**In Silico Study of Cucurbita maxima Compounds as Potential Therapeutics Against Schistosomiasis**

Floryn Lynorah Mtemeli1,2, Ryman Shoko1, Joice Ndlovu1 and Grace Mugumbate2

1Department of Biology, School of Natural Sciences and Mathematics, Chinhoyi University of Technology, Chinhoyi, Zimbabwe. 2Department of Chemical Technology, Midlands State University, Gweru, Zimbabwe.

**ABSTRACT:** Schistosomiasis, a disease usually related to poverty and poor sanitation, affects more than 200 million people worldwide. Since the 1970s, the medical sector has depended on a single drug, praziquantel, for the treatment of the disease. The emerging evidence of resistance of the Schistosoma parasite to praziquantel and the drug’s inefficacy against juvenile stages of the parasite makes the need to find alternative drugs an urgent matter. In this study, we explored the inhibition potential of compounds from *Cucurbita maxima* using molecular docking studies on *Schistosoma mansoni* purine nucleoside phosphorylase (SmPNP) and *Schistosoma haematobium* 28-kDa glutathione S-transferase (Sh28kDaGST). Following molecular docking studies and analysis of the active sites, the primary amino acids that were observed and shown to be involved in the SmPNP-ligand interaction are CYS 33, ARG 86, HIS 88, TYR 90, ALA 118, ALA 119, PRO 200, TYR 202, GLU 203, VAL 219, MET 221, THR 244, ASN 245, PRO 257 and HIS 259. For the Sh28kDa-ligand interaction, the primary amino acids were PHE 11, ARG 16, TRP 41, LEU 53, GLU 70 and SER 71. Momordiciside I aglycone binds to SmPNP with the lowest binding affinity of −7.9 kcal/mol by pi sigma bond interactions with HIS 88. Balsaminoside B binds to Sh28kDaGST with a binding affinity of −7.6 kcal/mol by hydrogen bond interaction with TRP 41, LEU 53 and SER 71. Pharmacokinetic studies showed favourable drug-like properties for the 10 compounds that exhibited the lowest binding energies. Therefore, we propose that bioactive compounds from *C. maxima* be considered as potential novel drug hits in the treatment of schistosomiasis.

**KEYWORDS:** Schistosomiasis, *Cucurbita maxima*, purine nucleoside phosphorylase, 28-kDa glutathione S-transferase, pharmacokinetics

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**INTRODUCTION**

*Schistosoma* species are digenetic blood trematodes and are the causal agents of schistosomiasis.1 The annual estimated number of deaths due to the disease varies between 24,000 and 200,000 globally.2 The 6 species responsible for morbidity are *Schistosoma mansoni*, *S. haematobium*, *S. japonicum*, *S. guineensis*, *S. mekongi*, and *S. intercalatum*.1 The most common species in sub-Saharan Africa are *S. mansoni* and *S. haematobium*.3 Since 1970, the treatment of schistosomiasis has greatly relied on the drug praziquantel.4 The reliance on a single drug for the treatment of the disease poses a threat to the medical sector as this can lead to drug resistance. Reduced efficacy of the drug following mass drug administration programmes and the reported laboratory-based resistance5 necessitates the need for the search for potential novel drug candidates.

Research in drug discovery based on natural products has been practised for a long time.6 Various plants have been investigated for anti-schistosomal activity *in vitro* and *in vivo*. These include *Zizinger officinale*,7 *Anomidiun mannii*,7 *Rauwolfia vomitoria*,8 *Pulatilla chinensis*,9 and *Artemisia annua*.10 *Cucurbita* cultivars such as *Cucurbita pepo* and *Cucurbita moschata* have also been tested for anti-schistosomal activity. *C. pepo* seed oil has been shown to induce microsatellite instability and tegumental damage to *S. mansoni in vitro*,11 while the curative effect of *C. moschata* was observed when patients infected with schistosomiasis were treated with daily doses of the powdered seeds.9

