J Herbmed Pharmacol. 2025; 14(2): 163-187.

http://www.herbmedpharmacol.com doi: 10.34172/jhp.2025.52888

Journal of Herbmed Pharmacology

Plant-derived extracts and conventional drugs: A new frontier in antimicrobial therapy

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ARTICLE INFO

Article Type:
Review

Article History:
Received: 26 Dec. 2024
Revised: 7 Feb. 2025
Accepted: 7 Mar. 2025
epublished: 1 Apr. 2025

Keywords:
Antimicrobial activity, Bacteria, Plant extract, Microbial resistance, Synergism

ABSTRACT

The discovery of novel therapies and the provenance of antimicrobial medication are critically important, as antimicrobial resistance is becoming more common because of the presence and continuous evolution of antimicrobial-resistant organisms. Studies regarding synergy in medicinal plant extracts with antimicrobials have emerged as a novel and important research field. The synergy itself can serve as a beneficial tactic to strengthen and replenish antimicrobial medications that are currently less effective in clinical settings when treating microbial infections that are multi-resistant. The current work is a web-based search performed using PubMed, which covered studies that were published over more than a 25-year period, specifically between 1997 and July 2024, and assessed the potential for synergy between plant extracts and conventionally prescribed antimicrobial medications. The findings of the current review held great promise for the development of novel plant-based remedies combined with clinical-in-use antimicrobial medications to be exceptionally successful in treating severe infections that are resistant to antimicrobial treatments alone.

Implication for health policy/practice/research/medical education:
Adding plant-based extracts to regular antibiotics might make people less reliant on taking large amounts of synthetic antimicrobials, which could lower the cost of healthcare and have fewer side effects. Policymakers can leverage this synergy to advocate for the development and supervision of combination therapies. This may lead to new ways to fight organisms that are resistant to more than one drug.

Please cite this paper as: Mustafa YF, Jebir RM. Plant-derived extracts and conventional drugs: A new frontier in antimicrobial therapy. J Herbmed Pharmacol. 2025;14(2):163-187. doi: 10.34172/jhp.2025.52888.

Introduction

Millions of people's health are severely impacted by antimicrobial resistance in developing nations as well as in developed ones, which in turn has significant economic consequences for the community (1). Microbial infections are becoming more resistant to nearly every known antimicrobial agent in the present antibiotic crisis, frequently by various mechanisms (2) and to numerous antibiotics within one specific organism (3), which inspired researchers to start conducting studies to find a way out of this trouble (4).

Over the past few years, there has been a global increase in the application of conventional herbal remedies for general medical treatments (5-7). Researchers are looking for novel natural products that may one day be developed into effective antimicrobial agents to treat infections (8-10). Investigations have switched to ethnopharmacology as a result of the emergence of microbial resistance as well as side effects from antibiotics. When combined with an antibiotic, a biologically active product obtained from plants could enhance its efficacy (11,12). One way that natural plant extracts may optimize their antimicrobial activity could be synergism, which refers to a valuable collaboration between a pair of substances (13,14). The combined-based therapy appears to have several benefits in this domain, including the mitigation of medication dosages, decreasing the likelihood of adverse effects, and avoiding the development and emergence of drug resistance (15,16). Research demonstrates that the minimum inhibitory concentration (MIC) values among antimicrobials regarding specific strains of pathogenic organisms may be significantly lowered by natural plant extracts in conjunction with antimicrobial agents (17,18). Because of their own biologically reactive products, plants are considered a wealthy resource for therapeutic substances with antibacterial (19,20), antifungal (21,22),

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as well as antiviral (23,24) properties. Investigations conducted *in vitro* (25,26) as well as *in vivo* (27,28) indicate that plant extracts could inhibit the proliferation of pathogenic microbes and fungi. Their actions are often associated with impeding the function or synthesis of vital elements within specific creatures (29,30). Furthermore, naturally occurring substances might interact with the mechanisms of microbial resistance, preventing viruses from attaching themselves to the host and infecting it (31,32). The current manuscript organizes the published articles into four main sections: synergism of plant extracts with antibacterial, antifungal, antiviral, and antiparasitic medications.

Synergism of plant extracts with antibacterial medications

Numerous studies have demonstrated that certain natural plant extracts, when used in conjunction with antibiotics, have a substantial positive effect on various pathogens, as shown in the subsections below and Figure 1.

Synergism against Staphylococcus aureus

In a study conducted in 2006 by Betoni and colleagues, the synergism between eight plant extracts and different classes of antimicrobials was demonstrated against *Staphylococcus aureus* strains. The disk approach was used to examine the antimicrobial susceptibility. The plant extracts were *Baccharis trimera* (carqueja), *Syzygium aromaticum* (clove), *Mikania glomerata* (guaco), *Psidium guajava* (guava), *Allium sativum* (garlic), *Zingiber officinale* (ginger), *Cymbopogon citratus* (lemongrass), and *Mentha piperita* (mint). Regarding the selected antimicrobial classes, they were β-lactam (ampicillin, oxacillin), chloramphenicol, tetracycline, aminoglycosides (netilmicin, gentamicin), macrolides (erythromycin), glycopeptides (vancomycin), cephalosporins (cephalothin, cefoxitin), fluoroquinolone (ofloxacin), and sulfonamides (cotrimoxazole). All of the tested antimicrobials exhibited potential for synergism but in a distinct fashion. Clove and guava exhibited the greatest synergistic potential with antimicrobials, whereas ginger and garlic displayed the least (33).

Many years later, in 2013, Diarra and colleagues looked into how cranberry extracts and beta-lactams could work together against four *Staphylococcus aureus* strains, both *in vitro* and *in vivo*. The *in vitro* study was done using the checkerboard dilution method, and its results showed an obvious synergism between the cranberry extracts with amoxicillin and oxacillin by reducing their minimum inhibitory concentrations. On the other hand, the *in vivo* study was performed utilizing the murine mastitis model (34). The mice were infected with *Staphylococcus aureus*-bovine strains. The findings of the study exhibited synergistic potential in the treatment of these mice with a combination of cranberry extracts and amoxicillin, resulting in a notable drop in the bacterial counts. The researchers expected that the presence of flavonoids, iridoids, or phenolic products in the extract was responsible for their antimicrobial potential (35).

One year later, in 2014, Teethaisong and colleagues assessed the *in vitro* synergism between the combination of *Stephania suberosa* root extract and ampicillin versus *Staphylococcus aureus* resistant to ampicillin. The research team at the end of the study concluded that the plant extract possesses a significant ability for restoring bacterial resistance to the initial drug susceptibility, and this could be associated with three mechanisms of action of the plant extract: first, it blocks the production of peptidoglycan, which causes morphological destruction (36). Second, it suppresses the activity of beta-lactamases (37). Third, it makes the bacterial cell membrane more permeable (38). Therefore, *Stephania suberosa* offers a good chance that an innovative adjunct medicinal product to ampicillin will be developed and used to treat ampicillin-resistant

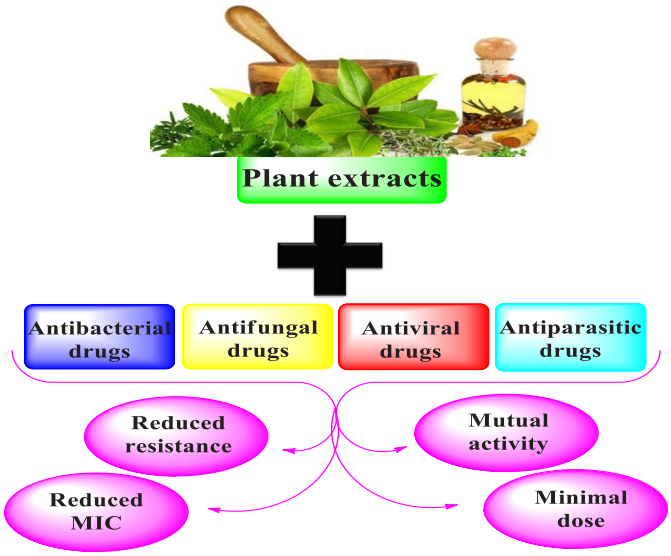


Figure 1. Graphical summarization of the work concept and outcomes. MIC: Minimum inhibitory concentration.

Staphylococcus aureus (39).

Subsequently, in 2015, Bezerra dos Santos and colleagues studied the synergistic potential of *Indigofera suffruticosa* leaves' organic extract in combination with erythromycin versus *Staphylococcus aureus*. This *in vitro* study found that the acetone and chloroform extracts of the plant boosted the antimicrobial potential of erythromycin against the mentioned bacterial strain; hence, the researchers concluded that the organic leaf extract represents a hopeful naturally occurring product in combination with erythromycin for the creation of novel anti-*Staphylococcus aureus* strategies (40).

In 2018, Buldain and colleagues assessed the synergistic antimicrobial potential of *Melaleuca armillaris* essential oils and cloxacillin against *Staphylococcus aureus*, utilizing the checkerboard technique. The research team has shown that this combination clearly works synergistically to lower cloxacillin's minimum inhibitory concentration versus *Staphylococcus aureus*. The medium's acidification promoted this interaction, as smaller concentrations of cloxacillin almost completely eradicated the bacteria when they were present in small quantities of the essential oil (41).

