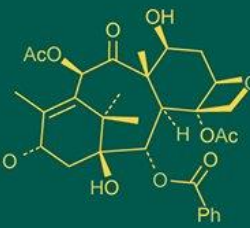
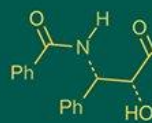
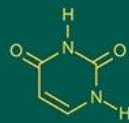


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In silico investigation of green tea (*Camellia sinensis*) phytochemicals as potential inhibitors of *Haemonchus contortus* cystatin-1 through Homology Modeling and Molecular Docking

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Abstract

The increasing prevalence of anthelmintic resistance has emphasized the need to identify novel therapeutic targets and alternative antiparasitic agents. Cystatin-1, a cysteine protease inhibitor of *Haemonchus contortus*, is a promising target for structure-based drug discovery based on their functions. Green tea (*Camellia sinensis*) contains a wide range of bioactive phytochemicals with reported pharmacological and antiparasitic properties. In the present study, the three-dimensional structure of *H. contortus* cystatin-1 was predicted by homology modeling in SWISS-MODEL server and validated in GalaxyRefine server prior to molecular docking with selected green tea phytochemicals. ADME and toxicity analyses was performed using SwissADME and ProTox-III, respectively, to select the phytochemicals for the docking study. Molecular docking identified cyanidin (−4.49 kcal/mol), epicatechin (−4.36 kcal/mol), caffeic acid (−4.18 kcal/mol), p-coumaric acid (−4.09 kcal/mol), catechin (−4.06 kcal/mol), and malvidin (−4.00 kcal/mol) as the compounds with the highest binding affinities toward cystatin-1. Protein-ligand interaction analysis further demonstrated that these phytochemicals formed multiple hydrogen bonds with key amino acid residues within the binding pocket, indicating stable protein-ligand complexes. These findings suggest that green tea phytochemicals, particularly cyanidin, epicatechin, caffeic acid, p-coumaric acid, catechin, and malvidin, possess promising inhibitory potential against *H. contortus* cystatin-1 and could serve as lead candidates for the development of novel anthelmintic agents. Further experimental validation through *in vitro* and *in vivo* studies is required to confirm their therapeutic efficacy.

Keywords: *Haemonchus contortus*, cystatin-1, *Camellia sinensis*, molecular docking, green tea phytochemicals

Introduction

Haemonchus contortus (Barber's pole worm) is prevalent globally that affects the small ruminants. The parasite resides in the abomasum of sheep and goats, sucks the blood causing anaemia, reduction in weight gain, decreased productivity, and in severe cases leading to death, makes the disease one of the most economically significant parasitic diseases [1]. Emergence of resistance to conventional anthelmintic drugs have become major challenges to sustainable livestock production. Consequently, the search for novel, effective, and environmentally safe antiparasitic agents has gained increasing attention.

The proteins of *H. contortus* mediate several important functions of the parasites, such as host-parasite interactions, nutrient absorption, immune evasion, reproduction, their survival and development, and cause pathogenesis. Several enzymes like cysteine proteases, glutathione transferases, and somatic proteins, excretory-secretory proteins are identified as potential therapeutic targets. Identification and functional characterization of the proteins as drug targets are corroborated by the advancement in genomics, proteomics, transcriptomic studies of *H. contortus* [2].

The identification and optimization of bioactive molecules against parasite diseases has been made possible by computer-aided drug discovery (CADD). Techniques such as molecular docking, molecular dynamics simulations, virtual screening, and ADMET (absorption, distribution, metabolism, excretion, and toxicity) prediction enable rapid evaluation of ligand-target interactions while reducing the time and cost associated with conventional drug development [3]. Prior to experimental validation, these *in silico* methods offer important insights into the pharmacokinetic characteristics, binding affinities, and interaction mechanisms of possible drug candidates.