*Cucurbita maxima* are rich in alkaloids, flavanoids, phenolics, carbohydrates, tannins, saponins, terpenoids, and proteins. The plant is cultivated for nutritional and medicinal purposes.12 For centuries, the plant has been used to treat intestinal infestations,13 renal failure,14 constipation, hyperplasia, and parasite infestation.15 Oral consumption of the seeds has also been used for blood pressure regulation.16 The molluscicidal potential and potency of *C. maxima* has been studied and successfully determined.17 However, there is a dearth of literature on the plant’s anti-schistosomal properties. Currently, 17 compounds from the plant are available on online databases such as PubChem (https://pubchem.ncbi.nlm.nih.gov/) and CHEMBL (https://www.ebi.ac.uk/chembl/). However, data on *in silico* studies on the anti-schistosomal activities of the plant is currently unavailable in the public domain.

Various schistosome protein and kinetic parameters have been studied as potential drug targets. Presently, 238 schistosome protein structures are registered in the Protein Data Bank and most of the proteins were obtained through X-ray...
crystallography.\textsuperscript{18} \textit{S. mansoni} purine nucleoside phosphorylase (\textit{SmPNP}) and \textit{S. haematobium} 28-kDa glutathione S-transferases (\textit{Sh28kDaGST}) are crucial targets in schistosomes.

Purine nucleoside phosphorylase (PNP) also known as inosine phosphorylase,\textsuperscript{19} plays a fundamental role in the maintenance of proper cellular function and metabolism, acting both in the \textit{de novo} purine synthesis and the purine nucleotide salvage pathway.\textsuperscript{20} One crucial component of the salvage pathway is the catalysis of the reversible phosphorolysis of the N-ribosidic bond of 6-oxopurine deoxynucleosides and nucleosides delivering their correspondent base and ribose-1-phosphate.\textsuperscript{21} PNP facilitates the metabolism of inosine into hypoxanthine, adenosine into adenine and guanosine into guanine, and in each case, a ribose phosphate is created. Mutations in the PNP enzyme lead to severe combined immunodeficiency (SCID).\textsuperscript{22}

The \textit{Sh28kDaGST} are enzymes associated with parasite metabolic cycles and host immune adjustment.\textsuperscript{23} In schistosomes, 28kDaGST have been shown to revoke the development of host epidermal Langerhans cells to the depleting lymph nodes.\textsuperscript{24} The protein is uncovered on the outer layer of the cercaria in the same manner as in adult worms, suggesting its inclusion in the parasite-host communication. First discovered in the 1980s, the protein is considered a promising candidate for a schistosomiasis vaccine, having undergone successful phases 1 and 2 clinical trials.\textsuperscript{25} It is hypothesised that the enzymes assist the schistosomes by protecting them from membrane damage and from toxins circulating in the host blood.\textsuperscript{24} This is achieved through immune-effector cells at the parasite surface, yielding lipid peroxidation products. Also, the increase in the solubility of haematin in the schistosome gut aids in the reduction of the \textit{constipation} of worms.\textsuperscript{24}

There is a need to control morbidity and eventually eliminate schistosomiasis as well as to attain the Sustainable Development Goal 3 ‘achieve health for all’.\textsuperscript{26} To achieve this goal, computational biology studies can be carried out to speed up drug discovery efforts against schistosomiasis. In this work, we screened the library of 17 \textit{Cucurbita maxima} bioactive compounds to determine their anti-schistosomal properties using molecular docking against \textit{SmPNP} and \textit{Sh28kDaGST}. Our results show that momordicoiside I aglycone and Balsaminoside B have the lowest binding affinity of $-7.9$ and $-7.6$ kcal/mol, respectively.

