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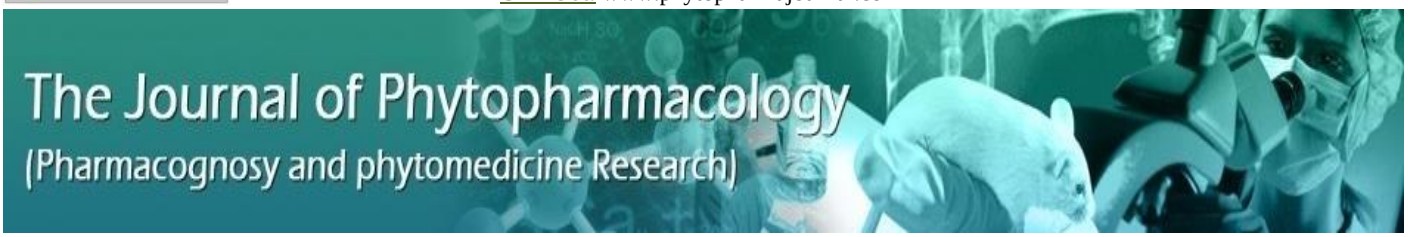

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In silico Assessment of Efficacy Against the Zoonotic Parasite *Echinococcus granulosus*, Pharmacokinetic and Toxicity Predictions for the Siddha Formulation Murukkanvithai Mathirai

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ABSTRACT

Background: Thioredoxin glutathione reductase (TGR) is essential for survival of the zoonotic tapeworm *Echinococcus granulosus*. Albendazole is the only promising drug for the treatment of cystic echinococcosis. To avoid the development of resistance to albendazole in the parasite, an herbal alternative to albendazole is the need-of-the-hour to combat the development of resistance. **Aim**: This study aimed to identify active compounds against the parasite Echinococcus granulosus from Murukkan Vithai Mathirai, an anthelmintic formulation used in Siddha practice. **Objectives**: To evaluate the efficacy of Murukkan Vithai Mathirai (MVM), a Siddha formulation against *Echinococcus granulosus*, a tapeworm of carnivores, by molecular docking, and to evaluate its ADMET properties using *in silico* tools. **Materials and Methods:** The 3D structure of *Echinococcus granulosus*-thioredoxin-glutathione systems (egTGR) and the phytoconstituents of Pi*per nigrum, Zingiber officinalis, Piper longum, Cuminum syminum, Coptis teeta, Butea monosperma*, and *Croton tiglium* were obtained from a curated database of Indian Medicinal Plants, Phytochemistry and Therapeutics (IMPPAT). 12 promising phytocompounds were selected based on their physicochemical properties, drug-likeness, bioavailability scores, and medicinal chemistry properties. These phytochemicals were docked individually with the egTGR using Autodock vina and binding affinity (kcal/mol) was recorded for each compound and compared with albendazole, a positive control drug. The results of docking were read using the Biovia Discovery studio visualizer. The ADMET properties of the phytochemicals were analysed using pkCSM and VEGA-QSAR tools. The toxicity score for each phytochemical was calculated by assigning weightage to the toxicities predicted and the weighted average was calculated to compare with the albendazole's weighted average. The geometric mean of NOAELs predicted for MVM phytochemicals was compared with the predicted NOAEL of albendazole. **Results:** The binding affinity (**ΔG**) scores of the selected phytocompounds were found to be higher than the albendazole and the phytocompounds with **ΔG** > -8.0 are as follows, aristolodione, berberastine and pluviatilol of *Piper longum*, apigenin of *Cuminum syminum* and prunetin of *Butea monosperma*, whereas the **ΔG** of albendazole was -6.7. The calculated toxicity score for MVM (0.56) was significantly lower than albendazole (1.08) and the predicted NOAELs was significantly higher (26.63 mg/kg) than albendazole (3.49), indicating that MVM is less toxic than albendazole. **Conclusion:** Murukkan Vithai Mathirai is a promising and safe anthelmintic in *in silico* studies, however, it needs to be validated by *in vitro* and *in vivo* studies**.**

Keywords: *Echinococcus granulosus*, Murukkan Vithai Mathirai, Docking, Toxicity score, ADME.

