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Review Article

Endophytic bacteria as a source of novel bioactive compounds

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ABSTRACT

The world is currently facing an increase in multi-drug resistance which is a serious threat to global health. Owing to this, and the scarcity of novel synthetic drugs on the market, the researchers are encouraged to find new means to combat the multi-drug resistance pathogens, directed towards utilizing natural bioactive products that have potent effectiveness and are harmless to humans. Microorganisms synthesize these compounds either alone or alongside plants. Endophytic bacteria colonize the inside tissues of the plant, with no disease symptoms appearing on plant tissues. The extensive colonization of endophytic bacteria inside plant tissues forms a barrier that prevents harmful pathogens from taking hold. This occurs by creating secondary metabolites that inhibit the growth of pathogenic organisms. In this regard, they have an essential role in plant defensive systems. Thus, the goal of this article is to provide a broad overview of novel bacterial endophytes-derived compounds that have antimicrobial, antibacterial, antifungal, antiviral, antioxidant, and anticancer activities, as well as to present their potential applications in the pharmaceutical, medicinal, agricultural, phytoremediation, and nanobiotechnology.

Keywords: *multi-drug resistance; endophytic bacteria; secondary metabolites; antimicrobial.*

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1. Multi-drug resistance (MDR)

Infectious illnesses are one of the most common prevalent reasons for morbidity and mortality among the global population, particularly in underdeveloped nations. Microbes are responsible for 25% of the world's 57 million annual fatalities, according to the World Health Organization (WHO); this figure is higher in underdeveloped countries [**1**]. Since the 1940s, antibiotics have been regularly utilized to cure bacterial diseases and to fight off infections in immunocompromised individuals, however, abuse or misuse of antibiotics causes the development of antibiotic-resistance or multidrug-resistance, which has serious consequences for global health **[2]**. Furthermore, as a result of modern lifestyle, human health deteriorates, with the presence of resistant bacteria and new versions of life-threatening viruses emerging with less control of existing drugs to combat disease development, treatment effectiveness is reduced, and morbidity and mortality rates are increased **[3]**. To combat the health impact of multi-drug resistance microbes, researchers and pharmaceutical companies have been focusing on discovering and developing new antimicrobial agents from natural sources that are active, readily available, and low in cost **[4]**.

The rise of microorganisms resistant to current antimicrobial treatments is owing to bacterial species' ability to acquire and transfer genetic resistance to available antibacterial medications. For millions of years, microbes have continually interacted with their biological, chemical, and physical environments, and some can interact with other living beings, a phenomenon known as sociomicrobiology. As a result, microorganisms have developed powerful metabolic capabilities that improve the chances of survival against scientific approaches used to eliminate these organisms **[5]**. Furthermore, the development of multidrug resistance (MDR) may arise from inappropriate use of antibiotics, poor hygiene conditions, inadequate food handling practices, and a lack of infection prevention and control (IPC), all of which may contribute to the spread of MDR **[6]**. Individuals with severe burns, diabetes, organ transplant recipients, and immunocompromised patients are more susceptible to hospital-acquired infections, which in turn promotes the spread of (MDR). Moreover, the expansion of worldwide transport and trade leads to a greater possibility of MDR spreading all over the world **[7]**.

New antibiotics are always necessary due to the rapid evolution of drug-resistant infections, the emergence of new diseases, the prevalence of naturally resistant bacteria, and the toxicity of some present drugs **[1]**. Natural products continue to be the most important resource for the discovery of novel effective therapeutic substances to solve the challenges of treating new strains of infectious diseases and controlling the spread of multidrug resistance. The identification of active new compounds to combat the emergence of resistant pathogens should be accelerated **[1, 29]**.

2. Medicinal plants and their importance to human health

The plant kingdom is a treasure home of potential drugs and nowadays, there has been increasing attention and awareness about the importance of medicinal plants. Medicinal plants refer to whole plants or plant parts that contain active ingredients or biologically active secondary metabolites. In ancient medicines, people utilized herbs and plants to cure a variety of illnesses, including gastrointestinal complaints, skin disorders, cardiovascular disease, hepatic disorders, respiratory disorders, and urinary issues **[8]**. According to the World Health Organization (WHO), medicinal plants are the best source for a wide range of medications **[9]**, and approximately 80% of the global population relies on traditional plants as remedies for diseases with many advantages as the natural products are considered safer, efficient, rarely have side effects, less toxic, inexpensive, and easily accessible **[4, 9, 12, 13]**. Furthermore, the basic requirements for using medicinal plants in the synthesis process of medications do not necessitate significant quality control for efficacy and safety compared to other drugs **[11]**.

Plants and herbs are considered the chief source of natural products and metabolites (biologically active compounds) used in medicines **[4],** as a result of these compounds the medicinal plants are either harvested for immediate use as herbal or alternative therapies in the presence of multiple adverse effects and drug resistance **[12]** or consumed for experimental use. The technique of preparing medicinal plants for experimental reasons entails collecting the plants at the appropriate time, drying and sterilizing them thoroughly, and then grinding them. Then extraction, fractionation, and purification of the natural bioactive compounds **[12]**.

Efforts to improve bioactive metabolite production have not yielded optimal results, necessitating the search for additional sources. Given the limitations of *in vivo* production and the need to preserve biodiversity, using a microbial source may be a more sustainable and cost-effective way to produce valuable metabolites, potentially lowering market prices.

For this reason, the study of microbial endophytes in medicinal plants has gained popularity and recognition in recent years **[14]**.

3. Natural compounds derived from plant sources

Plants produce natural chemical substances known as phytochemicals. Phytochemical compounds are synthesized by primary and secondary metabolism **[9]**. The primary metabolites are substances responsible for growth and are crucial for plant survival such as sugars, proteins, nucleotides, chlorophyll, and fatty acids **[15]**. Secondary metabolites are natural bioactive compounds or phytochemicals derived from microbes and medicinal plants including alkaloids, steroids, phenol, flavonoids, lectin, and tannins **[1],** to perform vital functions for their host plants **[15].** These compounds can be extracted and separated by using solvents and a standard extraction process **[16]**. Natural bioactive compounds have significantly impacted drug discovery, particularly for treating infectious disorders, cancer, cardiovascular disease, hyperlipidemia, and multiple sclerosis **[19].** Many of these compounds are considered ingredients of antibiotics, analgesics, anti-cancer agents, laxatives, diuretics, antihypertensive, heart drugs, anti-lipidemic, ulcer treatments, contraceptives, etc. **[10]**.

