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# *Insilico* analysis of cranberry proanthocyanidin Epicatechin-(4-beta-2)-phloroglucinol as an inhibitor for modelled Afimbrial adhesin virulence protein of uropathogenic *Escherichia coli*

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## ABSTRACT

Fimbrial adhesion is a Virulence Determinant which is classified under Adhesins category of virulence factor of uropathogenic Escherichia coli. Afimbrial adhesin Protein with swissprot accession number P12730, of length 181 amino was selected for modeling using Bioinformatics tools. Modelled protein has been submitted to protein model database and has been assigned an accession number of PM0075877. Docking analysis of Epicatechin -(4beta 2)-phloroglucinol a Proanthocyanin from cranberry against modelled fimbrial adhesion was carried out using hex docking tool. Some of the commonly used antibiotics to treat urinary tract infections caused by Uropathogenic E.coli which includes oflaxacin, sulfamethoxazole, Trimethoprim were subjected to docking analysis for comparative studies. © 2009 Trade Science Inc. - INDIA

## KEYWORDS

Uropathogenic E-coli;
Fimbrial adhesion;
Epicatechin;
Docking analysis.

## INTRODUCTION

Urinary tract infection is one of the most important causes of morbidity and mortality. E.coli is the most frequent urinary pathogen isolated from 50%-90% of all uncomplicated urinary tract infections. It has been traditionally described that certain serotypes of E.coli were consistently associated with uropathogenicity and were designated as Uropathogenic E.coli (UPEC)[1]. E. coli adhesion to host cells is important for bacterial infection and persistence in urinary fluxes[2]. The genes involved in biosynthesis of fimbria and adhesins present in UPEC are organized in operons denominated pap and sfa, coding for P and S fimbrial adhesins[3]. Two toxin types are associated to UPEC: the alfa-haemolysin (HLY) and cytotoxic necrotizating factor 1 (CNF 1) are involved in host cell destruction necessary to bacteria persistence in urinary tract[4].

Different virulence factors of E.coli which are thought to have a role in the pathogenesis of Urinary Tract Infections; they are O Antigens, K Antigens, Hemolysins, Serum resistance, Adhesins, Capacity to produce mannose sensitivity and resistant haemagglutination. Fimbrial adhesion is a Virulence Determinant which is classified under Adhesins category of virulence factor[5].

The adherence of Escherichia coli to uroepithelial cells is an important event in the pathogenesis of urinary tract infections[6]. The adhesion is generally mediated by Fimbriae (pili) which recognize cell sur-

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face carbohydrate structures on the epithelial cells[7].

Fimbria (plural-fimbriae) is a proteinaceous appendage in many gram-negative and gram positive bacteria that is thinner and shorter than a flagellum[8]. This appendage ranges from 3-10 nanometers in diameter and can be up to several micrometers long. Fimbriae are used by bacteria to adhere to one another and to adhere to animal cells. Their presence greatly enhances the bacteria's ability to attach to the host and cause disease[9]. Because of the possible role of the type 1 pilus in the pathogenicity of E. coli strains, there is now an urgent need for the preparation of specific and potent inhibitors of bacterial adhesion mediated by these pili[10].

Clinical trials have shown that cranberries are effective in the prevention of urinary tract infections, and may provide a way to stem the growing problem of antibiotic resistance.[11] A recent study showed that regular consumption of cranberry juice was also effective in cases in patients with UTI caused by antibiotic-resistant bacteria[12]. Cranberry has the potential to reduce the pace of antibiotic resistance development if taken on a regular basis to prevent UTIs before they occur[13]. Only the cranberry proanthocyanidins exhibit significant *in vitro* and *in vivo* bacterial anti adhesion activity when compared with other foods[14]. Cranberry proanthocyanidins act upon UPEC in the following ways:

- They Alter E. coli's cell membranes.
- Prevents the bacteria from making contact with cells or attaching to them even if they some how manage to get close enough.
- Change the shape of E.coli from rods to spheres.
- Disrupt bacterial communication[15]

## MATERIALS AND METHODS

Protein with Swiss-Prot primary accession number P12730, of length 181 amino Acid was selected for modelling of Afimbrial adhesin AFA-I.

