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Computational identification of potential bioactive compound from *Cassia auriculata* against urinary tract infection causative pathogen *E. coli*

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Abstract
In worldwide urinary tract infection is a second most common infection disease. Bacteria play on crucial role for UTI especially *E. coli*. In this present study to identify potential bioactive compounds from *Cassia auriculata* and their binding affinity was investigated against *E. coli* in computationally using Schrodinger suite. Based on the computational study, the following bioactive compounds 2, 4-Di-tert-butylphenol, 2H-Pyran-2-one, tetrahydro-6-tridecyl-, Diethyl phthalate, Palmitic acid Octadeca-9,12,15-trienoic acid, Pentadecanoic acid having better glide score and glide energy rather than other compounds. The compounds were taken into drug like evaluation by employing Qikprop. All compounds fall under desired ADME properties of six bioactive compounds are potential for further experimental analysis.

Keywords: diethyl phthalate, palmitic acid, qikprop, adme, *cassia auriculata*

Introduction

Microorganisms are chief factor for infection disease. Globally, urinary tract infection is one of the major public health concern and second most threatened infectious disasters and it mainly caused by bacteria. In worldwide, per year 150 million people were affecting by urinary tract infection. The major morbidityrate UTI occurs in infant boys, older men ad all ages of females. The morbidity rate of UTI high in women than men, in ratio 8:1. 10-20%, 25-50% of men were suffered by UTI age ranged between 25 to80 and above 80 respectively [1]. In clinically the UTI were categorized into several types these are acute, chronic, recurrent, asymptomatic, symptomatic, complicated and uncomplicated UTI. Around 80% of the gram-negative bacteria play on chief role for UTI especially *Escherichia coli, Klebsiella, Enterobacter ssp, Proteus mirabili s*and *Pseudomonas.* Even though, the 80-90% of UTI is caused by *E. coli*. Some gram positive bacteria also causative agents for life threatening UTI like *S. aureus, S. epidermidis, S. agalactiae, S. saprophyticus and Enterococcus, Yeast, Trematodes, Tapeworm* and some anaerobic bacteria lay on crucial role for urinary tract infection. The major routes of the bacteria for UTI are vaginal and perineal [2, 3].The major factors for UTI based on gender, age, race, HIV, diabetes, urinary catheter, genitourinary tract abnormalities, pregnancy, infants, elderly, and hospitalization status bear significant risk for recurrent UTIs. The major typical symptoms of UTI are fever, burning sensations while urinating, LAP, itching, formation of blisters and ulcers in the genital area, genital and suprapubic pain, and pyuria generally depend on the age of the person infected and the location of the urinary tract infected frequency of urination, dysuria, urgency, nocturia, suprapubic pain, hematuria, malaise, vague or mild abdominal pain, incontinence. The woman may feel unwell and her urine may be cloudy, odorous and might contain blood [4]. Medicinal plants play on crucial role in pharmaceutical filed and major sources of medicine to prevent and cure chronic illness, 85% of traditional medicine prepared from medicinal plants. Around 150000 higher plants existing in India, 9000 are commonly used and 7500 are having medicinal values, 3900 are edible, 700 are culturally significant, 525 are used for fiber, 400 are fodder, 300 for pest and insect killers, 300 are gum. Resin, dye purpose and remaining 100 are used for preparation of aromatic thinks preparation like cosmetics, perfume. *Cassia auriculata* Linn comm only known as *Tanners Senna* and belongs to family of Caesalpiniaceae and it widely distributed throughout hot deciduous forests and it possess high medicinal Values. The parts of *Cassia auriculata* having various medicinal properties especially the bark is used as astringent, leaves are used for ulcer, diarrhea and leprosy, the flowers are used in the treatment of urinary discharge, diabetes, dysentery, tumors, skin diseases, and asthma, leaves are anthelmintic, fruits are used anthelminthic, the *C. auriculata* is one of the major ingredients for preparation of kalpa herbal tea and consumed by people which is cure the diabetes mellitus, constipation and urinary tract infection [5, 6]. In this present work the computational tool for analysis the binding affinity of the bioactive compound from *Cassia auriculata* against *E. coli* and also drug likeness behavior were analyzed by Qikprop method.

Materials and Methods

Target Protein Structure Preparation

The target protein structure preparation is crucial for docking to minimize deterrent during docking the target protein structure of urinary tract infection causative microorganism *E. coli*from protein data bank (PDB ID: 1rx7) [7]. Then the protein structure was imported into protein preparation wizard panel of Schrödinger suite the assigning bond orders, treating metals, treating disulfidesre move the water molecule, hydrogen atom was added and energy minimization was done with the help of all OPLS3. [8].