The medicinal plant's quality is strongly affected by different environmental factors, such as temperature, soil condition, and moisture. Furthermore, it can be influenced by the connection between host plants and their unique microbes **[17]**. Medical plants face high demand for secondary metabolites, extinction threats to biodiversity, and commercial exploitation. Additionally, they require certain habitats for survival, which restricts their distribution **[18]**. The scientist discovered biotechnological approaches including tissue culture use and synthetic seed technology. These approaches have been used to reduce the overuse of medicinal plants, but these approaches can not produce high levels of bioactive compounds and need long growth periods **[142]**. So, researchers shift to an ideal substitute for medicinal plants, which depend on microorganisms (bacteria and fungi) that inhabit plants, as they have good handling features, short generation times, and high growth rates, resulting in high biomass production **[20]**. It is believed that most of these microorganisms synthesize some secondary metabolites similar to the host plant as they exchange fragments of their genomic DNA with that of their host plant **[21]**.

A wide range of bacteria have interactions with different plant tissues. These include the bacteria that live outside and inside their host plants. The bacteria that live outside the host plant tissues are either epiphytic (those bacteria live on the surface of the plant leaves), or rhizospheric, those bacteria colonize plant roots within the soil. However, bacteria that reside and thrive inside their host plant are known as endophytic bacteria **[22, 23]**.

4. Endophytes

4.1. Definition of Endophytes

The endophyte term was defined first in 1866 by De Bary **[4, 26, 27**; **28]**. They were initially described in the plant *Lolium temulentum*. The term endophytes, "endo" originates from the

Greek word "endon" referring to within, and "phyte" comes from the Greek word "phyton" which represents plant **[26**, **31]**. The term “endophytes” includes all non-pathogenic microorganisms colonizing and growing intra- and/or intercellularly in the tissues of healthy plants for a period of their life span without appearing external signs of infections or diseases on the plants in which they live **[22, 24, 27, 32]** and create a mutualistic relationship. Endophytes are considered rich sources of bioactive natural products **[29, 33]** such as alkaloids, flavonoids, phenols, steroids, terpenoids, benzopyranones, benzoquinones, and xanthones. They are considered highly potent producers of antibacterial, antifungal, antiviral, cytotoxic, and immunosuppressive agents **[25]**.

Endophytes in a single plant may consist of multiple species rather than just one. This could describe the beneficial effect of endophytes due to the combination of their activities **[37]**. Several scientists considered that the majority of microorganisms that interact with plants play an essential role in plant health, survival, and development, but only a small percentage of bacteria inhabiting the plants become harmful depending on the host genotype and environment, and sometimes they are neutral **[16]**.

Nearly 300,000 plant species on the earth, are considered hosts for one or more types of endophytes [**29**, **22, 33**] Various studies are focusing on the special colonization of endophytes in certain host plants, although it is estimated that there are around one million different endophyte species residing in plants. Only a few of them have been described **[29]**, which means that the opportunity to discover new natural products from interesting endophytic microorganisms isolated from different plant species is great.

4.2. The origin of the endophytes

The origin of endophytes is not determined exactly due to the complicated relationship between endophytes and plants and different environmental effects. Two major opinions on this, the first one is that endophytes are derived from the mitochondria of the plant's cell so can get the same genetic background as the host plants **[38]**. The second opinion is based on that endophytes can penetrate the plant tissue from outside environments like the soil due to injuries and openings in the host plants **[39]** as endophytes originate from the phylloplane micro-flora or rhizosphere bacteria which have a chance to penetrate and colonize root tissue **[41]**, providing a way into the xylem (vascular tissue). After that, the microbes could transport and reside in the plant systemically. Once the microbes enter the plant, endophytic populations can grow in different parts of the host plant. Endophytic microorganisms include bacteria, fungi, or actinomycetes, and in this article, we emphasize endophytic bacteria.

5. Endophytic bacteria

5.1. Entry of endophytic bacteria

The distribution and colonization of endophytic bacteria require the bacteria to enter the host plants in different ways. They can enter the plants through the root hairs or wounds caused by microbial phytopathogens [**31**, **32**] and the cracks that form in the lateral root junction and spaces between epidermal cells **[10]**. The roots are considered the primary gateway entrance of microorganisms to their host plants. Alternatively, some bacterial endophytes can secret cellulolytic enzymes such as cellulases, pectinases, xylanases, and endoglucanases which modify the cell wall of the host plant and facilitate the entry and spread of bacteria within the host plant tissues [**31, 36]**. The bacterial endophytes could also penetrate host plants through different places such as stomata, particularly on leaves and young stems, and lenticels, which are located in the periderm of stems and roots **[41]**. Furthermore, plants produce root exudate or attractive compounds (chemoattractants) that attract beneficial bacteria from the surrounding environment **[27]**. At the same time, endophytic bacteria recognize these compounds and show chemotactic movement toward them. Then, they can penetrate the plant through the root by using lateral root emergence or openings and wounds **[36]**.

5.2. Route of transmission of bacterial endophytes

Bacterial endophytes that inhabit inside plant tissue (intra- and/or intercellular) for a whole or a part of their life cycle can be transmitted from the parents to offspring or can be transmitted between two individual plants **[23]**. There are two different ways of transmission, horizontal and vertical, however, transmission can also be mixed (mixed–mode transmission) which involves both horizontal and vertical ways **[24, 42]**.

5.2.1. Horizontal transmission

Horizontal transmission occurs between individual plants in a community or in the same environment. The reproduction process through sexual or asexual spores **[43]** leads to horizontal transmission, where endophytic bacteria may transfer between plants in a community or a population in the environment **[23]**.

The majority of bacterial endophytes are horizontally transmitted as they are acquired from the surrounding environment **[42]**. Also, they can be transmitted through wounds and injuries of the root as well as the aerial parts of the plant **[10, 40]**. The beneficial properties of bacterial endophytes respond to changes in the environment, which depends on the soil type. The diversity of bacterial endophytes in the seeds of plants grown in the soil is higher than the diversity of bacterial endophytes in seeds grown under sterile conditions **[42]**. Soil is considered the main environmental factor impacting the diversity of bacterial endophytes, and pH is the most potential soil characteristic affecting the composition and structure of microorganism communities across different continents **[44]**.

