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Synergism Of Antibiotics With Plant Extract- A Brief Review

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1. ABSTRACT:

Antibiotic synergy is one of three possible responses that can occur when two or more antibiotics are used together to treat an infection. In a synergistic response, the antibiotics work collaboratively, leading to an overall effect that is significantly more potent than what each antibiotic could achieve individually. This enhanced effectiveness makes synergistic combinations particularly valuable in treating infections, especially in cases where bacteria exhibit resistance to one or more of the antibiotics. In contrast, there is the additive effect. When antibiotics have an additive response, their combined effectiveness is approximately equal to the sum of their individual effects. In this scenario, the antibiotics do not enhance each other's potency; instead, they simply contribute their effects together. The integration of plant extracts or pure natural compounds with conventional antibiotics offers a promising strategy for developing effective and affordable treatment options. This approach is particularly relevant in light of the growing challenge of antibiotic resistance. Several combination antibiotic therapies are already in clinical use, showcasing their potential to enhance therapeutic efficacy and broaden the spectrum of activity against resistant pathogens. This study reviews recent literature on these combinational therapies, highlighting their advantages, mechanisms of action, and clinical applications. By examining successful case studies and ongoing research, this review aims to shed light on the synergies between natural and conventional antibiotics. Furthermore, it seeks to inform and guide future investigations in this area, emphasizing the need for continued exploration of novel combinations that could lead to improved treatment outcomes for various infections. Ultimately, this research could contribute significantly to the fight against antibiotic resistance and the development of more effective therapeutic strategies.

Keywords : Synergy, Antibiotics, Additive response, Potency, Therapeutic efficacy, Plant extracts

2. Indroduction

The discovery of antibiotics was a crucial advancement in the fight against bacterial infections that once devastated human populations. Various antibiotics exert their inhibitory effects on different pathogenic organisms [1].

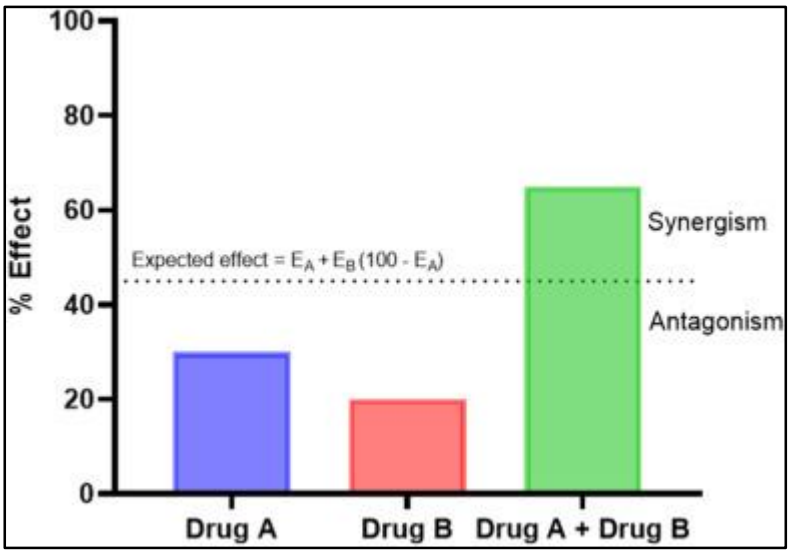

Figure 1: Evaluation of synergism [2]

However, in recent years, multidrug resistance has emerged in human pathogenic microorganisms, largely due to the indiscriminate use of commercial antimicrobial drugs commonly prescribed for infectious diseases. The rise of antibiotic resistance is influenced by multiple factors, including the specific interactions between bacteria and antibiotics, the patterns of antibacterial usage, host characteristics, and environmental conditions. This challenging scenario has prompted scientists to seek new antimicrobial substances from a variety of sources as potential novel therapeutic agents. Nevertheless, the production costs of synthetic drugs are high, and they often lead to adverse effects when compared to plant-derived alternatives [3]. About 20% of known plants have been studied for their pharmaceutical properties, positively influencing the healthcare system by aiding in the treatment of cancer and other serious diseases. Plants produce a wide variety of bioactive compounds, with fruits and vegetables containing high concentrations of phytochemicals that can help protect against free radical damage [14-15].

Numerous studies indicate that many plants are abundant in antioxidants. For example, vitamins A, C, and E, along with phenolic compounds like flavonoids, tannins, antignon's, present in plants, all serve as effective antioxidants [15]. Herbal medicines have garnered significant interest as a source of new antibacterial agents, as they are regarded as time-tested options that are relatively safe for both human use and the environment [4].

Figure 2: Antibiotics and plant extracts synergy [21]

Plant-derived medications remain a crucial resource, particularly in developing countries, for combating serious health challenges. These natural remedies have been used for centuries and are often more accessible and affordable than conventional pharmaceuticals. It is estimated that approximately 60-80% of the world's population relies on traditional medicine to treat common illnesses, highlighting the significance of these practices in everyday healthcare. In many regions, especially where healthcare infrastructure may be limited, people turn to local plants for their medicinal properties, relying on the knowledge passed down through generations. This reliance on traditional remedies underscores the importance of preserving plant biodiversity and promoting research into their therapeutic potential. As interest in holistic and natural treatments grows worldwide, there is a renewed focus on understanding the efficacy and safety of these plant-based medicines, which may offer valuable alternatives or complements to modern medical treatments [5-6]. Plants generate a diverse array of secondary metabolites, many of which have been documented for their therapeutic properties and a potential source of antibacterial compounds [7-8-9], raising hopes of discovering novel antibiotics that can help combat drug-resistant infections. These compounds are thought to contribute to the plant's defence against pathogens by working synergistically with intrinsic antimicrobials [10].

