

# Potential Role of Bioactive Phytochemicals in Combination Therapies against Antimicrobial Activity

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Since ancient times, plants have been a major source of novel drug molecules and have been used in the treatment of different infectious diseases. Secondary plant metabolites have miraculous healing properties and show potent therapeutic responses when used in combination drug therapy. The prime objective of this review is to summarize the concept of drug combination with special emphasis on the synergistic interactions between plant-derived bioactive phytochemicals with commercially available antimicrobial agents. The study also assesses the roles, importance, and applicability of phytochemicals in the management of different diseases. The review focuses on different aspects of combined antimicrobial activities, the possible mechanisms involved, and the current status of research in the field. The study was conducted based on an extensive literature survey that resulted in the following hypothesis: secondary metabolites derived from plants possess remarkable therapeutic activities. The study was designed as a systematic review that ensures unbiased and accurate representations of the relevant data and information. Jadad scale selection criteria were used for qualitative analysis of the articles to assess them based on the relevant score (minimum and maximum scores range between 1 and 5, respectively). Articles with score  $> 3$  were considered for the study. A comprehensive literature survey was conducted using resource databases including PubMed, Google Scholar, Bielefeld Academic Search Engine, Research Gate, Scopus, Medline, and Science Direct up to June 2019. This article contains concise information about the most commonly used bioactive phytochemicals with potent antifungal and antibacterial effects.

**Keywords:** antimicrobial, antifungal, bioactives, medicinal plants, phytochemicals, synergistic

## INTRODUCTION

Our ancestors effectively used natural resources as their sole means of healing infections and injuries. In fact, during the past few decades, plant-derived bioactive materials have played large roles in modern drug discovery. Traditional systems of medicine, such as Ayurveda and Charaka Samhita, described a list of 341 plant-derived medicines around 900 BC. Similarly, around 600 BC, Sushruta Samhita described 395 medicinal plants, and around 350 BC, traditional systems of Chinese medicine described 247 medicinal plants and 157 combinations of plant-derived medicines. This literature indicates that plants or plant-derived phytochemicals have remarkable healing capacities for

most challenging diseases of society [1]. Until the early 1900s, rational use of most plant-derived bioactive phytochemicals was not achieved due to the deficiency of modern research facilities. The introduction of modern research techniques and research tools provides the scope to explore the medicinal value of designated phytochemicals or bioactive molecules [2].

Combination drug therapy is a promising approach to treat complex diseases, such as cancer, fungal and bacterial infections, inflammation, and others [1-3]. Combination therapy is the use of two or more components together to generate a better therapeutic response against clinical conditions, in which one component may promote the pharmacological action of the other. An alternative drug delivery sometimes used syn-

onymously for combination drug delivery may be defined as one based on the therapeutic value of one chemical entity able to replace another. However, the phenomenon of combined drug interactions is still unpredictable. The most common interactions between two drugs are synergism, antagonism, and summation or additive action. Synergism is a phenomenon in which the pharmacological action of one therapeutically active molecule is increased in the presence of other molecules. The therapeutic activities of plant-derived phytochemicals and their roles in synergism may differ significantly [3]. Despite several controversies, it is possible to make an intense remark on the synergistic activity of therapeutically active phytochemicals in combination with synthetic molecules.

A modern concept like the “isobole method of Berenbaum,” highly efficient technologies like omic technology, pharmacokinetic and pharmacodynamic methods of estimation, biochemical pathway analysis of combinations are the most effective tools for monitoring synergism. The reported literature indicates that there are several mechanisms of synergistic activities [1, 4]. Therefore, the present study has been designed to summarize information about combinations of natural and synthetic compounds that have effective antifungal activity. Information related to compound types and their different mechanisms of action are also discussed.