INTRODUCTION

Echinococcus granulosus, a tapeworm of carnivores especially seen in dogs, is of zoonotic importance. Herbivores like sheep, goat, cattle, and pigs act as an intermediate host and harbours the larval or cyst stage which is commonly referred to as hydatid cysts in internal organs such as liver and lungs. This neglected tapeworm infection causes severe morbidity in humans in many developing countries associated with sheep rearing. Thioredoxin and glutathione systems are highly essential for the survival of the parasite, in terms of nucleic acid synthesis, proper protein conformation and defense against antioxidant activity, and key enzyme in various thiol-dependent redox pathways [1]. Thioredoxin glutathione reductase (TGR), a selenoenzyme of *Echinococcus granulosus* has a unique structural design and linked to thioredoxin–glutathione systems which is different from the individual thioredoxin and glutathione reductase enzymes of the host [2]. This makes them a promising target for the anthelmintic drug development. The control measures, treatment strategies and availability of vaccines against this fatal parasitic infection are limited [3]. Albendazole is the only promising drug against cystic echinococcosis. To avoid the development of resistance in the parasite for albendazole, it is essential to identify an herbal alternative to albendazole.

The traditional medicine system of Tamil Nadu is Siddha Medicine, in which the Murukkan Vithai Mathirai (MVM) is commonly used polyherbal formulation for intestinal parasitic infections, indigestion, bloating and ascites [4]. The herbal constituents of MVM are *Piper nigrum, Zingiber officinalis, Piper longum, Cuminum cyminum, Coptis teeta, Butea monosperma* and *Croton tiglium*. It also possesses the purgative action which may have a vermifuge activity too [4]. However, there is no scientific evidence for its anthelmintic activity.

Hence, in the current study, the drug target of this parasitic tapeworm linked TGR enzyme (5W1J) was docked with the selected phytoconsituents present in Murukkan Vithai Mathirai and the affinity was evaluated by an *in silico* approach. The ADME and toxicity properties are also evaluated to assess the pharmacokinetics and safety of MVM using *in silico* tools and compared with the standard drug, Albendazole, though the egTGR is not the natural target. However, albendazole is used to compare the pharmacokinetics and toxicity profiles, in addition to possible binding affinity against the egTGR.

MATERIAL AND METHODS

The 3D structure of *Echinococcus granulosus*- thioredoxin–glutathione systems (egTGR) was retrieved as PDB file (PDB Id-5W1J) from the protein databank. The protein target was converted from PDB to PDBQT formats using Autodock Vina.

The phytoconstituents of *Piper nigrum, Zingiber officinalis, Piper longum, Cuminum syminum, Coptis teeta, Butea monosperma* and *Croton tiglium* were obtained from a curated database of Indian Medicinal Plants, Phytochemistry and Therapeutics (IMPPAT) [5] were 509, 531, 259, 257, 10, 77 and 33 respectively. Using Swiss-ADME web tool[6], phytoconstituents of above plants were selected by applying filters such as physicochemical properties (lipophilicity, size, polarity, solubility, flexibility and saturation), drug-likeness (Lipinski rule-of-five, Ghose, Veber, Egan and Muegge filters), bioavailability scores and medicinal chemistry (structural alert, lead likeness and synthetic accessibility) properties. The chosen phytoconstituents with their Pubchem identifier were given in the table 1.

Table 1: Selected phytoconstituents of MVM against *Echinococcus granulosus* - thioredoxin–glutathione systems

