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Potential of endophytic bacteria as producers of antibiotics: A literature review

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Literature Review

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ABSTRACT

Microbial infection is a significant contributing aspect to the development of diseases, posing ongoing challenges in - healthcare. Numerous synthetic antibiotic agents have been used as therapeutic interventions; however, many microorganisms exhibit resistance to these synthetic agents. The rate at which microbes developed resistance to antibiotics has outpaced the discoveries and study of new treatments. The potential of endophytic bacteria to produce bioactive compounds or metabolites that can serve as the basis for developing new antibiotic drugs is promising is promising. This review aims to explore the metabolite potential of endophytic bacteria as a source of antibiotics. Understanding the mechanism and potential of endophytic bacteria offers opportunities for the advancing therapeutic interventions to mitigate the negative effects of various strains of antibiotic-resistant pathogenic bacteria.

INTRODUCTION

The issue of infection remains a significant global health concern, particularly in Indonesia, where bacterial infections are prevalent. Bacterial infections contribute to the development of many diseases and are a major concern in the daily lives of individuals. Bacteria are widely recognized in the scientific community for their capacity to serve as drug-producing organisms, particularly as makers of antibiotics. Antibiotics refer to compounds or chemical substances that are either naturally produced by microorganisms or artificially synthesized. The initial identification of the first microbial-produced antibiotic, penicillin (genus Penicillium), occurred in 1928 through the research efforts of Ian Fleming. From 1928 to 1962, commonly referred to as "the golden age", significant advancements were made in the field of antibiotic research. These substances play a crucial role in inhibiting the growth and proliferation of bacteria and other microorganisms.[1–3]

Throughout history, many types of antibiotics have been discovered, significantly contributing to the mitigation of infectious diseases. However, the widespread use of antibiotics has resulted in a consequential global rise in resistance. The phenomenon where microorganisms can withstand the effects of antibiotics is referred to as antibiotic resistance.[4–6] Resistance can be achieved through several mechanisms, such as the acquisition of resistance genes, genetic alteration, plasmid replacement, or gene transfer between different bacterial species.[7–9] The increasing incidence of antibiotic resistance demands the imperative task of discovering and nurturing novel antibiotics, as the pace of antibiotic discovery fails to keep pace with the annual rise in resistance.

The continual pursuit of identifying sources of bioactive chemicals persists in response to the emergence of many novel diseases resulting from bacterial resistance. Bioactive chemicals can be derived from a diverse range of living organisms, including microorganisms, plants, animals, marine organisms, and endophytic bacteria, which are bacteria that inhabit plant tissue. Endophytic bacteria reproduce inside the tissues of plants, specifically within the leaves, stems, and roots of plants. In Indonesia, there are an estimated range of 25,000 to 30,000 plant species with potential applications as herbal medicines.[1,4] The utilization of botanical resources as therapeutic constituents offers enhanced safety and facilitates the discovery of naturally occurring bioactive compounds. One method for isolating bioactive chemicals from medicinal plants involves extracting them from the specific plant parts used for therapeutic purposes. However, this approach is considered less efficient due to its protracted duration and substantial biomass requirements.[1,4,5]

Bacterial strains that exhibit higher resistance due to decreased antibiotic susceptibility can lead to negative impacts, including increased morbidity and mortality rates, as well as excessive health care costs.[9,10] Utilizing endophytic bacteria capable of synthesizing the necessary bioactive substances or compounds is widely regarded as the most effective approach for acquiring these bioactive chemicals. The objective of this review is to explore the potential of endophytic bacteria as agents for antibiotic therapy. Understanding the mechanism and potential of endophytic bacteria holds promise for advancing therapeutic strategies aimed at mitigating the negative effects associated with various forms of antibiotic-resistant pathogenic bacteria.