Finally, in 2019, the synergistic effect of the combination of several plant extracts with certain antimicrobials against *Staphylococcus aureus* was demonstrated by Silva and colleagues. The plant extracts included ethanolic extracts from *Senna macranthera*, *Salvia officinalis*, and *Plectranthus ornatus* leaves. The researchers documented that the simultaneous use of *Plectranthus ornatus* with ampicillin (the beta-lactam), gentamycin, and kanamycin (aminoglycosides) exhibited a synergistic effect, resulting in eight-fold drops in the MIC. Also, a similar drop had been shown with both extracts of *Senna macranthera* and *Salvia officinalis* that were expressed in the minimal MIC. So, it's interesting to note that utilizing such combinations led to a decrease in the smallest dosage needed to produce satisfactory anti-microbial impact, which might lower the medicines side effects risks and cost (17).

Synergism against methicillin-resistant Staphylococcus aureus (MRSA)

In 2009, Coutinho and colleagues studied the synergism between *Turnera ulmifolia* L. extract and two aminoglycoside antimicrobials, kanamycin and gentamicin, against MRSA using the checkerboard assay. This study approved that the use of herbal extracts with antimicrobials could significantly reduce the minimum inhibitory concentration of kanamycin and gentamicin, boosting their impact on aminoglycoside action and developing an innovative choice against these resistant bacterial strains (42).

In 2009, Kim and colleagues studied the synergism of a product isolated from *Achyranthes japonica* Nakai roots, called 20-hydroxyecdysone, when combined with gentamicin or ampicillin, employing the checkerboard dilution method. The results of the study exhibited an obvious synergistic potential between each of the antimicrobials used and the isolated product against MRSA, as evidenced by a marked drop in measured MIC (43).

After that, in 2012, Fernandes and colleagues assessed the synergism between *Psidium guineense* Swartz aqueous leaf extract and five antimicrobial drugs: meropenem, ciprofloxacin, cefoxitin, ampicillin, as well as amoxicillin/clavulanate, versus different resistant strains of *Staphylococcus aureus* using the checkerboard technique. The research team showed that when the antimicrobial drugs and the leaf extract of the plant were combined, the minimum inhibitory concentration of the drugs was reduced eight times, indicating a synergistic interaction versus MRSA (44). Furthermore, the minimum values of the fractional inhibitory concentration index were observed when *Psidium guineense* aqueous extract and cefoxitin were combined. Hence, the present study proved that the mentioned plant aqueous extract, when combined with beta-lactams, carbapenems, or fluoroquinolones, could work in concert to inhibit MRSA strains (45).

In 2012, Zuo and colleagues examined the *in vitro* synergistic potential of Isojacareubin that was extracted from *Hypericum japonicum* Thunb. aerial parts, the Chinese herb, and four antimicrobials towards MRSA. The checkerboard assay was used in this study and demonstrated that once isojacareubin was combined with ampicillin, ceftazidime, and levofloxacin, a notable synergistic impact was obtained, while unfortunately, the combination of isojacareubin and azithromycin resulted in indifference effects (46).

Following that, Santiago and colleagues in 2015 examined the synergistic potential of *Acalypha wilkesiana* when combined with ampicillin against MRSA's ability to form biofilms. The results of the study demonstrated that there was an inhibition of the biofilm matrix's ability to produce resistant proteins, which could result from blocking the preliminary cell surface adherence as well as lowering the level of penicillin-binding protein 2a within the matrix. It's thought that penicillin-binding protein 2a, which is present in the biofilm matrix, contributes to MRSA's virulence evolution. The researchers suggested that the presence of tannins in the extract is what causes the antibiofilm behavior that has been recognized (47).

In 2015, Liu and colleagues inspected the synergistic antimicrobial potential of salvianolate in combination with ten antimicrobial medications against multiple isolates of MRSA. Salvianolate refers to one of the prescribed remedies obtained from the herb *Salvia miltiorrhiza* Bunge, commonly known as the Chinese herb Danshen (48). The findings of the study revealed that salvianolate improved the *in vitro* potential of all the employed antimicrobial agents' against MRSA, but there was an obvious synergistic interaction between salvianolate and ampicillin, clindamycin, erythromycin, fosfomycin, and

piperacillin/tazobactam towards more than fifty percent of the isolates (49). The combination of salvianolate and ampicillin demonstrated the greatest synergistic impact regarding both bactericidal and bacteriostatic activities. whereas the combination of salvianolate and amikacin reverses MRSA's resistance to amikacin (50); hence, the researchers suggested that this combination could be a promising therapy for MRSA-infected patients, but with the need for additional investigation that is considered necessary (51).

One year later, Hong and colleagues conducted a study in 2016 in order to examine the synergism between *Phellinus baumii* extract, the medicinal mushroom, and particular antimicrobials versus MRSA using the time-killing technique. The antimicrobials used were cefazolin, cefepime, penicillin G, oxacillin, vancomycin, amikacin, erythromycin, and ciprofloxacin (52). The results of the study indicated that there were no synergistic effects recorded with non-beta lactams. On the other hand, the synergistic effects of the extract with beta-lactams, especially cefazolin and oxacillin, were obvious, as there was a significant reduction in MIC values for all tested beta-lactams, indicating that a key mechanism of synergy between the beta-lactams and the extract was the suppression of penicillin-binding protein 2a production. Finally, the researchers concluded that *Phellinus baumii* extracts can improve the effectiveness of beta-lactams when used in combination therapies to treat individuals with MRSA infections (53).

Thereafter, in 2017, Kuok and colleagues assessed the *in vitro* synergistic anti-MRSA potential of four medicinal plants: *Daphne genkwa*, *Magnolia officinalis*, *Momordica charantia*, and *Verbena officinalis* in conjunction with gentamicin or oxacillin. The study's findings demonstrated that, firstly, *Daphne genkwa* extract enhanced oxacillin's antibacterial activity versus MRSA. Secondly, *Magnolia officinalis* and *Verbena officinalis* developed limited synergistic responses in combination with oxacillin, and finally, *Momordica charantia* has been identified to possess no synergistic impact in suppressing MRSA (54). Catteau and colleagues performed a study to assess both the *in vitro* and *in vivo* anti-MRSA synergistic potential of *Vitellaria paradoxa* leaf extracts, commonly known as shea butter, and beta-lactamase antimicrobials. The triterpenoid compounds ursolic acid and oleanolic acid represent the major components of the leaf extracts. The findings of the *in vitro* study revealed that these terpenoids significantly synergized with ampicillin and oxacillin below their MIC values (55,56). On the other hand, the results of the *in vivo* study exhibited that locally administered ursolic acid worked synergistically with nafcillin in mice infected with subcutaneous MRSA, reducing the size of the lesion and the production of inflammatory cytokines (interleukin-1 beta). Therefore, these findings emphasize the possible utility of triterpenoids as agents that reverse resistance when combined with beta-lactamases to combat MRSA (57).

Subsequently, in 2018, Yang and colleagues examined the synergistic potential of the Tanreqing injection, a commercially available traditional Chinese medicine preparation made of different medicinal plants, which was utilized to manage infections of the upper respiratory tract with certain antimicrobials (linezolid and vancomycin) versus MRSA using the checkerboard dilution assay (58). The checkerboard analyses showed that by lowering the minimal inhibitory concentrations of the examined antimicrobial agents, Tanreqing significantly increased their effectiveness. Also, the synergistic antibiofilm impact of Tanreqing when combined with either linezolid or vancomycin below their MIC values was substantially greater than that of any of them alone. Hence, this gives a logical foundation for combining treatments for MRSA (59).

Then, in 2021, Sharaf and colleagues studied the synergism between the saponin fraction extracted from the plant *Zygophyllum album* and the antibiotic benzylpenicillin. The synergistic potential was assessed with the checkerboard technique and the time-kill method. The research team came to the conclusion that the combination of the saponin fraction of *Zygophyllum album* with concentrations of (312.5, 156.25, and 78.125) µg/mL and penicillin with a concentration of 62.5 µg/mL could work together as an alternative therapy versus MRSA and potentially act as a template for an innovative antimicrobial medication (60).Also, Jeong and colleagues examined the *in vitro* antimicrobial synergistic potential of aerial parts of *Sedum takesimense*-isolated active compound called "1,2,4,6-tetra-O-galloyl-glucose" with beta lactam antimicrobials: ampicillin, clavulanic acid, and oxacillin against MRSA. They demonstrated the synergism present with all antimicrobials used, but the best inhibition of MRSA growth was obtained when the plant extract was combined with oxacillin, as was obvious by the inhibition of MIC from 256 to less than 1 µg/mL (61).

Synergism against Pseudomonas aeruginosa

In 2020, Abu El-Wafa and colleagues evaluated the antimicrobial synergistic potential of rosemary and pomegranate extracts with particular antimicrobials against the development of *Pseudomonas aeruginosa* biofilms and antimicrobial resistance. The antimicrobials used were ceftazidime, gentamycin, imipenem, piperacillin, and levofloxacin. The findings of the study demonstrated a synergistic effect on the tested pathogens and point to the possibility of using rosemary, pomegranate, and antibiotic combinations as an effective treatment for managing *Pseudomonas aeruginosa* biofilm development as well as antimicrobial resistance. Also, the investigated isolate's susceptibility to the mentioned antimicrobials shifted from a resistant to a sensitive one. Finally, remarkably, the combined action of plant extracts

and antimicrobials employed has considerably lowered the antimicrobials' MIC values below their sensitivity limits (62).