### 1. Concept of synergism and its role in the management of infectious diseases

The term synergy comes from the Greek word “*synergos*,” which means “working together.” The concept of synergy refers to a combination of two or more compounds that generate outcomes greater than the additive impact of those individual compounds. This outcome is the result of interactions in which compounds enhance each other’s performance to achieve a desirable goal. However, if the interaction of bioactive agents or compounds leads to a result less than the sum of the individual effects, this would be designated antagonism. To understand the role and importance of synergism, one should understand the history and the present-day scenario of infectious diseases [5]. Available reports and literature indicate that since they were first recorded, infectious diseases caused by pathogenic bacteria and fungi have remained the most life-threatening issue for society. Infectious diseases affect millions of people worldwide, and a WHO report indicated that approximately 50,000 people die per day globally from these diseases. Hence, the discovery

of antimicrobial agents, such as antifungal compounds and antibiotics, was a major achievement in the history of medical sciences [6]. As time went on, new antimicrobial molecules against different active pathogens were introduced to the market. In the last few decades, the irrational and abundant misuse of antimicrobials has allowed clinically important microbes to become resistant to developed antimicrobial agents. Continual efforts by leading scientists are already underway to develop innovative and effective molecules or drugs that can effectively manage infectious diseases [7]. However, the invention of new molecules takes time. Therefore, the lack of new effective molecules and pathogenic resistance to existing molecules is a global health threat.

Several approaches have been taken to manage this situation; of them, multidrug therapy was comparatively more suitable for the effective treatment of infectious diseases [8, 9]. However, the use of synthetic antimicrobials in combination at higher strengths produces more side effects and greater toxicity; therefore, the rational use of multidrug therapy remains controversial.

Plant-derived bioactive phytochemicals have long been used, either singly or in combination, effectively against different life-threatening infectious diseases. Several studies have proposed that natural compounds can potentiate the activity of existing antibiotics and antifungal drugs. In this era, much research has been conducted to explore the medicinal values of different plants or plant-derived products. The results indicate the use of such bioactive materials will help to achieve superior pharmacological and therapeutic outcomes.

## MATERIALS AND METHODS

The current review is mainly focused on the role of bioactive phytochemicals in the treatment and management of antimicrobial activities in combination with synthetic drugs and the possibility of improved therapeutic responses. Furthermore, the mechanism involved in antimicrobial action and different strategies involved in disease management were also considered. Keywords, such as antimicrobial, antifungal, antibacterial, clinical trials, combination therapy, summation action, synergistic action, antagonistic effects, natural, plant resources, phytochemicals, bioactive, plant-derived therapeutic agents, synthetic antimicrobial agents, and all their possible combinations, were searched in the databases PubMed, Google Scholar, Bielefeld Academic Search Engine, Research Gate, Scopus, Medline, and

Science Direct. Most of the search contents ranged between the year 2000 and June 2017. Literature in the form of abstracts, structured reviews, clinical trial study reports, survey reports, and relevant research articles were collected for this review; however review articles, research articles, and clinical trial reports were prioritized for the write-up. Abstracts, non-relevant articles, repeated articles, and articles with inadequate and irrelevant information were excluded from the study (Fig. 1). Jadad scale selection criteria were used for qualitative analysis of the articles to assess the articles based on their relevant secure scores (minimum and maximum scores range between 1 and 5, respectively). Articles with secure scores > 3 were considered for this study.

## 1. Mechanism of synergism

The role of bioactive phytochemicals on modern therapy can only be justified through exact knowledge and understanding of the mechanisms underlying the therapeutic activity. Based on the latest developments in the fields of classic pharmacological, molecular biological, and clinical techniques, the mechanisms of synergism may be classified as follows.

### 1) Synergism due to pharmacokinetic or physicochemical interactions

This type of interaction can modify the normal solubility, absorption rate, reabsorption rate, and bioavailability of drugs [10]. Few examples that indicates pharmacokinetic and physicochemical interaction as shown in Table 1.

