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IN-SILICO CONSIDERATION OF ANTI-MICROBIAL PROSPECTIVE OF TANNIC ACID: MECHANISTIC INSIGHT

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ABSTRACT: Objective: Infections caused by pathogenic microorganisms present a significant risk to human health. The demand for novel, secure, and effective antimicrobial medications has been propelled by the increasing instances of drug resistance, adverse antibiotic reactions, and the resurgence of previously diagnosed diseases. Virtual screening techniques employed in the field of drug discovery, such as drug-likeness and ADMET analysis, utilize computational methods to rapidly and cost-effectively identify compounds that are probable to exhibit physiological activity.

Methods: The current research has focused on the discovery of antibacterial drugs by studying the enzymes aminoacyl-tRNA synthetase (IIes) and DHFR. Computational simulations were conducted to investigate docking. The process of molecular docking was conducted using AutoDock to analyze the interaction between tannic acid and aminoacyl-tRNA synthetase (AaRS) as well as dihydrofolate reductase (DHFR).

Results: The molecular docking analysis indicated that tannic acid exhibited a favorable docking score. Therefore, based on the aforementioned findings, it can be inferred that the tannin present in the plant extract shown strong inhibitory effects on the IleRS enzyme and DHFR synthase.

Keywords: Tannic acid, IIes, DHFR synthase and *in-silico* molecular docking.

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1. INTRODUCTION

Antibiotic resistance has become a significant public health concern in recent years due to the emergence, spread, and endurance of multidrug-resistant (MDR) bacteria, commonly referred to as "superbugs." These bacteria cause infections that are unresponsive to conventional treatments [1-2]. An important factor that leads to the development and expansion of antimicrobial resistance is the increasing utilization and misuse of antibiotics in both humans and animals, along with a lack of progress in antibiotic research (resulting in a decrease in the number of new types of antibiotics). There is a pressing requirement for the development of novel chemical compounds as antibacterial agents, together with the implementation of measures to limit the inappropriate and irrational utilization of antibiotics. A collection of multidrug-resistant microorganisms, collectively known as "ESKAPE", consists of both Gram-positive and Gram-negative species (Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter spp.). These microorganisms are frequently found in hospital settings and are responsible for the majority of healthcare-associated infections [3]. Gram-positive bacteria have developed widespread resistance to all available antibiotics, posing a significant problem not just in hospitals but also for the general population [4-5]. MRSA infections are a significant cause for concern. Tannic acid, being a phenolic acid, falls under the category of polyphenolic compounds. Due to its distinctive antiviral and antibacterial capabilities, this subject has been extensively researched in the biomedical realm of science. Tannic acid has been found to exhibit antiviral activity against Influenza A virus, Papilloma viruses, noroviruses, Herpes simplex virus type 1 and 2, and human immunodeficiency virus (HIV). It also shows antibacterial activity against both Gram-positive and Gram-negative bacteria such as Staphylococcus aureus, Escherichia coli, Streptococcus pyogenes, Enterococcus faecalis, Pseudomonas aeruginosa, Yersinia enterocolitica, and Listeria innocua. In contemporary times, substances derived from natural sources serve as the fundamental building blocks of material science, and this trend is referred to as "from nature to nature" [6-8]. Tannic acid is a crucial chemical component of *T. Chebula*. The compound is also known as Penta-(m- digalloyl)-glucose or gallotannin. It has a chemical formula of $C_{76}H_{52}O_{46}$ and a molecular weight of 1701.20 g/mol. Its melting point is 210°C (410°F), at which it begins to dissolve [9].

S.No.	**Description of Tannic acid [9]**	
1.	Molecular formula	$C_{76}H_{52}O_{46}$
2.	Molecular weight	1701.2 g/mol
3.	Source	Tara pods (Caesalpinia spinosa), gallnuts from Rhus semialata or Quercus infectoria or Sicilian sumac leaves (Rhus coriaria).
4.	Category	Gallotannin
5.	Pharmacology	Anti-inflammatory, neuroprotective, antitumor, cardioprotective, and anti-pathogenic effects [15].

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The current research has focused on the enzyme aminoacyl-tRNA synthetase (AaRS) and DHFR in the quest for antibacterial drugs. In this study, tannic acid is used as the active ingredient to investigate its antibacterial potential using molecular docking.

