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In silico Evaluation of Plant-Derived Phytochemicals as Potential Inhibitors of *Onchocerca volvulus*

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Abstract

Onchocerciasis (river blindness), caused by *Onchocerca volvulus*, remains a major neglected tropical disease with significant socioeconomic and public health impact in endemic regions. Current therapeutic options are constrained by adverse effects, emerging resistance concerns, and the inability of available drugs to effectively eliminate adult worms. This study applied a computational drug-discovery strategy to evaluate the inhibitory potential of selected phytochemicals against the *O. volvulus* pi-class glutathione S-transferase (GST), a key detoxification enzyme involved in parasite survival. The target protein (PDB ID: 1TU7) and reference ligand (GSH) were prepared using UCSF Chimera, PyMOL, AutoDockTools, and MGL Tools. A total of 6,500 phytochemicals sourced from Phytochemical databases were screened using Lipinski's Rule of Five, yielding 1,793 compounds for molecular docking. The reference ligand GSH exhibited a mean binding energy of -4.7 kcal/mol, whereas all screened phytochemicals demonstrated stronger binding, with affinities ranging from -8.0 to -7.1 kcal/mol. The top-ranking compounds are Daturamalakin B (-8.0 kcal/mol), Neveskone (-7.9 kcal/mol), and Daturametelin D (-7.8 kcal/mol) showed the most favourable interactions. All front-runner phytochemicals satisfied Lipinski's criteria and displayed no mutagenicity, tumourigenicity, reproductive toxicity, or irritant effects based on DataWarrior predictions, indicating good oral drug-likeness and preliminary safety. Overall, these findings indicate that the identified phytochemicals possess superior binding affinities compared to the reference ligand and may serve as promising lead compounds for the development of new anti-onchocerciasis therapeutics.

Keywords: *Onchocerca volvulus*; Glutathione S-transferase; Molecular docking; Phytochemicals; Binding affinity; Lipinski's Rule; Toxicity screening

1. Introduction

Onchocerciasis, commonly referred to as river blindness, is a neglected tropical disease caused by the filarial nematode *Onchocerca volvulus*, which is transmitted through repeated bites of infected blackflies (*Simulium* spp.) that breed near fast-flowing rivers and streams in rural communities across sub-Saharan Africa and parts of Latin America [1-3]. Globally, an estimated 37 million people are infected, with more than 600,000 individuals blind and approximately 500,000 visually impaired, making onchocerciasis the second leading infectious cause of blindness after trachoma [4].

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In addition to severe ophthalmic complications, chronic infection results in debilitating dermatological manifestations, reduced productivity, psychosocial stigma, and substantial socio-economic disruption in affected regions [3,5].

Ivermectin, introduced in the late 1980s, transformed onchocerciasis control and remains the cornerstone of mass drug administration (MDA) programmes due to its safety and potent microfilaricidal action [6,7]. However, ivermectin exhibits limited macrofilaricidal activity and does not eliminate adult worms, necessitating yearly or twice-yearly treatment for 10–15 years—the reproductive lifespan of *O. volvulus*—to interrupt transmission [4,6]. Reports of severe adverse events in individuals co-infected with *Loa loa*, emerging concerns regarding ivermectin resistance, and evidence of persistent transmission in certain endemic foci underscore the urgent need for novel therapeutic agents with macrofilaricidal or sterilising capabilities [2,7,8].

Natural products have historically served as a rich source of chemotherapeutic agents, offering remarkable structural diversity and a wide range of biologically active scaffolds [9-12]. Phytochemicals-bioactive secondary metabolites including terpenoids, flavonoids, alkaloids, phenolics, and saponins-exhibit diverse pharmacological properties such as antioxidant, antimicrobial, antiparasitic, anti-inflammatory, and antiviral activities [13-15]. Their long-standing use in traditional medicine, particularly in Africa, alongside their accessibility, low cost, and cultural acceptance, makes plant-derived compounds attractive candidates for antifilarial drug discovery [11,16,17]. Several studies have reported anti-*Onchocerca* activity in extracts and purified constituents from African medicinal plants, emphasising the potential of phytochemicals as promising leads for macrofilaricidal drug development [16,17].