S. No.	Plant name	Selected phyto-constituent	Pubchem Id	SMILES
1	*Butea monosperma*	Prunetin	5281804	COC1=CC(=C2C(=C1)OC=C(C2=O)C3=CC=C(C=C3)O)O
2		Butein	5281222	C1=CC(=C(C=C1C=CC(=O)C2=C(C=C(C=C2)O)O)O)O
3	*Piper nigrum*	Feruperine	131752909	COC1=C(C=CC(=C1)C=CC=CC(=O)N2CCCCC2)O
4		Moupinamide	5280537	COC1=C(C=CC(=C1)C=CC(=O)NCCC2=CC=C(C=C2)O)O
5	*Zingiber officinalis*	Gingerenone B	5317592	COC1=CC(=CC(=C1O)OC)CC/C=C/C(=O)CCC2=CC(=C(C=C2)O)OC
6		Gingerenone A	5281775	COC1=C(C=CC(=C1)CCC=CC(=O)CCC2=CC(=C(C=C2)O)OC)O
7	*Cuminum syminum*	Luteolin	5280445	C1=CC(=C(C=C1C2=CC(=O)C3=C(C=C(C=C3O2)O)O)O)O
8		Apigenin	5280443	C1=CC(=CC=C1C2=CC(=O)C3=C(C=C(C=C3O2)O)O)O
9	*Piper longum*	Pluviatilol	70695727	COC1=C(C=CC(=C1)C2C3COC(C3CO2)C4=CC5=C(C=C4)OCO5)O
10		Aristolodione	184116	CN1C2=CC3=CC=CC=C3C4=C2C(=CC(=C4OC)O)C(=O)C1=O
11		Berberastine	442180	COC1=C(C2=C[N+]3=C(C=C2C=C1)C4=CC5=C(C=C4C(C3)O)OCO5)OC
12		Jatrorrhizine	72323	COC1=C(C2=C[N+]3=C(C=C2C=C1)C4=CC(=C(C=C4CC3)O)OC)OC

The structure data files (SDF) of the selected phytoconstituents as shown in table 1 were downloaded from SwissADME and they were converted to PDB format using Biovia Discovery studio visualizer. The SMILES notation for each molecule was taken from the Pubchem database for Pharmacokinetics and Toxicity Predictions.

Docking

The PDB file of the protein target (5W1J) was converted to PDBQT formats and kept ready for docking using Autodock Vina [7]. Similarly, the selected phytoconstituents and albendazole, the standard drug, were prepared and saved in PDBQT formats for docking. Each ligand was docked individually with the egTGR and binding affinity (ΔG – Gibbs free energy) (kcal/mol) was recorded for each compound. The outputs were read using Biovia Discovery studio visualizer.

ADME and Toxicity Prediction

The pharmacokinetics parameters were predicted using pkCSM online tool [8] and the toxicities were predicted using VEGA-QSAR software, for the selected phytoconstituents and albendazole. The presence or absence of toxicity prediction was indicated as 1 or 0 and multiplied by weightage assigned for individual parameters based on the severity of the toxicity as given in Table 2, to derive the "Toxicity Score". The mean 'toxicity score' of MVM phytoconstituents is compared with the toxicity score of albendazole.

Table 2: Assigning weightage to the individual toxicity parameter

Toxicity Parameter	Weightage	Justification
Ames Mutagenicity	3	Due to its lack of a threshold effect, mutagenicity is the most severe genotoxicity parameter.
Chromosomal Aberration	3	Chromosomal aberration is another crucial measure of genotoxicity.
Micronucleus (*In vivo*)	3	Micronucleus induction *in vivo* is considered as the important genotoxicity effect.
Carcinogenicity	2	Carcinogenicity is a serious effect; however, anthelmintics are given for a shorter duration, hence being considered less important
Developmental Toxicity	3	Teratogenicity is a serious toxicity to the developing fetus, hence given a high score
Hepatotoxicity	2	As herbal drugs (complementary and alternative medicine) is the second major leading cause for the hepatotoxicity [9].
Cramer Class	1	The Cramer classification discerns the toxicity characteristics of a molecule, classifying it into categories I, II, and III, indicative of the escalating toxicity potential of the compound. Subsequently, this classification is transformed into a score for calculations, with no additional weighting assigned to the Cramer class.

Statistics

The geometric mean of the weighted averages of the phytoconstituents and the 95% confidence interval of the geometric mean are calculated and tabulated. D'Agostino & Pearson omnibus normality test was performed for the weighted average values and the predicted NOAELs of Phytoconstituents of MVM. One sample T-test was performed by comparing with the Albendazole's values. P value less than 0.05 is considered as statistically significant. The statistical analysis was performed using GraphPad Prism v 6.01.