2. MATERIALS AND METHODS

Ligand Preparation:

The 2D structure of tannic acid was created using ChemSketch [10]. The 2D structure of the ligand was then transformed into its 3D structure, which was optimized using 3D geometry. The optimized structure was saved in PDB format to ensure compatibility with AutoDock. Below are the fundamental structures of the ligand that was prepared:

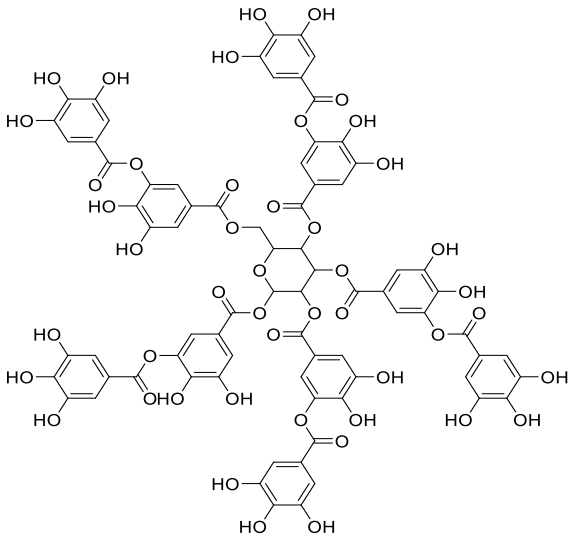

Figure 1: 2D structure of tannic acid.

Preparation of the grid file

Autodock defined the regions of interest by creating a grid box around the active sites and examining the grid area. The grid box is essential in the docking process as it encompasses all the amino acids found in the active sites that are required for binding, except those found in the receptor. The grid box contains three thumbwheel widgets that let us to modify the number of points in the x, y, and z dimensions. The table 1 [11-13] provides the spacing and grid points for the IleS receptor of S. aureus and DHFR of C. albicans in the current investigation.

Table 1. Grid parameters used in current docking analysis

S. No.	Receptor	x-axis	y-axis	z-axis	Spacing	x center	y center	z center
1	IleS	60	60	60	1.000	27.914	89.835	81.39
2	DHFR	40	40	40	0.758	3.334	-0.246	27.626

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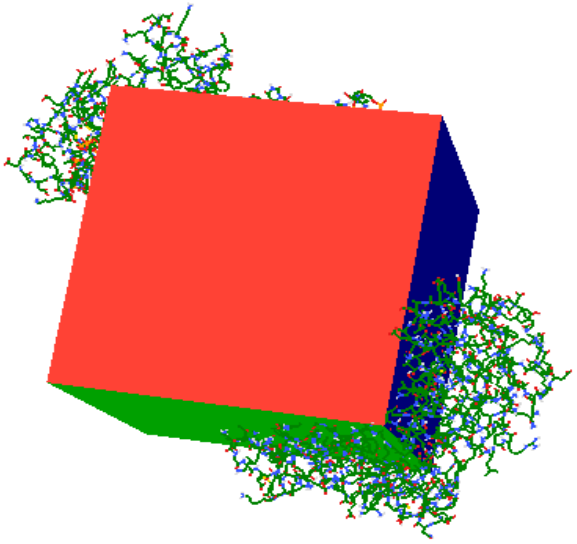

Figure 2: Grid box covering all active sites in IleS receptor.

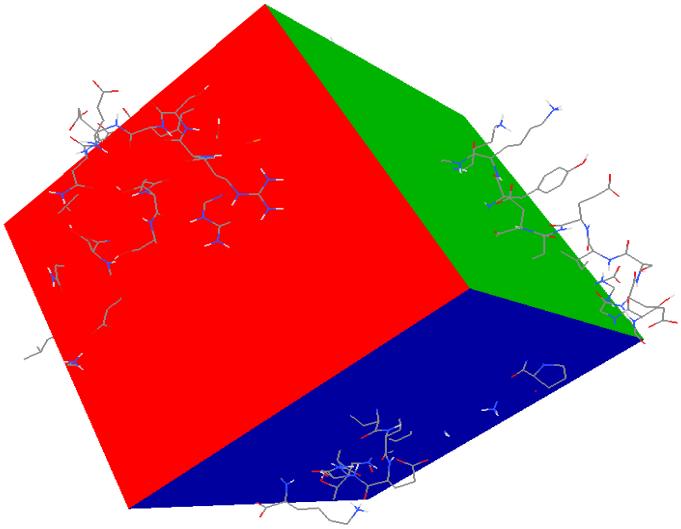

Figure 3: Grid box covering all active sites in DHFR receptor

Preparation of the docking file

The computations were performed using Autodock 4.2 as the docking tool. The docking studies were conducted using Pymol, Chimera, DS visualizer, and MMP Plus [14-17].

