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PLASMID-MEDIATED ANTIMICROBIAL DRUG RESISTANCE IN UROPATHOGENIC *ESCHERICHIA COLI* (ENTEROBACTERIALES: ENTEROBACTERIACEAE): A MINI REVIEW

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ABSTRACT
A common bacterial infection in the community is urinary tract infection (UTI). Women are more susceptible to UTIs. *Escherichia coli* are common uropathogenic bacteria (UPEC) in both complicated and uncomplicated UTIs. In recent years antimicrobial resistance (AMR) has been one of the paramount threats to civic health that happens nowadays, and it has been made worse by misuse and abuse of antimicrobial drugs in both humans and cattle, as well as by inadequate control of infection. This pathogen is gradually becoming resistant to single to multiple antibiotics due to the transfer of resistant (R) plasmid from one bacterium to another. In many countries, the standard treatment for UTIs depends on the practice of antimicrobial drugs including β-lactams, nitrofurantoin, trimethoprim, fosfomycin, and quinolones. The study showed that UPEC is completely susceptible to imipenem, vancomycin, carbapenem, and doxycycline whereas tetracycline, trimethoprim-sulfamethoxazole, cefepime, florfenicol, and sulfonamide are most susceptible antibiotics against this opportunistic pathogen. Quinolone and azithromycin resistance; and extended-spectrum β-lactamase (ESBL) enzyme synthesis are predominant plasmid-assisted AMR in UPEC. Therefore, co-resistance to β-lactams and fluoroquinolones hinders the treatment of UPEC-mediated infection. Cranberry extract and metallic nanosilver showed magnificent beneficial effects against UPEC. Therefore, it is of utmost necessity to search for new antimicrobial compounds from various natural sources including plants, or through using metallic nanoparticles (MNPs). The pathogenicity or virulence property of isolates can be reduced through the blocking of quorum sensing mechanisms or inhibiting biofilm formation.

KEYWORDS: Urinary tract infection; Uropathogen; *Escherichia coli*; Antimicrobial resistances; Plasmid.

INTRODUCTION

Antimicrobial resistance (AMR) is emerging more rapidly on a worldwide scale and also spreading from one country to the next. Several parts of the world are affected by superbugs and microorganisms that are multidrug-resistant (MDR). AMR has undoubtedly increased over the past 80 years due to extensive use, abuse, and overuse of antibiotics (Christaki et al., 2020; Some et al., 2021b). Bacteria may quickly spread the genes encoding for AMR both within and between the species via genetic recombination (Fig. 1). Use of antibiotics induces a selective evolutionary pressure that increases resistance (Septimus, 2018; Morrison & Zembower, 2020). In the prokaryotic cells, plasmids are genetic elements that settle there and self-replicate. They are considered a key factor in prokaryote evolution due to their capacity for population migration. Plasmids have also an important role in fundamental research as well as applications in biotechnology, synthetic biology, agriculture, and medicine, which extend their significance beyond microbial evolution (Wein & Dagan, 2020). The main factor of bacterial resistance is the existence of antibiotic resistance genes (ARG). Through plasmid interchange at the gene level, pathogenic bacteria get ARGs and support their antibiotic resistance. In bacteria, integrons, transposons, and plasmids harboring ARGs are accountable for horizontal gene transfer (HGT) between strains of the identical species and further species (Jian et al., 2021). *Escherichia coli* are responsible for acute urinary tract infection (UTI) in addition to urinary tract sepsis. It is the predominant uropathogen in both complicated and uncomplicated UTIs (Sood & Gupta, 2012; Lupindu, 2017). It is also associated with abscesses in multiple organ systems, sepsis, hemorrhagic colitis, and neonatal meningitis (Percival & Williams, 2014).

