Original Article

IN SILICO APPROACH TARGETING POLYPHENOL AS FABH INHIBITOR IN BACTERIAL INFECTION

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ABSTRACT

Objective: The aim of the study is to perform a computational study consisting of molecular docking for polyphenols subjected to *in silico* studies to identify a new lead for antimicrobial activity which has been reported yet or not been used yet.

Methods: The Schrödinger Maestro 11.3 performed molecular docking of the enzyme FabH (β-ketoacyl-acyl carrier protein synthase III) (PDB ID: 5BNR) with polyphenol. The targeted compounds were docked against FabH enzyme and also evaluated for MM-GBSA and ADMET analysis.

Results: The top hits shows remarkable results and good binding interactions with a pocket of the enzyme. The best binding score are as-8.6 (kcal/mol) of Geniestein,-8.579 (kcal/mol) of 4-naphthoquinone,-7.651(kcal/mol) of Pelargonidin. All the targeted compounds were found in the given limits of ADMET parameters. They also showed good free-binding energy.

Conclusion: The computational study reveals that the targeted polyphenols show good binding interactions and are also compatible with ADMET parameters. So, with this, we can conclude that the reported polyphenols can be potent against bacterial infection. In the future, if we derivatized these polyphenols with different substitutions, it can also lead to a potential drug moiety against bacterial infection.

Keywords*: E-coli*, Polyphenol, Antimicrobial, Molecular docking, MM-(GBSA), ADMET

INTRODUCTION

Bacteria are responsible for a variety of diseases in humans, seen in people of all ages [1]. However, a few factors such as infection, pestilential, acridity, and the complexity of infectious organism may get conditions with their palpable parcels similar as invasion, host hazard, vulnerability, poisons, etc. product, which increases the occurrence of developing bacterial illnesses as the number of effective antibacterial agents grows exponentially, these medications are used to treat the maturation of these infections [2, 3]. In the pharmaceutical market, many antibacterial agents are present and used for bacterial treatment, but over usage of antibiotics leads to antimicrobial resistance and it is becoming difficult to treat bacterial diseases with currently existing drugs [4-6]. Therefore, the development of new types of antibacterial agents is a very vital task and much of the research effort is oriented to the design of new antibacterial agents with high efficiency [7]. Recently, the research has been focused on the development of new antibacterial agents with a novel target [8]. A promising target is the fatty acid synthase (FAS) pathway in bacteria. β-ketoacyl-ACP-synthase III (FabH) is a key enzyme in bacterial fatty acid biosynthesis, catalyzing the committed step of the synthesis cycle. Considering this need, phytoconstituents are being researched for novel antimicrobial activity. The powerful antibacterial and antifungal properties of polyphenols are backed by a large body of evidence [9]. Microbial organisms are adapting to the condition and evolving their nature and acquiring resistance to the available anti-microbial drugs. So that there is need for developing novel anti-microbial agents [10]. It initiates fatty acid biosynthesis via a cysteine-mediated Claisen condensation reaction between malonyl-acyl carrier protein (MACP) and an acyl-enzyme intermediate formed by initial transacylation from the acyl-CoA primer to the active site Cys112. CoA is released from the enzyme after transacylation and replaced by MACP in the same binding pocket. FabH then catalyzes the decarboxylation of MACP, which reacts with the Cys112-bound acyl group to form β-ketoacyl-ACP. This product is released, reduced to the corresponding acyl-ACP, and subsequently elongated by other FAS condensing enzymes, including *FabB and FabF* [11]. The polyphenol inhibits the enzyme *FabH* which is responsible for bacterial cell wall synthesis.
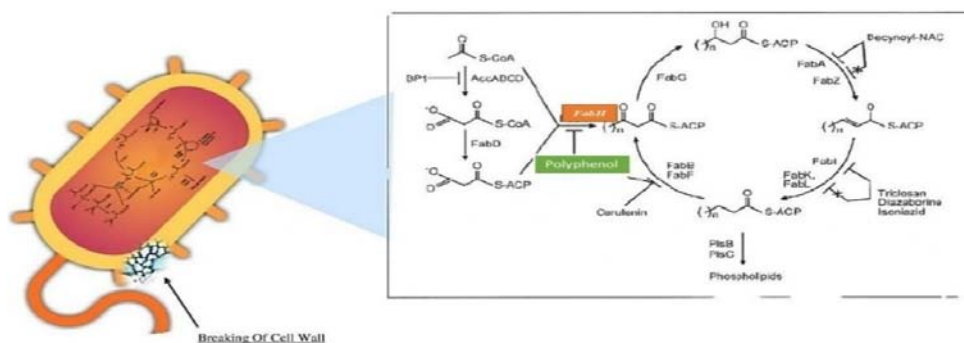

