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AN *IN-SILICO* APPROACH TOWARDS RUTIN FLAVONOID FROM *ABUTILON THEOPHRASTI* MAY BE A PROMISING INHIBITOR ACTIVITY AGAINST MICROBIAL AGENTS

Shreya Rane[1], Shankar Gharge [2], Rahul Koli[1], Anjana Adhyapak[1*]

[1]Department of Pharmaceutical Quality Assurance, KLE University's College of Pharmacy, Nehru Nagar, Belagavi 590010, Karnataka, India
[2]Department of Pharmaceutical Chemistry, KLE University's College of Pharmacy, Nehru Nagar, Belagavi 590010, Karnataka, India

***Corresponding author E-mail:** anjanaadhyapak@klepharm.edu

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ABSTRACT

Background: Microbial infections and diseases are frequently associated with several pathogenic strains of bacteria and fungi. Plants of the Abutilon genus are a notable source of new therapeutic agents including antimicrobial.

Methods: In present research article, usage of *in-silico* prediction of a number of available medications might prove to be effectual in inhibiting the antibacterial and antifungal proteins. Initially we screened phytoconstituents for their druggability and ADMET property, Furthermore, we got the 3D x-ray crystallographic strucutures of two antibacterial targets of *Escherichia Coli* (PDB ID: 4Y17), *Staphylococcus aureus* (PDB ID: 1JIJ) and one antifungal target of *Candida albicans* (PDB ID: 1IYL) from Protein Data Bank to use as protein targets for identification of potential drug candidates. We performed molecular docking study using AutoDock Vina by PyRx 0.8 software. BIOVIA Discovery Studio Visualizer v2021 was used to analyse ligand protein interaction. The probable protein targets of selected compound were predicted by SwissTargetPrediction. STRING and Gene Cards of Genes and Genomic pathways are utilized to identify molecular pathways modulated by predicted targets and network interaction between compounds and protein pathways was constructed by Cytoscape 3.6.1.

Results: The present investigation is very much helpful for researchers and readers, among all compounds, rutin showed druggable characteristic and scored lowest binding energy with target proteins **.**Enrichment analysis identified rutin to PI3K-Akt signaling pathway,Rap1 signaling pathway,HIF-1 signaling pathway,Shigellosis,NF-kappa B signalling pathway, Yersinia infection,Toxoplasmosis,Melanogenesis,Tuberculosis,Legionellosis,Pathogenic Escherichia coli infection, Prolactin signaling pathway, Bacterial invasion of epithelial cells, Salmonella infection,TNF signaling pathway, Epithelial cell signaling in Helicobacter pylori infection signaling pathways .Rutin may be a potent antimicrobial inhibitor and may inhibit severe antibacterial and antifungal infectious diseases.

Conclusion: This study suggests that the Rutin from Abutilon *theophrasti* an herbal drug which shows most promising antimicrobial activity.

INTRODUCTION

The genus Abutilon in the family Malvaceae includes about more than 160 species among them, one species, *Abutilon theophrasti*, grows in the Region of Uzbekistan and is mainly distributed in Central Asia and the European parts of the CIS and in the Caucases, Iran, India, China, Japan, north Africa, etc. The chemical composition of *Abutilon theophrasti* includes 2 to 3% tanning agents. Leaves contain180–200 mg% vitamin C, 24.3 mg% carotene and 0.28% of the air dried mass of rubber-like substances like glycosides and Flavonoids were present [1]. Rutin (2-(3,4-dihydroxyphenyl)-4,5-dihydroxy-3-[3,4,5-trihydroxy-6-[(3,4,5-trihydroxy-6 methyl-oxan-2-yl)oxymethyl]oxan-2-yl]oxy-chromen-7-one) and also known to be quercetin-3-rutinoside or sophorin is a flavonol glycoside comprised of the flavonol quercetin and the disaccharide rutinose. Rutin has significant scavenging properties on oxidizing species such as superoxide radical, OH radical and peroxyl radical Therefore, it shows several pharmacological activities including anti-inflammatory, antiallergic and vasoactive, antitumor, antibacterial, antiviral, and antiprotozoal properties. Moreover, it has also been reported that rutin has other therapeutic effects such as hypolipidemia, anticarcinogenic and antidiabetic effect. Natural products are being used for the development of novel drugs to treat various bacterial infections. Various secondary plant metabolites such as essential oils, flavonoids, and alkaloids have shown significant antimicrobial properties. Rutin has shown potent antimicrobial activity against a wide range of pathogens, i.e., bacteria, fungi, and viruses. In a study, rutin showed strong antibacterial and antifungal activities against standard strains of *Ecoli*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Staphylococcus aureus*, *Candida albicans andCandida krusei* when compared with control drug [2].