In recent years, *in silico* methodologies have become integral to early-stage drug discovery, allowing rapid screening of large compound libraries, prediction of protein–ligand interactions, and prioritisation of candidates prior to laboratory validation [18–22]. Computational approaches such as molecular docking, structure-based virtual screening, pharmacophore modelling, molecular dynamics simulations, and toxicity prediction help to reduce the cost, time, and attrition rates associated with conventional drug development pathways [20,23]. These tools have been widely applied in natural product research and have proven effective in identifying bioactive compounds with favourable drug-likeness, predicted safety, and strong binding affinity for validated therapeutic targets [21,23].

Given the limitations of current therapies and the need for new antifilarial agents, this study aimed to identify potential anti-*Onchocerca volvulus* compounds by virtually screening phytochemicals from African medicinal plants against a validated *O. volvulus* target protein (PDB ID: 1TU7). Molecular docking and computational analyses were performed to evaluate binding affinities, drug-likeness, and predicted interaction profiles. This approach provides a rapid, cost-effective, and scientifically robust strategy for identifying promising lead molecules for future experimental validation.

2. Materials and Methods

Several software programs were employed to investigate the activities of the selected phytochemicals against *Onchocerca volvulus* through molecular docking and post-docking analyses. These tools have demonstrated high reliability in computational drug-discovery workflows and are widely used in computer-aided drug design. The software included PyMOL, UCSF Chimera, AutoDock Tools (ADT), AutoDock Vina, Open Babel, GROMACS, and DataWarrior. Biological databases such as the Protein Data Bank (PDB) were utilised for bioinformatics mining, while phytochemicals were retrieved from Phytochemical databases for cheminformatics mining.

Supporting materials used in the docking workflow included:

- **Conf.txt** – An Ubuntu configuration file containing binding site coordinates derived from the grid box size and position.
- **bash binbash.sh** – A shell script used to automate and batch molecular docking runs in Ubuntu.
- **A Windows 10 Pro workstation** – Used for ligand and protein preparation in Chimera and AutoDock Tools.

2.1. Bioinformatics Mining – Identification of Target Sites

A systematic search of the Protein Data Bank (PDB) was conducted to identify a suitable *O. volvulus* protein target. Selection criteria were based on:

- A crystallographic resolution below 4.0 Å
- Presence of an organic ligand to help define the binding pocket
- Relevance to *O. volvulus* biology and pathogenesis

Based on these criteria, the glutathione S-transferase protein with PDB ID **1TU7** was identified and selected for further analysis.

2.2. Cheminformatics Mining

Phytochemicals were sourced from Phytochemical databases and downloaded in SDF format. These compounds were subjected to preliminary filtering using Lipinski's Rule of Five and toxicity parameters (mutagenicity, tumourigenicity, reproductive toxicity, irritancy, and undesirable functionalities) in DataWarrior. Only compounds passing these filters were retained and converted for downstream docking studies.

2.3. Selection and Preparation of Target Protein

The selected protein structure (PDB ID: 1TU7), with a resolution of 1.50 Å, contains two ligands: glutathione (GSH) and glycerol (GOL). The protein preparation steps were performed using UCSF Chimera and AutoDock Tools:

- **Chain simplification** – Duplicate chains were removed in Chimera, leaving only one chain. The file was saved as **"Deleted 1TU7"** in SDF format.
- **Retention of the ligand of interest** – All ligands except GSH were removed, and the structure was saved as **"Deleted 1TU7 + GSH"**.
- **Protein isolation** – GSH was subsequently removed, producing a ligand-free receptor saved as **"Filtered 1TU7"**.
- **Protein preparation in ADT** – The filtered protein was opened in AutoDock Tools, polar hydrogens were added, and Kollman charges were assigned. The prepared receptor was finally saved as a **PDBQT** file for docking.

