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SUGGESTION OF A FIMH INHIBITOR BY A MOLECULAR DOCKING METHOD FOR *ESCHERICHIA COLI* ISOLATED FROM CLINICAL SAMPLES OF PATIENTS WITH UTI

E. coli is one of the most important organisms that cause urinary tract infection (UTI) in more than 95 % of patients with UTI. ***The aim*** *of this study was to search for inhibitors of (fimH) by a docking method using computer programs and websites specialized for this purpose.* ***Materials and Methods.*** *This study involved 63 samples with positive E. coli collected from patients with UTI from February 2021 to October 2021 at the Iraqi hospital in Karbala. Full laboratory investigation for E. coli was made to detect FimH and predictsuitable inhibitors. The Fast Identification System VITEK-2, compact DNA extraction system, and PCR Molecular docking were used. Studies of FimH inhibitor for animals were performed as well.* ***Results.*** *FimH was found in most E. coli isolates, namely in 61 (96.82 %) of 63 samples. The principle of the experiment is dependent on activated infection on animals with/without feeding with our drug (chamomile), and then the counted E. coli in their urine chamomile appears to be a good FimH inhibitor, with a docking score of -9.4, and to be able to reduce UTI in roughly 50 percent of rats examined.* ***Conclusions.*** *The chamomile was predicted as a suitable inhibitor of (fimH) and then tested on rats. The results showed its good inhibitory properties.*

Keywords: *E. coli, molecular docking, FimH, UPEC, urinary tract infection.*

Uropathogenic *Escherichia coli* (UPEC) is a microorganism that most frequently causes urinary tract infections and is considered responsible for more than 95% of all urinary tract infections [1]. Most *E. coli* strains can produce type I fimbriae, which are rod-like appendages made up of roughly 1,000 FimA protein subunits and a few percents of minor components [2]. These fimbriae mediate the bacteria's attachment to D-mannose-containing structures, allowing

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them to bind in a variety of host tissues [3]. D-mannose and most of its derivatives were shown to be very strong antagonists of type 1 fimbria-mediated attachment in all cases, whereas all saccharides that did not contain D-mannose did not exhibit blocking properties. Each level in the UTI pathogenesis is kicked off by adhesion [4].

The UTI generally starts with an uropathogen infecting the periurethra in guts, accompanied by colonization of the urethra and then transfer of the bacteria to the bladder, necessitating the usage of appendages such as flagella and pili. In the bladder, the consequences of complex host-pathogen interaction ultimately decide whether uro-pathogens are spread or eliminated [5]. *E. coli*'s capacity to bind to uro-epithelial cells is greatly dependent on fimbriae type I, which are distinguished by the presence of an adhesion called FimH at the tip of the fimbriae [6]. FimH uses the catch—bond binding mechanism to bind to the epitope end of high mannosylated glycan attached to uro-plakin 1a (UP1a), a receptor exclusively expressed at the surface of urothelial cells [3].

The use of computational analysis to anticipate the physicochemical, spectral, and biological features of a newly synthesized drug is common [7]. The main goal of this research was to create new biologically active fimH inhibitor compounds and examine their binding affinities and interactions with *E. coli* FimH using computational techniques in order to identify an effective inhibitor of the bacterial function [8].

Molecular docking is useful in the development of drug, because it assists in the identification of active or lead compounds from a library of natural molecules [9]. It is one of the most used virtual screening techniques, especially when the target protein's three-dimensional structure is available. Docking allows for the prediction of ligand—target binding affinity as well as the structure of the protein—ligand complex, both of which are important for lead optimization. We examined the physicochemical attributes and toxicity potential of FimH antagonists before starting the molecular docking analysis [10].

After choosing some suitable medical compounds and docking them by Mcule web site, we chose medical drugs available in pharmacies and market on the basis of their high safety and appropriate efficacy to treat some diseases with no harm effect on the body's vital physiology, such as heart diseases, diabetes, and neurological diseases [11].

