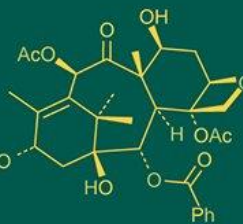
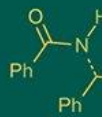


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In silico homology modeling and molecular docking analysis of phytochemicals against *Haemonchus contortus* galectin

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Abstract

Highly pathogenic *Haemonchus contortus*, is of global importance affecting small ruminants, particularly in tropical and subtropical regions. The parasite mainly cause disease through blood loss leading to anaemia, weakness and significant production losses. Use of anthelmintic drugs are the primary treatment for the helminth infection, however, improper usage of drug led to the development of anthelmintic resistance in the parasite. As a result, in recent decades, plant-based drugs are gaining attention as potential control strategies. This study uses computer-aided drug discovery approach to identify the possible new anthelmintic drug candidate. Phytochemicals from the commonly available plants with known anthelmintic activity such as *Coriandrum sativum* (Coriander), *Cinnamomum verum* (Cinnamon), *Terminalia bellerica* (Bahera), and *Ocimum sanctum* (Tulsi) were screened for the development of anthelmintic drug against *H. contortus*. The structure of the phytochemicals were obtained from PubChem database and evaluated for ADMET, and drug-likeness using SwissADME and ProTox-3.0 server. Compounds that pass all the filters are selected for the molecular docking study against *H. contortus* Galectin, which plays a crucial role in the host-parasite interaction. The result of the blind docking analysis identified that ellagic acid of *T. bellerica* had the most favorable interaction with a binding energy of -4.72 kcal/mol with highly stable and strong interaction within the binding pocket of the protein. This suggests its potential as a promising anthelmintic candidate against *H. contortus* Galectin.

Keywords: Anthelmintic resistance, galectin, *Haemonchus contortus*, molecular docking, phytochemicals

Introduction

Haemonchosis caused by *Haemonchus contortus* is a highly pathogenic gastrointestinal nematode affecting small ruminants. Distribution of the parasite is across the tropical and subtropical regions. The parasite is responsible for severe anemia, and significant economic losses in the livestock sector due to lower weight accretion, decline in milk production [1]. The control of *H. contortus* largely depends on the use of anthelmintics; however, the rapid emergence and global spread of drug resistance have significantly compromised the effectiveness of anthelmintics available [2, 3, 4]. In this context, medicinal plants have emerged as promising alternatives to available anthelmintics due to their rich diversity of bioactive compounds with antiparasitic properties [5, 6, 7]. India is particularly known for its long-standing tradition of indigenous medicinal systems such as Ayurveda, Siddha, and Unani, which utilize plant-based preparations for parasite control. Various phytochemicals, including alkaloids, flavonoids, tannins, and terpenoids obtained from medicinal plants such as *Azadirachta indica*, *Butea monosperma*, and *Vitex negundo*, have demonstrated notable anthelmintic potential against *H. contortus* [8, 9].

Among potential molecular targets, Galectin of *H. contortus* is involved in host-parasite interactions. Galectins are β -galactoside-binding lectins that play a key role in immune modulation, thereby promoting parasite survival through the alteration of host immune responses [10]. Targeting galectins may disrupt parasite establishment and persistence within the host, thereby making them promising candidates for drug discovery.

Molecular docking has become a powerful computational approach in structure-based drug design in recent years. It enables the prediction of binding affinity and interactions between

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ligands and target proteins, thereby accelerating the identification of potential therapeutic compounds [11]. This method is particularly useful for screening phytochemicals from medicinal plants, reducing the need for extensive time consuming experimental trials. Medicinal plants such as *Coriandrum sativum* (Coriander), *Cinnamomum verum* (Cinnamon), *Terminalia bellerica* (Bahera), and *Ocimum sanctum* (Tulsi) are reported to possess anthelmintic activity [12, 13, 14, 15].

Therefore, the present study aims to perform molecular docking analysis of *H. contortus* galectin with bioactive compounds derived from medicinal plants such as *C. sativum*, *C. verum*, *T. bellerica*, and *O. sanctum* available in India. This study seeks to identify potential plant-based anthelmintic compounds that may serve as effective, eco-friendly, and sustainable alternatives to conventional anthelmintics in controlling haemonchosis.

