International Journal of Pharmacognosy and Herbal Drug Technology (IJPHDT)
ISSN: 3049-1630, Vol.02, Issue No. 08, 2025 (pp.95-106)
AKT PUBLICATION
ORIGINAL ARTICLE
https://www.aktpublication.com/index.php/ijphdt

Exploring The Synergistic Effects of Plant-Derived Compounds with Conventional Antibiotics Against MDR Strains

Hiren Ravindra Shirsath[1*], Prachi Kamleshbhai Pandya[1], Twisha Mehulkumar Patel[1]

[1] S.S.Agrawal College of Commerce and Management, Navsari, Gujarat, Pin- 396445

***Corresponding Author E-mail: hirenshirsath@gmail.com**

ABSTRACT

Multidrug-resistant (MDR) bacterial pathogens are emerging and becoming a dire concern, and researchers are dependent on innovative solutions to the problem to reestablish antibiotic susceptibility. This paper examined synergisitc influences of plant-derived agents chosen to comprise of a conventional antibiotic against MDR pathogens. Phytochemicals had moderate anti-microbial activity against the same bacteria when administered separately, and their combination with antibiotics resulted in marked elevation of antimicrobial activity, decreased minimum inhibitory effect (MIC) and postponed resistance development. Bactericidal activity was demonstrated to be sustained over time by time-kill assays and cytotoxicity testing showed positive safety ratios at synergistic concentrations. These results were also justified statistically. Generally, these findings indicate the therapeutic potential value of phytochemical-antibiotic combination in curbing the menace of antimicrobial resistance as a cost effective and a sustainable method of managing this global emergency.

Key Words:

Multidrug Resistance, Phytochemicals, Antibiotic Synergy, Antimicrobial Resistance, Combination Therapy

Article History:

Received April 10, 2025

Revised June 15, 2025

Accepted July 28, 2025

Published Aug. 20, 2025

DOI: https://doi.org/10.64063/30491630.vol.2.issue8.8

1. INTRODUCTION

Multidrug-resistant (MDR) bacterial pathogens are appearing and spreading across the globe at a critical rate, and threatening to undermine the efficacy of currently available antibiotics and, as a consequence, inhibit treatment choices. The increased use (misuse and overuse) of the antimicrobial agents[1], in addition to the low rate of new antibiotic development, has increased resistance in clinically important pathogens including Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, and methicillin-resistant Staphylococcus aureus (MRSA)[2]. Appropriate in the backdrop of this crisis, recent interest has been swelling in alternative or complementary approaches to revive the efficacy of antibiotics. Of these, plant-derived bioactive compounds which have shown wide chemical structure and pharmacological activity have shown good potential[3]. Recent research indicates that such phytochemicals could improve the effects of

conventional antibiotics in synergistic interactions, thus decreasing levels necessary to effect, minimizing toxicity, and possibly postponing resistance. But despite this, their combinatorial potency against MDR strains has been researched systematically in only a few reports and therefore, more in-depth research is required to determine their therapeutic potential[4].

1.1.Background of the Study

The ever-growing epidemic of multidrug-resistant (MDR) bacterial pathogens has created an extremely harsh burden on worldwide health systems resulting in elevated morbidity, death rates, and health care expenditures[5]. Previously, very effective antibiotics have gradually lost their successful use as a result of an excess of excessive consumption, improper usage, and the quick strategies of bacteria. This has posed an imperative demand of identifying new methods of fighting resistant infections[6]. The development of phytochemicals that are natural constituents of healing herbs with antimicrobial and synergistic attributes is one of the promising ways. Besides having direct inhibitory effects towards the pathogens, these bioactive agents can be used to either repair or renew the activity of classical antibiotics. As more and more plant-derived molecules[7], like epigallocatechin gallate (EGCG), berberine, carvacrol, and quercetin, among others, show promise in being able to resist bacteria, the addition of phytochemicals to antimicrobial treatment might offer a sustainable and effective course of action against MDR pathogens.