\textbf{Materials and Methods}

\textbf{Protein preparation}

The crystal structures of \textit{SmPNP} (3FAZ) and \textit{Sh28kDaGST} (1OE7) were retrieved from the PDB (https://www.rcsb.org/) in complex with co-crystallised ligands. The proteins were prepared using Biovia Discovery Studio Visualiser v21.1.0.20298 (http://www.accelrys.com) through deletion of water molecules and addition of missing hydrogen atoms. The metal ionisation was corrected to certify formal charge and force field treatment using Autodock tools. All co-crystallised ligands were cut from the protein complexes and used in validating the molecular docking protocol through calculation of root mean square deviation (RMSD) using Biovia Discovery Studio. The proteins were optimised and refined for docking analysis using the Pyrx v 2008 to 2012 (Sargis Dallakyan, The Scripps Research Institute).

\textbf{Ligand preparation}

The phytochemicals of \textit{C. maxima} were retrieved from published literature,\textsuperscript{27} their structures were downloaded from the CHEMBL database (https://www.ebi.ac.uk/chembl/). The ligands were prepared using the Open Babel module of the Pyrx tool by using the force field uff.

\textbf{Molecular docking}

Molecular docking simulations were done using Autodock Vina integrated with the Pyrx software. \textit{C. maxima} phytochemicals were docked into the active sites of \textit{SmPNP}\textsuperscript{28} and \textit{Sh28kDaGST}\textsuperscript{24} proteins. The grid was generated using the receptor grid generation module of the Pyrx tool (coordinates are shown in Table 1). The grid box was adjusted to cover the catalytic site residues for \textit{SmPNP} and \textit{Sh28kDaGST} proteins.

The best 10 ligands according to the binding energy $\Delta G$ binding and RMSD values in each trial were chosen as novel inhibitors. The 17 compounds were docked against the catalytic site of the proteins using the binding pocket of the co-crystallised ligands which had been removed before docking. Visualisation of the protein-ligand complex was performed using Biovia Discovery Studio 2021.

\textbf{Toxicity analysis}

The SMILE structures of 10 compounds with the lowest binding energy were retrieved from CHEMBL. Using Lipinski’s rule of 5, the prediction of absorption, distribution, metabolism, elimination and toxicity (ADMET) analysis was done using the pkCSM server (http://biosig.unimelb.edu.au/pkcsms/).\textsuperscript{29} The following parameters were considered: human intestinal absorption (%), blood-brain barrier permeability.

\begin{table}[h]
\centering
\caption{The Pyrx grid box coordinates.}
\begin{tabular}{|l|c|c|c|}
\hline
PROTEIN & CENTRE X COORDINATES & CENTRE Y COORDINATES & CENTRE Z COORDINATES \\
\hline
\textit{SmPNP} & -6.4363 & 1.5792 & 30.1628 \\
\textit{Sh28kDaGST} & 15.6356 & 0.7630 & 26.34 \\
\hline
\end{tabular}
\end{table}

Abbreviations: \textit{Sh28kDaGST}, \textit{Schistosoma haematobium} 28-kDa glutathione S-transferase; \textit{SmPNP}, \textit{Schistosoma mansoni} purine nucleoside phosphorylase.
(log BB), metabolic interactions with cytochromes CYP2D6 and CYP3A4, total clearance (log mL/min/kg), Ames toxicity; human ERG I inhibition, oral rat acute toxicity (LD50) in mol/kg and oral rat long-term toxicity lowest adverse effect levels (LOAEL) in log mg/kg body weight/day. ADMET properties of praziquantel were also predicted for comparative studies.

Results and Discussion
Molecular docking
Virtual screening of a library of compounds from C. maxima was done using molecular docking against the targeted proteins SmPNP and Sh28kDaGST. Each of the generated docked complexes was observed centred on minimum binding energy values (kcal/mol). Pharmacokinetic profiling of the phytocompounds was further done to predict their drug-likeness properties. The interactions of the ligands within the binding pockets of SmPNP and Sh28kDaGST are shown in Table 3.