5.2.2. Vertical transmission

The transmission of bacterial endophytes is vertically directed from the parent plants to the offspring **[23]** via seeds and pollen, so different types of bacteria have been detected in the seeds of the parent plants [**24]**.

Endophytic bacterial distribution within plant tissue depends on the ability of bacterial endophytes to colonize and the allocation of plant resources. At the site of root injuries located below the root hair zone, the endophytic bacteria penetrate the epidermis and colonize there, grow, and become able to establish populations both inter- and intracellularly. After that, some bacterial endophytes can move systemically and enter the vascular tissue to reach other areas of the plants [**22, 23]**.

5.3. Distribution of endophytic bacteria

Endophytic bacteria seem to be distributed and colonized in different plant tissues, including roots, stems, leaves, flowers, seeds, ovules, and fruits **[45, 46]**. They are typically found in intercellular, intracellular areas, and xylem vessels, where the bacteria are transported to aerial parts of plants such as fruits and flowers. However, plants often have more bacterial endophytes in their roots than in their above-ground tissues.

Endophytic microorganisms are discovered in different plant species ranging from herbaceous plants such as rice, garlic, onion, ferns, mosses, and tomatoes to woody trees such as ginkgo, oak, etc. **[43]**. A single plant species may host diverse endophytic microorganisms **[32, 40]**. The classical approaches for studying microbial endophytes involve the isolation of endophytes from different plant parts, followed by phenotypic and genetic characterization of the isolates **[40]**. The variety of new endophytic species that may exist in numerous plants proves that endophytic microorganisms are significant components of microbial biodiversity **[43]**, and several studies have shown that there are few bacterial endophyte-free plants.

Recently, the study of endophytic bacteria has increased, as they play a serious role in agriculture by enhancing crop productivity; however, the major orientation now is to explore endophytic bacteria because they can produce valuable natural compounds with high efficacy, which can be used in the pharmaceutical and medicinal industries **[46]**.

The way of production of bioactive compounds by the endophytic bacteria is related to the genetic evolution of these microorganisms, while the genetic information incorporated with the host plants **[43]**, allows for better adaptation with the host plants and carries some prevention mechanisms against insects and pathogens **[33]**. So various types of bioactive metabolites are produced not only by endophytes but also can be produced by the host plant and associated endophytes together **[26, 69]**. For example, bacterial endophytes isolated from medicinal plants of *Solanum distichum*, *Calendula officinalis*, *Matricaria chamomilla*, and *Hypericum perforatum* showed sufficient antibacterial and antifungal activity **[47, 48]**. When the natural bioactive compound synthesized by endophytic microorganisms is the same produced by the host plant, this is supposed to be more beneficial for the environment by minimizing the need to harvest slow-growing and rare plants, and thus preserve the world's biodiversity. Also, this helps to get the natural bioactive compounds from microbial sources more easily and economically **[29]**.

Endophytic bacteria can synthesize extracellular enzymes such as pectinase, amylase, lipase, cellulase, and protease. These extracellular enzymes act as a defense mechanism against disease and help to obtain food from the host plants [**26]**.

Methods to obtain bioactive molecules synthesized by endophytes depend on the extraction process. The process starts with the isolation of endophytic microorganisms, followed by the production of endophytes through fermentation or microbial transformation **[29]**. More background information about the host plant species and microbial endophytes speeds up the research about natural bioactive metabolites **[29]**.

5.4. Diversity of endophytic bacteria

Endophytic bacteria are diverse, they belong to 16 phyla consisting of more than 200 genera of endophytic bacteria. However, a greater number of them belong to three phyla: *Actinobacteria, Proteobacteria, and Firmicutes* **[36, 45].** The diversity ranges from Gram-positive bacteria to Gram-negative bacteria, such as *Bacillus, Acinetobacter, Pseudomonas, Microbacterium, Achromobacter, Agrobacterium, Brevibacterium, Xanthomonas*, etc **[16]**. Endophytic bacteria were detected in various environments which include aquatic, temperate, tropic, deserts, xerophytic, Antarctic, rainforests, and coastal forests **[10]**. Endophytic bacteria have been detected in herbaceous plants such as aquatic weeds, noxious weeds, woody plants, reproductive structures of plants such as seeds and fruits, and perennial and annual grasses **[57]**.

5.4.1. Factors affecting the diversity of endophytic bacteria

The diversity of bacterial endophytes is strongly affected by host plant characteristics as well as biotic and abiotic environmental factors. The age, health, and growth stage of the host plant all have an impact on the diversity of endophytic bacteria. The host plant growth stages that are rich in nutritional resources are vulnerable to increased bacterial diversity **[58]**. The plant's surface structure and root architecture, as well as root exudate, all influence bacterial selectivity and the bacterial spectrum present in plant tissues.

Environmental factors such as soil management, geographic location, and climate changes have roles in determining the species of bacterial endophytes **[16, 17, 22, 44]**. For example, oxygen content in the environment critically influences bacterial endophyte diversity, especially aerobic bacterial species that require oxygen for survival and growth **[60]**. The variation in nitrogen fertilization, and elevated levels of CO_2, tend to have more bacterial diversity **[22]**. Moreover, Surette et al. **[61]** suggested that the abundance of bacterial endophytes in plant tissues may be associated with higher sugar content.

The nature of host plant species significantly impacts the type of bacterial endophyte community **[17]**. Varied species of plants growing in the same soil may yield diverse endophytic varieties. Germida et al. **[62]** found that canola and wheat plants growing in the same region had distinct bacterial endophytic species. This finding was validated by Ding et al. **[63]** who found that the host plant species was the most significant aspect in determining its bacterial endophytes community, next to the sampling location.

6. Technique used in studying endophytic bacteria

Two major techniques are used to investigate the occurrence of endophytic bacteria in plant tissues: the culture-dependent method (direct observation technique) and the culture-independent method.