1.2.Statement of the Problem

Although considerable progress has been made in the area of antibiotic therapy, one of the critical issues receiving the growing concerns of the global healthcare system is the problem of multidrug resistance that undermines the quality of the treatment process and enhances the pandemic of infectious diseases[8]. Further, the lack of a promising pipeline of new antibiotics coupled with the time and cost expendures associated with bringing them to market only helps to contribute to the crisis. Despite promising in vitro antimicrobial and synergistic effects, the use of phytochemicals in combination with conventional antibiotics to treat MDR pathogens is still insufficiently studied, and poorly standardized[9]. This is due to the absence of a detailed data concerning their minimum inhibitory concentrations (MICs), relationships, and practical usability that limits their incorporation in clinical practice[10]. As such, it is urgently necessary to methodically assess the antibacterial potential of the chosen phytochemicals and their synergetic interaction with the commonly used antimicrobes to find alternative options to the proliferating problem of MDR infections.

1.3.Research Objectives

- To determine the minimum inhibitory concentrations (MICs) of selected antibiotics and plant-derived compounds against multidrug-resistant (MDR) bacterial isolates.
- To evaluate the synergistic interactions between plant-derived compounds and conventional antibiotics using standardized in-vitro assays.
- To assess the impact of phytochemical-antibiotic combinations on bacterial resistance development and suppression of MIC drift.
- To examine the safety and therapeutic selectivity of phytochemical-antibiotic combinations.

2. RESEARCH METHODOLOGY

This experimental research paper established the effectiveness of using plant products in complementing the efficacy of conventional antibiotics in killing the multidrug resistant (MDR) bacteria. Synergy was determined in a standardised in-vitro test and the effects measured with accepted indices of interaction and responses were validated in different clinical isolates of the MDR phenotypes of priority.

2.1.Description of research design

The methodology that we used included a controlled and laboratory based cross sectional design. Synergy of phytochemicals-antibiotics was assessed in broth microdilution checkerboard and time-kill assays that were confirmed using E-test strips crossing. In all experiments, a combination treatment, solvent control, phytochemical-alone control, antibiotic-alone control, and combination replicates, were repeated on three separate days.

2.2.Sample details

The non-replicated clinical isolates were composed of 60 clinical isolates (purposive panel) from 20 MDR Escherichia coli, 15 Klebsiella pneumoniae, 15 Pseudomonas aeruginosa and 10 Staphylococcus aureus (MRSA isolates) archived in the microbiology repository of the hospital. Quality controls with reference strains (ATCC 25922, 27853, 29213 and 43300) were also added. Purified epigallocatechin gallate (EGCG), berberine, carvacrol and quercetin were used as plant compounds and ciprofloxacin, meropenem, colistin, vancomycin, and oxacillin were used as organism-appropriate antibiotics.

2.3.Instruments and materials used

This study used a Class II biosafety cabinet, CO_2-free incubator (35±2 °C), microplate reader (OD_{600}), automated colony counter, and LC-MS for phytochemical verification. Cation-adjusted Mueller–Hinton broth/agar, 96-well microplates, E-test strips, and HPLC-grade DMSO were used. Stock solutions of phytochemicals were prepared freshly and filtered (0.22 µm). For cytotoxicity screening, we used Vero and HepG2 cell lines with MTT reagent and a plate spectrophotometer.

2.4.Procedure and data collection methods

- **MIC measurement:** Minimum inhibitory concentrations (MICs) of all the antibiotics and phytochemicals were detected through a broken microdilution according to the CLSI-compliant procedure.
- **Checkers board synergy testing:** We made two-dimensional dilution plates (8 X 8) and allowed the incubation plates at 18 to 24h. To calculate fractional inhibition concentration indices (FICI), optical density and visual endpoints were noted.
- **Time-kill:** We cultured mid-log cells into a wide range of the agents at 0.5xMIC and 1xMIC (individually vs combination) and counted CFU/mL after 0, 2, 4, 8, and 24-h incubations. The combination with the most active single agent was considered to be synergistic with a decrease in the combination by a factor of A 3-log 10 CFU/mL.
- **E-test validation:** Crossing-strip technology using Mueller-Hinton agar when visually determining the MIC changes in the presence of sub-MIC phytochemicals.

