to a stronger and more stable interaction between the drug and its target, thereby enhancing therapeutic efficacy.

Table 3 presents selected multi-target drugs, with their predicted targets illustrated in figure 1(a-e). These drugs have binding energies above the reference drugs in protein targets used for the study. Multi-target drugs have gained considerable interest in the last 10 years due to their advantages in the treatment of complex diseases and health conditions linked to drug resistance issues. Prospective drug repositioning to treat comorbid conditions is another underutilized application of multi-target ligands (19).The option of multi-targeting assists to identify one drug that acts through several mechanisms to achieve a specific therapeutic effect. Although combination therapy may effectively treat certain conditions, multi-target ligands offer numerous benefits, including improved patient compliance, more predictable pharmacokinetics, and a lesser chance of drug interactions (19). The prediction of target is crucial in drug discovery, enabling researchers to identify potential disease therapeutic targets. The proteins of the target in this study were studied for their class of protein/enzyme. The Glutamate Chloride ion-gated Channel (GluClx) is a channel protein, while the 30s ribosomal target (30sR) is a structural protein. By prioritizing promising targets, researchers can focus their efforts on compounds with a higher likelihood of success, saving time and resources. Target prediction helps to streamline the drug discovery pipeline by identifying potential drug candidates earlier in the process (20, 21).We further assessed the amino acids in the protein targets of interest that interacted with the selected multi-targeting frontrunner drugs compared with the reference drugs in figure 2(a-f). From these 2D interaction assessments, it was observed that the frontrunner drugs have the same amino acid interactions and more at the binding pockets when compared to the reference drugs. This however, reinforced the observed higher binding energies by these drugs to the target. Recognizing these interaction patterns not only validates our computational predictions but also informs the selection of these compounds for further molecular dynamics simulations. The understanding of the specific interactions between a drug and the amino acids of its target protein is crucial for drug design and development. By identifying key amino acid residues involved in drug binding, researchers can optimize drug structure to increase affinity and selectivity. Understanding the interaction profile can help minimize interactions with unintended proteins, reducing side effects. Analyzing drug-protein interactions can provide insights into the underlying mechanisms of drug action and reveal potential new therapeutic applications for existing drugs. Researchers can modify the drug structure to improve its effectiveness for a new target by identifying the key interactions responsible for drug efficacy (22). Finally, we conducted molecular dynamics simulations for the selected frontrunner multi-targeting drugs (Diosmin, Azelastine and Adapalene) compared with the reference drugs (Ivermectin and Doxycycline) for the targeted proteins. One of the most efficient and best methods of studying biological macromolecules is the Molecular Dynamics (MD) simulation method (23, 24-25).

MD simulations of protein structure are performed in an aqueous medium to provide predicted adaptations of proteins under physiological conditions (26). In the molecular dynamics simulation, we looked at parameters like Root Mean Square Deviation (RMSD), Root Mean Square Fluctuations (RMSF) and Protein drug contacts. Root Mean Square Deviation (RMSD) is used for measuring the difference between the backbones of a protein from its initial structural conformation to its final position. The lesser observed the deviation, the better the stability of the system. (27)

In the MD simulations, the RMSD for complex A1, as shown in Figure 3a, was stable from 0- 10 and 40-92 nsec; and drifted at 10-40 and 92-100nsec. The RMSD values for both the GluClx and ivermectin complex were found within range. The protein highest RMSF during the complex A1 simulation in Figure 3b was 7.2 Å at 300nsec. The significance of Root Mean Square Fluctuation (RMSF) during molecular dynamics (MD) is that it measures the local flexibility of a protein or molecule over time, helping to identify protein residue stability (28). The higher the RMSF value, the more conformational change on the protein residue and the flexibility during MD. The protein ligand contact of the complex shown in figure 3c, showed that the reference compound (Ivermectin) exhibited hydrophobic interaction with TYR94, ALA90, PRO105, ILE149, and VAL108, Hydrogen bonding interaction with ASP152, GLY93, GLU95, ASN45, ASN46 and ARG96, Ionic bonding with ASP152, ASP99 and ARG43, and Water bridge interaction at ARG96, GLU95, ASP152, SER48, GLN121, ARG91, LEU47, ALA98, ARG43 and ASN45. Hydrogen bonds play a crucial role in drug-receptor interactions by determining binding specificity and stabilizing the drug-receptor complex**.** They are a key type of intermolecular force that contributes to the overall affinity between a drug and its target, and can also be involved in the dynamic activation of the receptor. The formation of a specific pattern of hydrogen bonds between a drug and receptor is critical