Natural products continue to serve as an important source of antiparasitic compounds. *Camellia sinensis* (green tea) has attracted considerable interest due to their diverse biological activities such as antioxidant, antimicrobial, anti-inflammatory, and antiparasitic effects. The green tea is a rich source of bioactive phytochemicals [4]. Previous study described the *in vitro* anthelmintic potential of green tea [5]. Several studies identified that catechins of green tea possess anthelmintic potential affecting the biotic activity of the helminths [6]. The present study explores the anthelmintic activity of phytochemicals of green tea against cystatin-1 of *H. contortus*. The findings may contribute to the development of novel plant-based therapeutic agents for the control of haemonchosis and help address the growing problem of anthelmintic resistance.

Materials and methods

Prediction of three dimensional structure of *H. contortus* cystatin-1:

The amino acid sequence of the cystatin-1 with 122 amino acid residues were obtained from NCBI database (Accession number: AAB95324.1). Three dimensional model of cystatin-1 was predicted in SWISS-MODEL server (<https://swissmodel.expasy.org/>) through automated homology modeling by submitting the retrieved amino acid sequence. The most appropriate structural template for the construction of protein three dimensional model was identified on the basis of sequence similarity, and favorable GMQE score [7].

Validation and refinement of predicted three dimensional model of *H. contortus* cystatin-1

The predicted cystatin-1 model was validated using ERRAT, and PROCHECK program of SAVESv6.1 server. GalaxyRefine (<https://galaxy.seoklab.org/cgi-bin/submit.cgi?type=REFINE>) server was used to refine the protein model [8]. This was followed by the validation of the refined model in SAVESv6.1 server [9].

Identification and selection of ligands for the molecular docking study:

Phytochemicals present in *Camellia sinensis* (green tea) were collected and compiled from previously published literature report [4, 10]. The SMILES representations of the identified phytochemicals of green tea were retrieved from PubChem database and submitted to SwissADME server. The server predicts the pharmacokinetic properties, physiochemical properties, lipophilicity, solubility, and druglikeness of the compounds. Based on the physiochemical properties, the drug-likeness of the compounds were determined using lipinski, veber, and egan's rule as filters. Lipophilicity, solubility, and pharmacokinetic properties i.e. absorption, distribution, metabolism, and excretion, druglikeness, and bioavailability score of the compounds were considered for the selection of the compounds for further molecular docking study. The toxicity of the phytochemicals were predicted in ProTox-III server (<https://tox.charite.de/protox3/index.php?site=home>) [11].

Preparation of *H. contortus* cystatin-1 and ligands for molecular docking study:

Preparation of the refined *H. contortus* cystatin-1 model was done in AutoDock tools by checking for missing atoms, polar hydrogen atom addition, and assigning AutoDock4 (AD4) atom type to the protein model.

Energy minimization of the ligands was performed using Merck Molecular Force Field 1994 (MMFF94) and minimization was run up to 250 steps. The SDF file of each ligand was converted into PDB file in OpenBabel tool. Ligands were then prepared in AutoDock tools by addition of polar hydrogens and gasteiger charges.

Molecular docking and interaction analysis

The prepared protein model and ligands were docked by placing them in the grid box. The grid box was set in a way to cover the entire protein surface to allow the ligand to bind to the binding pocket of the protein. Autogrid and Autodock programs were run to perform the blind docking of the *H. contortus* cystatin-1, and selected ligands. The binding energy (kcal/mol) of the protein-ligand binding and the amino acids involved in the interaction, type of interaction and their bond length were analyzed to find the binding stability of the ligands within the binding pocket of the protein. The interaction of the protein and ligand were analyzed in a web tool, PLIP (Protein - Ligand Interaction Profiler) [12] (<https://plip-tool.biotec.tu-dresden.de/plip-web/plip/index>). The protein-ligand complex was visualized using Discovery Studio Visualizer [13] in 2D and 3D formats and images of the complex were generated.