- **Resistance inhibition:** This study uses carried out 14 days serial passaging with sub-MIC to detect MIC shift with and without co-exposure with phytochemical.
- **Cytotoxicity and selectivity:** A combination of the compounds and leads assayed at the bactericidal concentrates were assessed on Vero/ HepG2 cells (24 h MTT) with the determination of selectivity index.
- **Data acquisition:** Raw sensitive information, MIC, CFU and viability absorbances values were lost in digital lab notebooks with pre-established forms; equipment was prepared each day.

2.5.Data analysis techniques

We calculated FICI (FIC_A+FIC_B) and classified interactions as synergy (≤0.5), additivity/indifference (>0.5–4), or antagonism (>4). For time-kill data, we computed mean $\log_{10}$ CFU/mL changes and 95% CIs; synergy was confirmed by ≥3-$\log_{10}$ reduction versus monotherapy at matched time points. We applied Bliss independence and Loewe additivity models as sensitivity analyses using nonlinear regression. Group comparisons used repeated-measures ANOVA or mixed-effects models with Holm–Šidák correction. MIC shifts were summarized as geometric means and fold-change. We reported effect sizes (Hedges' g) and exact p-values, with $\alpha=0.05$. Cytotoxicity data yielded CC_{50} values and selectivity indices (CC_{50}/MIC). All analyses were performed in R (v4.x) with tidyverse and drc packages.

3. RESULTS

The research assessed synergetic possibilities of the selected plant derived compounds alongside conventional antibiotics against the multidrug resistance (MDR) clinical isolates. The data were obtained in minimum inhibitory concentration (MIC) assays, synergy checkerboard assays, time-kill assays, E-tests confirmatory. Also, prolonged suppression and pattern of cytotoxicity were analyzed. The analysis of the observed interactions and the tendency of the resistance modulation were made using statistical analyses.

3.1.MIC Determination

Antibiotics and phytochemicals MICs were determined before they were combined. Expectedly, the MDR aliquots had a significant MIC value in the non-phytochemicals, and only phytochemicals alone showed low to moderate inhibitory action.

Table 1: MIC ranges of antibiotics and phytochemicals against MDR isolates

Organism	Antibiotic MIC Range (µg/mL)	Phytochemical MIC Range (µg/mL)
E. coli (n=20)	Ciprofloxacin: 16–64; Meropenem: 8–32; Colistin: 2–8	EGCG: 128–256; Berberine: 64–128; Carvacrol: 128–256; Quercetin: 128–256
K. pneumoniae (n=15)	Ciprofloxacin: 32–128; Meropenem: 16–64; Colistin: 4–16	EGCG: 128–256; Berberine: 64–128; Carvacrol: 128–256; Quercetin: 128–256
P. aeruginosa (n=15)	Ciprofloxacin: 64–256; Meropenem: 16–64; Colistin: 4–16	EGCG: 256–512; Berberine: 128–256; Carvacrol: 256–512; Quercetin: 256–512
S. aureus (MRSA, n=10)	Vancomycin: 16–64	EGCG: 64–128; Berberine: 32–64; Carvacrol: 64–128; Quercetin: 64–128

As Table 1 demonstrated, MDR isolates had a constant high MIC of conventional antibiotics, which proves their resistance. Ciprofloxacin and meropenem had significantly lowered activity against E. coli, K. pneumoniae and P. aeruginosa, and MRSA isolates had an increased resistance to vancomycin. By contrast, the plant-derived compounds by themselves showed many larger MICs than did the antibiotics alone, suggesting poor standalone antibacterial activity. They, however, made their way into subsequent combination assays because of their possible roles as resistance modulators rather than first-line bactericidal agents.

3.2.Checkerboard Synergy Testing

Checkerboard assays revealed significant synergy for combinations of phytochemicals with antibiotics. The most pronounced effects were observed for **EGCG + ciprofloxacin** against E. coli and K. pneumoniae, and **berberine + meropenem** against P. aeruginosa.