### Modelling

Modelling of target protein was carried out using Swiss-PdbViewer (or SPDBV). Modelling of protein refers to constructing an atomic-resolution model of the "target" protein from its amino acid sequence and an experimental three-dimensional structure of a related homologous protein ("template").The template with PDB accession number 2JTYA was selected for modelling.The sequence alignment and template structure are then used to produce a structural model of the target.

### Ligand

Epicatechin-(4beta 2)-phloroglucinol a Proanthocyanidin from cranberry was selected as lead molecule for Insilco analysis and comparative study of its inhibition activity against modelled fimbrial adhesion.

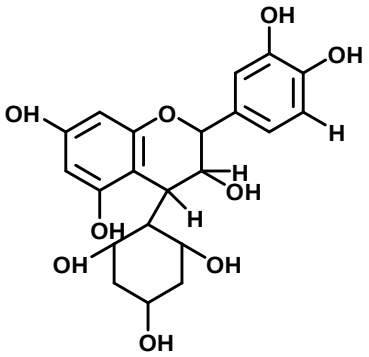


**Figure 1 : Epicatechin-(4beta 2)-phloroglucinol a Proanthocyanidin from cranberry**

### Lead validation

Validation assay for the lead molecule was carried out using OSIRIS Property Xplorer.

### Docking studies

Docking analysis was carried out using Hex 5.1. Analysis of Epicatechin-(4beta 2)-phloroglucinol a Proanthocyanidin from cranberry as an inhibitor against modelled fimbrial adhesion was carried out using Hex 5.1. Further Hex 5.1 was also used to visualize Interaction of Epicatechin-(4beta 2)-phloroglucinol with modelled fimbrial adhesion protein. Some of the commonly used antibiotics to treat urinary tract infections caused by Uropathogenic E.coli which includes Oflaxacin, sulfamethoxazole, Trimethoprim were subjected to docking analysis for comparative studies using Hex 5.1.

## RESULTS AND DISCUSSION

### Modelling

Modelling of fimbrial adhesin protein was done

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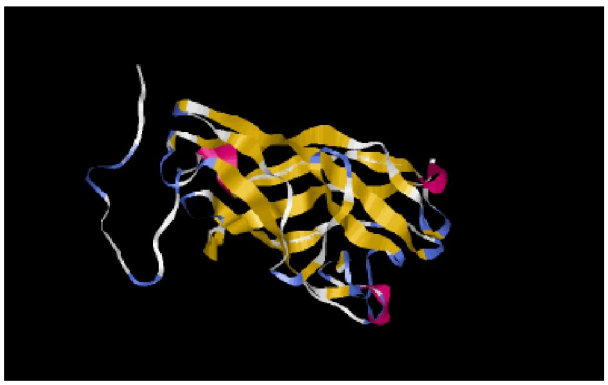


**Figure 2 : Structure of modelled fimbrial adhesin protein.**

using SPDBV tool. Modelled protein structure was submitted to protein model database. Submitted modelled structure has been assigned an accession number PM0075877.This accession number can be used to retreive the submitted protein structure.

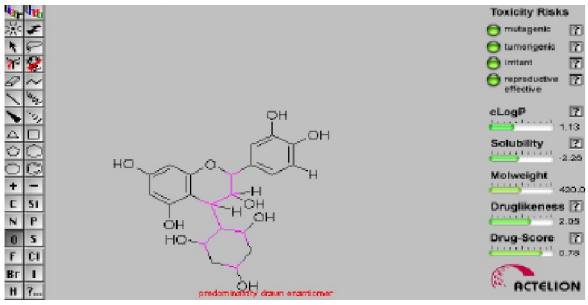



**Figure 3 : Result of validation assay**

## Lead validation

Validation assay for the lead molecule involving mutagenecity, drug likeliness, tumorogenic, irritant property was carried out using OSIRIS Property Xplorer.