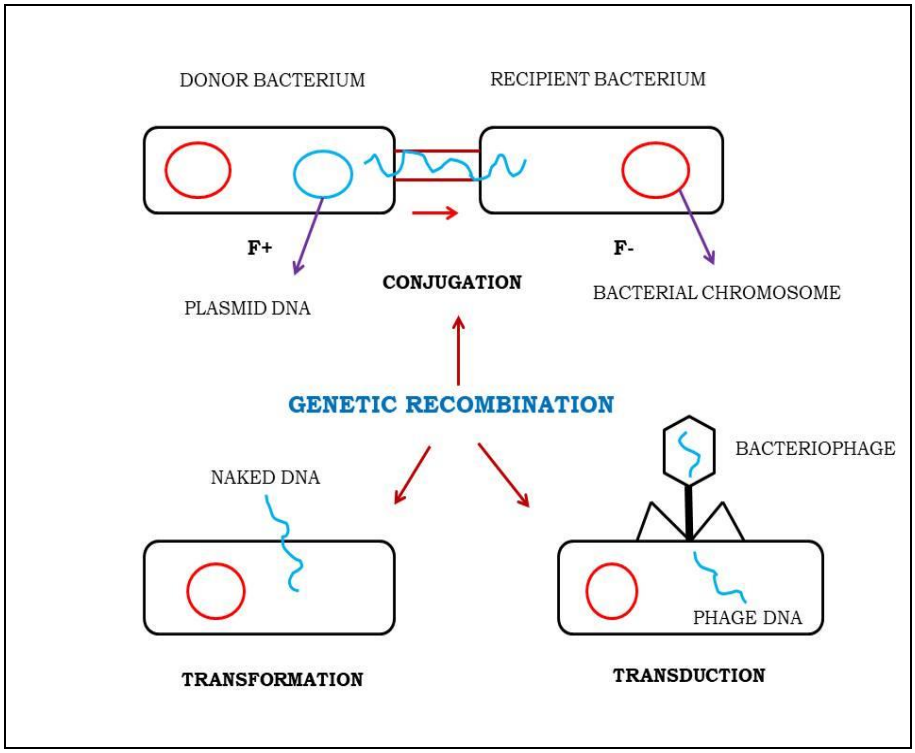

Fig. 1: Genetic recombination in bacteria through horizontal gene transfer (HGT).

AMR in *E. coli* is a universal problem in disease management. Drug resistance has progressively augmented against usually prescribed antibiotics. The multiple antibiotic resistance index (MARI) of an antibiotic indicates the susceptibility patterns of *E. coli*. The virulence factors in this pathogen are responsible for pathogenicity in *E. coli*-mediated ailments (Mandal et al., 2012; Prakash & Saxena, 2013; Guevara et al., 2015). Antibiotic resistance exhibited in plasmids, named drug-resistance (R) factors; usually also specify the development of sex pili, a filamentous appendage on the cell surface. The R factors are usually accountable for the epidemic feast of multiple drug resistances throughout a whole bacterial population (Stone, 1975). In this framework, several types of investigation have been conveyed concurrently in the research articles. A complete explanation is outside the scope of this analysis because the AMR in uropathogenic *E. coli* is irreplaceably covered by the current review. A brief account is summarized in this article regarding plasmid-mediated resistance with its remedial point of view.

FAMILY: ENTEROBACTERIACEAE

The family Enterobacteriaceae belongs to the domain Eubacteria under the order Enterobacteriales. This family contains more than 30 genera and 120 species. Ten genera and fewer than twenty-five species are responsible for more than ninety-five percent of the pathogenic relevant strains. The GI system of humans and other warm-blooded animals is the natural location for various members of the family Enterobacteriaceae (Rock & Donnenberg, 2014). The members of this family are gram-negative and characterized by facultative anaerobe, which means that they can thrive in both aerobic and anaerobic environments. The enteric bacteria are bacilli (rod-shaped), non-spore-forming, and normally 1–5 μm in length. Many species possess flagella and thus they are motile but little genera are non-motile. The members can produce acid and gas through the fermentation of lactose, glucose, and/or sucrose and are catalase positive, oxidase negative, and reducing nitrate to nitrite. Many are beneficial in human, animal, plant, and/or other pathogens that cause a variety of illnesses. Members of the Enterobacteriaceae have a wide range of uses, including bio-control in agriculture, the creation of several recombinant proteins and non-protein products, the prevention and treatment of infectious illnesses, the synthesis of anticancer medicines, the recycling of bio-waste, and bioremediation. (Octavia & Lan, 2014; Rogers, 2022).