#### RESEARCH WORK FLOW OF THE MANUSCRIPT

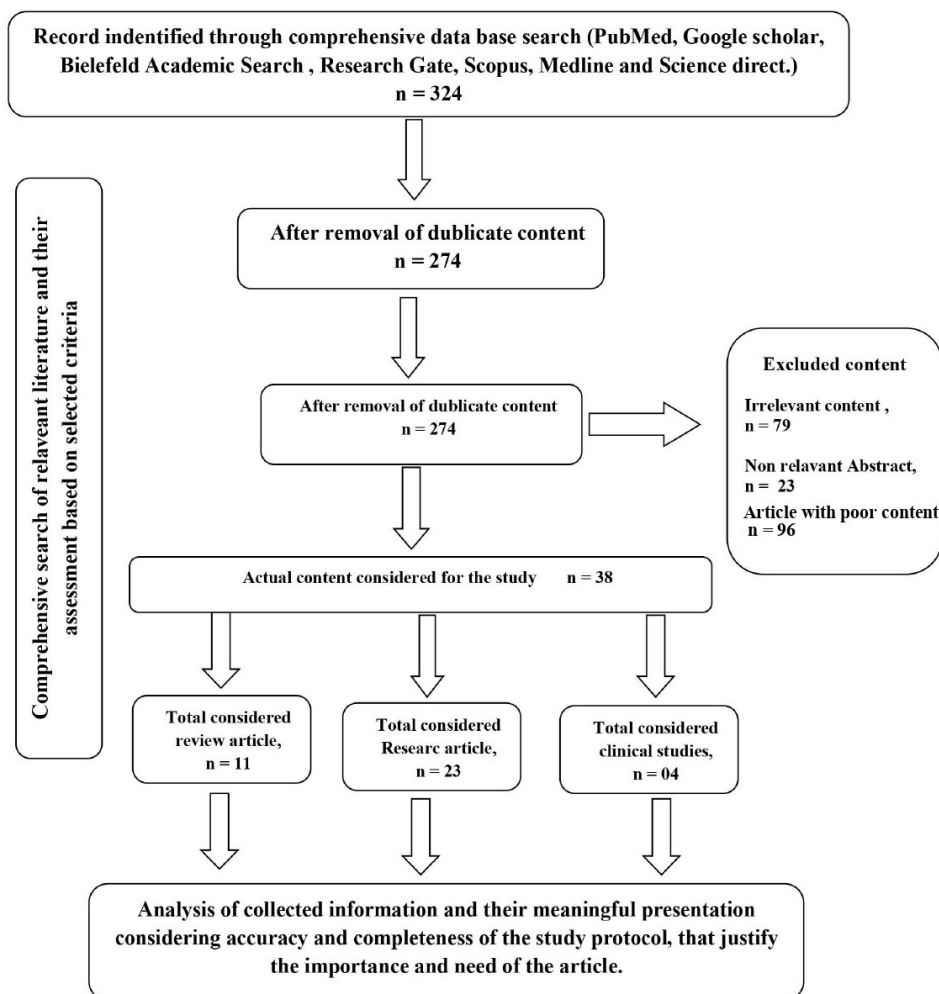


Figure 1. Research work flow.

**Table 1. Synergism due to pharmacokinetic or physicochemical interaction**

Drug A & its mechanism of action	Drug B & its mechanism of action	Reported effects	Possible mechanism of action
Amoxicillin (inhibits bacterial cell-wall synthesis)	Clavulanate ( $\beta$ -lactamase inhibitor)	Antibacterial synergy due to more effective drug distribution or localization	The presence of clavulanate improve the level of amoxicillin at bacterial cell wall by inhibiting its degradation enzyme $\beta$ -lactamase
Sulphamethoxazole (DHPs [Deoxyhypusine synthase] inhibitor)	Trimethoprim (DHFR [Dihydrofolate reductase] inhibitor)	No synergism is reported. The only one after other individual effects reflects in the response	Sulphamethoxazole targets the upstream DHPs whereas, trimethoprim targets the downstream DHFR. Trimethoprim act as a backup when the effect of sulphamethoxazole becomes less effective
Erythromycin (inhibit bacterial protein synthesis)	Penicillin (act on bacterial cell wall)	The combination shows both synergic and additive action due to facilitating action	Presence of penicillin boosts erythromycin penetration into bacterial cells, thereby improve its bioavailability

