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In Silico And In-Vitro Screening Of Flavonoids Against Different Pathogenic Microorganisms

Rajeev Kumar [1], Mrynal Chamoli [2], Shalini Singh Negi [3], Kamran Javed Naquvi, Maya Krishna Gupta [5], Nisha Shri Chengamaraju [6], Surya Pratap Singh [7], Avneet Kaur Lamba [8]*

1. Assistant Professor, Department of Biotechnology, Shivpadraj Mahavidyalaya Auraiya Affiliated to CSJM University, Kanpur, Pin-208001, U.P. India.
2. Assistant Professor, ICFAI School of Pharmaceutical Sciences, The ICFAI University, Dehradun, India
3. Assistant Professor, SVNIET, Barabanki Uttar Pradesh,225003
4. Assistant Professor, Pharmacy Department, Tishk International University, Erbil, Iraq
5. Principal, Sri Sai RR institute of Pharmacy, Phal Mandi, Sarsol, Aligarh, Uttar Pradesh 202001
6. Associate Professor, Gokaraju Rangaraju College of Pharmacy, Hyderabad, Telangana - 500090
7. Research Fellow, Department of Biotechnology and Life Sciences, Faculty of Sciences, Mangalayatan University, Aligarh, Beswan, (U.P.) 202145, India.
8. Assistant Professor, Gurugram University Address: Nirvana Rd, Mayfield Garden, Sector 51, Gurugram, Samaspur, Haryana 122003

Corresponding Author: Dr. Avneet Kaur Lamba
Designation and Affiliation: Assistant Professor, Gurugram University, Nirvana Rd, Mayfield Garden, Sector 51, Gurugram, Samaspur, Haryana 122003
avneetkaur.lamba@gmail.com

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ABSTRACT: *Human health was in grave danger due to antibiotic resistance, and new antimicrobial drugs are urgently needed. Flavonoids, one of the most abundant families of secondary metabolites found in plants, are widely distributed throughout the plant and are becoming more and more well-known for their antibacterial properties. Because it is essential to protein synthesis, the enzyme asparaginyl tRNA synthetase makes a great molecular target. This computer investigation was made possible by evidence from the literature that offered hints for finding flavonoids as possible antimicrobial leads. The potential antimicrobial properties of flavonoids are confirmed by computational factors such docking score, binding energy, intermolecular hydrogen bond interaction, and identical amino acids. The results demonstrate that they can be investigated further.*

Keywords: *Micro-organism, Flavonoids, Molecular Docking, Asparaginyl tRNA synthetase.*

INTRODUCTION

Global economic development and human public health have been gravely endangered by antimicrobial resistance (AMR), and novel antimicrobial drugs are critically needed [1,2]. Despite their remarkable antibacterial properties, antibiotics, which are secondary metabolites produced by several bacteria, actinomycetes, and fungi, also cause harmful side effects in humans and inevitably result in resistance [3]. While certain plant components can reverse the resistance of antimicrobial drugs, many have lesser antibacterial activities4. In addition, because they are found in a wide variety of meals and drinks made from plants, the majority of them are thought to be harmless to human health. [4, 5]

Flavonoids, one of the most abundant families of secondary metabolites in plants, are present in a wide range of plant components, including fruit, vegetables, nuts, and tea [6]. These substances have a variety of pharmacological properties, such as antioxidation, antibiosis, and the prevention of coronary heart disease. Notably, some flavonoids have the ability to reverse AMR and increase bacterial susceptibility to antibiotics [7, 8]. As a result, flavonoids' antimicrobial properties have drawn increasing interest. Numerous studies on the antibacterial properties of flavonoids have recently been conducted, and a summary of the likely connections between these compounds' chemical structures and antimicrobial properties has also been provided [8, 9, 10]. It is still necessary to investigate the regularity findings on the structure–activity relationships of flavonoids against bacteria.