RESULTS AND DISCUSSION

Twelve phytoconstituents namely prunetin, butein, feruperine, moupinamide, gingerenone B, gingerenone A, luteolin, apigenin, pluviatilol, aristolodione, berberastine and jatrorrhizine were chosen from the herbs of Murukkan Vithai Mathirai based on their physiochemical, drug-likeness and oral bioavailability properties, for docking against the target, egTGR enzyme. The anti-parasitic efficacy of these chosen phytoconstituents was compared with the standard anthelmintic, Albendazole. Upon molecular docking using Auto-dock Vina, the binding affinity (Gibbs free energy) and 3D pictures of the phytoconstituents of MVM and albendazole against thioredoxin glutathione reductase enzyme of *E. granulosus* were presented in table 3 and figure 1, respectively. Aristolodione and berberastine of *Piper longum* showed highest binding against egTGR followed by Pluviatilol of *Piper longum*, Apigenin of *Cuminum syminum* and Prunetin of *Butea monosperma showed* second highest binding affinity. The rest of the chosen phytoconstituents of MVM showed better binding affinity than albendazole and were presented in the descending order of binding affinity as Luteolin, Jatrorrhizine, Butein, Moupinamide, Gingerenone B, Gingerenone A, and Feruperine. Albendazole showed low binding affinity, because the egTGR is not its target, rather its mechanism of action is by binding to tubulin and preventing it from polymerization or microtubule assembly.

Table 3: Binding affinity of phytoconstituents of MVM against *Echinococcus granulosus* - thioredoxin–glutathione systems

S. No.	Plant name	Selected phytoconstituent	5W1J ΔG (Kcal/mol)	Interacting amino acids
1	*Butea monosperma*	Prunetin	-8.0 ± 0.24	Gln446, Lys449, Asn450, Arg453, Cys461, Asp564, Thr579, Arg581
2		Butein	-7.4 ± 0.21	Arg453, Asp564, Arg565, Leu580
3	*Piper nigrum*	Feruperine	-6.8 ± 0.18	Pro442, Ile445, Leu507, His570, Glu575
4		Moupinamide	-7.2 ± 0.23	Ile162, Pro442, Ile445, Leu507, His570, Pro571, Glu575, Thr579
5	*Zingiber officinalis*	Gingerenone B	-7.2 ± 0.08	Pro442, le445, Lys449, Leu507, His570, Glu575, Thr578, Thr579
6		Gingerenone A	-6.9 ± 0.18	Leu507, His570, Pro571, Cys156, Ile162, His204, Tyr212
7	*Cuminum syminum*	Luteolin	-7.7 ± 0.21	Lys449, Arg453, Cys461, Arg462, Asp564, Arg581
8		Apigenin	-8.0± 0.36	Tyr296, Gly323, Tyr438, Gln439, Leu440
9	*Piper longum*	Pluviatilol	-8.0± 0.27	Pro442, Lys449, Pro506, Thr572, Cys573, Glu575, Thr579
10		Aristolodione	-8.2± 0.32	Gln446, Asn450, Arg453, Asp564, Arg581
11		Berberastine	-8.2± 0.36	Lys56, Asn58, Gln446, Asn450, Asp459, Asp460, Cys461
12		Jatrorrhizine	-7.4± 0.16	Gln446, Asn450, Arg453, Asp564, Thr579, Arg581
13	Albendazole		-6.7 ± 0.33	Leu172, Tyr176, Glu508, Trp509, Pro541, Pro571, Cys573, Lys165, Gly544, Glu545