**Table 2. Synergism due to pharmacodynamics interaction**

Drug A & its mechanism of action	Drug B & its mechanism of action	Reported effects	Possible mechanism of action
Cycloserine (inhibits bacterial cell-wall synthesis)	Epigallocatechin gallate (interruption of bacterial cell wall integrity)	Destruction of bacteria cell wall due to the synergistic antibacterial action	The presence of both the component together complements each other. Epigallocatechin disrupts the integrity of bacterial cell wall and cycloserine act as an inhibitor for cell wall synthesis, which hampers the restoration of the cell wall
Ampicillin (interrupt bacterial cell-wall synthesis by blocking PBP2A (peptidoglycan transpeptidase)	Daptomycin (break down of bacterial cell membrane structure)	Strong synergistic antibacterial action	Membrane disruption due to daptomycin, perhaps supported by the presence of ampicillin
Artemisinin (disrupts parasite mitochondrial function, modulates host immune function)	Curcumin (generates ROs and produce cytotoxicity for malaria parasites)	Synergic/additive antimalarial activities	They act at different sites in a non-interfering manner
Ampicillin (inhibit bacterial cell-wall synthesis by blocking PBP2A)	Imipenem inhibits bacterial cell-wall synthesis by blocking PBP1A, 1B	Synergic/additive antibacterial effect	Both act at the same active site. Due to the presence of both at relatively high MICs (minimum inhibitory concentration), may make it responsible for the better antibacterial effect

## 2) Synergism due to pharmacodynamics interaction

This type of interaction involves two drugs, which are exerting their activity by joining to the same receptor [11, 12]. Few examples that indicates synergism due to pharmacodynamic interaction are shown in Table 2.

## 3) Synergism that overcomes resistance mechanisms of bacteria and fungi

In this type of interaction, the presence of one molecule may

improve or facilitate the fundamental mechanism of another chemical entity, which results in better therapeutic activity. This type of synergy occurs when antibiotics are combined with chemical entities that can partly or completely suppress bacterial resistance mechanisms. For example, the combination of penicillin with clavulanic acid (sulbactam or tazobactam) successfully overcomes penicillinase resistance due to three possible reasons: (i) modification of the active site; (ii) modification of antibiotic action by enzymes; and (iii) alteration in the efflux

**Table 3. List of some bioactive phytochemicals & their role in combination**

Sl no	Combination of active molecules	Observed effect	Mechanism	Ref
1	Curcumin with Amphotericin B	Antifungal & antibacterial action	A synergistically improve action was observed. In this case, the enzyme inhibitory effect of curcumin mainly reported being responsible for enhanced action	[13]
2	Garlic oil and allyl alcohol derived from garlic	Potent antifungal and anti-yeast effect	An additive action was observed. Garlic oil was reported to have cell damage capacity which facilitates the action of allyl alcohol, to show potential killing effect by affecting cytosolic components	[14]
3	Garlic extract with ciprofloxacin	Antibacterial action	The presence of garlic extract improves the inhibitory action of ciprofloxacin	[37]
4	Rifampicin with nalidixic acid	Anti-microbial action	The combination showed enhanced antimicrobial action may be due to synergistic action. Path of mechanism not reported	[15]
5	Fluconazole with cardamom oil & boswellia oil	Antifungal activity	Both the combination shows remarkable improved antifungal action may be due to synergism	[16]
6	Curcumin with fluconazole	Antifungal action against fluconazole-resistant pathogens	The curcumin modulates MDR by inhibiting the transport of fluorescent substrates that are actively effluxes from cells. It improves the sensitivity of fluconazole and, at the same time, practically abolishing cellular growth	[17]
7	Allicin with ketoconazole	Antifungal activity	The combination demonstrates potential antifungal activity due to synergism	[18]
8	Thymol with itraconazole (ITR) & fluconazole (FLU)	Potent antifungal action against resistant strain	Thymol enhances the action probably by disruption of the cell wall/membrane integrity mitogen-activated protein kinase (MAPK) system when used in combination with ITR. It probably creates lesions in the plasma membrane and disruption of ergosterol biosynthesis when used with FLU	[19]
9	Benzoic acid and its derivatives with fluconazole and itraconazole	Enhance antifungal action against resistant strain	Most effectively enhance the antifungal action of azole derivatives utilizing targeting of an oxidative stress response system	[19]
10	Caspofungin with ferulic acid	Antifungal action	The combination shows antifungal action due to synergism	[20]
11	Sulfamethoxazole with myricetin	Synergistic antimicrobial action	The potency of combination increases due to synergism. Myricetin act by DNA binding and induce enzymatic DNA breakage	[21]
12	Tetracycline with epigallocatechin gallate	Synergistic antimicrobial action	Enhances the activity tetracycline against resistant staphylococcal by impairment of tetracycline efflux pump activity and increased intracellular retention of the drug	[22]
13	Sulfamethoxazole with proto catechuic acid, ellagic acid, and gallic acid	Synergistic antibacterial and antifungal action	Improve activity may be due to DNA gyrase and topoisomerase IV enzymes	[21]
14	Sulfadiazine with proto catechuic acid and quercetin	Wide range of antimicrobial action	Reported to have synergism, however, exact mechanisms are unknown	[23]
15	Kaempferol with norfloxacin and ciprofloxacin	Potent antibacterial action	Combinations show synergism and reported possible mechanism involved may be DNA gyrase and DNA topoisomerase IV	[24]
16	Ceftazidime with quercetin analogs	Potent antimicrobial action	A possible reported mechanism states that cell wall damage due to leakage of potassium. Both the compound act at the same target either at different sites	[24]
17	Allium oils with ketoconazole	Fungi static activity	Reported to have synergism. The molecular mechanism was not reported	[18]

