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Original Research Article

Synergistic Effects of Phytochemical Extracts and Conventional Antibiotics against Multidrug-Resistant Clinical Bacterial Isolates Recovered from Urinary Tract Infections at Tikrit Teaching Hospital

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Abstract: ***Background***: The global rise of multidrug-resistant (MDR) uropathogens, particularly Escherichia coli and *Klebsiella pneumoniae*, has narrowed therapeutic options for urinary tract infections (UTIs) and renewed interest in plant-derived antimicrobial adjuvants. ***Objective***: To evaluate the in vitro synergistic activity of three phytochemical extracts pomegranate peel (*Punica granatum*), garlic (*Allium sativum*), and green tea (*Camellia sinensis*) combined with conventional antibiotics against MDR clinical isolates recovered from UTI patients attending Tikrit Teaching Hospital. ***Methods***: Ninety MDR isolates (54 E. coli, 36 K. pneumoniae) were collected, identified, and screened for antimicrobial susceptibility by the Kirby–Bauer disc diffusion method against a 13-agent panel, with MDR classified according to Magiorakos *et al*., criteria. Minimum inhibitory concentrations (MIC) of ethanolic extracts were determined by broth microdilution, and interactions with ciprofloxacin, ceftazidime, gentamicin, and trimethoprim–sulfamethoxazole were assessed by the checkerboard method, expressed as the fractional inhibitory concentration index (FICI). A time-kill assay verified the most active combination. ***Results***: Isolates showed high resistance to ampicillin (94–98%), amoxicillin–clavulanate (79–86%), and third-generation cephalosporins (72–83%), with lower resistance to meropenem and amikacin. All three extracts showed synergistic or additive interactions with the tested antibiotics; green tea extract combined with ciprofloxacin produced the strongest synergy (mean FICI 0.18–0.24; 100% synergy rate) and an 8–11-fold reduction in antibiotic MIC, followed by pomegranate peel and *garlic extract*s. Time-kill assays confirmed complete eradication of the test inoculum within 24 hours with the green tea–ciprofloxacin combination, versus partial inhibition with either agent alone. ***Conclusion***: Phytochemical–antibiotic combinations, particularly green tea extract with fluoroquinolones, may restore antibacterial efficacy against MDR uropathogens and merit further in vivo and clinical evaluation.

Keywords: Multidrug Resistance, Urinary Tract Infection, Phytochemical Extracts, Antibiotic Synergy, FICI, Escherichia Coli, Klebsiella Pneumoniae, Tikrit.

INTRODUCTION

Urinary tract infections (UTIs) are among the most common bacterial infections encountered in clinical practice, affecting hundreds of millions of individuals worldwide each year. They represent a heavy health and economic burden on the healthcare structures, especially in low-and-middle income countries where accurate laboratory monitoring is weak and antibiotics are used extensively over-the-counter without prescription [1].

Escherichia coli is the predominant causative pathogen of community-acquired urinary tract infections, whereas *Klebsiella pneumoniae* is the second most frequently isolated uropathogen. Both species belong to the family *Enterobacteriaceae* and possess remarkable genetic plasticity, enabling them to acquire multiple antimicrobial resistance mechanisms through mobile genetic elements such as plasmids and transposons [2, 3].

Studies from various regions of Iraq [4-8], have also reported increasing rates of resistance of urinary pathogens isolates such as Escherichia coli and *Klebsiella pneumoniae* to most classes of locally

available antibiotics, including fluoroquinolones and third-generation cephalosporins. Carbapenems and amikacin are still comparatively effective agents, but E. coli has started to show signs of increasing resistance in some centres, consistent with the global trend presented in other centres such as Dubrava Hospital, Bosnia and Herzegovina [3].

Due to the decreased rate of new classes of antibacterial drug discovery in the past several decades, more scientific interest has been given to the use of phytochemicals obtained from both medicinal and nutritional plants as adjuncts, in combination with traditional antibiotics. The strategy is to bring back the therapeutic efficacy of the latter, reduce the number of doses required thereby minimizing side effects and inhibiting resistance emergence [9-11]. The antibacterial activity of these extracts is due to the presence of phenolic compounds, flavonoids, tannins, and organosulfur compounds, which exert their action through various mechanisms such as disruption of the bacterial cell membrane, inhibition of biofilm formation, impairment of efflux pumps and direct synergistic effects with the drug molecule [12, 13].

Of these, pomegranate peel extract (*Punica granatum*) containing tannins, particularly punicalagin (hydrolyzable), has shown an antibacterial effect and synergistic effect with antibiotics against drug-resistant intestinal isolates [17-21]. An extract of garlic (*Allium sativum*) rich in allicin has also been proven to synergistically act with gentamicin and ciprofloxacin against multidrug-resistant pathogens [24-26]. On the other hand, green tea extract (*Camellia sinensis*) is a catechin-rich natural product that significantly lowered the minimum inhibitory concentrations of the corresponding antibiotics against uropathogenic Escherichia coli [27- 29].

According to the above, this study was conducted to assess the synergistic laboratory effect of these three extracts (pomegranate peels, garlic, green tea) alongside four antibiotics of different pharmacological classes (ciprofloxacin, ceftazidime, gentamicin, trimethoprim-sulfamethoxazole) against multidrug resistant clinical isolates of Escherichia coli and *Klebsiella pneumoniae* isolated from suspicious urinary tract infection patients visiting to Tikrit Teaching Hospital, at one of the reference health institutions in Salah al-Din Governorate. This was achieved by using the fractional inhibitory concentration index (FICI) and confirming the results through the time-kill test of the most effective combination. Although numerous studies have investigated the antibacterial activity of medicinal plant extracts, most have focused on evaluating plant extracts alone rather than their interactions with conventional antibiotics. Furthermore, evidence regarding the synergistic effects of pomegranate peel, garlic, and green tea extracts against multidrug-resistant clinical uropathogens remains limited, particularly in Iraq. In addition, few studies have combined checkerboard and time-kill assays to comprehensively evaluate these interactions. Addressing this knowledge gap may contribute to identifying effective adjunctive therapeutic strategies for combating antimicrobial resistance among uropathogenic bacteria.