6.1. Culture-dependent method

Most studies were carried out by culture-dependent method, which needs the isolation of bacterial endophytes from different parts of the plant which can performed by surface sterilization technique to confirm the killing of any other organisms, followed by culturing the plant tissue fragments, or ground tissue extract [**51]** on suitable media. The surface sterilization process is a mandatory and crucial step; it should be sensitive enough to preserve endophytic bacteria but at the same time should be strong enough to kill epiphytes from the plant surface **[28]**. In the culture-dependent method, the microscope is used to determine the morphological character of the organism. Isolating the microbial endophytes and culturing them in a laboratory is important for endophyte characterization, studying the endophyte's microbial communities and diversity, and identification of secondary metabolites produced by endophytic bacteria **[52]**.

6.2. Culture-independent method

In the culture-independent method, DNA fingerprinting and sequencing methods are used to determine the molecular character of the organism. This method is utilized when endophytic bacteria do not need to be cultivated; thus, this methodology is based on sequence analysis of bacterial genes resulting from DNA extracted from plant tissues **[51]**. A new molecular approach uses specific primers to characterize the specific genus and species of bacteria. This method relies on the amplification of the 16S ribosomal gene through the Polymerase Chain Reaction method (PCR) and aligning them with available databases which enables speedy and precise species identification of genetic material of the isolated bacteria [**55]**.

Culture-dependent and culture-independent approaches yielded similar microorganisms, with no significant differences **[53]**.

7. Classification of bacterial endophytes:

The classification of bacterial endophytes usually depends on their life strategies, including obligate, facultative, opportunistic, and passenger or passive endophytes.

Obligate endophytic bacteria are transmitted vertically via seeds to the host plant to complete their life cycle**,** while facultative which have a free-living phase of life in the soil as rhizosphere then enter the plants through emerging root hairs and root cracks or wounds **[36]**. Obligate bacterial endophytes are strongly dependent on their host plant for their growth, in contrast, facultative bacterial endophytes alternate between the soil and the host plant **[10]**. Others are opportunistic endophytes, which grow as epiphytic but occasionally enter the plant, and passenger or passive endophytes, which enter the host plant without actively seeking to colonize it **[30]**.

Other criteria for classifying endophytic bacteria are based on their diversity, taxonomy, transmission mode, and biology, which categorizes the endophytic bacteria into systemic bacterial endophytes (true) and non-systemic bacteria endophytes (transient).

Systemic bacterial endophytes are non-pathogenic microorganisms that have a symbiotic relationship with the plant **[64]**. However, these endophytes are not influenced by changing environmental conditions. In contrast, non-systemic endophyte diversity is influenced by changing environmental conditions **[65]**, and has a pathogenic effect on their host plant in stressful and deficit resource conditions.

8. Relationship between endophytic bacteria and host plants

The relationship between endophytes and host plants is characterized by symbiotic interactions, as both endophytes and host plants benefit from association **[17, 32]**. The plants supply the endophytes with nutrients, and the endophytes support the plants to settle in ecosystem restoration processes **[34]**, promoting the growth of the plants [**96]** directly by the production of secondary metabolites, which increase the ability of host plants to resist against biotic and abiotic stress such as osmotic stress, presence of heavy metals and xenobiotic compounds **[22, 32]**. Moreover, endophytes enhance root development by increasing nitrate uptake or solubilizing phosphorus and controlling soil-borne pathogens **[34]**. Furthermore, endophytic bacteria help the plants to adapt to their living environment **[44]**, and enhance tolerance to stressful factors such as high salinity in the soil, low temperature**,** low pH, and the presence of heavy metals **[43]**. In addition, the endophytic bacteria produce secondary bioactive metabolites that can inhibit the disease development of the host plants and fight the pathogens **[13]** and herbivores **[43]**, making them eligible for use in the pharmaceutical industry to control the growth of many pathogenic microorganisms **[67]**. Endophytes are one of the crucial organisms that develop beneficial associations with their host plants to thrive in the natural environments in the ecosystem and to tolerate multiple biotic and abiotic stresses that hamper the growth of the plants [**22]**. Endophyte-plant interaction involves a process of co-evolution controlled by colonization **[14]** which is managed by genes of the organism **[11]**, growth stage, type of plant tissue, physiological status, agricultural practices, and environmental conditions such as nutrients, temperature, and water supply **[32]**.

Most of the modern research demonstrates that the health and survival of plants are very much dependent on these microorganisms **[27],** so, in general, the endophytes-free plants are less healthy than the endophytes-infected plants **[43]** and the chance of endophytes-free plants to survive under natural conditions is low **[41, 30]**. This may be because the endophytes help the host plants to absorb the beneficial nutrients from the surrounding environment like nitrogen and phosphorus, **[17]** and or maybe because the endophytes produce phytohormones such as cytokines, indole-3-acetic acid (IAA), and vitamins which promote the growth of the plants **[17**, **31**, **36**, **43]**.

In addition, endophytic bacteria demonstrated great antibacterial activity against many plant pathogens such as *Bacillus sp.*, *Paenibacillus polymyxa*, *and Pseudomonas poae* **[66]**. *Burkholderia glumae and Xanthomonas oryzae* **[66]**. Endophytic bacteria colonize an ecological niche similar to that of phytopathogens that invade the plants, thus allowing them to be suitable biocontrol agents **[68]**. For this reason, numerous researches have shown that endophytic bacteria can control plant pathogens. In addition, bacterial endophytes can also speed up seedling emergence, enhancing plant establishment and growth under adverse conditions. Due to the great biological properties of bioactive metabolites produced by endophytes, the interest of researchers in studying these metabolites increased. According to Stelmasiewicz et al., **[69]** there was a significant increase in the number of articles published on endophytes and their bioactive substances between 2000 and 2022.

9. Application of Endophytic bacteria

Bioactive compounds synthesized by endophytic bacteria have wide applications in pharmaceutical, medical, environmental, agricultural, and nanobiotechnology.

9.1. Pharmaceutical and Medical Applications

Endophytes colonizing medicinal plants are known as a good source of bioactive compounds such as alkaloids, peptides, terpenoids, antibiotics, flavonoids, quinones, and phenols **[39]**. **Fig. 1** and **Table 1**, summarize examples of bioactive compounds produced by endophytic bacteria and their biological activities.