Fig. 1: Mechanism of action of bacteria and polyphenols

Polyphenols are phytochemicals that are organically diverse compounds of fragrances that contain many hydroxyl groups [12]. These bioactive compounds not just promote good health but play a major role in the prevention of chronic diseases [13]. Polyphenols are secondary metabolites which produce by the plant and are not widely distributed in all developed stores, which have important properties such as protection from factory viruses and animal fury as well as reactions to colourful stresses, such as falls and ultraviolet radiation [14]. The plants naturally produced secondary metabolite to protect against bacteria, viruses, fungi, protozoa, and UV radiation [15]. Various studies have presently known the properties of plant polyphenols towards human health, as a complete number of polyphenols have undeniable anti-fungal, antitumor, and anti-oxidant, actions that are both antimicrobial and anti-allergic [16]. 20 y ago, studying polyphenols was done for their clear participation in the prevention of common conditions, such as nausea, cancer, osteoporosis, polygenic disorder Mellitus, and neurodegenerative conditions. Therefore, in order to further investigate its application, we have employed an insilico approach to discover new leads against bacterial diseases [17].

MATERIALS AND METHODS

Maestro 11.3 Schrödinger module was used to perform all computational simulations consisting of all segment recreation, in that we utilize the protein preparation wizard, ligand planning, docking, MM-GBSA, and ADMET. The Schrödinger is digital screening has confirmed to be a completely successful technique for locating ligand activity supporting optimization primarily depending completely on drug discovery venture with the aid of using docking a big library of compounds into one extra excessive-decision shape of goal receptor [16-19].

Protein preparation

The PDB ID: 5BNR was imported from the RCSB Site and created prior to docking with the assistance of the protein preparation wizard. This process contains a three-step import and process, then review and modification and after that, alter and the last refinement of the protein structure. The Pre-processing protein included expansion, production of zero-order metal bond, hydrogen bond, bond order, and disulfide bonds with the filling of missing side chains and loops. Under 5 Å, water is removed and created utilizing Epik pH 7.0±0.0. In the refinement step, there is the advancement of protein and evacuation of water atoms followed by minimization involving OPLS4 force field performed [20-22].

Preparation of ligands

The structural representation of polyphenols is imported as ligands for docking purpose. The ligands 2D structure were downloaded from the chemical database i. e PubChem database in the. mol format. We can also design a 2D structure by using Chem Draw 8.0. Ligand preparation done by performing on Ligprep module Maestro software. Mostly 257 polyphenols were selected for performing docking, such as Geniestein (Pubchem ID-5280961) Naringin (442428) Silybinin (31553) Oleocanthal (11652416). In the ligprep module, import structures of polyphenol and set up the maximum molecular size, which is 500D. The ionization of ligands by using target PH: 7.00 with Epik format. The stereochemically active fragments retain chiralities of compounds and run the program [23, 24].

Receptor grid generation

The ligand was preserved within the crystal structure of the ready supermolecule that was used for receptor grid generation. The form and properties of the receptor are diagrammatic in an exceeding grid by fields that become continuous a lot of discerning throughout the tying up process. Bond constraints in the receptor grid are well-defined [25]. Selection of the coordination tail end of intricate using ligand supply a three-dimensional grid containing measurements and dimensions are X, Y, and Z (10, 12, and 14 Å respectively) to duplicate the active area of the receptor [26].

Molecular docking

The minimum necessities for running a Glide virtual screen are a grid file and a ligand file. It's powerfully counseled that the grid file is generated from the receptor grid generation and also the ligand file is prepared using LigPrep. The results of tying up poses, scores, and co-crystallized ligand interactions in contrast to the original crystal formations guide use of a hierarchy of criteria to search the active-site space of the receptor for potential ligand locations [27].