METHODS

From June to October 2023, the authors conducted a comprehensive literature review searching multiple for scientific articles and research findings. These databases included Science Direct, PubMed, and Google Scholar. The reviews only included studies that met the predefined search criteria. The search terms used were: "antibiotics", "antibiotic resistance", "endophytic bacteria", "metabolites", and "pathogenic bacteria". The inclusion criteria were articles containing these five keywords, resulting from observational and laboratory research, discussing various sources of endophytic bacteria from plants and their antibotic effects against various pathogenic bacteria, and being the latest articles from the past 5-10 years. The exclusion criteria included duplicate articles. Duplicate articles were detected and removed by manually checking search results or bibliographic databases. Identical or very similar articles were searched by title, author, and year of publication, duplicates were removed by comparing and verifying each record. The authors analyzed previous studies to gain a deeper understanding of the latest discoveries concerning endophytic bacteria, focusing specifically on their potential as antibiotics.

A comprehensive search of all databases using the specified keywords, resulting in a total of 105 articles being retrieved (30 from Science Direct, 50 from PubMed, 20 from Google Scholar, and 5 from books and governmental report). Duplicate articles were then removed. From the abstract screening to full-text publications, articles were evaluated based on research objectives and results. Out of the initial selection of 50 articles, 30 were

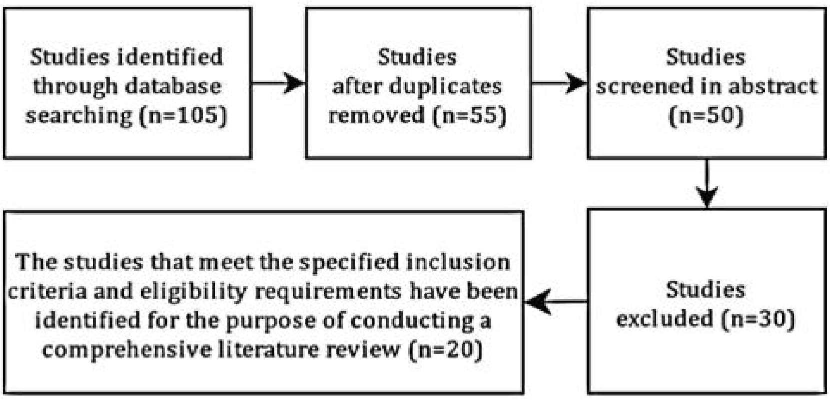

Figure 1. Process of Article Selection

excluded for not meeting the predetermined criteria, tsuch as sources that do not originate from plant endophytic bacteria. Consequently, a comprehensive set of 20 publications met the established criteria for inclusion and were considered appropriate for assessment.

RESULTS AND DISCUSSION

Antibiotics

The initial development of antibiotics, commonly referred to as the "magic bullet," was pioneered by Paul Ehrlich in 1910 with the discovery of Salvarsan, a treatment for syphilis. In 1928, Alexander Fleming made the groundbreaking discovery of penicillin. Gerhard Domagk initiated the pursuit of anti-tuberculosis treatments with the discovery of isoniazid, while the discovery of streptomycin as an anti-tuberculosis agent is attributed to Selman Waksman and Albert Schatz in 1943. Since then, antibiotics have been employed to treat a variety of infectious diseases. Antimicrobials are pharmaceutical substances used to eliminate microbial illnesses. These bioactive chemicals can be synthesized artificially or produced by microorganisms and are capable of inhibiting bacterial growth or killing bacteria and other organisms. Such compounds are commonly referred to as antibiotics.[1–3]

Mechanism of Antibiotics

Antimicrobials are pharmaceutical substances used to eliminate microbial illnesses. Bioactive substances can be synthesized artificially or produced by microorganisms. These compounds inhibit bacterial growth or kill bacteria and other organisms, thus are referred to as antibiotics. Antimicrobial compounds affect essential cellular components, including cell membranes, structural proteins, and enzymes. The mechanisms involved includes cell wall damage, inhibition of protein, ribonucleic acid (RNA), and deoxyribonucleic acid (DNA) production, suppression of enzyme function, modification of proteins and nucleic acids, and alteration of cell permeability.[11,12]