Materials and Methods

Homology modeling of three dimensional model of *H. contortus* Galectin amino acid sequence

The 283 amino acid sequence of *H. contortus* Galectin was retrieved from NCBI database (Accession number: AAP05998.1). The amino acid sequence was submitted to SWISS-MODEL (<https://swissmodel.expasy.org/>) server to identify the template similar to the *H. contortus* Galectin. The suitable structural template was identified based on the percentage of identity of sequence, and GMQE score to build the three dimensional model. The three-dimensional structure of the target protein was constructed using the selected template through automated homology modeling [16].

The initial protein model was refined in GalaxyRefine (<https://galaxy.seoklab.org/cgi-bin/submit.cgi?type=REFINE>) to improve the structural quality and conformations [17]. The refined model was then validated in SAVESv6.1 server using ERRAT, VERIFY3D, and PROCHECK program to perform the structural validation (<https://save.mbi.ucla.edu/>). The PROCHECK program generates Ramachandran plot which was used to assess backbone dihedral angles and overall model quality [18].

Preparation of three dimensional model of *H. contortus* Galectin for docking study

The validated protein structure was further prepared for molecular docking analysis using AutoDock Tools [21]. The preparation steps included removal of water molecules, checking for missing atoms and repair of them, addition of polar hydrogen atoms, and assignment of AutoDock4 (AD4) atom type to the protein structure.

Ligand identification, ADMET analysis, and preparation for the docking study

The phytochemical constituents of plants with known anthelmintic property such as *C. sativum*, *C. verum*, *T. bellerica*, and *O. sanctum* were identified through literature survey of published articles [14, 20, 21, 22, 23, 24]. The SMILES representations of the selected phytochemicals were retrieved from the PubChem database, and their pharmacokinetic properties were evaluated using the SwissADME server (<https://swissadme.ch/>). The ADMET (Absorption, Distribution, Metabolism, Excretion, Toxicity) analysis was performed to assess drug-likeness,

pharmacokinetic behavior and toxic property of the compounds. Drug-likeness was evaluated based on key physicochemical and pharmacokinetic parameters, including lipophilicity, aqueous solubility, gastrointestinal absorption, P-glycoprotein substrate, cytochrome P450 1A2, 2C19, 2C9, 2D6, 3A4 and compliance with Lipinski's rule of Five, Veber's rule, and Egan's rule. The toxicity (T) of the ligands were analysed in ProTox-III server (<https://tox.charite.de/protox3/index.php?site=home>) [25].

The chemical structures of the identified ligands were retrieved in SDF format from the PubChem database (<https://pubchem.ncbi.nlm.nih.gov/>). The SDF format of the ligands were then converted into PDB format using OpenBabel tool [26]. The energy minimization of the ligand was performed using Merck Molecular Force Field 1994 (MMFF94) and minimization was run up to 250 steps [27]. The ligands were subsequently prepared for the molecular docking study in AutoDock tool by addition of polar hydrogens and gasteiger charges.

Molecular docking study of *H. contortus* Galectin and ligands

A grid box was defined to encompass the entire protein structure with appropriate dimensions, ensuring full ligand flexibility within the docking space and complete exploration of potential binding sites by the ligands. Molecular docking study was performed using AutoDock to predict the binding affinity and interaction pattern between galectin and selected ligands. The docking algorithm uses a scoring function based on binding free energy (kcal/mol) to evaluate ligand conformations.

Analysis of Docking study results

The best docked conformations were selected based on the lowest binding energy. Protein–ligand interactions were analyzed for hydrogen bonds, hydrophobic interactions, and other non-covalent interactions using visualization tool, Discovery Studio Visualizer [28], and a web tool, PLIP (Protein – Ligand Interaction Profiler) [29] (<https://plip-tool.biotech.tu-dresden.de/plip-web/plip/index>). Key interacting amino acid residues involved in ligand binding were identified and bond distance were analyzed to evaluate the strength and stability of protein-ligand binding.

Visualization

The docked complexes were visualized in 3D and 2D formats to analyze binding orientation and interaction patterns in Discovery Studio Visualizer and PyMol structural images were generated for presentation and interpretation.

Results

The 283 amino acid sequence of *H. contortus* Galectin was modeled using SWISS-MODEL (Fig 1). The server identified a 32 kDa Beta-galactosidase-binding lectin alpha fold DB model of LEG1_HAECO(gene: GAL-1) as template with the sequence identity of 98.94% and GMQE score of 0.95, indicating the higher reliability. The generated model was refined using GalaxyRefine server. The refined model was validated using SAVESv6.1 server, yielding an ERRAT score of 93.609 (Fig 2). ERRAT score indicated the model is highly reliable non-bonded atomic interactions. Generally, models with ERRAT score of more than 90% indicates high quality of the model. Generally, protein models with an

ERRAT quality factor greater than 90% are considered to be of high quality, indicating a low level of errors in non-bonded atomic interactions and good overall structural reliability^[30].