Free binding energy computation (MM-GBSA)

To evaluate the intensity of their free binding and establish, if the listing remained long enough to evoke any potential natural reaction, in XP of top docked complex mode were placed through Energy free calculation (MM-GBSA) calculations using the high module [28, 29].

ADMET studies

The top eight hits on molecular arrival were put via QikProp's ADMET analysis. Lipinski's method was used in a process study for the prediction of ADMET characteristics and to get novel drug-like leads. Rule of 5 for the compound was assessed using the Schrodinger ADMET program and the data are shown in table 2 for analysis of Human Oral Absorption, predicted permeability of barriers in the brain, oral assimilation and Lipinski Rule. [30] Each compound has octanol-water partition and permissible binary compound solubility limits. Constants, according to ADMET analysis. The top eight hits from molecular arrival had been put via QikProp procedure investigation for ADMET property prediction and to discover new ones [31].

RESULTS AND DISCUSSION

Polyphenol is powerful against bacterial disease that which is demonstrated with the assistance of the Insilico approach. We did molecular docking on the protein synthase III known as FabH (-ketoacyl-acyl carrier) complex (PDB-5BNR). Docking of the ligand with the protein which is imported from the protein data bank (PDB-5BNR). Practically around 257 polyphenols docked against the FabH and 11 polyphenols are found to hit [32]. Ligand was docked on Protein and investigation of dock score with properties. The outcome is the docking of these 11 polyphenols as ligands 5BNR show ligand-target. We observed that the compound genistein against 5BNR has a docking score of-8.6cal/mol and a decent hydrogen bonding connection. The protein 5BNR is a great dock with the polyphenol as 4-naphthoquinone with a docking score of-8.579. Naringin shows a great interaction with amino acids and also a good hydrophobic interaction with the docking score of-6.634 kcal/mol [33].

Docking and MM-GBSA

Docking changed into performed to recognize ligand-protein interaction, and molecular docking look has been carried out for compounds polyphenol docked in opposition to protein FabH Protein Synthetase III, also known as (Beta-ketoacyl-acyl provider) FabH (protein synthase III, Beta-ketoacyl-acyl supplier) (PDB ID: 5BNR) the use of Glide (grid-primarily based ligand docking) software integrated within side the Schrodinger molecular modeling with the aid of using 11.3 [34-36]. The FabH is the primary issue of the Synthesis of fatty acids in gram-negative microorganisms *Escherichia coli and Streptococcus pneumonia*. The docking results found that each one of the compounds had been energetically favorable in Glide dock score. (table 1) After analysing docking results of polyphenol, Naringin with FabH synthase protein formed of hydrogen bonds between ASP-150, MET-207, ARG-151, ASP-150, ARG-298 Show in table 1 and fig. Additionally, the molecule has been stabilized with amino acids such as MET-207, and ALA-208. The docking results of the polyphenol confirmed that the polyphenol shows good binding interactions. All the ligands confirmed interactions of hydrogen bond and hydrophobic interactions with amino acids [37-39].

Table 1: Molecular docking scores of selected polyphenols participating in hydrogen bonding with 5BNR