Various Group of Antibiotics

Several types of antibiotics impair the integrity of bacterial cell walls or impede their production,such as Vancomycin, Beta Lactams, and Bacitracin. Others modify or impede the production of proteins, DNA, and RNA, including aminoglycosides, clindamycin, chloramphenicol, macrolides, mupirocin, spectinomycin, and tetracycline. Antibiotics like sulfonamide and trimethoprim inhibit enzyme activity, while quinolones and nitrofurans modify proteins or nucleic acids.[11,12] Antimicrobials are also classified into two : bactericidal agents, which kill bacteria, and bacteriostatic agents, which inhibit bacterial proliferation. Bactericidal agents include penicillins, cephalosporins, aminoglycosides at high concentrations, co-trimoxazole, rifampicin, and isoniazid. Bacteriostatic agents include sulfonamides, tetracycline, chloramphenicol, erythromycin, trimethoprim, lincomycin, clindamycin, and paraaminosalicylic. The utilization of this particular bacteriostatic antibiotic depends on the patient's immune condition.[11,12]

Antibiotics are available in various forms and can be administered intravenously, orally, or topically. The diversity of classifications, typologies, bacterial susceptibility patterns, and the continuous emergence of novel antibiotics present challenges for clinicians in selecting the most appropriate treatment,[13,14] contributing to the occurrence of resistance. Given bacteria’s evolutionary history of approximately 3.8 billion years, their ability to adapt to antibiotics is remarkable. Resistance consistently occurs prior to drug exposure, and even a few surviving bacteria can lead to the emergence of novel resistant strains, potentially causing epidemic. The transmission is facilitated by inadequate infection control measures and the extensive antibiotics use.[13,14]

Challenges of Antibiotic Resistance

Resistance occurs when bacterial growth is minimally or not inhibited by systemic antibiotics at typical doses. Multidrug resistance refers to resistance towards multiple drugs or pharmacological classes. The phenomenon of developing resistance to a second drug, which has not been previously characterized, subsequent to resistance to a first drug, is referred to as cross-resistance. Resistance arises when bacteria undergo alterations in mechanisms, diminishing or eliminating the efficacy in chemicals, drugs, or other substances used to prevent or treat bacterial infections. Bacterial strains that exhibit sustained viability and reproductive capacity present an enhanced level of risk.[14,15]

The development of antibiotic resistance can occur through several methods. Bacteria can synthesis of enzymes that impair or eliminate the effectiveness of antibiotics, such as the production of beta-lactamase by Staphylococci, which degrade penicillin G. Bacteria can also alter the permeability of pharmaceutical substances, as withtetracycline. Additionally, bacteria can alter medication targets such as changes in proteins within the 30-s subunit of bacterial ribosomes targeted by aminoglycoside.[15,16] Antibiotics can impede and modify metabolic pathwayswith bacteria exhibiting resistance to sulfonamides by alterating enzymes that disrupt metabolic processes.

Potential of Endophytic Bacteria

Endophytic bacteria reproduce within plant tissues , residing in the leaves, stems, and roots. The bacteria can synthesize bioactive chemicals with antibacterial, anticancer, and antimalarial properties, making them valuable for industrial and agricultural applications. Endophytic bacteria show promise in producting bioactive substances,[17] offering potential for future research in discovering novel pharmaceutical agents targeting diverse diseases. Endophytic bacteriaestablish colonization within plant tissue without causing harm, and every higher plant possesses several endophytes capable of synthesizing secondary metabolites. These compounds may result from genetic transfer or co-evolution between the host plant and the endophyte.[17,18]

Most vascular plants contain endophytes within their tissues, typically entering through the root system. Bacterial colonization primarily occurs in the roots, stomata, and plant injury sites. Microbes can infiltrate plant tissue through several entry points, including stems, blossoms, and cotyledons. However, the primary mode of entry is predominantly through the roots. Bacterial infiltration into tissue primarily occurs via shoot or sprout tissue, stomata, roots, and areas of tissue that have been compromised or injured.[19–21]

