Biomedical & Pharmacology Journal, March 2023. Vol. **16**(1), p. 595-604

Comparative Docking Studies of Potential Candidates from Kokum and Cranberry as Anti-Adhesins Against UTI

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https://dx.doi.org/10.13005/bpj/2642

(Received: 15 March 2022; accepted: 03 August 2022)

Most frequently affecting women and those with diabetes, urinary tract infections (UTI) are a prevalent illness. Inappropriate management of the acute stage of the illness leads to pyelonephritis, which makes the condition chronic. Multiple medications are ineffective against the microorganisms that cause UTIs, due to multi-drug resistance. Escherichia coli fimbria contains the bacterial adhesin protein FimH, which is responsible for adhering bacteria to the host urinary tract's epithelial cells. Therefore, FimH becomes a crucial target for the development of drugs since it plays a key role in bacterial infections like UTIs. In the context, phytochemical intervention using Garcinia indica (Kokum) and Vaccinia macrocarpon (Cranberry) proves to be an effective alternative. Garcinia indica is a tropical plant endemic to India, particularly in the Karnataka, Kerala, and Maharashtra coastal regions. The fruit is abundant in anthocyanins and benzophenones, which have antibacterial properties against a variety of pathogens. Because the fruit includes antiadhesive flavonoids and proanthocyanins, Vaccinia macrocarpon fruit syrup is currently utilized as a treatment for UTIs and the fruit is native to America. The current study contrasts the inhibitory effects of secondary metabolites from Vaccinia macrocarpon and Garcinia indica on E. coli FimH protein. According to the study, garcinol and kaempferol from the plants' Garcinia indica and Vaccinia macrocarpon, respectively, showed the highest affinities for the protein FimH.

Keywords: Anti-adhesin activity; Garcinia indica; Garcinol; kaempferol; Urinary Tract Infection; Molecular Docking Simulation; Molecular Dynamics Simulation; Vaccinia macrocarpon.

Urinary tract infection (UTI) is one of the prevalent diseases that affects females and people suffering from type II diabetes[1]. Around 50-60% of the women have suffered from UTI at least once in their lifetime[2]. Uropathogenic *E. coli* (UPEC) is considered to be responsible for the majority of the infection, can form the biofilm, and invade the host immune response[3]. Apart from *E. coli* which causes around 80% of the total infection, other pathogens like *Klebsiella spp., Staphylococcus saprophyticus, Enterobacters* and *Proteus spp.* can also contribute to the same[4]. The threat posed by the uropathogens' due to the rise in antibiotic resistance makes therapy challenging and expensive. This

increases the likelihood of recurring infection[5]. Genetic polymorphism in the pathogens' has made them resistant to multiple drugs[6]. Another worrying trend is the rise in the prevalence of multidrug-resistant infections among pregnant women[7].

Pathogens causing UTI possess type-1 fimbriae that facilitates attachment of the bacterial cell to the epithelial cells of the urethra. Due to its interaction with the mannosylated receptors expressed by urothelial cells, type-1 pili is considered to be mannose sensitive. This peculiarity of the pili is due to the activity of the adhesin protein FimH located at the tip of type-1 fimbriae[8,9].

Several attempts are being carried out to find a potent drug that can inhibit the action of pathogens without altering the host immunity. As the protein FimH is mannose sensitive, D-Mannose was used as vaccine to mask the FimH but it was found to be ineffective[10]. Drugs that target the protein FimH and its mannose specificity are currently the subject of experiments to cure UTI because the treatment functions without killing the pathogen and uropathogens are unlikely to develop resistance. Moreover drugs targeting FimH will be selective in their effect, leaving host microflora intact[11]. Even though there are many alternative medical treatments for UTI, current research on the condition is concentrating on the antiadhesive properties of various secondary metabolites from herbal sources because they are linked to a lower risk of side effects[12,13].

Flavonols and Proanthocyanidins from cranberry and kokum as antimicrobial agents

The production of flavonoids varies from plant to plant and depends on the environment, type of soil, and other physiological parameters. Flavonoids are generated in different sections of plants at varied amounts. They guard against biotic and abiotic stressors on the plants. Plants produce flavonoids to help them defend themselves[14]. Berries include flavonols and their derivatives, which are known for their antibacterial properties among other health advantages[15]. Their antiadhesive properties are proving to be an efficient defense mechanism against pathogens that can withstand antibiotic action[16].

