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In-Silico Consideration of Anti-Microbial Prospective of Plant Phenolic and Flavonoids

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ABSTRACT: ***Background:*** Pathogenic microorganism infections pose a serious threat to human health. The need for innovative, safe, and efficient antimicrobial medicines has been driven by rising drug resistance cases, unfavorable antibiotic side effects, and the reemergence of previously identified illnesses. Virtual screening techniques used in drug development, such as drug-likeness and ADMET analysis, use computation to quickly and cheaply identify compounds that are likely to demonstrate physiological activity. ***Methods*:** In this regard, the enzyme aminoacyl-tRNA synthetase (AaRS) has been the focus of recent research in the discovery of antibacterial agents. Docking studies were performed Molecular docking of aminoacyl-tRNA synthetase (AaRS) with chlorogenic acid, rutin, quercetin and gallic acid was carried out by AutoDock. ***Results*:** The molecular docking result revealed that chlorogenic acid, gallic acid, quercetin and rutin showed encouraging docking score. Hence from above finding it can be predicted that phenolics and flavonoids found in the plants extract exhibited good inhibitor of IleRS enzyme.

Keywords: Chlorogenic acid, rutin, quercetin, gallic acid and *in-silico* molecular docking.

RESEARCH PAPER

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INTRODUCTION

The rise, dissemination, and persistence of multidrug-resistant (MDR) bacteria, colloquially known as "superbugs," which cause infections that do not respond to traditional therapies, has led to antibiotic resistance being one of the most important public health challenges of this century [1-2]. One of the main factors contributing to the emergence and spread of antimicrobial resistance is the rising use and abuse of antibiotics in both humans and animals, as well as the lack of innovation in antibiotic research (reduction in the number of new antibiotic classes). There is an urgent need for new chemical entities to be developed as antibacterial agents, as well as policies to restrict the improper and irrational use of antibiotics. A group of MDR micro organism together acknowledged as "ESKAPE", which incorporates Gram-effective and Gram-terrible species (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter spp.*), are regularly remoted in sanatorium environments, in which they're accountable for the bulk of nosocomial infections [3]. In precise, Gram-effective micro organism have predominantly advanced resistance to all of the to be had antibiotics and pose a critical trouble now no longer simplest in hospitals however additionally for the overall population [4, 5]. Infections of methicillin-resistant Staphylococcus aureus (MRSA) are of precise concern. In plants, Flavonoids are widely distributed as a naturally occurring polyphenols. Being both dietary and biologically active compounds, flavonoids have attracted much attention of investigators as potent species capable of affecting various biological processes in living organisms. They are able to modulate various enzymes present in biological system. Flavonoids and the other phenolic compounds are generally referred to as plant secondary metabolites that maintain an aromatic ring bearing as a minimum one hydroxyl groups. More than 8000 phenolic compounds as obviously going on materials from vegetation were pronounced [6]. It may be very thrilling to word that 1/2 of of those phenolic compounds are flavonoids offering as aglycone, glycosides and methylated derivatives [7]. These phytochemical materials are provided in vitamins and natural medicines, each flavonoids and lots of different phenolic additives were pronounced on their powerful antioxidants, anticancer, antibacterial, cardioprotective agents, anti-inflammation, immune

gadget promoting, pores and skin safety from UV radiation, and thrilling candidate for pharmaceutical and scientific application [8-9]. Since some many years ago, the studies research specializing in flavonoids and the other phenolics compounds from medicinal plant species have improved considerably, due to their flexible advantages for human health. In this consideration, the enzyme aminoacyl-tRNA synthetase (AaRS) has been the focus of recent research in the discovery of antibacterial agents. With this endeavor chlorogenic acid, rutin, quercetin, and gallic acid are taken as active compound for elucidation of antimicrobial potential *via* molecular docking.

Experimental works

Ligand Preparation

2D Structure of ligand like chlorogenic acid, rutin, quercetin, and gallic acid was drawn using ChemDraw [10]. The two-dimensional structures of ligands were converted into 3-D structures with optimized 3D geometry by using Chem3D software. The optimized structure was saved in PDB format for AutoDock compatibility [11].