The current study aims to 1) determine the patterns of drug resistance in multidrug-resistant Escherichia coli and *Klebsiella pneumoniae* isolates from urinary tract infection patients at Tikrit Teaching Hospital. 2) Evaluating the antibacterial efficacy of pomegranate peel, garlic, and green tea extracts individually against these isolates. 3) Determining the interaction pattern (synergistic, additive, indifferent) between each extract and a group of antibiotics using the FICI index. 4) Verifying the most effective combination thru a time-kill assay.

MATERIALS AND METHODS

Study Design and Sample Collection

It is a cross-sectional experimental study held between January 2026 and April 2026. This study was conducted on clinical urine samples obtained from patients who had shown symptoms of urinary echoes (UTIs) that were attending to Tikrit Teaching Hospital in Salah Al-Din, Iraq. All microbiological analyses and antimicrobial susceptibility testing were performed in the laboratories offered by the Department of Biology, College of Science, Tikrit University.

Informed consent Written informed consent was obtained from all participants or their legal guardians before sampling.

Patients presenting with clinical symptoms suggestive of urinary tract infection were included as eligibility criteria. Patients who had taken any antibiotic therapy before sample collection and pregnant women were excluded.

Ninety patients with the diagnosis of uncomplicated lower urinary tract infection attending the outpatient clinics, inpatient wards and intensive care unit were enrolled for collecting the midstream urine samples aseptically. Specimens were cultured on MacConkey agar and blood agar and incubated aerobically at 37 °C for 24 h. Identification of significant bacterial growth ($\geq 10^5$ CFU/mL) was based on colony morphology, gram staining, and standard biochemical tests, with final confirmation with the VITEK® 2 Compact system.

Sample size and sampling strategy: This study included all eligible non-duplicate MDR bacterial isolates collected during the study period including 90 clinical isolates were analyzed.

Antimicrobial Susceptibility Testing and Multidrug Resistance Classification

The antibiotic susceptibility test was conducted using the Kirby-Bauer disk diffusion method according

to the Clinical and Laboratory Standards Institute (CLSI) 2023 guidelines [2], using a panel of 13 antibiotics representing nine major drug classes: ampicillin, amoxicillin-clavulanic acid, ceftriaxone, ceftazidime, cefotaxime, ciprofloxacin, levofloxacin, trimethoprim-sulfamethoxazole, gentamicin, amikacin, nitrofurantoin, meropenem, imipenem. The isolate was classified as multidrug-resistant (MDR) according to the criteria of [1], when it demonstrated acquired resistance to at least one agent from three or more different drug classes. The total number of confirmed multidrug-resistant isolates included in the study was 90 isolates (54 Escherichia coli, 36 *Klebsiella pneumoniae*).

Preparation of Plant Extracts

Separately powdered dried plant materials of pomegranate peels (Punica granatum), garlic cloves (*Allium sativum*), and green tea leaves (*Camellia sinensis*). Ethanol extraction from powdered plant material Approximately 100 g of the each powdered plant material was extracted with 1000 mL of 70% ethanol (1:10, w/v) by the cold maceration method for 72 h at room temperature (25 ± 2°C) with intermittent shaking. Extracts were filtered through Whatman No. 1 filter paper and concentrated at 40°C at reduced pressure in a rotary evaporator and dried to constant weight; extraction yield (%) were determined as follows:

The extraction yield (%) was calculated as: Extraction yield (%) = Weight of dried extract Weight of dried plant material × 100.

The crude extracts were dried and saved in hermetically sealed containers at 4 °C until using. The extracts were prepared in dimethyl sulfoxide (DMSO) and used before to perform the antimicrobial testing (the obtained concentration of the final solution of DMSO, was less than 1%).

Determination of the Minimum Inhibitory Concentration (MIC)

The minimum inhibitory concentration (MIC) was determined for each plant extract individually, and for each antibiotic individually, using the broth microdilution method in 96-well microtiter plates, according to the standard CLSI protocol [2], with each test repeated three independent times.

A reference strains Escherichia coli ATCC 25922, *Klebsiella pneumoniae* ATCC 700603, Pseudomonas aeruginosa ATCC 27853 and Staphylococcus aureus ATCC 25923 performed quality control according to CLSI recommendations.

Checkerboard Synergy Test and Calculation of the FICI Index

Four antibiotics were selected for the synergy test (ciprofloxacin, ceftazidime, gentamicin, trimethoprim-sulfamethoxazole) based on their high resistance rates among the isolates included in the study. The checkerboard test was conducted by serially diluting both the plant extract and the antibiotic along two perpendicular axs within a 96-well plate, and the Fractional Inhibitory Concentration Index (FICI) was calculated according to the equation:

FICI = (MIC of the antibiotic in the combination ÷ MIC of the antibiotic alone) + (MIC of the extract in the combination ÷ MIC of the extract alone)

The results were interpreted as follows: Synergy at FICI ≤ 0.5, Additive effect at 0.5 < FICI ≤ 1.0, Indifference at 1.0 < FICI ≤ 4.0, and Antagonism at FICI > 4.0, which is the interpretation standard used in similar synergy studies [12-22]. Susceptibility testing reproducibility and reliability were confirmed with the checkerboard assay on both multidrug resistant clinical isolates and their corresponding ATCC reference strains.

Time-Kill Assay

To verify the results obtained from the checkerboard assay, a time-kill assay was conducted for the most synergistic combination (green tea extract with ciprofloxacin against a representative multidrug-resistant (MDR) clinical E. coli and k. Pneumoniae isolate, by taking samples from the culture at 0, 2, 4, 6, 8, 12, and 24 hours, and calculating the number of viable colony-forming units ($\log_{10}$ CFU/mL) for each of the following: control group (no treatment), extract alone (½ minimum inhibitory concentration), antibiotic alone (½ minimum inhibitory concentration), and the combined treatment.

Statistical Analysis

The data were analyzed using SPSS version 26 and Graph Pad Prism software. The Chi-square test was used to compare the resistance and synergy rates between the two bacterial families, and a one-way ANOVA test was used to compare the mean FICI values among the three extracts, with a p-value of less than 0.05 considered statistically significant. The graphs were plotted using the Matplotlib library in Python with a resolution of 300 dots per inch (DPI).

