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REVIEW ARTICLE

Uropathogenic *Escherichia coli* in India—an Overview on Recent Research Advancements and Trends

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Abstract

Urinary tract infection (UTI), a prevalent disease in India, also ranks among the most common infections in developing countries. The rapid emergence of antibiotic-resistant uropathogenic *Escherichia coli* (UPECs), the leading etiologic agent of UTI, in the last few years, led to an upsurge in the health care cost. This caused a considerable economic burden, especially in low-middle income country, India. This review aimed to provide an explicit overview of the recent advancements in *E. coli*–mediated UTI in India by incorporation of valuable information from the works published in PubMed and Google Scholar in the last six years (2015 to August, 2020). The literature survey demonstrated UPECs as the most predominant uropathogen in India, especially among females, causing both asymptomatic bacteriuria (ABU) and symptomatic UTI. An overall increasing national trend in resistance to penicillins, cephalosporins, aminoglycosides, fluoroquinolones, and sulfonamides was perceived irrespective of ABU and symptomatic UPECs during the aforementioned study period. High incidences of multidrug resistance, extended-spectrum β-lactamases, metallo β-lactamases, and AmpCs in UPECs were reported. Notable information on the pathogenic profiles, phylogroups, pathogenicity islands, and evidence of pathoadaptive FimH mutations was described. Alternative therapeutics and potential drug targets against UPECs were also reconnoitered. Therefore, the nationwide widespread occurrences of highly virulent MDR UPEC together with the limited availability of therapeutics highlighted the urgent need for promotion and invention of alternative therapeutics, search for which had already been started. Moreover, investigation of several mechanisms of UPEC infection and the search for potential drug targets might help to design newer therapeutics.

Keywords Uropathogenic *Escherichia coli* · Urinary tract infection, multidrug resistance · Alternative therapeutics · India

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Introduction

Escherichia coli (*E. coli*) was the most common cause of all forms of urinary tract infections (UTIs) that included symptomatic infections as well as asymptomatic bacteriuria (ABU), over the last few years in India [1–4]. UTIs, caused by uropathogenic *E. coli* (UPECs), although more prevalent in women mainly due to their anatomy (shorter urethra), were found to be a significant cause of hospital visits for people of all ages and both genders [3, 5].

Multidrug-resistant variants of UPECs with either inherited or transmissible resistance were on the rise for the last few years in India [4, 6, 7]. Moreover, infections caused by the aforementioned resistant UPEC strains were the leading cause of mortality in India as well as in the rest of the world [8–12]. India had witnessed a dramatic increase in resistance to several groups of antibiotics like penicillins, cephalosporins, aminoglycosides, quinolones/fluoroquinolones, and sulphonamides in the last decade [2, 3, 9, 13]. However, the patterns of antibiotic resistance with respect to one or more antibiotics of the same or different groups showed considerable intra [2, 14–16] and inter-regional difference [1–3, 17].

Incidence of extended-spectrum β-lactamase (ESBL) [4, 6, 7, 17–19], metallo β-lactamase (MBL) [4, 20], and AmpC producers [4] among MDR UPECs had also been on the rise in the last few years. The increasing trend of MBL and AmpC producers among MDR variants of UPECs in a resource-poor country India was highly alarming as, in addition to other groups of antibiotics, MBL and AmpC producers were also found to be resistant to carbapenems and/or β-lactamase inhibitors, unlike the ESBL producers. Thus, infections caused by these MDR UPECs are increasingly becoming very difficult to treat and this might lead to a therapeutic dead-end in the future. Earlier reports [9, 14] stated that several factors are responsible for the dissemination of antimicrobial resistance genes in UPECs and among them, the plasmid-mediated transfer is the most important mechanism for the horizontal transfer of multidrug resistance.

Several studies conducted in the recent past suggested that colonization of UPECs in the human urinary bladder for the establishment of UTI is mediated by the usage of several virulence factors like adhesins (type 1 fimbriae, P fimbriae, and S fimbriae), flagellin, lipopolysaccharides, and secreted virulence factors (α-hemolysin, cytotoxic necrotizing factor, secreted auto-transporter toxin) [2, 7, 11, 12]. Moreover, Miryala et al. [19] and Rubini et al. [11] stated that the type I pili adhesion is an important event in the pathogenesis of UPECs that also helps in biofilm formation which is considered a universal and the most effectual strategy adopted by UPECs for survival [7]. Likewise, earlier reports [1, 21–24] also advocated the fact that biofilm production in UPECs promotes bladder colonization, thereby leading to an increase in the rate of UTIs, and such infections might be difficult to treat as they display MDR. Furthermore, earlier studies also characterized asymptomatic [2, 25] and symptomatic [2] UPECs, with their phylogenetic background and distribution of pathogenicity islands (PAIs).

India saw the emergence of MDR UPEC strains, an increase in ESBL-, MBL-, and AmpC-producing UPEC strains and a high incidence of UPEC biofilm formers in the last few years. This shifted the attention of clinicians and researchers to several alternative therapeutic options [3, 10, 11, 21, 24, 26–28], which might help to cope with the upcoming therapeutic limitations and combat the spread of MDR UPECs. Therefore, this review aimed to provide an overview of recent advancements in UPEC-mediated UTI, in a resource-poor country like India.

Evidence Acquisition and Synthesis

An extensive literature hunt was performed using the electronic databases, PubMed and Google Scholar from 2015 to 2020 (last 6 years), using the following keywords: uropathogenic *Escherichia coli* and India in association with urinary tract infections in humans, multidrug resistance, pathogenicity, and therapeutics. Database search for articles of the year 2020 was restricted until the month of August. Articles written in English were considered in this review. Preprints were not considered in this review. Statistical significance of the data collected was analyzed using Prism software package (GraphPad Prism version 9) [29] and also further validated using SPSS version 21.0 (SPSS Inc., Chicago, IL, USA) [2, 30]. The correlation coefficient [29, 30] was determined to find the degree of association between different states (variables) of India with respect to the incidence of urine culture–positive symptomatic *E. coli* and their resistance against different antibiotics. Heat maps were constructed from the correlation matrices using the GraphPad Prism version 9 (GraphPad Software, La Jolla California USA) [29]. However, correlation coefficient values < 0.2 were found to be statistically insignificant according to SPSS version 21.0 software package. Moreover, values < 0.2 are considered a negligible or poor correlation [31]. Therefore, correlation coefficient values < 0.2 were not considered when ascertaining the highest and lowest correlations.

Incidence of *Escherichia coli* in Urine Culture–Positive Samples Isolated from Individuals with Symptomatic UTI or ABU

Escherichia coli (*E. coli*) is one of the most prevalent pathogen liable for more than 80% of all urinary tract infections (UTIs) and can cause both asymptomatic bacteriuria (ABU) and symptomatic UTI [2]. Results from the literature search also revealed that *E. coli* was one of the predominant uropathogen of this era responsible for symptomatic UTI in people residing in different states of India (Table 1).

Moreover, a statistically significant positive correlation that ranged from low to very high with p values ≤ 0.05 was observed in the incidence of urine culture–positive symptomatic *E. coli* among 14 different states during the time period (2015–2020). Two different Indian states and/or union territories between which the highest correlation with respect to the incidence of symptomatic UPECs was observed were Bihar (2015) [BH' 15]; Kerala (2017) [KL' 17], Andhra Pradesh (2016) [AP' 16]; Tamil Nadu (2019—1st) [TN' 19 (1)], Madhya Pradesh (2017) [MP' 17]; West Bengal (2018—1st) [WB' 18 (1)], Delhi (2017) [DL' 17]; Tamil Nadu (2019—2nd) [TN' 19 (2)], Kerala (2018) [KL' 18]; West Bengal (2019—3rd) [WB' 19 (3)], Maharashtra (2019) [MH' 19]; Chandigarh (2019) [CG' 19], West Bengal (2019—2nd) [WB' 19 (2)]; Telangana (2020) [TL' 20], Uttar Pradesh (2019) [UP' 19]; Delhi (2019) [DL' 19], Himachal Pradesh (2019) [HP' 19]; Delhi (2017) [DL' 17] and Tamil Nadu (2019—2nd); and Bihar (2015) respectively. Furthermore, three different Indian states and/or union territories among which the highest correlation was observed were Odisha (2016) [OD' 16]; Uttar Pradesh (2019) [UP' 19]; Delhi (2019) [DL' 19], West Bengal (2016) [WB' 16]; Kerala (2018) [KL' 18]; West Bengal (2019—3rd) [WB' 19 (3)], Kerala (2017) [KL' 17]; Bihar (2015) [BH' 15]; West Bengal (2018—1st) WB' 18 (1)], West Bengal (2018—1st) [WB' 18 (1)]; Madhya Pradesh (2017) [MP' 17], West Bengal (2018—2nd) [WB' 18 (2)]; West Bengal (2019—2nd) [WB' 19 (2)]; Telangana (2020) [TL' 20], Haryana (2018) [HR' 18]; Maharashtra (2019) [MH' 19]; Chandigarh (2019) [CG' 19] and West Bengal (2019—1st) [WB' 19 (1)];

Table 1 Incidence of *Escherichia coli* in urine culture–positive isolates obtained from urinary tract infected patients from different Indian states during the years 2015–2020

Sl. no.	*E. coli* (%)	Union territory/state of report	Reference
1	50	Bihar	[32]
2	26.3	Andhra Pradesh	[37]
3	21.37	Odisha	[36]
4	39.9	West Bengal	[13]
5	45.4	Manipur	[34]
6	48.9	Kerala	[35]
7	56.22	New Delhi	[44]
8	67.5	West Bengal	[42]
9	46.15	West Bengal	[52]
10	37.45	Kerala	[45]
11	76.60	Haryana	[43]
12	32.26	West Bengal	[2]
13	75	Maharashtra	[3]
14	70.1	West Bengal	[14]
15	22.01	Uttar Pradesh	[41]
16	74.95	Chandigarh	[8]
17	21.5	New Delhi	[48]
18	25.93	Tamil Nadu	[15]
19	59.8	Himachal Pradesh	[19]
20	38	West Bengal	[9]
21	54.29	Tamil Nadu	[16]
22	69.9	Telangana	[17]

Kerala (2018) [KL' 18]; and West Bengal (2019—3rd) [WB' 19 (3)] respectively. However, 10 (Bihar (2015) [BH' 15], Delhi (2017) [DL' 17], West Bengal (2018—2nd) [WB' 18 (2)], Haryana (2018) [HR' 18], Maharashtra (2019) [MH' 19], West Bengal (2019—2nd) [WB' 19(2)], Chandigarh (2019) [CG' 19], Himachal Pradesh (2019) [HP' 19], Tamil Nadu (2019—2nd) [TN' 19 (2)], and Telangana (2020) [TL' 20]) and 12 (Andhra Pradesh (2016) [AP' 16], Odisha (2016) [OD' 16], West Bengal (2016) [WB' 16], Madhya Pradesh (2017) [MH' 17], Kerala (2017) [KL' 17], West Bengal (2018—1st) [WB' 18 (1)], Kerala (2018) [KL' 18], West Bengal (2019—1st) [WB' 19 (1)], Uttar Pradesh (2019) [UP' 19], Delhi (2019) [DL' 19], Tamil Nadu (2019—1st) [TN' 19 (1)], and West Bengal (2019—3rd) [WB' 19 (3)]) different states and/or union territories were found to show their lowest correlation with Odisha (2016) [OD' 16] and Haryana (2018) [HR' 18] respectively (Fig. 1).