Therapeutic uses

Abutilon theophrasti has been used in ethnomedicine against various ailments. Aerial parts of *Abutilon theophrasti* are used in folk medicine as an expectorant and emollient and the drug exhibits anti-inflammatory and carminative properties and is mainly used to treat rheumatic pains, arthrosis, bruises, sprains, dysentery, otitis media, tinnitus and deafness [3].

Phytochemistry

Phyto constituents have been rarely reported as Roseoside, Kaempferol, P-hydroxy benzoic acid, P-coumaric acid, Syringic acid, Vanillic acid, Luteolin, Catechin, Ferulic acid, Rutin, Caffeic acid, Quercetin and other compounds have been isolated from *Abutilon theophrasti* by thin-layer chromatography (TLC), preparative paper chromatography, cellulose columns, Sephadex LH-20 and spectroscopic methods. In the roots, stems, leaves, seeds and exocarps of *Abutilon theophrasti* Medic Roseoside, Kaempferol, P-hydroxy benzoic acid, P-coumaric acid, Syringic acid, Vanillic acid, Luteolin, Catechin, Ferulic acid, Rutin, Quercetin and Caffeic acid were generally found to be primary phenol components in an earlier report [4].

Materials and Methods

Determination of drug-likeness and ADMET profile

In our study, Drug likeness score of each phytoconstituents was calculated based on Lipinski's rule of five using MolSoft (https://www.molsoft.com/**).** Likewise, the probability for pharmacokinetic properties such as Blood Brain Barrier (BBB), P-glycoprotein, plasma protein binding, skin permeability, buffer solubility and Human intestinal absorption along with Toxicology and other important aspects of ADMET was predicited using admetSAR2.0(http://lmmd.ecust.edu.cn/admetsar2) [5-9].

Preparation of ligand

The 3D structures of all ligand molecules were retrived from PubChem chemical database (https://pubchem.ncbi.nlm.nih.gov/) in structural data format is converted to PDB format by using Discovery Studio Visualizer (DSV) 2021.PubChem is a universal database that stores chemical structural information, including their biological activities. Furthermore, we minimized ligand's free energy using the MMFF94 force field. In the

present study, Roseoside, Kaempferol, P-hydroxy benzoic acid, P-coumaric acid, Syringic acid, Vanillic acid, Luteolin, Catechin, Ferulic acid, Rutin and Caffeic acid, Quercetin, Gallic acid, Syriacusin A and Procatechuic acid as *Abutilon theophrasti* phytoconstituents[10].

Preparation of target protein

We got the 3D x-ray crystallographic strucutures of two antibacterial targetsof *Escherichia Coli* (PDB ID: 4Y17) [11], *Staphylococcus aureus* (PDB ID: 1JIJ) [12] and one antifungal target of *Candida albicans* (PDB ID: 1IYL) [13]. These macromolecule was retrieved from PDB (https://www.rcsb.org/), website in pdb format. The retrieved protein is associated with water molecules and hetero atoms. All hetero atoms, water molecules and native ligand were removed using Discovery studio 2021 to avoid docking interference and saved in the PDB format [14].