Synergism against Escherichia coli

In 2021, Jaktaji and colleagues performed an *in vitro* study to investigate the synergism of honey and *Sophora alopecuroides* alkaloidal extract with ciprofloxacin against *an Escherichia coli* mutant strain that demonstrated elevated activity of the AcrAB-TolC efflux pump. The researchers found that the mentioned combination exhibited total synergistic interactions versus strains of *Escherichia coli* that are extremely resistant to ciprofloxacin, as seen in the minimum inhibitory concentration that was measured, and there was a notable reduction in the extent of gene expression (63).

Recently, Mitra and colleagues assessed the *in vitro* antimicrobial synergistic potential of guava leaf extract and a number of antibacterial medications against uropathogenic *Escherichia coli* employing Muller-Hinton agar. The antimicrobial medications used were amikacin, tobramycin, amoxicillin/clavulanate, cefotaxime, cefuroxime, ceftizoxime, cephalothin, levofloxacin, ofloxacin, norfloxacin, nitrofurantoin, and trimethoprim. The research team found that the addition of guava leaf extract enhanced the sensitivity of all the antimicrobials employed in the study (64). At the end of this study, the researchers concluded that the guava leaf extracts showed the greatest synergistic impact when combined with the antibacterial ofloxacin (65). So, this discovery suggests that the extract of guava increases the potency of widely prescribed antimicrobials for the management of urinary tract infections. This effect is primarily ascribed to the flavonoid constituents and related derivatives found in the extract of guava leaves, which suppress the growth of pathogenic bacteria. Consequently, it is reasonable to assume that taking antimicrobial agents along with guava extract may help prevent the appearance of microbial resistance (66).

Synergism against Klebsiella pneumonia

In 2016, Cai and colleagues examined the synergistic potential of baicalein with cefotaxime versus *Klebsiella pneumoniae*. Baicalein represents a kind of flavonoids derived from the roots of *Scutellaria lateriflora* and *Scutellaria baicalensis*, which are among the most utilized Chinese herbs throughout China for the management of infections caused by bacteria. The results of the investigation revealed that baicalein, when coupled with cefotaxime, showed synergistic potential versus certain *Klebsiella pneumoniae* strains that were positive for extended-spectrum beta-lactamases by suppressing the expression of CTX-M-1 mRNA. The synergistic behavior, nevertheless, was not mediated by any direct bacteriostatic or bactericidal activities. It appears that baicalein is an innovative, potent, and synergistic antimicrobial compound (67).

After that, last year, in 2023, the synergism between *Ulva lactuca*, seaweed, and different classes of antimicrobials was approved by EL-Sayed and colleagues. The researchers deduced that the extract of *Ulva lactuca* possesses the potential to assist antimicrobials in diminishing the growth of the resistant bacterial strains of *Klebsiella pneumonia* using the agar well diffusion approach. The antimicrobial classes employed were beta-lactam, aminoglycoside, and chloramphenicol. The best synergistic effect was seen with the administration of the mentioned extract with chloramphenicol and gentamicin (68).

Synergism against Mycobacteria

More than two decades ago, specifically in 1999, the impact of "mao-bushi-saishin-to," the traditional Chinese medicine, on benzoxazinorifamycin's ability to treat mice infected with the *Mycobacterium avium* complex was investigated by Shimizu and colleagues. The results of the current research showed that the new benzoxazinorifamycin's medicinal effectiveness on *Mycobacterium avium* infection could be somewhat enhanced by the used Chinese medicine's mao-bushi-saishin-to, which represents a combination made from three medicinal herbal extracts: hou-bushi, mao, and saishin (69). The impact of the used medicinal herbal extract seems to be associated with its capacity to modify murine peritoneal macrophage anti-*Mycobacterium avium* complex action, as the herbal usage on mice peritoneal macrophages promoted benzoxazinorifamycin's microbicidal action towards intra-murine peritoneal macrophage *Mycobacterium avium* complex (70).

Then, many years later, specifically in 2016, Aro and colleagues examined the synergism between six extracts of *the Rubiaceae* family, which were *Cephalanthus natalensis*, *Cremaspora triflora*, *Pavetta lanceolata*, *Psychotria capensis*, *Psychotria zombamontana*, and *Oxyanthus speciosus,* with rifampicin, versus three mycobacterial strains, including *Mycobacterium tuberculosis*, *Mycobacterium smegmatis*, and *Mycobacterium aurum*, employing the checkerboard technique. The results of the study proved that, when given with rifampicin, each of the tested leaf extracts displayed synergistic effects at varying concentrations; no antagonistic effects were seen (71).

Subsequently, in 2018, Rahgozar and colleagues assessed the *in vitro* synergistic effects of five plants, which were *Thymus vulgaris*, *Rosmarinus officinalis*, *Lavandula stoechas*, *Datura stramonium*, and *Boswellia serrate,* on *Mycobacterium bovis*. The potential for synergism with regard to antimycobacterial activity was explored by combining the extracts from the mentioned plants with ethambutol and isoniazid (72). The researchers demonstrated that, when combined with ethambutol, *Datura stramonium* and *Lavandula stoechas* produced the greatest synergistic effects; however, the other combinations still exhibited synergistic impact, but in a

distinct fashion, except for isoniazid when combined with *Rosmarinus officinalis*, and *Datura stramonium* showed no interacting potential (73).

Synergism against Acinetobacter baumannii

The synergistic potential of plant extract with antimicrobials against *Acinetobacter baumannii* was only assessed in a single study by Chusri and colleagues in 2014. The researchers performed an *in vitro* study to determine the effectiveness of a variety of seventeen medicinal plants belonging to *the Apocynaceae* family when employed together with standard antimicrobials of varied classes versus *Acinetobacter baumannii* strains, which were extensive drug-resistant, multidrug-resistant, as well as non-multidrug-resistant. The most important results of the study were as follows: When combining the *Apocynaceae* extracts with rifampicin or cefazolin, the most significant synergistic potential was seen. Remarkably, more than half of the combinations of the extracts with rifampicin showed either partial synergistic or synergistic potential. Furthermore, *Holarrhena antidysenterica* extract evidently recovered the rifampicin action against extensive drug-resistant, multidrug-resistant *Acinetobacter baumannii* strains (74).

Synergism against Salmonella

In 2008, Jang-Gi and colleagues assessed the *in vitro* synergistic potential of methyl gallate derived from Galla rhois with ciprofloxacin versus *Salmonella* isolates. The results of the study were promising and proved that the utilized combination could work synergistically to inhibit Salmonella growth *in vitro* (75).

The synergistic potential of *Ocimum sanctum* leaves' extracts with trimethoprim and chloramphenicol towards *Salmonella enterica* serovar *typhi* was assessed by an *in vitro* study conducted in 2012 by Mandal and colleagues using the disk diffusion method. The bacterial isolates in the current study were resistant to the selected antimicrobial drugs. The research team found that the herbal leaf extract combined with trimethoprim and chloramphenicol exhibited synergistic potential against the employed *Salmonella typhi* isolates. Consequently, *Ocimum sanctum* offers promise in countering *Salmonella typhi* strains resistance to conventional antimicrobial medications and also in the evolution of non-antimicrobial therapy for typhoid fever infections (76).

Synergism against certain bacteriological conditions

The followings are studies of synergy between specific plants and antimicrobial medicines used in particular medical conditions.

Synergism against chronic rhinosinusitis

In 2018, Lopatin and colleagues assessed the synergistic potential of *Cyclamen europaeum* in the treatment of chronic rhinosinusitis. Intranasal *Cyclamen europaeum* extract, combined with an oral antimicrobial, was administered to patients in Group 1. Group 2 received monotherapy with intranasal *Cyclamen europaeum*, while Group 3 received oral antimicrobials only (77). There were no strict rules for empirical antimicrobial treatment, and each of the contributing physicians chose an oral first-line prescribed antimicrobial based on institutional instructions as well as their own clinical observations, such as amoxicillin, amoxicillin/clavulanate, clarithromycin, as well as first- and third-generation cephalosporins. *Cyclamen europaeum* was applied topically to every nostril (2.6 milligrams only once per day) for eight consecutive days. Following the initiation of therapy, every patient underwent a routine examination every six months by the assigned observer (78). The present observational study's findings indicate that, in comparison to antimicrobials used alone, *Cyclamen europaeum* in combination with oral antimicrobials or as a monotherapy improves amelioration of symptoms and minimizes future chronic rhinosinusitis recurrence in patients with moderate intensity. Therefore, intranasal *Cyclamen europaeum* may be taken into consideration as a substitute for conventional antimicrobial medication in the treatment of non-complicated, non-severe cases. It could also contribute to reducing disease-related expenses and minimizing the misuse of antibiotics, which in turn lowers the rise in antimicrobial resistance (79).