Results and Discussion

In SWISS-MODEL server, cystatin domain-containing protein AlphaFold DB model of AOA714YZ14_Haeco, *H. contortus* was identified as template sequence based on the sequence identity of 94.26%, and GMQE score of 0.93 to generate *H. contortus* cystatin-1 model (Fig 1). The GMQE score expressed between 0 and 1, higher number indicates the very high expected quality of the model [7].

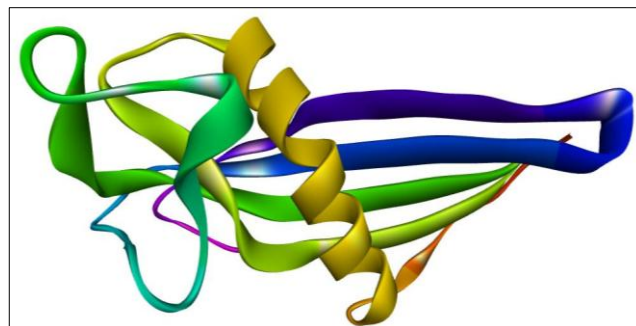


Fig 1: *Haemonchus contortus* cystatin-1 model predicted in SWISS-MODEL server using the protein sequence obtained from NCBI database (Accession number: AAB95324.1)

Validation of the predicted *H. contortus* cystatin-1 model using SAVESv6.1 server resulted in an ERRAT score of 81.25, and Ramachandran plot generated by PROCHECK exhibited 92.4% residues in most favored region, 6.7% residues in allowed region, 1% residues in the generously allowed region, and 0% residues in the disallowed region (Fig 2). More than 90% residues in the most favored region, and no residues in the disallowed region indicated the good stereochemical quality of the model [14]. Generally, the ERRAT score of the three dimensional model more than 90, considered as the highest quality model [15]. Therefore, the predicted *H. contortus* cystatin-1 model, was refined in GalaxyRefine server to improve the quality and reliability of the protein model before the downstream application (Fig 3).

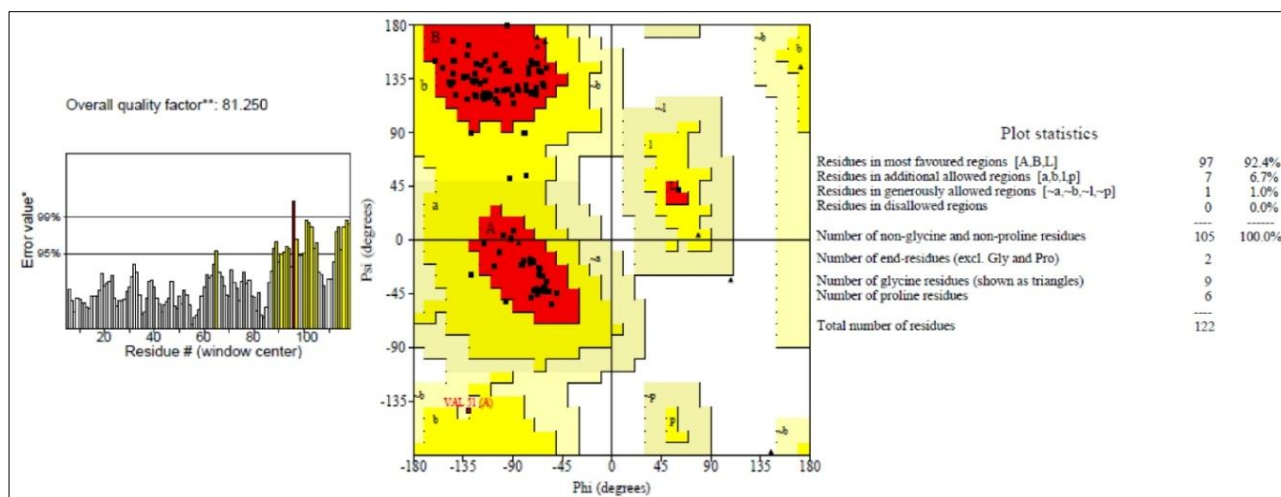


Fig 2: Validation of the predicted *H. contortus* cystatin-1 model using SAVESv6.1 server. The model achieved an ERRAT score of 81.25. Structural validation by the PROCHECK-generated Ramachandran plot revealed that 92.4% of residues were located in the most favored regions, 6.7% in the additionally allowed regions, 1.0% in the generously allowed regions, and 0% in the disallowed regions.