HUMAN URINARY SYSTEM DISORDER

The human urinary system is affected by different reasons. An infection in the urinary tract is called UTI. It can also occur in different portions of the urinary system. The infection in the bladder and urethra is known as cystitis and urethritis (Flores-Mireles et al., 2015). According to Karlowsky et al. (2002), 150 million persons are affected by UTIs every year across the globe. Females are suffering more from UTI than males because of the structure of the urethra. Sexual activities are also considered a significant risk factor in this infection (Minardi et al., 2011). The clinical manifestations of the UTI are presented in Table 1 (Mayo Clinic, 2023).

Table 1: Clinical manifestations of UTI.

Sl. No.	Part of the Urinary System	Clinical Appearance	Symptoms
1.	Kidney	Acute pyelonephritis	High fever, back pain, nausea, and vomiting
2.	Bladder	Cystitis	Pain in the lower abdomen, feeling irritation during urination, and blood in the urine
3.	Urethra	Urethritis	Burning micturition and frequent urination

CULTURAL TECHNIQUES OF UPEC

Morning urine samples are collected in a 20 ml screw-capped pre-sterilized bottle. Mid-stream clean catch process is used for sampling. Boric acid (0.2 mg) is mixed to stop the growth of bacteria in the sample. The sample is analyzed within 6 hours after sampling. The total bacterial population in the sample is calculated on nutrient agar (NA) plates using the standard plate count (SPC) technique (Fig. 2). A calibrated loop of platinum wire (4 mm) is used for the streak plate technique on cysteine lactose electrolyte deficient (CLED) medium. Pure microorganisms at a concentration of $>10^5$ cfu/ml indicate a positive result. The Levine medium and MacConkey agar medium are used for the inoculation of Gram-negative bacteria including *E. coli* (Mandal et al., 2012; Prakash & Sexana, 2013; Rahman et al., 2014). Antimicrobial susceptibility of this paramount pathogen is accomplished by the Kirby-Bauer disc diffusion method in Mueller-Hinton (MH) agar (Sagar, 2022). The inoculated plate is placed in an incubator at 37 ºC for 24 hours. The zones of inhibition are determined and interpreted by clinical standards using *E. coli* ATCC 25922 strains as control. Multiple antibiotic resistance index (MARI) is calculated for antibiotic sensitivity and resistance using the formula 1. Antibiotic resistance is directly proportional to the index values (Sood & Gupta, 2012; Prakash & Sexana, 2013).

MAR index of antibiotic = number of antibiotic, resistant to the isolate / total number of antibiotics used × total number of isolates (1)

MORPHOLOGICAL AND BIOCHEMICAL PROPERTIES OF UPEC

As a member of the coliform group, *Escherichia coli* are a rod-shaped, non-spore-forming, Gram-negative bacterium that is typically motile by peritrichous flagella. It is a member of the Enterobacteriaceae family. They can ferment lactose at 37 ℃ to 44 °C. The bacteria can also grow on specific kinds of selective culture media and show color colonies. It has pink colonies on MacConkey agar plates. An *E. coli* culture that is positive will have a characteristic metallic green sheen when grown on an eosin methylene blue (EMB) plate (Fig. 2) (Paramesh et al., 2018). The biochemical characterization of *E. coli* for its identification is presented in Table 2 (Lehman, 2005; Lupindu, 2017; Batra, 2018). The monovalent O-antisera are used for serotyping of UPEC (Vranes et al., 2001).