2.4. Selection and Preparation of Ligands

The reference ligand for docking was selected based on two criteria:

- The ligand must be an organic molecule
- It must occupy a defined binding pocket in the receptor (confirmed using PyMOL and Chimera)
- Glutathione (GSH) met these requirements and was downloaded from the PDB in ideal SDF format.
- Ligand preparation was carried out using Open Babel (Ubuntu) and AutoDock Tools (Windows 10):
  - **Format conversion in Ubuntu** –
    - Obabel ligand.sdf -O ligand.mol2
  - **Transfer to Windows** – MOL2 files were moved to Windows for further processing.
  - **Preparation in ADT** –
    - Gasteiger charges were computed
    - All bonds were set to non-rotatable
    - Ligands were saved in PDBQT format for docking

2.5. Validation of Docking Protocol

Docking validation involved identifying the binding pocket of the target protein. The reference ligand (GSH) was isolated in Chimera to determine its orientation within the active site.

In AutoDock Tools:

- The prepared receptor and isolated GSH ligand were loaded
- A grid box was generated to completely enclose the binding site
- The grid centre and dimensions were documented (Table 1)

Table 1 Centre and Size of Grid Box

Grid box	Centre	Dimension
X	17.06	14
Y	-1.057	12
Z	24.028	12

2.6. Molecular Docking

- Molecular docking simulations were performed using AutoDock Vina on Ubuntu.
- All receptor and ligand PDBQT files were placed into a single directory
- The directory was opened in the terminal
- Docking simulations were executed using the command:
- bash binbash.sh
- Each ligand generated an output log containing its predicted binding affinity values.

2.7. Post-Docking Analysis

Upon completion of the docking runs:

- Binding affinity values for each ligand were extracted and compiled in Microsoft Excel
- Mean docking scores and standard deviations were calculated across four replicates (A1–A4)
- Ligands were ranked, and the top 20 compounds exhibiting the strongest affinities were designated as the **front-runner phytochemicals**

These compounds were visualised in PyMOL to examine their binding orientation within the active site. Each ligand was assigned a unique colour for clarity.

Protein–ligand interactions were assessed based on:

- Hydrogen bond formation
- Hydrophobic contacts
- Active-site amino acid residues involved
- Relevant binding-site interactions were captured and saved as PNG images for documentation and reporting.

3. Results

3.1. Screening and Selection of Phytochemicals

A total of 6,500 phytochemicals were initially retrieved from Phytochemical databases. After filtering using Lipinski's Rule of Five and toxicity parameters in DataWarrior, 1,793 compounds satisfied the drug-likeness criteria and were retained for molecular docking against *Onchocerca volvulus* glutathione S-transferase (GST; PDB ID: 1TU7).

3.2. Molecular Docking Analysis

All 1,793 phytochemicals were docked against the prepared receptor using AutoDock Vina on Ubuntu, alongside the reference ligand glutathione (GSH). Docking was conducted in quadruplicate (A1-A4), and mean binding energies were calculated for each compound.

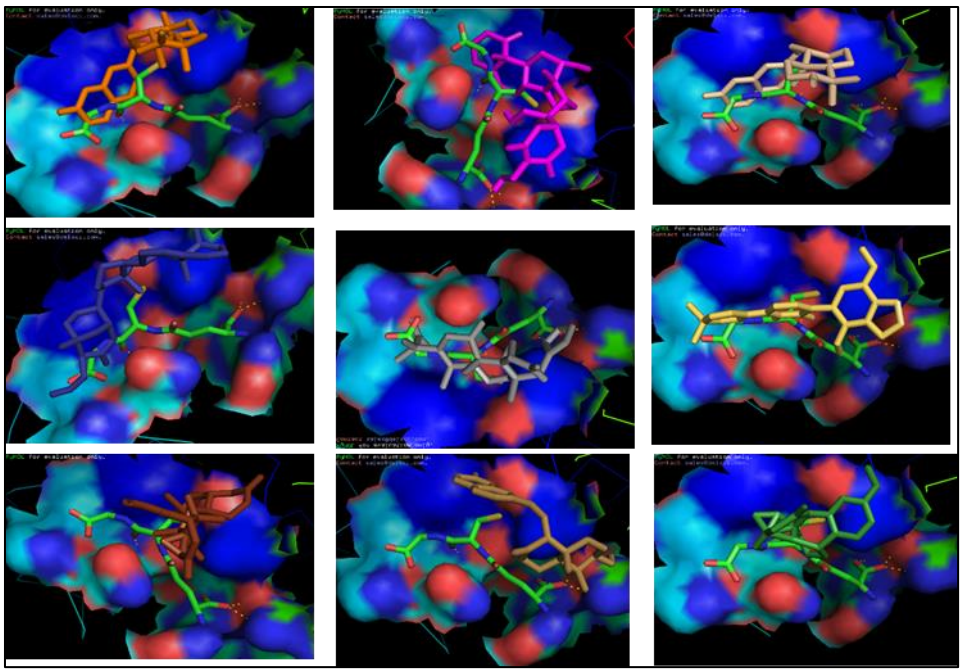
The top 20 phytochemicals exhibiting the strongest binding affinities ranging from -8.0 to -7.1 kcal/mol were identified as lead candidates. All top compounds demonstrated significantly stronger binding than the reference ligand GSH (mean = -4.7 kcal/mol).