Docking Study

Crystal structure

The protein's crystal structure, which includes the IleS and DHFR receptor, was obtained via the Protein Data Bank portal. The Protein Data Bank [18-22] has comprehensive information on the structure of all receptors. The intricate ligand was isolated using Chimera software for each of the target receptors.

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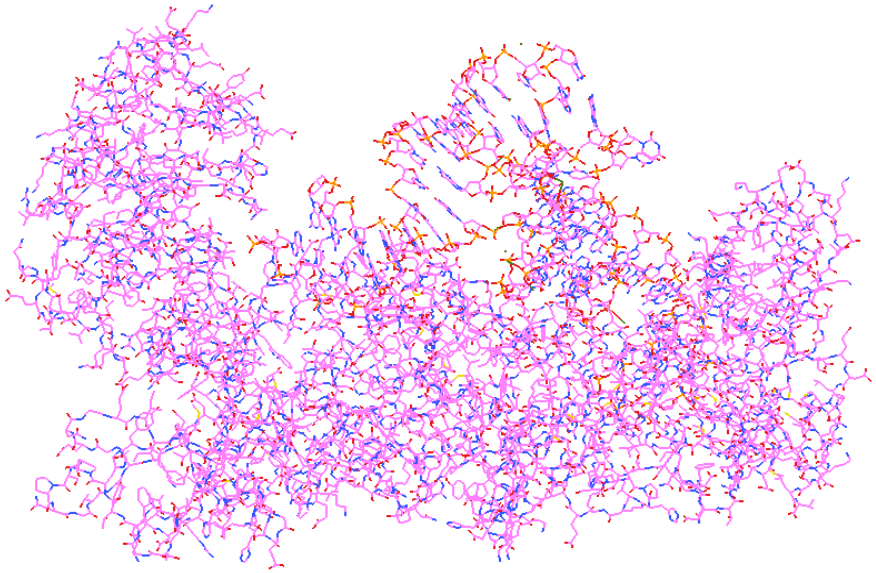

Figure 4: Crystal structure of IleS receptor (PDB ID-1ffy)

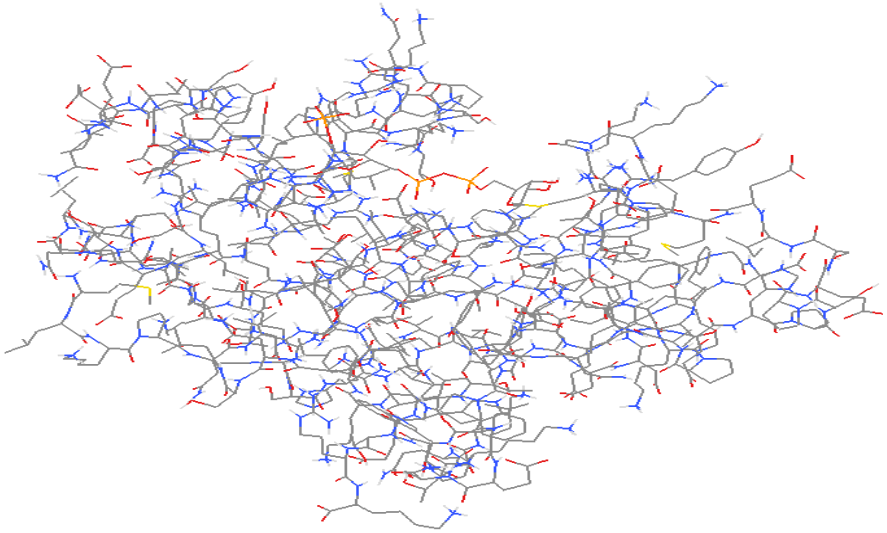

Figure 5: Crystal structure of DHFR receptor (PDB ID-4hoe)

Processing of Protein

All of the downloaded receptor proteins consist of a single chain, specifically chain A, which has been chosen for experimental purposes. The complex ligand has been extracted from it. The ligand that was attached to the macromolecular complex was isolated using the Chimera software [23-26].

Molecular Docking Simulation Studies

The docking of tannic acid against the IleS and DHFR receptors was conducted using Autodock. The flexibility of all ligand bonds was maintained, whereas no flexibility was introduced to the receptor residues [27-30].

Toxicity & ADME-T Studies

The ligand molecules, specifically tannic acid, were analyzed using the online tool OSIRIS to anticipate the existence of any hazardous groups and evaluate their ADME-T characteristics [31].