Determination of active pocket sites

The amino acids in the active pocket site of a protein were determined by using the Biovia Discovery Studio 2021 and the determination of the amino acids in the active pocket site was used to analyse docking evaluation results [15]

Ligand-protein docking study

For molecular docking interaction, we used AutoDock Vina by PyRx 0.8. The target protein and ligand PDB files were loaded into PyRx software, and AutoDock Vina preferences were obtained for both ligand and protein in PDBQT format. The grid box was generated to the active site, and the exhaustiveness was set to 100. After completion of docking algorithm, the ligand-protein complexes that have the best conformation and lowest binding affinity were selected and visualized in DSV 2021 for their hydrophobic interactions.

Mining and network analysis

The phytoconstituent of *Abutilon theophrasti* were retrived from Dr. Duke's Phytochemical and Ethnobotanical databases (https://phytochem.nal.usda.gov/phytochem/search). The targets of rutin were identified using SwissTargetPrediction (http://www.swisstargetprediction.ch/) database for proteins at pharmacological activity (Pa)>0.7 [16].

Enrichment and network analysis

The list of most probable targets was obtained from Gene Cards and most of the pathways are obtained from STRING database, and enrichment analysis of protein-protein interaction was performed for biological process, molecular function and cellular components. Further, the probably modulated pathways were also identified concerning the KEGG pathway database. Cytoscape was used to construct the network among the plant and its phytoconstituents, modulated proteins, and regulated pathways, and network between them was constructed using Cytoscape 3.6.1 software. The network is treated as directed by using the command "network analyzer", and topological parameter "edge count" was applied to identify the connections [17-18].

Results

Drug-likeness and ADMET profile of bioactive phytoconstituents

MolSoft online server was used to screen the phytoconstituents druggable characteristics Among selected compounds, only rutin showed potent drug-like properties. The drug-likeness score of rutin was found to be 0.91 mentioned in [Table 1] Furthermore, all the phytocompounds were predicted to get absorbed from intestinal tract among all syringic acid, vanillic acid and ferulic acid were predicted to cross BBB and also to have highest oral bioavailability and was also less toxic as compared to other phytoconstituents mentioned in [Table 2].

Ligand-protein interaction

AutoDock by PyRx 0.8v was used to perform a molecular docking study to identify the possible binding affinity and molecular interactions of phytoconstituents with antimicrobial proteins. Among all phytocompounds rutin has showed highest binding affinity with antibacterial and antifungal proteins, that is, -8.6kcal/mol with *Escherichia Coli* (PDB ID: 4Y17), -9 kcal/mol with *Staphylococcus aureus* (PDB ID: 1JIJ) and -9.4 kcal/mol with antifungal target *Candida albicans* **(**PDB ID: 1IYL). Docking score is mentioned in [Table 3] and the 3D and 2D structure of protein-ligand interaction showed in [Figure 1].

Target prediction, gene set enrichment and network analysis

A total of 45 probable protein targets of rutin were identified SwissTargetPredicition (P≥0.09). The gene set enrichment analysis of predicted targets identified 70 protein targets to modulate 102 pathways. Among them, 16 molecular pathways were potentially involved in antimicrobial and other viral infections, inflammation, hypertension, diabetes mellitus etc. And scored the highest edge count with the network via modulating 10 protein targets, namelyPTGS2,SERPINE1,HSP90AB1,SYK, PRKCA,PRKCD,MMP9,MPO,CYP19A1 and SRC .Following intracellular signalling pathways such as PI3K-Akt signaling pathway,Rap1 signaling pathway,HIF-1 signaling pathway,Shigellosis,NF-kappa B signaling pathway,Yersiniainfection,Toxoplasmosis,Melanogenesis,Tuberculosis,Legionellosis,Pathogenic Escherichia coli infection, Prolactin signaling pathway, Bacterial invasion of epithelial cells, Salmonella infection,TNF signaling pathway, Epithelial cell signaling in Helicobacter pylori infection were identified to be next highly enriched molecular pathways by rutin presented in [Table 4] and the network representation of rutin, protein targets, and pathways mentioned in [Figure 2].