Synergism against oral bacteria

In 2017, Lee and colleagues assessed the synergism of *Sophora flavescens* root extract with ampicillin and gentamicin versus multiple oral bacteria, including *Streptococcal* strains, *Aggregatibacter actinomycetemcomitans*, *Fusobacterium nucleatum*, *Porphyromonas gingivalis*, and *Prevotella intermedia,* using the checkerboard and time-kill methods. The current study approved that the combination of butanol extract with either ampicillin or gentamicin, along with the combination of ethyl acetate fraction in combination with either of the mentioned antimicrobials, could result in synergistic effects against all tested bacterial strains (80).

Synergism against periodontopathic bacterial strains

In 2021, Saquib and colleagues conducted a study to assess the synergistic potential of *Azadirachta indica*, *Commiphora molmol*, and *Punica granatum* in conjunction with amoxicillin, azithromycin, metronidazole, and tetracycline towards periodontopathic bacteria, including *Aggregatibacter actinomycetemcomitans*, *Porphyromonas gingivalis*, *Tannerella forsythia*, and *Treponema denticola.* By determining the zone of inhibition diameters', the synergistic potential of plant extract and antimicrobials was evaluated for each microbe individually. The results of the study exhibited that combining plant extracts with antimicrobials has been shown to have a synergistic

antibacterial impact against all of the tested bacteria. However, the superior synergism that has been shown between *Punica granatum* and amoxicillin towards the bacterium *Aggregatibacter actinomycetemcomitans* (11,81,82).

Synergism against bacterial-related wound infections

Aiyegoro and colleagues performed a study in 2009 that examined the synergism of *Helichrysum pedunculatum* leaf extracts with particular antimicrobials against bacteria-linked wound infections. Time-kill procedures were used to examine the effects of combinations containing the methanolic leaf extract of *Helichrysum pedunculatum* and eight of the first-line antimicrobials on a set of bacterial strains known to cause wound infections (83). The bacterial strains employed were: *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus faecalis*, *Bacillus pumilus*, *Bacillus subtilis*, *Proteus vulgaris*, *Micrococcus kristinae*, *Micrococcus luteus, and Klebsiella pneumoniae*. The results of the study revealed that, first, the plant extract was able to increase the antimicrobials' bactericidal impact against all examined bacterial strains. Second, the greatest bactericidal potential was demonstrated for *Staphylococcus epidermidis* once the extract was combined with penicillin G. Third, approximately 60% of the extract and antimicrobial combinations examined for all of the tested microbes had a synergistic reaction in general. Fourth, across all combinations tested versus *Staphylococcus aureus*, there was no evidence of synergy or antagonistic behavior among the total number of tests that were conducted (84). At the end of the study, the researchers suggested that leaf extracts from *Helichrysum pedunculatum* could potentially be relevant for combined treatment as well as a source of therapeutic concepts that modify resistance, which may be helpful in treating chronic wound infections (85).

Synergism against Leptospirosis

Leptospirosis represents one of the most significantly prevalent zoonotic infectious illnesses globally, brought about by spirochete bacteria related to the genus *Leptospira*. In 2013, Seesom and colleagues examined the synergistic potential of γ-mangostin extracted from *Garcinia mangostana* in combination with penicillin G versus leptospirosis. By determining the fractional inhibitory concentration index, the synergistic potential was assessed (86). The research team revealed that the combination used produced a synergistic potential towards the pathogenic *Leptospira interrogans* serovars Bataviae, Javanica, and Autumnalis, but there was an absence of interaction with the nonpathogenic strain *Leptospira biflexa* serovar Patoc. On the other hand, the pathogenic *Leptospira interrogans* serovar Saigon exhibited antagonistic behavior. So, they concluded that the combined administration of *Garcinia mangostana* extract along with the antimicrobial improves its anti-leptospiral efficiency (87).

Synergism against caprine and bovine mastitis

The term mastitis refers to breast tissue inflammation that may involve a bacterial infection resulting from particular bacteria that exist in the mammary glands. In 2019, Procópio and colleagues performed a study to examine the synergism of lectin extract from *Calliandra surinamensis* leaves together with certain antimicrobials, ampicillin and tetracycline, against fifteen strains of mastitis-causing bacteria obtained in cows and goats, including *Corynebacterium*, *Escherichia coli*, and thirteen different strains of *Staphylococcus aureus* (88). The researchers concluded that for certain mastitis isolates, the plant extract acted as an antibiofilm and bacteriostatic agent, and the combination of the plant extract with ampicillin and tetracycline was effective against one and two isolates of *Staphylococcus aureus,* respectively. The findings encourage further research on lectin leaf extract's potential as a mastitis therapy, especially when combined with antimicrobial medications (89).

Synergism against multiple bacterial strains

In 2007, Horiuchi and colleagues performed a study to inspect the synergism between the phenolic diterpene product, carnosol, and the related product, carnosic acid, which derives from *Salvia officinalis* leaves, and certain antimicrobials against four strains of vancomycin-resistant *Enterococci*, MRSA, and *Staphylococcus aureus*. The researchers found that, firstly, carnosol and carnosic acid could potentiate tetracycline, erythromycin, and aminoglycosides' antimicrobial efficacy against vancomycin-resistant *Enterococci*. Secondly, although carnosol and carnosic acid enhanced the aminoglycosides' antimicrobial effect against MRSA, it was not as strong as against vancomycin-resistant *Enterococci*. Thirdly, carnosol and carnosic acid could also enhance the efficacy of erythromycin and tetracycline against *Staphylococcus aureus*, but with tetracycline, there was just a minor impact noticed (90).

After that, in 2012, Stefanovi and colleagues assessed the synergism between the extracts of *Cichorium intybus* and *Salvia officinalis* and the antimicrobials amoxicillin and chloramphenicol using the checkerboard technique. The organisms tested were *Bacillus subtilis*, *Enterobacter cloacae*, *Escherichia coli*, *Proteus mirabilis*, and *Klebsiella pneumoniae*. The researchers showed that, first, compared to *Cichorium intybus*, *Salvia officinalis* demonstrated a higher capacity for synergy. Second, there have been synergistic effects detected between *Salvia officinalis* extract and amoxicillin, as well as chloramphenicol. Third, with the exception of *Escherichia coli*, synergism was seen against all of the examined bacteria. Fourth, on the other hand, *Cichorium intybus* extract and the antimicrobials produced additive and indifferent impacts on the examined bacteria. Ultimately, the antimicrobial capacity of plant extracts from *Cichorium intybus* and *Salvia officinalis* has been verified, and the extracts' synergistic

potential with the examined antimicrobials may indicate a different approach to combating the issue of bacterial infections (91).

Subsequently, in 2013, Olajuyigbe and Afolayan investigated the *in vitro* synergistic potential of *Ziziphus mucronata* bark extracts when combined with certain antimicrobials against different bacterial strains. The antimicrobials used include amoxicillin, chloramphenicol, ciprofloxacin, kanamycin, nalidixic acid, and tetracycline. The bacterial strains employed were the gram-negative bacteria, including *Acinetobacter calcoaceticus*, *Bacillus cereus*, *Bacillus subtilis*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Serratia marcescens*, and *Shigella flexneri*, as well as the gram-positive ones, which were *Enterococcus faecalis*, *Proteus vulgaris*, and *Staphylococcus aureus*. The results of the study revealed that the bacterial strains examined showed varying degrees of response to the combinations used, with *Shigella flexneri* exhibiting the greatest susceptibility, with the exception of *Bacillus cereus* and *Escherichia coli*, which were more susceptible to only nalidixic acid. Regarding the zones of inhibition that developed by the extract-antimicrobial combinations, they were generally greater than those of the extract or any of the individual antimicrobials utilized independently (92).

Then, in 2014, Araújo and colleagues studied the synergistic antibacterial potential of some plant extracts of *the Lamiaceae* family and streptomycin versus six bacterial strains. The plants used were *Rosmarinus officinalis*, *Plectranthus barbatus*, *Ocimum basilicum*, *Mentha spicata*, and *Melissa officinalis*. While the bacteria employed were three gram-negative bacterial strains, including *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *and Escherichia coli*, there were also three gram-positive bacterial strains, including *Streptococcus mutans*, *Staphylococcus aureus*, and *Enterococcus faecalis*. The results obtained demonstrated the synergistic potential of the ethanolic extract with streptomycin for all tested microorganisms. The researchers indicated that this effectiveness could be attributed to the compound phytol present in all the obtained extracts (93).

Thereafter, in 2016, Manosalva and colleagues studied the *in vitro* antimicrobial synergistic effect of *Berberis microphylla* alkaloids extracted from the plant's roots, leaves, and steam with certain antimicrobials versus different gram-positive bacteria. The current study concluded the following findings about the synergism of the extract with ampicillin: first, the alkaloidal extract of the plant exhibited synergism towards *Staphylococcus epidermidis*, *Bacillus subtilis*, and *Bacillus cereus* with the combination of the leaf alkaloidal extract and ampicillin. Second, synergism was also obtained versus *Staphylococcus epidermidis* and *Staphylococcus aureus* using the combination of the stem alkaloidal extract and ampicillin; also, the combination of the root alkaloidal extract and ampicillin displayed similar effects towards *Bacillus subtilis*. Third, on the other hand, the synergistic effect of the alkaloidal extracts and cephalothin has been demonstrated to be effective in the subsequent combinations: leaves alkaloidal extract and cephalothin towards *Staphylococcus aureus*, *Bacillus cereus*, and *Staphylococcus epidermidis*; stem alkaloidal extract and cephalothin towards *Staphylococcus aureus* and *Bacillus subtilis*; as well as roots alkaloidal extract and cephalothin towards *Bacillus cereus* and *Staphylococcus epidermidis*. Fourth, as a result of the synergism between *Berberis microphylla* alkaloidal extracts and antimicrobials, the adverse effects of using either antimicrobial alone would be reduced (94).