By using the «Mcule website», the ligands were docked to the Chamomilla and FimH proteins, as reported by our study.

To minimize the amount of energy consumed by the ligand molecules, a Merck molecular force field (MMFF94) was applied [12].

Gasteiger partial charges were augmented using ligand atoms. On the target proteins, calculations for docking were performed [13].

Materials and methods. This study involved 63 samples with positive *E. coli* collected from patients with UTI of both sexes and different ages, who attended hospitals of Karbala Province from February 2021 to October 2021.The age of patients ranged from 15 to 60 years.

Fast Identification System by VITEK-2 Compact System. The automated VITEK-2 compact system successfully identified *E. coli*. It is a gadget that uses a methodology to identify an organism based on the characteristics of information and knowledge about the microbe and reaction in question. The producers' instructions were followed in order to develop a confirmatory tool for biochemical tests [14].

DNA extraction and PCR. DNA was extracted from clinical isolates. Each isolate's colony was grown overnight at 37 ºC after cultivation and put into 5 ml of BHI (Brain Heart Infusion) [15]. A genomic DNA kit provided by the manufacturing company was used to harvest DNA from bacterial cells in these isolate cultures [16]. The DNA acquired as templates was used in all PCR assays. The virulence gene listed in Table 1 was found in PCR utilizing nucleic acid (DNA) extracted from *E. coli* cells as a template. A single

reaction combination contained 2.5 of upstream primers, 2.5 of downstream primers, 5 of DNA extraction, 12.5 of master mix, and 2.5 of nuclease-free water. After that, the PCR products were run on a 1.5% agarose gel [17].

Molecular docking. The molecular docking method was used to describe the molecular level connection among fine molecules and a protein, making us to notice fine molecule's behavior at specific protein-binding sites and deduce critical biochemical processes. Molecular docking can be performed in Mcule.com, which is a web-based drug discovery service [18].

Animals study. Four groups of rats were taken, weighted 150—200 g and inoculated with 10^8—10^{10} colony forming units (CFU) of UPEC bacteria directly into the bladder by transurethral catheterization [19] (using an angio-catheter of 24G, diameter 0.7 mm, length 19 mm) and small injection [20].

FimH inhibitor study. FimH inhibition was studied via determination of the bacterial contents in rat's urine upon giving chamomile as a FimH inhibitor. To collect urine samples in a volume appropriate for routine urinary testing techniques, rats are usually single-housed in metabolic cages for 16 to 24 hr [21]. The collected urine was diluted in 0.85% NaCl, plated on nutrient agar supplemented with 0.1% yeast extract and 0.1% glucose, and incubated at 37°C for 20 hr. The colonies formed and then were counted. The extent of bacteriuria was graded as follows: no excretion of bacteria (<10^3 cells/mL), occasional excretion (10^2—10^3 cells/mL), and excretion of bacteria (10^{10} cells/mL) [22].

Bacterial cell count. A photopette® portable spectrophotometer was used to count *E. coli* cells at OD600. The approach is simple and quick to execute in a bio reactor or cell culture hood. In the cell culture flask, *E. coli* may be directly detected at 600 nm. The procedure may be carried out anywhere and does not need a laboratory [23].

Results. Fig. 1 demonstrates that uropathogenic *E. coli* samples are identified using screened PCR technique. The fimH gene was amplified using specific primers and showed a band about 903 bp. FimH's high quality was found in 61 of 63 samples of the UPEC strain samples (96.82%),

Table 1. **Forward and reverse primers used in this study**

Primer	Sequence	Product size (bp)	Reference
FimH forward	5'-ATGAAACGAGTTATTACCCT-3'	903	[25]
FimH reverse	5'-TTATTGATAAACAAAAGTCACG-3'		