Validation of the refined model, yielded an ERRAT score of 92, and 95.2% residues were found in the most favorable region in Ramachandran plot. The refinement of the protein model had enhanced the non-bonded atomic interactions, and reduced the structural errors, and few of the residues from the

allowed region were redistributed into the most favored region (Figure 4). This process improved the overall geometric and stereochemical quality of *H. contortus* cystatin-1 model, made this protein model suitable for the molecular docking study.

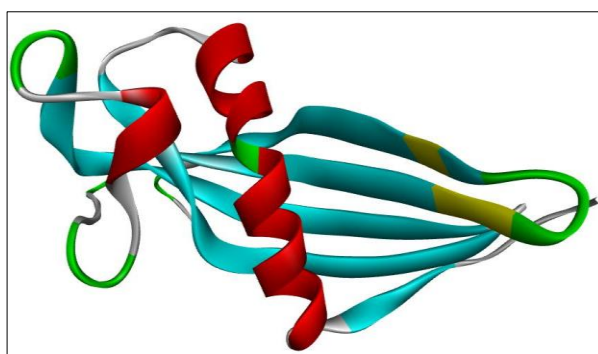


Fig 3: *Haemonchus contortus* cystatin-1 model refined in GalaxyRefine server

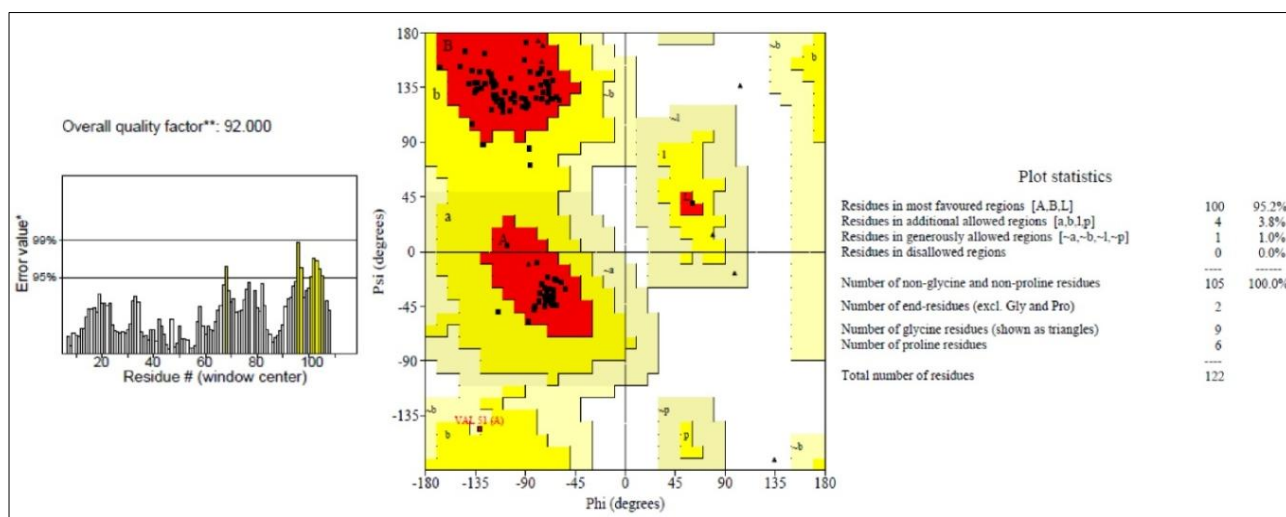


Fig 4: Validation of the refined *H. contortus* cystatin-1 model using SAVESv6.1 server. The model achieved an ERRAT score of 92. Structural validation by the PROCHECK-generated Ramachandran plot revealed that 95.2% of residues were located in the most favored regions, 3.8% in the additionally allowed regions, 1.0% in the generously allowed regions, and 0% in the disallowed regions, indicating good stereochemical quality of the predicted protein model