Afterward, in an in-depth study conducted in 2017 by Sanhueza and colleagues, the synergism between the use of grape pomace extract in different concentrations and multiple antibiotics belonging to various classes against strains of *Staphylococcus aureus* and *Escherichia coli* that are multidrug resistant was demonstrated employing the checkerboard technique. The selected classes were quinolone, fluoroquinolone, β-lactam, amphenicol, and tetracycline. The researchers found that this combination could result in a significant reduction in MIC ranging from 75 to 30 times for different *Staphylococcus aureus* strains. Likewise, the results are somewhat comparable for *Escherichia coli*, as the mentioned combination resulted in a reduction in MIC spanning from 67 to 4 times. These findings were observed for all employed combinations in different concentrations, regardless of whether the bacteria under test was resistant to the antimicrobial or not (95).

Again, in 2017, Haroun and colleagues performed a study to examine the synergism of *Thymbra spicata* L. extract when combined with particular antimicrobials against strains of *Klebsiella pneumoniae* and *Staphylococcus aureus* that were multidrug resistant, utilizing the checkerboard assay. The results of the study revealed that, based on the strain examined, various impacts—synergistic, additive, or even indifference—of the combination used were recognized. Regarding *Staphylococcus aureus*, firstly, for all strains of *Staphylococcus aureus* that have been examined, the combination of amikacin, ampicillin, and cefotaxime with *Thymbra spicata* L. extracts demonstrated synergistic potential. Secondly, cefotaxime showed the greatest synergistic potential when used versus the mentioned strains, increasing its efficacy from eight to one hundred twenty-eight times. On the other hand, the combined effects of plant extract and ciprofloxacin were primarily additive or indifferent. In comparison to *Staphylococcus aureus* strains, *Klebsiella pneumoniae* strains were less susceptible to the combined effects of plant extracts, with the majority of combinations showing indifferent impact. However, plant extracts and ampicillin showed the greatest synergistic potential for *Klebsiella pneumoniae*-resistant strains. Yet, this combination demonstrated an additive impact with sensitive ones. Furthermore, the

plant extract and cefotaxime combination resulted in synergism for multi-drug *Klebsiella pneumoniae*-resistant strains, besides additive impact for the other ones. Finally, the combination of plant extract and ciprofloxacin showed an indifferent and additive impact on both sensitive and resistant strains (96).

Once again in 2017, Rao and colleagues assessed the *in vitro* potential of *Geophila repens* essential oil when combined with certain common antimicrobials (ampicillin, chloramphenicol, and streptomycin) against two gram-negative bacterial strains, including *Pseudomonas aeruginosa* and *Escherichia coli*, as well as two gram-positive ones, including *Staphylococcus aureus* and *Bacillus subtilis*. The research team showed that the combination used in the current study produced synergistic potential in the majority of cases; the strongest synergistic impact was observed once the herbal extract was combined with streptomycin when examined versus *Escherichia coli*. In finality, the researchers concluded that the amalgamation of *Geophila repens* essential oil and commercially available antibiotics holds substantial promise for the advancement of novel antimicrobial therapies and the mitigation of antimicrobial resistance (97).

Then, in 2019, Maheshwari and colleagues investigated the antimicrobial synergism of *Carum copticum* L. seed extract with ciprofloxacin versus extended-spectrum beta-lactamase bacteria utilizing the checkerboard technique. The researchers found that there was a significant reduction in the MIC of ciprofloxacin in the presence of the herbal extract, demonstrating a synergistic improvement in antibacterial action. The current research illustrates the potential application of the herbal extract in combination treatment for the investigated bacterial infections (98).

Again, in 2019, Manoraj and colleagues examined the synergistic impacts of Triphala extract and two antimicrobials, oxacillin and gentamicin, versus MRSA as well as multi-drug-resistant gram-negative bacilli. Triphala is referred to as a traditional herbal remedy consisting of three fruits: *Emblica officinalis* L., *Terminalia bellirica*, and *Terminalia chebula* Retz, incorporated in the same proportions. The study was performed *in vitro,* utilizing the checkerboard technique. At the end of the study, the researchers concluded that Triphala exhibits synergistic impact when combined with oxacillin to combat MRSA strains and with gentamicin to combat particular multi-drug-resistant gram-negative bacteria. The particular gram-negative bacteria mentioned were *Pseudomonas aeruginosa*, *Acinetobacter* species, *Klebsiella pneumonia*, *Enterobacter cloacae*, *Serratia* species, and *Proteus* species (99).

Following that, recently in 2023, Jesus and colleagues inspected the synergism of stems and leaves ethanolic extracts for *Miconia albicans*, a Brazilian herbal remedy, with ciprofloxacin and ampicillin towards *Staphylococcus aureus* and *Acinetobacter baumannii* resistant strains. The results of this study demonstrated the noticeable antimicrobial characteristics of *Miconia albicans*, especially in its capacity for synergizing antimicrobials. These findings may pave the way for the creation of new, effective treatments targeted at curing and halting the spread of antimicrobial-resistant microbial infections (100).

Again in 2023, Atta and colleagues using the checkerboard assay evaluated the antimicrobial synergistic effects of nine plant extracts: *Chamomilla recutita*, *Curcuma amada*, *Gentian lutea*, *Mentha longifolia*, *Momordica charantia*, *Murraya koenigii*, *Nigella sativa*, *Terminalia chebula*, and *Terminalia arjuna* with cefixime. The tested microorganisms were four resistant gram-negative strains: *Acinetobacter*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*. Besides three gram-positive strains: *Staphylococcus aureus*, *Staphylococcus haemolyticus*, and MRSA. It was concluded that the synergistic effects were variable on each tested organism, but each extract obviously enhanced the cefixime efficiency, especially on resistant strains (101).

Then recently, in the current year 2024, Abrar and colleagues examined the plant *Fagonia indica Burm*.f. as a synergistic therapy with cefixime for MRSA and *Escherichia coli*-resistant strains. Utilizing bacterial protein estimation research as well as time-kill kinetics, synergism was assessed. Concerning MRSA and *Escherichia coli* resistance strains, topographic images showing synergism have been determined via electron microscope scanning (102). The present study showed that this combination of plant extract and cefixime exhibited an obvious antimicrobial potential, with significant destruction of the structures of bacterial cells and a reduction in the contents of bacterial proteins. The use of this combination treatment proved to have fewer adverse effects and was biocompatible, suggesting its use as a successful treatment choice in the future (103).

Synergism of Berberis alkaloids with antibiotics

In 2018, Ramos and colleagues investigated the *in vitro* synergistic antibacterial and antifungal potentials of *Alpinia purpurata* inflorescences with antimicrobials. The bacterial strains employed included *Pseudomonas aeruginosa* and *Staphylococcus aureus*, while the fungal strains were *Candida parapsilosis* and *Candida albicans*. The findings of the study showed that, firstly, the combination of *Alpinia purpurata* and oxacillin resulted in synergistic potential towards *Staphylococcus aureus* strains resistant to oxacillin alone (104). Secondly, *the Alpinia purpurata* and ceftazidime combination exhibited synergistic potential for *Pseudomonas aeruginosa* (105). Thirdly, *Alpinia purpurata* and fluconazole combinations resulted in synergistic and additive characteristics versus *Candida parapsilosis* and *Candida albicans*, respectively (106). It was interesting to note that the synergistic potential

towards *Candida parapsilosis* expressed a decrease of more than eight times the fluconazole minimum inhibitory concentration (107). Table 1 gives a simple tabulated summary of the above-mentioned studies included in this manuscript.

Synergism of plant extracts with antifungal medications

Due to the fact that infectious fungal strains have been continuously increasing their resistance to antimicrobials, a dire need arose to investigate unfamiliar potential strategies for improving antifungal medicinal products, such as the synergism of antifungal medication with natural plant extract (108). Studies that have approved synergistic impacts are summarized below.

In 2012, Ouédraogo and colleagues investigated the *in vitro* synergistic potential of alkaloids from *Sida cordifolia* L. with clotrimazole and nystatin versus five different *candida* strains, which were *Candida albicans*, *Candida krusei*, *Candida parapsilosis*, and *Candida tropicalis*. The findings of this study were intriguing and suggested that the combination of alkaloids from *Sida cordifolia* L. and antifungals, including clotrimazole and nystatin, could be effective against the strains examined. So, according to the findings, such plants can be utilized for managing infectious diseases, especially infections caused by candida (109).

In 2013, Santos and colleagues examined the *in vitro* synergism between Eugenia uniflora L. leaves and four antimicrobial medications, which were amphotericin B, nystatin, metronidazole, and mebendazole, versus *Candida albicans*, *Candida glabrata*, *Candida krusei*, *Candida parapsilosis*, and *Candida tropicalis*. The study's findings demonstrated that the plant extract exhibited synergistic antifungal potential with metronidazole versus *Candida tropicalis*, but no synergistic potential towards the other strains was seen, as was noticed once the extract was combined with other antifungal medications, not improving their efficacy (110).