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3. RESULTS AND DISCUSSION

Throughout history, plants have been a source of optimism for discovering new medicinal compounds due to the significant enhancement of human health through herbal treatments derived from plants. The widespread utilization of plants as remedies for many infectious disorders has prompted a continuous pursuit for plant components possessing antibacterial properties. There is an urgent requirement to identify and develop new compounds to combat potentially fatal bacterial, fungal, and viral illnesses due to the ability of these infections to develop resistance to current treatment methods. These substances must exhibit high bioavailability, possess a defined action, and demonstrate low toxicity. Optimal compounds for this type of task generally originate from natural sources, such as plants, animals, or even microbiological organisms. Tannins are polyphenols with a high molecular weight (MW) that can be found in plants from all kingdoms. Their molecular weight ranges from 500 to 30,000 Da. Tannin is a primary compound found in plants that has potential health benefits. Tannins have been demonstrated to hinder bacterial growth by many mechanisms, such as iron chelation, disruption of the cell membrane, suppression of cell wall construction, and inhibition of fatty acid biosynthesis pathways. Tannins possess the capacity to interfere with quorum sensing and diminish the expression of many genes associated with the virulence factors, such as biofilms, enzymes, adhesins, motility, and toxins. Tannic acid was selected as the primary compound for in-silico molecular docking with the target proteins, DHFR and isoleucyl-tRNA synthetase (IleRS), in the present investigation. Aminoacyl-tRNA synthetases (ARSs) play a crucial role in protein synthesis and have conserved enzymatic pathways across different species. Scientists have developed effective anti-infective drugs by exploiting the structural differences in the catalytic clefts of ARSs found in both infections and people, even though these structures are similar across different taxa. Advancements in genomic, proteomic, and functionomic research have uncovered other biological functions of human ARSs, going beyond their primary involvement in protein synthesis. These activities encompass the identification of unforeseen disease-associated mutations, as well as changes in expression, secretion, and interactions. These studies have demonstrated the potential of ARS proteins and their components as a valuable and untapped resource for new therapeutic targets and agents. This has been achieved through methods such as directly targeting the catalytic sites, regulating disease-associated protein-protein interactions, and developing novel biologics from the secreted ARS proteins or their parts. Bacterial, protozoan, and other microbial disorders typically exhibit a shared heightened metabolic rate. In these cases, the rate of folate metabolism is also increased to ensure proper cell replication and synthesis of proteins and nucleic acids. Due to the metabolic difference between folic acid antagonists and human cells, these compounds have been used to treat many microbial illnesses since their discovery. Dihydrofolate reductase has been extensively studied due to its crucial role in maintaining the folate pathway. The reduction of dihydrofolate (DHF) helps to maintain a collection

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of various tetrahydrofolate (THF) derivatives inside cells. These derivatives are used in biosynthetic activities and reactions involving the transfer of one-carbon units. Due to its essential role in bacterial growth, dihydrofolate reductase (DHFR) inhibitors have demonstrated potential in treating bacterial infections. Tannic acid was selected as the primary compound for in-silico molecular docking with the target proteins, DHFR and isoleucyl-tRNA synthetase (IleRS), in the present investigation. Aminoacyl-tRNA synthetases (ARSs) play a crucial role in protein synthesis and have conserved enzymatic pathways across different species. Scientists have developed effective anti-infective drugs by exploiting the structural differences in the catalytic clefts of ARSs found in both infections and people, even though these structures are similar across different taxa. Advancements in genomic, proteomic, and functionomic research have uncovered other biological functions of human ARSs, going beyond their primary involvement in protein synthesis. These activities encompass the identification of unforeseen disease-associated mutations, as well as changes in expression, secretion, and interactions. These studies have demonstrated the potential of ARS proteins and their components as a valuable and untapped resource for new therapeutic targets and agents. This has been achieved through methods such as directly targeting the catalytic sites, regulating disease-associated protein-protein interactions, and developing novel biologics from the secreted ARS proteins or their parts. Bacterial, protozoan, and other microbial disorders typically exhibit a shared heightened metabolic rate. In these cases, the rate of folate metabolism is also increased to ensure proper cell replication and synthesis of proteins and nucleic acids. Due to the metabolic difference between folic acid antagonists and human cells, these compounds have been used to treat many microbial illnesses since their discovery. Dihydrofolate reductase has been extensively studied due to its crucial role in maintaining the folate pathway. The reduction of dihydrofolate (DHF) helps to maintain a collection of various tetrahydrofolate (THF) derivatives inside cells. These derivatives are used in biosynthetic activities and reactions involving the transfer of one-carbon units. Due to its essential role in bacterial growth, dihydrofolate reductase (DHFR) inhibitors have demonstrated potential in treating bacterial infections. The results of the in-silico molecular docking research indicate that tannic acid effectively attaches to the IIes and DHFR proteins, with binding energies of -3.13 and -3.29, respectively. The outcome was computed and recorded in tables 2 and 3. The figure 6-7 (2D) and 8-9 (3D) demonstrate the manner in which lead molecules interact with receptors. The binding pattern was succinctly outlined in table 4. The IC50 value of tannic acid against both selected target proteins are identical, measuring 0.19. The pharmacokinetic profile of the selected lead compounds indicates that they have favorable pharmacokinetic characteristics. However, there are no significant adverse effects such as tumorogenicity, irritating and reproductive impacts, save for mild mutagenicity. The figure 12 displays the pharmacokinetic and toxicity profiling data of the ligand. The pharmacokinetic profiles of several substances were compared and presented in table 6-8, indicating that tannic acid had the