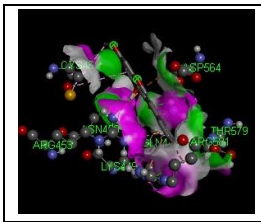
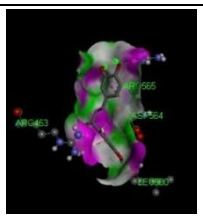
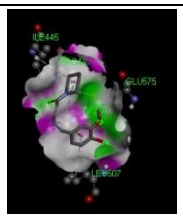
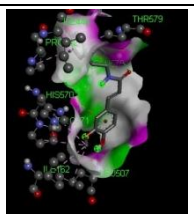
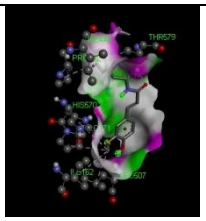
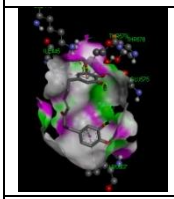
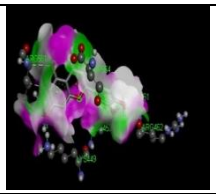
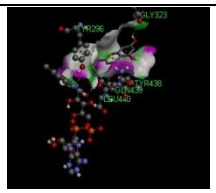
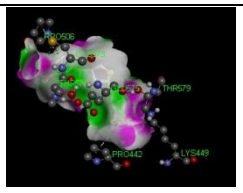
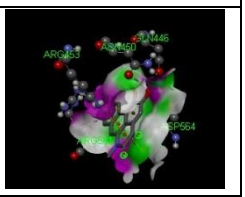
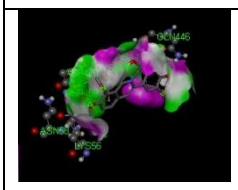
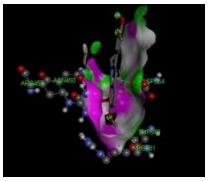
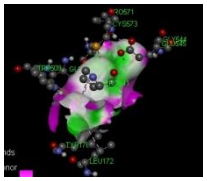
				
Prunetin	Butein	Feruperine	Moupinamide	Gingerenone B
				
Gingerenone A	Luteolin	Apigenin	Pluviatilol	Aristolodione
				
Berberastine	Jatrorrhizine	Albendazole		

Figure 1: 3D pictures of the phytoconstituents of MVM and albendazole against thioredoxin glutathione reductase enzyme of *E. granulosus.*

The increase in human morbidity and mortality recently was attributed to neglected parasitic diseases. Among the helminthic infection, cestode infection primarily echinococcosis was responsible for serious illness in humans and livestock [10]. Zoonotic nature of this tapeworm, the unavailability of an effective treatment regime, and the curtailing usage of a single drug make echinococcosis a big concern among researchers. This *in silico* work revealed MVM, a traditional siddha formulation as an effective choice of medicine against echinococcosis. The selected phytoconstituents of herbs *Butea monosperma, Piper nigrum, Zingiber officinalis, Cuminum syminum* and *Piper longum* present in MVM exhibited better binding affinity against TGR of *Echincoccus granulosus* than the standard drug of choice albendazole. In Siddha, MVM is being given as purgation therapy against endoparasitic infection, digestive disorders and muscular cramps [11]. Purgation in Siddha system of medicine is believed to be an internal cleansing process to remove impurities for better digestion and to stay strong and healthy [4]. MVM is recommended for digestive disturbances in children, helminth infection, abdominal distension and respiratory disorders and is consumed along with jaggery, tender coconut water ghee or milk. From this *in silico* study, it is evident that the phytoconstituents of this herbal formulation is having binding affinity to the target enzyme which may be correlated to its claimed anthelmintic activity in the Siddha literature.