Binding Site Analysis and Grid Generation

Identification of active site information is crucial for docking were collect the active PHE 31, TRP 2, ARG 52, GLU 17, ASP 27, LEU 24site amino acids from research articles [9]. The following residues involved in the formation of various intermolecular interactions. The prepared protein was subsequently imported into receptor grid generation panel for generate grid for target protein were generated grid fore target protein around the active site region of the structure and the grid box size was at X=0.782, Y= 2.171, Z= 1.21 [10].

Preparation of *Cassia Auriculata* Chemical Structure

More than 10 different bioactive compounds from *Cassia auriculata* by employing GC-MS were obtained the chemical structure of *Cassia auriculata* from Pub Chem database in the form of SDF [11]. The structure was further imported for ligands preparation. The proper charges for the ligands and their structure energy were minimized with the help of force filed OPLS3 [12].

Molecular Docking Studies

Molecular docking is one of the significant tool for evaluate the protein-ligand interaction in computationally, hence by applying glide extra precision method embedded in glide were applied for docking. Finally, the various interaction using glide XP visualize panel and analyzed [13].

Adme Properties Filtration

In order to reduce the failure and increase the success rate of drug discovery project and to predict the ADME properties of the ligands by evaluating Qikprop for ADME filtration. It is one of the fast and accurate tools for computational ADME filtration [14, 15, 16]. The following ADME properties partition coefficient (Q Plog P octanol/water), predicted aqueous solubility (QP log Sb), apparent MDCK permeability (QPPMDCK), Vander Waals surface area of polar nitrogen and oxygen atoms (PSA), Lipinski's rule of five (LROF), gut-blood brain barrier (QPP Caco2), Log IC 50 value for blockage of K+ channels (QP log HERG), Percentage of human were predicted for *Cassia auriculata* compounds.

Results and Discussion

Docking Studies

In these docking studies were identified ten effective bioactive compounds from *Cassia auriculata* using GCMS analysis. The further taken into explore the binding affinity against urinary tract infection causative microorganism *E.coli* using Insilco docking. The structures of ten bioactive compounds from Pub Chem database in the form of SDF were downloaded the compounds were imported into ligprep for ligands preparation and the three-dimensional structure urinary tract infection causative microorganism *E.coli* were retrieved from PDB and imported into protein preparation panel for protein preparation. The prepared bioactive compounds were docked into active site of the *E.coli*.

Binding Mode of 7311

By analysis from the binding mode of 7311, the ligand 7311 formed only two hydrogen bond interactions with *E. coli*, and the residues held hydrogen bonds with *E. coli*. These are TRP 22 and ASP27 with bond distance 1.63Å, 1.79Å. The glide score and glide energy were measured -4.751kcal/mol and -28.350kcal/mol.

Binding Mode of 860

Binding mode of compound 860 was investigated; it displayed the 860 formed only two hydrogen bond interactions with *E. coli*. The residue involved in hydrogen bond formation ARG 57 with a bond distance 1.74Å and 1.58Å. The residues LUE 54, PHE 31, ALA 6 and ILE 5 involved hydrophobic interaction and also increase the binding of ligand with protein. The compound 860 glide score and glide energy were noted -3.434kcal/mol -40.807kcal/mol respectively.

Binding Mode of 985

Binding mode of compound 985 was investigated; it displayed the 985 formed only two hydrogen bond interactions with *E. coli*. The residue involved in hydrogen bond formation ARG 57 with a bond distance 1.85Å and 1.75Å. The residues LUE 54, PHE 31, ALA 6 and ILE 5 involved hydrophobic interaction and also increase the binding of ligand with protein. The compound 985 glide score and glide energy were noted -3.597kcal/mol -41.694kcal/mol respectively.

Binding Mode of 6781

Binding mode of compound 6781 was investigated; it displayed the 6781 formed only two hydrogen bond interactions with *E. coli*. The residues involved in hydrogen bond formation ALA 7 with a bond distance 1.90Å were reported in figure 1. The residues LUE 54, PHE 31, ALA 6 and ILE 5 involved hydrophobic interactions and also increase the binding of ligand with protein. The compound 985 glide score and glide energy were noted -4.214kcal/mol -46.885kcal/mol respectively.