Recent studies have suggested that these compounds could significantly enhance the efficacy of antibiotics in combating multidrug-resistant (MDR) bacterial pathogens. The action mechanisms of plant extracts and their natural components are multifaceted and involve several critical processes that contribute to their antibacterial properties. First, these compounds can degrade the bacterial cell wall, a vital structure that maintains the integrity and shape of the cell. By compromising this barrier, they weaken the bacteria, making them more susceptible to antibiotics. Second, they can disrupt the cytoplasmic membrane and its associated proteins.

This disruption can lead to the leakage of intracellular contents, including essential nutrients and cellular components, which are crucial for bacterial survival and replication. Additionally, these extracts may cause coagulation of the cytoplasm, further hindering bacterial function. They also interfere with active transport mechanisms and metabolic enzymes, disrupting essential biochemical pathways that bacteria rely on for energy and growth. Moreover, these natural compounds can dissipate cellular energy, primarily in the form of ATP, which is essential for various cellular processes. They can also deplete the proton motive force (PMF) and interfere with electron flow, both of which are critical for maintaining the electrochemical gradients that drive many physiological processes in bacteria. Collectively, these mechanisms can lead to bacterial cell death, underscoring the potential of plant-derived compounds in enhancing the effectiveness of existing antibiotics against resistant strains [11-12].

Combining essential oils with antibiotics presents a promising approach to tackling infectious diseases, particularly in the context of rising antibiotic resistance. This strategy utilizes the unique properties of essential oils—rich in bioactive compounds—alongside traditional antibiotics to enhance their effectiveness against various pathogens, especially those that have developed resistance.

Recent studies have focused on the synergistic effects that arise when antibiotics are paired with plant extracts, including essential oils. These extracts contain a range of bioactive compounds, such as phenolics and terpenes, which can interact with bacterial cells to enhance antibiotic action. Research indicates that these compounds may disrupt bacterial cell membranes, inhibit biofilm formation, and increase cell permeability, making bacteria more susceptible to antibiotics. Such interactions can lead to significantly improved treatment outcomes, particularly for infections caused by resistant strains.

Scientists are actively investigating various combinations of essential oils and antibiotics to identify the most effective pairings. This involves determining optimal dosages and understanding the underlying mechanisms of these synergistic interactions. For example, some studies have shown that combining certain essential oils with specific antibiotics can enhance the penetration of antibiotics through bacterial cell walls. Additionally, essential oils may help overcome resistance mechanisms, such as efflux pumps that expel antibiotics from bacterial cells.

The implications of this research are substantial, as antibiotic resistance poses a major threat to public health globally. As conventional treatments become less effective against resistant pathogens, there is a critical need for new strategies that can bolster existing antimicrobial therapies. Integrating essential oils into treatment regimens not only enhances antibiotic efficacy but also opens avenues for developing novel therapeutic strategies.

Moreover, the combination of essential oils and antibiotics has shown potential in reducing bacterial resistance, addressing a key challenge in modern medicine. By weakening bacteria's ability to resist antibiotics, this approach could lead to more successful treatment outcomes and lower rates of treatment failure. Overall, the integration of essential oils with antibiotics represents a significant advancement in the fight against infectious diseases, offering hope for more effective therapies in the face of escalating resistance [16-17-18].

3. Materials and Methods

3.1. Plant material:

Samples of Origanum compactum (O. compactum), Chrysanthemum coronarium (C. coronarium), and Thymus willdenowii Boiss (T. willdenowii) were collected in Khénifra, while Melissa officinalis (M. officinalis) and Origanum majorana L. (O. majorana) were gathered from the Marrakech Region. The collection took place between May and June 2014. After harvesting, the samples were dried in the shade for 10 days prior to steam distillation.

The drying process aimed to preserve the essential oils and aromatic compounds within the plants. Care was taken to ensure the samples were protected from direct sunlight to maintain their quality. Following drying, steam distillation was conducted to extract the essential oils for further analysis. These oils are often studied for their potential medicinal properties and applications in aromatherapy. The careful collection and preparation of these samples were crucial for ensuring accurate and reliable results in subsequent research [22].

3.2. Extraction of plant material:

The essential oils were extracted using hydrodistillation with a Clevenger-type apparatus. They were then stored at 4°C in a dark environment, along with anhydrous sodium sulfate to maintain their quality. This method ensures that the oils remain free from moisture and other contaminants that could affect their properties. The use of dark storage helps prevent degradation caused by light exposure. Additionally, careful handling and storage conditions are crucial for preserving the oils' aromatic compounds and potential therapeutic benefits for future analysis and applications [23].

3.3. Collection of samples:

From April to August 2012, a thorough collection of medical specimens was conducted at Sidnawy Hospital in Zagazig, Egypt. The specimens, which included pus, sputum, blood, stool, and urine, were collected from inpatients to ensure quality and integrity. Following Miller’s (1999) protocols, the samples were transported to maintain their viability and prevent degradation, which is vital for accurate laboratory analyses. This meticulous process played a key role in providing reliable clinical information and supporting patient care needs [13].