A total of 49 phytochemicals compounds were identified from the literature study (Table 1). SMILES of the

compounds that were available in the PubChem database were obtained and submitted to SwissADME server.

Phytochemical compounds were selected for the molecular docking study based on the predicted lipophilicity score, solubility class, gastrointestinal absorption, cytochrome P450 inhibitors, lipinski's rule, veber's rule, and egan's rule, and bioavailability score of the compounds. Lipophilicity score (LogP) of the compounds should be between 0 and 5, moderately soluble to highly soluble with high gastrointestinal absorption, bioavailability score of 0.5 or more than 0.5, non-inhibitor of all five CYP450s (CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4), or inhibitor of any one or two of the three CYP450s, CYP1A2, CYP2C19, and CYP2C9, except CYP3A4 and CYP2D6^[16, 17, 18].

In the present study, 19 compounds were selected for the further study. Molecular weight and lipophilicity score (LogP) of the selected compounds ranged from 62.13 to 331.30 kDa, and 0.08 to 3.69, respectively. The solubility of the compounds was estimated by three methods namely ESOL, Ali, and SILICOS-IT in SwissADME server. The compounds that are soluble atleast in two methods were selected. All the selected phytochemicals were predicted as non inhibitors of all five CYPs. However, three compounds such as cyanidin, malvidin, ellagic acid were identified as CYP1A2 inhibitors, and dibutylphthalate was predicted to inhibit both CYP1A2, and CYP2C19 inhibitor. All the compounds obeyed lipinski rule, veber rule, and egan rule

except ellagic acid which obeyed lipinski's rule but did not obey veber's and egan's rule due to topological polar surface area (TPSA) greater than 140 Å². The compound ellagic acid satisfied other parameters for selection, hence, it was selected for the further study. Physicochemical properties, lipophilicity, water solubility, pharmacokinetics, druglikeness of 16 compounds that were selected for the docking against *H. contortus* cystatin-1 were listed in Table 2.

The toxicity study of the phytochemical compounds revealed that the selected compounds were in the toxicity class 3, 4, 5, and 6. Caffeine, pentanal, and 1-pentanol belonged to toxicity class 3, these compounds are toxic if swallowed, and were not selected for the molecular docking study. The predicted LD₅₀ and toxicity class of selected phytochemical compounds are given in Table 3. The docking study of 16 compounds showed that cyanidin, epicatechin, caffeic acid, p-coumaric acid, catechin, and malvidin had better binding energy of -4.49, -4.36, -4.18, -4.09, -4.06, and -4.00 kcal/mol, respectively, compared to other ligand molecules. The protein-ligand complexes were generated and analyzed for the stability of ligand within binding pocket. The interaction study of the protein-ligand complex analyzed in PLIP server revealed the multiple hydrogen bonds formed by all the six ligand molecules (Figure 5).