Table 1: Drug-likeness properties of selected drugs and ligands

The server has a strong data base to predict the druggability of phytocompounds by Lipinski's rule of five.

Sl.No	Phytoconstituents	Molecular Formula	Mol Weight (>500)	HBA (>10)	HBD (>5)	Log P (>5)	Drug likeness Score
1	Roseoside	$C_{19}H_{30}O_8$	386.19	8	5	-0.13	0.33
2	Kaempferol	$C_{15}H_{10}O_6$	286.05	6	4	1.61	0.50
3	P-hydroxy benzoic acid	C_7H_6O3	138.03	3	2	1.43	-0.37
4	P-coumaric acid	$C_9H_8O_3$	164.05	3	2	1.66	-0.81
5	Syringic acid	$C_9H_{10}O_5$	198.05	5	2	0.82	-0.81
6	Vanillic acid	$C_8H_8O_4$	168.04	4	2	1.40	-0.18
7	Luteolin	$C_{15}H_{10}O_6$	286.05	6	4	2.78	0.38
8	Catechin	$C_{15}H_{14}O_6$	290.08	6	5	0.53	0.64
9	Ferulic acid	$C_{10}H_{10}O_4$	194.06	4	2	1.61	-0.61
10	Rutin	$C_{27}H_{30}O_{16}$	610.15	16	10	-1.55	0.91
11	Caffeic acid	$C_9H_8O_4$	180.04	4	3	1.27	-0.35
12	Quercetin	$C_{15}H_{10}O_7$	302.04	7	5	1.19	0.52
13	Gallic acid	$C_7H_6O_5$	170.02	5	4	7.8	-0.22
14	Syriacusin A	$C_{13}H_{12}O_4$	232.07	4	2	2.51	-0.54
15	Procatechuic acid	$C_7H_6O_4$	154.03	4	3	1.30	0.32
16	Neomycin	$C_{23}H_{46}N_6O_{13}$	614.31	19	19	-10.8	0.82
17	Miconazole	$C_{18}H_{14}C_{l4}N_2O$	413.99	2	0	6.16	0.62

Table 1: Drug-likeness properties of selected drugs and ligands

Table 2 ADMET Profile

The server has a strong data base to predict physicochemical properties like pharmacokinetics, water solubility, lipophilicity, drug likeness, Toxicity and medicinal properties with high correctness of phytoconstituents which shown most binding affinity towards antimicrobial proteins.

Parameters		Compounds														
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
ABSORPTION	HIA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
	Caco-2	-	-	+	+	-	+	+	-	+	-	+	-	-	+	-
	HOB	-	-	+	-	+	+	-	-	+	-	+	-	-	+	-
DISTRIBUTION	BBB	+	-	-	-	+	+	-	-	+	-	-	-	-	-	-
	P-glycoprotein (i)	-	-	-	-	-	-	-	-	-	-	-	+	-	-	-
	P-glycoprotein (s)	-	-	-	-	-	-	-	-	-		-	-	-	-	-
	PPB	0.91	0.83	0.94	0.89	0.97	0.82	0.62	0.85	0.8	0.7	0.95	0.8	0.85	0.65	0.9
METABOLISM	CYP3A4 (s)	+	+	-	-	-	-	-	-	-	+	-	-	-	-	-
	CYP2C9 (s)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	CYP2D6 (s)	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-
	CYP3A4 (i)	-	+	-	-	-	-	+	-	-	-	-	-	-	-	-
	CYP2D6 (i)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	CYP1A2 (i)	-	+	-	-	-	-	+	-	-	-	-	+	-	+	-
EXCREATION	Plasma t1/2	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Renal clearance	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
TOXICITY	HERG	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Hepatotoxicity	-	+	-	-	-	-	+	-	-	-	-	-	-	-	-
	AOT	III	III	III	III	II	III	II	IV	IV	III	IV	II	III	III	III
	Eye corrosion	-	-	+	+	+	+	-	-	+	-	-	-	-	-	-
	Carcinogenicity	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Ames mutagenesis	-	+	-	-	-	-	-	+	-	-	-	-	-	-	-