The amino acid residues involved in the interactions and each of their position in their ligand-binding site were identified. Hydrophobic, pi-pi stacking, hydrogen bonding and many other interactions between the protein and the ligands were demonstrated through molecular docking. The primary amino acids that were observed and shown to be involved in the SmPNP-ligand interaction are CYS 33, ARG 86, HIS 88, TYR 90, ALA 118, ALA 119, PRO 200, TYR 202, GLU 203, VAL 219, MET 221, THR 244, ASN 245, PRO 257, and HIS 259. For the Sh28kDaGST-ligand interaction, the primary amino acids were PHE 11, ARG 16, TRP 41, LEU 53, GLU 70 and SER 71.

Among the 10 compounds docked against proteins, Momordicoside I aglycone and Balsaminoside B were predicted to have the lowest binding energy values when bound to SmPNP and Sh28kDaGST, respectively. Momordicoside I aglycone is a triterpenoid saponin found in the Cucurbitaceae family and previous studies have shown the compounds’ anti-diabetic properties and anti-obesity properties through reduction of fat accumulation.31-33 Following the docking of Momordicoside I aglycone against SmPNP, it displayed pi sigma bonding with amino acid residue HIS 88 with a binding affinity of −7.9 kcal/mol. Balsaminoside B is a triterpene that has been shown to have antimalarial and anticancer activity.34 The docking results from Balsaminoside B docked against Sh28kDaGST displayed a binding affinity of −7.69 kcal/mol. Hydrogen bond interactions with the amino acid residues TRP 41, LEU 53, SER 77 and carbon-hydrogen bonds with ARG 16 were observed. Our results are in agreement with studies that have shown the in vitro anti-schistosomal activity of triterpenes in plants such as Argemone mexicana,35 Momordica balsamina, Actinopyga echinites, and Holothuria polii.30,36

Balsaminol E showed affinity on both SmPNP and Sh28kDaGST with binding energies of −7.6 and −7.5 kcal/mol, respectively. For SmPNP, the amino acid residue interactions observed with Balsaminol E were hydrogen bonds with ARG 86 and ASN 244, alkyl and pi alkyl bonds with TYR 202, VAL 219 and PRO 257. For Sh28kDaGST, the interactions observed with Balsaminol E were hydrogen bonds with TRP 41, pi sigma bonds with PHE 11, pi alkyl and alkyl bonds with LEU 53 and carbon-hydrogen bonds with ARG 16.

CHEMBL468165 binds to SmPNP with a binding affinity of −7.0 kcal/mol by hydrogen bond interactions with PRO 200 and pi sigma bond interactions with TYR 90 and HIS 259. Charantadiol A interacts with SmPNP through hydrogen bonds with amino acid residues at CYS 33, VAL 219; alkyl and pi alkyl bonds at TYR 202 and MET 221. 3beta,25-diol had a binding affinity of −6.6 kcal/mol exhibiting pi sigma bonds with SmPNP amino acid residues at HIS 259 and pi alkyl and alkyl bonds at TYR 202 and MET 221.

Neither visible interactions nor Lipinski violations were observed between Balsaminol C and Sh28kDaGST. Balsaminol E and Balsaminoside C, both triterpenoids, had the same binding affinities of −7.5 kcal/mol with Sh28kDaGST amino acid residues exhibiting pi sigma and hydrogen bonds. CHEMBL249658 binds to Sh28kDaGST with a binding affinity of −7.1 kcal/mol showing pi sigma bond interaction with PHE 11 and TRP 41. Docking results showed that compounds generally exhibited good docking energy values with the highest binding energy values of −6.6 kcal/mol for SmPNP and −7.1 kcal/mol for Sh28kDaGST. Table 1 shows the Pyx grid box coordinates; Table 2 shows the drug-like properties of the 10 best ligands and Table 3 shows the interactions between the ligands and the proteins in three-dimensional images.