Figure 3: Collection of samples [19].

The antibacterial activity was assessed using Gram-positive bacteria, specifically Staphylococcus aureus (S. aureus), as well as Gram-negative bacteria, including Escherichia coli (E. coli), E. coli (ATCC 25921), Klebsiella pneumoniae (K. pneumoniae), Proteus mirabilis (P. mirabilis), Pseudomonas aeruginosa (P. aeruginosa), Pseudomonas aeruginosa (ATCC 27853), Pseudomonas putida (P. putida), Salmonella enteritidis (S. enteritidis), and Enterobacter aerogenes (E. aerogenes).

All bacterial strains were sourced from the microbiology laboratory at Hospital Mehemmed VI. The bacterial strains were maintained through subculturing on nutrient agar, which supports their growth, incubated in the dark for 24 hours at 37°C [22].

3.4. Isolation and purification of bacteria:

The collected swabs were systematically streaked onto the surface of Nutrient agar to initiate the growth of microorganisms. In addition to Nutrient agar, various diagnostic and selective media were employed to enhance the isolation of specific bacterial species. These included cystine lactose electrolyte deficient (C.L.E.D) agar, which is designed to facilitate the growth of gram-negative bacteria while inhibiting others, as well as MacConkey agar, which differentiates lactose fermenters from non-fermenters.

Mannitol salt agar was also used, particularly effective for isolating staphylococci due to its high salt concentration, while Blood agar provided a rich medium for growing a wide range of bacteria and allowed for the observation of haemolytic activity [13].

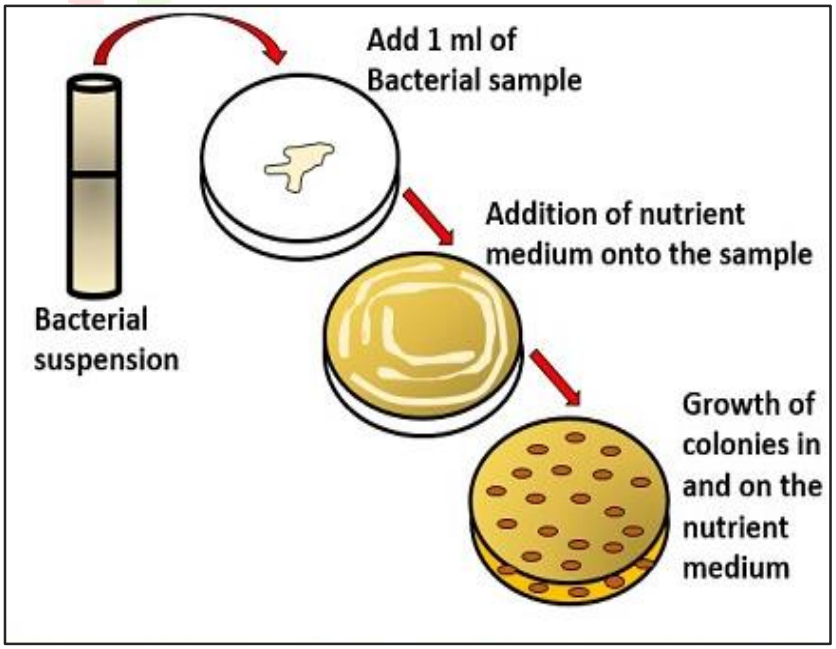

Figure 4: Isolation and purification of bacteria [20]

This comprehensive approach involved a process of streaking each swab across a range of different growth media, allowing for careful observation and monitoring of microbial growth over time. The primary objective was to isolate pure, single colonies from the mixed microbial populations present in the specimens collected. To achieve this, the streaking technique was employed systematically, with each swab carefully drawn across the surface of the agar plates in specific patterns to ensure even distribution and to facilitate the separation of individual bacterial colonies. This process required not only precision but also patience, as the incubation period needed to be closely observed.

The method continued until distinct colonies could be identified, characterized by their unique morphology and growth patterns. These identified colonies were then confirmed as pure cultures, which play a vital role in ensuring the accuracy of subsequent identification processes and testing in clinical microbiology. Pure cultures are crucial for a range of applications, including susceptibility testing, where the effectiveness of various antibiotics against the isolated bacteria is determined. Ultimately, this approach helps in providing reliable data that informs clinical decisions and enhances our understanding of microbial behaviour in healthcare settings [13].

Figure 5: Bacterial growth on agar plate [24].

3.5. Antibiotics:

The antibiotics used included standard gentamicin (10 mg), tobramycin (30 mg), imipenem (10 mg), and ticarcillin (75 mg). These antibiotics were selected for their effectiveness against a range of bacterial infections. Each antibiotic was carefully measured to ensure accurate dosing for testing. The choice of these specific agents reflects their relevance in clinical treatment and research regarding antimicrobial susceptibility [22].

