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Original Article

POTENTIAL ROLE OF BIOACTIVE PHYTOCHEMICALS IN COMBINATION THERAPIES AGAINST ANTIMICROBIAL ACTIVITY

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Abstract:

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 secure score (minimum and maximum scores range between 1 and 5, respectively). Articles with secure scores > 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, Synergestic

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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 Saṃhita, 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]. 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 synonymously 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. 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,]. 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.

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. 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. 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. 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,

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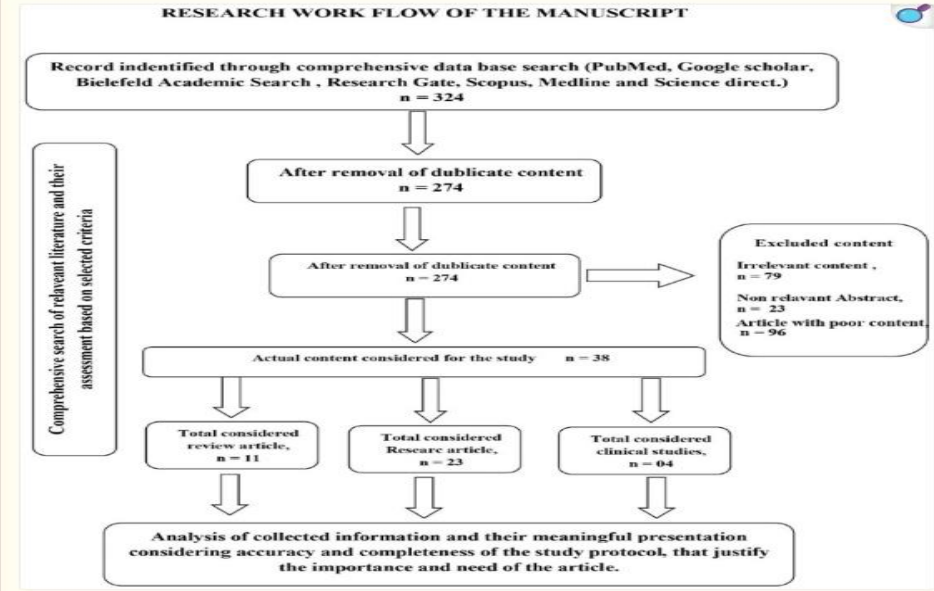
clinical trials, combination therapy, summation action, synergistic action, antagonistic effects, natural, plant resources, phytochemicals, bioactive, plant-derived therapeutic agents, synthetic antimicrobial agents, and all their possible combinations, were searched in the databases PubMed, Google Scholar, 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. 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.

Figure 1.



Results and Discussion:

1. Synergism that overcomes resistance mechanisms of bacteria and fungi.
2. 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 of antibiotics from the cell.

3. Few examples of potential bio-active phytochemicals that played significant role in enchaining therapeutic activity as well.

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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