Endophytic bacteria have a symbiotic relationship with plants, residing within the plant tissue without causing any negative impacts to the host plant. These bacteria can undergo sporulation and exhibit gram-positive characteristics,enhancing their resilience to environmental stressors. Cell metabolism may enter a dormant state in inhospitable environment.[17,18]

Endophytes influence host plants by enhancing nutrient absorption, modulating stress-related plant hormones (green box, Figure 2), combating

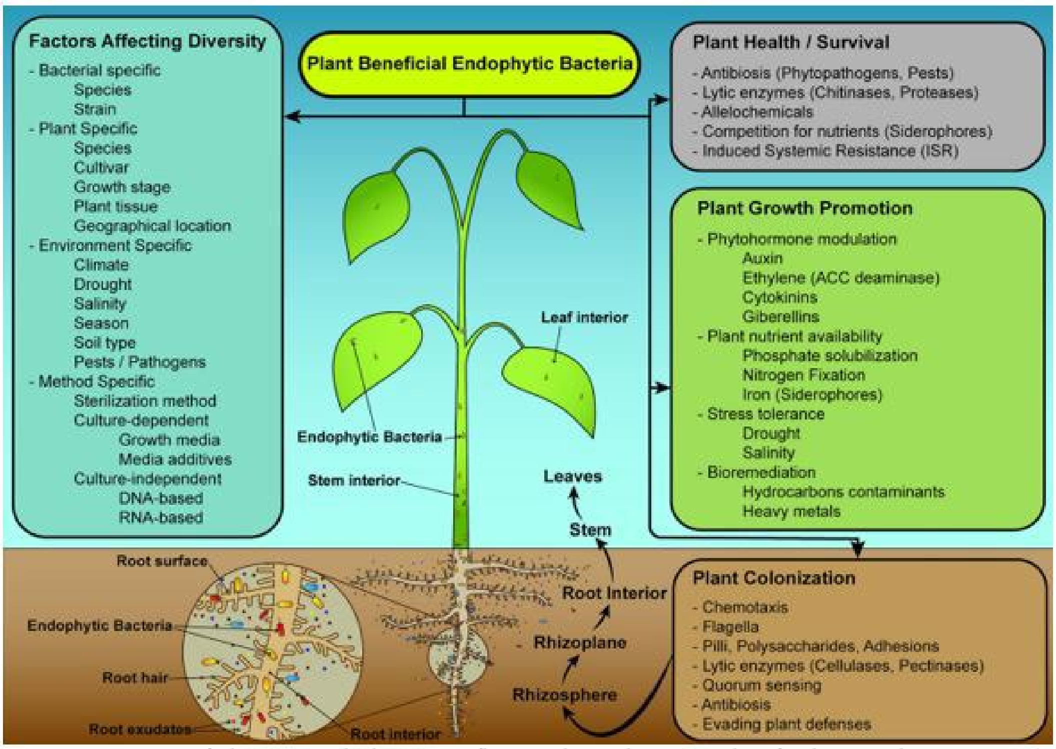

Figure 2. Aspects of plant growth that are influenced, mechanisms that facilitate colonization, and the diversity of endophytes on host plants (Elsevier: www.elsevier.com).[11]

infections or pests, and inhibiting the growth of competitive plants (gray box). These interactions benefit the host plant. Competitive colonization within the internal regions of the plant is essential for these benefits, facilitated by a colonization trait battery (shown by the brown box). The initial stage involves bacteria responding to root exudates, followed by the colonization of both the surface and interior of the roots. Proficient endophytes can migrate to aboveground components, such as the stems and leaves. The diversity of endophyte colonization is influenced by bacteria, plants, and environmental factors (as depicted in the blue box), with the method of assessment impacting bacterial diversity.[11]