Table 2. **Different results for animal groups treated with chamomile**

Test Animals group	General Urine Examination of rats	Bacterial Cell Count in rats urine
(G1) Control (without drug, without infection)	20 (100%) All negative*	20 (100%) All negative <10^4
(G2) Animals taking Drug before infection for 2 days	10 from 20 (50%) negative 10 from 20 (50%) positive**	10 from 20 (50%)-ve<10^4 CFU 10 from 20 (50%)+ve>10^7 CFU
(G3) Animals taking Drug after infection for 2 days	7 of 20 (35%) negative 13 of 20 (65%) positive	7 of 20 (35%) -ve<10^4 CFU 13 of 20 (65%) +ve>10^7 CFU
(G4) Animals infected without drug given	20 (100%) all positive	20 (100%) > 10^7 CFU

* Negative (-ve) = No infection, **Positive (+ve) = Infection

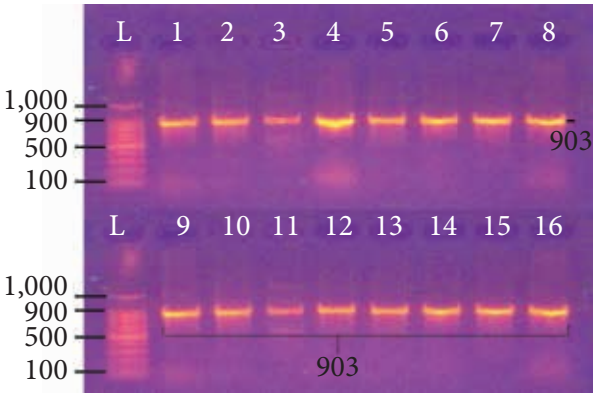

Fig. 1. FimH PCR results in ultraviolet light at 300 nm after staining with E.B stain on a 1% agarose gel electrophoresis at 71 V for 51 min. (L): 1000 bp ladder; lane (1—16) was positive; the product size was 903 bp

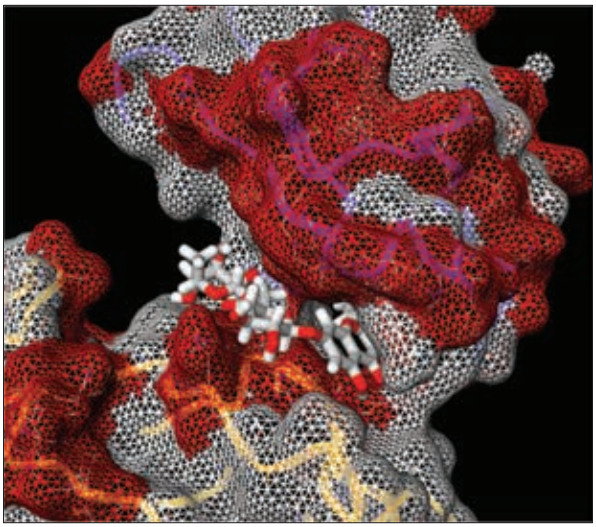

Fig. 2. Electron density map for prediction of FimH-target binding with fimH protein

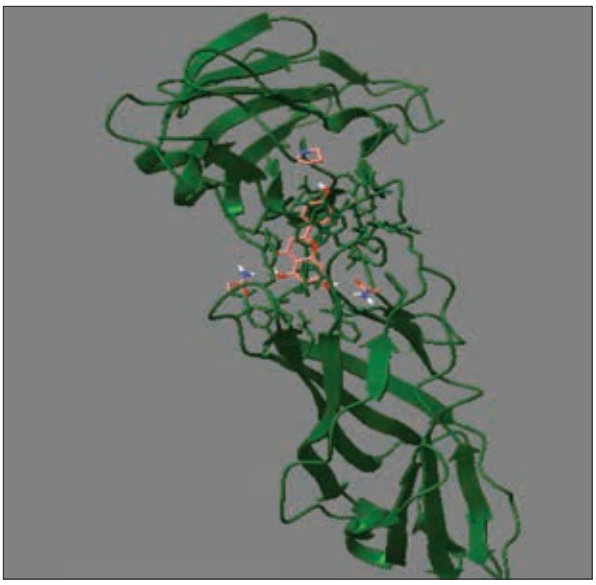

Fig. 3. Crystal structure of FimH (green) complexing with Chamomilla (colored)

indicating that fimH is one of the most important virulence factors in UPEC bacteria to cause a UTI [24].