Proanthocyanidins, also known as condensed flavonols, are extensively dispersed in different areas of the plant and have a number

Table 1. Virtual screening results of cranberry phytocompounds with target protein FimH lectin domain (PDB ID: 6GTX)

S. No.	Name of the ligand	Binding Affinity (kcal/mol)	Non-bonded interaction	Hydrogen bonds
1.	Apigenin	-6.1	6	3
2.	I3-II8-Biapigenin	-6.6	2	1
3.	Kaempferide	-5.9	6	2
4.	Kaempferol	-7.9	7	3
5.	*Luteolin*	-6.9	4	1
6.	Quercetin	-6.1	5	2

Table 2. Binding affinity and non-bonding interactions of secondary metabolites of *Garcinia indica* with target protein crystal structure of the FimH lectin domain

S. No.	Name of the ligand	Binding Affinity (kcal/mol)	Total no of non-bonded interaction	Total no of hydrogen bond
1.	(-)-Hydroxycitric acid	-4.4	4	3
2.	Isogarcinol	-7.2	7	4
3.	Xanthochymol	-5.6	5	2
4.	cyanidin 3-glucoside	-6.9	-6.9	-6.9
5.	*cyanidin 3-sambubioside*	-5.7	5	3
6.	Garcinol	-8.5	12	3

Table 3. Interaction details of experimental molecules with the binding residues with their respective distance in Å (Angstrom)

S. No.	Compound	Binding affinity (kcal/mol)	Hydrogen bond interactions	Electrostatic bond interactions	Hydrophobic bond interactions		
					Pi-sigma bonds	Alkyl bonds	Pi-alkyl bonds
1	Garcinol	-8.5	ASN A: 135 (2.38), ASP A: 54 (1.87), ASP A: 47 (2.95)	PHE A: 1 (4.22)	ILE A: 52 (3.91)	ILE A: 13 (4.61)	TYR A: 48 (4.15), TYR A: 48 (5.08), TYR A: 48 (5.00), TYR A: 48 (4.71), TYR A: 137 (4.45), TYR A: 137 (5.29)
2	Kaempferol	-7.9	ASN A: 138 (2.82), UNL1:H (1.79), ASN A: 138 (3.27)	PHE A: 1 (4.12), ASP A: 140 (3.35), ASP A: 140 (3.98)	ILE A: 52 (3.99)	-	-

of positive health effects, such as anticancer, neuroprotective, and antibacterial capabilities[17]. They have a very low Minimum Inhibitory Concentration (MIC) and can suppress microbial growth[18]. Even nanoparticles synthesized from chitosan and proanthocyanidins along with gentamicin are proven to be bactericidal[19]. The antiadhesive properties polyphenols and flavanols (kaempferol, quercetin, and myricetin) of cranberry make them effective against a variety of infections[20]. The flavones apigenin, i3-ii8-biapigenin, and luteolin are among the promising anti-adhesive chemicals because they exhibit a notable anti-adhesive action on uropathogens[21]. Cranberry syrup is a highly suggested alternative to antibiotics among the different herbal remedies for UTI since it hinders the pathogen's adherence to the urinary system[22]. Several studies on antiadhesive property of secondary metabolites of cranberry shows that flavonoids and proanthocyanidins inhibit the FimH mediated interaction of uropathogens with the epithelial cells of the urethra and bladder[23]

Garcinia indica is a plant that is commonly found in the coastal region of India specially in the coastal areas of Karnataka, Maharashtra and Kerala[24]. It is endemic to Western and Eastern Ghats and also to North-eastern regions of India[25]. The fruit is used for domestic purpose in the preparation of curry, pickles and juice. The secondary metabolites of *G. indica* is believed to have health benefits that can be considered as efficient herbal drug for future therapeutics[26,27]. Kokum extracts are also being studied for various biological activities. Studies have revealed that Kokum extracts have antibacterial property against several pathogens and Benzophenones of kokum especially garcinol, isogarcinol and xanthochymol that are included in the study contributes to the antimicrobial property of kokum[28,29]. Benzophenones derivatives from *Garcinia species* have shown chemotherapeutic activities against bacteria, fungi and mycobacteria[30]. Kokum fruit rinds are also rich in flavonoids and proanthocyanidins[31]. Cyanidin 3 sambubioside and cyanidin 3 glucoside are the anthocyanins that are present in Kokum that make kokum as a promising agent for therapeutics (28). Pathogens that were resistant to antibiotics have been susceptible to the synergistic effect when the same antibiotics are combined[32].