Binding Mode of 13849

Binding mode of compound 13849 was investigated; it displayed the 13849 formed only two hydrogen bond interactions with *E. coli*. The residue involved in hydrogen bond formation ARG 57 with a bond distance 1.85Å and 1.75Å. The residues LUE 54, PHE 31, ALA 6 and ILE 5 involved hydrophobic interactions and also increase the binding of ligand with protein. The compound 13849 glide score and glide energy were noted -2.923 kcal/mol -34.890kcal/mol respectively.

Binding Mode of 518573

The binding mode of 518573, the ligand 518573 formed only two hydrogen bond interactions with *E. coli* and the residues held hydrogen bonds with *E. coli* TRP 22 and LEU 24 with bond distance 2.22Å, 1.70Å. The glide score and glide energy were measured -4.495kcal/mol and -36.678kcal/mol. The docking of the six *Cassia auriculata* bioactive compound were depicted in figure 1.

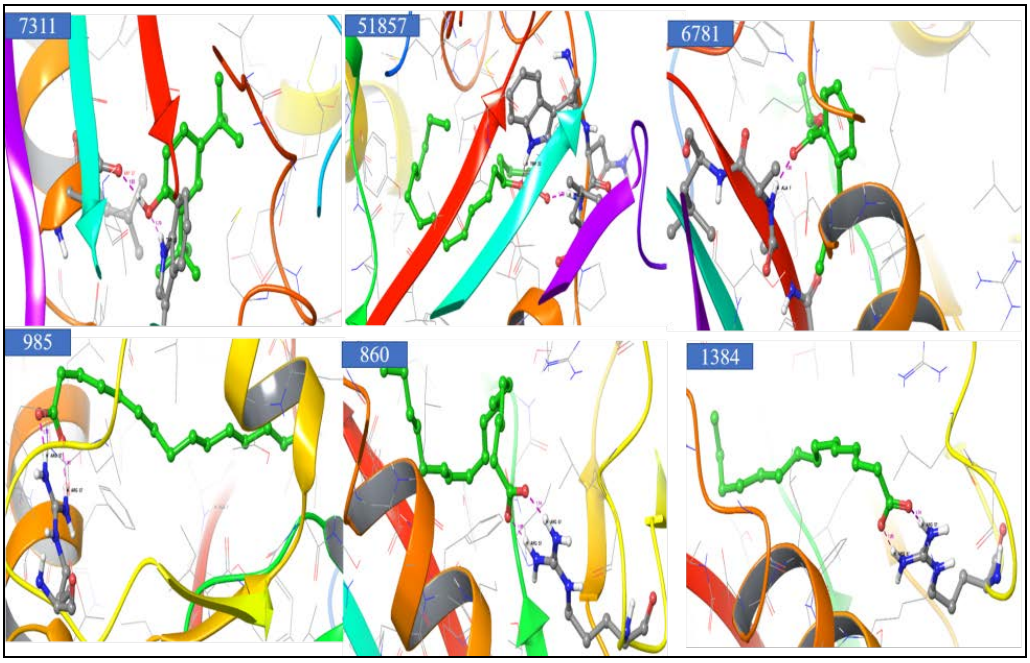

Fig 1: The docking site *Cassia auriculata* bioactive compounds against *E. coli*.