Figs. 2 and 3 show an electron density map and the crystal structure for oligomannose-3 in the FimH receptor binding site, bound with the Chamomilla active site to the blocking FimH active site (with a mean docking score of -9.4). More negative values indicate higher binding affinity. In Table 2, animal's groups show different results before and after giving chamomile. Table 2 shows the experimental results on rats. Four groups of rats were taken; each group contained 20 animals of 150—200 g in weight. The principle of the experiment is dependent on the activated infection on animals with/without feeding them with chamomile, and then *E. coli* in their urine is counted. The first group served as a control; these rats were not inoculated by bacteria and not fed with chamomile, so they were healthy, with no disease, and all laboratory tests revealed a negative infection. The second group was pre-fed with chamomile for three days and then inoculated with 10^7—10^9 CFU of UPEC by intraurethral catheterization. The concentration of chamomile used in this experiment was prepared by adding 5 drops of 1.2% liquid extract in 100 ml of water [26], and animals should be fed with this solution throughout the day without being given water. The result from 20 animals showed that 10 (50%) of rats were not infected with UTI and 10 (50%) of them caught an infection [27]. The third group had been infected before two-day feeding with chamomile.

Discussion. Various germs, including uropathogenic *E. coli* (UPEC), cause urinary tract infections (UTIs). UPEC strains have unique virulence characteristics, such as type 1 fimbriae, which can exacerbate UTIs [28]. The previous result shows that type 1 fimbria is very important for *E. coli* in UTI due to its ability to be attached to a uroepithelial cell by the FimH protein, to render elimination by urine, and to facilitate colonization and pathogenicity. The essential step in the infection process is the colonization to the urinary tract [29]. Ordinarily, without binding to epithelium cells, bacteria can be washed out by the urination process [30]. Type 1 fimbriae are coded in the genome of almost 95% *E. coli* strains [24].

The presence of fimbriae is required for colonization of the urinary system. The fimbriae (P, type 1, S, and F1C) are among the stickiest organelles expressed by uropathogenic *E. coli*. More than 90% of all uropathogenic *E. coli* develop type I, or mannose sensitive fimbriae [31]. Bacteriuria with UTI symptoms was considered serious if a voided urine culture revealed at least 100,000 uropathogens per mL [32]. Table 2 demonstrates that the *E. coli* expression of type I fimbriae is a virulence factor in urinary tract pathogenesis for most isolates. Since FimH's receptor-binding site is highly specialized mannose-binding pockets with tyrosine gates (Tyr.48, Ile.52, and Tyr.137) at one side and a hydrophobic ridge (Ile13, Phe1, and Phe142) surrounding its entry, a FimH inhibitor should be overlaid onto the FimH lectin domain combination with oligomannose-3 [33]. The chemical structure of D- mannose permits it to stick to *E. coli* bacteria much more tenaciously than *E. coli* sticks to human cells. Although the mechanism of this action is unclear, we may speculate that if enough D-mannose is present in the urine, it will stick to bacteria and prevent them from sticking to the lining of the urinary tract. The affinity (grid) maps sized at (60° × 60° × 60°) were generated using an auto grid algorithm in order to target the grid coordinates in the target protein's catalytic site (chamomilla and FimH). The FimH protein targeting the catalytic region had x, y, and z coordinate values of -16.519, 50.643, and 27.017, respectively. The ligands' initial positions, directions, and torsions were chosen at random [34].