In the field of drug discovery molecular

docking is having a great importance and application as the study is directed towards computer aided drug designing. Protein ligand interaction study is increasing possibilities of discovering new drugs with greater accuracy. Considering the antimicrobial properties and antiadhesive property of proanthocyanidins, flavonoids, anthocyanins and benzophenones, the present study compares the inhibitory binding interactions of proanthocyanidins and flavonols from cranberry with anthocyanins, benzophenones and other potential secondary metabolites of *G. indica* while binding with the protein FimH[33]. For selected compounds, molecular dynamics simulation was also done to The virtual screening helps to identify the potential drug candidates from diverse nature of sources[34,35].

METHODOLOGY

Data retrieval

The crystal structure of the FimH protein was downloaded from RCSB PDB database (https://www.rcsb.org/) (PDB ID: 6GTX). The 3D structures of the ligands from *G. indica* (garcinol, isogarcinol, (-)-hydroxycitric acid, xanthochymol, cyanidin 3-sambubioside, cyanidin 3-glucoside) and from cranberry (apigenin, i3-ii8-biapigenin, kaempferide, quercetin, luteolin and kampferol) were retrieved from PubChem chemical database (https://pubchem.ncbi.nlm.nih.gov/).

Molecular docking simulation

AutoDock Vina 1.1.2, a command-based software was employed for the docking studies[36,37]. The pre-preparation of protein and ligand required for docking study was conducted based on authors previous work[38]. By using BIOVIA Discovery Studios Visualizer 2021, a GUI based software for the screening for best conformation was done, based on their binding affinity, non-boding interactions, and total number of hydrogen bonds.

Molecular dynamics (MD) simulation

To get the better understanding of conformational changes and their stability over a period of time, MD study was conducted using the GROMACS biological software package. The pre-requisite and the MD experiments were performed based on previous work[39]. Using the XMGRACE software[40], the trajectory plots were analysed.

Binding free energy (MMPBSA) calculations

The calculation of binding free energies was performed based on work[41,20]. The study was performed to understand formation of energy after dynamic study. The calculation was done using, g_mmpbsa programme, by using GROMACS trajectories as input[43].

RESULTS AND DISCUSSION

Molecular docking simulation

Based on virtual screening results, garcinol from *G. indica* showed a higher (most negative) binding affinity of -8.5 kcal/mol with 12 non-bonded interactions, out of which 3 were found to be hydrogen bonds (Table 1). However, kaempferol from *V. macrocarpon* showed the binding affinity of -7.9 kcal/mol with 7 non-bonded interactions and 3 of them were found to be hydrogen bonds (Table 2). Visualization of binding interactions garcinol and kaempferol with FimH protein has been given in Figure 1, whereas the details of binding residues along with their respective distances have been depicted in Table 3.

Table 4. Results from binding free energy (MMPBSA) calculations of experimental molecules with complexed with the target protein

	Garcinol-FimH complex		Kaempferol- FimH complex	
	Values (kj/mol)	Standard deviation kj/mol	Values (kj/mol)	Standard deviation kj/mol
Van der Waal's energy	- 37.584	+/- 17.357	-35.952	+/- 49.039
Electrostatic energy	- 19.990	+/- 12.655	-7.083	+/- 0.647
Polar solvationenergy	38.908	+/- 29.180	29.271	+/- 55.147
SASA energy	- 5.720	+/- 1.880	-3.084	+/- 4.731
Binding energy	- 24.385	+/ 20.763	-9.682	+/- 82.308

Molecular dynamics simulation

The molecular dynamics simulation studies were employed for validation of the docked structure of garcinol bound FimH complex and kaempferol bound FimH complex. The result was analysed by plotting the graphs for protein-ligand complex RMSD, RMSF, Rg, SASA, and ligand hydrogen bonds (Figure 2). Based on the RMSD