In VERIFY3D, 92.58% of residues are located in favorable structural environments, indicating the good compatibility between the amino acid residues sequence and the predicted three dimensional structure (Fig 2). Residues with $\geq 80\%$ of residues with score ≥ 0.2 , the protein model is considered structurally reliable^[31]. Ramachandran plot evaluates the stereochemical quality of protein structures based on backbone dihedral angles (ϕ and ψ), and a reliable model typically exhibits more than 90% residues in the most favored regions with minimal residues in disallowed regions^[32]. Ramachandran plot generated had 95.5% residues in most favored region, 4.1% residues in allowed region, 0.0% residues in generously allowed region, and 0.4% residues in disallowed region. 0.4% residue in disallowed region indicating the overall stereochemical quality of the model (Fig 2). Collectively, these validation metrics indicate that the modeled protein possesses high structural integrity and is well-suited for downstream molecular docking studies. The refined *H. contortus* Galectin was then prepared for the docking study.

The phytochemicals of *C. sativum*, *C. verum*, *T. bellerica*, and *O. sanctum* identified through literature study are enlisted in Table 1. These phytochemicals were then evaluated for their physiochemical and pharmacokinetic properties in SwissADME. The initial screening was based on lipophilicity, solubility, gastrointestinal (GI) absorption, and bioavailability score. Lipophilicity was calculated by five prediction methods (iLOGP, XLOGP3, WLOGP, MLOGP, SILICOS-IT) and average of these methods were obtained as consensus LogP value. The compounds with LogP value between 0 and 5 were selected^[33].

The solubility (Log S) of the compounds was predicted by three methods (ESOL, Ali, and SILICOS-IT). The solubility of the compounds were categorized as Insoluble, poorly soluble, moderately soluble, soluble, very soluble, and highly soluble in SwissADME. The compounds that were categorized as moderately soluble, soluble, very soluble or highly soluble in at least two methods were selected^[34]. Gastrointestinal (GI) absorption was classified as high or low absorption, and the compounds with high GI absorption were filtered. Bioavailability score of at least 0.5 or above was considered good, the drug compounds which has more than 0.55 score in SwissADME was selected^[34, 35]. These parameters supported the selection of compounds with favorable pharmacokinetic profiles.

The selected phytochemical compounds were further screened based on drug-likeness criteria such as Lipinski's rule (Molecular weight ≤ 500 Da, LogP ≤ 5 , Hydrogen bond donors ≤ 5 , hydrogen bond acceptors ≤ 10 , Veber's rule (Number of rotatable bonds ≤ 10 , Topological Polar Surface Area (TPSA) ≤ 140 Å²), and Egan's rule (WLOGP ≤ 5.88 , TPSA ≤ 131 Å²). Only phytochemicals that obeyed the above three rules were selected. Furthermore, the compounds were analyzed for cytochrome (CYP) P450 enzyme inhibition, including CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4. The compounds that were non-CYP enzyme inhibitors or inhibitor of only one of the CYPs excluding CYP3A4, and CYP2D6 are considered acceptable. Inhibitor of multiple CYPs and inhibitor of CYP3A4, and CYP2D6 individually were excluded. The

compounds were also evaluated for P-glycoprotein (P-gp) substrate potential, all compounds except catechin are found not to be P-gp substrates. Toxicity assessment of the selected phytochemicals using ProTox 3.0 categorized them into 6 classes. Compounds belonging to toxicity classes 5 and 6 were considered for further study due to their relatively lower toxicity profiles, whereas class 4 compounds (harmful category) were considered with caution depending on overall ADMET properties. This multi-step screening strategy enabled the identification of compounds with optimal pharmacological properties and acceptable safety profiles.

A total of 29 ligands were docked against the prepared protein using AutoDock, where ellagic acid demonstrated the most favorable binding energy of -4.72 kcal/mol, compared to the other molecules. The molecular interaction analysis of ellagic acid was carried out using Biovia Discovery Studio and the PLIP server, revealed a well-defined binding pattern supported by multiple interaction types. Analysis using Biovia Discovery Studio identified key interacting amino acids, including LYS 225, PRO 227, GLU 249, GLU 252, and PHE 254, indicating that the ligand is positioned within a functionally relevant binding pocket (Fig 3).