3.6. Antimicrobial activity:

The antimicrobial activity of the extracts was assessed using the disk diffusion method, which relies on the diffusion of antimicrobial compounds through a solid medium. In this technique, paper disks impregnated with the extracts are placed on the agar surface, allowing the compounds to spread and inhibit bacterial growth. The resulting inhibition zones are then measured to evaluate the effectiveness of the extracts [25]. Mueller–Hinton agar was placed in sterile Petri dishes (90 mm in diameter). Paper discs (6 mm in diameter) were soaked with 2 mL of each essential oil and antibiotic, along with standard test discs, and then placed on the agar surface. The dishes were left at room temperature for 30 minutes before being incubated at 37°C for 24 hours. The effectiveness of the essential oils was shown by a clear zone around the disc where bacteria did not grow. The size of this inhibition zone was measured in millimetres; a larger zone indicated that the strain was more susceptible [26]. To assess the synergistic effect of combining essential oils and antibiotics, which were in the form of ready-to-use discs, 2 mL of each essential oil was applied to the antibiotic discs to measure the zones of inhibition [27]. The results obtained were compared with those of the antibiotics

tested on the same strains using the same method. This allowed for a clear assessment of the efficacy of the essential oils in relation to the antibiotics.

4. Discussion:

4.1. T. willdenowii Boiss:

The essential oil derived from *T. willdenowii Boiss* has demonstrated significant antibacterial activity against various microorganisms, except for *P. putida*, *P. aeruginosa*, and *P. aeruginosa* ATCC 27853. Notably, when combined with tobramycin, the essential oil resulted in an antagonistic effect against six tested bacteria. However, a synergistic effect was observed with *K. pneumoniae,* P. aeruginosa, *P. aeruginosa* ATCC 27853, *P. putida,* and *E. aerogenes*, indicating enhanced antibacterial efficacy.

The combination of ticarcillin with the essential oil produced a synergistic effect against *E. coli (*ATCC 25921), *E. coli*, *P. putida, S. enteritidis*, *E. aerogenes*, and *P. aeruginosa*. This suggests that the essential oil can augment the action of ticarcillin, potentially leading to more effective treatment strategies. Conversely, this combination exhibited antagonistic effects against other bacteria, indicating variability in interaction outcomes.

When the essential oil was paired with imipenem, antagonistic effects were observed on *K. pneumoniae*, *E. aerogenes*, and *P. mirabilis*, while synergistic effects were noted against *E. coli*, *P. putida*, and *S. enteritidis*. Additionally, the combination with gentamicin showed synergistic effects on *P. putida* and *S. enteritidis*, but yielded antagonism with other strains. These findings highlight the complex interactions between *T. willdenowii Boiss* essential oil and antibiotics, suggesting potential for optimized combined therapies while cautioning against combinations that may inhibit effectiveness. Further research is needed to refine these interactions and develop effective treatment strategies [22].

Figure 6: T. willdenowii Boiss[30].

Microorganism	Essential Oil	TOB	TIC	IPM	G	Essential Oil + TOB	Essential Oil + TIC	Essential Oil + IPM	Essential Oil + G
E. coli	12.33 ± 0.57	20.33 ± 0.57	_	24.33 ± 0.57	20.33 ± 0.57	23.00 ± 1.00 (A)	16.00 ± 1.00 (S)	37.33 ± 0.57 (S)	20.33 ± 0.57 (I)
E. coli (ATCC 25921)	12.33 ± 0.57	22.33 ± 0.57	_	20.00 ± 0.00	22.66 ± 0.15	27.33 ± 1.52 (A)	14.33 ± 0.57 (S)	34.33 ± 1.52 (S)	24.00 ± 0.15 (A)
K. pneumoniae	20.00 ± 0.00	10.00 ± 0.00	20.66 ± 1.15	24.33 ± 0.57	22.00 ± 0.00	32.00 ± 0.00 (S)	34.33 ± 1.52 (A)	26.00 ± 0.57 (A)	32.00 ± 0.00 (A)
E. aerogenes	19.00 ± 0.00	10.00 ± 0.00	7.00 ± 0.00	17.66 ± 0.57	10.33 ± 0.57	30.00 ± 2.00 (S)	34.66 ± 0.57 (S)	22.66 ± 0.57 (A)	24.00 ± 0.57 (A)
S. aureus	13.00 ± 0.00	21.33 ± 0.57	_	_	22.33 ± 0.57	25.33 ± 0.57 (A)	_	_	23.00 ± 0.57 (A)
P. mirabilis	10.33 ± 0.57	9.00 ± 0.00	19.00 ± 0.57	27.00 ± 0.00	8.33 ± 0.57	10.66 ± 0.57 (A)	17.33 ± 0.57 (A)	26.00 ± 0.00 (A)	9.00 ± 0.57 (A)
P. putida	_	7.33 ± 0.57	14.00 ± 0.00	26.66 ± 0.57	_	20.00 ± 1.73 (S)	21.33 ± 0.57 (S)	27.00 ± 0.57 (S)	12.00 ± 0.00 (S)
P. aeruginosa	_	21.33 ± 0.57	24.00 ± 0.00	24.00 ± 0.00	20.33 ± 0.57	32.33 ± 0.57 (S)	17.00 ± 0.00 (A)	25.00 ± 0.00 (S)	7.00 ± 0.57 (A)
P. aeruginosa (ATCC 27853)	_	23.00 ± 1.00	23.66 ± 0.57	30.66 ± 1.15	18.66 ± 0.57	26.00 ± 0.00 (S)	22.33 ± 1.52 (A)	32.00 ± 0.00 (S)	17.00 ± 0.57 (A)
S. enteritidis	13.00 ± 0.00	21.33 ± 0.57	_	_	12.33 ± 0.57	22.66 ± 0.57 (A)	18.33 ± 0.57 (S)	20.00 ± 1.00 (S)	16.00 ± 0.57 (S)

Values are presented as mean ± SEM; I indicate indifference, S denotes synergy, A signifies antagonism, and the abbreviations stand for: TOB for tobramycin, TIC for ticarcillin, IPM for imipenem, and G for gentamicin.