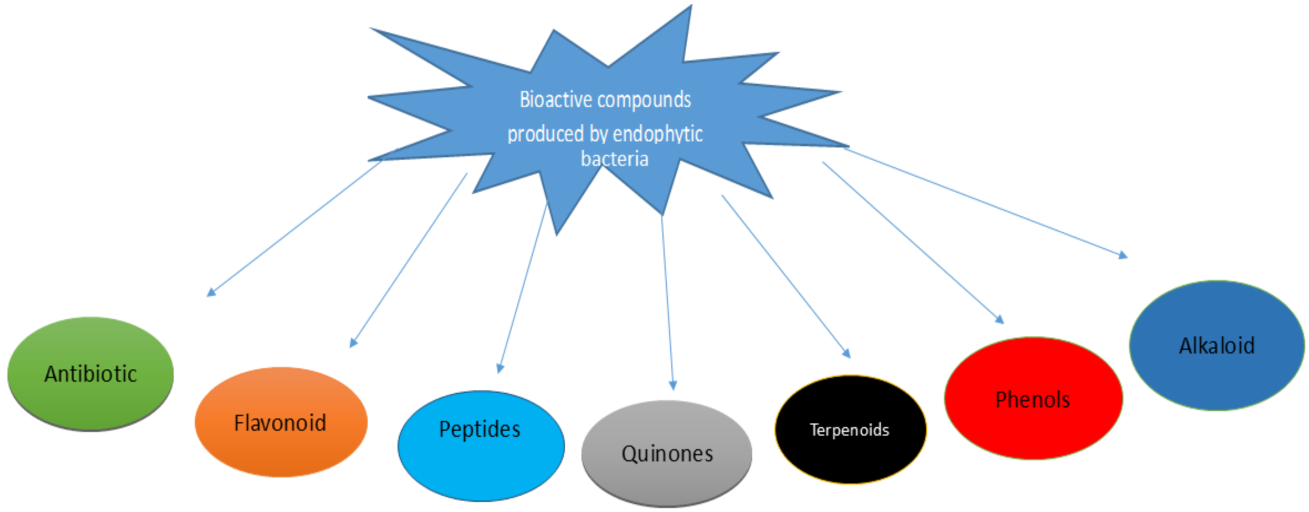

Fig. 1. Examples of bioactive compounds produced by endophytic bacteria

Table 1. Example of bioactive compound produced by endophytic bacteria and their therapeutic applications

Endophytic bacteria	**Host plant**	**Active component**	**Therapeutic application**	**References**
P. aeruginosa CP43328.1	*Anredera cordifolia CIX1*	dioctyl phthalate (50.51%) and [1, 2, 4] oxadiazole, 5-benzyl-3 (10.44%)	antibacterial and antioxidant	**[49]**
Pseudomonas aeruginosa strain UICC B-40	*Neesia altissimo*	phenyltetradeca-2,5-dienoate	inhibitory activity on the growth of Gram-positive bacteria.	**[50]**
B. megaterium MTCC446	*Phyllanthus amarus Schumach.* and *Thonn.*	Phenolic content	antioxidant activity	**[35]**
Streptomyces *sp. LJK109*	*Alpinia galangal* root	3-methyl carbazole	anti-inflammatory activity	**[56]**
Paenibacillus sp. IIRAC-30	*Cassava*	Surfactin	Antibacterial	**[106]**
Methylobacterium radiotolerans MAMP 4754	Combretum erythrophyllum	9-octadecene, 3-eicosene, 11-tricosene, hexadecane	antibacterial and antioxidant	**[116]**
Micromonospora sp. PC1052	*Puereria candollei*	*S*-adenosyl-*N*-acetylhomocysteine	Antioxidant, antibacterial	**[130]**
B. amyloliquefaciens sp.	*Ophiopogon japonicus*	exopolysaccharides	antitumor activity against the human gastric carcinoma cell lines MC-4 and SGC-7901	**[129]**

9.1.1. Antimicrobial agents from Endophytes

Antimicrobial agents are the most bioactive natural compounds with low molecular weight made by endophytes and have activity at low concentrations against other organisms**.** Endophytic bacteria associated with medicinal plants are abundant sources of bioactive compounds with antimicrobial action. These antimicrobial compounds belong to multiple structural classes such as steroids, phenols, alkaloids, peptides, flavonoids, and quinines [**29]**, and used not only as drugs for the treatment of diseases but they can also be used as food preservatives in the food industry to prevent spoilage and food-borne diseases **[6, 29]**.

Ecomycin is a potent antimicrobial compound, which is composed of some amino acids such as homoserine and β-hydroxy aspartic acid and has activity against human pathogens *Candida albicans* and *Cryptococcus neoformans*. According to Miller et al., **[70]** Ecomycin can be produced by the endophytic bacteria *Pseudomonas viridiflava*, which was isolated from some grass species. An endophytic bacteria *Pseudomonas aeruginosa* which lives within the tissue of *Brassica oleracea (Cabbage)*, exhibits considerable antibiotic action against *Escherichia coli*, *Staphylococcus aureus*, *Salmonella Typhi*, and *Klebsiella pneumoniae* **[71]**.

A further study was performed on the antibacterial activity of a metabolic extract of endophytic bacteria isolated from the medicinal plant *Andrographis paniculata* **[72]**. Other research reported that *Bacillus* species endophytes including *B. cereus*, *B. subtilis*, *B. licheniformis*, *B.circulans*, and *B. pumilus* produced antimicrobial metabolites with high efficacy against different bacteria and fungi **[73]**. Another study focused on munumbicins compounds, which were obtained from an endophytic bacteria *Streptomyces NRRL 30562* that was found in a medicinal plant, Snake Vine *[Kennedia nigriscans]*. The munumbicins A, B, C, and D, are newly described antibiotics that have potent activity against gram-positive bacteria such as *Streptococcus pneumoniae*, *Bacillus anthracis,* *Staphylococcus aureus*, and *Enterococcus faecalis* **[74]**. Moreover, the endophytic bacteria *Bacillus megaterium*, which was isolated from the roots of the medicinal plant *Pongamia glabra*, possesses great antifungal activity **[75]**.