The antibacterial properties of flavonoids are not associated with their unique structure, however they may be associated with their polarities or lipid-water partition coefficients, according to our research on antimicrobial compounds [11, 12]. Numerous plant flavonoid data, including their chemical structures and antibacterial properties documented in earlier studies, were looked up and examined to support this. [13] Plant flavonoids' inhibitory effects on gram-positive bacteria, particularly Staphylococcus aureus, can be extensively studied, but there have been few reports of their effects on gram-negative bacteria and fungi to conduct statistical analysis [14, 15, 16]. Therefore, we concentrated on the former in this study. Since a compound's inhibitory activities against various harmful bacteria vary, this research will focus primarily on the flavonoids' inhibitory activities against Staphylococcus aureus, a species that has been the subject of the most literature reports [17, 18]. Numerous biological advantages for human health are provided by flavonoids, including anti-inflammatory, antioxidant, antibacterial, antifungal, and antiviral properties as well as antifilarial properties [19]. Several types of flavonoids, including luteolin, baicalein, quercetin, kaempferol, plumbagin, and rutinto, have been effectively demonstrated in numerous studies to be very active against a variety of infections [20, 21, 22]. We investigated certain synthetic flavonoid derivatives as possible anti-microbial leads for our current work after searching for leads for different therapeutic targets.

MATERIALS AND METHODS:

Protein preparation: Fig. 1 shows the crystal structure of AsnRS (PDB ID: 4ZYA). The Protein Data Bank provided the X-ray crystallographic coordinates of AsnRS in its complex state with the ligand NSS, at a resolution of 1.9A°. Together with chain B, water molecules, ligands, and other heteroatoms were extracted from the protein molecule. The CHARMm force field was used to add hydrogen atoms to the protein. Using the conjugate gradient approach and an RMS gradient of 0.01 kcal/(A° mol), energy minimisation was carried out on Accelyrs Discovery studio client (version 2.5) (2009) San Diego. [24, 25]

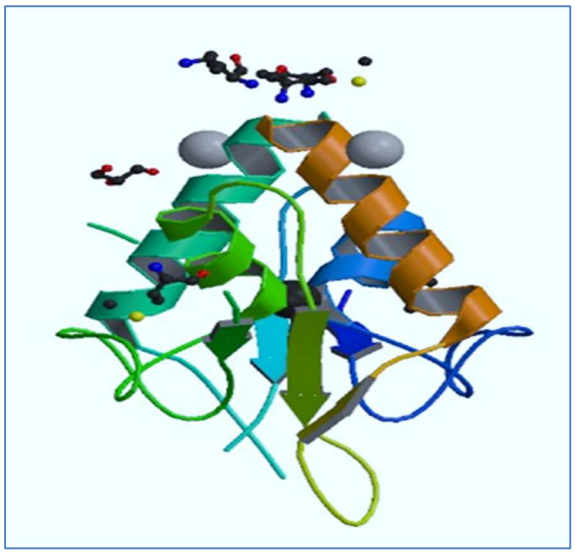

Fig. 1: The Crystal Structure of AsnRS (PDB ID: 4ZYA)

Ligand preparation: Fig. 2 lists the flavonoid compounds taken into consideration for this investigation. SMILES notation (Simplified Molecular Input Line Entry Specification) was used to create the chemical structures after the molecules were obtained from the Pubchem database using Discovery Studio 2.5. [26, 27]

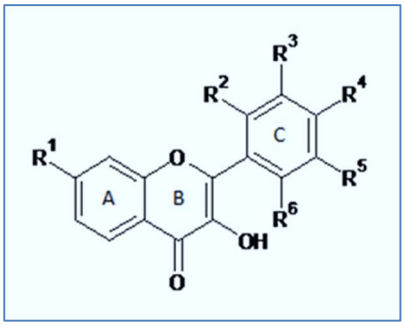

Fig. 2: Flavonoid Derivatives Used for Study

Table 1: Derivatives of flavonoids for study

Compound	R^1	R^2	R^3	R^4	R^5	R^6
1	H	H	H	H	H	H
2	H	H	$-NO_2$	H	H	H
3	H	H	H	$-CH_3$	H	H
4	H	H	-OH	$-OCH_3$	H	H
5	H	-Cl	H	H	H	H
6	H	H	$-OCH_3$	$-OCH_3$	H	H
7	H	H	$-OCH_3$	-OH	H	H
8	H	H	$-CH_3$	H	H	H
9	H	H	H	$-NO_2$	H	H

10	H	H	H	-Br	H	H
11	-OH	H	H	H	H	H
12	-OH	H	-Br	H	H	H
13	-OH	$-NO_2$	H	H	H	H
14	-OH	H	H	$-CH_3$	H	H
15	-OH	-Cl	H	H	H	H
16	-OH	H	$-NO_2$	H	H	H
17	-OH	H	H	-Cl	H	H
18	-OH	H	$-OCH_3$	$-OCH_3$	H	H
19	-OH	H	$-OCH_3$	-OH	H	H
20	-OH	H	-OH	$-OCH_3$	H	H