Furthermore, a remarkable incidence of *E. coli* was also reported in urine culture–positive samples isolated from the asymptomatic individuals besides the symptomatic ones [2, 25]

Age-Sex Parameter in Relation to UPECs

Reports from several Indian states like Haryana, Bihar, Jharkhand, West Bengal, Kerala, Tamil Nadu [2, 7, 15, 16, 20, 23, 32], and Karnataka [1] indicated a higher prevalence of female and male respectively among patients affected with *E. coli*–mediated symptomatic UTI. However, a study [2] from West Bengal conducted on asymptomatic UPECs proclaimed equal incidence of male and female individuals.

Moreover, Mittal et al. [22] and Karigoudar et al. [1] revealed that the maximum age group affected by symptomatic UPECs among both male and female patients was 21–30 years. However, Ghosh et al. [2] indicated the mean age as 48.2 years (range 7–82 years) among the

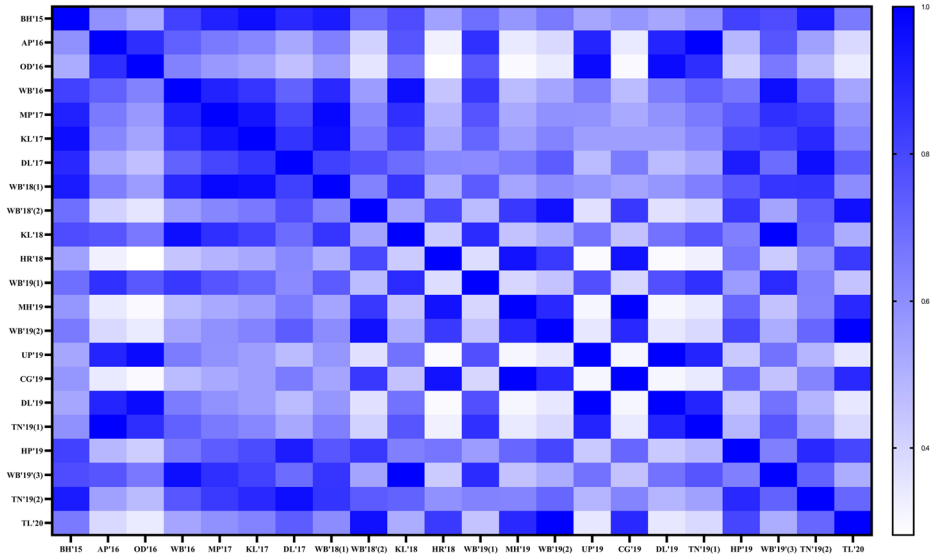


Fig. 1 Statistical significance of the incidence of symptomatic UPEC in the different Indian states was analyzed by GraphPad Prism version 9 (Prism software package). Heat maps were generated on the correlation coefficient values represented by the color keys that ranged from zero (white) to 1 (deep blue)

hospitalized individuals affected by symptomatic UPECs. Nonetheless, a study [32] found the mean age of their population as 33.1 years, though the mean age of the male and female population was 43.3 and 31.1 years respectively. Nevertheless, another study [15] conducted on symptomatic UPECs reported a higher prevalence of females and males in the age group 21–30 and 31–40 years respectively. Withal, Muraleetharan et al. [16] showed a higher prevalence of symptomatic UPECs above 35 years of age among both the affected males and females. Furthermore, studies by Mukherjee et al. [25] and Ghosh et al. [2] from West Bengal showed the mean age as 25.14 years (18–38 years) and 44.8 (22–82 years) respectively among individuals with ABU *E. coli*.

UPECs in Pregnant Females

A study from West Bengal [25] reported a remarkable incidence of *E. coli* in urine culture–positive samples isolated from the asymptomatic pregnant females

UPECs' Drug Resistance Pattern Nationwide

Antibiotic resistance in UPECs and the dissemination of the MDR UPECs is presently a global public health problem [5]. Moreover, the increasing frequency of MDR UPECs, especially in a developing country like India in the last few years, resulted in the increase in the cost of treatment and hospitalization. The literature search indicated resistance of UPECs to different groups of antibiotics.

Resistance to β-Lactam Antibiotics

At present, resistance of symptomatic UPECs to penicillin, aminopenicillin, and **antipseudomonal penicillin** groups of antibiotics is immensely high, especially to aminopenicillins (ampicillin and amoxicillin) and **antipseudomonal penicillin like** carbenicillin [1, 3, 15, 23, 24, 33–35]. Moreover, a study by Pullanhi et al. [7], during a period of 1 year, indicated a very high level of resistance of UPECs to aminopenicillin (amoxicillin) and **antipseudomonal penicillin (**piperacillin), even when used in combination with clavulanic acid (β-lactam inhibitors).

Moreover, literature search revealed that resistance to cephalosporins, especially to first and third generations, was moderate to [33, 36] extremely high among symptomatic UPECs [1, 2, 4, 9, 13, 16, 37–40]. Furthermore, studies by Mukherjee et al. [25] and Ghosh et al. [2] reported moderate and extremely high resistance, respectively, of asymptomatic UPECs to third-generation cephalosporins. However, Kammili et al. [17] and Vasudevan et al. [24] reported moderate resistance to second- and third-generation cephalosporins (cefuroxime and cefotaxime). A study [6] showed a significant increase in cephalosporin resistance of symptomatic UPECs from 51 to 58% over a period of 5 years (2013–2017). High resistance of symptomatic UPECs to cephalosporins was observed even when used in combination with β-lactam inhibitors [1, 23].

Presently, resistance of both asymptomatic [2, 25] and symptomatic UPECs [1–4, 7, 16, 33, 34, 39–41] to carbapenems (imipenem and/or meropenem) is quite low. Moreover, Kammili et al. [17] stated that none of the UPECs tested were resistant to meropenem. However, other studies [23, 42] showed much higher resistance against imipenem and meropenem in their population. Withal, a report by Prasada et al. [6] revealed an increasing trend in carbapenem resistance in symptomatic UPECs from 0 to 5.9% over a period of 5 years (2013–2017).

UPECs as ESBL Producers

β-Lactam antibiotics are one of the most commonly used antibiotics for the treatment of *E. coli*–mediated UTI. *E. coli* has developed a particular resistance mechanism for inactivation of the β-lactam groups of antibiotics by the production of ESBL enzymes. ESBL-producing *E. coli* have been known to be capable of hydrolyzing all penicillins, cephalosporins (first to third generations), mainly oxyimino cephalosporins, and monobactams. However, ESBLs are inhibited by β-lactamase inhibitors such as tazobactam, sulbactam, and clavulanic acid. However, over the past 6 years, low [37], moderate [6, 7, 19], and high incidence [4, 17, 43] of ESBL producers among the symptomatic UPECs was found from Andhra Pradesh; Karnataka, Kerala, and Himachal Pradesh; and Pondicherry and Telangana respectively. Moreover, a report by Prasada et al. [6] from Karnataka indicated an increase in the rate of ESBL production from 45.2 to 59.6% during the years 2013–2017.

Resistance to β-Lactam-β-Lactamase Inhibitors

Low to a high level of resistance to β-lactamase inhibitors like tazobactam, sulbactam, and clavulanic acid was observed among symptomatic UPECs [1, 6, 23, 34, 40]. Diversity in symptomatic UPECs' response to two different β-lactamase inhibitors was reported by

Karigoudar et al. [1] that showed very high and moderately low resistance against clavulanic acid and sulbactam respectively when used in combination with amoxicillin and piperacillin. However, Kammili et al. [17] reported similitude in UPECs' response to different β-lactamase inhibitors. The aforementioned study showed an extremely low level of resistance to both the β-lactamase inhibitors: clavulanic acid and tazobactam when used in combination with amoxicillin and piperacillin respectively. Moreover, Prasada et al. [6] specified an increasing (9.4 to 23%) trend in resistance to β-lactamase inhibitors over the 5 years duration. Furthermore, the same study revealed an overall increase (5.6 to 9.04%) and a decrease (33 to 31%) in resistance to sulbactam when used in combination with cefoperazone and ampicillin respectively over the aforementioned period; however, the trends were inconsistent.

UPECs as MBL Producers

MBL-producing *E. coli* are known to hydrolyze a broad range of β-lactam antibiotics that includes penicillins, cephalosporins, carbapenems, cephamycins, and even certain β-lactamase inhibitors (clavulanate, tazobactam, and sulbactam). However, they are found to be sensitive to aztreonam (monobactam). Over the last 6 years, low incidence of MBL producers was observed among symptomatic MDR UPECs in Haryana and Pondicherry [4, 20].

UPECs as AmpC Producers

E. coli AmpC producers are known to be capable of hydrolyzing penicillins, broad and extended-spectrum cephalosporins (first to third-generation), cephamycins, and β-lactamase inhibitors, but are found to be sensitive to fourth-generation cephalosporins and carbapenems. Moderate incidence of AmpC producers among symptomatic MDR UPECs has been reported in four (Haryana, West Bengal, Jharkhand, Pondicherry) different states or union territories of India, over the last 6 years [2, 4, 20, 23].

Co-production of ESBL, MBL, and AmpC in UPECs

Low to very high incidence of AmpC and ESBL co-production was observed in two different studies conducted in two different states (Haryana, West Bengal) [13, 20]. Moreover, a study Gopichand et al. [4] performed on samples collected over a period of 1 year (2016–2017) from Pondicherry revealed the incidence of co-production of ESBL, MBL, or AmpC among MDR UPECs.