**Table 3. Continued**

Sl no	Combination of active molecules	Observed effect	Mechanism	Ref
18	Berberine with 5'-methoxyhydrnocarpin	Potent antimicrobial action	5'-methoxyhydrnocarpin (1 mg/mL) inhibited the berberine effluxing multidrug pump and thus increased berberine bioavailability. When combined with subinhibitory amounts of berberine, 5'-methoxyhydrnocarpin caused complete inhibition of growth at a concentration of 1 mg/mL	[4]
19	Curcumin with 5-fluorouracil	Anticancer activity	Enhance the capacity of 5-fluorouracil due to synergism. Molecular path not reported	[35]
20	Quercetin with doxorubicin	Anticancer activity	Quercetin combined with cisplatin, exhibited a proapoptotic effect toward human laryngeal carcinoma cells	[25]
21	Resveratrol with doxorubicin	Anticancer activity	Resveratrol facilitates doxorubicin uptake by the cells, probably by downregulation of the expression of <i>mnp-1</i> ( <i>mnp-1</i> belongs to ATP-binding cassette transporter family, involved in multidrug resistance). It acts as an energy-dependent efflux pump whose overexpression causes a decrease in doxorubicin concentration in the cells	[26]
22	Silibinin with aminoglycosides	Antibacterial action	Improve the action efficacy of aminoglycosides through a significant inhibitory effect on DNA topoisomerase activity due to the formation of complexes that alter enzyme binding	[27]
23	Kaurenoic acid derivatives with fluconazole	Enhance antifungal action against the fluconazole-resistant strain	Kaurenoic acid derivatives enhance the capacity of fluconazole probably due to inhibition of topoisomerase I	[28]
24	Glabridin combination with fluconazole	Effectively improve antifungal activity (fungicidal) of fluconazole	Glabridin facilitates membrane permeability & damage cell wall, hence increase the performance of fluconazole	[29]
25	Lactoferrin with fluconazole & itraconazole	Synergistic antifungal activity	Lactoferrin shows synergistic activity in combination with azole derivatives. A possible mechanism may be by promotion or suppression of ergosterol synthesis in the candida cell membrane. Again the iron-chelating function of lactoferrin reported contributing in the synergism	[30]
26	Nisin with thymol	Synergistic antimicrobial activity	Destabilization of bacterial membrane structure resulting in an increased permeability for nisin which leads to bacterial cell lysis	[31]
27	Carnosic acid with tetracycline	Antimicrobial activity	Possible mechanism reported inhibiting the MDR pumps	[3]

of antibiotics from the cell [1, 10].

Few examples of potential bio-active phytochemicals that played significant role in enchaining therapeutic activity as well as minimizing microbial resistance in combination therapy are shown in the Table 3 [13-35].

#### 4) Synergistic multi-target effects

Synergistic multi-target effects mean that single constituents may show combination effects not only against a single target but also several targets; therefore, they may act in both antagonistic and synergistic ways. Investigation of synergism describes the evidence of multi-targeting that affects gene expression, e.g.,

methotrexate targets a multitude of genes involved in apoptosis, mismatch repair, cell cycle control, and stress responses [1, 10].