Preparation of the grid file

The regions of interest used by Autodock were defined by considering grid area by making a grid box around the active sites. Grid box plays a central role in process of docking as it is made to cover all the amino acids present in active sites necessary for binding other than those present in receptor. Grid box has 3 thumbwheel widgets which let us change the number of points in the x, y and z dimensions. The spacing between grid points can be adjusted with another thumbwheel, the value in the study taken is 0.392 Å and No. of points considered are 40, 40 and 40 points in the x, y, and z dimensions are67.561, 31.934 and 19.359 as x, y, z centers [12].

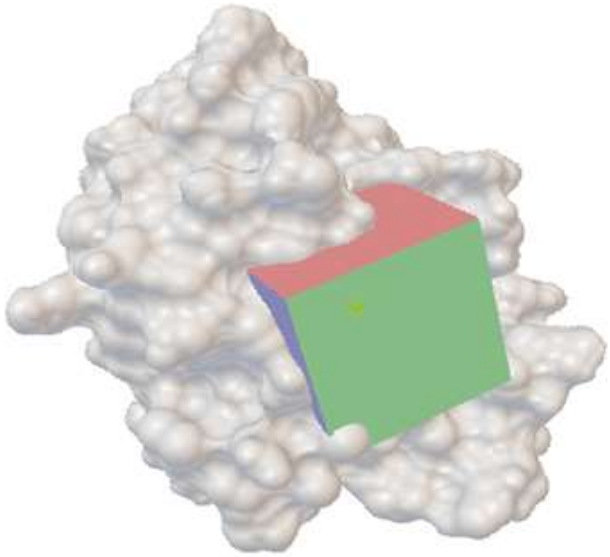


Figure 1: Grid box covering all active sites in receptor

Preparation of the docking file

All the calculations were carried out by using Autodock4.2 as docking tool. The visualization and other programs necessary for docking studies were performed out by means of Pymol, Chimera, DS visualizer, MMP Plus [13].

Docking of Isoleucyl-transfer RNA (tRNA) synthetase (IleRS)

Crystal structure

The crystal structure of the protein consisting of receptor associated with bound ligand is downloaded from the Protein Data Bank portal. All the primary information regarding receptor and structure (1WNZ.pdb) registered in the Protein data bank was used. The bound ligand 2'-(L-valyl) amino-2'-deoxyadenosine (2VA) was found within the receptor [14].

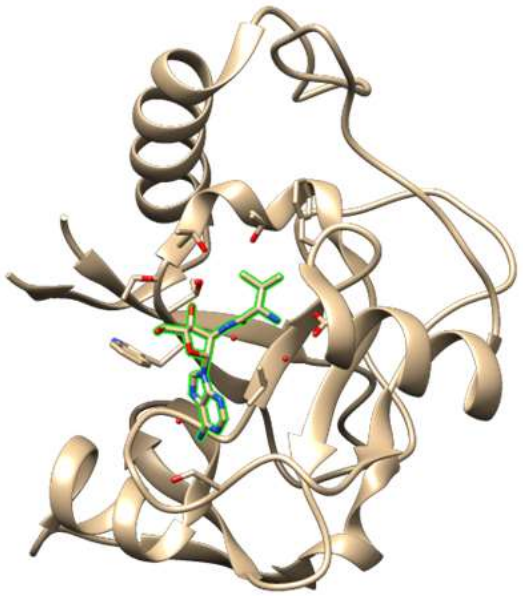


Figure 2: Crystal structure of IleRS enzyme with bound ligand 2VA(PDB ID-1WNZ)

Processing of Protein

The downloaded receptor protein is having a single chain A, which has been selected for the experimental purpose. The bound ligand 2VA was separated from the macromolecular complex by using software Chimera [15].

Molecular Docking Simulation Studies

Docking of ligand like chlorogenic acid, rutin, quercetin, and gallic acid against IleRS enzyme was performed by Autodock. All the bonds of ligand were kept flexible, while no residues in receptor were made flexible [16].