Resistance to Other Cell Wall Synthesis Inhibitors

A high level of resistance to different cell wall inhibitors like fosfomycin, vancomycin, and bacitracin was observed among symptomatic UPECs [8, 15]. Moreover, Kaza et al. [8] revealed the prevalence of polymyxin like colistin (an antibiotic regarded as the last resort for MDR gram-negative bacteria) resistance (3.52%) among MDR UPECs. However, Singh et al. [23] found 100% sensitivity against colistin. Nonetheless, [4, 22] reported the incidence

of 100% fosfomycin sensitivity among highly MDR (UPECs), which included ESBL, carbapenemase, and/or AmpC producers.

Resistance to Aminoglycosides and Tetracyclines

Varied pattern of resistance of symptomatic UPECs to different aminoglycosides was observed since the last 6 years. Several studies reported a very low level of resistance to aminoglycosides: amikacin, kanamycin tobramycin, or streptomycin [7, 15–17, 24, 32–34, 44]. Moderate to a moderately high level of resistance of symptomatic UPECs against amikacin, gentamicin, kanamycin, or neomycin was also reported by various other studies [1–3, 13, 36–38, 45]. However, Gopichand et al. [4] indicated a low and very high level of resistance to two (amikacin and gentamicin respectively) different antibiotics of the aminoglycoside class. A report by Prasada et al. [6] indicated a decreasing (8.8 to 6.5%) trend in resistance to aminoglycoside netilmicin from 2013 to 2017. However, the same study reported an overall increase in gentamicin resistance from 31 to 34% over a period of 5 years. Studies conducted [2, 25] on asymptomatic UPECs reported low and moderate to moderately high level of resistance, respectively, to different antibiotics of the aminoglycoside group.

Kaza et al. [8] proclaimed susceptibility of UPECs towards tetracycline. However, a study by Gnanasekaran et al. [15] revealed an extremely high level of resistance of UPECs to tetracyclines.

Resistance to Macrolides and Chloramphenicol

A high level of resistance to macrolide (erythromycin) was reported in the recent past [15]. However, another study [3] indicated a low level of resistance to chloramphenicol.

Resistance to Quinolones/Fluoroquinolones

Resistance to first-generation quinolones/fluoroquinolones had been very high for the last few years among symptomatic UPECs [1, 15, 17, 24, 37, 41] except a study by Muraleetharan et al. [16] that reported moderate resistance against nalidixic acid, a first-generation quinolone. However, the resistance of asymptomatic [2, 25] and symptomatic [1, 2, 4, 13, 15, 23, 24, 32–34, 37, 38, 40, 41] UPECs to second-generation fluoroquinolones, i.e., ciprofloxacin, levofloxacin, and norfloxacin, was found to be very high for the last 6 years. Though a study by Wabale et al. [33] found a very low level of resistance against ciprofloxacin in their population, another report [6] stated a statistically significant rise (48 to 64%) in resistance to second-generation fluoroquinolone, i.e., norfloxacin, over a period of 5 years (2013–2017).

Resistance to Sulfonamides

Varied level of resistance of asymptomatic and symptomatic UPECs to sulfonamides like trimethoprim, cotrimoxazole, and trimethoprim/sulfamethoxazole had been observed for the last 6 years. Several studies reported low [24], moderate [1, 17, 36, 37], and high incidence [2,

3, 8, 13, 15, 23, 25, 32, 33, 38] of sulfonamide-resistant symptomatic UPECs. Moreover, Ghosh et al. [2] also reported a high incidence of sulfonamide-resistant asymptomatic UPECs. Furthermore, two studies [6, 44] reported a rising trend (35.5 to 63.3% and 52 to 59%) in resistance to cotrimoxazole during the time period of 2009–2014 and 2013–2017 respectively.

Resistance to Nitrofurans

Resistance to nitrofurans group of drugs like nitrofurantoin (synthetic drug) was found to be very low since 2015 among both asymptomatic [2, 25] and symptomatic [1, 2, 4, 7, 13, 17, 32, 37, 41] UPECs, except a study by Wabale et al. [33] that reported incidence of moderate nitrofurantoin resistance in symptomatic UPECs. Another study [15] reported 100% sensitivity of the tested symptomatic UPECs. However, Prasada et al. (2019) [6] reported an overall rise (12.8 to 13.3%) in resistance to nitrofurantoin from 2013 to 2017.

Multidrug Resistance in UPECs

Low [7, 8, 32], moderate [17, 33, 36], and very high [2, 16, 22–24, 41] levels of MDR were observed among the symptomatic UPECs from various union territories or states of India like Chandigarh, Kerala, Telangana, West Bengal, and Tamil Nadu respectively. Moreover, moderate [25] and extremely high [2] levels of MDR among asymptomatic UPECs were reported especially from Kolkata, West Bengal.

Trends in UPECs' Antibiotic Resistance Nationwide

India was broadly divided into six zones mainly North, South, East, West, Central, and Northeast zone. Antibiotic resistance trends of asymptomatic and symptomatic UPECs over the last 6 years in different regions/states of India were illustrated in Fig. 2a and b respectively.

A rise in resistance of asymptomatic UPECs to third-generation cephalosporins (cefotaxime and ceftazidime), aminoglycoside (amikacin), second-generation fluoroquinolone (ciprofloxacin), and sulfonamide (cotrimoxazole) in two reports from the eastern state, West Bengal, after a period of 4 years was observed. Moreover, both studies indicated a high level of resistance against cotrimoxazole (sulfonamide) and least resistance against amikacin (aminoglycoside) and nitrofurantoin (nitrofuran) respectively (Fig. 2a). However, during the present study period (2015–2020), there were no data on the resistance pattern of the asymptomatic *E. coli* collected from urine culture–positive isolates from the other parts of the Indian sub-continent.

Current trends in resistance to different groups of antibiotics among symptomatic UPEC were quite similar to their asymptomatic counterparts. Reports from different states of Northern, North Eastern, Eastern, and/or Southern India showed moderately high to very high level of aminopenicillin (ampicillin, amoxicillin) resistance over the last 6 years (2015–2020). One hundred percent resistance against ampicillin was reported from Tamil Nadu (Southern India) consecutively in 2019 and 2020. Moreover, very recently, two different states of southern India, i.e., Kerala and Tamil Nadu, reported a very high (80% and 100%) incidence of resistance respectively against piperacillin and carbenicillin of the antipseudomonal class (Fig. 2b).

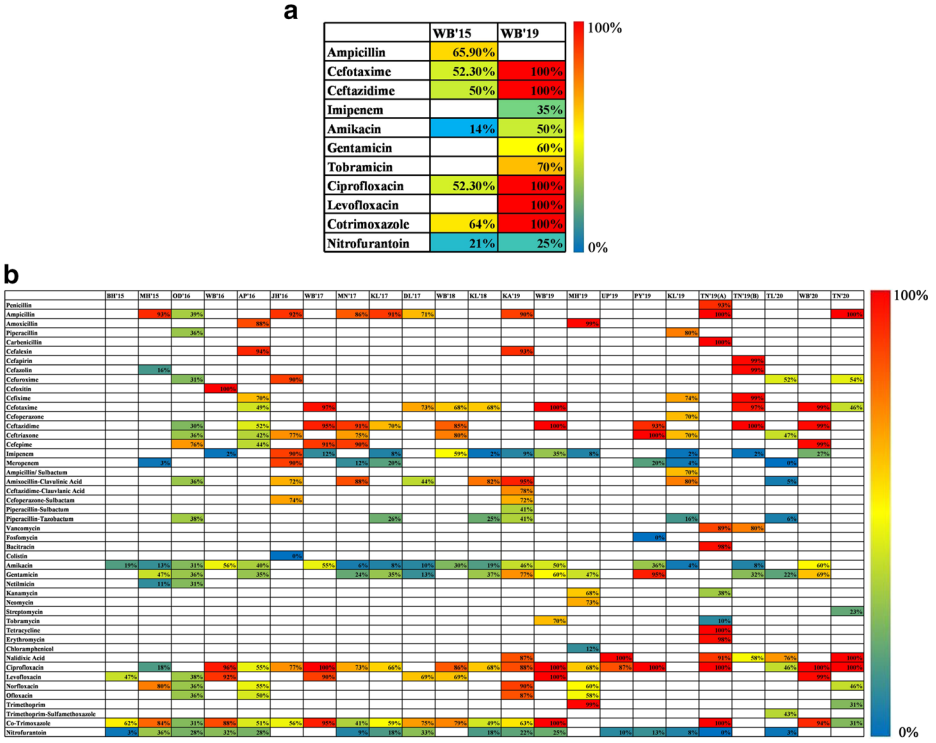


Fig. 2 Reports on percentage of resistance among **a** asymptomatic *E. coli* obtained from urine culture–positive isolates to different antibiotics in West Bengal in 2015 (WB'15), and in 2019 (WB'19), and **b** percentage of resistance among symptomatic uropathogenic *E. coli* to different antibiotics in various Indian states during the years 2015–2020 respectively. Color key represents the variation in colors from red to blue illustrating the percentage of resistance from 100 to zero

Furthermore, late reports from southern India (Karnataka and Tamil Nadu) showed very high (93 to 99%) first-generation cephalosporin resistance especially against cefalexin, cefazolin, and cefapirin with the highest being from Tamil Nadu, but moderate cefuroxime (second generation of cephalosporin) resistance from states of Telangana and Tamil Nadu. However, two reports from two different (Odisha and Jharkhand) states of eastern India in 2016 reported completely different (lowest and highest respectively) levels of cefuroxime resistance. Ninety-three percent cefoxitin resistance was reported only from West Bengal (2016). Resistance to third-generation cephalosporins, especially cefixime, cefotaxime, ceftazidime, and ceftriaxone, was reported to be from low to moderate ranges in the north-eastern, eastern, and southern regions of India between the years 2015–2016. However, a rising trend in third-generation cephalosporins (cefixime, cefotaxime, cefoperazone, ceftazidime, and ceftriaxone) resistance was noticed from the year 2017 to 2020 in almost all regions of India which included the states of West Bengal, Manipur, Delhi, Pondicherry, Kerala, Karnataka, and Tamil Nadu. Nonetheless, lately, Telangana and Tamil Nadu, parts of southern India, reported moderate resistance against ceftriaxone and cefotaxime (third-generation cephalosporins) respectively. One hundred percent resistance against cefotaxime and ceftazidime (third-generation cephalosporins) was reported from West Bengal and Tamil

Nadu in 2019. Cefepime (fourth-generation cephalosporin) resistance was found to be quite high (76 to 98.70%) over the last 5 (2016–2020) years in different states of India, except a report from Andhra Pradesh (2016) that stated moderately low (44%) incidence of cefepime resistance. However, the highest resistance was reported recently from West Bengal (Fig. 2b).