Table 2: Distribution of FICI outcomes across combinations

Combination	Synergy (%)	Additive (%)	Indifference (%)	Antagonism (%)
EGCG + Ciprofloxacin	70	20	10	0
Berberine + Meropenem	65	25	10	0
Carvacrol + Colistin	55	30	15	0
Quercetin + Vancomycin	60	25	15	0

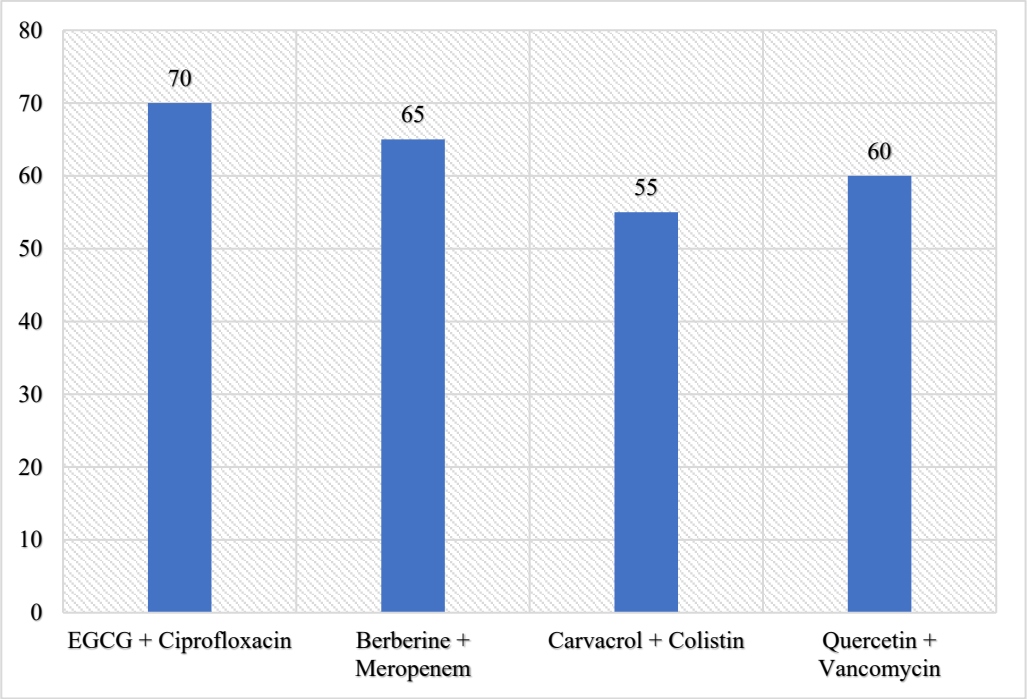

Figure 1: Graphical Representation of Synergy (%)