9.1.2. Antioxidant agents from endophytes

Antioxidants are substances that can prevent, inhibit, or significantly delay the oxidation of rapidly oxidizable materials at low concentrations **[76]**. The oxidation reactions involve the exchange of hydrogen or electrons between molecules and the oxidizing agent, forming free radicals. These free radicals can initiate chain reactions in a cell which harm or cause death in a cell. Oxygen-derived free radicals can also cause adverse consequences such as DNA damage, cellular degeneration, and carcinogenesis **[77]**. Antioxidants prevent chain reactions by eliminating free radicals and inhibiting other oxidative reactions.

Natural antioxidant compounds commonly exist in medicinal plants, vegetables, and fruit including phenolics, tocopherols, carotenoids, flavonoids, tannins, lignins, and anthocyanins **[78]**. Plant-derived antioxidants aid in preventing degenerative disorders induced by oxidative stress, including cancer, atherosclerosis, Alzheimer's, and Parkinson's disease **[79]** Endophytes play a crucial role in the defense mechanism against infectious disease, as they produce a significant amount of antioxidant metabolites which inhibit the oxidative damage of human cells **[25]**.

Endophytic bacteria are a potential source of natural antioxidant compounds **[33]**. Endophytic bacteria isolated from Papaya leaves were able to synthesize the same secondary metabolites of Papaya plants including alkaloids, flavonoids, tannin, saponin, and triterpenoids, which have high antioxidant activity and reduce free radicals **[82]**. Moreover, Sogandi et al., **[80]** reported that the endophytic *Staphylococcus sp.* isolated from clove *(Syzygium aromaticum L.),* produced alkaloids with high antioxidant activity.

9.1.3. Anticancer agents from endophytes

Cancer is a group of disorders where the aberrant cells proliferate and spread uncontrollably. There are over a hundred different forms of cancer. This illness occurs when aging cells cannot be substituted by new ones and aggregate in an accumulation of tissue called a tumor.

The main issue with anticancer drugs is that they have nonspecific toxicity against normal cells, resulting in considerable side effects and limited efficacy against cancer cells. Therefore, careful medicine selection, combined with early diagnosis, improves the outcome of cancer treatment.

One of the most important anticancer agents is Taxol which was initially isolated from trees related to the Taxus family *(Taxus brevifolia)* **[84]**. These trees are slow-growing, scarce, and produce low amounts of Taxol. These reasons limited the supply of this drug, and new sources for Taxol production were needed. Taxol production by the microbial fermentation of *Taxomyces andreanae* endophytes isolated from *yew* trees [**85]**, offers an economical, and readily available alternative drug source**.** *Bacillus safensis* extracts obtained from sea sponges showed antitumor efficacy against hepatocellular carcinoma, breast carcinoma, colon carcinoma **[86],** and lung cancer **[15]**. The endophytic bacteria *Raoultella ornithinolytica* produced an extract composed of a protein complex, which exhibited cytopathic, cytotoxic, and apoptotic effects on the human endometrioid ovarian cancer line, and the human breast adenocarcinoma line, leading to cell number reduction **[87]**.

9.2. Agriculture application

9.2.1. Plant Growth Promotion

Most current research clearly shows that plant health and ability to survive are heavily reliant on microbial endophytes **[11, 27],** so endophyte-free plants are generally less healthy than endophyte-infected plants **[43],** and also have a low chance of survival under poor environmental conditions [**41]**.

Plant-growth-promoting bacterial endophytes (PGPBEs) promote plant growth either directly, through phytohormone production, phosphate solubilization, nitrogen fixation **[32],** and inhibition of ethylene biosynthesis in response to biotic and abiotic stress (drought, salinity, flood, etc.), as well as enhance the nutrient's availability such as iron, phosphorus, nitrogen, and minor elements that are crucial for plant growth, or indirectly by increasing the resistance to pathogens and induce systemic resistance of plants **[41, 46]**. **Fig. 2**. shows direct and indirect mechanisms of plant growth promotion. **Table 2**. includes examples of different endophytic bacteria promoting plant growth through different mechanisms.

Table 2. Examples of endophytic bacteria promoting plant growth through different mechanisms

Endophytic bacteria	**Host plant**	**Plant growth promotion mechanism**	**References**
Bacillus subtilis and Paenibacillus sp.	*Tomato*	Antifungal	**[119]**
Bacillus sp., Pseudomonas sp., and Stenotrophomonas sp.	*rhizome of ginger*	Siderophore production	**[120]**
Stenotrophomonas maltophila, Pseudomonas geniculata, Bacillus amyloliquefaciens, Bacillus licheniformis, and Bacillus subtilis	*Tomato*	IAA production	**[117]**
Pseudomonas aeruginosa.	*chilli fruits*	IAA, ammonia, siderophore production and phosphorous Solubilization, and pathogen biocontrol activity	**[116]**
Acenitobacter calcoaceticus, Paenibacillus polymaxa, and Psuedomonas resinovorans	*G. procumbens leaves*	Cytokinin production	**[113]**
Actinobacteria, Bacteroidetes, Proteobacteria	*Suaeda maritima (L.) Dumort*	nitrogen-fixing	**[125]**
Bacillus Serratia	*tomato and chilli*	Antifungal activity, IAA, and Siderophore production	**[124]**
Enterobacter sp.	*Allium macrostemon Bunge*	Phytoremediation (remediate hydrocarbon-contaminated soils)	**[126]**
Acinetobacter sp. LSE06, Enterobacter aerogenes LRE17, Enterobacter sp. LSE04, and Serratia nematodiphila LRE07	*S. nigrum*	aminocyclopropane-1-carboxylic acid deaminase, indole acetic acid, siderophores, and P solubilizing activity	**[127]**