Presently, in carbapenem (meropenem and imipenem) resistance in symptomatic UPECs in different regions (northern, eastern, western, southern) of India, although found to be low, a rising trend from 2016 to 2019 could be noticed especially from the eastern state of India, West Bengal. However, moderately high and exceptionally high level of resistance to carbapenem (meropenem and/or imipenem) was reported from eastern Indian state West Bengal (2018) and Jharkhand (2016) respectively. Lately, a report from Telangana, a south Indian state, proclaimed 0% resistance against meropenem (Fig. 2b).

Resistance to one or more of the β-lactam-β-lactamase inhibitor combinations like ampicillin/sulbactam, amoxicillin/clavulanic acid, ceftazidime/clavulanic acid, and cefoperazone/sulbactam was reported to be high or very high in various Indian states like Jharkhand, Manipur, Kerala, and Karnataka that belonged to eastern, north-eastern, and southern parts of India. Moreover, the highest resistance to three β-lactam-β-lactamase inhibitor combinations amoxicillin/clavulanic acid, ceftazidime/ clavulanic acid, and cefoperazone/sulbactam was reported from Manipur, 2017, and Karnataka in 2019. However, resistance against piperacillin/tazobactam was consistently reported to be quite low especially during the years 2016–2020, in Odisha, Kerala, Karnataka, and Telangana but the least resistance to β-lactam-β-lactamase inhibitor combination (amoxicillin/clavulanic acid) was reported in the recent past from Telangana. Moreover, the national trend in resistance to β-lactamase inhibitors when used in combination with penicillins or cephalosporins over the last 6 years was found to be inconsistent (Fig. 2b).

High resistance against vancomycin and bacitracin (cell wall inhibitors other than β-lactam) was reported from the south Indian state of Tamil Nadu lately. However, reports from an Eastern (Jharkhand) and Southern part (Pondicherry) of India stated 100% sensitivity to cell wall inhibitors colistin and fosfomycin respectively (Fig. 2b).

Resistance to one or more of the several antibiotics of aminoglycoside group like amikacin, gentamicin, neomycin, netilmicin, kanamycin, tobramycin, and streptomycin was found to range from low to very high over the last 6 years. The trend in amikacin resistance was found to be low to moderate in various regions of India that included states and union territories like Bihar, West Bengal, Maharashtra, Odisha, Andhra Pradesh, Manipur, Kerala, Delhi, Karnataka, Pondicherry, Telangana, and Tamil Nadu. However, recently, very low (4%) amikacin resistance was reported from the south Indian state of Kerala, which was in contrary to the report from the eastern Indian state of West Bengal that reported moderately high (60.25%) resistance of symptomatic UPECs against amikacin. An almost similar pattern of resistance against gentamicin was observed from most of the aforementioned states of India, but of late, a report from Pondicherry showed extremely high resistance against gentamicin. Resistance to one/more aminoglycoside (amikacin, gentamicin, kanamycin, tobramycin, streptomycin) class of antibiotics was reported to be low in the south Indian states of Kerala, Tamil Nadu, and Telangana (Fig. 2b).

An extremely high level of resistance of symptomatic UPECs to tetracycline and erythromycin (macrolide) was reported from the south Indian state of Tamil Nadu. However, a report from the western region of India (Maharashtra) indicated immensely low chloramphenicol resistance (Fig. 2b).

Resistance against nalidixic acid (first-generation quinolones) was very high except for a report from Tamil Nadu (southern India) that reported moderate nalidixic resistance lately. One hundred percent resistance against nalidixic acid was reported from the north Indian state of Uttar Pradesh and the south Indian state of Tamil Nadu (Fig. 2b).

Reports from the eastern, northern, and southern regions of India covering states like West Bengal, Karnataka, Uttar Pradesh, and Pondicherry stated very high resistance to second-generation fluoroquinolones, especially against ciprofloxacin and levofloxacin, over the last 5 years (2016–2020). However, moderate ciprofloxacin resistance was reported from Telangana (Southern region of India). However, reports from most of the aforesaid Indian states showed comparatively lower resistance to two other second-generation fluoroquinolones (norfloxacin or ofloxacin) (Fig. 2b).

Resistance against cotrimoxazole (sulfonamide) was found to have an increasing trend from 2015 to 2020; however, the trend was inconsistent. One hundred percent resistance against cotrimoxazole was reported recently from the eastern Indian state of West Bengal and the south Indian state of Tamil Nadu. However, surprisingly, another recent report from Tamil Nadu stated a low incidence of cotrimoxazole resistance among symptomatic UPECs (Fig. 2b).

Resistance against nitrofurantoin (nitrofuran) was found to be very low in almost all parts of India. However, in the recent past, a report from Tamil Nadu (South India) proclaimed 0% resistance against nitrofurantoin. Notably, recent reports especially those published in and after 2019 showed a decrease in nitrofurantoin resistance (Fig. 2b).

Moreover, a statistically significant positive correlation that ranged from low to very high with p values ≤ 0.05 was observed in the incidence of resistance of symptomatic UPECs against 20 (ampicillin, cefuroxime, cefixime, cefotaxime, ceftazidime, ceftriaxone, cefepime, imipenem, meropenem, amoxicillin-clavulanic acid, piperacillin-tazobactam, amikacin, gentamicin, nalidixic acid, ciprofloxacin, levofloxacin, norfloxacin, ofloxacin, co-trimoxazole, nitrofurantoin) different antibiotics over a period of 5 (2015–2020) years. However, the highest and the lowest correlation with respect to resistance against ampicillin was observed between the states of Jharkhand (2016), Manipur (2017) and Maharashtra (2015), and Odisha (2016) respectively (Fig. 3a). Furthermore, in case of resistance against second-generation cefuroxime, the highest correlation was observed between Telengana (2020) and Tamil Nadu (2020) and the lowest between Odisha (2016) and Jharkhand (2016) respectively (Fig. 3b). However, a statistically significant (p values ≤ 0.05) positive correlation with a correlation coefficient of 0.91 was perceived in the incidence of resistance against cefixime (third-generation cephalosporin) only between Andhra Pradesh (2016) and Kerala (2019) (Fig. 3c). Nevertheless, West Bengal (2017), Tamil Nadu (2019—second) and West Bengal (2018), and Kerala (2018) showed the strongest correlation with respect to the resistance against cefotaxime, another third-generation cephalosporin. Moreover, West Bengal (2017), West Bengal (2018), Kerala (2018), and Tamil Nadu (2019—second) was found to have the weakest correlation with West Bengal (2018), Kerala (2018) and West Bengal (2017), Tamil Nadu (2019—second) and West Bengal (2017), Tamil Nadu (2019—second) and West Bengal (2018), and Kerala (2018) respectively (Fig. 3d). However, with respect to another third-generation cephalosporin, ceftazidime, the highest and lowest correlation was perceived between Manipur (2017), Pondicherry (2019) and Odisha (2016), and Manipur (2017) respectively (Fig. 3e). To boot, resistance against another third-generation cephalosporin, ceftriaxone, in Jharkhand (2016), Manipur (2017) and Odisha (2016), and West Bengal (2018) respectively was found to be most strongly and weakly correlated (Fig. 3f). Withal, with respect to resistance against cefepime (fourth-generation cephalosporin), the highest and

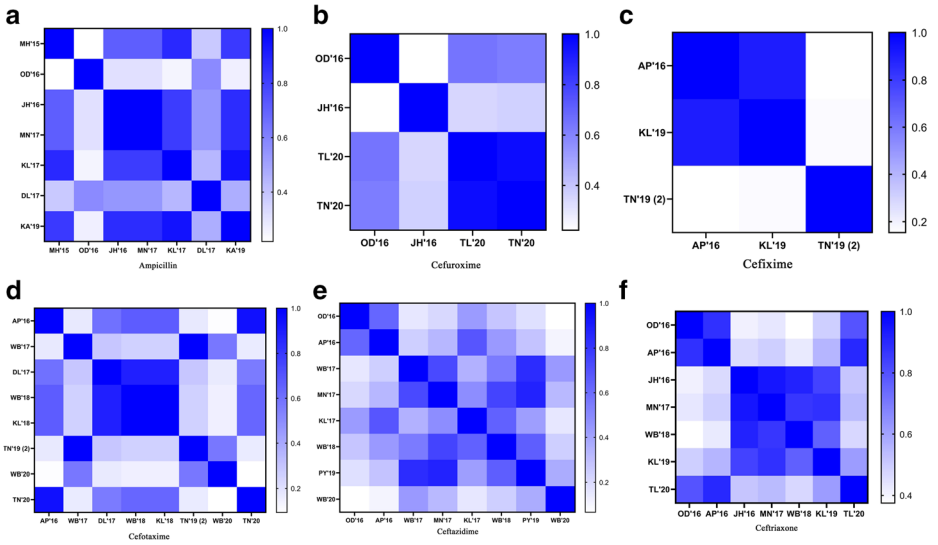
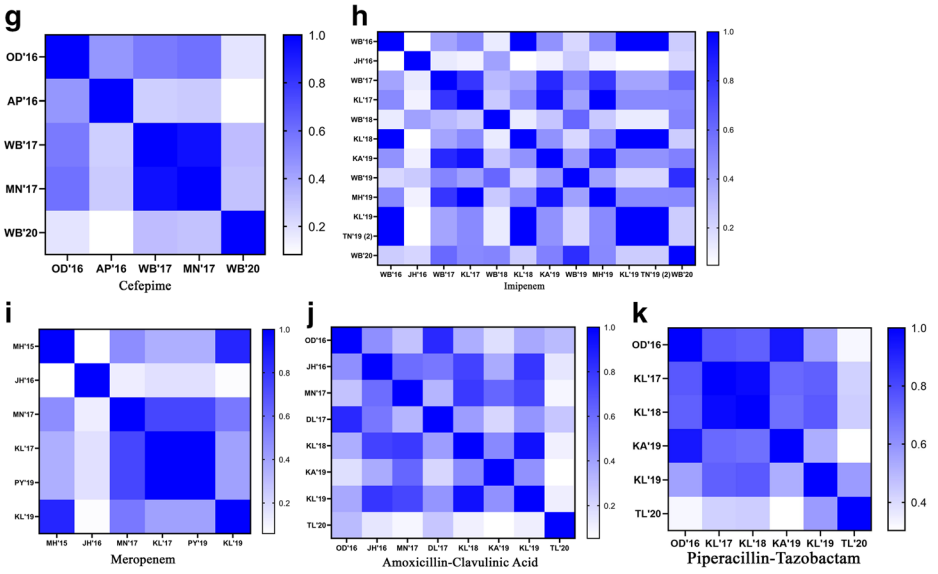