Table 2: ADMET profile of bioactive phytoconstituents

1-Roseoside, 2-Kaempferol, 3-P-hydroxy benzoic acid, 4-P-coumaric acid, 5-Syringic acid, 6-Vanillic acid, 7-Luteolin, 8-Catechin, 9-Ferulic acid, 10-Rutin, 11-Caffeic acid, 12-Quercetin, 13- Gallic acid, 14-Syriacusin A, 15- Procatechuic acid.

Human either-a-go-go inhibition: HERG, Plasma protein binding: PPB, Blood Brain Barrier: BBB, Human Intestinal Absorption: HIA, Human Oral Bioavailability: HOB, Acute Oral Toxicity: AOT, (i): Inhibiter, (s): Substrate

Table 3 score of Binding affinity

Binding score of highest bonded phytoconstituents to targets Binding affinity with antibacterial and antifungal proteins that is, -8.6kcal/mol with *Escherichia Coli*, -9.0 kcal/mol with *Staphylococcus aureus* and -9.4 kcal/mol with antifungal target *Candida albicans.*

		Binding energy(kcal/mol)		
		Antibacterial		Antifungal
Compounds	PubChem ID	Escherichia Coli	Staphylococcus aureus	Candida albicans
		4Y17	**1JIJ**	**1IYL**
Roseoside	9930064	-6.4	-7.4	-8.3
Kaempferol	5280863	-7.3	-7.6	-9
Parahydoxybenzoic acid	135	-5	-5.6	-6.4
Paracoumaric acid	322	-5.9	-6.1	-6.9
Syringic acid	10742	-5.3	-5.6	-6.4
Vanillic acid	8468	-5.3	-5.5	-6.4
Luteolin	5280445	-8	-7.5	-9.3
Catechin	1203	-8	-7.1	-8.9
Ferulic acid	709	-5.8	-6.1	-7.2
Rutin	5280805	**-8.6**	**-9**	**-9.4**
Caffeicacid	68904311	-5.8	-6.1	-7.3

Quercetin	5280343	-8.1	-7.7	-9.1
Gallic acid	370	-5.6	-5.4	-6.3
Syriacusin A	9991528	-6.3	-6.8	-7.5
Procatechuic acid	19	-5.4	-6.1	-6.3
Neomycin	8378	-5.2	-6.5	-7.2
Miconazole	4189	-5.8	-6.3	-7.3

Table 3: Ligand-protein Binding interaction Score

Table 4 Target prediction, gene set enrichment and network analysis: Highly enriched molecular pathways and proteins, gene count is mentioned by using Cytoscape 3.7.2