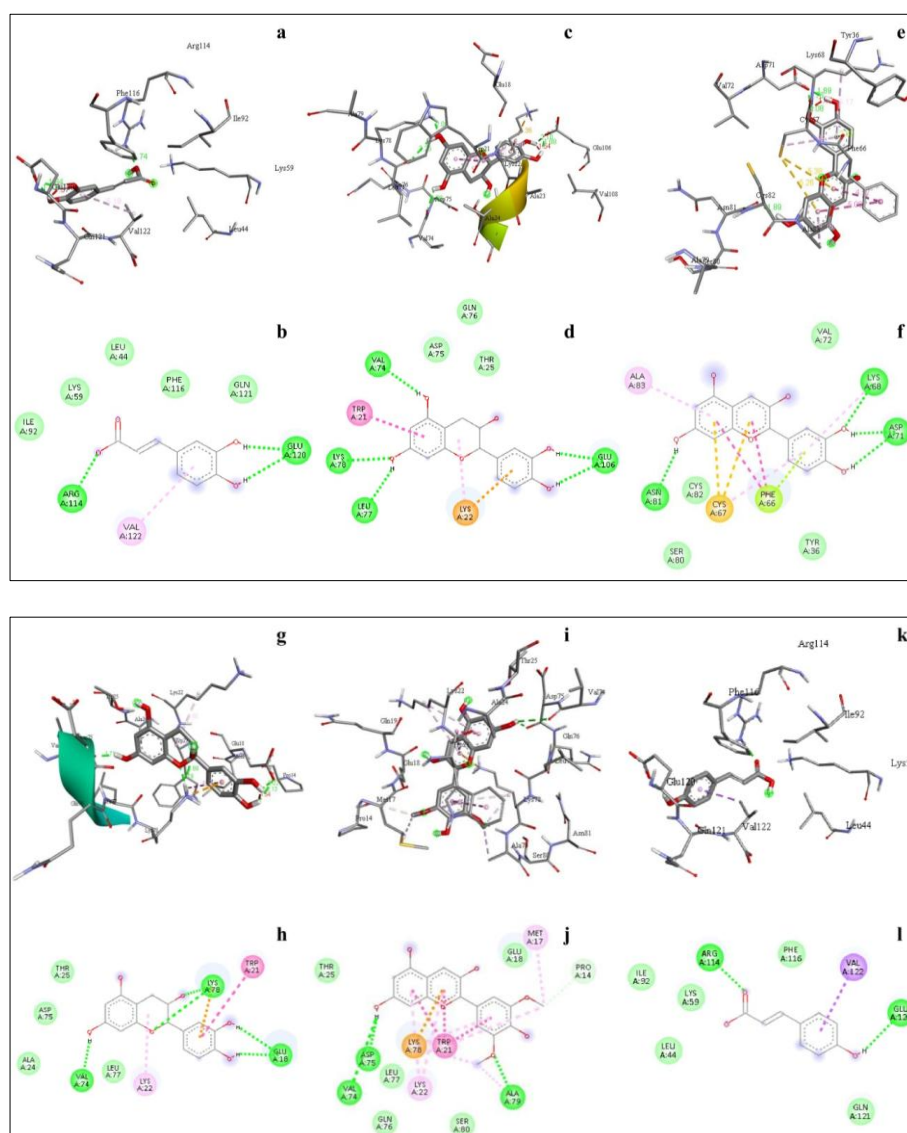


Fig 5: Protein–ligand interactions of cystatin-1

Fig 5: The interaction of six Ligands with *Haemonchus contortus* cystatin-1 was analyzed using BIOVIA Discovery Studio. a) Three-dimensional interaction of the cystatin-1-caffeic acid, b) Two-dimensional interaction of the cystatin-1-caffeic acid, c) Three-dimensional interaction of the cystatin-1-catechin, d) Two-dimensional interaction of the cystatin-1-catechin, e) Three-dimensional interaction of the cystatin-1-cyanidin, and f) Two-dimensional interaction of the cystatin-1-cyanidin, g) Three-dimensional interaction of the cystatin-1-epicatechin, h) Two-dimensional interaction of the cystatin-1-epicatechin, i) Three-dimensional interaction of the cystatin-1-malvidin, j) Two-dimensional interaction of the cystatin-1-malvidin, k) Three-dimensional interaction of the cystatin-1-p-coumaric acid, and l) Two-dimensional interaction of the cystatin-1-p-coumaric acid illustrating the key interactions and pocket atoms

Catechin followed by epicatechin had the highest number of eight and seven hydrogen bonds indicating stable interaction of Ligands within the binding pocket of the protein. Malvidin had the highest number of six hydrophobic interactions and well as five hydrogen bond interactions and their favorable bond length indicating the strong binding of the ligand. Numbers of hydrogen and hydrophobic bonds formed, their bond length are given in Table 4.