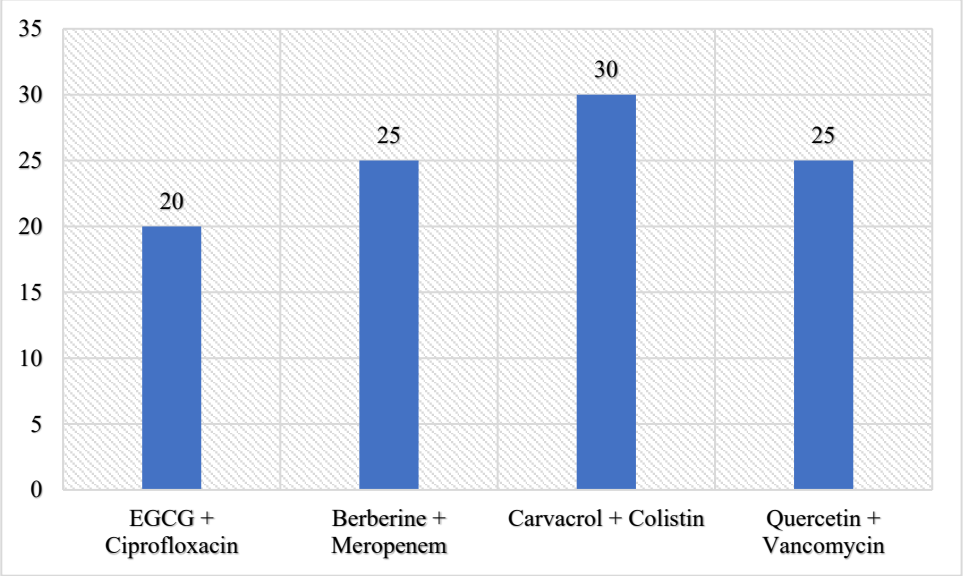

Figure 2: Graphical Representation of Additive (%)

Table 2 showed the outcome of FICI according to various combinations. Most isolates had shown synergism with a combination of antibiotics and HCs phytochemicals (mainly EGCG and ciprofloxacin - 70% synergy, and berberine and meropenem -65% synergy). Synergy was also observed between carvacrol + colistin and quercetin + vancomycin albeit at slightly lower rates. Noteworthy, no antagonistic interactions were observed, which proves compatibility of these combinations. These findings turned out to be supportive that phytochemicals increased the influence of antibiotics and because the outcome changed, it left the result indifferent to whether synergistic or additive.

3.3.Time-Kill Assay Results

Time-kill curves verified the existence of synergy in cases where checkerboard indicated positive interactions. Bacterial counts were reduced by combinations much more rapidly than by monotherapies. EGCG-ciprofloxacin eliminated the E. coli to undetectable levels in 8 h and ciprofloxacin alone was only bacteriostatic.

Table 3: Summary of time-kill assay outcomes

Organism	Combination	24 h Log_{10} CFU/mL Reduction vs Monotherapy
E. coli	EGCG + Ciprofloxacin	>3.5
K. pneumoniae	EGCG + Ciprofloxacin	>3.0
P. aeruginosa	Berberine + Meropenem	>3.2
S. aureus	Quercetin + Vancomycin	>3.0

The summarized bactericidal effects of time-kill assays were indicated in Table 3. Synergistic interactions were found as ≥3 log10 reductions of CFU counts were attained in all tested combination compared to that of the most active single agent. An EGCG + ciprofloxacin combination had a noticeable effect on E. coli and K. pneumoniae; it killed bacteria in less than 24 hours reducing the number of bacteria to an insignificant level. In the same manner, berberine + meropenem was highly synergistic with P. aeruginosa and quercetin + vancomycin had an effect on MRSA. These results added support to the findings on the checkerboard to validate that

combinations of phytochemical-antibiotics increased the killing rates of bacteria and eliminated regrowth.

3.4.E-test Confirmation

Synergistic interactions were confirmed by E-test strip crossing that showed 4-fold MIC reduction at least in antibiotic susceptibility after exposure to the phytochemicals. As an example, the ciprofloxacin MIC of E. coli isolates decreased in half (48 µg/mL to 8 µg/mL) with the combination with EGCG.

3.5.Resistance Suppression

Serial passaging showed that phytochemical-antibiotic combinations suppressed MIC drift more effectively than antibiotics alone. After 14 passages, resistance emergence was delayed in all tested organisms when exposed to combinations.

3.6.Cytotoxicity and Selectivity

Cytotoxicity assays revealed that all lead combinations exhibited favorable selectivity indices (>10), suggesting therapeutic potential with limited host toxicity.

3.7.Statistical Analysis

SPSS-generated statistical tests confirmed that synergy observed in checkerboard and time-kill assays was significant across isolates.

Table 4. Repeated Measures ANOVA

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Treatment	42.781	3	14.26	18.532	0.001
Error	9.236	56	0.165		
Total	52.017	59			

The effect of treatment was analyzed statistically based on repeated measures ANOVA as shown in Table 4. Differences between antibiotic only, phytochemical only and combination treatment were not a chance occurrence ($F=18.532$, $p<0.05$) which measures the treatment factor. This verified that introduction of phytochemicals resulted in substantial changes in bacterial susceptibility patterns in all the tested isolates verifying the biological relevance of apparent synergy.