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most favorable effects.

Table 2: Results of docking of ligand tannic acid against IleS and DHFR receptor

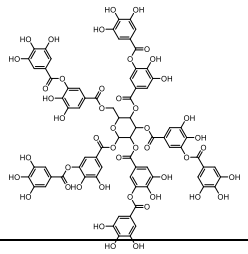
Sl. No	Compound	Structure	Binding Energy (kcal/mol)	
			IleS (1ffy)	DHFR (4hoe)
1	Tannic Acid		-3.13	-3.29

Table 3: Determination of Ki value and IC50 value

S.No.	Compound	IleS (1ffy)		DHFR (4hoe)	
		Ki	IC 50	Ki	IC 50
1	Tannic Acid	5.28	0.19	5.5	0.19

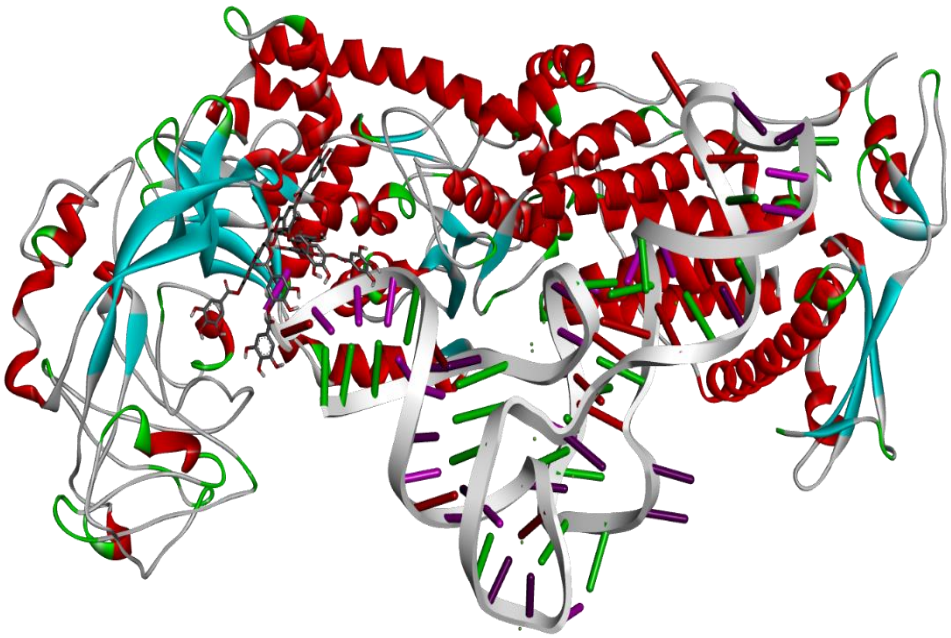


Figure 6: Binding mode of tannic acid within the active site of IleS receptor.

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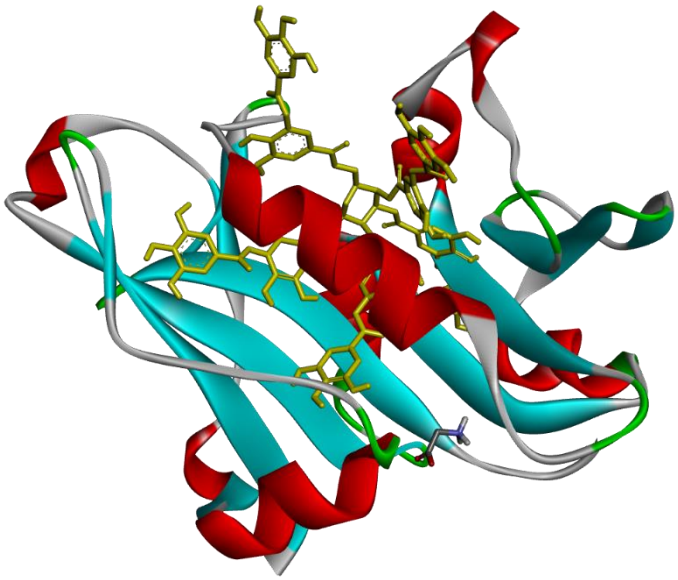

Figure 7: Binding mode of tannic acid within the active site of DHFR receptor.