Overall, the interaction analysis revealed that all six phytochemicals formed stable complexes with the target

protein through synergistic hydrophobic and hydrogen-bond interactions, which are essential determinants of ligand binding affinity and stability of the complex. The orientation of the ligand within the binding pocket is contributed by hydrophobic interactions by reducing the solvent accessibility, and the hydrogen bonds increases the specificity of binding and stability of the ligand within the binding pocket of the protein [19, 20]. The hydrogen bond distances observed in the present study (H-A: 1.71-3.62 Å and D-A: 2.59-4.10 Å) are within the acceptable range reported for biologically relevant protein-ligand interactions, indicating favorable binding of the selected compounds. Among the evaluated compounds, catechin, epicatechin, caffeic acid, and malvidin displayed comparatively stronger interaction networks, suggesting greater inhibitory potential than the remaining phytochemicals. These findings support the molecular docking results and provide a structural basis for the potential biological activity of the selected phytochemicals. Nevertheless, molecular docking provides only a static representation of protein-ligand interactions; therefore, molecular dynamics simulations and experimental validation are necessary to confirm the stability, binding behavior, and inhibitory efficacy of these compounds under physiological conditions.

Table 1: Phytochemicals of *C. sinensis* (green tea)

Phytochemicals of <i>C. sinensis</i> (green tea)	
Catechin, Epicatechin, Epigallocatechin, Epicatechin gallate, epigallocatechin gallate, Myrecetin-3- rhamnosyl glucoside, Myrecetin-3- galactoside, Myrecetin-3- glucoside, Kaempferol-3-galactoside, Kaempferol-3-glucoside, Cyanidin, Delphinidin, Pelargonidin, Malvidin, Petunidin, Gallic acid, Chlorogenic acid, Caffeic acid, p-Coumaric acid, Ellagic acid, Quinic acid, Caffeine, Theophylline, Theobromine, Oxalic acid, Tartaric acid, Formic acid, L-malic acid, Ascorbic acid, Lactic acid, Citric acid, succinic acid, Fumaric acid, Dimethyl sulfide, Pentanal, 8-octadecanoic acid methyl ester, Dibutyl phthalate, Hexanal, Acetone, Hexadecane, 1-Pentanol, Heptanal, 2-methylbutyraldehyde, 3-methylbutyraldehyde, Heptadecane, 1-ethylpyrrole, 2-methylpropionaldehyde, Naphthalene, Acetic acid	

Table 2: In silico ADMET profiling of phytochemicals showing molecular weight, lipophilicity (LogP), Solubility, Lipinski's rule, Veber's rule, Egan's rule, and oral bioavailability score prediction to evaluate drug-likeness and pharmacokinetic behavior

S. No	Phytochemicals	Molecular weight	Lipophilicity	Solubility			Lipinski's rule	Veber's rule	Egan's rule	Bioavailability score
				ESOL	Ali	Silicos-IT				
1	Catechin	290.27	0.83	S	S	S	Y	Y	Y	0.55
2	Epicatechin	290.27	0.85	S	S	S	Y	Y	Y	0.55
3	Epigallocatechin	306.27	0.42	S	S	S	Y	Y	Y	0.55
4	Cyanidin	287.24	0.32	S	S	S	Y	Y	Y	0.55
5	Malvidin	331.30	0.92	S	MS	S	Y	Y	Y	0.55
6	Caffeic acid	180.6	0.93	VS	S	S	Y	Y	Y	0.56
7	p-Coumaric acid	164.16	1.26	S	S	S	Y	Y	Y	0.85
8	Ellagic acid	302.19	1.00	S	S	S	Y	N(1)	N(1)	0.55
9	Dimethyl sulfide	62.13	0.90	VS	VS	S	Y	Y	Y	0.55
10	Dibutyl phthalate	278.34	3.69	S	MS	MS	Y	Y	Y	0.55
11	Hexanal	100.16	1.66	VS	VS	S	Y	Y	Y	0.55
12	Acetone	58.08	0.40	VS	HS	S	Y	Y	Y	0.55
13	Heptanal	114.19	2.05	VS	S	S	Y	Y	Y	0.55
14	2-methyl butyraldehyde	86.13	1.20	VS	VS	S	Y	Y	Y	0.55
15	3-methyl butyraldehyde	86.13	1.14	VS	VS	S	Y	Y	Y	0.55
16	2-methyl propionaldehyde	72.11	0.82	VS	VS	S	Y	Y	Y	0.55