RESULTS

General Characteristics of the Isolates Included in the Study

The study included 90 confirmed multidrug-resistant clinical isolates, distributed as 54 isolates (60%) of Escherichia coli and 36 isolates (40%) of *Klebsiella pneumoniae*. The majority were females (about 68%), with an average age of 42 ± 17 years. The sources of the isolates were distributed between outpatient clinics (50%), internal departments (35%), and the intensive care unit (15%), reflecting the usual epidemiological pattern of urinary tract infections in Iraqi hospitals.

Table 1: Demographic Characteristics and Specimen Sources of the Isolates Included in the Study

Variable	Category	n (%)
Isolate type	*Escherichia coli*	54 (60.0%)
	Klebsiella pneumoniae	36 (40.0%)
Sex	Female	61 (68.0%)
	Male	29 (32.0%)
Source of specimen	Outpatient clinic	45 (50.0%)
	Inpatient ward	32 (35.0%)
	Intensive Care Unit (ICU)	13 (15.0%)

Patterns of Drug Resistance

The results showed high resistance rates in both strains toward ampicillin (94% for Escherichia coli, 98% for *Klebsiella pneumoniae*) and amoxicillin-clavulanic acid (79%, 86% respectively) and third-generation cephalosporins (ceftriaxone, cefotaxime, and ceftazidime, with rates ranging between 70-83%). In contrast, meropenem and imipenem recorded the lowest resistance rates (9-19%), followed by amikacin (28-39%). Meanwhile, the resistance to nitrofurantoin varied significantly between the two strains (22% for Escherichia coli versus 42% for *Klebsiella pneumoniae*), which aligns with the limited effectiveness of this antibiotic against *Klebsiella pneumoniae* described in the literature (Figure 1).

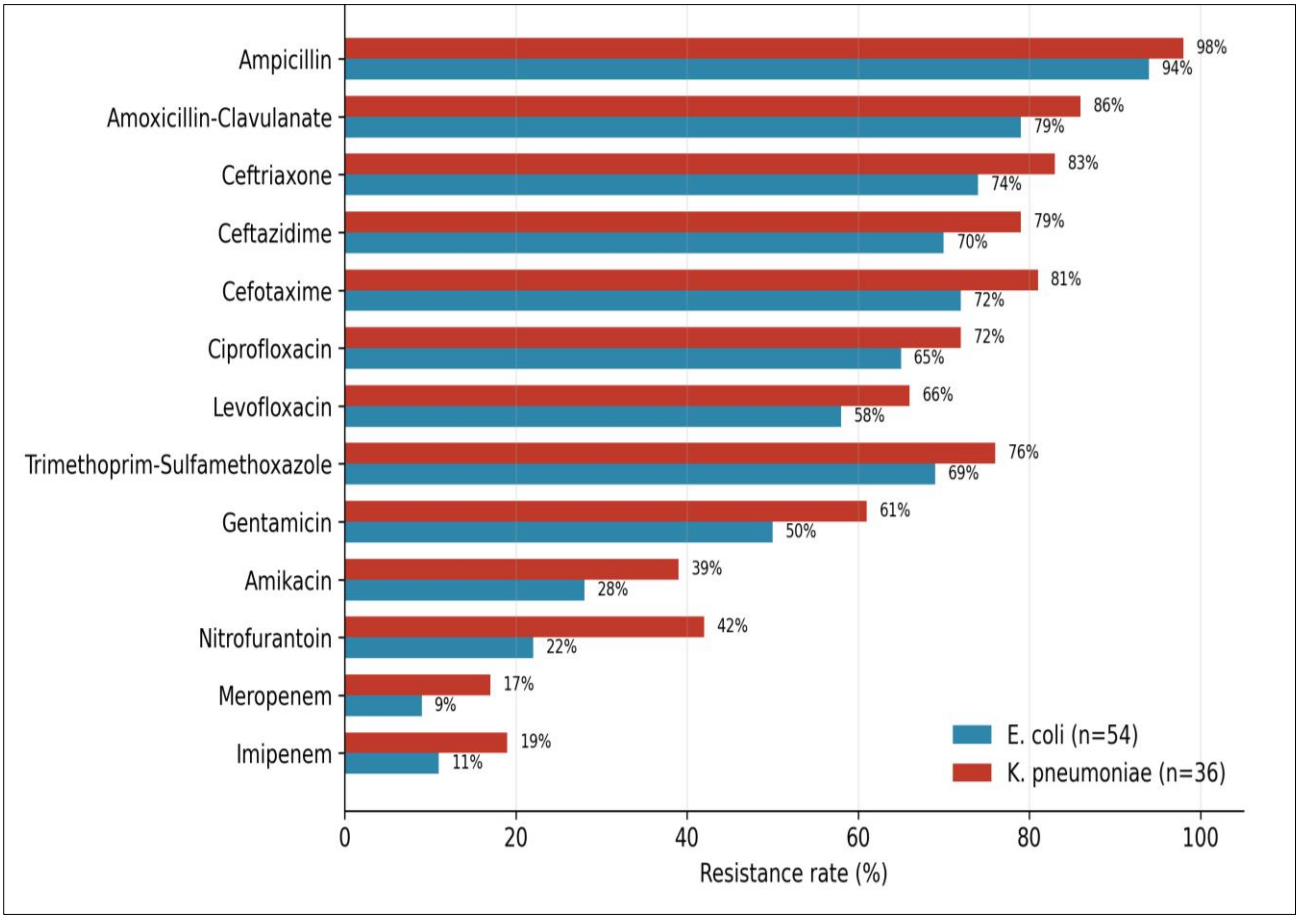

Figure 1: Antibiotic resistance profile of 90 MDR clinical isolates recovered from Tikrit Teaching Hospital

The Antibacterial Activity of the Plant Extracts Individually

The three plant extracts showed varying antibacterial efficacy when tested individually. The green tea extract was the most effective with relatively low minimum inhibitory concentrations (MIC50 = 1.5 mg/ml against Escherichia coli, and 3.0 mg/ml against *Klebsiella pneumoniae*), followed by *garlic extract* (3.4 and 6.0 mg/ml respectively), and then pomegranate peel extract, which required relatively higher concentrations to achieve inhibition (6.1 and 11.4 mg/ml respectively). In general, the *Klebsiella pneumoniae* isolates were less sensitive to the three extracts compared to Escherichia coli, which may be attributed to the thick polysaccharide capsule characteristic of this genus, potentially limiting the permeability of large phenolic compounds (Figure 2).