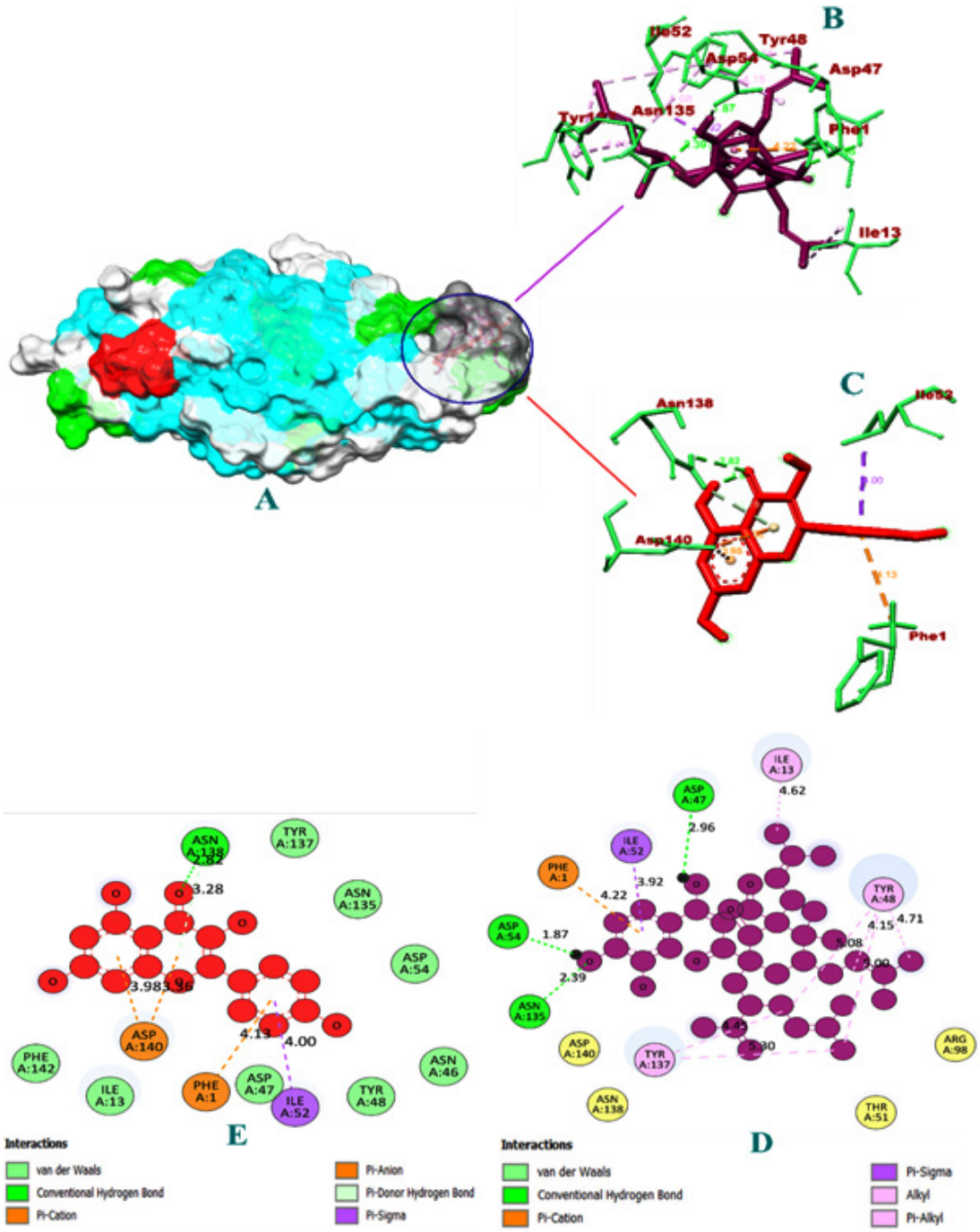

Fig. 1. (A) surface representation of the binding site of FimH lectin domain target protein bound to garcinol and kaempferol. (B) 3D representation of bound garcinol (sticks model). (C) 3D representation of bound kaempferol (sticks model). (D) 2D representation of bound garcinol (E) 2D representation of bound kaempferol

plot prediction it is understood that the garcinol complex and protein is within the range of 0.2 – 0.25 nm, whereas kaempferol complex is within the range of 0.3-0.35 nm. Both the protein as well as garcinol complex shows the similar pattern at around ~80 ns and attains stability. While the RMSF plot for protein, garcinol and kaempferol are on par and show similar fluctuation pattern. Further, based on the Rg plot and SASA analysis shows the similar pattern, thus it can be said that