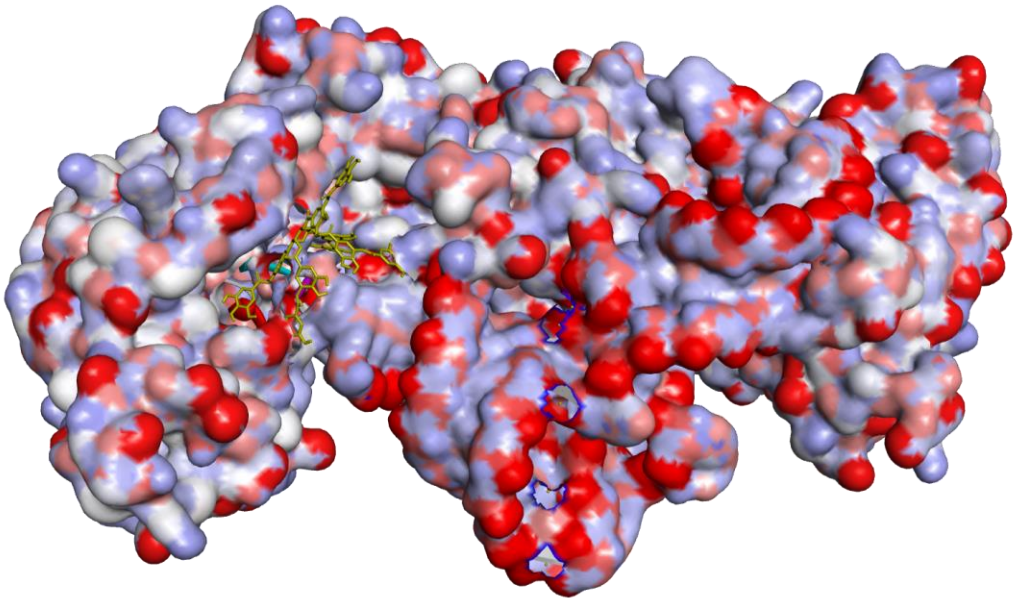

Figure 8: Three-dimensional binding mode of tannic acid within the active site of IleS receptor.

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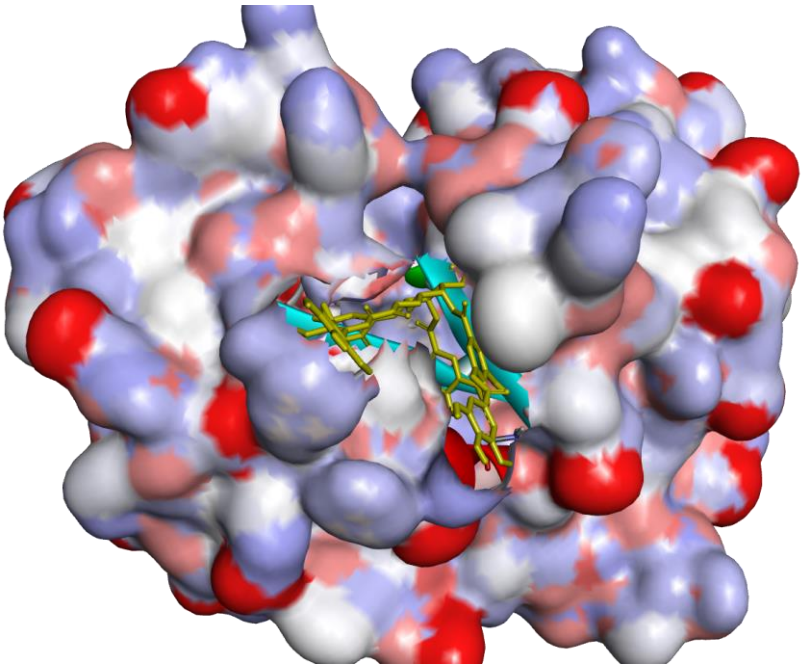

Figure 9: Three-dimensional binding mode of tannic acid within the active site of DHFR receptor.