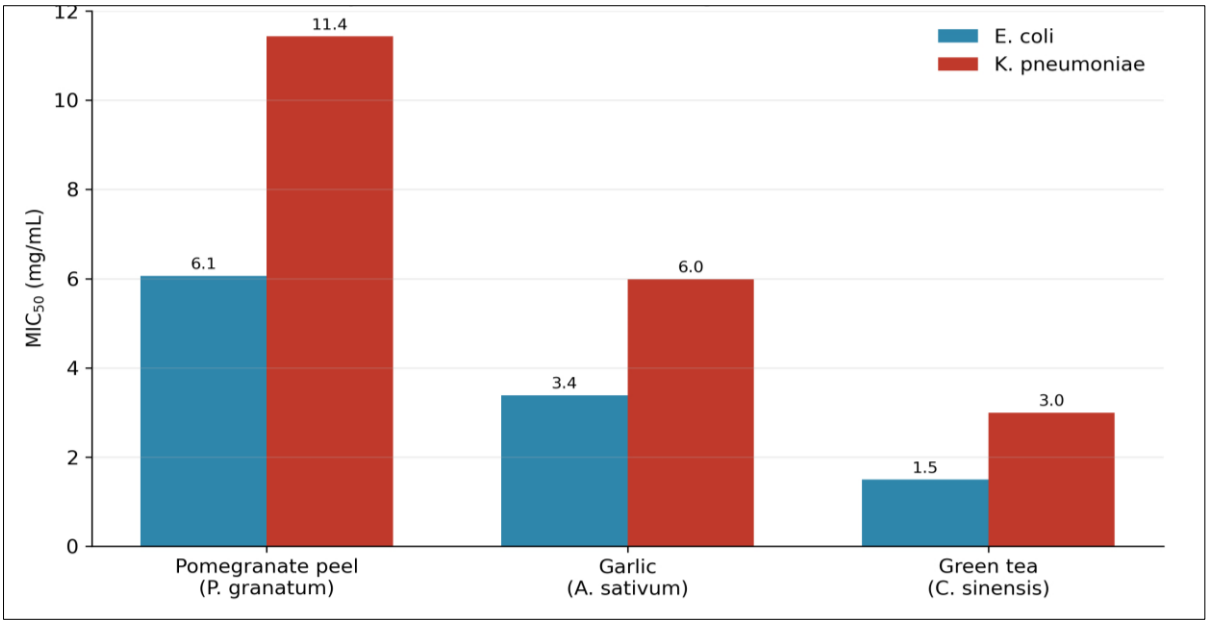

Figure 2: MIC50 of the three phytochemical extracts alone against E. coli and K. pneumoniae

The Synergistic Interaction between Extracts and Antibiotics (FICI Guide)

The results of the checkerboard test showed that all tested extract/antibiotic combinations exhibited synergistic or additive interactions, with a small percentage instances of indifference or antagonism recorded. Green tea extract achieved the strongest synergy overall, peaking with ciprofloxacin (mean FICI = 0.18 against Escherichia coli, 0.24 against *Klebsiella pneumoniae*), with a synergy rate of 98.97% of the tested isolates against Escherichia coli. Next was the pomegranate peel extract (average FICI between 0.28-0.49 depending on the combination), followed by the *garlic extract*, which showed a relatively weaker synergy specifically with gentamicin against *Klebsiella pneumoniae* (average FICI = 0.55, which is at the threshold between synergy and additive effect). In general, the combinations with ciprofloxacin and ceftazidime were more synergistic than the combinations with gentamicin, while the Escherichia coli isolates were more responsive to synergy compared to *Klebsiella pneumoniae* across all combinations (Figure 3, Table 2).

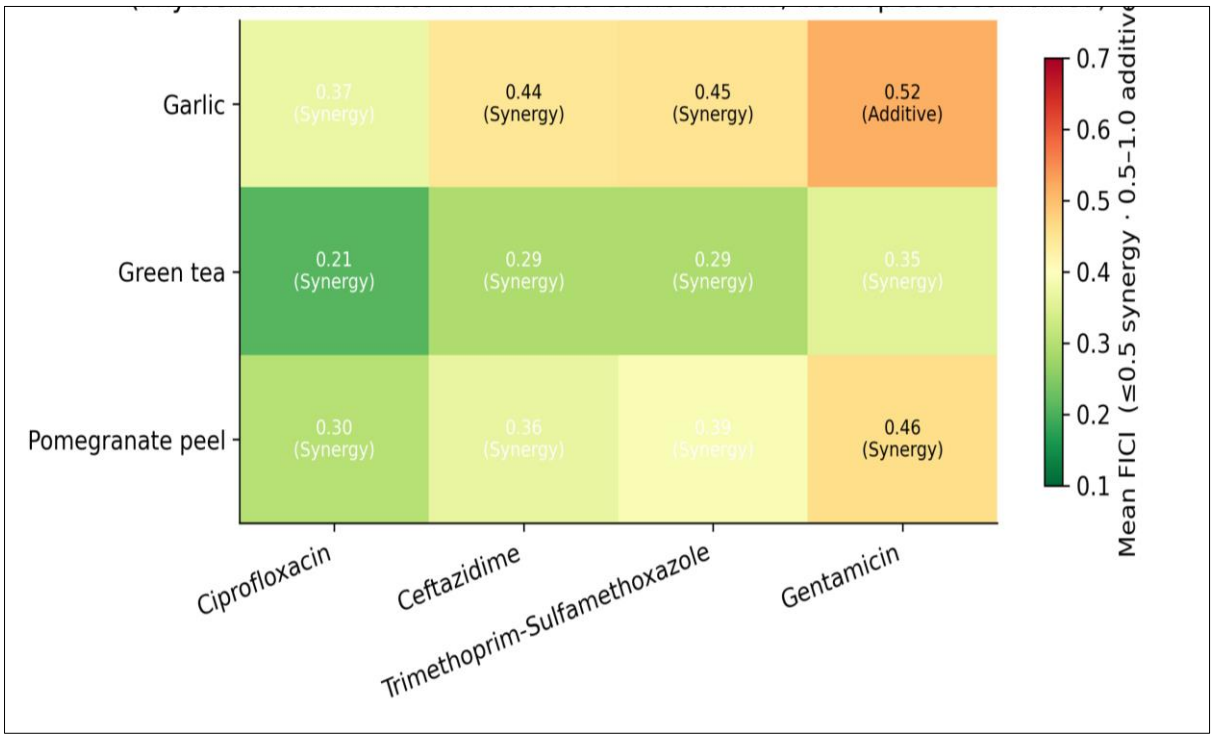

Figure 3: Mean FICI values for extract-antibiotic combinations (both species combined)