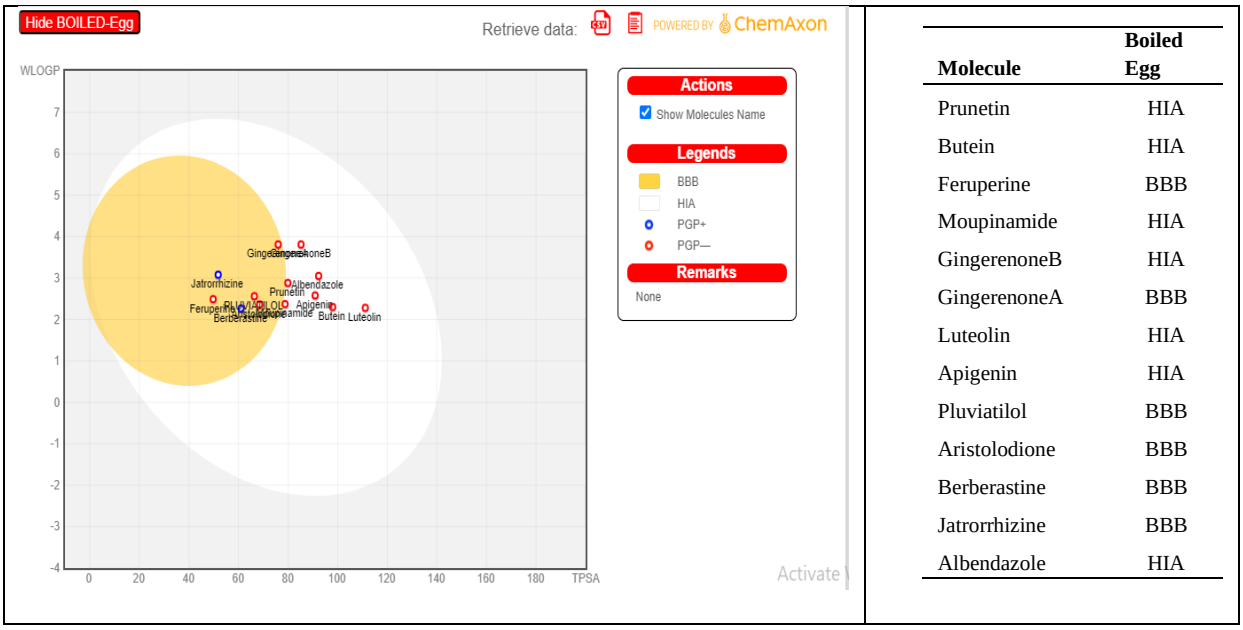
The pharmacokinetic prediction of MVM phytoconstituents are presented in the table 4 and it showed favourable PK parameters similar to Albendazole. The boiled egg representation of the phytoconstituents of MVM and albendazole was given in the figure 2. It showed that 6 molecules cross blood brain barrier whereas other showed only intestinal absorption.

Table 4: Predicted Pharmacokinetics Parameters of MVM phyto-constituents

Active Ingredients	**Absorption**		**Distribution**			**Metabolism**	**Excretion**
	Oral BA (%)	**Pgp substrate/ inhibitor**	**FU**	**Vd (L/Kg)**	**CNS Penetration (logPS)***	**CYP substrate/inhibitor**	**Total Clearance (ml/min/kg)**
Prunetin	95.5	+/-	0.064	0.86	-2.188	3A4/1A2,2C19,2C9,3A4	1.87
Butein	72.6	+/-	0.232	5.51	-2.395	Nil/1A2	1.04
Feruperine	91.3	+/-	0.104	2.29	-2.265	3A4/2C19	2.36
Moupinamide	90.2	+/-	0.045	1.34	-2.547	3A4/1A2,2C19,3A4	1.86
GingerenoneB	90.9	+/+	0.004	1.29	-2.871	3A4/2C19,2C9,3A4	1.66
GingerenoneA	91.6	+/-	0	1.05	-2.566	3A4/1A2,2C19,2C9,3A4	1.60
Luteolin	81.1	+/-	0.168	14.22	-2.251	Nil/1A2,2C9	3.13
Apigenin	93.3	+/-	0.147	6.64	-2.061	Nil/1A2,2C19	3.68
Pluviatilol	94.7	-/+	0	0.76	-2.899	3A4/2C19,2C9,3A4	0.88

Aristolodione	96.0	+/+	0.089	0.92	-2.028	3A4/1A2,2C19,2C9	1.21
Berberastine	95.4	+/-	0.204	2.68	-2.248	3A4/1A2,3A4	13.55
Jatrorrhizine	94.5	+/-	0.182	3.46	-2.142	3A4/1A2,2D6	16.67
Albendazole	81.1	+/-	0.246	0.69	-2.392	Nil/1A2	10.07

FU- Fraction unbound; *log PS <-2 penetrate CNS; + substrate or inhibitor; - not substrate or not inhibitor;



Molecule	Boiled Egg
Prunetin	HIA
Butein	HIA
Feruperine	BBB
Moupinamide	HIA
GingerenoneB	HIA
GingerenoneA	BBB
Luteolin	HIA
Apigenin	HIA
Pluviatilol	BBB
Aristolodione	BBB
Berberastine	BBB
Jatrorrhizine	BBB
Albendazole	HIA