## 2. Most common methods for *in vitro* evaluation of synergy

The accurate estimation of synergy between commercial drug molecules or between a drug and bioactive phytochemical based on the results of *in vitro* testing is essential. Several methods are used to detect synergy. An in-depth understanding of molecular biology, implementation of new clinical and statistical tools for accurate estimation, and introduction of modern technologies, such as omic methods and gene microassay tech-

nology, improves the accuracy of *in vitro* evaluation of synergy. However, for infectious disease concerns, the checkerboard and time-kill curve methods are the two most easily and widely used techniques [36]. In the checkerboard method, microtiteration plates are used; for multiple combinations of two antimicrobial agents at different concentrations (equal to, above, and below), their minimal inhibitory concentrations for the microorganism are tested. The combination for which growth is completely inhibited is the effective MIC for the combination [36, 37]. However, the time-kill method assesses the bactericidal activity of the individual and the different concentrations of the drug combinations as a function of time. Tubes containing the individual, as well as the combinations of, compounds with different concentrations ranging from one-quarter to twice the MIC for the bacterial strain are prepared as per NCCLS (National Committee for Clinical Laboratory Standards) guidelines and incubated overnight. Aliquots of samples at 0 h of incubation (reflecting the initial inoculum) and 24 h of incubation (reflecting exposure of bacteria to the compound) are estimated. If a 100-fold or greater decrease in colony count is observed at 24 h by the combination of agents, synergism would be concluded [36-38]. The E-test (Epsilometer test) is another method used for evaluating synergy. It consists of two plastic strips coated with a continuous gradient of each compound on one side. The first compound strip is placed onto an agar plate for 1 h and then removed, and the second compound strip is placed on top of the gradient left behind by the first strip. The MIC of the combination is taken as the value at which the two inhibition zones intersect [38].

Further standardization of these techniques for routine laboratory testing is required for effective and accurate estimation of drug combinations.

## DISCUSSION

Combination drug therapy is not a new concept; however, innovative and rational use of phytochemicals to develop safe and effective combination therapies may be the future of infectious disease management. Although the term synergism may be considered a type of combination therapy, in which the presence of one component effectively improves the activities of others, there are several mechanisms. The introduction of modern and improved technologies, statistical tools, and in-depth knowledge of molecular mechanisms may be key to understanding the phenomenon of synergism and its different

types. In this article, we have attempted to present a summary of the most effective and often used bioactive compounds in the management of infectious diseases, along with their possible reported mechanisms of action. Again, detailed information about documented synergistic effects of some plant-derived bioactive molecules in combination with synthetic drugs is also discussed. Despite enormous efforts, proper information on the molecular mechanisms underlying the effectiveness of most bioactive phytochemicals is limited. Therefore, a proper understanding of the mechanisms will be the key deciding factor. As far as activities of plant-derived phytochemicals are concerned, in most cases, the appropriate molecular mechanisms remain undefined. Although researchers have reported that different plant extracts show significant therapeutic effects, the lead molecules responsible for their observed activities or their mechanisms of action are yet to be explored. Safe and effective therapies from plant-derived bioactive compounds mainly depend on the toxicity profiles of molecules. Therefore, the concentrations of phytochemicals in a combination and the frequency of use of those combinations are two key factors that should be strictly followed to obtain optimum benefits. Resistance against available synthetic antibacterial and antifungal drugs by pathogenic stains is the most important issue of this era, but it can easily be countered by proper scientific investigations, explanations of the holistic approaches of traditional medicine, and effective utilization of natural resources.

## CONCLUSION

This review highlights several aspects of synergism and the role of plant-derived bioactive phytochemicals in developing effective drug combinations for infectious disease management. From the above discussion, it can be concluded that bioactive phytochemicals obtained from different medicinal plants show promising healing capabilities and may effectively treat different diseases. Clear understanding of the molecular mechanisms of such bioactive compounds will enable better disease management. Although the rational design of drug combinations with synergistic effects is challenging, it may become a treatment strategy in the future.

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