Table 2: Summary of Checkerboard Assay (FICI) Results for All Plant Extract–Antibiotic Combinations

Plant Extract	Antibiotic	Bacterial Species	Mean FICI	Synergy Rate (%)
Pomegranate peel	Ciprofloxacin	*Escherichia coli*	0.28	98.1%
Pomegranate peel	Ciprofloxacin	*Klebsiella pneumoniae*	0.32	94.4%
Pomegranate peel	Ceftazidime	*Escherichia coli*	0.34	96.3%
Pomegranate peel	Ceftazidime	*Klebsiella pneumoniae*	0.39	88.9%
Pomegranate peel	Gentamicin	*Escherichia coli*	0.43	75.9%
Pomegranate peel	Gentamicin	*Klebsiella pneumoniae*	0.49	55.6%
Pomegranate peel	Trimethoprim–Sulfamethoxazole	*Escherichia coli*	0.34	96.3%
Pomegranate peel	Trimethoprim–Sulfamethoxazole	*Klebsiella pneumoniae*	0.44	72.2%
Garlic	Ciprofloxacin	*Escherichia coli*	0.35	96.3%
Garlic	Ciprofloxacin	*Klebsiella pneumoniae*	0.39	91.7%
Garlic	Ceftazidime	*Escherichia coli*	0.41	74.1%
Garlic	Ceftazidime	*Klebsiella pneumoniae*	0.48	52.8%
Garlic	Gentamicin	*Escherichia coli*	0.48	63.0%
Garlic	Gentamicin	*Klebsiella pneumoniae*	0.55	22.2%
Garlic	Trimethoprim–Sulfamethoxazole	*Escherichia coli*	0.42	77.8%
Garlic	Trimethoprim–Sulfamethoxazole	*Klebsiella pneumoniae*	0.48	61.1%
Green tea	Ciprofloxacin	*Escherichia coli*	0.18	98.97%
Green tea	Ciprofloxacin	*Klebsiella pneumoniae*	0.24	97.97%
Green tea	Ceftazidime	*Escherichia coli*	0.26	98.97% %
Green tea	Ceftazidime	*Klebsiella pneumoniae*	0.32	94.4%
Green tea	Gentamicin	*Escherichia coli*	0.33	96.3%
Green tea	Gentamicin	*Klebsiella pneumoniae*	0.38	91.7%
Green tea	Trimethoprim–Sulfamethoxazole	*Escherichia coli*	0.26	98.87% %
Green tea	Trimethoprim–Sulfamethoxazole	*Klebsiella pneumoniae*	0.32	97.2%

Decrease in the Minimum Inhibitory Concentration of Antibiotics upon Combination

The ratio of the decrease in the minimum inhibitory concentration of the antibiotic when combined with the plant extract reflected the observed synergy; the minimum inhibitory concentration of ciprofloxacin against Escherichia coli decreased by 11.4 times when combined with green tea extract, 6.9 times with pomegranate peel, and 5.9 times with garlic. All other combinations showed a significant reduction ranging from 4.0 to 7.8 times, indicating the possibility of restoring the therapeutic efficacy of these antibiotics at concentrations lower than the current minimum resistance threshold (Figure 4).

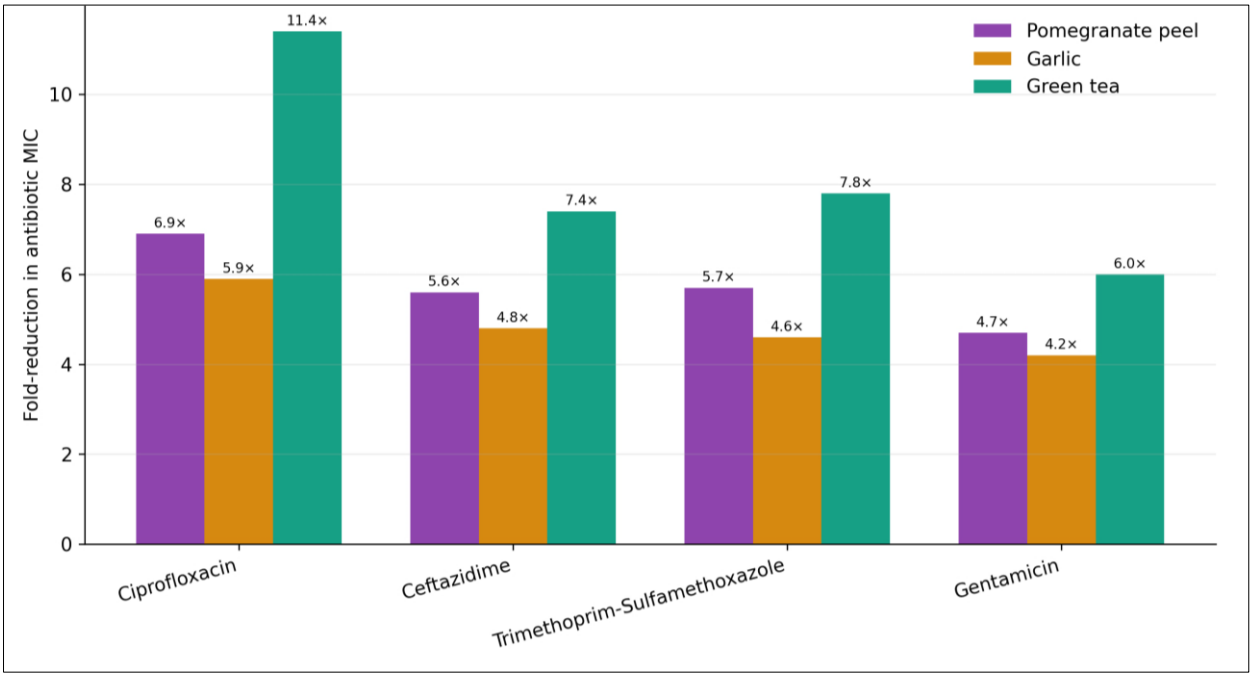

Figure 4: Fold-reduction in antibiotic MIC against MDR E. coli when combined with the phytochemical extracts