Fig. 3 Statistical significance of the incidence of resistance of symptomatic UPECs against 20 different antibiotics (**a**–**t**) in the various Indian states was analyzed by GraphPad Prism version 9 (Prism software package). Heat maps were generated on the correlation coefficient values represented by the color keys that ranged from zero (white) to 1 (deep blue)

lowest correlation was observed between West Bengal (2017), Manipur (2017) and Andhra Pradesh (2016), and West Bengal (2017) respectively (Fig. 3g). Moreover, West Bengal



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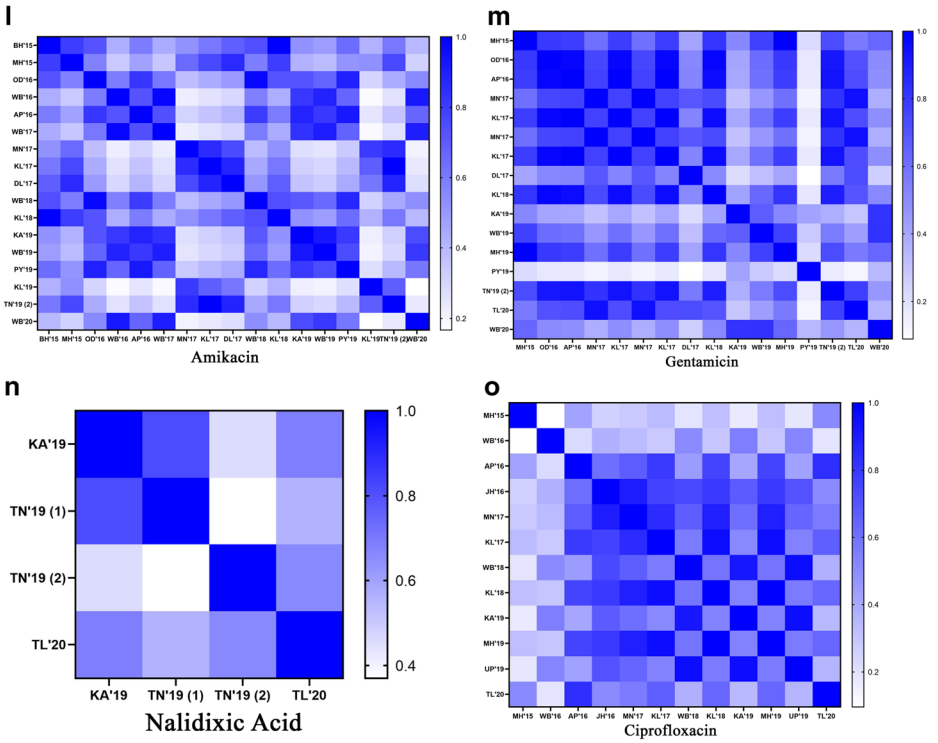

Fig. 3 continued.

(2016), Kerala (2018), Kerala (2019), Tamil Nadu (2019—second) and Kerala (2017), and Maharashtra (2019) respectively showed the highest correlation with respect to resistance against a carbapenem group of antibiotic: imipenem. However, lowest correlation was observed between Jharkhand (2016) and West Bengal (2020) (Fig. 3h). Moreover, the highest and lowest correlation with respect to resistance meropenem from carbapenem group was observed between Kerala (2017), Pondicherry (2019) and Maharashtra (2015), Kerala (2017), and Pondicherry (2019) respectively (Fig. 3i). Furthermore, in case of resistance against amoxicillin/clavulanic acid (Fig. 3j) and piperacillin/tazobactam (Fig. 3k) (β-lactam-β-lactamase inhibitor), the highest correlation was observed between Kerala (2018), Kerala (2019) and Kerala (2017), and Kerala (2018) and lowest between Delhi (2017), Karnataka (2019) and Karnataka (2019), and Telengana (2020) respectively. Bihar (2015) and Kerala (2017) were found to show the strongest correlation with Kerala (2018) and Tamil Nadu (2019—second) respectively with respect to resistance against an aminoglycoside group of antibiotic: amikacin. Notwithstanding, the lowest correlation was perceived between West Bengal (2019) and Kerala (2019) (Fig. 3l). In addition, Maharashtra (2015) and Andhra Pradesh (2016) displayed the strongest correlation with Maharashtra (2019) and Kerala (2017) respectively with respect to the resistance against gentamicin (aminoglycoside). However, the weakest correlation against gentamicin was perceived between Delhi (2017) and

Karnataka (2019) (Fig. 3m). Moreover, the highest and lowest correlation with respect to resistance against first-generation quinolone, nalidixic acid, was observed between the states of Karnataka (2019), Tamil Nadu (2019—first) and Tamil Nadu (2019—first), and Tamil Nadu (2019—second) respectively (Fig. 3n). Furthermore, in case of resistance against ciprofloxacin, a second-generation quinolone, the highest correlation was observed between Kerala (2018) and Maharashtra (2019) and lowest between West Bengal (2016) and Andhra Pradesh (2016) respectively (Fig. 3o). However, the strongest and weakest correlation in the incidence of resistance against two other second-generation fluoroquinolone, i.e., ofloxacin (Fig. 3p) and norfloxacin (Fig. 3q), was found between the states Andhra Pradesh (2016) and Maharashtra (2019) and Odisha (2016) and Karnataka (2019) respectively. Moreover, the highest and lowest correlation with respect to resistance against levofloxacin (second-generation quinolone) was observed between the states or union territories of Delhi (2017), West Bengal (2018) and Odisha (2016), and West Bengal (2016) respectively (Fig. 3r). Odisha (2016) and Manipur (2017) showed the highest and lowest correlation in the incidence of resistance against cotrimoxazole (sulfonamide) with Tamil Nadu (2020) and West Bengal (2020) respectively (Fig. 3s). Moreover, Bihar (2015) and Odisha (2016) and Kerala (2017) showed the strongest correlation with Tamil Nadu (2020), Andhra Pradesh (2016), and Kerala (2018) respectively with respect to the resistance against nitrofurantoin from the nitrofuran group (a synthetic drug). However, Maharashtra (2015) showed the lowest correlation both with Bihar (2015) and Telengana (2020) respectively (Fig. 3t).

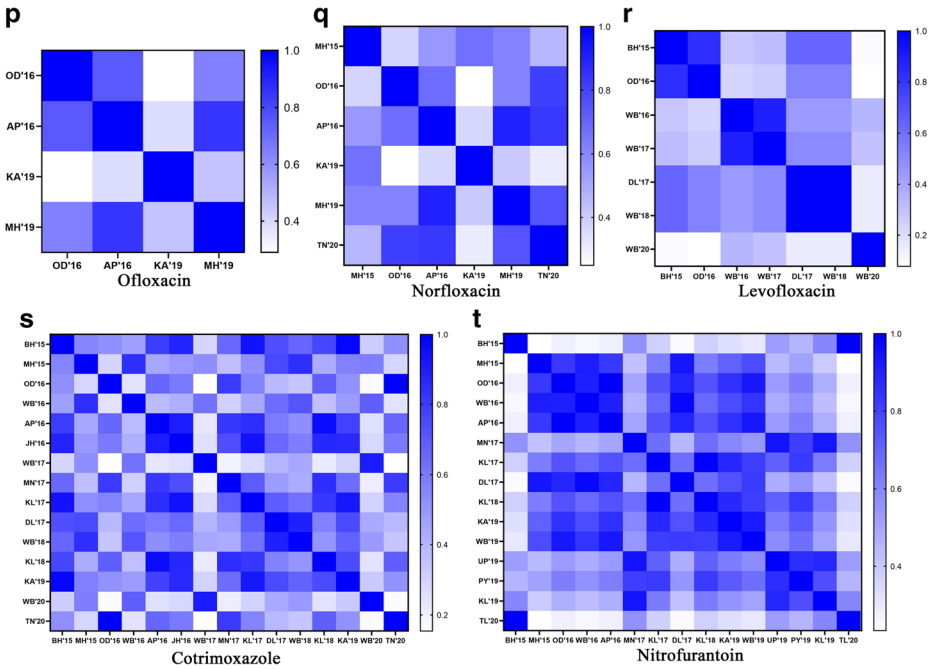

Fig. 3 continued.

Distribution of Plasmid-Mediated Antibiotic Resistance Genes in UPECs

Distribution of ESBL and AmpC Genes

UPEC isolates that exhibited AmpC phenotypes were reported to haborbla_{CMY-2} and bla_{DHA-1} genes either alone or in combination. However, isolates that showed co-production of AmpC and ESBL were found to harbor bla_{CMY-2} and bla_{DHA-1} genes in combination with bla_{TEM} and bla_{CTX-M} genes [13]. Among the phenotypically confirmed ESBL *E. coli* isolates, the most common ESBL gene was *TEM* followed by *SHV* and *CTX-M.* Co-occurrence of *TEM*, *SHV*, and *CTX-M* was reported from Odisha [46]. However, Kammili et al. [17] from Telangana reported that among the phenotypically confirmed ESBL *E. coli* isolates, the most common ESBL gene was *TEM-1* followed by *CTX-M-15* and *SHV-38*. Moreover, the co-occurrence of *CTX-M-15* and *TEM-1* and *TEM-1+SHV-38* genes was also observed among the isolated UPECs.

Distribution of PMQR Genes

Among the phenotypically confirmed quinolone-resistant ESBL *E. coli*, the most common gene identified was *qnrS* followed by *aac (6')-Ib-cr* [17]. Moreover, other studies [9, 14, 42] from Kolkata, West Bengal, reported a high prevalence of *aac(6')-1b-cr* alone and also in combination with *qnrB* and *qnrB* with *oqxB*.