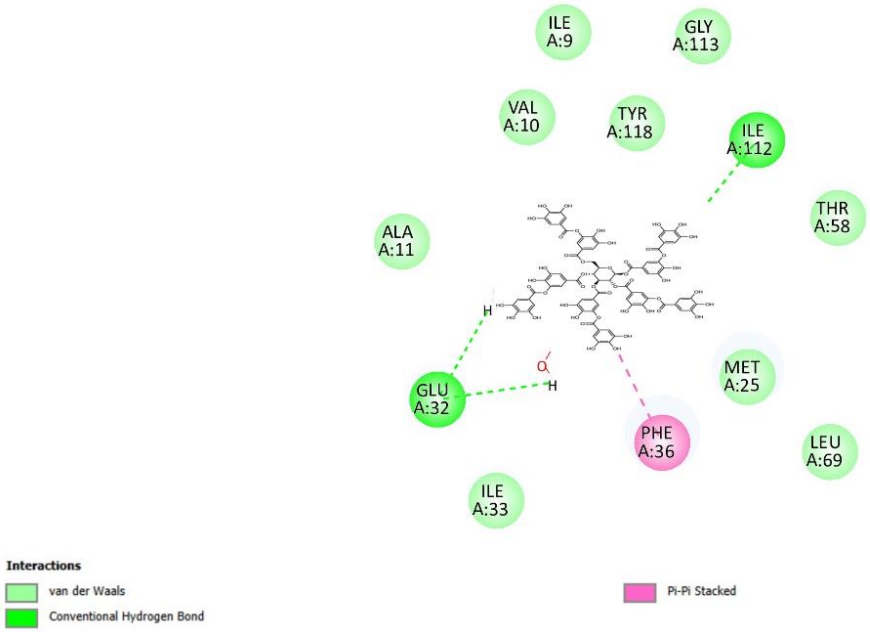

Figure 10: Two-dimensional binding mode of tannic acid within the active site of IleS receptor.

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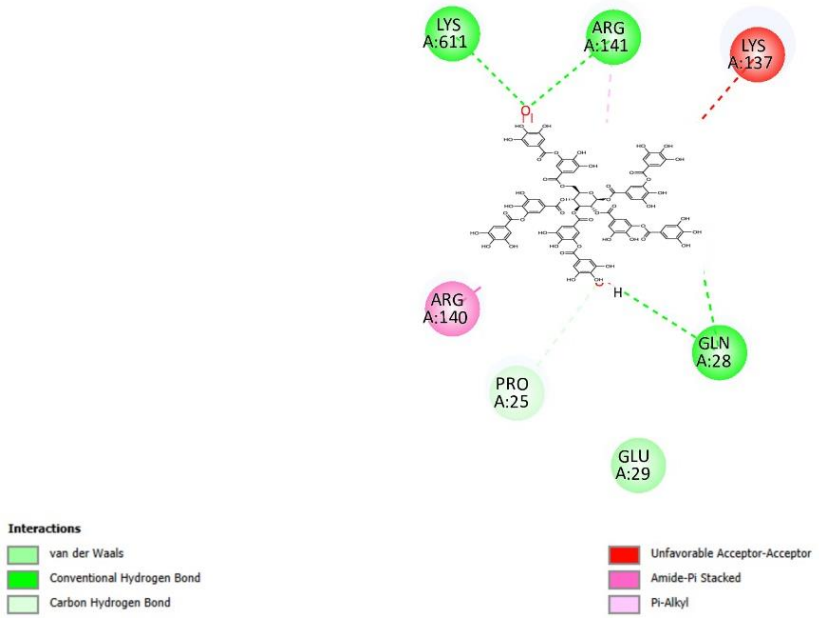

Figure 11: Two-dimensional binding mode of tannic acid within the active site of DHFR receptor.

Table 4: Binding interaction of lead molecule with IIes protein

Compound	Conventional H bounding	Vander waals	Pi-Pi	Pi-Alkyl
Tannic acid	Glu 32 Ile 112	Ile 9 Gly 113 Val 10 Tyr 118 Thr 58 Leu 69 Met 25 Ile 33 Ala 11	Phen 36	-

Table 5: Binding interaction of lead molecule with DHFR protein

Compound	Conventional H bounding	Vander waals	Pi-Pi	Pi-Alkyl
Tannic acid	Gln 28 Lys 611 Arg 141	Pro 25 Glu 29	-	Arg 140