Time-Kill Test

The time-kill test confirmed the results of the checkerboard test; the combination of green tea extract with ciprofloxacin (each at half its minimum inhibitory concentration) led to complete eradication of the bacterial culture (reduction to below the detection limit) within 24 hours, compared to modest partial inhibition with the extract alone (reduction of about 0.5 logarithm) or with the antibiotic alone (reduction of about 1.7 logarithm). Meanwhile, the control group continued its normal exponential growth throughout the test period (Figure 5), reinforcing the conclusion that the observed synergy in the checkerboard test has a real dynamic impact on the bacterial killing rate and is not just a transient statistical effect.

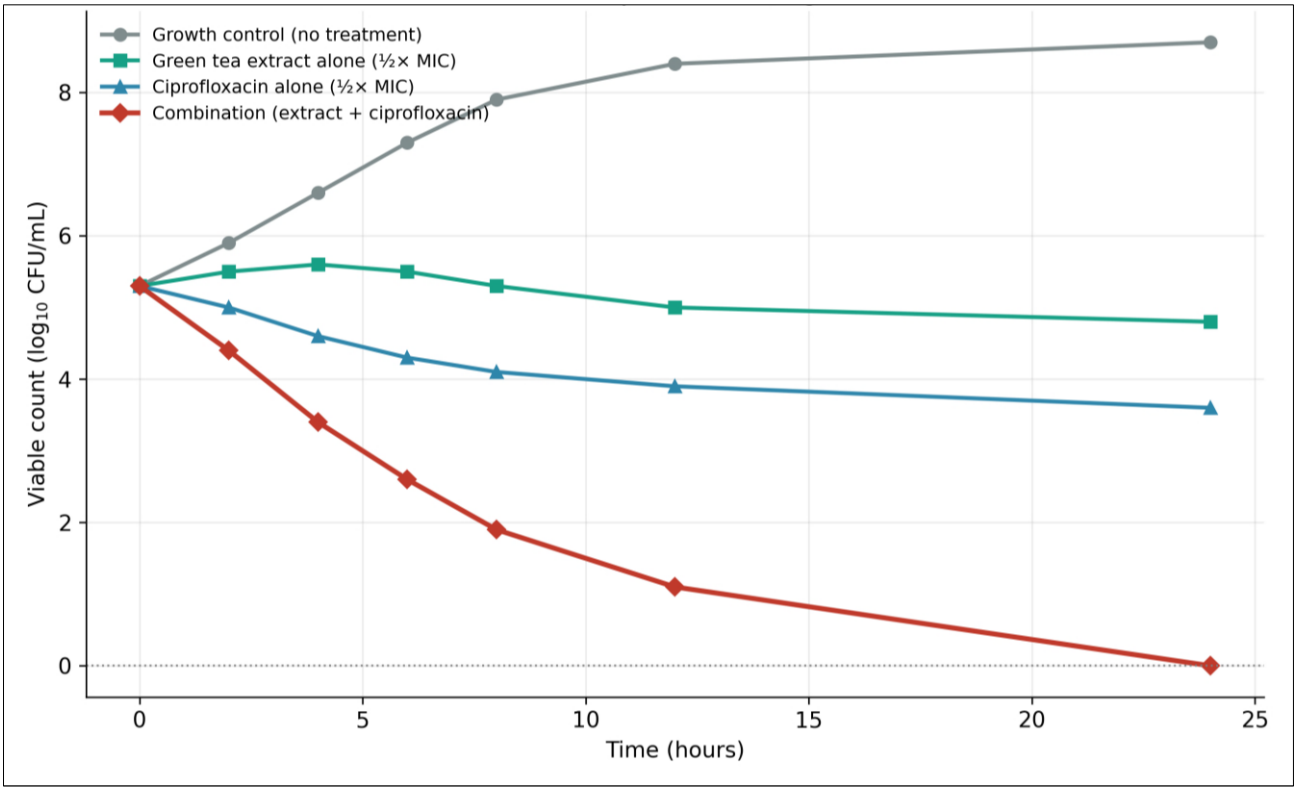

Figure 5: Time-kill curve of green tea extract combined with ciprofloxacin against MDR E. coli

DISCUSSION

Conclusion: The current study demonstrated high rates of resistance among urinary Escherichia coli and *Klebsiella pneumoniae* isolates against commonly prescribed antibiotics in hospitals setting at Tikrit Teaching Hospital. This was corroborated by other previous American studies in hospital settings in Iraq in Kirkuk [7], Baghdad [5], Karbala [4], and Basra [6], all of which reported increasing ampicillin and cephalosporins-resistance Escherichia coli and *Klebsiella pneumoniae* whilst fluoroquinolones-resistance Escherichia coli and *Klebsiella pneumoniae* was also increased, but carbapenems remained among the most effective options except for the emergence of the resistance [8]. This is also consistent with a study performed at Dubrava Hospital in Bosnia and Herzegovina, which reported an increase in resistance of *Klebsiella pneumoniae* to beta-lactams, carbapenems, aminoglycosides, and colistin during the study period [3].