Table 3: In silico toxicity prediction of phytochemicals of green tea. Predicted acute toxicity (LD₅₀) and toxicity classification of selected phytochemicals are provided.

S. No	Phytochemicals	Predicted LD ₅₀ (mg/kg)	Predicted toxicity class
1	Catechin	10000	6
2	Epicatechin	10000	6
3	Epigallocatechin	10000	6
4	Cyanidin	5000	5
5	Malvidin	5000	5
6	Caffeic acid	2980	5
7	p-Coumaric acid	2850	5
8	Ellagic acid	2991	4
9	Dimethyl sulfide	3300	5
10	Dibutyl phthalate	3474	5
11	Hexanal	3240	5
12	Acetone	3000	5
13	Heptanal	5000	5
14	2-methyl butyraldehyde	2490	4
15	3-methyl butyraldehyde	2490	5
16	2-methyl propionaldehyde	960	4

Table 4: Hydrophobic and hydrogen bond interactions of the top-ranked green tea (*Camellia sinensis*) phytochemicals with *Haemonchus contortus* cystatin-1, indicating the interacting amino acid residues and bond distances (Å).

Hydrophobic bonds		Hydrogen bonds		
Residues	Distance	Residues	Distance H-A	Distance D-A
Caffeic acid				
PHE 116	3.77	LYS 59	2.15	3.15
VAL 122	3.09	ARG 114	1.74	2.59
		ARG 114	3.50	4.00
		GLU120	1.91	2.77
		GLU 120	1.84	2.76
		GLN 121	3.45	3.78
Catechin				
LYS 22	3.28	THR 25	3.04	3.83
		LEU 77	2.25	3.12
		LEU 77	3.26	3.89
		LEU 77	3.33	4.00
		LYS 78	2.08	2.96
		GLU 106	1.84	2.61
		GLU 106	1.89	2.61
		GLU 106	2.10	2.67
Cyanidin				
PHE 66	3.95	LYS 68	2.08	3.07
LYS 68	3.84	ASP 71	1.89	2.76
		ASP 71	1.76	2.70
		ASN 81	1.89	2.86
Epicatechin				
GLU 18	3.51	GLU 18	2.13	2.91
		GLU 18	2.22	2.85
		THR 25	3.33	3.73
		THR 25	2.93	3.73
		VAL 74	1.71	2.59
		LEU 77	3.01	3.48
		LYS 78	2.19	3.03
P-Coumaric acid				
PHE 116	3.25	LYS 59	1.81	2.80
PHE 116	3.99	ARG 114	3.35	3.91
VAL 122	3.26	ARG 114	1.84	2.71
		GLU 120	1.94	2.88
		GLN 121	3.16	3.94
Malvidin				
TRP 21	3.37	GLU 18	3.30	3.79
TRP 21	3.08	ASP 75	2.03	2.89
LYS 22	3.67	LEU 77	3.62	4.10
LYS 78	3.33	LYS 78	2.04	3.03
LYS 78	4.00	ALA 79	1.88	2.87
ALA 79	3.81			

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