Docking Studies: Schrodinger AutoDock 4.2 docking computations were used to determine the binding affinity between the AsnRS and flavonoid molecules. For each type of atom in the ligand being docked, AutoDock needs a pre-calculated grid map. The auxiliary program AutoGrid was used to calculate these maps. The six spatial degrees of freedom for orientation and torsional degrees of freedom inside the grid box were open to the compounds that were considered as flexible molecules. H-bonds and van der Waals interactions were modelled using the program's implementation of Lennard-Jones parameters 12-10 and 12-6, respectively. [28, 29, 30]

RESULTS AND DISCUSSION

The binding energy and their corresponding docking score, the interaction of substituents with different amino acids for each class of flavonoids with AsnRS are given in Table 2. All the energies are reported in kcal/mol. Fig. 3 shows the lowest binding energy conformation of flavonoid (compound 3). Their interacting residues in the binding site of AsnRS are represented in elemental coloured ball and stick model. The coloured lines between the atoms represent the hydrogen bonds which links the substituents with amino acid of the protein. Among all the studied compounds, the flavonoid ligand, [3-hydroxy-2-(3-nitro)-4H-chromen-4-one] (compound 3), showed best docking scores, best molecular properties and bioactivity.

Table 2: Binding Energy, Docking Score and Interaction Of Substituents With Different Amino Acids

Comp	Docking score	Binding Energy	Substituents			Amino acids
			Ring A	Ring B	Ring C	
1	-6.365	-21.044		-OH		LYS64
2	-5.355	-22.643		-OH		ZN101
3	-4.373	-21.354		-OH		LYS64
4	-4.072	-24.359		-OH		LYS67
5	-4.154	-23.764		-OH		LYS67
6	-4.853	-21.852		-OH		LYS64
7	-3.914	-25.464		-OH		LYS67
8	-5.474	-20.662		-OH		ZN101
9	-5.376	-26.279		-OH		ZN101
10	-3.853	-25.638			-OH	LYS22
11	-4.456	-23.153			-OH	LYS38

12	-4.153	-21.274	-OH			ZN101
13	-4.13	-21.164	-OH			ZN101
14	-3.32	-22.911	-OH			MET3
15	-4.062	-21.536	-OH			ZN101
16	-3.533	-25.143	-OH			MET3
17	-3.945	-19.273	-OH			ZN101
18	-4.353	-23.053	-OH			ZN101
19	-3.325	-26.184				ZN101
20	-4.223	-27.575		-OH		GLU12

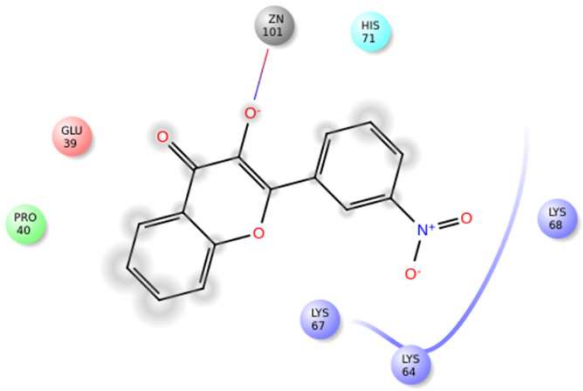

Fig. 3: The Lowest Binding Energy Conformation Of Flavonoid (Compound 3).

CONCLUSION

Molecular docking calculations have been used to study the binding and interactions of flavonoid compounds with AsnRS. Significant binding interactions with the AsnRS have been demonstrated by the majority of the substances. Unfavourable interactions with the binding site residues could be the cause of the drop in activity when compared to other classes of chemicals. The flavonoid ligand, [3-hydroxy-2-(3-nitro)-4H-chromen-4-one] (compound 3) demonstrated the best docking scores, best molecular properties, and best bioactivity; as a result, it can be regarded as having the best antimicrobial activity. This conclusion can be drawn from the compounds' docking scores, molecular properties, and bioactivity scores. The results demonstrate that their promise as antimicrobial agents can be confirmed by additional in vitro and in vivo research.

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