for the drug to bind effectively and produce the desired effect, such as initiating or blocking a biological response (29).Hydrophobic interactions play a crucial role in drug-receptor binding by providing stability to the complex, increasing binding affinity, and contributing to specificity. These interactions occur between non-polar regions of a drug and a receptor, driving them to associate in an aqueous environment to minimize their contact with water. This leads to a thermodynamically favorable interaction that helps stabilize the folded structure of proteins and lock the drug into the receptor's binding site (30).Ionic interactions, which are electrostatic attractions between oppositely charged ions, play a crucial role in initial, long-range drug-receptor binding by attracting charged molecules from a distance. Most receptors have ionizable groups, and many drugs contain ionized functional groups that can form these bonds, contributing to the specificity and affinity of the interaction. While strong and often dominant initially, the strength of these bonds is influenced by the surrounding medium's dielectric constant and are generally considered reversible, contributing to a drug's duration of action. These interactions varied in their intensities, as shown in the second chart in Figure 3c and the deeper the colour, the more intense the interaction at specific times of the dynamic simulation. The most effective binding generally involves a favourable combination of these forces that fit precisely into the protein's binding pocket, leading to a stable complex. However, these interactions provide crucial insights into the stability, binding affinity, specificity and dynamic behaviour of the molecular complex

In the Complex A2 (Adapalene+GluClx complex), the RMSD shown in Figure 3a revealed a significant drift at the beginning of the simulation, but reversed to stability towards the end of the simulation. The protein highest RMSF was 7.8 Å at 244nsec, which is slightly higher in the residue fluctuation when compared to the reference drug. This highlights the conformational change experienced by the target during the simulation. The complex contact shown in figure 3c revealed Hydrogen bonding (with TYR36, GLY44, ASN45, ASN46, SER48, TRP49, ASP51, ANS88, ARG91, ARG96, LEU97, THR119, ASP152 & VAL201), Hydrophobic interaction (with TRP49, LEU57, ALA90, LEU92, TYR94, VAL104, PRO105, VAL109, LEU110 & ILE149), Ionic bonding(GLN103) and Water bridge interaction (with TYR36, ARG43, ASN45, ASN46, LEU47, ASN88, ARG96, LEU97, GLN103, ASP152, GLN154 & LYS202). Crucially, the ligand maintained more numerous and stable contacts throughout the trajectory, including persistent hydrogen bonds with new residues, which underpins its robust binding pose and these new H-bond interactions may contribute to the additional stability of the complex.

In the Complex A3 (**Diosmin+GluClx- complex), the RMSD** showed an initial drift from 0-30nsec; eventually, the complex got stabilised at 30-50nsec. Additionally, in the complex, a drift was observed from 50-100 during the simulation. The protein highest RMSF value was 6.4 Å at 80nsec, which indicates lesser perturbation by the ligand binding and residue rigidity than the reference drug. The protein ligand contact shown in Figure 3c revealed mainly hydrogen bonding (with ASN45&46, LEU47, GLN154, ASN88, ASP51, & ARG43), water bridge interactions (with ARG43, LEU47, GLY44, ASN88, ALA90, GLU86, TRP47, & ASP45) and a trace interaction of Hydrophobic interaction at TRP49 &LEU47. The ligand retained the observed interaction in the 2D assessment and formed a new interaction in the MD simulation.

In the Complex A4 (Azelastin +GluClx complex), the RMSD showed a slight drift within the simulation but got stabilised towards the end of the simulation. The observed drifts were within the acceptable range of 1-3 Å. The protein highest RMSF was 9.0 Å at 247nsec, thus indicating higher residue flexibility than the reference drug. The complex contact shown in Figure 3c revealed Hydrogen bonding (interactions with GLU198, ARG43, ANS88 and ANS45), Hydrophobic interaction (with LEU57 and ALA90), Ionic bonding (GLU198) and Water bridge interaction (with ARG43, GLY44, ASP51, ASN88, ALA90 & ASP153). The ligand retained a similar with the reference compound and formed crucial ionic bonding during the MD simulation.

From the MD simulation results for GluClx, Azelastine and Adapalene vis-à-vis the reference compound ivermectin, exhibited good interactions with the target, considering their binding affinity, stability and interaction during the MD simulation.