Table 1: The antimicrobial properties, measured as zones of inhibition, of the essential oil from *T. willdenowii* and its synergistic effects when combined with antibiotics [22].

4.2. O. compactum L:

The essential oil of *O. compactum* L. exhibited a significant inhibitory effect on various microorganisms, with notable exceptions including *Pseudomonas aeruginosa, P. aeruginosa* (ATCC 27853), *Proteus mirabilis*, and *P. putida* (refer to Table 2). In certain cases, a synergistic effect was observed when *O. compactum L.* was combined with tobramycin, particularly against *Klebsiella pneumoniae, P. putida, P. aeruginosa* (ATCC 27853), *P. aeruginosa, and P. mirabilis.* Conversely, other bacterial strains exhibited antagonistic effects under similar conditions.

When paired with ticarcillin, *O. compactum* L. showed a synergistic effect against the majority of tested bacteria; however, antagonism was observed specifically with *K. pneumoniae* and *Enterobacter aerogenes*. Additionally, combining the essential oil with imipenem produced a synergistic response against *P. putida* and *Salmonella enteritidis,* while other bacteria displayed antagonistic interactions. A further synergistic

effect was noted in combinations of O. compactum L. essential oil with gentamicin against *P. putida*, *P. mirabilis*, *P. aeruginosa* (ATCC 27853), and *P. aeruginosa*. Nonetheless, antagonistic effects were also recorded with other bacterial strains. These findings highlight the complex interactions between the essential oil of *O. compactum* L. and various antibiotics, suggesting that while synergistic effects can enhance antimicrobial efficacy against specific pathogens, there are instances where antagonistic interactions may limit effectiveness. This underscores the importance of further research to explore the mechanisms behind these interactions and to optimize combinations of essential oils and antibiotics for better therapeutic outcomes. Understanding these dynamics could lead to more effective strategies in combating antibiotic-resistant bacterial strains [28].

Figure 7: O. compactum L[31].

Microorganism	Essential Oil	TOB	TIC	IPM	G	Essential Oil + TOB	Essential Oil + TIC	Essential Oil + IPM	Essential Oil + G
E. coli	15.33 ± 0.57	20.33 ± 0.57	20.33 ± 0.57	_	22.00 ± 0.00	20.33 ± 0.57 (A)	16.33 ± 0.57 (S)	32.33 ± 2.51 (A)	22.00 ± 0.00 (A)
E. coli (ATCC 25921)	13.00 ± 0.00	22.33 ± 0.57	20.00 ± 0.00	_	22.66 ± 0.15	25.33 ± 0.57 (A)	15.00 ± 0.57 (S)	31.33 ± 1.52 (A)	23.00 ± 1.00 (A)
K. pneumoniae	25.66 ± 0.57	10.00 ± 0.00	20.66 ± 1.15	24.33 ± 0.57	_	22.00 ± 0.00 (S)	36.00 ± 0.00 (A)	40.00 ± 0.57 (A)	38.00 ± 0.00 (A)
E. aerogenes	28.00 ± 0.00	10.00 ± 0.00	7.00 ± 0.00	17.66 ± 0.57	_	10.33 ± 0.57 (I)	26.00 ± 2.00 (A)	26.00 ± 1.00 (A)	27.33 ± 0.57 (A)
S. aureus	18.33 ± 0.57	21.33 ± 0.57	_	_	_	22.33 ± 0.57 (A)	_	_	26.00 ± 0.57 (A)
P. mirabilis	_	9.00 ± 0.00	15.00 ± 0.57	27.00 ± 0.00	_	8.33 ± 0.57 (S)	11.00 ± 0.00 (S)	24.00 ± 0.00 (A)	9.00 ± 0.00 (S)
P. putida	_	7.33 ± 0.57	14.00 ± 0.00	26.66 ± 0.57	_	10.00 ± 0.57 (S)	18.00 ± 0.00 (S)	28.33 ± 0.57 (S)	9.66 ± 0.57 (S)
P. aeruginosa	_	21.33 ± 0.57	24.00 ± 0.00	24.00 ± 0.00	_	20.33 ± 0.57 (S)	32.66 ± 1.52 (S)	23.00 ± 0.00 (A)	22.00 ± 1.00 (S)
P. aeruginosa (ATCC 27853)	_	23.00 ± 1.00	23.66 ± 0.57	30.66 ± 1.15	_	18.66 ± 0.57 (S)	27.00 ± 1.00 (S)	_	21.00 ± 0.57 (S)
S. enteritidis	14.00 ± 0.00	21.33 ± 0.57	_	_	_	12.33 ± 0.57 (A)	24.00 ± 0.57 (S)	28.33 ± 0.57 (S)	17.00 ± 0.57 (A

Values are presented as mean ± SEM; I indicate indifference, S denotes synergy, A signifies antagonism, and the abbreviations stand for: TOB for tobramycin, TIC for ticarcillin, IPM for imipenem, and G for gentamicin

Table 2: The antimicrobial properties, measured as zones of inhibition, of the essential oil from O. compactum L and its synergistic effects when combined with antibiotics [28]

4.3. O. majorana L:

The essential oils of *O. majorana* L. demonstrated moderate antimicrobial activity against several microorganisms, including *E. coli, E. coli* (ATCC 25921), *K. pneumoniae, E. aerogenes, S. aureus*, and *S. enteritidis*. The zones of inhibition ranged from 8.00 ± 1.00 mm to 10.00 ± 1.00 mm. However, no inhibitory effects were detected against *P. putida*, *P. mirabilis*, and *P. aeruginosa* (ATCC 27853), as detailed in Table 3.