Toxicity & ADME-T Studies

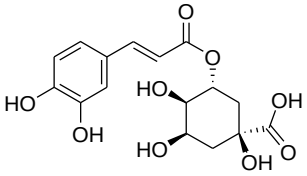
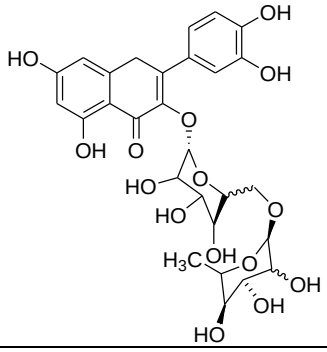
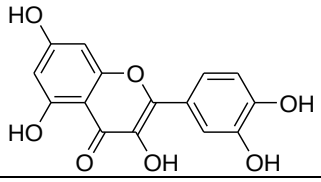
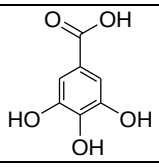
The modified lead molecules are studied by online program OSIRIS, for prediction of presence of any toxic group as well as presence of any toxic group and ADME- T properties [17].

RESULTS AND DISCUSSION

The current sensational increase within the unfold of antimicrobial resistance in microorganisms poses a true threat to the well-being of the general public round the world. Of explicit concern are contamination with methicillin-resistant staphylococci aureus (MRSA), antibiotic drug *staphylococci aureus*, vancomycin-resistant enterococci and mycobacteria. Tuberculosis, several of those creatures are impervious to some categories of medication agents. This scenario facilitates the explored for novel antimicrobial agents that block essential targets for microorganism that don't seem to be littered with current therapy resistance mechanisms. During this regard, the protein aminoacyl-tRNA synthetase (AaRS) has been the focus of recent analysis within the discovery of medication agents. These enzymes play a very important role in super molecule synthesis by catalyzing the synthesis of aminoacyl-RNA (aarRNA). Once these enzymes are suppressed, protein biosynthesis ceases, leading to restricted bacterial growth underneath each *in-vitro* and infectious conditions. These enzymes are attention-grabbing targets for antibacterial drugs. The result of *in-Silico* molecular docking revealed that binding energy ($Kcalmol^{-1}$) of chlorogenic acid, rutin, quercetin, and gallic acid against IleRS enzyme were found to be -4.20,-5.06,-7.42 & -4.56 respectively (Table 1). Molecular stimulation interaction showed in following pattern Rutin> Chlorgenic acid > Gallic acid > Quercetin (Figure 3-10).

The pharmacokinetic profiling of the ligand has revealed that chlorogenic acid and rutin are having good pharmacokinetic profile without presence of any major toxic effects, while quercetin is associated with some mutagenic and tumorogenic properties. The Gallic acid is also associate with mutagenic and reproduction effects. The pharmacokinetic and toxicity profiling results were shown in Figure 11-14.

Table 1: Result of docking of against IleRS enzyme.

S. No	Compound	Structure	B.E.	H-Bond	Residual Interaction	
					Pi-Interaction	van der Waals
1	Chlorogenic acid		-4.20	Gly316, Ser310, Thr229, His319, Asp328, Thr230	Val318	Asp313, Val309, Trp227, Thr228, Tyr308, Thr233
2	Rutin		-5.06	Thr229, Trp227, Thr315, Ile317, Ser310, Tyr308, Asp328	Trp227, Val318	Gly314, Val309, Thr230, Thr228, Glu327, Gln320, Ala321
3	Quercetin		-7.42	Thr315, Ser310, Ile317	Val318, Asp313	Gly316, Gly314, Thr228, Thr229, Thr230, Tyr308
4	Gallic acid		-4.56	Asp313, Ser310, Trp227, Ile317, Gly316	Val318, Trp227	Thr315, Thr228, Val309, Ile226