Endophytic bacteria can be utilized for medicinal purposes through the production of bioactive molecules or chemicals. Their beneficial characteristics include their cultivability, short life cycle, and ability to generate substantial quantities of bioactive chemicals via fermentation. Certain plant species can convert their bioactive molecules or compounds into endophytic bacteria, enabling the production of the same compounds found in the host plants. Identifyinng antibiotic-producing endophytic bacteria requires careful consideration and systematic methodology, avoiding any accidental or random approaches. Plants are undergo specialized selection based on factors such as age, environmental conditions, host plant's history, and the ethnobotanical utilization.[17]

Endophytic bacteria protect plant tissue against pathogenic bacteria by synthesizing bioactive chemicals while fulfilling their nutritional requirements from plant tissue. These microorganisms promote plant growth by modulating hormone production, and enhancing nutrients availability, including phosphate and nitrogen. They synthesize bioactive chemicals with significant pharmacological properties, such as antifungal, antibacterial, antidiabetic, antiviral, anticancer, anti-immunosuppressive, and antimalarial activities.[19,20] Endophytic bacteria promote plant resistance against pathogenic bacteria through Induced System Resistance (ISR), enhancing the plant's capacity to survive disease attacks. They can synthesize a diverse range of metabolites, including quinones, alkaloids, flavonoids, terpenoids, phenols, steroids, peptides, isocoumarin derivatives, phenolic acids, and other compounds.[19]

Utilizating endophytic bacteria as bioactive chemical biofactories is advantageous due to their accelerated life cycle enabling large-scale production. This approach saves production time and reduces spatial requirements. Additionally, endophytic bacteria contribute to conserving medicinal plants, preserving rare species, and mitigating exploitation risk.[22]

Isolation of Endophytic Bacteria

Endophytes can be obtained through the extraction of internal plant tissues and isolation from sterile plant surfaces. They can be cultivated in suitable growth media to synthesize metabolic chemicals. Endophytic bacteria synthesize host plant chemicals within the incubation medium through enzymatic activity.[22]

The bacterial isolation technique involves transferring bacteria from their original media or habitat into another medium, allowing growth in controlled conditions and enabling isolation in culture or pure culture. This process yields data on specific bacterial strain, analyzed for morphology, characteristics, and biochemical properties. Aseptic method are crucial during the transfer process to ensure sterility, devoid of microbes.The direct plating approach involving placing the sample onto a solid media, is a viable technique for isolating endophytic bacteria.[17,22]

Bacterial Metabolites

Microbial metabolites are classified into primary and secondary metabolites. Primary metabolites are produced within cells during the metabolic processes, essential for organisms function, including lipids, proteins, and carbohydrates. Overproduction of primary metabolites is avoided due to detrimental effects on microbial growth. Primary metabolism involves the synthesis and transformation of these metabolites, occuring alongside cellular proliferation and aligning with population growth.[23]

Secondary metabolites, including antimicrobial and antibiotic compounds are synthesized by endophytic bacteria inhabiting plant tissues. An estimated 300,000 plant species harbor endophytic bacteria within their biological makeup. Secondary metabolites play crucial role in the development and growth of plants, enhancing stem elongation, root hair development, root branching, root length, and root dry weight. Rapid root growth facilitates water and nutrients uptake, promoting accelerated growth in immature plants. Plants synthesize secondary metabolite molecules to protect againts high temperatures and rain.[23]

Antibiotic Activity Test

To determine and classify compounds with the capacity to function as antimicrobial agents against bacteria, it is important to assess the efficacy of microorganisms. There are various methodologies for antibiotic activity test that can be used.[24] The first method is dilution method. The dilution technique is a quantitative method. The experimental procedure involves the initial preparation of antimicrobial compounds at various concentrations. These compounds are then added to the medium, which has been inoculated with the test organism, using a dropper. This approach represents the basic concept. The process of dilution can be accomplished by two distinct methods, specifically liquid dilution, and solid dilution.[24,25]