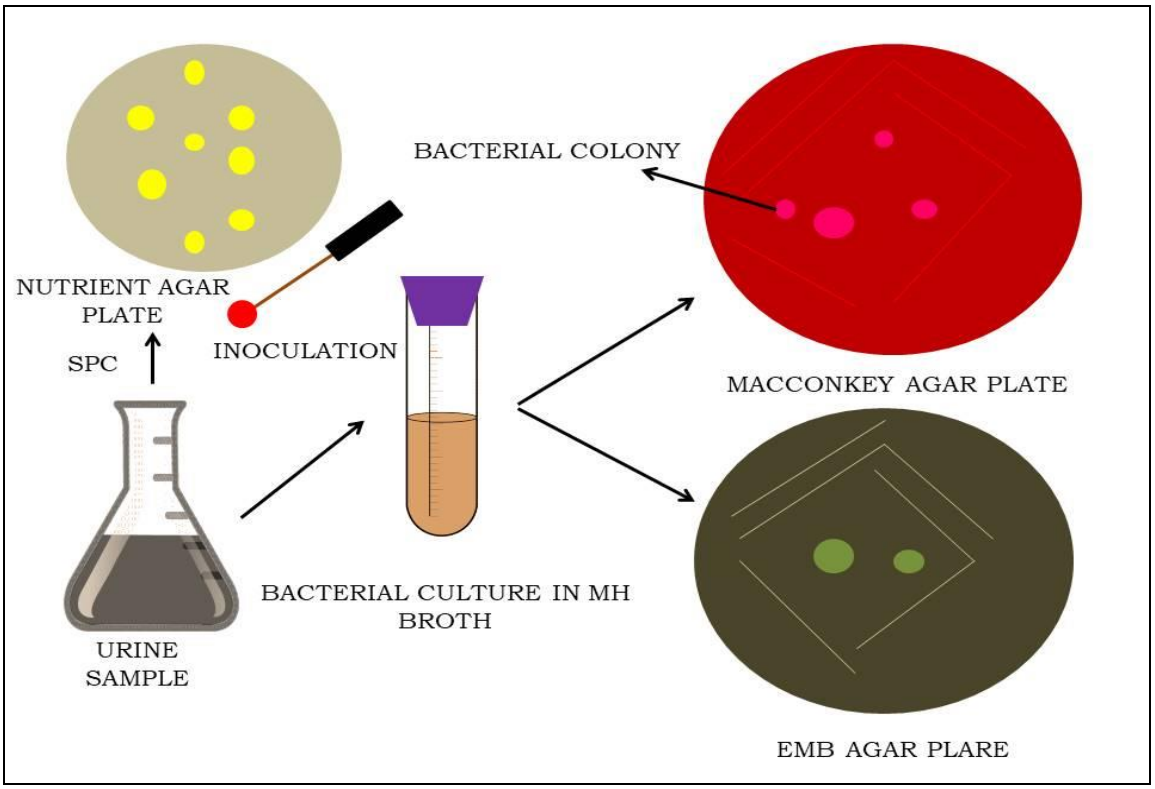

Fig. 2: Standard plate count (SPC), and inoculation with isolation of UPEC in selective media.

Table 2: Bio-chemical characterization of *Escherichia coli.*

Sl. No.	Name of the Test	Reaction
1.	Indole production	(+)
2.	Methyl red reaction	(+)
3.	Citrate utilization	(-)
4.	Voges – Proskauer test	(-)
5.	H_2S production	(-)
6.	Urease production	(-)
7.	Catalase production	(+)
8.	Oxidase production	(-)
9.	Nitrate reduction	(+)
10.	Lactose fermentation	(+)
11.	Glucose utilization	(+)
12.	Sucrose utilization	(+)