Interactions

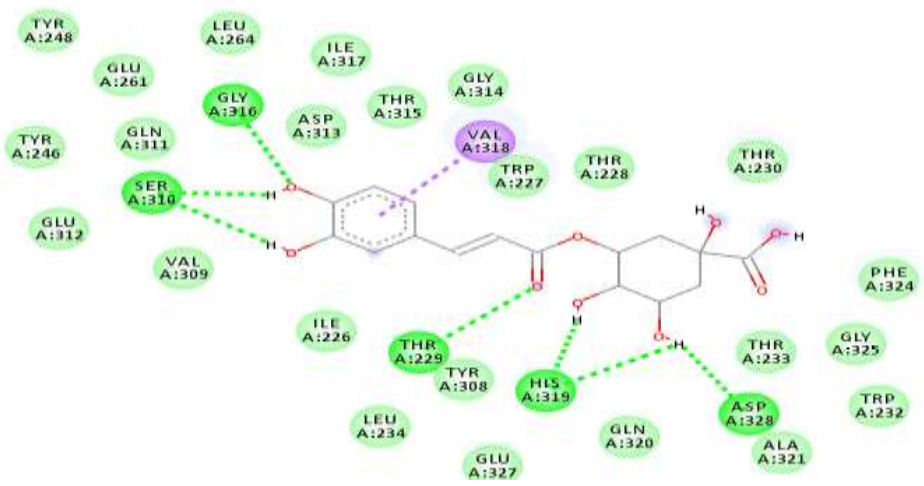


Figure 3: Binding interaction of chlorogenic acid with IleRS

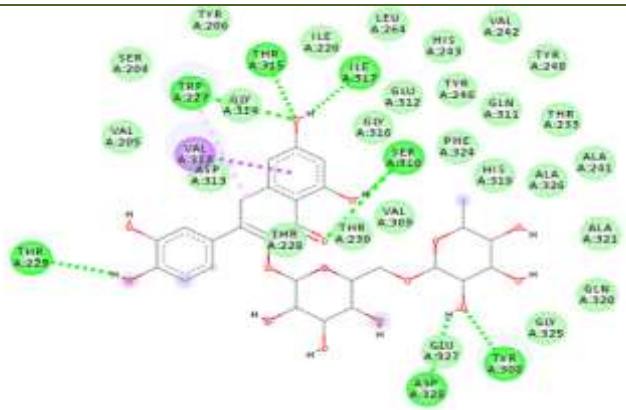


Figure 4: Binding interaction of rutin with IleRS

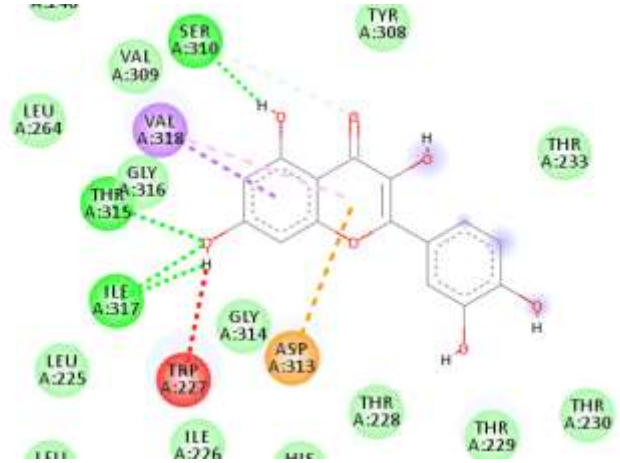


Figure 5: Binding interaction of quercetin acid with IleRS

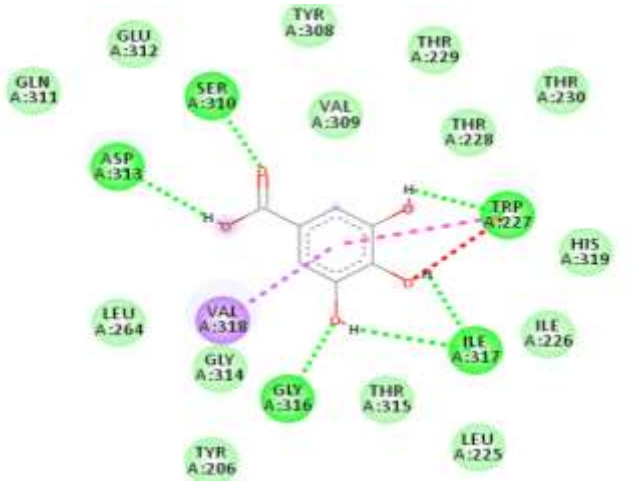


Figure 6: Binding interaction of gallic acid with IleRS