The second is the diffusion method. This method is employed for assessing the efficacy of antimicrobial drugs. The agar medium, which has been inoculated with the test bacteria, is supplemented with an antibacterial agent. Subsequently, the diffusion of the antibacterial agent inside the agar media is enabled. The observation of a separate area devoid of microbial growth on the agar surface signifies the inhibitory effect of antimicrobial drugs on microorganisms. One limitation of this method is the inability to calculate the minimum inhibitory concentration (MIC) value for an antibacterial agent against the specific organism being studied. Two commonly used methods for doing diffusion antibiotic testing are the well method and the Kirby Bauer method.[24,26]

The third method is bioautography method. The technique used for this procedure exhibits similarities to the agar diffusion method. The bioautography technique involves the diffusion of the test substance from the chromatography paper into the agar medium that has been inoculated with the test bacteria. This characteristic distinguishes it from the agar diffusion method. The methods of bioautography can be categorized as contact bioautography, direct bioautography, and immersion.[24,27]

Antibiotic-producing endophytic bacteria isolates can also be identified using molecular techniques. A study was conducted to determine the molecular identities of OOH-1 and STG-1 isolates, as well as to identify antibiotic compounds generated by STG-1 isolates. The selected isolates were identified molecularly using the 16S rRNA gene and primers 27F and 1492R. The resultant sequences were then used to generate a phylogenetic tree by comparing them to Gene Bank data using the nucleotide Basic Local Alignment Search Tool (BLAST-N) tool. Antibiotic compounds are identified by purifying and separating them. Antibiotic activity was also assessed using the Lethal Concentration (LC50) on *Fusarium oxysporum*, which ranged between 0.01 to 0.02%.[26]

The increasing prevalence of drug-resistant microorganisms necessitates the exploration of a greater number of endophytic bacteria in order to find out their potential as sources of bioactive natural compounds with antimicrobial properties. The example of a novel antibacterial agent derived from endophytic bacteria is 7-amino-4-methylcoumarin obtained from *Xylaria* sp.[28] The inhibitory effect of *Bacillus amyloliquefaciens*, an endophytic bacterium derived from the stem bark of clove plants, has been shown on the pathogens *Streptococcus mutans* and *Staphylococcus aureus*.[29] The endophytic bacterial isolates derived from green betel exhibit antibacterial action against *Staphylococcus aureus*. An additional benefit associated with endophytes is to their capacity to synthesize indoleacetic acid (IAA), a growth regulator, within banana cultivars.[30] Other research also shows that jawer kotok plant is used to treat diarrhea and has been shown to be able to inhibit the growth of *S. enteritidis* bacteria.[26] Furthermore, there exist studies that confirm the presence of various endophytic bacteria derived from the medicinal plant *Solanum xanthocarpum*. Among these bacteria, three specific strains have been found that have antimycobacterial properties, such as *Mycobacterium tuberculosis*.[31]

CONCLUSION

There is significant potential to develop techniques to combat bacterial resistance to antibiotics by utilizing endophytic microbes. Metabolites from endophytic bacteria can potentially suppress the growth of germs or harmful bacteria through various mechanisms. These actions include damaging cell walls, blocking

DNA, RNA, and protein production, hindering enzyme function, altering proteins and nucleic acids, and affecting cell permeability. Endophytic bacteria have symbiotic connections with their host plants, interacting without causing harm or disruption. Continuous research is crucial to enhance the efficacy of endophytic bacteria sourced from different plant sections, providing alternative solutions to the issue of antibiotic resistance in Indonesia and worldwide.

CONFLICT OF INTEREST

There is no conflict of interest.

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AUTHOR CONTRIBUTIONS

The authors confirm their contribution to the paper, as follows: Study conception and design: AES and FI; methodology: AES and FI; draft manuscript preparation: AES; and visualization: AES. Validation: AES and FI. All authors evaluated and approved the final version of the article.

LIST OF ABBREVIATIONS

RNA: ribonucleic acid; DNA: deoxyribonucleic acid; ISR: induced system resistance; BLAST-N: nucleotide basic local alignment search tool; IAA: indoleacetic acid.

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