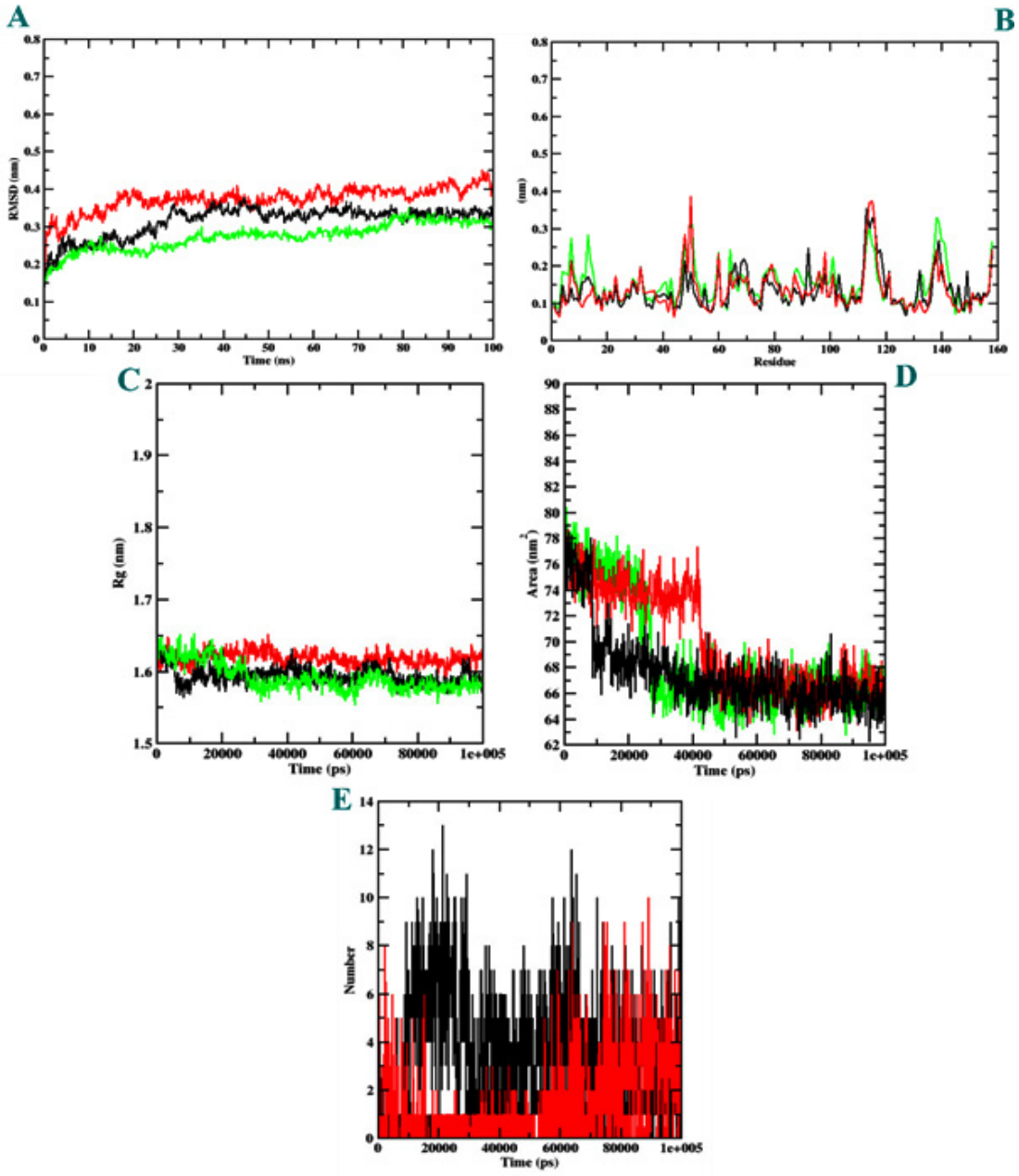

Fig. 2. Visualization of MD trajectories of bound garcinol and kaempferol with the target protein for 100 ns. RMSD, RMSF, Rg, SASA, and number of hydrogen bonds of garcinol (black) and kaempferol (red) with FimH (green) at 100 ns. (A) Time evolution of backbone RMSD of the complex structure. (B) RMSF of protein and ligand. (C) Radius of gyration (Rg) (D) SASA (E) ligand hydrogen bonds. Protein backbone atoms: green, protein-garcinol complex: black, and protein-kaempferol complex (red)