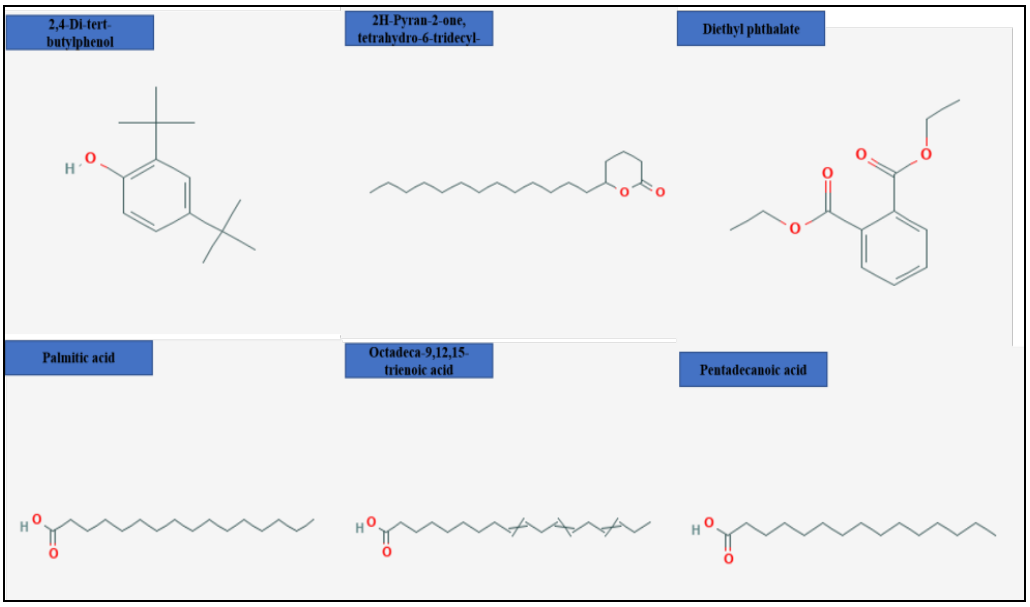

Fig 2: The 2D structure of the six *Cassia auriculata* bioactive compounds.

Table 1: Glide extra-precision (XP) results for the six *Cassia auriculata* bioactive Compound, by use of Glide.

Compound ID	Glide Score	Glide Energy	No of H-bond interaction	Interacting residues	Distance (Å)
7311	-4.751	-28.350	2	TRP22 ASP27	1.63 1.79
518573	-4.495	-36.678	2	TRP22 LEU24	2.22 1.70
6781	-4.214	-46.885	1	ALA 71	1.90
985	-3.597	-41.694	2	ARG 57 (2)	1.75 1.85
860	-3.434	-40.807	2	ARG 57 (2)	1.58 1.74
13849	-2.923	-34.890	2	ARG 57 (2)	1.75 1.85

The IDs are of the Pub Chem database

Glide score (Kcal/mol); Glide energy (Kcal/mol); No of hydrogen bond interaction; Interacting residues; Distance between the protein and ligand (Å).

Adme Properties Assessment

Assessment of ADME in crucial step in drug discovery project. Most of the drug attains failure due to lack of adequate ADME properties were appraised five most efficient bioactive compounds of *Cassia auriculata*. According the Lipinski rule of five, the five bioactive compounds possess adequate value. All the bioactive compounds having under 500 Dalton molecular weight, below 5 hydrogen bond donors, below 5 hydrogen bond acceptors and log p value also below 5 and analyzed some additional ADME properties. All compounds having excellent predicted MDCK values ranges from 134 to 2659,

the predicted Caco2 value range from 239 to 15451 and also predicted BBB properties are under adequate ranges i.e., 0.105 to -1.485.Percentage of human oral absorption ranged from 88 to 100. From this Insilco ADME analysis were highly recommended all the bioactive compounds suitable for human use.

Table 2: The drug-like properties of the six *Cassia auriculata* bio active compounds were evaluated by Qik Prop.

Compound ID	MW	HBD	HBA	Log P	MDCK	Caco 2	Aqueous solubility	Human oral absorption in %	BBB
7311	206.327	1.000	0.750	3.828	2659	4740	-3.956	100	0.105
518573	282.465	0.000	3.000	5.194	1241	2342	-6.038	100	-0.893
6781	22.240	0.000	4.000	2.278	792	1545	-2.864	100	-0.460
985	256.428	1.000	2.000	5.314	134	239	-5.648	88	-1.476
860	278.434	1.000	2.000	5.895	134	239	-6.788	91	-1.485
13849	242.401	1.000	2.000	4.923	134	239	-5.198	100	-1.385

Molecular weight (< 500Da); Hydrogen bond donor (< 5); Hydrogen bond acceptor (< 10);Predicted octanol /water partition co-efficient log p (acceptable range; -2.0 to 6.5). Predicted aqueous solubility; S in mol/L (acceptable range; -6.5 to 0.5). Percentage of human oral absorption; (<25% is poor and >80% is high); Prediction of brain/blood; (acceptable range; -3.0 to 1.2).

Conclusion

Urinary tract infection is major health problem in globally and it is caused by microorganism. Every year several thousand people were infected and died by Urinary tract infection to identify potential bioactive from *Cassia auriculta*. Then, the molecular docking studies were carried out for identification of their binding affinity against *E.coli*, the following compounds 2,4-Di-tert-butylphenol, 2H-Pyran-2-one, tetrahydro-6-tridecyl-, Diethyl phthalate, Palmitic acid Octadeca-9,12,15-trienoic acid, Penta decanoic acid having excellent glide score and glide energy compared with other bioactive compounds and to evaluated drug likeness of the bioactive compounds. All the bioactive compounds having better predicted ADME properties and it' shaving computationally efficient biological barrier penetration and expose their biological activity. From this Insilco analysis, hence by conclude the following bioactive compounds suitable for further *in vitro* and *in vivo* investigation.

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