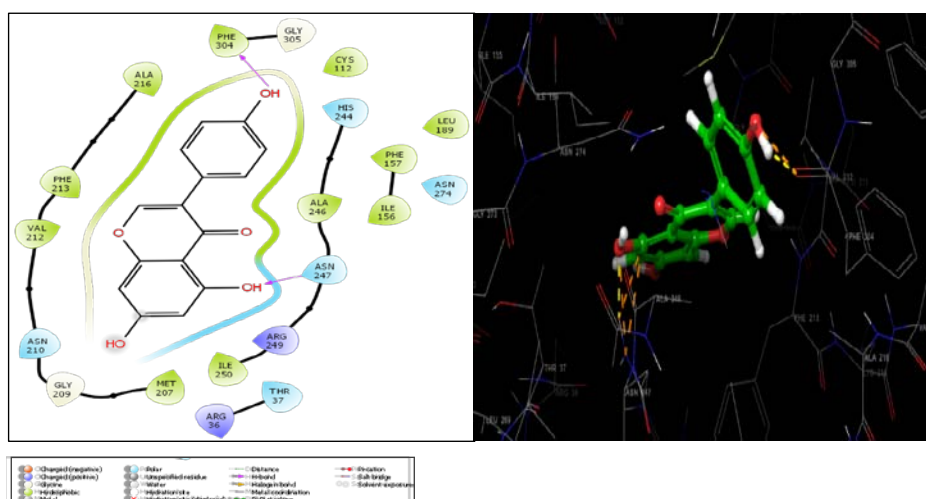| S. No.	Compound name	Pubchem ID	Docking score	Dg Bind MM-GBSA	Hydrogen bonding interaction	Hydrophobic interaction
1.	Geniestein	5280961	-8.6	-87.48	ASN-247, PHE-304	PHE-213,ALA-216,PHE-301,ALA-246
2.	4-naphthoquinone	8530	-8.579	-86.75	CYS-112,ASN-274	ILE-156,ILE-189,ALA-246,ILE-250
3.	Pelargonidin	440832	-7.651	-76.56	-	-
4.	P-Coumaric acid	637542	-7.384	-74.66	-	
5.	Anthocyanin	145858	-7.128	-71.47	HIS-244	ALA-246,ALA-216,PHE-213
6.	Oleocanthal	11652416	-6.983	-67.43	ASN-274,HIS-244,ARG-249	ALA-246,ALA-216,VAL-212,MET-207
7.	Peonidin	441773	-6.669	-65.47	CYS-112,GLY-209	ALA-246,ALA-216,PHE-213,VAL-212
8.	Naringin	442428	-6.634	-70.68	ASP-150, MET-207, ARG-151, ASP-150, ARG-298	MET-207,ALA-208
9.	Silybinin	31553	-6.507	-58.21	CYS-112, ARG-236, ARG-151, ARG-249	VAL-212,PHE-212,ALA-216,PHE-157
10.	Kaempferol	5280863	-5.712	-	ARG-249	VAL-212,ILE-250
11.	Ptrotocatechuic Acid	72	-5.361	-	ARG-151	PHE-157
12.	Petunidin	441774	-5.116	-	MET-207	VAL-212
13.	Malvidin	159287	-4.283	-	-	-
14.	Marsdenin	15560118	-4.181	-	-	-
15.	Berberine	2353	-3.669	-	-	-
16.	Nobiletin	72344	-3.536	-	-	-

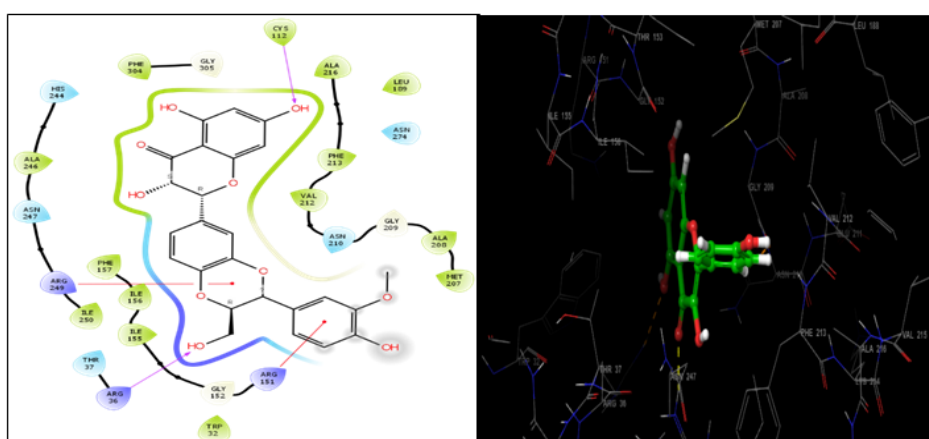**Fig. 2: 2D and 3D interaction of naringin with 5BNR protein**