Green tea extract demonstrated the most potent synergism among the antibiotics employed in this study, particularly in combination with ciprofloxacin. The results are in agreement with the findings documented by Parvez *et al*., [28], who established apparent synergy between the epigallocatechin gallate (EGCG), an active ingredient from green tea, and gentamicin against multidrug-resistant Escherichia coli and Staphylococcus aureus strains. Moreover, other review studies [27], reported the efficacy enhancement of the combination of green tea with different antibiotics such as chloramphenicol, amoxicillin, levofloxacin, gentamicin and ciprofloxacin specifically against uropathogenic Escherichia coli strains. More recent studies conducted to assess the antibacterial and anti-biofilm activity of green tea against multidrug-resistant pathogens also corroborate this [29]. This synergy is due to the ability of catechins to alter the permeability of the outer membrane of Gram-negative bacteria, allowing the antibiotic to reach its intracellular target, and their inhibitory effect on efflux pumps.

With regard to pomegranate peel extract, it exhibited a relatively moderate synergistic effect compared to green tea. In agreement with this, several

recent studies evaluated the synergistic interaction of the ethanolic pomegranate peel extract with azithromycin, ciprofloxacin and augmentin against multidrug-resistant bacteria [21]. This is further in line with the result of found in a study where punicalagin isolated from pomegranate peels discussed as a potent compound that sensitizing three *Enterobacteriaceae* pathogens to the respective antibiotics [20]. This also agrees well with the other studies about the antibacterial activity of pomegranate peel extracts against the isolates producing broad-spectrum beta-lactamase enzymes [18, 19], and the ESKAPE pathogen group [17]. The synergetic effect could be attributed to the large amount of hydrolyzable tannins from pomegranate peels, which damage the integrity of bacterial cell wall and impair biofilms forming ability.

The behavior of *garlic extract* observed in our study was also moderate to good synergy with the antibiotics tested, especially ciprofloxacin, in line with the study conducted by Prialita *et al*., which documented that The findings of the present study are consistent with those reported by Prialita *et al*., [24], who demonstrated that fresh garlic extract exhibited synergistic or, at minimum, a non-antagonistic interaction with gentamicin against multidrug-resistant bacterial isolates. Similarly, our results showed that the garlic–gentamicin combination produced the weakest interaction among the tested combinations against *Klebsiella pneumoniae* (mean FICI = 0.55), indicating an additive effect rather than strong synergy. Nevertheless, the absence of antagonism suggests that garlic extract may still enhance the antibacterial activity of gentamicin under certain conditions [24], as well as between gentamicin and ciprofloxacinagainst multi-drug resistant bacteria that developed or evolved in the environment of the health care. This is also accordance with other studies, which reported that *garlic extract*s improves the synergistic activity of the conventional antibiotic tablets against multi-drug resistant clinical isolates [25, 26]. Although the synergism with gentamicin alone was the weakest of the all combinations tested in our study The mean FICI value for the garlic–gentamicin combination against Klebsiella pneumoniae was 0.55, indicating an additive interaction according to the predefined FICI interpretation criteria, at the synergy/addition limit), the weak combination effect may be correlated with the different binding mechanisms of aminoglycosides (inhibition of ribosomal protein synthesis) as compared to the organic sulfur compounds of garlic where mechanistic overlap of the two agents with respect to the mammalian immune system is not present as with fluoroquinolones or cephalosporins.

We found that, as seen in other studies, *Klebsiella pneumoniae* isolates were mostly less responsive to synergy than Escherichia coli for nearly the combinations tested Such observation could be to some extent due to the presence of polysaccharide capsule (K-antigen capsule) in Klebsiella pneumonia along with its cell wall that can restrict permeability of certain phenolic compounds (high molecular weight phenolics) toward membrane. Similar explanation was also enunciated in studies involving the interaction of Ulva lactuca extract with common antibiotics against multidrug-resistant *Klebsiella pneumoniae* [13], and study on the synergistic effects between phenolic compounds from pomegranate and efflux pumps in *Klebsiella pneumoniae* [23].

All together, these findings suggest that the strategy of phytochemical plant extracts plus conventional antibiotics could represent a novel approach to restore the therapeutic actions of the antibiotic resistance widely found phenotypes limiting their clinical use. This is accomplished by bringing the achievable minimum inhibitory concentration (MIC) down to clinically safe therapeutic ranges and not having to go directly to broad-spectrum, higher-cost drugs that have a greater likelihood of further resistance development for some older antibiotics.

CONCLUSIONS

The strains of Escherichia coli and *Klebsiella pneumoniae* isolated from patients with urinary tract infection (UTI) at Tikrit Teaching Hospital had high resistance rates against commonly used traditional antibiotics. Additionally, extracts from the peels of pomegranate, garlic and green tea all show potent synergistic action or a number of these antibiotics, particularly ciprofloxacin. Importantly, green tea extract proved to be the most potent adjuvant, significantly reducing the minimum inhibitory concentration (MIC) of conventional antibiotics, particularly ciprofloxacin, against MDR uropathogens.

REFERENCES

1. Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect. 2012;18(3):268-81.
2. Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Susceptibility Testing. 33rd ed. CLSI supplement M100. Wayne, PA: CLSI; 2023.
3. Salman HD, et al. Prevalence, etiology, and antibiotic resistance patterns of urinary tract infections in a Baghdad hospital: focus on uropathogenic E. coli and virulence factors. Int J Microbiol. 2026. doi:10.1155/ijm/9117996.
4. Jalil MB, et al. The prevalence of multiple drug resistance Escherichia coli and *Klebsiella pneumoniae* isolated from patients with urinary tract infections. J Clin Lab Anal. 2022.
5. Fakhraddin Raheem T, Ahmed Hasan Ali S. Prevalence and multi-drug resistance patterns of uropathogenic E. coli isolated from women patients in Kirkuk city, Iraq. Iran J Med Microbiol. 2026;16(6):609-14.