Dissemination of Antibiotic Resistance Genes

A study by Ghosh et al. [13] reported a high incidence of AmpC-ESBL co-production among the p-AmpC-producing isolates. bla_{AmpC} and ESBL genes were harbored on transmissible plasmids which were successfully transmitted by conjugation. The transconjugants showed resistance to cephalosporins, fluoroquinolones, amikacin, and co-trimoxazole, which validated the rapid propagation of the different plasmid-mediated resistance genes along with the bla_{AmpC} genes. The predominance of IncF-type plasmid replicons Frep (65%), F1B (87%), followed by IncI (26%), IncH1 (8.7%), and IncN (4%) plasmids was found, harboring bla_{CMY-2}, bla_{TEM}, and bla_{DHA-1} genes. It was also found that plasmids carrying bla_{CMY-2} and bla_{DHA-1} genes were variants of IncF replicon family followed by IncF in combination with incI1, IncH1, and IncN, signifying a selection in plasmids, which contributed to the spread of AmpC beta-lactamases in combination with other ESBL genes. Moreover, an *in vitro* study conducted by [14] from Kolkata, West Bengal, reported efficacious transmission of PMQR genes, *aac(6')-Ib-cr*, *qnrA*, *qnrB*, *qnrS*, and *oqxB*, to susceptible *E. coli* J53Azide-resistant strain from ciprofloxacin-resistant UPECs in presence of high selection pressure of ciprofloxacin that generated transconjugants which further displayed varied MIC levels towards the drug with acquired mutations, Ser83Leu and Asp87Asn in the quinolone-resistant determining regions (QRDR) of *gyrA* gene (*E. coli* DNA gyrase subunit A). Moreover, another study [9] from Kolkata, West Bengal, revealed the successful transmission of the β-lactamase genes (*blaTE*M, *blaCTX-M*, *blaOXA*) and the PMQR genes (*aac(60)1b-cr*, *oqxAB*, *qnrB*) respectively in various combinations to the *E. coli* J53AziR recipients strain from all the tested UPECs against ceftazidime/ciprofloxacin selection. Furthermore, [9] proclaimed the predominance of *traF* irrespective of drug selection which indicated that F-type conjugation system was responsible for the transmission of the resistant plasmids resulting in the expeditious dissemination of antibiotic resistance in the isolated UPEC.

UPECs' Alternative Response Towards Survival

A study performed by Bandyopadhyay et al. [38] Kolkata, West Bengal, reported the incidence of the generation of reactive oxygen species (ROS) in response to the sub-inhibitory concentration of certain bactericidal antibiotics (ceftazidime, gentamicin, and ciprofloxacin) in the highly MDR UPECs that conveyed a protective function towards cell lethality, thereby suggesting an alternative mechanism of selection of the drug-resistant UPECs. Moreover, the study also portrayed the fact that the production of ROS assisted in the survival of the MDR UPECS by alteration in the transcription profile of different genes encoding the bacterial protective proteins, thereby affecting the core cellular functions. Additionally, a statistically significant correlation between *uspA* over-expression and ROS production at the sub-inhibitory dosage of ceftazidime, gentamicin, and ciprofloxacin among MDR UPECs was reported, also suggesting an alternative mechanism of selection of the drug-resistant UPECs.

UPEC Phenotypic Characterization

Evidence of hemolytic activity, hemagglutination activity, slime activity, β-lactamase activity, and biofilm formation capacity in UPECs.

Hemolytic Activity, Slime Activity, β-Lactamase Activity, Hemagglutination Activity by UPECs

Moderate incidence of hemolysin production was detected in studies conducted from two different states (Kerala, Tamil Nadu) of India on tested UPECs [7, 15, 16]. Gnanasekaran et al. [15] also reported the notable incidence of slime and β-lactamase activity in the tested UPECs. A remarkable incidence of mannose-resistant hemagglutination (MHRA) was observed in a study conducted from Haryana, Jharkhand, and Kerala [7, 22, 23].

UPECs as Biofilm Producers

The biofilm formation capacity ranged from a weak to very high level among the studied symptomatic UPECs from five different Indian states (Haryana, Jharkhand, Karnataka, Kerala, and Tamil Nadu) [1, 7, 22–24, 39]. Biofilm formation in UPECs was reported to be facilitated by type I fimbriae, especially the adhesion mediated by the FimH [21, 23]. Biofilm-producing UPECs were found to be more resistant to multiple groups of antibiotics as compared to the non-biofilm producers [1, 39] which was contrary to the report by Pullanhi et al. [7] that indicated similar antibiotic susceptibility pattern among both biofilm-producing and non-biofilm-producing *E. coli*. Moreover, a study by Vasudevan et al. [24] indicated high incidence of strong biofilm formers among the highly MDR UPECs.

Phylogenetic Background, Pathogenic Islands Distribution, and Genetic Makeup of UPECs

India, a country of diversity in geography, culture, religion, climate, race, and language, also exhibits diversity in phylogenetic background, distribution of pathogenic island (PAI) markers, and virulence characteristics of UPECs [2].

UPEC Phylotypes

Studies [25, 40] from Kolkata stated significant incidence of phylogroups B2, B1, and B2, D among the asymptomatic and symptomatic MDR UPECs respectively when analyzed by triplex PCR-based phylogenetic assay. However, another study from Kolkata by Ghosh et al. [2] demonstrated a significant incidence of asymptomatic and symptomatic MDR UPECs that could not be assigned to any of the eight known phylogroups (unknown phylogroup) when analyzed by quadruplex PCR-based phylogenetic assay.

Distribution of PAIs in UPECs

A study from Kolkata [2], West Bengal, reported a significant predominance of PAI IV536 and PAI I CFT073 among both asymptomatic and symptomatic UPECs.

Virulence Characteristics of UPECs

Moderate to a high incidence of several virulence factor genes including the fimbrial and afimbrial adhesins, and toxins was reported from two different Indian states (West Bengal and Tamil Nadu) in case of symptomatic [2, 19] and only from the state West Bengal in case of asymptomatic UPECs respectively [2].

Incidence of Mutation/Polymorphisms of Chromosomal Genes in UPECs

FimH Mutations

A study [2], from Kolkata, West Bengal, proclaimed the incidence of several synonymous and nonsynonymous mutations (NSMs) in the lectin and pilin domain of FimH of both asymptomatic and symptomatic UPECs, some of which were pathoadaptive. A very high prevalence of hot spot mutation V27A was observed among both the asymptomatic and symptomatic UPECs.

gyrA Mutations

A high incidence of *gyrA* mutations was observed among the studied UPECs from Kolkata, West Bengal [14].

Understanding Mechanisms for UPEC-Mediated UTI in Human

Role of Osmoregulatory Protein Pair in Transcription Regulation

A report by Narayan et al. [47] from Tamil Nadu stated that in all the pathogenic bacteria including UPECs, osmolarity alterations signal successful invasion in a mammalian host apart from temperature. UPECs were found to experience striking changes in external osmolarity that range from ~0 Osm in the soil to 1 Osm (~0.5 M ionic strength) upon infection. Moreover, Narayan et al. [47] reported that at high ionic strength (a condition generally observed after a successful invasion), Cnu (a member of the Hha-family of proteins), and H-NS (a transcription repressor) in 1:1 combination preferentially formed a complex with very weak affinity, thereby causing the expression of virulent genes. However, at low ionic strength, Cnu affinity for H-NS was found to increase and that also resulted in subsequent repression of virulence genes. Therefore, the study [47] showed that Cnu could act as a perfect molecular sensor of solvent ionic strength. Furthermore, the aforementioned study also depicted that the order-disorder transitions in H-NS could act synergistically with molecular swelling of Cnu, thereby giving way to a salt-driven switch in binding cooperativity.

Role of Inflammasomes and Their Components in UPEC-Mediated UTI

Verma et al. [48] from New Delhi stated that the inflammatory regulators (NLRP3, NAIP, NLRC4, ASC, and CASPASE-1) were upregulated at both mRNA and protein levels in the UPEC-infected UTI patients. Moreover, pro-inflammatory cytokines like IL-6, IL-8, IFN-g, TNF-a, and MCP-1 were also found to be upregulated in the patients' group. However, no significant difference was perceived in the expression of AIM2 and CASPASE-4 genes at both mRNA and protein levels. Additionally, the involvement of NLRC4 inflammasome in UPEC-infected UTI was also observed. Moreover, Verma et al. [12] also reported that active α-hemolysin (HlyA) could induce the formation of the NLRP3 inflammasome by initiating deubiquitination of NLRP3-dependent potassium efflux, whereas the inactive form proHlyA was unable to do so, which suggested that the UPEC α-hemolysin's pore-forming property is an essentiality for initiation of pro-inflammatory response. Furthermore, Verma et al. [12] also displayed that disturbance in potassium homeostasis as a result of HlyA stimulation led to mitochondrial dysfunction which was followed by an acute inflammatory response that ensued in cell death. Previously, Verma et al. [49] demonstrated the most simple but perfect way for the production of active and inactive recombinant a-hemolysin for the aforementioned kind of functional studies.

Role of YadV in Pilus Biogenesis

A study [50] from New Delhi showed that the monomeric form of YadV, the chaperone component of the CU pathway of Yad pili, is the preferred state for its interaction with pilus subunits. Moreover, it was observed that the closed conformation for the proline lock was an important structural element for chaperone–pilus subunit interaction and the closed state of the proline lock was found to be energetically unstable. Therefore, the aforementioned report demonstrated that the monomeric YadV with its closed proline lock might act as an intermediate state to support suitable access to pilus subunits and also pilus biogenesis.

Alternative Therapeutic Strategies Against UPECs

The ineptitude of conventional antibiotics against UPECs demanded newer therapeutic interventions. The literature search yielded several reports that indicated various newer alternative therapeutic options that might help to combat the spread of UPECs.

Phage Therapy

Bacteriophages are viruses that are capable of infecting and killing bacteria without affecting humans. Phage therapy uses bacteriophages for the treatment of bacterial infections. A study [27] from the state of Maharashtra reported very high lytic activity of *Escherichia* virus myPSH2311 against UPECs which were found to be resistant to last-resort antibiotics like meropenem and colistin.

Sulfur Nanoparticles

Sulfur nanoparticles are widely used antimicrobial agents. A study by Paralikar et al. [3] from Maharashtra displayed the antibacterial potential of sulfur nanoparticles (SNPs) alone and in combination with antibiotics such as amoxicillin, norfloxacin, and trimethoprim against UPECs. Maximum zone of inhibition was observed when SNPs were used in combination with amoxicillin. Moreover, the aforementioned study also revealed a decrease in zeta potential when UPECs were exposed to SNPs that indicated an alteration in their surface potential owing to membrane damage.