In PLIP, hydrophobic interactions were observed with PRO 227 (3.35 Å) and PHE 254 (3.33 Å), contributing to the stabilization of ellagic acid within the binding cavity through van der Waals forces (Fig 4). These interactions likely assist in maintaining the ligand orientation and reducing solvent exposure.

Hydrogen bond analysis from both Biovia Discovery Studio and the PLIP server demonstrated consistent interactions with critical residues. Hydrogen bond interactions in molecular docking studies are typically considered significant when the bond distance is ≤ 3.5 Å, as shorter distances indicate stronger electrostatic attraction and improved ligand-protein binding stability. Strong hydrogen bonds were formed with GLU 249 (H-A: 1.99 Å; D-A: 2.71 Å), and PHE 254 (H-A: 2.20, D-A: 3.10), while an additional hydrogen bond with LYS 225 (H-A: 2.41 Å; D-A: 3.28 Å) was identified by PLIP. The short hydrogen bond distances, particularly with GLU 249, suggest high stability and specificity of these interactions, which play a crucial role in ligand binding affinity.

A salt bridge interaction with LYS 225 (5.31 Å) further contributes to electrostatic stabilization, although the relatively longer distance indicates a weaker interaction compared to the hydrogen bonds. In docking studies, interactions within a distance of ≤ 4 Å are generally considered significant, although their strength is influenced by solvent effects and is typically less directional than hydrogen bonds^[36, 37]. Additionally, pocket analysis revealed the involvement of neighboring residues such as GLY 224, MET 226, ASN 250, and ARG 253, which may indirectly support ligand binding by shaping the binding environment.

Overall, the interaction profile indicates that ellagic acid is stabilized within the galectin binding site through a combination of hydrogen bonding, hydrophobic interactions, and electrostatic forces. This multi-faceted interaction network supports favorable ligand accommodation and suggests that ellagic acid can serve as a potential lead compound. However, the moderate binding energy suggests that while ellagic acid is a promising

candidate, it may not act as a strong inhibitor in its current form. Instead, it can be considered a potential lead compound for further optimization through structural modification or derivatization.

In conclusion, the study identifies ellagic acid of *T. bellerica* as a biologically relevant and pharmacokinetically favorable

ligand with moderate binding affinity toward *H. contortus* Galectin. These findings provide a foundation for future experimental validation and rational drug design efforts aimed at enhancing binding affinity and therapeutic efficacy.

Table 1: Phytochemicals from plants with known anthelmintic activity

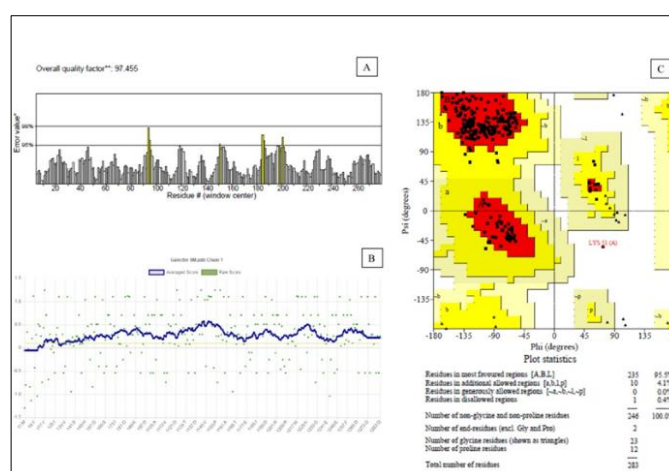
Plant names	Phytochemical constituents
<i>Coriandrum sativum</i>	α -pinene, Borneol, Garenolol Acetate, Geraniol, Camphor, Citronellol, Coriandrin, Coriandrone A, Coriandrone B, Coriandrone C, Coriandrone D, Coriandrone E, Dihydrocoriandrin, Diligustilide, Furan, Isocoumarin, Linalool, Neocnidilide, p-cymene, Pyrazine, Pyridine, Thiazole, γ -terpinene
<i>Cinnamomum verum</i>	Cinnamaldehyde, Eugenol, Camphor, Trans-cinnamyl acetate, β -caryophyllene, α -bergamottin, α -copaene, Cinnamyl acetate, Trans- α -bergamotene, Caryophyllene oxide, Catechin, Kaempferol, Isorhamnetin, Procyanidin, Cinnamic acid
<i>Terminalia bellerica</i>	Termilignan, Thannilignan, Hydroxy-3'4' (methylenedioxy) flavan, Anolignan B, Gallic acid, Ellagic acid, Methyl gallate, Ethyl gallate, Chebulagic acid, Hexahydroxydiphenic acid, Punicalagin, Terflavin A, Terchebulin
<i>Ocimum sanctum</i>	β -ocimene, cis- α -terpineol, Estragole, E- α -bergamotene, Isovitexin, Rosmarinic acid, Trans phytol, 1,8-cineole, 2-camphanone, 3,-dimethylocta-1,6-dien-3-ol, 4-hydroxybenzoic acid, 5-isopropyl-2-methyl phenol, Aesculetin, Apigenin, Apigenin-7-o-glucuronide, Borneocamphor, Borneol acetate, Camphene, Carvene, Chavicol, Chlorogenic acid, Eicosane, Elemene, Ethyl gallate, Eugenol, Farnesene, Farnesyl alcohol, Gallic acid, Galuteolin, Germacene A, Germacrene D, Heptyl alcohol, Humelene oxide, Isocaryophyllene, Isoorientin, Luteolin, Methyl cinnamate, Methyl eugenol, Methyl gallate, Molludistin, Myristaldehyde, n-butyl benzoate, Orientin, p-4(10) thujene, Protocatechuic acid, Selin-11-en-4- α -ol, Ursolic acid, Vanillic acid, Vanillin, Vicenin, Vicenin-2, Vitexin, Z- α -bisabolene, α -amorphene, α -bisabolol, α -caryophyllene, α -murelone, β -bisabolene, β -caryophyllene, β -caryophyllene epoxide, β -eudesmene, β -guaiane, β -gurjunene, β -pinene, β -stigmaterol