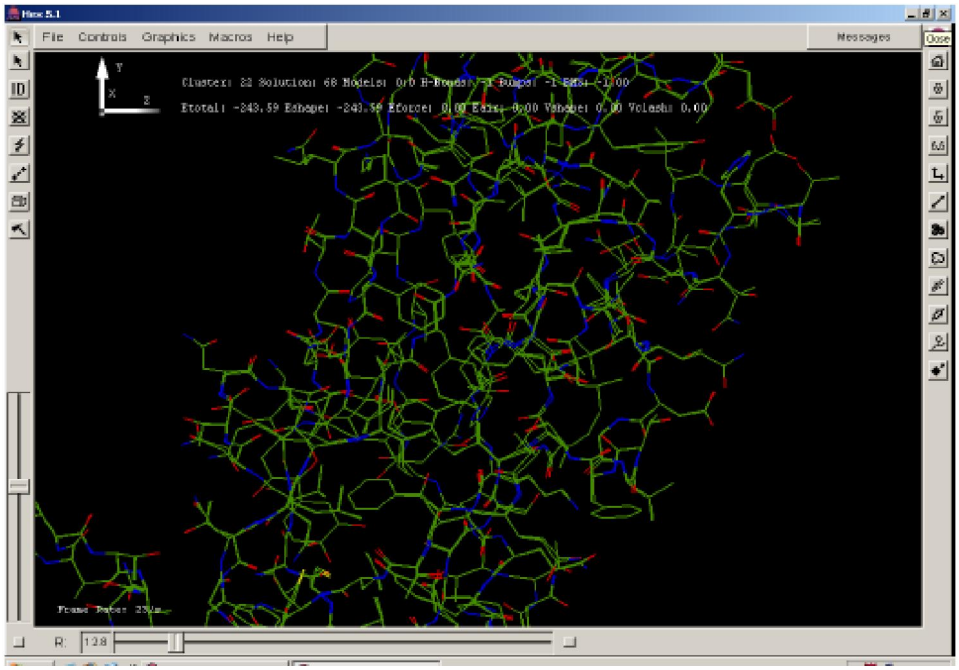
It is observed that Epicatechin-(4beta 2)-phloroglucinol clears mutagenecity, druglikeness, tumorogenic, irritant assays. Hence, can be considered as potential inhibitor for further analysis.

## Docking analysis

Docking analysis of Epicatechin-(4beta 2)-phloroglucinol a Proanthocyanidin from cranberry as an inhibitor against modelled fimbrial adhesion was carried out using Hex 5.1.

Interaction of Epicatechin-(4beta 2)-phloroglucinol with the modelled target protein and its E value is shown in Figure 4.

Some of the most commonly used antibiotics such as Oflaxacin, Sulfamethoxazole and Trimethoprim, to treat Urinary Tract Infections were subjected to Docking Analysis to compare them with the lead molecule. The Binding Energy values obtained for the lead molecule and these




**E Value: -243.59 kcal/mol**

**Figure 4 : Interaction of Epicatechin-(4beta 2)-phloroglucinol a proanthocyanidin from cranberry with modelled fimbrial adhesion virulence protein.**

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**TABLE 1 : Comparison of E values between existing antibiotics to treat UTI and the lead molecule**

| Sl. No. | NAME OF THE COMPOUND | ΔG kcal/mol |
|---|---|---|
| | Lead Molecule | |
| 1 | Epicatechin(4beta-2) phloroglucinol | -243.59 |
| | Commonly used Antibiotics | |
| 1 | Ofloxacin | -190.88 |
| 2 | Trimethoprim | -183.28 |
| 3 | Sulfamethoxazole | -170.00 |

antibiotics are shown in TABLE 1.

## CONCLUSION

Since its reported that Uropathogenic E Coli have developed antibiotic resistance(Gupta et al 2002), Epicatechin Proanthocyanidin from cranberry with many evidences of its activity against virulence proteins of Uropathogenic E.coli has a very good prospective of being used as a medicine for Urinary tract infections caused by Escherichia coli. Comparative docking analysis of commonly used antibiotics used for treatment of urinary tract infections caused by Uropathogenic E.coli also suggest that Epicatechin can be an alternative for the treatment.

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