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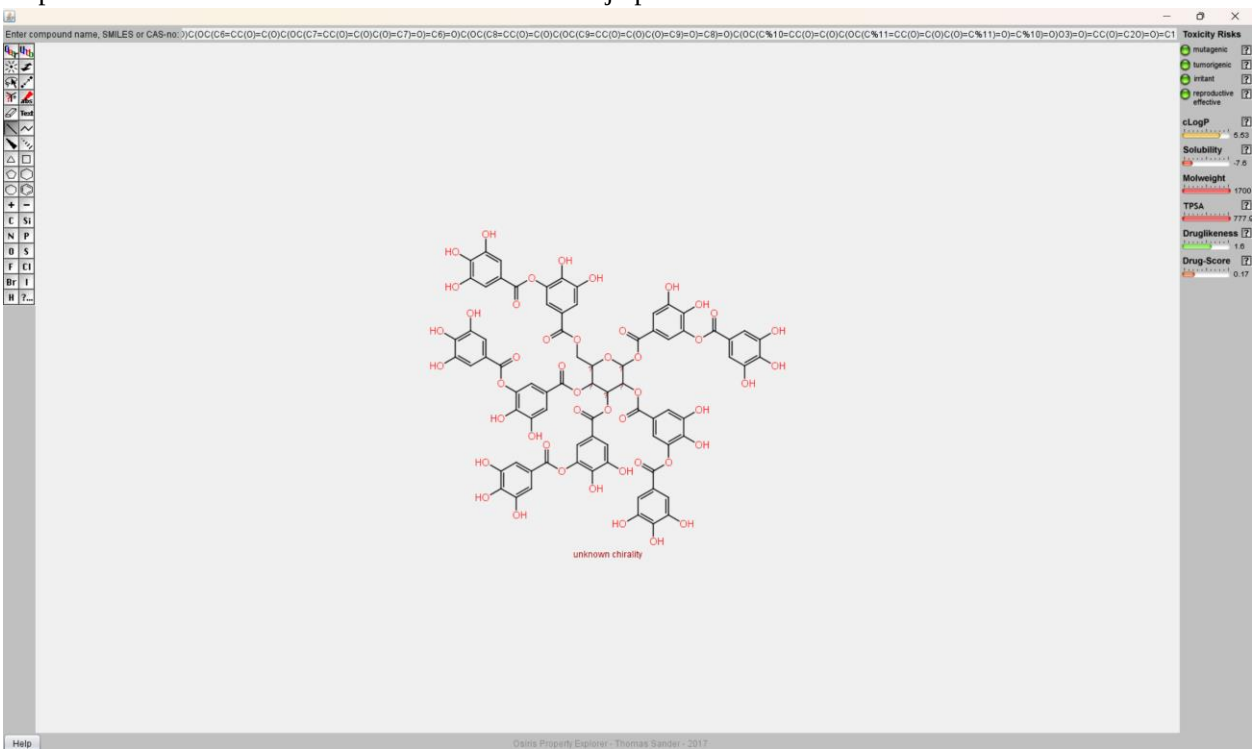

Figure 12: Pharmacokinetic and toxicity profiling of tannic acid.

Table 6: Pharmacokinetic Profiling of lead molecules

Compound	ADMET			
	Mutagenic	**Tumorigenic**	**Irritant**	**Reproductive effectivity**
Tannic acid	NO	NO	NO	NO

Table 7: Lipinski Properties of lead molecules

Compound	*cLogP*	Solubility	Mol.wt.	TPSA	Drug likeness	Drug score
Tannic acid	5.53	-7.0	1700	71.7	0.14	0.17

Table 8: Drug likeness of lead molecules

Compound	Lipinski rule of five	H bond donar(<5)	H bond acceptor (<10)
Tannic acid	No	25	36

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4. CONCLUSION

Tannins are a group of polyphenolic compounds that are found in large quantities in many parts of plants. They possess a variety of biological characteristics, including immunological modulation, antioxidant activity, antiviral effects, antibacterial effects, and anti-parasitic effects. Tannins are the primary area of research when it comes to finding natural alternatives to antibiotics used in animal feed. Plant tannins are widely recognized for their notable ability to strongly bind to proteins. This property has been successfully utilized in ruminant nutrition to decrease protein degradation in the rumen and improve animal production efficiency and protein utilization. The present study employed DHFR and IIes proteins to assess the antibacterial efficacy of tannic acid by in-silico molecular docking analysis. The results indicated that the tannic acid had about identical affinity towards both the DHFR and IIes protein. The concurrent inhibitory effect of tannin on the chosen proteins showcased the antibacterial capability of tannic acid.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No animals or humans were used for the studies that are based on this research.

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

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CONFLICT OF INTEREST

The authors declare that no conflict of interest exists.

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