From the data in Table 3, it is evident that the combination of *O. majorana* L. essential oil with tobramycin produced a synergistic effect against *K. pneumoniae* and *P. putida*, while showing antagonistic interactions with the other bacteria tested. When *O. majorana* essential oil was combined with ticarcillin, an additive effect was observed against *E. aerogenes*. Additionally, a synergistic effect was noted against *E. coli* (ATCC 25921), *S. enteritidis,* and *E. coli*, while antagonism occurred with other bacterial strains. The combination of imipenem and *O. majorana* essential oil resulted in a synergistic effect against *E. coli* (ATCC 25921), *P. aeruginosa* (ATCC 27853), *P. aeruginosa, S. enteritidis and P. putida.* Antagonistic effects were recorded against the remaining bacteria tested. Furthermore, when combined with gentamicin, the essential oil exhibited a synergistic effect against *K. pneumoniae*, an additive effect against *E. aerogenes*, and antagonism against other bacterial strains. Overall, no inhibitory effects were observed for *P. putida, P. mirabilis, and P. aeruginosa*, suggesting that while *O. majorana* essential oil shows promise in certain combinations, its efficacy may be limited against specific pathogens. Further exploration of these interactions could provide insights into effective antimicrobial strategies [28].

Figure 8: O. majorana L[32].

Microorganism
E. coli
E. coli (ATCC 25921)
K. pneumoniae
E. aerogenes
S. aureus
P. mirabilis

P. putida
P. aeruginosa
P. aeruginosa (ATCC 27853)
S. enteritidis

Values are presented as mean ± SEM; I indicate indifference, S denotes synergy, A signifies antagonism, and the abbreviations stand for: TOB for tobramycin, TIC for ticarcillin, IPM for imipenem, and G for gentamicin

Table 3: The antimicrobial properties, measured as zones of inhibition, of the essential oil from O. majorana L and its synergistic effects when combined with antibiotics [28].

4.4. M. officinalis L:

The essential oils derived from *M. officinalis* L. demonstrated limited antibacterial activity, with inhibition zones ranging from 8.00 ± 1.00 mm to 11.00 ± 1.00 mm against most tested bacterial strains. Notably, *M. officinalis L*. exhibited no antibacterial effects against *P. putida*, *P. aeruginosa* (ATCC 27853), *S. enteritidis*, and *P. aeruginosa*, indicating that while the essential oil possesses some antibacterial properties, its effectiveness is constrained against certain resistant strains.

In a series of experiments combining ticarcillin with the essential oil of *M. officinalis L*, a synergistic effect was observed against *E. coli, P. putida*, and *K. pneumoniae*. This suggests that the essential oil enhances the efficacy of ticarcillin when used in tandem, highlighting its potential as an adjunctive therapy for these specific bacteria. Conversely, an antagonistic effect was noted for *E. coli* (ATCC 25921), *P. mirabilis,* and *P. aeruginosa*, indicating a more complex interaction that diminishes the antibacterial activity in these cases. For the remaining bacterial strains tested, no significant inhibitory effect was detected, further emphasizing the need for tailored approaches in antibiotic therapy. Additionally, synergistic effects were identified with other antibiotics: gentamicin displayed enhanced effectiveness against *P. mirabilis*, while imipenem showed synergy with *S. enteritidis*. An additive effect was observed in *P. putida* and *P. aeruginosa,* underscoring the variability in how these bacteria respond to different antibiotic combinations. Furthermore, a synergistic interaction was confirmed for *K. pneumoniae* and P. mirabilis, indicating that certain pairings can significantly enhance antibacterial effectiveness. When assessing the interactions between the essential oil of *M. officinalis L*. and tobramycin, the results varied; an indifferent effect was noted on S. *aureus*, whereas antagonistic effects were recorded in other bacterial strains. These findings illustrate the importance of comprehending the specific interactions between essential oils and antibiotics, which could inform future therapeutic strategies and the development of more effective treatments against resistant bacterial strains. Overall, while *M. officinalis* L. shows potential, further research is essential to clarify its role and efficacy in antibacterial therapies, particularly in the context of multi-drug resistance [29].

Figure 9: M. officinalis L[33].