Table 2: In silico ADMET profiling of phytochemicals showing molecular weight, lipophilicity (LogP), aqueous solubility, oral bioavailability score, cytochrome P450 enzyme inhibition profile, and P-glycoprotein (P-gp) substrate prediction to evaluate drug-likeness and pharmacokinetic behavior

Phytochemicals	Molecular weight (g/mol)	LogP	Solubility class			Bioavailability score	Cytochrome P450 Inhibitors					P-gp substrate
			ESOL	ALI	SILICOS-IT		CYP1A2	CYP2C19	CYP2C9	CYP2D6	CYP3A4	
4-hydroxybenzoic acid	158.12	1.05	S	S	S	0.55	N	N	N	N	N	N
Borneol	154.25	2.38	S	S	S	0.55	N	N	N	N	N	N
Camphor	152.23	2.37	S	S	S	0.55	N	N	N	N	N	N
Carvacrol	150.22	2.82	S	S	S	0.55	Y	N	N	N	N	N
Carvene	136.23	3.37	S	MS	S	0.55	N	N	Y	N	N	N
Catechin	290.27	0.83	S	S	S	0.55	N	N	N	N	N	Y
Cinnamaldehyde	132.16	1.97	S	VS	S	0.55	N	N	N	N	N	N
Cinnamic acid	148.16	1.79	S	S	S	0.85	N	N	N	N	N	N
Cinnamyl acetate	176.21	2.33	S	S	S	0.55	N	N	N	N	N	N
Cis-alpha-terpineol	154.25	2.58	S	S	S	0.55	N	N	N	N	N	N
Coriandrone D	352.38	2.25	S	MS	S	0.55	N	N	N	N	N	N
Coriandrone E	248.23	1.55	S	S	S	0.55	N	N	N	N	N	N
Ellagic acid	302.19	1	S	S	S	0.55	Y	N	N	N	N	N
Estragole	148.20	2.78	S	S	S	0.55	Y	N	N	N	N	N
Ethyl gallate	198.17	0.92	S	S	S	0.55	N	N	N	N	N	N
Eucalyptol	154.25	2.67	S	S	S	0.55	N	N	N	N	N	N
Eugenol	164.20	2.25	S	S	S	0.55	Y	N	N	N	N	N
Furan	68.07	0.86	VS	VS	S	0.55	N	N	N	N	N	N
Gallic acid	170.12	0.21	VS	S	S	0.56	N	N	N	N	N	N
Heptyl alcohol	116.20	2.08	VS	S	S	0.55	N	N	N	N	N	N
Isocoumarin	146.14	1.93	S	S	S	0.55	Y	N	N	N	N	N
Linalool	154.25	2.66	S	S	S	0.55	N	N	N	N	N	N
Luteolin	286.24	1.73	S	MS	S	0.55	N	N	N	N	N	N
Methyl cinnamate	162.19	2.22	S	S	S	0.55	N	N	N	N	N	N
Methyl eugenol	178.23	2.58	S	S	S	0.55	Y	N	N	N	N	N
Methyl gallate	184.15	0.57	VS	S	S	0.55	N	N	N	N	N	N
Pyrazine	80.09	0.25	VS	HS	S	0.55	N	N	N	N	N	N
Sabinene	136.23	3.25	S	S	S	0.55	N	N	N	N	N	N
Thiazole	85.13	0.73	VS	VS	S	0.55	N	N	N	N	N	N
Vanillic acid	168.15	1.08	S	S	S	0.85	N	N	N	N	N	N
Vanillin	152.15	1.20	VS	VS	S	0.55	N	N	N	N	N	N