In 2014, Fu and colleagues studied the synergistic antifungal impact between baicalein and amphotericin B versus thirty isolates of *Candida albicans*. Baicalein is the product that was first isolated from the root of *Scutellaria baicalensis*. By employing the checkerboard method, the synergistic impact was assessed (111). The researchers found that the reactive oxygen species increased in tandem with an acceleration of the apoptosis of *Candida albicans* as a result of the combination of baicalein and amphotericin B (112). Additionally, they discovered that amphotericin B elevated *Candida albicans* caspase action as well as the corresponding gene expression, CaMCA1; the existence of baicalein amplified these impacts. Amphotericin B prompt apoptosis was evidently mitigated by the CaMCA1 deletion, suggesting a synergistic role for the CaMCA1-mediated caspase system in amphotericin B prompt apoptosis (113).

In 2016, Han and colleagues looked into how well the *Rubus chingii* fruit extract and fluconazole worked together versus *Candida albicans* strains resistant to fluconazole. The results of the *in vitro* study were promising, as the combination of the extract and fluconazole exhibited stronger antifungal potential against the strains tested when taken together than that of either of them alone (114).

After that, in 2017, Moraes and colleagues performed a study to assess the antifungal synergistic potential of an aquatic-not-soluble portion of *Uncaria tomentosa* bark with fluconazole and terbinafine against resistant non-*Candida albicans* isolates of *Candida krusei* and *Candida glabrata*, utilizing the checkerboard approach. The results of the study revealed that there was a synergistic potential between the combinations of an aquatic-not-soluble portion with each of fluconazole and terbinafine. The research team concluded that this portion primarily consists of proanthocyanidins that interact unquestionably with fluconazole and terbinafine, resulting in an obvious synergistic antifungal activity (115). Also, Cardoso and colleagues performed a study to assess the synergism of *Ocimum basilicum* var. Maria Bonita leaf extract together with amphotericin B against *Cryptococcus neoformans*. The synergism tested in this study was performed through the checkerboard technique. The research team found that the combination of the extract with amphotericin B could result in reducing the concentration of each of the components required to eradicate one hundred percent of the inoculum, boosting their antifungal potential (116).

Following that, in 2020, Liu and colleagues examined the synergistic antifungal impacts between gypenosides and fluconazole versus *Candida albicans* strains both *in vitro* and *in vivo*. The *in vitro* investigation demonstrated that gypenosides and fluconazole had a synergistic antifungal potential against fluconazole-resistant *Candida albicans* while showing no apparent effects on fluconazole-susceptible ones (117). Furthermore, this *in vitro* synergism showed anti-biofilm potential towards fluconazole-resistant *candida albicans* at the initial phase. On the other hand, the *in vivo* synergistic examination of gypenosides and fluconazole for their antifungal potential was done using *Galleria mellonella* larvae. The research team found that gypenosides, along with fluconazole, decreased the invasion of tissues and expanded the rate of survival for fluconazole-resistant *Candida albicans*-infected larvae. Gypenosides refers to a group of triterpenoid saponins that were isolated from *Makino's Gynostemma pentaphyllum* and utilized for the treatment of various illnesses in Chinese medicine (118).

Recently, in a study conducted by Ogidi and colleagues in 2021, the synergism between the antifungal impact of a combination of antifungal creams and *Aloe vera* gel or *Curcuma longa* essential oil was assessed *in vitro* utilizing the agar well diffusion technique. The combination of antifungal creams used was (0.5%) fluconazole, (1%) clotrimazole, (1%) terbinafine, and (2%) ketoconazole.

Table 1. Tabulated summary of the synergistic studies of natural compounds and antimicrobial agents on pathogenic bacterial strains

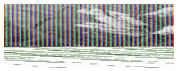
Natural source	Part used	Antimicrobial used	Targeted bacteria	Result and reference	Value of synergism	Illustrative picture
Baccharis trimera "Carqueja"	Different dried plant material	Ampicillin Oxacillin Chloramphenicol tetracycline Netilmicin Gentamicin Erythromycin Vancomycin Cephalothin Cefoxitin Ofloxacin Cotrimoxazole	*Staphylococcus aureus*	*Syzygium aromaticum* "clove" and *Psidium guajava* "guava" showed the greatest synergistic potential with all antimicrobials used (33)	Not determined	
Syzygium aromaticum "Clove"						
Mikania glomerata "guaco"						
Psidium guajava "Guava"						
Allium sativum "garlic"						
Zingiber officinale "Ginger"						
Cymbopogon citratus "Lemongrass"						
Mentha piperita "Mint"						
Vaccinium macrocarpon Ait "Cranberry"	Fruits	Amoxicillin Oxacillin	*Staphylococcus aureus*	The best result obtained with amoxicillin (35)	Drop of amoxicillin MIC by 512 times	
Stephania suberosa	Roots	Ampicillin	*Staphylococcus aureus*	Significant synergism Obtained (39)	Dropping from 512 to 0.15 µg/mL in ampicillin concentration required for growth inhibition	
Indigofera suffruticosa	Leaves	Erythromycin	*Staphylococcus aureus*	Hopeful synergism obtained against ampicillin-resistant strains (40)	Dropping of erythromycin MIC by 4 times	
Melaleuca armillaris	Herbaceous branches Leaves	Cloxacillin	*Staphylococcus aureus*	Lower cloxacillin's minimum inhibitory concentration versus *Staphylococcus aureus* (41)	MIC of cloxacillin from 0.125 to 0.031 µg/mL	

Table 1. Continued

Natural source	Part used	Antimicrobial used	Targeted bacteria	Result and reference	Value of synergism	Illustrative picture
Senna macranthera	Leaves	Ampicillin Gentamycin Kanamycin	*Staphylococcus aureus*	Eightfold drops in the MIC (17)	Dropping of MIC by eight times with each plant extract	
Salvia officinalis						
Plectranthus ornatus						
Turnera ulmifolia L	Leaves	Kanamycin Gentamicin	MRSA	A significant reduction in MIC (42)	Dropping of MIC from (1024 to 128 and 8 to 1) µg/mL, respectively	
Achyranthes japonica	Roots	Gentamicin Ampicillin	MRSA	A marked drop in MIC (43)	Dropping of MIC from (512 to 128 and 256 to 64.0) µg/mL, respectively	
Psidium guineense "Guava"	Leaves	Meropenem Ciprofloxacin Cefoxitin Ampicillin Amoxicillin/Clavulanate	MRSA	The best result was obtained with cefoxitin (45)	Dropping of MIC of cefoxitin from 400 to 0.78 µg/mL	
Hypericum japonicum	Aerial parts	Ampicillin Ceftazidime Levofloxacin Azithromycin	MRSA	The best result was obtained with ampicillin, ceftazidime and levofloxacin (46)	Dropping of MIC from (128, 512, 16 to 16, 64, 4) µg/mL, respectively	
Acalypha wilkesiana	Whole plant	Ampicillin	MRSA	Significant synergism effect (47)	Not determined	
Salvia miltiorrhiza	Whole plant	Ampicillin Clindamycin Erythromycin Fosfomycin Piperacillin/Tazobactam	MRSA	Ampicillin showed the greatest synergistic impact regarding both bactericidal and bacteriostatic activities (51)	Dropping of MIC of ampicillin from 64 to 0.75 µg/mL	
Phellinus baumii	Mushroom	Cefazolin, Cefepime, Penicillin G, Oxacillin, Vancomycin, Amikacin, Erythromycin, Ciprofloxacin	MRSA	Improvement of the beta-lactam effectiveness (53)	Reducing the MICs of various beta-lactams by 8-128 times	

Table 1. Continued

Natural source	Part used	Antimicrobial used	Targeted bacteria	Result and reference	Value of synergism	Illustrative picture
Daphne genkwa	Different plant parts	Gentamicin Oxacillin	MRSA	Significant synergism was obtained when *Daphne genkwa* was combined with oxacillin (54)	Lowering MIC from 128 to 48 µg/mL	
Magnolia officinalis						
Momordica charantia						
Verbena officinalis						
Vitellaria paradoxa "Shea butter tree"	Leaves	Ampicillin Oxacillin	MRSA	Significant synergism was obtained (57)	Not determined	
Tanreqing injection	Different dried plant material	Linezolid Vancomycin	MRSA	Significant reduction of MIC values (59)	Lowering MIC from (4125 to 516 and 2063) µg/mL, respectively	
Zygophyllum album	Dried plant material	Penicillin	MRSA	A hopeful result obtained (60)	Reducing MIC from 125 to 39.06 µg/mL	
Sedum takesimense	Aerial parts	Ampicillin Clavulanic Acid Oxacillin	MRSA	The best synergism was obtained in combination with oxacillin (61)	Dropping of MIC from 128 to 64 µg/mL	
Rosmarinus officinalis "Rosemary"	Peels	Ceftazidime Gentamycin Imipenem Piperacillin Levofloxacin	*Pseudomonas aeruginosa*	Significant reduction in the antimicrobials' MIC values; the best result was shown in the combination of piperacillin (62)	Lowering MIC from 1.024 to 0.032 µg/mL	
Punica granatum "Pomegranate"						
Honey *Sophora alopecuroides*	Seeds	Ciprofloxacin	*Escherichia coli*	Significant synergism obtained (63)	Dropping of MIC from 100 to 10 µg/mL	