Microorganism	Essential Oil	TOB	TIC	IPM	G	Essential Oil + TOB	Essential Oil + TIC	Essential Oil + IPM	Essential Oil + G
E. coli	8.66 ± 0.57	20.33 ± 1.52	_	24.33 ± 0.57	20.33 ± 0.57	26.33 ± 1.52 A	39.33 ± 0.57 S	26.00 ± 0.57 A	21.00 ± 0.57 A
E. coli (ATCC 25921)	8.00 ± 1.00	22.33 ± 0.57	_	20.00 ± 0.00	22.66 ± 0.15	21.00 ± 0.57 A	7.33 ± 0.57 A	28.00 ± 0.00 Ad	19.00 ± 0.15 A
K. pneumoniae	11.33 ± 0.57	10.00 ± 0.00	20.66 ± 1.15	24.33 ± 0.57	22.66 ± 0.15	24.00 ± 0.00 S	38.00 ± 1.15 S	9.33 ± 0.57 A	23.00 ± 0.00 A
E. aerogenes	8.00 ± 1.00	10.00 ± 0.00	7.00 ± 0.00	17.66 ± 0.57	10.33 ± 0.57	11.00 ± 0.00 A	_	17.00 ± 0.57 I	14.00 ± 2.00 A
S. aureus	8.33 ± 0.57	21.33 ± 0.57	_	_	22.33 ± 0.57	21.00 ± 0.57 I	_	_	19.00 ± 0.57 A
P. mirabilis	11.00 ± 1.00	9.00 ± 0.00	19.00 ± 0.57	27.00 ± 0.00	8.33 ± 0.57	26.00 ± 0.00 S	14.00 ± 0.57 A	9.00 ± 0.00 A	21.00 ± 1.73 S
P. putida	_-	7.33 ± 0.57	14.00 ± 0.00	26.66 ± 0.57	_	8.00 ± 0.00 S	15.00 ± 0.00 S	24.00 ± 0.57 A	_
P. aeruginosa	_	21.33 ± 0.57	24.00 ± 0.00	24.00 ± 0.00	20.33 ± 0.57	21.00 ± 0.00 A	_	23.00 ± 1.15 A	19.33 ± 1.52 A
P. aeruginosa (ATCC 27853)	_	23.00 ± 1.00	23.66 ± 0.57	30.66 ± 1.15	18.66 ± 0.57	19.00 ± 0.00 A	21.00 ± 0.57 A	28.66 ± 1.15 A	15.00 ± 0.57 A
S. enteritidis	_	21.33 ± 0.57	_	_	12.33 ± 0.57	18.00 ± 0.57 A	_	24.00 ± 0.00 S	_

Values are presented as mean ± SEM; I indicate indifference, S denotes synergy, A signifies antagonism, and the abbreviations stand for: TOB for tobramycin, TIC for ticarcillin, IPM for imipenem, and G for gentamicin

Table 4: The antimicrobial properties, measured as zones of inhibition, of the essential oil from M. officinalis L and its synergistic effects when combined with antibiotics [29].

4.5. C. coronarium L:

The essential oil extracted from *C. coronarium* L. exhibited limited antibacterial activity, showing no effects against most tested bacterial strains except for *K. pneumoniae*, which displayed a small zone of inhibition measuring 9.66 ± 1.15 mm. This indicates that while the essential oil may have some antibacterial potential, its effectiveness is primarily restricted to this particular pathogen. When combined with tobramycin, the essential oil demonstrated a synergistic effect against *K. pneumoniae, P. mirabilis, P. putida*, S. *aureus*, *E.*

aerogenes, and *E. coli.* This suggests that the essential oil can enhance the effectiveness of tobramycin against these bacteria. However, an antagonistic effect was observed against E. *coli* (ATCC 25921), P. *aeruginosa* (ATCC 27853), P. *aeruginosa,* and *S. enteritidis*, indicating that the combination may hinder antibacterial activity for these particular strains.

Additionally, when ticarcillin was used in conjunction with the essential oil, synergistic effects were noted against E. coli, E. coli (ATCC 25921), K. pneumoniae, P. mirabilis, and S. aureus. This finding highlights the potential of using ticarcillin alongside the essential oil to enhance antibacterial efficacy against certain bacteria. In contrast, the combination of imipenem with the essential oil led to antagonistic effects against E. coli (ATCC 25921), E. aerogenes, K. pneumoniae, and P. mirabilis. Despite this, synergistic effects were observed in other tested bacteria, emphasizing the variability in response to antibiotic combinations. Furthermore, a synergistic interaction was specifically noted for E. coli (ATCC 25921) and E. aerogenes when the essential oil of C. coronarium L. was combined with gentamicin. Conversely, an antagonistic effect was identified in the other bacterial strains tested. These findings illustrate the complexity of interactions between the essential oil and various antibiotics, indicating that while certain combinations may be beneficial, others could potentially hinder effectiveness. Overall, these results suggest that further research is essential to optimize the use of C. coronarium L. essential oil in conjunction with antibiotics, particularly in addressing antibiotic-resistant bacterial infections [29].

Figure 10: C. coronarium L[34].

Microorganism	Essential Oil	TOB	TIC	IPM	G	Essential Oil + TOB	Essential Oil + TIC	Essential Oil + IPM	Essential Oil + G
E. coli	–	20.33 ± 1.52	–	24.33 ± 0.57	20.33 ± 0.57	21.66 ± 2.08S	10.00 ± 0.57S	26.00 ± 0.57S	19.33 ± 0.57A
E. coli (ATCC 25921)	–	22.33 ± 0.57	–	20.00 ± 0.00	22.66 ± 0.15	23.00 ± 0.57A	11.33 ± 0.57S	19.00 ± 0.00A	27.00 ± 0.15S
K. pneumoniae	9.66 ± 1.15	10.00 ± 0.00	20.66 ± 1.15	24.33 ± 0.57	22.00 ± 0.00	24.66 ± 2.08S	28.00 ± 1.15S	27.66 ± 1.15A	18.00 ± 2.00A
E. aerogenes	–	10.00 ± 0.00	7.00 ± 0.00	17.66 ± 0.57	10.33 ± 0.57	13.33 ± 0.57S	–	14.00 ± 0.57A	17.33 ± 2.51S
S. aureus	–	21.33 ±	–	–	22.33 ±	22.66 ± 1.	23.00 ± 0.	26.00 ± 1.	20.33 ± 0.