1-Amino-4-Hydroxyanthraquinone (Disperse Red 15 or DR15)

A study [21] from Tamil Nadu stated that DR15, a natural product often found in wastewaters when derivatised into *N*-(4-hydroxy-9, 10-dioxo-9, 10-dihydroanthracen-1-yl) undec-10-enamide and self-assembled with linseed oil, could be used to inhibit biofilm formation in UPECs which could potentially help to reduce catheter-acquired UTI incidents and their subsequent healthcare costs.

Antimicrobial Peptides

Antimicrobial peptides (AMPs) are small proteins known to have effective antibacterial, antifungal, and antiviral activity. A report by Biswas et al. [26] from Telangana had shown that 2 mg/kg dose of recombinant Defensin 21 (DEFB21) when administered with 50 μg gentamycin for 3 days in UPEC-infected rats significantly decreased the bacterial load in the caput and cauda epididymis and testis of infected rats. A study [28] from Tamil Nadu declared that a synthetic analog of the membranolytic AMPs of the tritrpticin family significantly lowered solvation energy in the *E. coli* membrane, thereby showing higher antibacterial activity against *E. coli*, which might be used as alternative solutions for the treatment of *E. coli*–mediated UTI.

Lectins

Lectins are proteins that are found in fungi, bacteria, and viruses. The exclusive feature of lectin to recognize and bind specific carbohydrate structures makes it relevant for use in

targeted drug delivery. A study conducted from Tamil Nadu [10] revealed that the interaction between silver nanoparticles (AgNPs) and *Buteamonosperma* seed lectin (BMSL) formed efficient surface-functionalized AgNPs with exemplary antibiofilm competency against UPEC. The aforementioned study also displayed that BMSL–AgNP conjugate affected the integrity of the bacterial outer membrane and generated an imbalance in the antioxidant defense which induced cell death.

Chitosan

Chitosan is a linear polysaccharide (derived from chitin shells of shrimp and other crustaceans with an alkaline substance such as sodium hydroxide) composed of randomly distributed β-(1→4)-linked D-glucosamine (deacetylated unit) and *N*-acetyl-D-glucosamine. Another study [11] from Tamil Nadu displayed the fact that commercial chitosan (CC) and extracted chitosan (EC) showed a high inhibitory percentage of 60–75% and 80–85% respectively on young biofilm and were also found to disrupt biofilm formation. Moreover, hemolysis assay exhibited a high inhibition potential of 79% against EC. Both the chitosan presented remarkable activity in suppression of the phenotypic virulence factors like swarming motility, mediated by type I pili, and were also found to repress cellulose production in UPEC. EC also downregulated the virulent genes responsible for the invasion in UPECs.

Type A Procyanidin

Type A procyanidin (TAP) are members of the proanthocyanidin class of flavonoids. A report from Tamil Nadu by [24] showed that TAP caused 70% inhibition in biofilm formation of MDR UPECs. The study also reported that at pH 5.8, TAP alone and in combination with nitrofurantoin downregulated the major fimbrial adhesins of UPEC, thereby affecting their ability to invade the host uroepithelial cells.

Potential Drug Targets to Combat Drug-Resistant UPECs

FimH

A study from Uttar Pradesh indicated successful repression of the fimH gene, a major virulent factor in UPEC infection by the CRISPRi technique that might be implemented in vivo to prevent UTI [51]. A computational screening was performed by Miryala et al. [21] from Tamil Nadu for identifying potential inhibitors against the FimH-mediated UPEC adhesion. The compounds, 1-amino-4-hydroxyanthraquinone (Disperse Red 15 or DR15) and 4-(4′-chloro-4-biphenylylsulfonylamino) benzoic acid (CB1), could enfeeble adhesion and biofilm formation without impeding the planktonic growth.

β-Lactamase

A study [52] from West Bengal identified a potent inhibitor-resistant TEM (IRT) β-lactamase inhibitor (naringenin triacetate) that was reported to hinder the growth of UPECs effectively in vitro and thus might act as a therapeutic alternative to the classical β-lactams and β-lactam–β-lactamase inhibitor combinations.

Discussion

In this review, an overview of the recent articles (from 2015) that dealt with the main and current developments and progress in the field of UPEC research that were published was presented. This included the national trends in incidence of UPEC-mediated UTIs, their age and gender-wise distribution, antibiotic resistance patterns, distribution of resistance genes, phenotypic characters, phylogenetic background, distribution of PAIs, and infection mechanisms. Moreover, the current alternative therapeutic strategies to fight against UPECs and their potential drug targets were also reviewed.

The literature search indicated that in the last 6 years, *E. coli* was the most predominant uropathogen causing symptomatic UTI in people residing in different (eastern, western, northern, southern) regions of India especially in the states and union territories like Bihar, West Bengal, Maharashtra, Haryana, Himachal Pradesh, Tamil Nadu, Telangana, New Delhi, and Chandigarh respectively. Moreover, the incidence of urine culture–positive symptomatic *E. coli* among different (northern, eastern, and southern) regions of India during the time period (2015–2020) was found be statistically correlated (Fig. 1). However, the prevalence of UPEC-mediated symptomatic UTI was comparatively lower in the states like Manipur, Uttar Pradesh, and Kerala. The highest incidence of UPEC-mediated UTI was reported from the north Indian state, Haryana, in the year 2018 (Table 1). Moreover, although in West Bengal, Tamil Nadu, and New Delhi the main causative agent of UTI was UPECs, the disparity in the percentage of UPEC-mediated UTI in the same or different years was also observed (Table 1). However, a striking incidence of UPECs in asymptomatic individuals was only reported from the eastern region, West Bengal [2, 25]. This indicated that in current times, highest predominance of UPECs in both ABU and symptomatic UTI poses a public health concern in West Bengal which is in the eastern region of India where a major population lies below the poverty level.

Moreover, the literature study also displayed a higher prevalence of UPEC infections among the female population from various regions (northern, eastern, southern) covering states of Haryana, Bihar, Jharkhand, West Bengal, Kerala, and Tamil Nadu as compared to the males [2, 7, 15, 16, 20, 23, 32] except a report from a southern state, Karnataka [1], that indicated the predominance of the males. The maximum age group affected with UPEC-mediated UTI from various Indian states was found to be 21–40 years in case of both male and female populations with asymptomatic or symptomatic infections [1, 2, 15, 16, 20]. However, the prevalence of UPECs was also observed in pediatric and geriatric populations that consisted of both asymptomatic and symptomatic patients, especially from the eastern region, West Bengal [2].

Recent reports indicated an overall increasing trend in drug resistance in both asymptomatic (Fig. 2a) and symptomatic (Fig. 2b) UPECs to several groups of antibiotics like penicillins, cephalosporins, aminoglycosides, quinolones/ fluoroquinolones, and sulphonamides in various parts of India covering several Indian states over the last 6 years (2015–2020). Two different (2015 and 2019) reports from an eastern region of India, West Bengal, displayed a striking rise in resistance of asymptomatic UPECs to third-generation cephalosporins (cefotaxime and ceftazidime), aminoglycoside (amikacin), second-generation fluoroquinolone (ciprofloxacin), and sulfonamide (cotrimoxazole) after a period of 4 years (Fig. 2a). Although the two aforesaid studies were conducted on separate patient populations, the rising trend of resistance in these groups of antibiotics, especially among asymptomatic UPECs, was highly alarming and also indicated the rise in unprescribed usage of antibiotics in recent times. Later of the two reports stated the least resistance against nitrofurantoin (nitrofuran) (Fig. 2a) which betokened the

need to use it as a first-line antibacterial agent. Moreover, further studies also must be initiated to explore the antibiotic susceptibility pattern of asymptomatic *E. coli* obtained from urine culture–positive isolates from the different regions of the Indian sub-continent to cease the unprecedented use of antibiotics across the country.

National trends in resistance among symptomatic UPECs to various groups of antibiotics were quite similar to the asymptomatic ones. Moreover, a varied level of statistically significant positive correlation in the incidence of resistance against different antibiotics that belonged to various groups like aminopenicillin, cephalosporin, carbapenem, β-lactam–β-lactamase inhibitors, aminoglycosides, quinolone/ fluoroquinolones, sulfonamides, and nitrofuran among various Indian states over a period of 5 (2015–2020) years was observed (Fig. 3a–t). High incidence of penicillin resistance in different states of Northern, North Eastern, Eastern, and/or Southern India over the last 6 years (2015–2020) along with a rising trend from 2015 to 2020 (Fig. 2b) indicated that overuse of this group of antibiotics in last few years had rendered them ineffective.

Reports from different regions of India (northern, north-eastern, eastern, and southern) revealed a very high level of resistance to first–fourth-generation cephalosporins. Likewise, an overall rising trend in resistance to third (cefixime, cefotaxime, cefoperazone, ceftazidime, and ceftriaxone)- and fourth (cefepime)-generation cephalosporins in the aforementioned regions of India was noticed from 2017 to 2020 (Fig. 2b). This indicated to the ineffectiveness of first- and second-generation cephalosporins in the last decade due to which usage of third- and fourth-generation cephalosporins increased rapidly. Moreover, among all these four generation cephalosporins, the least resistance was observed against ceftriaxone from various Indian states (Fig. 2b) which suggested that ceftriaxone might be the last resort antibiotic of the third-generation cephalosporin group. However, the highest incidence of cefepime (fourth-generation cephalosporin) resistance recently among symptomatic UPECs (Fig. 2b) was exceedingly disquieting especially, when it was from one of the poorest Indian state, West Bengal.

Low incidence of resistance to carbapenems like imipenem and meropenem in symptomatic UPECs in different regions (northern, eastern, western, and southern) of India (Fig. 2b) indicated that these antibiotics can be the drugs of choice for treatment of symptomatic patients resistant to other classes of antibiotics. However, a rising trend in carbapenem resistance from 2016 to 2019 especially in an eastern state West Bengal (Fig. 2b) was highly alarming as indicated extra usage of these drugs in recent times.

Among the β-lactam-β-lactamase inhibitor combinations, resistance against piperacillin/ tazobactam was consistently reported to be quite low especially during the years 2016–2020, in eastern (Odisha) and southern (Kerala, Karnataka, and Telangana) regions (Fig. 2b), thereby suggestive of the fact that aforementioned combination can be a suitable way to treat infections caused by ESBL-producing symptomatic UPECs. Moreover, the inconsistent increase in resistance to β-lactam-β-lactamase inhibitors combination from 2015 to 2020 (Fig. 2b) might be due to the diverse sample population with great disparity in age, sex, and environmental factors.