(+): Positive result; (-): Negative result

ANTIMICROBIAL DRUG RESISTANCE IN UPEC

The need for novel strategies based on fundamental biological research is driven by the increase of AMR in UPEC. AMR is a paramount health problem across the globe that is frequently evolving and differs spatially and temporally (McLellan & Hunstad, 2016). A study noted that all UPEC isolates displayed susceptibility to fosfomycin and nitrofurantoin, however, they are resistant to sulfamethoxazole (31.8%) and ciprofloxacin (15.9%) (Nüesch-Inderbinen et al., 2017). Spindola et al. (2018) reported that 98% of UPEC isolates have been recorded as MDR bacteria, and the maximum levels of resistance displayed against florfenicol, sulfonamides, ampicillin, and tetracycline. In this inquiry, these bacteria have also been classified into four phylogenetic groups such as B1 (34.4%), D (33.9%), E (30.1%), and A (1.6%). A study noted that AMR has indicated an extraordinary grade of resistance toward norfloxacin, ampicillin, and co-trimoxazole. The resistance has been perceived at a noteworthy higher grade in biofilm formers as related to non-formers (Shah et al., 2019). According to an investigation, UPEC isolates are sensitive to vancomycin (100%), imipenem (100%), and doxycycline (100%), but resistant to cefepime (100%) and cephalothin (74%). The genes hemolysin (*hlyA*), fimbriae type I (*fimH*), and aerobactin (*aer*) are the most pathogenic among these UPEC (Raeispour & Ranjbar, 2018). As the first line of treatment for pyelonephritis, the practice of amoxicillin-clavulanic acid is advised by the physician. Regional variations exist in the prevalence of amoxicillin-clavulanic acid resistance in UPEC. The pathogen has a degree of resistance to this antibiotic of 5.3% in Germany, while in France; the data has a level of 37.6%. However for the curing of uncomplicated cystitis, fosfomycin, and nitrofurantoin are advised as first-line therapies, and there is a little bit of resistance to these antimicrobial drugs (Kot, 2019). It is reported that UPEC is also resistant to ciprofloxacin, fosfomycin, trimethoprim-sulfamethoxazole and it was also an extended spectrum β-lactamase (ESBL)-producing strain (Behzadi *et al*., 2020). A study showed that 64.7% of UPEC isolates are resistant to cephalosporins. The next most resistant groups are to aminoglycosides (15.3%), β-lactams (13.3%), quinolones (7.8%), carbapenems (4.4%), trimethoprim-sulfamethoxazole (34%), and fluoroquinolones (31%) (Ghavidel et al., 2020). Javed et al. (2020) conveyed that 68% of UPEC are completely resistant to quinolones but sensitive to fosfomycin, imipenem, and colistin drugs. Out of that 92% of MDR UPEC exhibited generally resistant phenotype of fluoroquinolones, cephalosporins, sulfamethoxazole/trimethoprim, and aminoglycosides having 1-3 plasmids of more than 1kb length and 82% bearing class 1 integron genes. According to an analysis, tetracycline has the highest AMR rates of any antibiotic class (69.1%), followed by sulphonamides (59.3%), quinolones (49.4%), and beta-lactams (36.9%). Among the beta-lactams, high resistance has been witnessed for aminopenicillins (74.3%) and first-generation cephalosporins (38.8%) (Bunduki et al., 2021). No carbapenem-resistant UPEC isolates were discovered in Zeng et al.'s (2021) investigation; nevertheless, 62.25% and 42.38% of the strains were fluoroquinolone-resistant and MDR UPEC strains, respectively. The study is dominated by phylogenetic group B2 (58.94%), with phylogenetic group D (26.49%) following closely after. The most prevalent sequence type, ST1193 (25.83%), was initially identified in Shanghai, China. The majority ESBL genotype is *blaCTX*-M-14, followed by *blaCTX*-M-55. The percentage of ESBL-positive isolates is 39.74%. Most isolates that are resistant to fluoroquinolones contain mutations in their *gyrA* genes, which are then followed by *parC* and *parE*. Eighty-five percent of isolates with aminoglycoside resistance also contain the *aac (3) -IIa*. However, high incidences of multi-drug resistance, ESBL, Metallo β-lactamases, and AmpCs in UPECs have been conveyed in India (Ghosh et al., 2021). An additional investigation revealed that UPEC isolates had a high rate of resistance to tetracycline (92.86%), sulfonamide (71.43%), ampicillin (52.38%), trimethoprim-sulfamethoxazole (47.62%), and 28.57% to each of the antibiotics streptomycin, erythromycin, and chloramphenicol (Rahman et al., 2022). Furthermore, it has been observed that >70% of bacteria harbor the MDR ST131 plasmid-mediated resistance gene, which codes for the AAC(6')-Ib-cr enzyme that deactivates the fluoroquinolone group (FQ) drug ciprofloxacin (Phan et al., 2022).