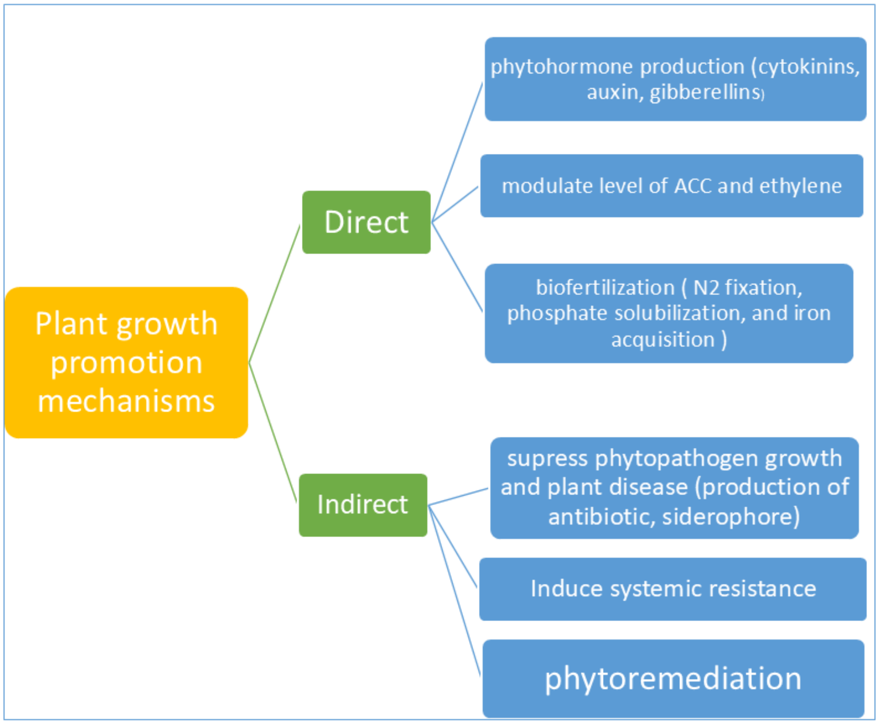

Fig. 2. Direct and indirect mechanisms of plant growth promotion

9.2.2. Direct Mechanism

9.2.2.1. Phytohormones production

Phytohormones are organic substances or plant growth regulators, which enhance plant growth and development at low concentrations **[32]**. For agricultural purposes, phytohormones are chemically manufactured, extracted from plant sources, or generated through microbial fermentation. The main phytohormones synthesized by bacterial endophytes are auxins, gibberellins, cytokinins, ethylene, abscisic acid, strigolactones, brassinosteroids, jasmonates, and indole-3- acetic acid (IAA). **[41]**. Indole-3- acetic acid (IAA) is widely recognized as an essential growth regulator molecule generated by endophytic bacteria, which play a role in increasing root surface area and providing soil nutrients to plants **[31, 39]**. It is capable of developing the gene regulation process as well as cell expansion, division, and differentiation **[46]**. Gibberellins regulate plant growth and development by delaying plant aging, increasing seed germination, and promoting stem, leaf, flower, and fruit growth and development [**96]**. Cytokinin regulates cell division and differentiation, stimulates axillary bud growth, and enhances resistance to biotic and abiotic stress **[97]**. Another phytohormone produced by endophytic bacteria is the 1-aminocyclopropane-1-carboxylate (ACC) deaminase enzyme, which belongs to a group of auxins. This enzyme hydrolyzes ACC into α-ketobutyrate and ammonia. Lowering the level of ACC in soil results in the reduction of ethylene level **[83],** therefore enhancing plant growth by minimizing the abiotic stress caused by the imbalance in plant ethylene-level production. Elevated amount of ethylene levels inhibits DNA synthesis and cell division **[32]**. Moreover, the plant could use the ammonia and energy released during ACC breakdown for growth [**98]**.

9.2.2.2. Biofertilization

9.2.2.2.1. Nitrogen fixation

Biofertilization occurs due to nitrogen fixation, which involves the conversion of atmospheric nitrogen N_2 into useful forms of nitrogen such as ammonia, ammonium, and nitrate **[31],** to enhance the biomass and length of host plants, especially in environments with high salinity**.** While chemical pesticides have been the objects of real criticism, especially due to their adverse effects on human health and the environment **[83],** the recognition and realization of the beneficial use of biological pesticides increased.

9.2.2.2.2. Phosphate solubilization

Phosphorous (P) is a vital element that helps in root development, glucose transport, and other physiological functions **[91]**. About 90-95% of soil phosphorus is present in precipitated or insoluble forms **[92]**, making it difficult for plants to absorb. In this case, the phosphorus deficit can be balanced using organic or chemical phosphate fertilizers **[93]**. Bacterial endophytes boost phosphorus availability in plants by dissolving insoluble phosphate through acidification, ion exchange, chelation (i.e., PO_4^{3-}), and organic acid secretion, such as citric acid, glycolic, acetic, tartaric, malonic, or fumaric acid, or phosphate solubilizing enzymes such as phosphatase, C—P lyase, and phytase enzymes **[103]**. Furthermore, the secretion of exopolysaccharides by bacterial endophytes breaks down phosphate-containing substances **[36]**.

9.2.2.2.3. Siderophore production

The majority of soil iron is insoluble, which makes it difficult for plants to absorb. This results in an iron deficiency for plant uptake. Endophytic bacteria create a siderophore, which has a propensity for binding to iron and forming a siderophore -Fe^{3+} complex, making it available to plants **[95]**.

9.2.3. Indirect Mechanism

9.2.3.1. Biocontrol

Endophytes can prevent pathogen penetration into plants through both direct and indirect methods. The direct method explains a competition between phytopathogens and bacterial endophytes in which endophytic bacteria produce inhibitory molecules such as 2,4-diacetyl phloroglucinol (DAPG), rhamnolipids, phenazine-1-carboxamide, viscosinamide, neomycin, pyroluteorine, pyrrolidine, neomycin, butyroaminectone, and cepafungins to suppress pathogen growth **[27, 101]**. In the indirect method, endophytic bacteria can regulate the host plant's genetic expression, affecting the plant’s physiological responses and defensive mechanism by inducing systemic resistance **[99]**, increasing its resistance to phytopathogens. Furthermore, endophytic bacteria produce biocidal substances known as siderophores such as chelate iron which provides enough amount of iron to endophytes and host plants but not to pathogens, which restricts the growth of pathogens by limiting mycelial growth and spore germination **[99, 45]**. Salicylic acid and Jasmonic acid have been reported as Siderophores produced by endophytic bacteria. These play critical roles in inducing systemic resistance of plants that stimulate local and systemic defensive responses against pathogens attacks **[100]**. **S**ome endophytes produced Gibberellin to enhance the resistance against the attack of insects and phytopathogens **[88]**.