A recent report from the southern (Pondicherry) part of India that stated 100% sensitivity to fosfomycin (Fig. 2b), a cell wall inhibitor, lighted a glimmer of hope as this might turn out as a treatment option for patients resistant to other groups of antibiotics in future.

West Bengal (eastern India) recently reported moderately high (60.25%) resistance of symptomatic UPECs against amikacin unlike other reports from different regions that stated comparatively lower incidence of amikacin resistance. Moreover, a recent report from southern India (Pondicherry) showed extremely high resistance against gentamicin unlike the other states (Fig. 2b). This suggested the increase in the use of amikacin and gentamicin respectively

in recent years in these two states particularly. However, of late, resistance to aminoglycoside was reported to be low in the south Indian states of Kerala, Tamil Nadu, and Telangana (Fig. 2b) which implied to the controlled use of this antibiotic group in the recent past.

A very high incidence of tetracycline and erythromycin (macrolide) resistance among symptomatic UPECs was reported from the south Indian state of Tamil Nadu recently (Fig. 2b). This pointed out the fact that resistance to the aforementioned protein synthesis inhibitors also started rapidly in south India. However, a report from the western (Maharashtra) region (Fig. 2b) indicated immensely low chloramphenicol resistance which might be a ray of hope for future researchers and clinicians.

This literature survey showed that usage of nalidixic acid (first-generation quinolone) for treatment of UPEC-mediated symptomatic UTIs was not very common from 2015 to 2018. However, right from 2019, prevalence of nalidixic acid resistance was quite evident in the northern and southern parts of India (Fig. 2b). Moreover, reports from different regions, (northern, eastern, and southern) covering various Indian states demonstrated very high resistance to second-generation fluoroquinolones, especially against ciprofloxacin and levofloxacin, over the last 5 years (2016–2020) (Fig. 2b). This suggested that excessive use of nalidixic acid, the first synthetic quinolone antibiotic in the first few years of the past decade, had rendered them ineffective in the last few years, thereby causing a decline in their usage. However, the present scenario of resistance against nalidixic further affirmed the persistent futile nature of this drug. Furthermore, current evidence of the emergence of ciprofloxacin- and levofloxacin (second-generation fluoroquinolones)-resistant UPECs along with a somewhat rising trend in different parts of India is highly appalling as it limits the choice of antibiotics to a great extent.

Present trend in cotrimoxazole (sulphonamide) resistance was found to be very high from almost all regions of India with the highest (100%) being from the eastern Indian state of West Bengal and the south Indian state of Tamil Nadu. However, strangely another recent report from Tamil Nadu stated low (31%) incidence of cotrimoxazole resistance among symptomatic UPECs (Fig. 2b). The aforementioned reports suggested even the use of sulfonamides became rampant in recent years and thus the empiric usage of these drugs should be restricted in the future. However, numerous reports from various regions of India indicated nil or very low resistance against nitrofurantoin (nitrofuran), and strikingly recent reports, especially those published on and after 2019, implied a decrease in nitrofurantoin resistance which indicated the need for wise and proper prescription usage of this drug as this remained as the most effective oral agent for the treatment of symptomatic UPEC infections.

Extremely high incidence of MDR symptomatic UPECs [2, 16, 20, 23, 24, 42] was reported from the northern, eastern, and southern regions of India. This indicated the inappropriate antibacterial treatment and uncontrolled use of antibiotics nationwide that contributed to the emergence of MDR in UPECs. Moreover, a report from Kolkata, West Bengal, that stated exceedingly high [2] levels of MDR among asymptomatic UPECs was highly alarming and this furthermore justified the need to surcease dissemination of antibiotic resistance by immediate implementation of proper prescription policies in one of the poorest Indian states.

National trends of moderate to the high incidence of ESBL [4, 6, 7, 17, 19], MBL [4, 20], and/or AmpC [4, 13, 20, 23] producers among symptomatic UPECs from different regions (northern, eastern, and southern) of India were really alarming. Moreover, the incidence of co-production of ESBL, MBL, or AmpC among MDR UPECs was also reported in the recent past from southern India (Pondicherry) [4]. This incidence is highly worrisome as it poses a serious threat to the health care setting of a resource-poor country as India by limiting the

therapeutic options since unlike ESBL producers, MBL and AmpC producers were also found to be resistant to carbapenems and β-lactam inhibitors. Withal, the presence of ESBL [17], AmpC [13], and/or PMQR [9, 14, 17, 42] genes among the phenotypically confirmed symptomatic UPECs from southern and eastern India further pointed out to the dreadful implications of inappropriate clinical management in the aforementioned areas that led to the spread of these plasmid-mediated resistance genes through horizontal gene transfer.

A very recent report [38] from the eastern region (West Bengal) of India threw the spotlight on an alternative strategy that might be adopted by symptomatic MDR UPECs for their survival when exposed to sub-inhibitory concentration of different bactericidal antibiotics and this was really daunting as this might cause treatment failures in the future.

Moreover, the notable incidence of hemolytic activity [7, 15, 16]/slime activity [15]/β-lactamase activity [15]/hemagglutination activity [7, 20, 23] by symptomatic UPECs was reported from northern, eastern, and southern regions of India in the last few years. Furthermore, a high incidence of several virulence factors genes (fimbrial, afimbrial adhesins, and toxins) was also reported from eastern and southern India [2, 16] in case of asymptomatic and/or symptomatic UPECs. These reports highlighted the high adherence and colonization potential of the circulated UPECs in India irrespective of their asymptomatic and symptomatic nature.

Weak to high biofilm formation capacity was recognized in various UPEC isolates in different parts of India (northern, north-eastern, and southern) [1, 7, 20, 23, 24, 39]. Moreover, incidences of PAI markers and pathoadaptive FimH mutations were reported from eastern India in both asymptomatic and symptomatic UPECs. To boot, a recent report from eastern India stated a very high incidence of asymptomatic and symptomatic UPECs that belonged to undesignated and/or pathogenic phylogroups [2]. The aforementioned reports drew attention to the enhanced virulence potential, survival, and fitness capacity of UPECs currently prevalent in various regions of India.

In the last few years, India had perceived the emergence of highly virulent MDR and mutated β-lactamase-producing UPEC strains due to indiscriminate use of unprescribed antibiotics, which further led to limitations in therapeutic options, thereby threatening the current health care setting, especially of a developing country, like India. Moreover, high-dosage administration of antibiotics was found to cause several adverse effects on humans [10]. It is therefore of urgent necessity to develop alternative therapeutic strategies to fight against these virulent MDR microbes. Very recently, several researchers especially from western [3, 27] and south Indian state [10, 11, 21, 24, 28] of Maharashtra and Tamil Nadu displayed the usage of several alternative therapeutics which might have preached the way to cope with the upcoming therapeutic challenges and combat the spread of MDR UPECs.

In the recent past, especially during 2019–2020, several mechanisms by which UPECs mediate UTI in the host [12, 47, 49, 50] and potential drug target against UPECs mediated UTI [21] were explored by several researchers from the northern, eastern, and southern regions of India. The exploration of various mechanisms of UPEC infections and the search for potential drug targets might turn to be a boon in the future, as this might help to design new therapeutics.

Last but not the least, this literature survey attempted to bring to the forefront the current trends and advancements in UPEC-mediated UTI in a resource-poor country like India by incorporating relevant information from most of the published reports (PubMed, Google Scholar); however, this could lack some available information. Nevertheless, reports included in this review successfully provided a well-defined overview of present developments of UPECs in India, which was further lucidly represented by a graphical model (Fig. 4).

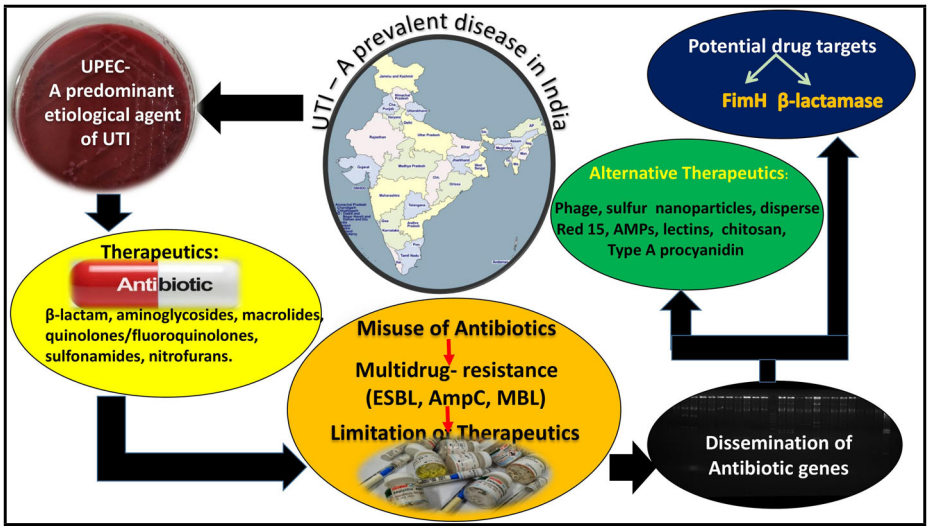

Fig. 4 Graphical model on present developments of UPECs in India

Conclusion

The present review based on the recent developments in UPECs, the most predominant uropathogen in India, threw the spotlight on the nationwide expeditious emergence and dissemination of antibiotic-resistant UPEC strains that included ESBL, MBL, and AmpC producers, in the last few years. Moreover, the incidence of symptomatic UPECs and their resistance against different groups of antibiotics was found to be statistically correlated at a significance level of ≤ 0.05 among various Indian states that covered different regions of India. This pointed out the atrocious implications of improper clinical management, thereby causing a significant rise in health care expenses and the consequent economic burden in a resource-poor country like India. Moreover, this review also displayed the high adherence and colonization potential of the circulated MDR UPECs currently prevalent in India. The present Indian scenario of limited availability of therapeutic options for treatment of UPEC-mediated UTI but the prevalence of the highly virulent MDR UPEC strains might have instigated several researchers, especially from southern India in the search of alternative therapeutic strategies to cope with the imminent therapeutic challenges and encounter the spread of virulent MDR UPECs. Furthermore, exploration of several mechanisms of UPEC infections and the quest for potential drug targets might aid in UPEC research in the future with successful novel therapeutic interventions.

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Materials Availability Not applicable

Author Contribution A. Ghosh, D. Bandyopadhyay, and S. Koley contributed equally in the data collection, compilation, and writing of this manuscript. M. Mukherjee participated in the preparation and correction of the manuscript.

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