VIRULENCE FACTOR FOR DRUG RESISTANCE

Plasmid-mediated quinolone resistance (PMQR) factors have been investigated in Tunisia using 300 UPEC isolates. PMQR genes are recognized in 22.7% of isolates including *aac (6')-Ib-cr*, *qnrB1*, *qnrA6*, and *qnrS1*. The gene *aac (6')-Ib-cr* is frequently found on IncF-type plasmids and is often connected with *blaCTX-M-15* (Sana et al., 2014). In UPEC, plasmid-assisted AmpC (pAmpC) and ESBL co-production are also observed. Of the 148 isolates found in the urine sample, 39.86% have been identified as UPEC, and 93.22% of them are cefoxitin-resistant. Twenty-five isolates were found to produce pAmpC, exhibiting a heterogeneous distribution of *blaCMY-2* and *blaDHA-1* type genes

either independently or in combination. ESBL co-production has been detected in 88% of pAmpC-producing isolates with *blaTEM* predominance. Twenty-three trans-conjugants displayed transmission of pAmpC-and ESBL-resistant genes with co-carriage of *blaCMY-2* and *blaTEM* in the plasmids of *IncF* type being predominant, followed by *IncI1* and *IncH1* in grouping (Ghosh & Mukherjee, 2016). According to reports, 50.0% of ciprofloxacin-resistant isolates had PMQR, 42.9% produced ESBL, and 51.4% had a β-lactamase inhibitor-resistant phenotype. It has been observed that *aac (6')-Ib-cr* co-occurs most frequently (37.1%) and co-transmits with *blaTEM*, *blaCTX-M*, and *blaOXA*. Replicon types *FrepB/FrepB+F1B* are the most common among the conjugal plasmids; *A/C, N, X, I1, FIIS, L/M,* and *H1* are sporadically found. It has been discovered that integrons, ISEcp1 and IS26, either singly or in combination, are disseminated independently of PMQR and ESBL gene types. Therefore, treatment problems for UPEC infections are hindered by co-resistance to fluoroquinolones and β-lactams (Basu & Mukherjee, 2018). According to a study by Zogg et al. (2018), among UPEC, the azithromycin resistance gene *mph(A)* (20.3%), the plasmid-facilitated fluoroquinolone resistance genes *aac (6')-Ib-cr* (26.6%), and *qnrB* (1.6%) have been found often. The frequency of O-antigen serogroup and quinolone-resistance plasmid genes among UPEC, isolated from kidney transplant patients (KTPs) and non-KTP with UTI in Iran, has been investigated by Sadeghi et al. (2020). The investigation's results indicates that the O1, O2, O4, O16, and O25 serogroups are dispersed at rates of 3.5%, 2.6%, 3.5%, 3.5%, and 20.2%, in that order. Antibiotic susceptibility patterns showed that norfloxacin (43.9%) and nalidixic acid (69.3%) had the lowest and highest resistance rates, respectively. The prevalence of the *qnrA* gene was not found in any isolates, although the *qnrS* and *qnrB* genes are present in 33.3% and 15.8% of patients, respectively. The presence of *qnr* genes did not appear to be associated with increased antibiotic resistance. Muriuki et al. (2022) found that *blaCTX-M* (95.6%), *blaTEM* (95.6%), and *blaSHV* (21.7%) genes were discovered in 24% of UPEC isolates from Kenya that are ESBL producers. While five isolates have *blaTEM/CTX-M/SHV*, sixteen isolates have *blaCTX-M/TEM*. Of the twenty-three isolates that produce ESBLs, five are resistant to cefoxitin; nonetheless, the *AmpC* gene remains unidentified. The majority of UPECs are found in phylogenetic groups D (31.6%) and B2 (32.6%), whereas groups B2 and A include the greatest number of ESBL producers.