Pharmacokinetic Studies
Tables 4 and 5 show the pharmacokinetics and drug-likeness parameters of each experimental compound. Momordicoside I aglycone’s toxicity study confirms that it has an excellent intestinal absorption of 96.373% and acceptable blood-brain barrier permeability of log BB −0.117. The log BB value of Momordicoside I aglycone and all the compounds was less than the standard (log BB 0.3) which suggests that the compounds do not readily cross the blood-brain barrier. The compounds do not inhibit the cytochrome P3A4 and cytochrome 2D6 enzymes and can be easily excreted. The pharmacokinetic predictions suggest that none of the compounds was Ames toxic and none inhibited the potassium channels encoded by the human ether-a-go-go gene 1 (herG1). The pharmacokinetic properties of the favourable compounds were comparable to that of praziquantel with 70% of the compounds showing better intestinal absorption than praziquantel. The predicted intestinal absorption of all the 10 compounds was greater than the set standard of 30%. All of the compounds exhibited a total drug clearance prediction that was greater than 0. Also, all the compounds showed maximum tolerated values that were less than the standard (0.477 mg/kg/day) and in the same range as praziquantel. The highest predicted rat LD50 value of the
Table 2. The drug-likeness properties and binding affinities in kcal/mol of the 10 best ligands.

| PROTEIN-LIGAND COMPLEX | MOLECULAR WEIGHT | LOG P | ROTATABLE BONDS | ACCEPTORS | DONORS | SURFACE AREA | LIPINSKI VIOLATIONS | BINDING AFFINITY IN kcal/mol |
|------------------------|------------------|-------|-----------------|-----------|--------|--------------|----------------------|-----------------------------|
| SmPNP CHEMBL3264665 Momordicoside I aglycone | 456.711 | 6.2946 | 4 | 3 | 2 | 201.616 | 1 | −7.9 |
| SmPNP CHEMBL1254849 Balsaminol E | 456.711 | 6.4848 | 4 | 3 | 2 | 201.670 | 1 | −7.6 |
| SmPNP CHEMBL 468165 | 440.712 | 7.2259 | 4 | 2 | 2 | 7.2259 | 1 | −7.0 |
| SmPNP Charantadiol A CHEMBL3264664 | 454.695 | 6.4182 | 4 | 3 | 2 | 201.616 | 1 | −6.7 |
| SmPNP CHEMBL3264663 3beta,25-diol | 486.737 | 6.2671 | 5 | 4 | 2 | 213.095 | 1 | −6.6 |
| Sh28kDaGST CHEMBL1928850 Balsaminoside B | 620.868 | 4.1008 | 7 | 8 | 6 | 264.096 | 2 | −7.6 |
| Sh28kDaGST CHEMBL1254849 Balsaminol E | 456.711 | 6.4848 | 4 | 3 | 2 | 201.670 | 1 | −7.5 |
| Sh28kDaGST CHEMBL1254762 Balsaminoside C | 620.868 | 4.1008 | 7 | 8 | 6 | 2 | −7.5 |
| Sh 28kDaGST CHEMBL1254761 Balsaminol | 470.694 | 5 | 4 | 2 | 205.832 | 0 | −7.2 |
| Sh 28kDaGST CHEMBL349658 | 468.722 | 7.0723 | 5 | 3 | 1 | 207.611 | 1 | −7.1 |

Abbreviations: Sh28kDaGST, S. haematobium 28-kDa glutathione S-transferase; SmPNP, S. mansoni purine nucleoside phosphorylase.

Table 3. Shows the interaction between the docked ligands and the proteins in 3-dimensional images.
Table 3. (Continued)

| PROTEIN-LIGAND COMPLEX | 3D INTERACTION |
|------------------------|----------------|
| SmPNP                  | CHEMBL468165   |

![SmPNP - CHARANDIOL A](image1)

SmPNP Charantadiol A (CHEMBL3264664)

![SmPNP - Charantadiol A](image2)

SmPNP 3beta,25-diol (CHEMBL3264663)

![SmPNP - 3beta,25-diol](image3)
Table 3. (Continued)

| PROTEIN-LIGAND COMPLEX | 3D INTERACTION |
|-------------------------|----------------|
| Sh 28kDaGST             | Balsaminoside B (CHEMBL1928850) |
| Sh28kDaGST              | Balsaminol E (CHEMBL1254849) |
| Sh28kDaGST              | Balsaminoside C (CHEMBL1928851) |
| Sh 28dkaGST             | Balsaminol C (CHEMBL1254762) |
Table 3. (Continued)

| PROTEIN-LIGAND COMPLEX | 3D INTERACTION |
|------------------------|----------------|
| Sh 28dkaGST            | CHEMBL249658   |

Abbreviations: Sh28kDaGST, S. haematobium 28-kDa glutathione S-transferase; SmPNP, S. mansoni purine nucleoside phosphorylase.