		0.57			0.57	15S	00S	73S	57A
P. mirabilis	–	9.00±0.00	19.00±0.57	27.00±0.00	8.33±0.57	10.000±0.00S	20.000±0.57S	25.00±0.00A	–
P. putida	–	7.33±0.57	14.00±0.00	26.66±0.57		8.000±0.57S	7.000±1.00A	27.00±0.57S	–
P. aeruginosa	–	21.33±0.66±1.1557	24.00±0.00	24.00±0.00	20.33±0.57	9.333±0.57A	19.66±2.08A	27.66±1.15S	–
P. aeruginosa (ATCC 27853)	–	23.00±1.00	23.24.33±0.57±	30.66±1.15	18.66±0.57	21.000±1.00A	–	32.33±1.52S	12.66±1.15A

			0.57						
S. enteritidis	–	21.33±0.57	–	–	12.33±0.57	19.00±0.57A	14.00±0.00S	27.33±0.57S	10.66±2.08A

Values are presented as mean ± SEM; I indicate indifference, S denotes synergy, A signifies antagonism, and the abbreviations stand for: TOB for tobramycin, TIC for ticarcillin, IPM for imipenem, and G for gentamicin

Table 4: The antimicrobial properties, measured as zones of inhibition, of the essential oil from C. coronarium L and its synergistic effects when combined with antibiotics [29].

5. Future prospect:

Throughout human history, plants have played a crucial role in treating infections, long before the advent of modern antibiotics. For example, colchicine, an organic compound extracted from Colchicum autumnale, is widely used in cancer therapy, while ajmaline, a glycoside from Rauwolfia serpentina, serves as a treatment for cardiac arrhythmias. These historical uses illustrate the potential of plant-based compounds in medicine and highlight a pathway for future research. Despite this rich history, most commercially available antibiotics today are sourced from bacteria and fungi. The notable exceptions are artemisinin from Artemisia annua and quinine from Cinchona officinalis, both effective against malaria. The limited inventory of plant-derived antibiotics can largely be attributed to the fact that many plants do not produce highly effective secondary metabolites suitable for antibacterial purposes. Instead, they have evolved various defense mechanisms that may inhibit the synthesis of potent antimicrobial compounds. However, the rise of antimicrobial resistance among pathogens underscores an urgent need for new therapeutic options. As bacteria evolve and acquire resistance genes, there is growing pressure on plants to produce more effective antibiotics capable of combating multidrug-resistant organisms that produce β-lactamase. This challenge opens up exciting possibilities for discovering new antibiotics from plant sources, particularly in environments contaminated with antimicrobial substances.

The future of antibiotic discovery could significantly benefit from research into plant secondary metabolites. As noted by Segal et al. (2006), unique histone proteins interact with specific DNA sequences to form nucleosomes that may influence how these metabolites exert their effects. Understanding these interactions could lead to identifying novel therapeutic agents. However, a more comprehensive investigation into the activities of secondary metabolites is necessary to facilitate their use as substitutes for conventional antimicrobials.

To explore the mechanisms of action of plant-derived antibiotics effectively, several methodologies should be employed. Proteomics in particular offers a promising approach. By assessing changes in protein expression following treatment with plant-derived compounds, researchers can elucidate the mechanisms of action and regulatory pathways involved. Techniques such as two-dimensional gel electrophoresis, stable isotopic labeling, and mass spectrometry will be crucial in these investigations.

Additionally, transcriptomic methods can provide insights into gene expression profiles related to specific proteins. Quantitative RT-PCR is a valuable tool for comparing gene expression between treated and untreated control groups, revealing the potential of plant-derived antibiotics. By integrating proteomic and transcriptomic approaches, future research could unlock new therapeutic possibilities, making plant secondary metabolites a viable alternative in the fight against antibiotic-resistant infections. This multidimensional research strategy holds great promise for advancing our understanding of plant-derived compounds and their potential as effective antibacterial agents, paving the way for innovative treatments in an era of increasing resistance[35-36-37-38-39].

6. Conclusion:

This study highlights the potential of combining essential oils from five medicinal plants with standard antibiotics to develop new antimicrobial treatments and reduce drug resistance. The results indicate that these essential oils work synergistically with the antibiotics tested, enhancing their effectiveness against various microorganisms. This synergy could provide new avenues for treating infectious diseases, especially in the context of increasing drug resistance.

However, to fully understand this beneficial interaction, further research is needed to explore the molecular mechanisms behind it. Understanding how the essential oils enhance antibiotic action is crucial for developing new pharmacological agents to combat bacterial infections.

Future studies should focus on identifying additional medicinal plants that exhibit similar synergistic properties. By doing so, researchers can expand the options available for effective treatments, addressing the urgent need for alternatives in the face of rising antibiotic resistance. Overall, this approach not only holds promise for improving health outcomes but also offers a strategy for sustainable and natural treatment options in medicine.

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