Figure 2: Boiled egg representation of Phytoconstituents and Albendazole

The toxicity parameters predicted for the phytoconstituents are presented in Table 5. A statistically decrease in the weighted average of toxicity parameters was identified for MVM phytoconstituents when compared to the weighted average of albendazole, indicating a comparatively lower level of toxicity for MVM (see Table 6). Furthermore, the geometric mean of NOAELs predicted for MVM phytoconstituents was statistically higher than the predicted NOAEL for albendazole, signifying that MVM is anticipated to be less toxic than albendazole. The comparative safety profile of herbal formulations, commonly perceived as safer than allopathic drugs, becomes challenging to affirm due to the unavailability of toxicity data for individual phytoconstituents within the formulation. To address this limitation, a methodology involving the assignment of a toxicity score was implemented. This approach facilitated a direct comparison of the formulation's safety with the toxicity score associated with the allopathic active ingredient. The results of the toxicity score analysis unequivocally indicate that MVM is deemed to be a safer alternative than albendazole.

Table 5: Toxicity Prediction using VEGA-QSAR *In silico* Tool

Active Ingredients	Ames Mutagenicity	Chromosomal Aberration	Micronucleus (*In vivo*)	Carcinogenicity	Developmental Toxicity	Hepatotoxicity	NOAEL (mg/kg)	Cramer Class
Prunetin	0	1	1	0	1	1	37.46	III
Butein	0	1	1	1	1	0	125.96	III
Feruperine	0	1	0	0	0	0	12.70	III
Moupinamide	0	0	0	1	0	0	22.47	III
GingerenoneB	0	0	1	0	0	0	60.45	III
GingerenoneA	0	0	0	0	0	0	48.02	III
Luteolin	0	1	1	0	1	1	152.24	III
Apigenin	0	1	1	1	1	1	67.32	III
Pluviatilol	0	1	0	1	1	0	16.63	III
Aristolodione	1	0	0	0	1	0	6.59	III
Berberastine	1	1	0	1	1	1	5.30	III
Jatrorrhizine	1	1	0	1	1	1	5.47	III
Albendazole	1	0	1	0	1	1	3.49	III

0 indicates absence of the toxic effect; 1 indicates the presence of toxic effect; III - severe toxicity under Cramer Class.

Table 6: Comparison of Toxicity Score and NOAEL of the MVM phytoconstituents with the Toxicity Score and NOAEL of the Albendazole

Parameter	Geometric Mean (95% CI of Geo. Mean)	D'Agostino & Pearson omnibus normality test
Toxicity Score of MVM Phytoconstituents	0.56* (0.39-0.80)	Passed
Toxicity Score of Albendazole	1.08	-
NOAEL (mg/kg) of MVM Phytoconstituents	26.63* (12.58 – 56.36)	Passed
NOAEL of Albendazole	3.49	-

*P<0.05 in One Sample T-test against the Albendazole

CONCLUSION

In conclusion, the development of an effective treatment strategy for tapeworm infection is imperative for both animal and human well-being. Encouraging the use of herbal-based medicine is crucial to mitigate the emergence and dissemination of drug resistance. In this study, molecular docking of phytocompounds with egTGR was conducted, revealing higher binding affinity (ΔG) scores for selected phytocompounds from the Siddha formulation Murukkan Vithai Mathirai compared to albendazole. Notably, aristolodione, berberastine, Pluviatilol of *Piper longum*, apigenin of *Cuminum syminum*, and Prunetin of *Butea monosperma* demonstrated elevated binding affinities. These compounds potentially contribute to the anthelmintic activity of MVM, although validation through *in vitro* and *in vivo* studies is imperative for efficacy confirmation in target species.

Furthermore, the pharmacokinetic and toxicity parameter predictions indicate favorable properties and enhanced safety compared to albendazole. Nevertheless, additional experimental investigations are warranted to comprehensively assess the safety profile and pharmacokinetics of the Murukkan Vithai Mathirai formulation, providing a foundation for its potential application in clinical settings.

Conflict of interest

The authors have declared no conflict of interest.

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