Table 4. The pharmacokinetic properties of the best 10 compounds.

| COMPOUND         | INTESTINAL ABSORPTION, % | BLOOD-BRAIN BARRIER PERMEABILITY, LOGBB | CYP3A4 INHIBITOR | CYP2D6 INHIBITOR | TOTAL CLEARANCE LOG (MIL/MIN/KG) |
|------------------|--------------------------|----------------------------------------|------------------|------------------|----------------------------------|
| CHEMBL3264665    | 96.373                   | −0.117                                 | NO               | NO               | 0.292                            |
| CHEMBL1254849    | 96.753                   | −0.644                                 | NO               | NO               | 0.334                            |
| CHEMBL468165     | 95.149                   | −0.207                                 | NO               | NO               | 0.33                             |
| CHEMBL3264664    | 97.319                   | −0.001                                 | NO               | NO               | 0.401                            |
| CHEMBL3264663    | 97.757                   | −0.424                                 | NO               | NO               | 0.32                             |
| CHEMBL1928850    | 50.312                   | −1.118                                 | NO               | NO               | 0.492                            |
| CHEMBL1928851    | 50.312                   | −1.118                                 | NO               | NO               | 0.492                            |
| CHEMBL1254762    | 99.995                   | 0.254                                  | NO               | NO               | 0.359                            |
| CHEMBL249658     | 98.037                   | 0.107                                  | NO               | NO               | 0.423                            |
| Praziquantel     | 93.386                   | 0.3                                    | NO               | NO               | 1.182                            |

compounds was 4.256 mol/kg exhibited by the compounds CHEMBL1928850 and CHEMBL19288.

The calculated RMSD values and the superimposed co-crystallised and docked ligands are shown in Figures 1 and 2.

Our results are in agreement with studies that have shown that Balsaminol F, a closely related tripetene to the promising compounds from this study, has anti-anthelmintic properties against *S. mansoni* in vitro with an LC50 value of 15 μM.

Balsaminoside B and Balsaminoside C had similar pharmacokinetic properties. The compounds had the lowest intestinal absorption of 50.312%. This can be attributed to the fact that they are both triterpenes with similar molecular formulae and their differentiation is difficult as also observed by Serala et al. The ligands Momordicoside I aglycone, Balsaminol E, CHEMBL468165, Charantadiol A, 3β,25-diol, Balsaminol E and CHEMBL249658 violated the ROF with log P values greater than 5. Although the log P value, which affects the compound’s lipophilicity, is a major determining factor in a compound’s penetration across vital membranes and biological barriers, some researchers argue that these rules can be done away with at least during a virtual screening protocol, because
it is essential to first look for a potent molecule and once potency is validated, improved kinetics can then be sought.

Hit to lead compound identification may take time, making it impossible for most current hit compounds to reach the market. However, various approaches are being brought forward in coming up with novel anti-schistosomal agents. An interesting iterative drug development process successfully identified derivatives of the OXA drug that are effective against all three species of the Schistosoma parasite. Evaluation of 6-Gingerol and its modified analogues as therapeutic candidates against \textit{S. mansoni} phosphofructokinase\textsuperscript{41,42} has also been done. Molecular docking methods showed oxadiazole-2-oxides derivatives furoxan exhibiting significant anti-schistosomal activity against \textit{S. japonicum}.\textsuperscript{43} These \textit{in silico} studies, including ours, lay a crucial foundation in the development of novel drugs against schistosomiasis.