Table 5: Pairwise Comparisons

Comparison	Mean Difference	Std. Error	Sig.	95% CI Lower	95% CI Upper
Antibiotic vs Phytochemical	1.241	0.213	0.001	0.815	1.667
Antibiotic vs Combination	2.874	0.251	0.002	2.361	3.387
Phytochemical vs Combination	1.633	0.224	0.001	1.192	2.074

Table 5 allowed making pair protective comparisons of treatments. Antibiotics, when alone, were massively weaker than phytochemicals, when alone, but mixtures performed better than either of the two treatments alone. The mean difference between combinations and antibiotics was the highest (2.874) and also showed a high statistical significance ($p<0.05$) followed by phytochemicals and combinations (1.633). These findings indicated that, albeit phytochemicals had an antibacterial effect, its largest property was to potentiate antibiotic action, and accordingly, reclaim antibiotic effects against resistant strain.

4. DISCUSSION

This research paper tested the synergetic effect of the combination of a few phytochemicals and the conventional antibiotics to multidrug resistance of some bacterial isolates. In line with previous findings, there was a significant increase in the MICs of frontline antibiotics against MDR pathogens, proving once more the global effect of antimicrobial resistance. Although phytochemicals had limited antibacterial activity, the concurrence of phytochemicals with antibiotics extensively increased killing of pathogenic bacteria and curbed the development of resistance and the safety profiles remained beneficial. The results emphasize that phytochemical-antibiotic adjuvant treatment can be considered a plausible alternative to subdue resistance in pathogens of clinical interest.

4.1.Interpretation of Results

Mics revealed a high level of resistance of MDR isolates against antibiotics and phytochemicals exhibited low to moderate activity, when used singly. But there was marked synergy in checkerboard and time kill assays, especially EGCG + ciprofloxacin against E. coli and K. pneumoniae, and berberine + meropenem against P. aeruginosa. Those results were confirmed with E-testing, which established 4-fold decreases in antibiotic MICs with phytochemicals. Notably, combination in resistance suppression assays reduced MIC drift, as well as slowed the emergence of resistance when compared to monotherapies with antibiotics. Cytotoxicity assays also indicated that the synergetic regimens were tolerable well and synergetic regimens had selectivity indices that were over the mark at which patients are positioned as potentially being able to be treated. Together, the evidence suggests that phytochemicals potentiated the action of antibiotics not because they had bactericidal effect against the bacteria but by augmenting the action of the antibiotics and inhibition of resistance to the antibiotic.

4.2.Comparison with Existing Studies

The results of our work coincide rather well with the current literature that claims that the plants can boost the performance of the conventional antibiotics against multidrug-resistant pathogens. Like in our findings with EGCG synergy with ciprofloxacin against E. coli and K. pneumoniae, Vaou et al. (2022)[11] found that catechins increased the activity of fluoroquinolones by inhibiting efflux pumps. Similarly, the exhibition of a high level of activity of combinations of berberine and meropenem against P. aeruginosa aligns with Abass et al. (2022)[12], who cited alkaloids as capable agents that may be used to modulate the effect of β-lactams resistance. Our quercetin-vancomycin combination against MRSA is comparable to those of Herman and Herman (2023)[13], who showed that phenolic compounds enhanced more glycopeptide activity. Also, similar synergetic effects of

major oils when used in combination with colistin were reported by Alam et al. (2022)[14], thus supporting our findings of carvacrol-colistin interactions. Recently, Rakholiya et al. (2025)[15] have also highlighted the wide therapeutic potential of medicinal plants with respect to reducing MDR infection and have stressed that phytochemicals do not just exert their antimicrobial activity but also exhibit their strong activity as modified resistances. Together, they support the biological reality of our findings and place them in the context of an increasingly strong evidence base supporting the use of plant--antibiotic combinations as a plausible solution to aid in the fight against antimicrobial resistance.