Table 3: Predicted acute toxicity (LD₅₀) and toxicity classification of selected phytochemicals based on in silico toxicity prediction

Phytochemicals	Predicted LD50 (mg/Kg)	Predicted Toxicity class
4-hydroxybenzoic acid	2200	5
Borneol	500	4
Camphor	775	4
Carvacrol	810	4
Carvene	4400	5
Catechin	10000	6
Cinnamaldehyde	1850	4
Cinnamic acid	2500	5
Cinnamyl acetate	3300	5
Cis-alpha-terpineol	2830	5
Coriandrone D	2170	5
Ellagic acid	2991	4
Estragole	1230	4
Ethyl gallate	5810	6
Eucalyptol	2480	5
Eugenol	1930	4
Gallic acid	2000	4
Heptyl alcohol	1000	4
Linalool	2200	5
Luteolin	3919	5
Methyl cinnamate	2610	5
Methyl eugenol	810	4
Methyl gallate	1700	4
Pyrazine	1020	4
Sabinene	5000	5
Thiazole	983	4
Vanillic acid	2000	4
Vanillin	1000	4

**Fig 1:** Refined three-dimensional model of *H. contortus* Galectin**Fig 2:** Structural validation of the refined three-dimensional model of *H. contortus* Galectin. A) ERRAT analysis showing the distribution of non-bonded interaction errors across the protein sequence, with the majority of residues falling within acceptable quality limits with ERRAT score of 97.455. B) VERIFY3D analysis showed 92.58% of residues have acceptable 3D-1D scores, demonstrating the compatibility between the amino acid sequence and the predicted 3D structure. C) Ramachandran plot illustrating 95.5% of residues in the most favored region, 4.1% residues in the additional allowed region, and one residue in the disallowed region

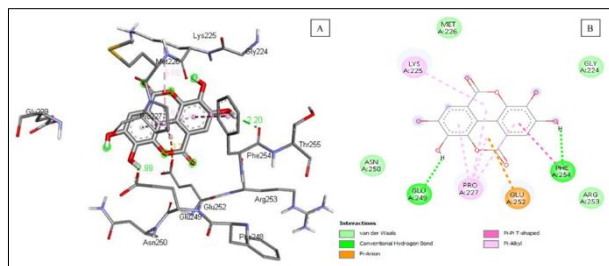


Fig 3: *H. contortus* Galectin and ellagic acid interaction was analyzed using BIOVIA Discovery Studio. A) Three-dimensional interaction of the protein-ligand complex, and B) Two-dimensional interaction of protein and ligand illustrating the key interactions and pocket atoms

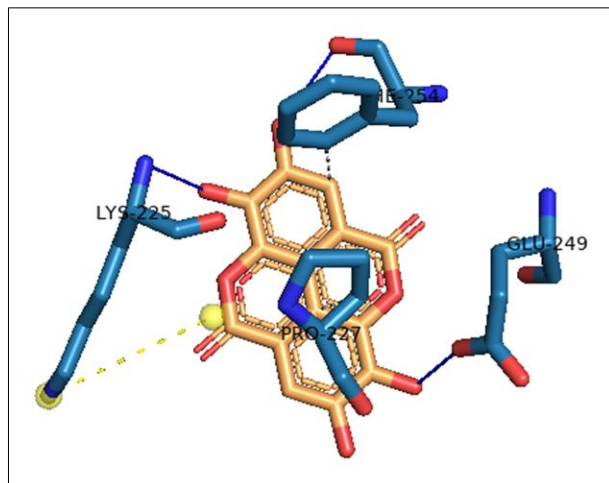


Fig 4: *H. contortus* Galectin and ellagic acid interaction was analyzed using PLIP web tool. Blue lines indicate the hydrogen bonds formed and the yellow line indicate the salt bridge formed

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Conflict of Interest

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

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