3.3. Binding Affinity Profiles of Lead Compounds

Table 2 Binding energies (kcal/mol), mean values, and standard deviations for the top-ranking phytochemicals compared with the reference ligand GSH

S/N	Molecule Name	A1	A2	A3	A4	Mean	SD
1	Daturamalakin B	-8	-8	-8	-8	-8.0	0
2	Neveskone	-7.9	-7.9	-7.9	-7.9	-7.9	0
3	Daturametelin D	-7.8	-7.8	-7.8	-7.7	-7.8	0.05
4	Feselol	-8	-7.3	-7.4	-7.9	-7.7	0.35

5	Foetidin	-7.6	-7.6	-7.6	-7.6	-7.6	0
6	Limonin	-7.5	-7.5	-7.5	-7.5	-7.5	0
7	Gummosin	-7.5	-7.5	-7.4	-7.5	-7.5	0.05
8	Farnesiferol A	-7.4	-7.5	-7.5	-7.4	-7.5	0.06
9	Jamaicin	-7.5	-7.3	-7.2	-7.6	-7.4	0.18
10	Ferulsinaic Acid	-6.8	-7.6	-7.6	-7.5	-7.4	0.39
11	Mexicanolide	-7.3	-7.2	-7.5	-7.5	-7.4	0.15
12	Latrunculin A	-7.3	-7.3	-7.3	-7.3	-7.3	0.00
13	Galbanic Acid	-7.4	-7.3	-7.4	-6.8	-7.2	0.29
14	Ekeberin C1	-7.2	-7.2	-7.2	-7.2	-7.2	0.00
15	Ferrugone	-7.2	-7.2	-7.2	-7.2	-7.2	0.00
16	Isoschizogaline	-7.2	-7.2	-7.2	-7.2	-7.2	0.00
17	Marmaricin	-7.4	-7.1	-7.1	-7.1	-7.2	0.15
18	Lanuginosine	-7.1	-7.2	-7.2	-7.2	-7.2	0.05
19	Demethoxyexcelsin	-7.2	-7.2	-7.1	-7.1	-7.2	0.06
20	Fumariline	-7.1	-7.1	-7.1	-7.1	-7.1	0.00
414	GSHligand	-4.7	-4.8	-4.8	-4.5	-4.7	0.12



A - Neveskone, B - Daturamalakin B, C - Feselol, D - Daturametelin D, E - Ekeberin C1, F - Ferrugone, G - Limonin, H - Farnesiferol A, I - Isoschizogaline

Figure 1 Docked conformations of the top-ranking phytochemicals within the active-site pocket of *O. volvulus* GST (PDB ID: 1TU7)

3.4. Lipinski Drug-Likeness Evaluation

All 20 lead compounds satisfied Lipinski's Rule of Five, indicating favourable oral drug-likeness. Molecular weight, cLogP values, hydrogen bond donors, hydrogen bond acceptors, and molecular formulae are summarised in **Table 3**.