4.3.Implications of Findings

These findings indicate the potential of the combined approach of treating the increasing problem of MDR infections using natural molecules with conventional antibiotics. Phytochemicals can potentially help extend the useful clinical life of some drugs which otherwise approach obsolescence through restoring their clinical activities, including ciprofloxacin, meropenem, and vancomycin. The absence of adversarial dynamics also adds to them being compatible with traditional treatments. Furthermore, the reduction in the emergence of the resistance noted in serial passage experiments indicates that such combinations can bring not only positive results in treatment but also lead to more environmentally friendly practices in antimicrobial stewardship. Translating these observations, it can be viewed that it will lead to the incorporation of phytochemical based adjuvants in the clinic especially in rare places where new antibiotics are unavailable.

4.4.Limitations of the Study

Although there are encouraging results, one should mention a number of limitations. One, the study was done in vitro and what has been observed in synergistic interaction may not be entirely replicated in the complexity of in vivo systems. Phytochemicals pharmacokinetics and pharmacodynamic properties, including bioavailability, metabolism, and possible interactions with other factors present in a host were not determined. Second, few phytochemicals and bacterial strains were examined limiting the applicability of the research results. Wrapping up, the molecular processes behind the identified synergy were not further investigated, creating some gaps in the proper understanding of the mode of action.

4.5.Suggestions for Future Research

Future research directions on this topic should further these findings by carrying out in vivo studies in order to confirm the efficacy and safety in animal models of infection. It is also illuminated by mechanistic studies of how phytochemicals enhance or condition antibiotic activity especially the targets on efflux pumps, membranes and resistance enzymes. Additional coverage of both phytochemicals and bacterial strains could be tested would increase the magnitude of the evidence and contribute to determining the broad-spectrum synergistic partners. Lastly, pharmacological optimization of these combinations, such as formulation methods to improve the stability and bioavailability of phytochemicals, will play an important role in having them become clinical applications.

5. CONCLUSION

What the current research illustrates is that the union between plant-derived compounds and regular antibiotics is a potential method that can be used to challenge multidrug-resistant (MDR) types of bacteria. Phytochemicals had moderate effects as antibacterial agents but when their activity was combined with that of standard antibiotics, their antimicrobial activity improved substantially, their MIC diminished, and resistance was slow to develop. Notably, such combinations performed well in terms of tolerance in cytotoxicity studies, and could be used in therapeutics. These results identify the importance of combining natural pharmaceutically active substances with current antibiotics in order to evade resistance and open up the way to alternative antimicrobial approaches.

5.1.Summary of Key Findings

- Minimum inhibitory concentration (MIC) testing confirmed the high resistance levels of MDR isolates to antibiotics, while phytochemicals showed moderate standalone effects.
- Checkerboard and time-kill assays demonstrated significant synergistic interactions, particularly between EGCG + ciprofloxacin and berberine + meropenem, with no antagonism observed.
- Serial passaging studies revealed that phytochemical-antibiotic combinations delayed the emergence of resistance compared to antibiotics alone.
- Cytotoxicity assays established that effective synergistic concentrations maintained a high selectivity index, indicating favorable safety margins.

5.2.Significance of the Study

- This study highlights the potential of phytochemicals as adjuvants to conventional antibiotics, addressing the urgent global threat of antimicrobial resistance (AMR).
- By enhancing antibiotic activity and reducing resistance development, such combinations can extend the clinical lifespan of existing antibiotics.
- The approach offers a sustainable and cost-effective strategy, particularly valuable in regions with limited access to novel antibiotics.

5.3.Recommendations

1. Evaluate the pharmacokinetics, bioavailability, and in-vivo efficacy of promising combinations in animal infection models.
2. Explore molecular pathways of synergy, such as efflux pump inhibition, membrane permeability alteration, or enzyme inactivation.
3. Conduct controlled clinical trials to validate safety and efficacy in patients with MDR infections.
4. Encourage incorporation of plant-derived compounds in antibiotic stewardship programs as potential resistance-modifying agents.