FUTURE VISION FOR MONITORING OF UPEC

Global healthcare systems are extremely concerned about the onset and quick spread of AMR in bacterial pathogens along with the advent of unique MDR strains of disease-causing microorganisms. As a result, the plant extract's antibacterial characteristics may offer a significant therapeutic alternative to traditional medications (Parveen & Some, 2021). The antibacterial effects of cranberry (*Vaccinium macrocarpon*) and propolis could decrease the incidence of UTIs and the emergence of AMR. Cranberry is a splendid origin of polyphenols as phenolic acids and flavonoids and has beneficial effects against UPEC-mediated UTI. Therefore flavonoid is considered a natural antibiotic (Ranfaing et al., 2018; González de Llano et al., 2020). Sarshar et al. (2018) conveyed that the fruit decoction of *Apium graveolens* (Celery) has been traditionally used in European and Persian drugs to treat uncomplicated UTIs. The secondary metabolites of this plant have an excellent anti-adhesive and anti-quorum sensing effect against UPEC. It was also noted that phthalides are the main bioactive compounds in *Apium graveolens* fruit extract, and have wonderful anti-biofilm activity against UPEC (Grube et al., 2019). It has been reported that the cranberry bioactive compound, proanthocyanins (PACs) may act as wonderful anti-virulence approach for the treatment through down-regulation of the *CTX-M* gene that causes ESBL production by UPEC strain CTX-M_{15} (Samarasinghe et al., 2019). It was noted that the volatile oil of *Rosmarinus officinalis*, *Thymus zygis*, and *Origanum majorana* exhibited excellent antibacterial effects against UPEC. Additionally, the oils had remarkable biofilm inhibitory exploit, with percentages of inhibition ranging from 14.94 to 94.75. The anti-biofilm activity of *R. officinalis* oil was highest, followed by *T. zygis* and *O. majorana* (Lagha et al., 2019). A study noted that polymethoxylated flavones in the leaf extract of *Orthosiphon stamineus* abridged the gene expression of *csgA*, *focG*, *fimH*, *fimC*, and *fimD* which are strongly deployed for the establishment of UPEC-facilitated adhesion in the urinary bladder (Deipenbrock & Hensel, 2019). The leaf extract of *Orthosiphon stamineus* has been extensively used as traditional medicine in Asia and Europe for the curing of complicated and uncomplicated UTIs. The aqueous leaf extract inhibited the gene expression of multiple iron-acquisition systems (*fep*, *ent*, *feo*, *chu*, *fhu*, *sit*, *ybt*) (Beydokhti et al., 2019). Crude polysaccharides in the aqueous seed extract of *Vaccaria segetalis* have been traditionally used in China for the treatment of benign prostatic hyperplasia (BPH) and UPEC-mediated cysto-urethritis (Mao et al., 2020). Probiotics like *Bifidobacterium* and *Lactobacillus* are valuable microorganisms that may perform by the competitive exclusion principle to protect against infections in the urogenital tracts (Das, 2020). Rutin and saponins are predominant bioactive compounds in *Phaseaoli pericarpium* and exhibited wonderful anti-adhesive activity in UPEC-mediated cystitis (Popowski et al., 2021). Extract of *Orthosiphon stamineus* leaves (Java tea) is also traditionally used for the curing of UTI. The bioactive compound polymethoxylated flavones, rosmarinic acid, cichoric acid, and caffeic acid in Java tea extract showed excellent anti-adhesive activity against UPEC (Deipenbrock et al., 2021). Silver nanoparticles (AgNPs) or metallic nanosilver can be suitable for the management of UPEC contagions due to their excellent physico-biochemical properties that

discuss their antibacterial action against biofilm formers. A study noted that the minimum inhibitory concentration (MIC) of biomolecule functionalized metallic nanosilver on planktonic UPEC cells is 25 mg/ml, however a sub-MIC concentration (7.5 mg/l) is enough to inhibit the UPEC-biofilm creation of about 97%, or produce the interference of an 80% of mature UPEC-biofilms representing the potential of fungal-derived metallic nanosilver to inhibit UPEC infections (Rodríguez-Serrano et al., 2020). The plausible mechanism and mode of action of bioactive compounds and AgNPs against MDR bacteria are presented in Fig. 3. AgNPs generate reactive oxygen species (ROS) and free radicals within the cell which may damage the plasma membrane, ribosome functions, and nucleic acids and also activate the inhibition of cell proliferation of MDR UPEC (Some et al, 2021a). The bioactive compounds become also prolific against MDR UPEC via inhibiting cell wall, protein, and nucleic acid synthesis or disrupting the cell-membrane (Parveen & Some, 2021).