Table 1. Continued

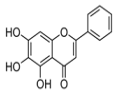
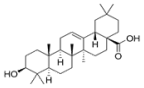
Natural source	Part used	Antimicrobial used	Targeted bacteria	Result and reference	Value of synergism	Illustrative picture
Psidium guineense "Guava"	Leaves	Amikacin, Tobramycin, Amoxicillin/Clavulanate, Cefotaxime, Cefuroxime, Ceftizoxime, Cephalothin, Levofloxacin, Ofloxacin, Norfloxacin, Nitrofurantoin, Trimethoprim	*Escherichia coli*	The best synergism was obtained in combination with ofloxacin (66)	Changing ofloxacin sensitivity from 70% to 100%	
Baicalein "Flavonoid product"	Roots	Cefotaxime	*Klebsiella pneumonia*	Significant synergism resulted (67)	Not determined	
Ulva lactuca	Alga	Gentamicin Chloramphenicol	*Klebsiella pneumonia*	Significant synergism was obtained (68)	Changing the bacteria response from resistance to sensitivity	
Mao-bushi-saishin-to	Dried herbal material	Benzoxazinorifamycin	*Mycobacterium avium complex*	Significant synergism was obtained (70)	Not determined	
Six plants of the *Apocynaceae* family	Leaves	Rifampicin	*Mycobacterium tuberculosis, Mycobacterium smegmatis, Mycobacterium aurum*	Synergistic effects at varying degrees (71)	Reduction of MICs by two to four times	
Oleanolic acid extracts of five different plants	Different plant parts	Ethambutol Isoniazid	*Mycobacterium bovis*	Best result in combination with ethambutol (73)	Not determined	
Seventeen medicinal plants of the *Apocynaceae* family	Various plant parts	Rifampicin Cefazolin	*Acinetobacter baumannii*	Rifampicin exhibited the most significant synergism (74)	Not determined	
Galla rhois	Dried plant material	Ciprofloxacin	*Salmonella*	Promising result obtained (75)	Dropping of MIC from 31.25 to7.8 µg/mL	
Ocimum sanctum "Holy basil"	Leaves	Trimethoprim Chloramphenicol	*Salmonella*	Promising result obtained (76)	Increasing in the zone of inhibition from about 6 to 20 mm	

Table 1. Continued

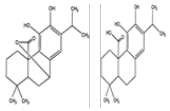
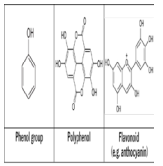
Natural source	Part used	Antimicrobial used	Targeted bacteria	Result and reference	Value of synergism	Illustrative picture
Cyclamen europaeum	Different plant parts	Amoxicillin, amoxicillin/ clavulanate clarithromycin, First- and third-generation cephalosporins	Bacteria causing chronic rhinosinusitis	Improvement and amelioration of symptoms and minimization of future chronic rhinosinusitis recurrence (79)	Reduction of chronic rhinosinusitis recurrence by about four times	
Sophora flavescens	Roots	Ampicillin Gentamicin	Multiple pathogenic oral bacteria	Obvious synergistic effect produced (80)	Reduction of MICs of about one half and one quarter	
Azadirachta indica	Different dried plant material	Amoxicillin, Azithromycin, Metronidazole, Tetracycline	Various periodontopathic bacteria	Superior synergism shown between *Punica granatum* and amoxicillin (11)	Reduction in the zone of inhibition of about three times	
Commiphora molmol						
Punica granatum “Pomegranate”						
Helichrysum pedunculatum	Leaves	Penicillin G, Amoxicillin, Chloramphenicol, Oxytetracycline, Ampicilin, Tetracycline, Erythromycin, Ciprofloxacin	Multiple bacteria-linked wound infections	The greatest bactericidal potential was demonstrated for *Staphylococcus epidermidis* in combination with penicillin G (85)	Reduction in bacterial count to zero	
Garcinia mangostana	Fruits	Penicillin G	*Leptospira*	Significant improvement in antileptospiral efficiency (87)	Droppin of MIC from 6.25 to 3.13 µg/mL	
Calliandra surinamensis	Leaves	Ampicillin Tetracycline	Multiple mastitis-causing bacteria	Tetracycline exhibited better results (89)	Reduction of MICs by about two times	
Phenolic diterpene products of *Salvia officinalis*	Leaves	Gentamicin Streptomycin Erythromycin Tetracycline	Vancomycin-resistant enterococci MRSA *Staphylococcus aureus*	Synergism with various potentials obtained (90)	Not determined	

Table 1. Continued

Natural source	Part used	Antimicrobial used	Targeted bacteria	Result and reference	Value of synergism	Illustrative picture
Cichorium intybus	Roots	Amoxicillin Chloramphenicol	*Bacillus subtilis* *Enterobacter cloacae* *Escherichia coli* *Proteus mirabilis* *Klebsiella pneumoniae*	Synergism with various potentials obtained (91)	Dropping of MIC values by about two to ten times	
Salvia officinalis	Leaves					
Ziziphus mucronata	Bark	Amoxicillin, Chloramphenicol, Ciprofloxacin, Kanamycin, Nalidixic Acid, Tetracycline	Multiple gram-positive and gram-negative bacteria	Greatest zone of inhibition obtained (92)	Increase in the zone of inhibition by about 20 mm	
Six plants of the *Lamiaceae* family	Different dried plant material	Streptomycin	Multiple gram-positive and gram-negative bacteria	Significant synergism obtained (93)	Not determined	
Berberis microphylla	Roots Leaves Steams	Ampicillin Cephalothin	Different gram-positive bacteria	Synergism with various potentials obtained (94)	Reduction of MIC from about 250 to 62.5 µg/mL	
Cabernet Sauvignon grape	Fruits	Multiple antimicrobial classes	*Staphylococcus aureus* *Escherichia coli*	Significant reduction in antimicrobials MIC (95)	Increasing the activity of the drug from 8 to 128 times	
Thymbra spicata	leaves	Amikacin Ampicillin Cefotaxime	*Klebsiella pneumoniae* *Staphylococcus aureus*	Best synergism obtained with cefotaxime (96)	the activity of cefotaxime was increased from 8- to 128-fold.	
Geophila repens	Fresh plant material	Ampicillin, Chloramphenicol, Streptomycin	*Pseudomonas aeruginosa Escherichia coli Staphylococcus aureus Bacillus subtilis*	The strongest synergistic impact was observed in combination with streptomycin when examined versus *Escherichia coli* (97)	Dropping of MIC from 1000 to 62.5 µg/mL	

Table 1. Continued

Natural source	Part used	Antimicrobial used	Targeted bacteria	Result and reference	Value of synergism	Illustrative picture
Carum copticum	Seeds	Ciprofloxacin	Extended-spectrum beta-lactamase bacteria	Significant reduction in ciprofloxacin MIC (98)	Reduction of MIC value by about eight times	
Triphala extract	Fruits	Oxacillin Gentamicin	Multi-drug-resistant gram-negative bacilli	Synergism with various potentials obtained (99)	Dropping of MIC value from (8-64) to (1-32) µg/mL	
Miconia albicans	Steams Leaves	Ciprofloxacin Ampicillin	*Staphylococcus aureus* *Acinetobacter baumannii* *"Resistant strains"*	Significant synergism effect (100)	Not determined	
Polyphenolic extracts of nine different plants	Different plant parts	Cefixime	*Acinetobacter*, *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa,* "Resistant strains"	Variable synergistic effects (101)	Reduction of MIC by two to eight times	
Fagonia indica Burm	Aerial parts	Cefixime	MRSA *Escherichia coli* "Resistant strains"	An obvious antimicrobial potential, significant destruction of the bacterial cell structures, and a reduction in the bacterial proteins contents (103)	Reduction of MIC by about one half	
Alpinia purpurata	Bracts	Oxacillin Ceftazidime	*Pseudomonas aeruginosa* *Staphylococcus aureus* *Candida parapsilosis* *Candida albicans*	Significant synergism effect (107)	Not determined	

MIC: minimum inhibitory concentration; MRSA: methicillin-resistant *Staphylococcus aureus.*

On the other hand, nine species of fungi were examined: *Candida albicans*, *Candida tropicalis*, *Aspergillus flavus*, *Aspergillus fumigatus*, *Aspergillus niger*, *Trichophyton mentagrophytes*, *Trichophyton rubrum*, *Trichophyton violceum*, and *Penicillium notatum*. The researchers discovered the presence of eighteen and thirty-six phytochemicals in the extracts of *Aloe vera* gel and *Curcuma longa* essential oil, respectively. These products participate in the antifungal activity of the extracts, which include alkaloids, cardiac glycosides, flavonoids, phenols, saponins, steroids, and terpenoids. Finally, the researchers concluded that using antifungal creams together with one of these extracts gives better results than if the cream or extract were used alone (119). Table 2 provides an overview of the previously mentioned studies.