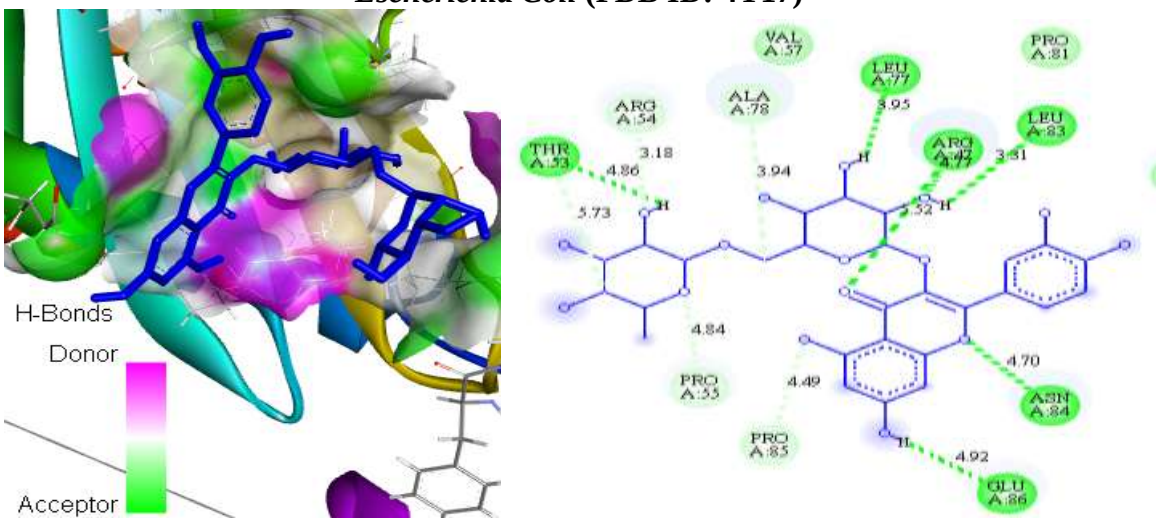
Pathway name	Gene count	Set of genes with the pathways
PI3K-Akt signaling pathway	12	IL2, FLT3, KDR, TP53, EGFR INSR, PTK2, PIK3CG, MCL1 HSP90AB1, SYK, PRKCA
Rap1 signaling pathway	8	PRKCG, KDR, EGFR, INSR, PRKCB, SRC PRKCZ, PRKCA
HIF-1 signaling pathway	6	SERPINE1, PRKCG, EGFR, INSR PRKCB, PRKCA
Shigellosis	7	TP53, EGFR, PRKCE, PTK2, SRC, PRKCD TNF
NF-kappa B signaling pathway	5	CSNK2A1, PRKCB, PTGS2, SYK, TNF
Yersinia infection	4	IL2, PTK2, SRC, TNF
Toxoplasmosis	3	PIK3CG, ALOX5, TNF
Melanogenesis	3	PRKCG, PRKCB, PRKCA
Tuberculosis	3	SRC, SYK, TNF
Legionellosis	2	VCP, TNF
Pathogenic Escherichia coli infection	3	F2, SRC, TNF
Prolactin signaling pathway	2	SRC, ESR1
Bacterial invasion of epithelial cells	2	PTK2, SRC
Salmonella infection	3	PIK3CG, HSP90AB1, TNF
TNF signaling pathway	3	PTGS2, MMP9, TNF