the complexes are stable. Finally, based on the hydrogen bond evaluation, structural re-agreement in protein-ligand complex could be expected, as the number of hydrogen bonds is increased compared to docked structure.

Binding free energy (MMPBSA) calculations

Free-binding energy was calculated based on the MM-PBSA method. The predicted values of the calculation along with the energy being formed during the last 50 ns are given in Table 4. Since more negative energy reflects more stability, from the obtained results it can be predicted that protein-garcinol complex shows better stability compared to protein-kaempferol complex.

The study reveals that among the compounds taken for the study kaempferol from cranberry and garcinol from kokum have shown better inhibitory binding action against FimH. Kaempferol derivatives of cranberry are antibiofilm agents that inhibit colonization of microbes[44,45]. Kaempferol is one of the bioactive substances found in cranberry extract that has the ability to function as an anti-adhesin and prevent the development of biofilm by interfering with the anchoring of microbial cells. Despite not being a biocidal agent, kaempferol's antiadhesion activity can stop microbial development[46]. Garcinol demonstrated a higher affinity to bind FimH than the other benzophenones and anthocyanins of kokum included in the study. When the antiadhesive properties of kaempferol and garcinol were evaluated, the results revealed that garcinol's potential to be an anti-adhesin is equal to that of kaempferol. Garcinol can considerably inhibit FimH and can be prospected for drug discovery against UTI. So further studies are required to check for synergism of secondary metabolites with antibiotics and confirm the action.

Urinary Tract Infection is becoming more prevalent among various age groups and the risk of recurrent infection is increasing due to the resistance of pathogens to various antibiotics. Females and diabetic patients are more susceptible to infection (Yu and Pieper, 2019; Sekhar et al., 2020). There are several studies being carried out to develop drug against UTI without altering the host immunity. Being an antiadhesive agent, cranberry extract is coming out to be effective for treating UTI. The fruit comes from a native American plant that grows in wetlands[48] and currently it is being used as a herbal drug against UTI.[49]

G. indica is considered as an underutilized fruit and it is being used traditionally[50]. According to the findings of this study, *G. indica* can be used as an antiadhesive agent and may be investigated for therapeutic development against UTI because Garcinol has shown to have the same affinity for FimH as Kaempferol.

Further studies have to confirm the same as cranberry has shown synergistic effect against uropathogens in combination with few natural borne-antimicrobials[51]. Because of its health benefits, garcinol is a metabolite of interest that is being examined for drug development[52,53]. More research into this area could turn an underutilized fruit into a local bio resource.

CONCLUSION

Cranberry and kokum are potent plants to treat uropathogens as they contain secondary metabolites which are having antiadhesive property. Inhibition of the protein FimH of uropathogenic *E. coli* by the bioactive compound can be considered for drug discovery as alternative to the antibiotic treatment. The present study has indicated that both garcinol and kaempferol from kokum and cranberry, respectively could act as the potential FimH inhibitors (anti-adhesins). The compounds have been reported with extensive binding efficiency and stability. With these outcomes, *in silico* investigations prove that both the compounds could be taken for biological assays. Therefore, *in vitro* and *in vivo* studies can be used to validate on the mode of action of these anti-adhesins.

ACKNOWLEDGMENT

This research work is self-funded and no external financial assistance were taken. The authors express their gratitude to the late Secretary of SDME Society Dr. B Yashovarma for encouragement and motivation. All the authors express sincere gratitude to JSS Academy of Higher Education and Research, Mysuru for encouragement and support to carry out the research work.

Conflict of interest

No conflicts of interest associated with this work.

Funding Sources

There is no funding sources.

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