Table 3 Molecular descriptors (Lipinski parameters) of the top-ranking phytochemicals

S/N	Molecule Name	Molecular Weight (MW)	cLogP	HBA	HBD	Molecular Formula
1	Daturamalakin B	470.604	2.5837	6	3	C28H38O6
2	Neveskone	396.525	4.8231	4	1	C25H32O4
3	Daturametelin D	468.632	3.5588	5	0	C29H40O5
4	Feselol	382.498	4.3522	4	1	C24H30O4
5	Foetidin	382.498	4.5462	4	1	C24H30O4
6	Limonin	470.516	1.0279	8	0	C26H30O8
7	Gummosin	382.498	4.4305	4	1	C24H30O4
8	Farnesiferol A	382.498	4.4305	4	1	C24H30O4
9	Jamaicin	378.379	3.7324	6	0	C22H18O6
10	Ferulsinaic Acid	398.497	4.8707	5	1	C24H30O5
11	Mexicanolide	468.544	3.2076	7	0	C27H32O7
12	Latrunculin A	421.556	4.138	6	2	C22H31NO5S
13	Galbanic Acid	398.497	4.9176	5	1	C24H30O5
14	Ekeberin C1	440.534	2.8183	6	0	C26H32O6
15	Ferrugone	408.405	3.6624	7	0	C23H20O7
16	Isoschizogaline	322.407	2.8745	4	0	C20H22N2O2
17	Marmaricin	382.498	4.4305	4	1	C24H30O4
18	Lanuginosine	305.288	3.4648	5	0	C18H11NO4
19	Demethoxyexcelsin	384.383	3.1546	7	0	C21H20O7
20	Fumariline	351.357	3.4324	6	0	C20H17NO5

3.5. Toxicity Prediction

All lead phytochemicals showed favourable toxicity profiles. None demonstrated mutagenicity, tumourigenicity, reproductive toxicity, irritant effects, or undesirable functionalities, as shown in Table 4.

Table 4 Toxicity profile of the top-ranking phytochemicals

S/N	phytochemicals	Mutagenicity	tumorigenicity	Effect on Reproduction	Irritant Effect	Nasty functions
1	Daturamalakin B	None	None	None	None	None
2	Neveskone	None	None	None	None	None
3	Daturametelin D	None	None	None	None	None
4	Feselol	None	None	None	None	None
5	Foetidin	None	None	None	None	None
6	Limonin	None	None	None	None	None
7	Gummosin	None	None	None	None	None
8	Farnesiferol A	None	None	None	None	None
9	Jamaicin	None	None	None	None	None

10	Ferulsinaic Acid	None	None	None	None	None
11	Mexicanolide	None	None	None	None	None
12	Latrunculin A	None	None	None	None	None
13	Galbanic Acid	None	None	None	None	None
14	Ekeberin C1	None	None	None	None	None
15	Ferrugone	None	None	None	None	None
16	Isoschizogaline	None	None	None	None	None
17	Marmaricin	None	None	None	None	None
18	Lanuginosine	None	None	None	None	None
19	Demethoxyexcelsin	None	None	None	None	None
20	Fumariline	None	None	None	None	None

4. Discussion

The strength and stability of a protein–ligand complex are governed by the intermolecular interactions formed within the binding pocket, and molecular docking provides a computational means of estimating these interactions through predicted Gibbs free energy (ΔG) values [24-27]. More negative binding energies indicate stronger and more thermodynamically favourable interactions, reflecting higher affinity and greater potential for biological efficacy [28]. These predictions have become central to early-stage drug discovery, particularly for identifying natural compounds with high complementarity toward parasite-specific protein targets [29,30].

In the present study, all twenty selected phytochemicals demonstrated considerably stronger binding affinities toward *O. volvulus* glutathione S-transferase (GST; PDB ID: 1TU7) than the reference ligand, glutathione (GSH), which recorded a mean docking score of -4.7 kcal/mol. The top-scoring compounds-Daturamalakin B (-8.0 kcal/mol), Neveskone (-7.9 kcal/mol), and Daturametelin D (-7.8 kcal/mol)-exhibited remarkedly improved affinities, suggesting superior binding complementarity. GST plays a key role in parasite detoxification, oxidative stress defence, and immune evasion, making it an attractive chemotherapeutic target in filarial parasites [31,32]. The strong binding energies observed for these phytochemicals indicate their potential to interfere with GST catalytic function, thereby compromising parasite survival mechanisms.