Table 4: Highly enriched molecular pathways by Rutin molecule

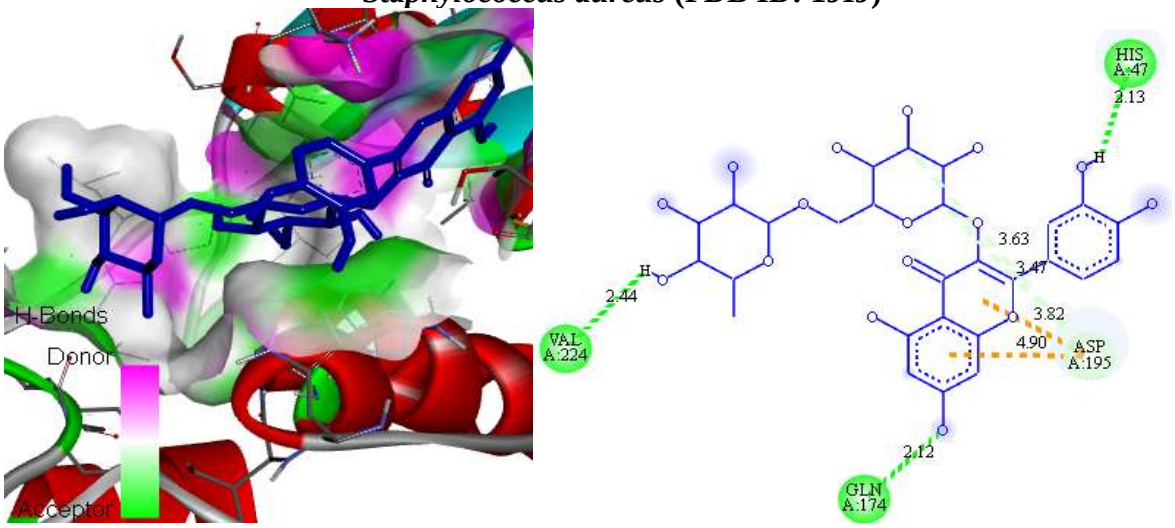
Figure Legend

Figure 1 Complex structure of molecular binding affinity: Binding affinity with antibacterial and antifungal proteins, that is, -8.6kcal/mol with *Escherichia Coli* (PDB ID: 4Y17), -9 kcal/mol with *Staphylococcus aureus* (PDB ID: 1JIJ) and -9.4 kcal/mol with antifungal target *Candida albicans* **(**PDB ID: 1IYL).

Figure 1: Complex structure of molecular binding affinity
***Escherichia Coli* (PDB ID: 4Y17)**