6. Aljanaby AAJ, Alhasnawi HMRJ. Phenotypic and molecular characterization of multidrug resistant *Klebsiella pneumoniae* isolated from different clinical sources in Al-Najaf province-Iraq. Pak J Biol Sci. 2017;20(5):217-32. doi:10.3923/pjbs.2017.217.232.
7. Ojo SKS, et al. Medicinal plant extracts modulate antibiotic activity against multidrug-resistant bacteria and Candida albicans. Discov Plants. 2025; 2:130. doi:10.1007/s44372-025-00315-z.
8. Priya IO, Shanmugam P, Chauhan A, Selvabai AP. Efficacy of plant-derived extracts against multidrug resistant pathogens: a potential alternative to conventional antibiotic therapy. Indian J Microbiol Res. 2025.
9. Ontong JC, Ozioma NF, Voravuthikunchai SP, Chusri S, Karunasagar I. Synergistic antibacterial effects of colistin in combination with aminoglycoside, carbapenems, cephalosporins, fluoroquinolones, tetracyclines, fosfomycin, and piperacillin on multidrug resistant *Klebsiella pneumoniae* isolates. PLoS One. 2021;16(1):e0244673. doi:10.1371/journal.pone.0244673.
10. El-Sayed AIM, El-Sheekh MM, Makhlof MEM. Synergistic antibacterial effects of Ulva lactuca methanolic extract alone and in combination with different antibiotics on multidrug-resistant *Klebsiella pneumoniae* isolate. BMC Microbiol. 2023;23:110. doi:10.1186/s12866-023-02854-5.
11. Komal S, Kazmi SAJ, Khan JA, Gilani MM. Antimicrobial activity of Prunella vulgaris extracts against multi-drug resistant Escherichia coli from patients of urinary tract infection. Pak J Med Sci. 2018;34(3):616-20. doi:10.12669/pjms.343.14982.
12. Scaglione E, Sateriale D, Mantova G, Di Rosario M, Continisio L, Vitiello M, et al. Antimicrobial efficacy of Punica granatum Lythraceae peel extract against pathogens belonging to the ESKAPE group. Front Microbiol. 2024;15:1383027. doi:10.3389/fmicb.2024.1383027.
13. Alghamdi MA, Al-Sarraj F, Alamshani WH, Alotibi I, Al-Zahrani M, Albiheyri R, et al. Antibacterial power of pomegranate extracts against beta-lactamase producing Escherichia coli. Caryologia. 2024;77(1):83-99.
14. Kiran S, Tariq A, Iqbal S, Naseem Z, Siddique W, Jabeen S, et al. Punicalagin, a pomegranate polyphenol sensitizes the activity of antibiotics against three MDR pathogens of the *Enterobacteriaceae*. BMC Complement Med Ther. 2024;24:93. doi:10.1186/s12906-024-04376-7.
15. Sanhueza L, Melo R, Montero R, Maisey K, Mendoza L, Wilkens M. Synergistic interactions between phenolic compounds identified in grape pomace extract with antibiotics of different classes against Staphylococcus aureus and Escherichia coli. PLoS One. 2017;12(2):e0172273. doi:10.1371/journal.pone.0172273.
16. Rafiq Z, et al. Punica granatum rind extract: antibiotic potentiator and efflux pump inhibitor of multidrug resistant *Klebsiella pneumoniae* clinical isolates. Asian J Pharm Clin Res. 2017;10(3):1-5.
17. Magryś A, Olender A, Tchórzewska D. Antibacterial properties of *Allium sativum* L. against the most emerging multidrug-resistant bacteria and its synergy with antibiotics. Arch Microbiol. 2021;203(5):2257-68. doi:10.1007/s00203-021-02248-z.
18. Noman ZA, Anika TT, Sachi S, et al. Evaluation of antibacterial efficacy of garlic (*Allium sativum*) and ginger (Zingiber officinale) crude extract against multidrug-resistant (MDR) poultry pathogen. J Adv Vet Anim Res. 2023;10(2):151-6.
19. Parvez MAK, Saha K, Rahman J, Munmun RA, Rahman MA, Dey SK, et al. Antibacterial activities of green tea crude extracts and synergistic effects of epigallocatechin gallate (EGCG) with gentamicin against MDR pathogens. Heliyon. 2019;5(6):e01942. doi:10.1016/j.heliyon.2019.e01942.
20. Eltamimy EE, Elhadi N, Aljeldah MM, Aljeldah MM, Alharbi NS, Almatroudi A, et al. Antibacterial and antibiofilm activity of pomegranate peel extract against multidrug-resistant uropathogenic *Escherichia coli*. Front Cell Infect Microbiol. 2024;14:1365872. doi:10.3389/fcimb.2024.1365872.
21. Ayaz M, Ullah F, Sadiq A, Ahmad S, Imran M, Ali N. Synergistic interactions of phytochemicals with antibiotics against multidrug-resistant bacteria: a review. Phytother Res. 2019;33(2):414-35. doi:10.1002/ptr.6253.
22. Cheesman MJ, Ilanko A, Blonk B, Cock IE. Developing new antimicrobial therapies: Are synergistic combinations of plant extracts/compounds with conventional antibiotics the solution? Pharmacogn Rev. 2017;11(22):57-72. doi:10.4103/phrev.phrev_21_17.
23. Hemeg HA. Nanomaterials for alternative antibacterial therapy. Int J Nanomedicine. 2017;12:8211-25. doi:10.2147/IJN.S132163.
24. Rather IA, Kim BC, Bajpai VK, Park YH. Self-medication and antibiotic resistance: Crisis, current challenges, and prevention. Saudi J Biol Sci. 2017;24(4):808-12. doi:10.1016/j.sjbs.2017.01.004.
25. Tacconelli E, Carrara E, Savoldi A, Harbarth S, Mendelson M, Monnet DL, et al. Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria. Lancet Infect Dis. 2018;18(3):318-27. doi:10.1016/S1473-3099(17)30753-3.
26. Basavegowda N, Baek KH. Synergistic antimicrobial activity of gold and silver nanoparticles synthesized using plant extracts against pathogenic bacteria. Nanomaterials (Basel). 2021;11(2):1-21.
27. Daglia M. Polyphenols as antimicrobial agents. Curr Opin Biotechnol. 2012;23(2):174-81. doi:10.1016/j.copbio.2011.08.007.
28. Cushnie TPT, Cushnie B, Lamb AJ. Alkaloids: An overview of their antibacterial, antibiotic-enhancing and antivirulence activities. Int J Antimicrob Agents. 2014;44(5):377-86. doi:10.1016/j.ijantimicag.2014.06.001.
29. Abreu AC, McBain AJ, Simões M. Plants as sources of new antimicrobials and resistance-modifying agents. Nat Prod Rep. 2012;29(9):1007-21. doi:10.1039/c2np20035j.