Drug-likeness assessment is a critical component of rational drug development, with the Lipinski Rule of Five widely used to predict oral bioavailability and desirable pharmacokinetic properties [33-35]. All twenty front-runner phytochemicals satisfied Lipinski's criteria without violations, indicating favourable physicochemical characteristics associated with adequate membrane permeability, solubility, and systemic absorption. Compliance with these thresholds is generally associated with improved absorption, distribution, and oral pharmacokinetics *in vivo* [36,37]. This finding aligns with previous research demonstrating that natural products adhering to Lipinski parameters often progress successfully into experimental development pipelines [37].

Toxicity prediction is equally essential, as many candidate molecules are eliminated due to safety concerns. While traditional toxicological assessment relies heavily on *in vivo* models, *in silico* toxicity screening provides a rapid, cost-efficient, and ethically acceptable method for early identification of harmful compounds [38,39]. All selected phytochemicals exhibited no predicted mutagenicity, tumorigenicity, reproductive toxicity, irritant effects, or undesirable functions, strengthening their potential suitability for further development. The absence of mutagenic or carcinogenic alerts is particularly important, as compounds with genotoxic liability are typically rejected at early discovery stages [40]. These favourable toxicity predictions therefore reduce the likelihood of late-stage attrition.

Structural visualisation of the docked complexes further clarified the molecular basis of ligand binding. The top candidates formed hydrogen bonds and hydrophobic interactions with key active-site residues such as TYR-106, THR-107, HIS-98, THR-102, and TYR-7. Hydrogen bonding enhances ligand specificity and stabilises orientation within the binding cleft, while hydrophobic contacts contribute to shape complementarity and overall complex stability [41,42]. For instance, Daturamalakin B interacted strongly with TYR-106 and THR-107, whereas Foetidin formed key

interactions with HIS-98 and TYR-7. These residues may act as functional hotspots within the GST active site and have been similarly implicated in GST inhibition in other parasitic helminths [43].

Collectively, the strong binding affinities, compliance with drug-likeness criteria, absence of toxicity alerts, and favourable binding interaction profiles position Daturamalakin B, Neveskone, and Daturametelin D as promising lead candidates for GST inhibition in *O. volvulus*. These findings demonstrate the effectiveness of computational screening as a rapid and cost-efficient strategy for identifying natural product-based antifilarial agents. Nevertheless, as with all *in silico* approaches, these results require further validation through biochemical assays, in vitro parasite inhibition studies, and comprehensive ADMET profiling to confirm their therapeutic potential.

5. Conclusion

This study employed an *in silico* drug-discovery approach to identify potential anti-onchocercal agents by screening phytochemicals against the *Onchocerca volvulus* glutathione S-transferase (GST) enzyme (PDB ID: 1TU7). From an initial library of 6,500 phytochemicals, 1,793 compounds met Lipinski's Rule of Five and were subjected to molecular docking. All twenty front-runner phytochemicals demonstrated stronger binding affinities than the reference ligand glutathione, with Daturamalakin B, Neveskone, and Daturametelin D emerging as the most promising candidates.

The front-runner ligands exhibited favourable physicochemical properties, compliance with drug-likeness criteria, and no predicted mutagenic, carcinogenic, reproductive, or irritant toxicity. Structural analysis revealed stable hydrogen bonding and hydrophobic interactions with key catalytic residues of the GST active site, indicating strong inhibitory potential.

Together, these findings highlight the value of computational screening in natural product-based drug discovery and identify three lead phytochemicals with promising therapeutic relevance for onchocerciasis. However, *in silico* predictions alone are insufficient for drug development. Therefore, further validation through molecular dynamics simulations, biochemical enzyme inhibition assays, and in vitro and in vivo antiparasitic evaluations is essential to confirm the efficacy, safety, and pharmacokinetic behaviour of these candidate molecules.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare that there are no conflicts of interest regarding the publication of this work.

Data availability

No new experimental data were generated. All computational data used in this study are available upon reasonable request.

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