In the MD simulations for the second target 30sR protein, the RMSD of the Complex B1 (Doxycycline+ 30sR complex), as shown in Figure 3a, began with a drift a 0-7nsec and tended towards stability at 8-15nsec cum 30nsec. Eventually, it drifted throughout the simulation. The protein RMSF showed a peak value of 8 Å at 225nsec and indicates the limit of protein residue reconfiguration caused by the complex interaction. The complex contact shown in figure 3c revealed Hydrogen bonding (with ARG100, LYS120, GLN190, GLY191, PHE235, GLY237, HIS316 and GLU328), Hydrophobic interaction (with ILE238, &PRO 331), Ionic bonding (with GLU328, LYS80 & ARG112) and Water bridge interaction (with ARG100, ARG112, GLU113, LYS120, GLY153, LYS189, GLN190, GLY191, GLY233, PHE235, GLY237, HIS316, GLU328, LEU329, LYS330 and GLU360). New interactions were observed in the MD simulation, which contributed to the stability of the complex. Also there was couple of ionic interaction formed in the MD simulation which not observed in the 2D assessment.

In the Complex B2 (Adapalene +30sR complex), the RMSD revealed that the complex was stable from 0nsec to 10nsec and drifted afterwards till the end of the simulation. The protein RMSF (value, 9.5 Å at 157nsec) revealed the highest conformational change in the target. The complex contact shown in Figure 3c revealed Hydrogen bonding (with LYS314, GLU360, GLN190, SER155, GLY153, ARG112 & ANS192), Hydrophobic interaction (with TRY104, ILE116, PHE235 & VAL236) and Water bridge interaction (with ARG112, GLU113, SER115, GLN190, GLY191, LYS314, HIS316 & GLU360). The ligand retained a similar interaction with the compound and formed new interactions that resulted in its stability at the binding pocket.

In the Complex B3 (Diosmin +30sR- complex), the RMSD showed that the ligand (Diosmin) drifted from the beginning of the simulation till the end. This could be a result of natural dissociation resulting from an initial conformational change in the protein. However, the average drifting distances of the ligand are within an acceptable range of 1.3 Å.

The observed protein highest RMSF was 9.5 Å at 220nsec and indicates higher structural perturbation when compared to the reference complex. The complex contact shown in figure 3c revealed Hydrogen bonding (with ASP103, GLU113, LYS120, ASP152, LYS189, GLN190, GLY191, ASN192 & LEU329), Hydrophobic interaction (with TYR105 & PHE235), Ionic bonding(with LEU110) and Water bridge interaction (with ASP103, TYR105, LEU110, ARG112, GLU113, LYS120, ASP152, GLY191, ASN192, LYS314, GLY237, HIS316, THR318, GLU328, LEU329, ARG357 & GLY358). The drug maintained and formed new hydrogen bonding which was crucial to it specificity and binding affinity.

In the Complex B3 (30sR-Azelastine complex), the RMSD shown in Figure 3a revealed that the drug drifted from the beginning of the simulation till the end. Again, this could also be due to the conformational changes in the target structure, and the drifting distance is within the acceptable range. The observed protein's highest RMSF value was 14.1 Å at 225nsec, which indicates higher conformational changes in the protein residues and flexibility during the simulation. The complex contact shown in Figure 3c revealed Hydrogen bonding (with LYS330, LYS189, & LEU329), Hydrophobic interaction (with ILE116, PHE235, TYR313, & LEU329) and Water bridge interaction (with ARG112, GLU119, LYS188, LYS189, GLN190, VAL236, GLN294, ANS298, LYS314, & LYS330). The drug complemented the few hydrogen bonding interaction by forming more of water bridge interactions. Water bridge interactions play a crucial role in drug-receptor binding by acting as intermediaries to form hydrogen bonds, which can stabilize the complex, enhance specificity, and influence the drug's conformation. These water molecules form intricate networks that can either directly link the drug and receptor or indirectly stabilize the binding site by holding other water molecules in position (31). From the MD simulation results for 30sR, Adapalene Diosmin and Azelastine vis-à-vis the reference compound Doxycycline, exhibited good interactions with the target, considering their binding affinity, stability and interaction during the MD simulation.

5. Conclusion

From this study, It can be concluded that Adapalene, Diosmin, Azelastine and other frontrunner compounds were predicted to have activity against onchocerciasis causative agents due to their ability to bind with Glutamate Chloride ion-gated channel and 30s ribosomal protein. The essence of this study was to identify a readily available therapeutic option in the case of onchocerciasis and prevent the possible emergence of drug resistance. We recommend further studies, especially using clinical trials to ascertain the appropriate doses at which the activities of these drugs will be effective and the extent of their activity or duration, possible side effects and adverse effects. Possibly, other identified frontrunner drugs should be evaluated.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors have no conflicts of interest to declare. All co-authors have seen and agree with the contents of the manuscript. We certify that the submission is original work and is not under review at any other publication.

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