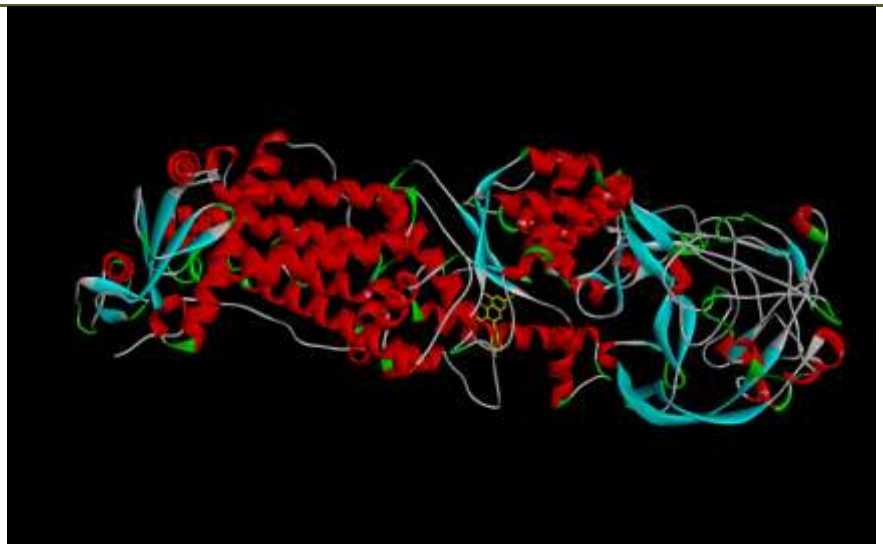


Figure 7: Binding mode of quercetin within the active site of IleRS receptor

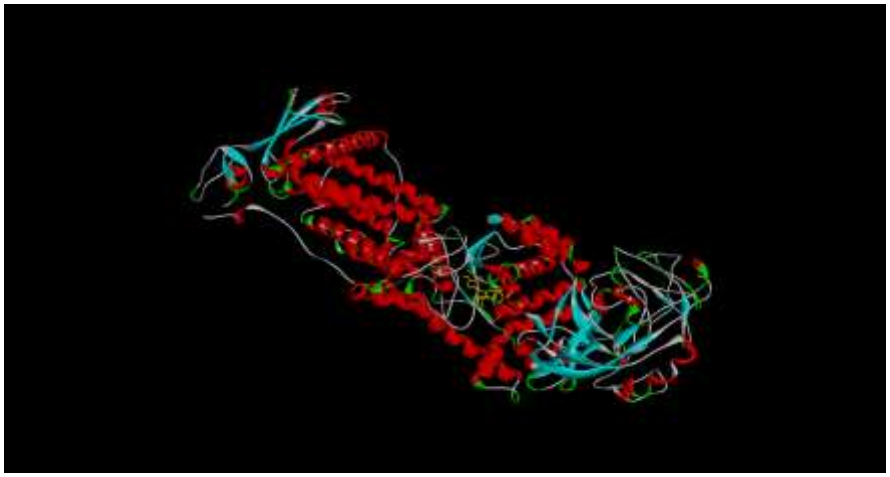


Figure 8: Binding mode of rutin within the active site of IleRS receptor

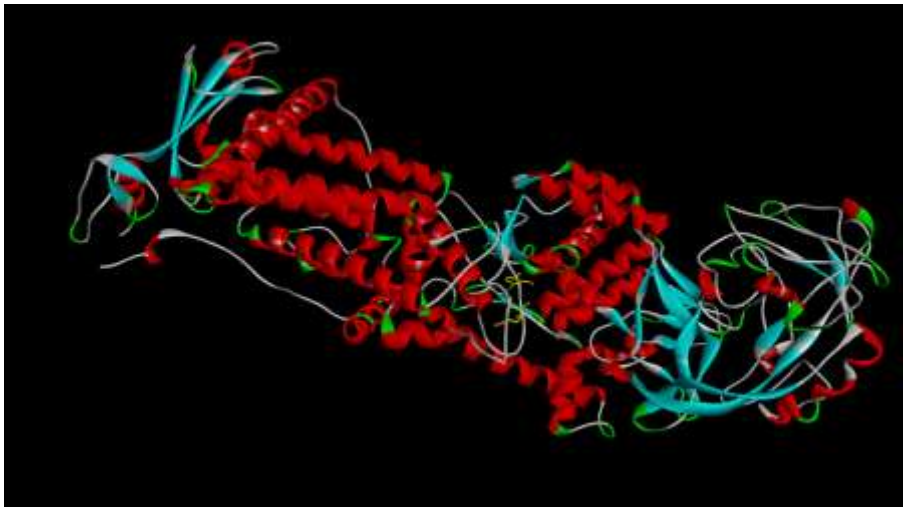


Figure 9: Binding mode of chlorogenic acid within the active site of IleRS receptor