Figs. 2 and 3 show the molecular docking of binding between FimH and chamomile. Chamomile, known as Matricaria recutita, is a medicinal plant that is native to Western Europe and North Asia. It is distinguished by its herbaceous bearing and flowering [35].

In the systemic molecular genetics and computer-assisted drug design, molecular docking is an important technique [36]. The aim of ligand protein docking is to expect ligand's interaction mode with protein molecules having a defined 3D shape. Good docking algorithm efficiently explores high dimensional domains and employs a scoring system that scores proposed dockings precisely [37]. Docking may be used to perform virtual scanning in large libraries of drugs, rank the findings, and supply structural hypotheses for how ligands obstruct the targets, all of which are very beneficial in optimization of leads [38]. Molecular docking between fimH and chamomile give high degree of binding (docking score is –9.4), as compared to molecular docking with D-mannose with a score of –5.5. This means a lower energy needed for molecule binding (ligand and target) to form a more stable complex than with D-mannose [39].

Table 2 shows that 13 (65%) rats get an infection and 7 (35%) are not infected. We notice that the infection can be increased when chamomile is not given before infection, which is due to the ability of *E. coli* to be bound onto bladder epithelial cells by fimH in the absence of drug [3]. When the concentration of the drug increases after two days, we can notice the healing effect of chamomile on the one-third number of animals in the third group [27].

In the fourth group, all animals could be infected without any treatment, so all animals getting an infection showed more than 10^8 CFU in

their urine, because no FimH antagonist (chamomile) was present.

Conclusions. This study explains a good effect of chamomile in UTI treatment. Also, chamomile refers to a safer therapy and can be given in treatment for many diseases, such as cold and chest disease, as well as for prophylaxis in case of high-risk factors for UTI. Chamomile can provide protection from UTI in rats by 50% when it is taken as prophylaxis, and protect about 35% of rats after getting an infection, so in our study, we have recommended using chamomile as a natural herbal product in adjuvant therapy with other drugs or products in the UTI treatment.

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ПОШУК ІНГІБІТОРА FIMH МЕТОДОМ МОЛЕКУЛЯРНОГО ДОКІНГУ ДЛЯ *ESCHERICHIA COLI*, ВИДІЛЕНОЇ З КЛІНІЧНИХ ЗРАЗКІВ ПАЦІЄНТІВ З ІСШ

Кишкова паличка є одним із найважливіших мікроорганізмів, яка викликає інфекцію сечовивідних шляхів (ІСШ) у понад 95% пацієнтів. **Метою** даного дослідження є пошук інгібіторів (fimH) методом докингу з використанням комп'ютерних програм та спеціалізованих для цього веб-сайтів. **Матеріали та методи.** У цьому дослідженні відібрано 63 зразки кишкової палички у пацієнтів з ІСШ у період з лютого 2021 року по жовтень 2021 року з іракської лікарні в Кербелі. Для виявлення FimH та прогнозування відповідних інгібіторів було проведено повне лабораторне дослідження на *E. coli.* Була використана система швидкої ідентифікації VITEK-2, проведено виділення ДНК, ПЛР молекулярний докінг, а також дослідження інгібітора FimH на тваринах. **Результати.** FimH виявлено в більшості ізолятів *E. coli*, а саме в 61 (96, 82%) з 63 зразків. Показано, що ромашка є хорошим інгібітором FimH з показником докингу –9,4 і зменшувала прояви ІСШ приблизно у 50 відсотків досліджених щурів. **Висновки.** Було зроблено припущення, що ромашку можна використовувати як відповідний інгібітор (fimH), і були проведені її випробування на щурах. Результати показали, що ромашка має гарну інгібуючу властивість; крім того, вона безпечна і має інші переваги.

***Ключові слова**: E. coli, молекулярний докінг, FimH, UPEC, інфекція сечовивідних шляхів.*