Synergism of plant extracts with antiviral medications

In order to examine the synergistic potential of plant extracts with certain antiviral medications, a number of studies were conducted. Piras and colleagues conducted a study to assess the potential of Sho-Saiko-To, "a conventional Kampo medicine, which is made up of seven crude constituents that are derived from herbs," to inhibit the replication of the human immunodeficiency virus type I within the peripheral blood mononuclear cells in combination with certain antiviral medications. The researchers found that when "Sho-Saiko-To" was combined with lamivudine, zidovudine, or both, "Sho-Saiko-To" could boost the efficacy of the anti-human immunodeficiency virus type I of lamivudine. On the other hand, lamivudine plus zidovudine anti-human immunodeficiency virus type I effectiveness was modestly increased by Sho-Saiko-To, but zidovudine's own activity was unaffected when used alone with Sho-Saiko-To. These findings imply that "Sho-Saiko-To" and lamivudine together have the possibility of being an effective chemotherapy treatment for patients with AIDS (120).

In 2015, Hong and colleagues performed a study to investigate the therapeutic approach of concurrent administration of *Hedera helix* L. leaf extract with oseltamivir, "an established neuraminidase suppressant", to increase its antiviral effectiveness. The current work examined the possible antiviral capabilities of *Hedera helix* L. leaf extract toward influenza A/PR/8 virus using mice that resemble an inadequate therapeutic response to oseltamivir treatment. The research team concluded that the concurrent orally administered herbal extract with oseltamivir could result in enhanced antiviral activity for the latter. Also, they mentioned that the cytopathic impact of oseltamivir on influenza A/PR/8 virus-infected cells was considerably inhibited by *Hedera helix* L extract and its constituents, especially hedrasaponin F. The co-administration of hedrasaponin F-rich herbal extract with oseltamivir could significantly reduce the pulmonary inflammation in the infected mice; beside that, there was a reduction in the inflammatory cytokines as well as chemokines like tumor necrosis factor-alpha (121).

In 2017, Houston and colleagues conducted a study to examine the effects of the concomitant administration of pomegranate rind extract with zinc ions on the *Herpes simplex virus*. The outcomes of this research verified that zinc citrate, zinc gluconate, zinc sulfate, and zinc stearate all showed comparable enhanced viral-destroying potential with pomegranate rind extract towards *Herpes simplex virus* type-1, reaching as much as a fourfold increase without any cytotoxic adverse effects. Finally, based on their own personal observations, the research team came to the conclusion that the co-administration of pomegranate rind extract and zinc could potentiate viral-destroying efficacy, making it a promising, unique, topically medicinal product with multiple actions for treating *Herpes simplex virus* infections, including cold sores (122).

Subsequently, in 2018, Mor and colleagues examined the synergistic impact of polyphenol-rich extracts derived from Mexican seaweeds with ribavirin as antivirals against the measles virus. These seaweeds were *Solieria filiformis* and *Ecklonia arborea*. This examination was done *in vitro* using the syncytia-reduction technique. The results of this study regarding synergism were unexpected; despite the success of polyphenolic extracts as antivirals, there was no synergism with ribavirin, as this conbination results in antagonistic effects (15). The studies mentioned above are summarized in Table 3.

Synergism of plant extracts with antiparasitic medications

Studies that approved the synergism between plant extracts and antiparasitic medications are discussed here. In 2013, Adegbolagun and colleagues examined the synergistic antimalarial impact of concomitant administration of the leaves aqueous extract of *Telfaria occidentalis* and the antimalarial agent artesunate using mice infected with *Plasmodium berghei*. The researchers found that following forty-eight hours, artesunate, the herbal aqueous extract, and the combination of them reduced parasitemia by 70%, 72%, and 85%, respectively. So, the results of this research conclude that the concomitant administration had a synergistic impact on the rate at which *Plasmodium berghei* infections in mice were cleared of parasites, with a notable improvement in hematological variables observed within forty-eight hours of administration. This suggests that infections with *Plasmodium* can be treated quickly with this concomitant administration (123).

Then in 2016, Williams and colleagues examined for the first time the synergistic antiparasitic effects of ajoene oil, an organosulphur extract of *Allium sativum*, commonly known as garlic, when combined with metronidazole. Ajoene oil and metronidazole worked together synergistically *in vitro* against *Spironucleus vortens*, lowering the medication individual's MIC by 16 times and the ajoene oil's MIC by 200 times. This synergy was also verified *in vivo*. Oral administration of metronidazole

Table 2. Tabulated summary of the synergistic effects of natural compounds and antifungal agents against fungal strains

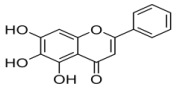
Natural source	Part used	Antifungal used	Targeted fungi	Value of synergism	Illustrative picture
Sida cordifolia L	Leaves Steams	Clotrimazole Nystatin	*Candida albicans Candida krusei Candida parapsilosis Candida tropicalis* (109)	Reduction of MICs by about three times	
Eugenia uniflora L	Leaves	Amphotericin B Nystatin Metronidazole Mebendazole	*Candida albicans Candida glabrata Candida krusei Candida parapsilosis Candida tropicalis* (110)	Not determined	
Baicalein "Flavonoid product"	Roots	Amphotericin B	*Candida albicans* (113)	Reduction of MIc from 0.375 to 0.0117 µg/ml	
Rubus chingii	Fruits	Fluconazole	*Candida albicans* (114) "Fluconazole-resistant strains"	Not determined	
Uncaria tomentosa	Bark	Fluconazole Terbinafine	*Candida krusei* *Candida glabrata* (115)	Not determined	
Ocimum basilicum var. Maria Bonita "Common basil"	Leaves	Amphotericin B	*Cryptococcus neoformans* (116)	Reduction of MIC by about seven times	
Makino's Gynostemma pentaphyllum	Whole plant	Fluconazole	*Candida albicans* (118) "Fluconazole-resistant and susceptible strains"	Reduction of MIC by about four times	
Aloe vera	Leaves	Fluconazole Clotrimazole Terbinafine Ketoconazole	*Candida albicans, Candida tropicalis, Aspergillus flavus, Aspergillus fumigatus, Aspergillus niger, Trichophyton mentagrophyte, Trichophyton rubrum, Trichophyton violceum, Penicillium notatum* (119)	Reduction of MICs by about one to five times	
Curcuma longa	Rhizomes				

Table 3. Tabulated summary of the synergistic effects of natural compounds and antivirus agents against virus strains

Natural source	Part used	Drug used	Targeted virus	Value of synergism	Illustrative picture
Sho-Saiko-To	Mixture of seven herbal constituents	Lamivudine Zidovudine	Human immunodeficiency virus type I (120)	Not determined	
Hedera helix L.	Leaves	Oseltamivir	Influenza A/PR/8 virus (121)	Not determined	
Punica granatum "Pomegranate"	Rind	Zinc preparations	*Herpes simplex virus* type-1 (122)	The virucidal activity of pomegranate increased by four times	
Solieria filiformis	Whole seaweed	Ribavirin	Measles virus (15)	Not determined	
Ecklonia arborea					

Table 4. Tabulated summary of the synergistic effects of natural compounds and antiparasitic agents against parasites

Natural source	Part used	Antimicrobial used	Targeted organism	Value of synergism	Illustrative picture
Telfaria occidentalis	Leaves	Artesunate	*Plasmodium berghei* (123)	Not determined	
Allium sativum	Cloves	Metronidazole	*Spironucleus vortens* (124)	Lowering the MIC of the drug by 16 times	

plus ajoene for *Pterophyllum scalare* (angelfish) infected with *Spironucleus voters* results in significantly reduced trophozoites in the feces compared to those given metronidazole alone. Finally, it is important to mention that *Spironucleus vortens* refers to a kind of protozoan parasite responsible for substantial mortality in freshwater angelfish (124). The above findings are summarized in Table 4.

Conclusion

The results of this review draw attention to the enormous potential of plant-based extracts when mixed with common antimicrobials. These combinations are promising against many types of multidrug-resistant microorganisms, such as *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Candida albicans*. Some bioactive compounds, like berberine, thymol, and baicalein, consistently made antibiotics work better or restored their effectiveness. They also lowered MICs and weakened resistance mechanisms like biofilm formation and efflux pumps. The review talks about the therapeutic benefits of these interactions, such as lower doses of synthetic drugs, fewer side effects, and slower development of resistance. Despite these advancements, the translation of these findings into clinical settings remains a challenge. Standardization of plant-based extract formulations, pharmacokinetic and pharmacodynamic studies, and clinical trials are crucial to validate their safety and efficacy. Going forward, research across disciplines should focus on finding underused plant species, figuring out how molecular synergy works, and making formulations that can be used by many people at a low cost. Using these natural strategies that work well together in antimicrobial stewardship programs is a new and sustainable way to deal with the worldwide problem of antibiotic resistance.

Acknowledgement

The authors are very grateful to the University of Mosul/ College of Pharmacy for their provided facilities, which helped to improve the quality of this work.

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Resources: Yasser Fakri Mustafa.
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Supervision: Yasser Fakri Mustafa.

Validation: Yasser Fakri Mustafa.
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Conflict of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethical considerations

Not applicable.

Funding/Support

Self-funded.

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