Endophytic bacteria serve as effective bio-control agents as they colonize an ecological niche similar to phytopathogens **[68]** and have a close relationship with the plant, resulting in limiting pathogen entrance into the host cells and reliable prevention of vascular diseases in plants **[90]**, thereby minimizing pesticide use.

Numerous research reported that endophytic microorganisms have been shown to control plant pathogens, insects, nematodes, and fungal pathogens such as the inhibitory effect of *B. pumilus SE34* on *Fusarium oxysporum* on roots of black pepper **[81]**.

9.2.3.2. Phytoremediation

Phytoremediation is the utilization of plants and their accompanying microbes to remediate a site. Plants and their associated bacteria endophytes interact in complex and varied ways, which have been extensively researched and exploited to promote soil fertility, plant growth, and phytoremediation of polluted water and soil **[131]**. Trace elements (TEs) which include diverse metals such as arsenic, chromium, mercury, cadmium, nickel, zinc, lead, and copper are the main inorganic soil and water contaminants; which become hazardous to health at high quantities. Many efforts have been undertaken to develop soil and water remediation technologies that employ thermal, or physicochemical strategies. The common feature of such strategies is their high expense, especially when applied across wide areas **[133]**. Hence, phytoremediation which is based on plants and their associated bacterial endophytes is an environmentally acceptable and cost-effective approach but requires long-term supervision **[134]**. Using endophytic bacteria with plant growth-promoting activity may help plants adapt and develop in contaminated soil [**136]**. According to Shehzadi et al.[**137]**, utilizing bacterial endophytes in pollutant-degrading pathways produces metabolic activities that aid in lowering both phytotoxicity and evapotranspiration of volatile organic molecules.

Furthermore, plant-endophyte collaborations can also be utilized to purify (ground) water polluted with organic substances **[135]**. Bacterial endophytes are more effective at eliminating toxins than plants, as plants do not fully break down pollutants, leaving hazardous decomposition products. Recently, several endophytic bacteria were isolated from diverse plants, and a number of them displayed pollutant-degrading and plant growth-promoting properties **[104]**.

9.3. Nanobiotechnology

Nanotechnology is an interdisciplinary scientific field that involves biology, chemistry, physics, and bioengineering to create novel molecules termed nanoparticles (NPs) with sizes smaller than 100 nm [**138]**. Nanoparticles have a wide range of technical and industrial uses, including medicine, agriculture, environmental waste treatment, disinfection, cosmetics, electronics, energy, and biotechnology **[139]**. Biological approaches for nanoparticle production (Nanobiotechnology) have numerous benefits over physical and chemical processes, including the absence of significant energy requirements and the absence of toxic waste, making them easy, and cost-effective **[139]**. Currently, metal nanoparticles have significant potential for fighting multi-drug resistance. Nanoparticles provide numerous advantages over traditional antibiotics, including higher stability, higher accuracy in infected tissues, more solubility, extended antibiotic activity duration, greater capacity to penetrate epithelial barriers, and reduced risk of adverse effects **[140]**. Utilizing bacterial endophytes in metal nanoparticle biosynthesis is an example of nanobiotechnology. Endophytic bacteria cause a reduction in metallic ions for metal nanoparticle production **[141]**. Nanosilver particles (AgNPs) synthesized by *Pantoea ananatis* exhibited antimicrobial activity against multidrug-resistant pathogens **[89].** Examples of endophytic bacteria-mediated nanoparticle biosynthesis and their biological activities are shown in **Table 3**.

Table 3. Examples of endophytic bacteria-mediated nanoparticle biosynthesis and their biological activities

Endophytic bacteria	Host plant	nanoparticles	Biological activity	References
Bacillus cereus	*Garcinia xanthochymus*	Ag-NPs	Antibacterial	**[107]**
Streptomyces laurentii	*A. fragrantissima*	Ag-NPs	Antibacterial and Anticancer	**[112]**
Actinomycete	Marine	CuO NPs	antibacterial and anticancer (lung cancer)	**[111]**
Brevibacillus brevis PI-5	*Pulicaria incisa*	CuO-NPs	antifungal and anticancer (breast cancer cell lines (T47D)), larvicidal activity	**[110]**
Bacillus zanthoxyli GBE11	*Ginkgo biloba*	AgNPs	Antibacterial	**[109]**
Streptomyces coelicolor	*Ocimum sanctum*	MgO	Active against multidrug-resistant microbes	**[132]**
Pseudomonas fluorescens 417	*Coffea arabica*	Au	Antibacterial	**[132]**

Conclusion and prospects

With the rise of multi-drug-resistant pathogens, as well as the emergence of novel viruses and bacteria, there is a significant interest in discovering novel sources of bioactive compounds with high efficacy, minimal side effects, and cheap cost. Nowadays, researchers emphasize studying the natural biological substances and the processes of extraction of these products from the plants, then utilize them for the creation of innovative active medications with greater safety than the old synthetic medications. Endophytic bacteria's unique ability to synthesize bioactive compounds, whether alone or alongside plants is becoming more widely recognized. Understanding how endophytes affect plant physiology, growth, metabolism, and development, and how they utilize the primary and secondary metabolites as nutrition and as precursors of new compounds are still largely studied.

Endophytic bacteria are an alternative biological tool that is effective and useful in the pharmaceutical and medicinal industries. They can also be used to promote plant growth and as natural biocontrol agents, which makes them a viable option for organic farming. Endophytic bacteria can be utilized in Nano biotechnology field for the synthesis of novel antimicrobial agents to fight multi-drug resistance situations.

List of abbreviations

Multi-drug resistance (MDR); World health organization (WHO); infection prevention and control (IPC); Plant-growth-promoting bacterial endophytes (PGPBEs); Indole-3- acetic acid (IAA); 2,4-diacetyl phloroglucinol (DAPG); Trace elements: (TEs); 1-aminocyclopropane-1-carboxylate (ACC); nanoparticles (NPs).

Declarations

Ethics Approval and Consent to Participate

Not applicable

Consent to Publish

Not applicable.

Availability of Data and Materials

All data generated and analyzed in this study are included in the main published article and this manuscript.

Competing Interests

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