***Staphylococcus aureus* (PDB ID: 1JIJ)**



***Candida albicans* (PDB ID: 1IYL)**

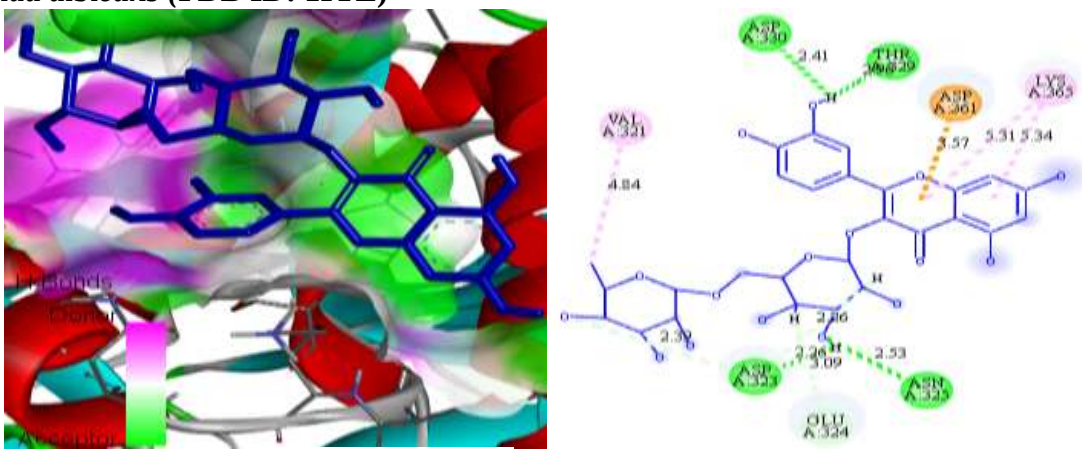
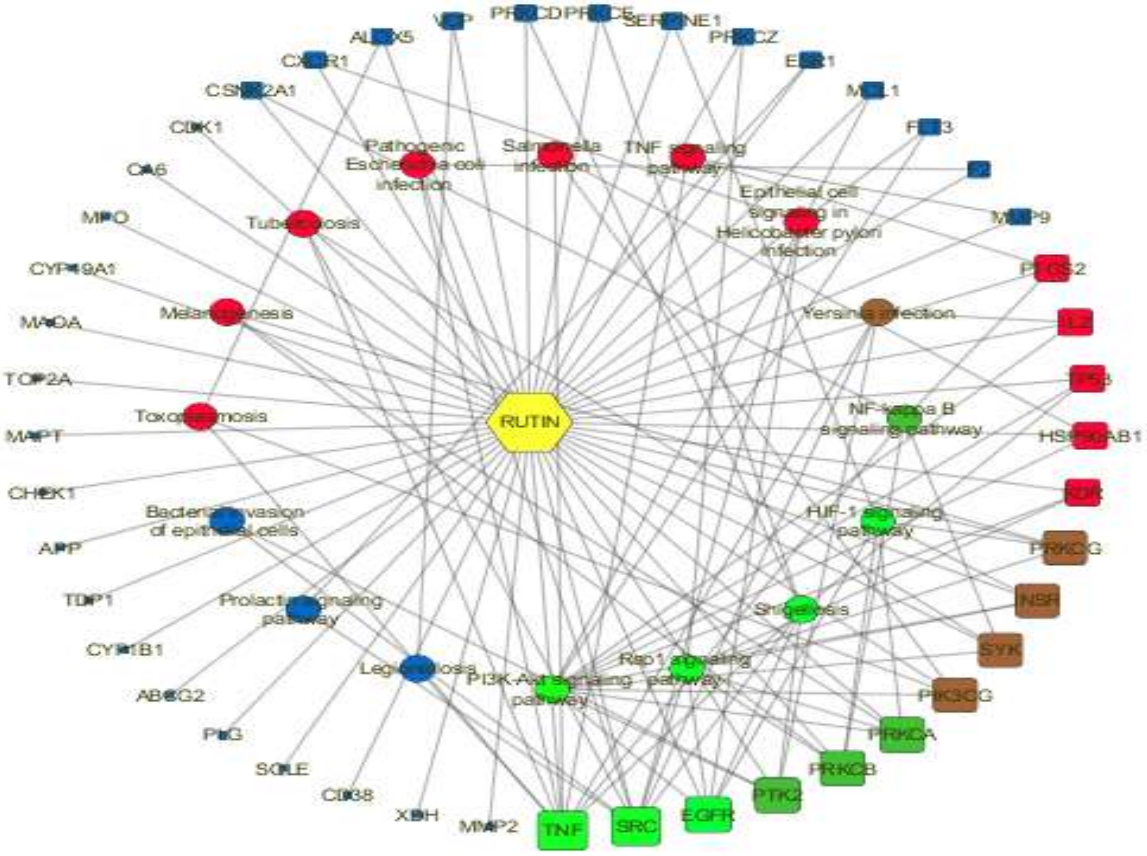


Figure 2 Complex network representation
A complex protein-protein network representation of Rutin, protein targets, and pathways towards microbial agents.

Figure 2: The network representation of rutin, protein targets, and pathways



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DISCUSSION

The present study shows that Rutin flavonoid from *Abutilon theophrasti* could be used as a potent antimicrobial agent. Further exploration of the function of the compound will facilitate a better understanding toward developing Rutin flavonoid from *Abutilon theophrasti* as an antimicrobial agent like antibacterial and antifungal activity. Further, the study also identified the regulation of multiple signalling pathways PI3K-Akt signaling pathway,Rap1 signaling pathway,HIF-1 signaling pathway,Shigellosis,NF-kappa B signalingpathway,Yersiniainfection,Toxoplasmosis,Melanogenesis,Tuberculosis,Legionellosis,Pathogenic Escherichia coli infection, Prolactin signaling pathway, Bacterial invasion of epithelial cells, Salmonella infection,TNF signaling pathway, Epithelial cell signaling in Helicobacter pylori infection signaling pathways and ligand protein interaction predicted that among four immune-modulating herbal medicines the phytocompound Among all phytocompounds rutin has showed highest binding affinity with antibacterial and antifungal proteins, that is, -8.6kcal/mol with *Escherichia Coli*, -9.0 kcal/mol with *Staphylococcus aureus* and -9.4 kcal/mol with antifungal target *Candida albicans.*

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Consent for publication:

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