Fig. 3: 2D and 3D Interaction of silybinin with 5BNR protein

***In silico* ADMET**

Qikprop model is used to study ADMET. The ADMET's property is Absorption, Distribution, Metabolism, Excretion, and Toxicity including the pharmacokinetics of the drug particles. It contains the properties of bioavailability, oral assimilation, cerebrum entrance, cancer-causing nature, and human digestive ingestion properties. QikProp has become used to take a look at if they are verified like as standard medicine function or not [40]. All the hits of polyphenol found active also follow all the parameters of ADMET properties. Less active polyphenols deviated from the original criteria. The detailed analysis of each polyphenol is listed in table 2.
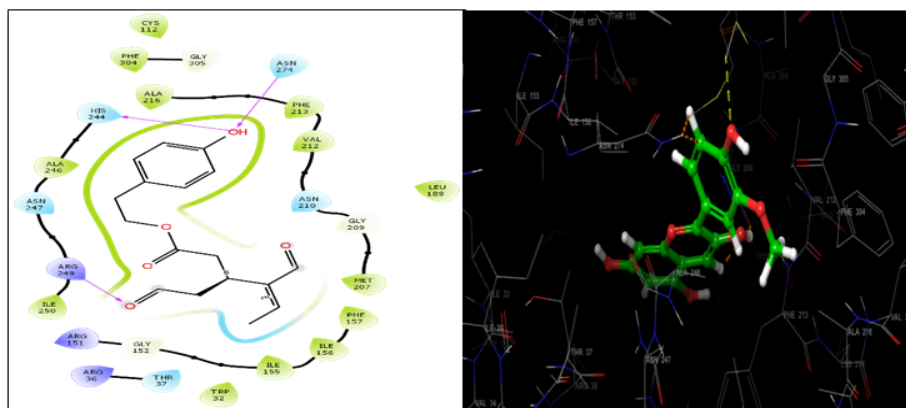
Fig. 4: 2D and 3D interaction of oleocanthal with 5BNR protein

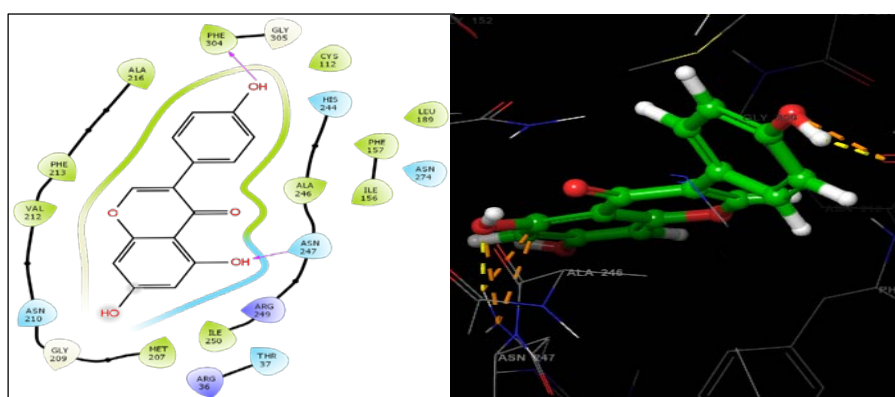Fig. 5: 2D and 3D interaction of peonidin with 5BNR protein

Fig. 6: 2D and 3D Interaction of geniestein with 5BNR protein

Table 2: The acceptance criteria for ADMET-listed polyphenols

Abbreviations	Full form	Acceptance criteria
QPlogp o/w	Qikprop of partition coefficient in octanol/water	-2.0–6.5
QPlogS	Qikprop of solubility in aqueous medium (mol/l)	-6.5–0.5
QPPCaco	Qikprop of permeability of cell caco (nm/s)	<25 is poor and>500 is great
QPlogBB	Qikprop of permeability across the blood-brain barrier	-3–1.2
QPPMDCK	Qikprop apparent cell permeability of MDCK (nm/s)	<25 is poor and>500 is great
Human Oral Absorption	-	0-3
Rule of five	violations of Lipinski's rule	1-2