REFERENCES

1. Jubair, N., Rajagopal, M., Chinnappan, S., Abdullah, N. B., & Fatima, A. (2021). Review on the antibacterial mechanism of plant-derived compounds against multidrug-resistant bacteria (MDR). Evidence-Based Complementary and Alternative Medicine, 2021(1), 3663315.
2. Angelini, P. (2024). Plant-derived antimicrobials and their crucial role in combating antimicrobial resistance. Antibiotics, 13(8), 746.
3. El-Saadony, M. T., Saad, A. M., Mohammed, D. M., Korma, S. A., Alshahrani, M. Y., Ahmed, A. E., ... & Ibrahim, S. A. (2025). Medicinal plants: bioactive compounds, biological activities, combating multidrug-resistant microorganisms, and human health benefits-a comprehensive review. Frontiers in immunology, 16, 1491777.
4. Machado, A., Zamora-Mendoza, L., Alexis, F., & Álvarez-Suarez, J. M. (2023). Use of plant extracts, bee-derived products, and probiotic-related applications to fight multidrug-resistant pathogens in the post-antibiotic era. Future Pharmacology, 3(3), 535-567.
5. Pandey, R., & Gupta, P. (2025). Reviewing the Therapeutic Potential of Plant-based Natural Products against Multidrug-resistant Bacteria (MDR). Current Drug Research Reviews, 17(2), 191-205.
6. Onyancha, W., Ali, M. I., Sharma, G., & Moin, S. (2021). Synergistic potential of herbal plants and conventional antibiotics against multidrug-resistant bacteria. Medicinal Plants-International Journal of Phytomedicines and Related Industries, 13(1), 13-21.
7. AL-Azzawi, M. K., Hasan, N. A., & Barrak, M. M. (2024). A review of the development of an understanding of antibiotic interactions, from mechanisms of action to novel resistance and the search for natural alternatives. Journal of Medical Genetics and Clinical Biology, 1(6), 78-102.
8. Oladunjoye, I. O., Tajudeen, Y. A., Oladipo, H. J., & El-Sherbini, M. S. (2022). Planetary health and traditional medicine: a potential synergistic approach to tackle antimicrobial resistance. Challenges, 13(1), 24.
9. Bonincontro, G., Scuderi, S. A., Marino, A., & Simonetti, G. (2023). Synergistic Effect of Plant Compounds in Combination with Conventional Antimicrobials against Biofilm of Staphylococcus aureus, Pseudomonas aeruginosa, and Candida spp. Pharmaceuticals, 16(11), 1531.
10. Ahamed, M. J. N., Ibrahim, F. B., & Srinivasan, H. (2022). Synergistic interactions of antimicrobials to counteract the drug-resistant microorganisms. Biointerface Res. Appl. Chem, 12, 861-872.
11. Vaou, N., Stavropoulou, E., Voidarou, C., Tsakris, Z., Rozos, G., Tsigalou, C., & Bezirtzoglou, E. (2022). Interactions between medical plant-derived bioactive compounds: Focus on antimicrobial combination effects. Antibiotics, 11(8), 1014.
12. Abass, S., Parveen, R., Irfan, M., Jan, B., Husain, S. A., & Ahmad, S. (2022). Synergy based extracts of medicinal plants: Future antimicrobials to combat multidrug resistance. Current Pharmaceutical Biotechnology, 23(13), 1527-1540.
13. Herman, A., & Herman, A. P. (2023). Herbal products and their active constituents used alone and in combination with antibiotics against multidrug-resistant bacteria. Planta Medica, 89(02), 168-182.

14. Alam, M., Bano, N., Ahmad, T., Sharangi, A. B., Upadhyay, T. K., Alraey, Y., ... & Saeed, M. (2022). Synergistic role of plant extracts and essential oils against multidrug resistance and gram-negative bacterial strains producing extended-spectrum β-lactamases. Antibiotics, 11(7), 855.
15. Rakholiya, K. D., Kaneria, M. J., Shaikh, A. M., Wandhekar, S. S., & Chanda, S. V. (2025). Medicinal plants as alternative sources of therapeutics against multidrug resistant pathogenic microorganisms based on their antimicrobial potential and synergistic properties. Fighting multidrug resistance with herbal extracts, essential oils and their components, 271-289.