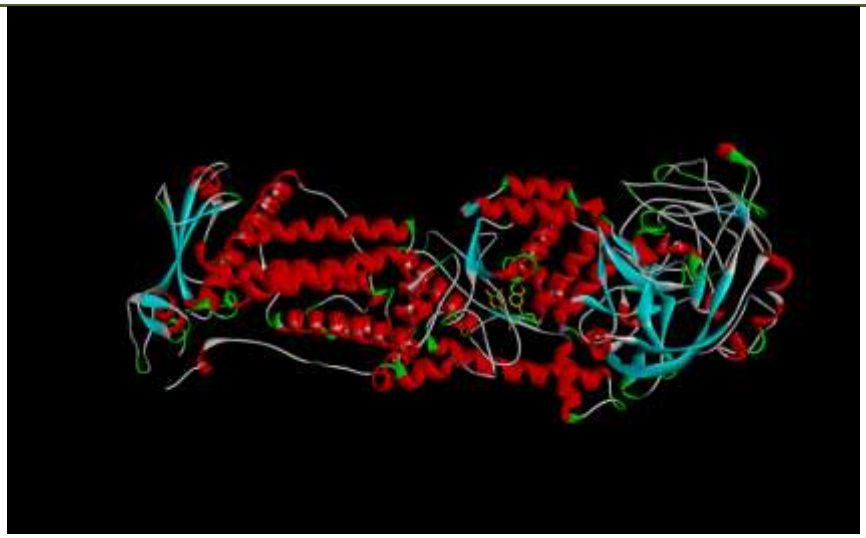


Figure 10: Binding mode of Gallic acid within the active site of IleRS receptor

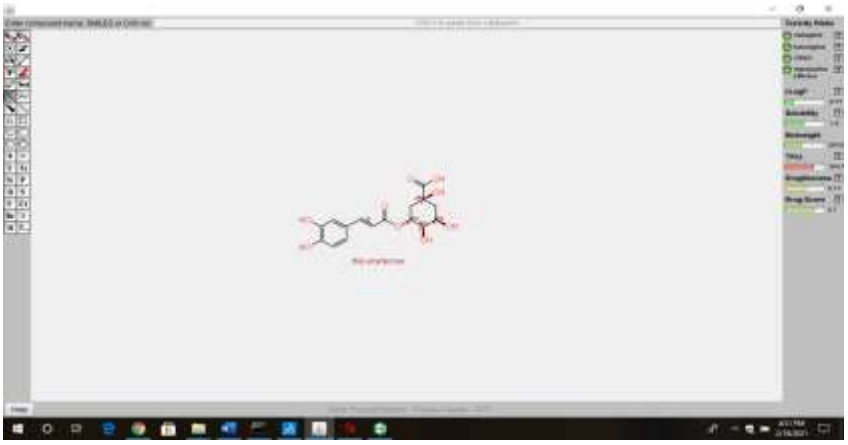


Figure 11: Pharmacokinetic and toxicity profiling of chlorogenic acid

Figure 12: Pharmacokinetic and toxicity profiling of rutin

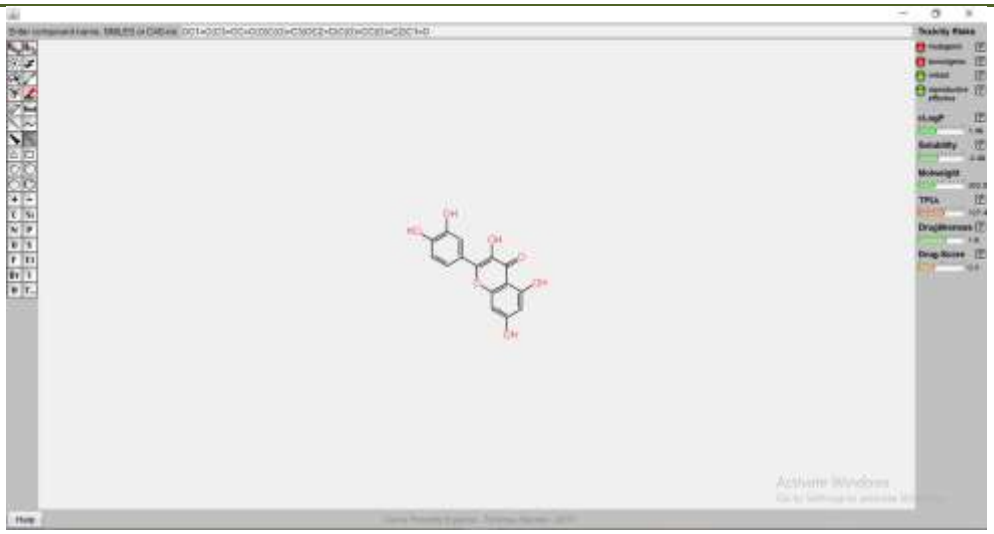


Figure 13: Pharmacokinetic and toxicity profiling of quercetin

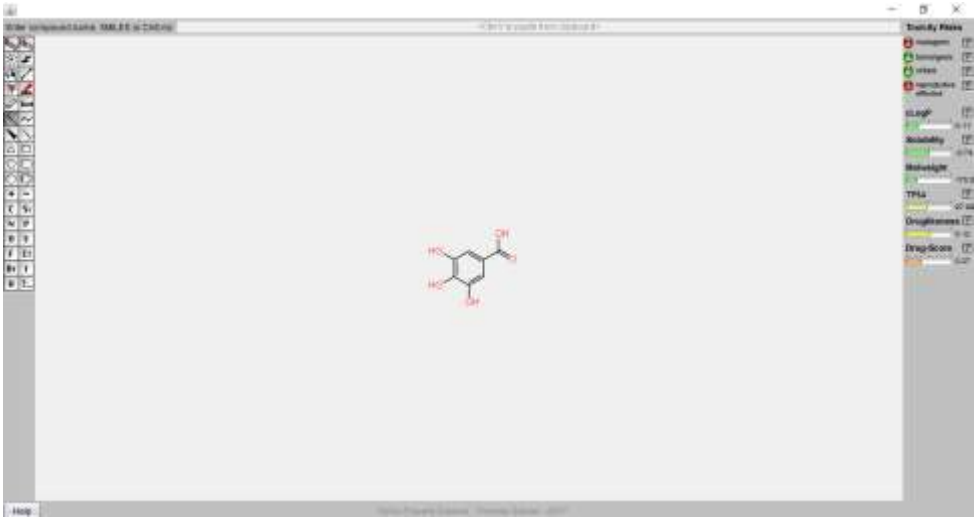


Figure 14: Pharmacokinetic and toxicity profiling of gallic acid

CONCLUSION

With this attempt, natural plant Phenolics & flavonoids found in extracts of the plants known as, gallic acid, chlorogenic acid rutin and quercetin has been identified as ligand and their aminoacyl-tRNA synthetase (AaRS) enzymes inhibitory activity has been checked *in-silico* with the facilitated of docking approach. The molecular docking result revealed that chlorogenic acid, gallic acid, quercetin and rutin showed encouraging docking score. Hence from above finding it can be predicted that phenolics and flavonoids found in the plants exhibited good inhibitor of IleRS enzyme.

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