Table 3: The top 18 compounds' ADMET characteristics are listed

S. No.	Entry ID	Compound name	QPlogp o/water	QikPlogS	QikPPCaco	QikPlog BB	QikPPM DCK	Oral absorption in humans
	5BNR _PREP_COMPLEX	5BNR_others 5BNR_ligand						
1	5280961	Geniestein	1.688	-3.018	171.791	-3.54	73.701	3
2	4naphthoquinone. cdx	naphthoquinone	0.323	-0.14	589.205	-2.76	279.277	3
3	440832	Pelargonidin	-	-	-	-2.44	-	-
4	catechin. mol	coumaric acid	0.468	-1.313	172.005	-3.66	73.801	2
5	P-Coumaric-3-o-glucoside. cdx	P-Coumaric acid	0.468	-1.313	172.005	-3.73	73.801	2
6	145858	anthocyanin	-	-	-	-2.88	-	-
7	11652416	oleocanthal	1.853	-3.423	99.337	-1.33	40.771	3
8	441773	Peonidin	-	-	-	-1.54	-	-
9	442428	Naringin	-1.574	-3.169	2.441	-2.45	0.742	1
10	31553	Silybinin	1.836	-5.079	29.956	-3.45	11.159	2
11	5280863	Kaempferol	1.054	-3.133	53.288	-1.23	20.797	3
12	Ptrotocatechuic acid	Ptrotocatechuic acid	-0.281	-1.187	15.658	-1.99	7.039	2
13	441774	Petunidin	-	-	-	-2.34	-	-
14	159287	Malvidin	-	-	-	-3.92	-	-
15	15560118	Marsdenin	1.079	-2.847	228.62	-3.55	100.376	2
16	2353	Berberine	-	-	-	-2.55	-	-
17	72344	Nobiletin	3.649	-4.297	3799.21	-1,22	2093.774	3
18	107935	Deguelin	4.218	-5.441	4703.515	-1.03	2637.298	3

The normal range of lipophilicity according to the partition coefficient in octanol/water is QPlogp o/w is-2.0 to 6.5 and active polyphenols have the most relevant QPlogP values. The aqueous solubility (QPlogS) of compounds having normal range of about-6.5 to 0.5. The cell permeability prediction (QPPCaco) of some selected polyphenols having good range according to acceptable range (less than 25 is poor and more than 500 is great). BBB permeability necessary for action of CNS system with QPlogBB range from-3 to 1.2. There are the number of metabolic reactions of the compounds, which are in the scale of 2-5. The normal range of rule of Lipinski is about 1-2. The targeted polyphenols have oral absorption from 1-3 (3-best oral absorption, 2-better oral absorption and 1-good oral absorption).

CONCLUSION

Polyphenol is a secondary metabolite, produce by the higher plant. Polyphenol is reported in different categories like antioxidant, antifungal, anti-inflammatory, antimalarial, etc. Our objective was to find out the polyphenols which are active against bacterial infection but have not been reported yet. The insilico study of polyphenol against bacterial infection shows a remarkable result. Polyphenols show good binding interactions with the targeted FabH enzyme which is mainly responsible for the production of bacteria. ADMET property criteria were also fulfilled by best interacting polyphenols. So, with this, we can conclude that the reported polyphenols can be potent against bacterial infection. In the future, if we derivatized these polyphenols with different substitutions, it can also lead to a potential drug moiety against bacterial infection.

AVAILABILITY OF DATA AND MATERIAL

Yes

CODE AVAILABILITY

Not applicable

ABBREVIATION

(QPlogPo/w)-Predicted octanol/water partition coefficient, (QPlogS)-Predicted aqueous solubility, log S, (QPlogBB)-The blood-brain barrier permeability parameter, (QPPCaco)-predicating Caco-cell permeability in nm/s-+, (QPPMDCK)-predicating MDCK Cell permeability in nm/s.

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AUTHORS CONTRIBUTIONS

Sachin Dhawale-Main concept, software handling with data analysis.

Manuscript drafting and visualization.

Sachin Gawale-Data interpretation and Parameter evaluation.

Akash Jadhav-fig. and tables with formatting.

Kalyani Gethe-Manuscript writing and editing.

Nikita Hiwrale-Manuscript writing and editing.

Prashant Raut-Editing and formatting.

Pallavi Bhosale-Manuscript drafting and analysis of work.

Ganesh Tapadiya-Supervision and Phytoconstituent analysis.

CONFLICT OF INTERESTS

The authors affirm that they have no known financial or interpersonal conflicts that would have seemed to have an impact on the research presented in this study.

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