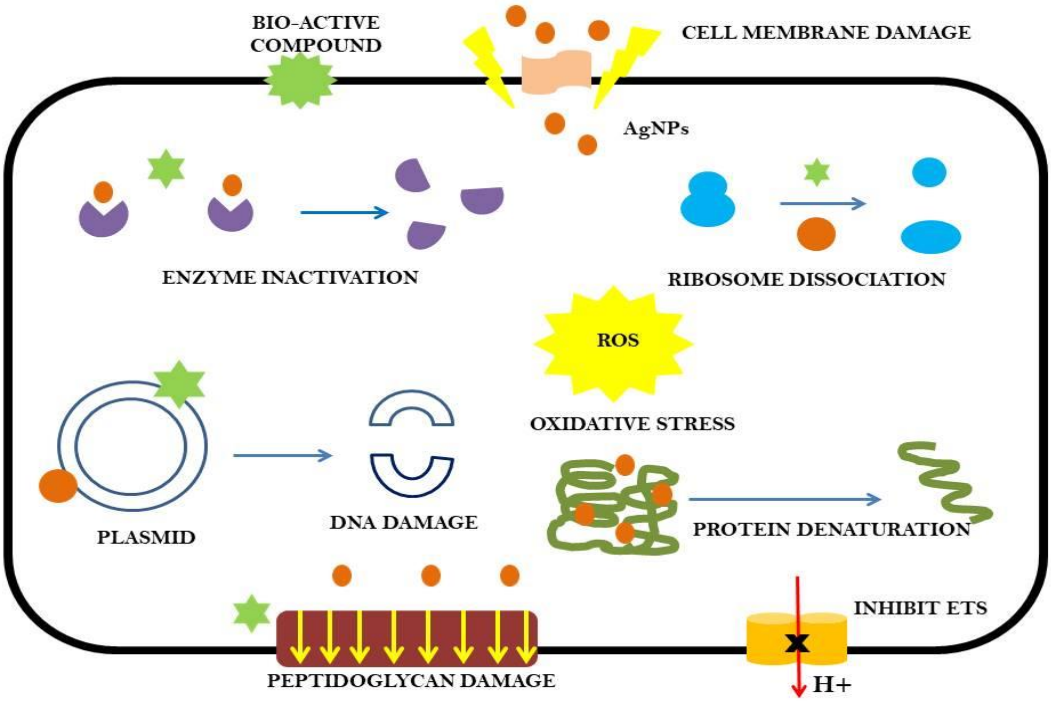

Fig. 3: Antimicrobial activity of bioactive compounds and silver nanoparticles.

Another study showed that the amalgamation of *Butea monosperma* seed lectin (BMSL) with AgNPs results in effective surface-functionalized AgNPs with an outstanding anti-biofilm capability against UPEC. It has been recorded that metallic nanosilver and the biogenic BMSL-metallic nanosilver conjugate (B-AgNP) have a minimum biofilm inhibitory concentration of 75 and 9.37 µM against UPEC, respectively. B-AgNPs exhibit anti-biofilm activity as well as anti-microbial bustle at 18.75 µM, which is four times lower than the MIC of metallic nanosilver (Bala Subramaniyan et al., 2020).

CONCLUSION

One of the most prevalent medical conditions, UTI afflicts daily patients in a regular family care practice. The majority of the time, an antibiotic is prescribed, and this practice is probably causing an increase in antibiotic resistance globally. Clinicians must identify their local bacterial resistance trends and antibiograms, correctly diagnose and treat UTIs when necessary, and understand their responsibility for antibiotic stewardship to assist address this issue. With attention to the improvement of vaccines and small-biomolecule inhibitors affecting virulence factors, numerous alternative approaches are being pursued both the anticipation and treatment of UTIs with the hope of reducing the burden of urogenital tract infections while minimizing the use of antibiotics. The epidemiological study on UPEC showed a robust link between multidrug resistance and the existence of class 1 integron. Multiple plasmid bands and a high incidence of class 1 integrons in MDR UPEC strains suggest that plasmids and integrons perform a key role in the horizontal communication of ARG among the species. Further investigation is immediately required to explain the mechanism of resistance, aspect for new goals for anti-microbial drugs, determine more operative ways for using our current drugs, and diminish the expansion of resistance, to launch the most convenient treatment for infection due to MDR organisms and to learn how to avert this infection. This is an important challenge in this millennium.

Author's Contribution

SS designed the concept. DB and SS have contributed equally to writing the final version of the MS.

Conflict of Interest

The authors declare that they have no conflict of interest.

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None.

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