\textbf{Conclusion}

Praziquantel has been the only drug used to treat schistosomiasis since 1970 making it vital to look for novel drugs to treat the 

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### Table 5. Pharmacokinetic properties of the best 10 compounds.

| COMPOUND       | AMES TOXICITY | MAX. TOLERATED DOSE (HUMAN) \(\text{LOG (mg/kg/day)}\) | HERG I INHIBITOR | ORAL RAT ACUTE TOXICITY (LD50) \(\text{(MOL/kg)}\) | ORAL RAT LONG-TERM TOXICITY (LOAEL) \(\text{(mg/kg_bw/day)}\) |
|----------------|---------------|----------------------------------------------------------|-----------------|-------------------------------------------------|----------------------------------------------------------|
| CHEMBL3264665 | NO            | -0.869                                                   | NO              | 3.398                                          | 1.796                                                   |
| CHEMBL1254849 | NO            | -0.734                                                   | NO              | 3.996                                          | 1.949                                                   |
| CHEMBL468165  | NO            | -0.976                                                   | NO              | 3.548                                          | 2.26                                                    |
| CHEMBL3264664 | NO            | -0.863                                                   | NO              | 3.085                                          | 1.818                                                   |
| CHEMBL3264663 | NO            | -0.441                                                   | NO              | 3.104                                          | 1.376                                                   |
| CHEMBL1928850 | NO            | -1.559                                                   | NO              | 4.256                                          | 2.923                                                   |
| CHEMBL1928851 | NO            | -1.559                                                   | NO              | 4.256                                          | 2.923                                                   |
| CHEMBL1254762 | NO            | -0.426                                                   | NO              | 3.45                                           | 1.693                                                   |
| CHEMBL249658  | NO            | 0.072                                                    | NO              | 2.251                                          | 1.752                                                   |
| Praziquantel   | NO            | -0.554                                                   | NO              | 2.469                                          | 1.248                                                   |

Abbreviation: LOAEL, lowest adverse effect levels.

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\textbf{Figure 1}. Superimposed SmPNP co-crystallised, docked ligand and RMSD values used as a validation of docking protocol. RMSD indicates root mean square deviation; SmPNP, \textit{S. mansoni} purine nucleoside phosphorylase.
disease. *C. maxima* seeds have been used in different parts of the world as traditional medicine for treatments of gastrointestinal parasites such as anthelmintic, urinary dysfunctions, hyperplasia of prostate, dysuria, cardiovascular disease, enuresis, and lowering blood glucose. This *in silico* study was aimed at exploring *Cucurbita maxima* compounds as potential therapeutics against schistosomiasis. We used computational modelling techniques to predict the inhibitory potential of *C. maxima* against SmPNP, a crucial protein in purine synthesis and Sh28kDaGST which is involved in parasite metabolic cycles. The binding of *C. maxima* compounds with SmPNP and Sh28dKa, pharmacokinetic properties as established by docking studies, demonstrate that the *C. maxima* ligands are promising anti-schistosomal agents. Momordicoside I aglycone and Balsaminoside B exhibited the highest binding affinities with favourable drug-like properties. The ADMET properties of the compounds favour their consideration as drug candidates. We propose that *C. maxima* compounds be considered as potential therapeutics against schistosomiasis. We suggest that future research should involve molecular dynamic simulations to validate the structural stability of the selected ligands. Thereafter, *in vitro* and *in vivo* assays are required to get a more detailed analysis of the activity of the compounds within live organisms.

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**Author Contributions**
All authors contributed to the study conception and design. Primary investigation, formal analysis and data interpretation were carried out by FLM. The first draft of the manuscript was written by FLM and all authors commented on the previous versions of the manuscript. RS obtained funding and supervised the study. All authors have read and agreed to submit the final version of the manuscript.

**Data Availability Statement**
Data can be made available upon request.

**ORCID iD**
Floryn Lynorah Mtemeli [https://orcid.org/0000-0001-8755-8477](https://orcid.org/0000-0001-8755-8477)

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