

REVIEW ON:ENDOPHYTIC BACTERIA AS A SOURCE OF DRUGS AGAINST VARIOUS DISEASES

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Abstract :

Beneficial microorganisms called endophytic bacteria live inside plant tissues and are a promising source of natural products with biological activity. With antibacterial, antifungal, antiviral, anticancer, antioxidant, anti-inflammatory, antidiabetic, and neuroprotective properties, they generate structurally varied secondary metabolites. Novel bioactive compounds have been found more quickly thanks to recent developments in genome mining, metagenomics, metabolomics, synthetic biology, and bioinformatics. Additionally, they provide sustainable substitutes for direct extraction from medicinal plants by using microbial fermentation to produce valuable metabolites. Endophytic bacteria have great potential for the creation of innovative treatments for a range of illnesses, despite difficulties with cultivation, metabolite yield, safety assessment, and clinical validation.

Key words :-

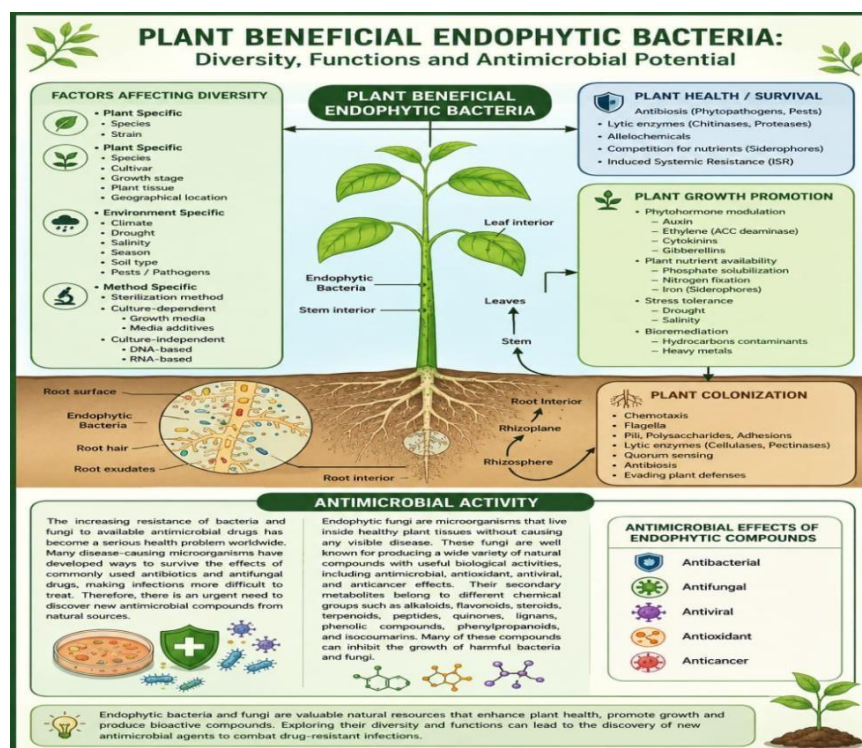
Endophytic bacteria , natural products , secondary metabolites , bioactive compounds , anti microbial activity , genome mining , metabolomics , fermentation , novel therapeutics , sustainable production.

Introduction :

Microorganisms referred as endophytic bacteria reside in the internal structures of healthy plants and form beneficial bonds living in their host without causing disease. In practically every kind of plant, they colonize the various plant parts including roots ,stems ,leaves ,flowers, fruits ,and seeds. These bacteria are essential for increasing plant growth, facilitating nutrient uptake, enhancing stress tolerance, and protecting plants from pathogens by producing a range of bioactive metabolites. Recently, endophytic bacteria have attracted a lot of interest as a valuable source of natural products with substantial pharmaceutical potential. Natural products have historically played a major role in drug discovery, many clinically important drugs are derived from microorganisms and plants. However, the rapid emergence of antimicrobial resistance and the increasing prevalence of diabetes, cancer, inflammatory diseases, and other chronic illnesses necessitate the development of novel therapeutic agents. Endophytic bacteria have emerged as appealing candidates due to their production of structurally diverse secondary metabolites such as alkaloids, polyketides, non-ribosomal peptides, terpenoids, lipopeptides, phenolic compounds, and volatile organic compounds. These metabolites display a wide range of biological activities, including antibacterial, antifungal, antiviral, anticancer, antioxidant, anti-inflammatory, antidiabetic, and immunomodulatory effects. A unique ecological niche that fosters the synthesis of novel bioactive compounds is created by the close relationship

between endophytic bacteria and medicinal plants. Among the bacterial genera that have shown exceptional potential for producing metabolites with therapeutic value are *Bacillus*, *Pseudomonas*, *Streptomyces*, *Paenibacillus*, *Burkholderia*, *Enterobacter*, and *Microbacterium*. Advances in genome sequencing, metagenomics, metabolomics, and bioinformatics have accelerated the identification of biosynthetic gene clusters responsible for these compounds, increasing opportunities for new drug discovery. In addition to being helpful in the pharmaceutical industry, endophytic bacteria promote sustainable biotechnology by providing renewable and environmentally friendly sources of bioactive compounds. Unlike direct extraction from medicinal plants, bacterial fermentation enables the large-scale production of beneficial metabolites while lessening the burden on natural plant resources. Advances in synthetic biology, metabolic engineering, and AI-assisted genome mining have further enhanced the capacity to identify, optimize, and commercialize compounds derived from endophytes for therapeutic use. Despite significant advancements, problems persist, including the requirement for extensive pharmacological, toxicological, and clinical testing before commercialization, uneven metabolite production in laboratory settings, and difficulties in growing a variety of endophytic bacteria. Research continues to uncover the enormous potential of endophytic bacteria as a rich source of novel bioactive compounds to combat cancer, metabolic disorders, inflammatory conditions, infectious diseases, and other serious health issues, for various diseases. Recent advancements in drug discovery, current challenges, and possible future.

FIG:



2. Historical Background :

2.1 The Early Identification of Plant Endophytes:

In the late 19th century, German scientist Heinrich Friedrich Link coined the term "endophytes" to refer to microorganisms that live inside plant tissues. The classical definition of endophytes was established in 1866 by the famous botanist Anton de Bary, who defined them as organisms that live inside plants but do not exhibit outward signs of disease. Due to their ease of microscopic observation, fungal endophytes were the primary focus

of early research. The challenges of isolating and identifying bacterial endophytes have limited research on these microorganisms.

Researchers were able to separate bacterial endophytes from healthy plants during the 20th century thanks to developments in microbiology and plant pathology. It became evident that these bacteria form advantageous relationships by colonizing a variety of plant parts, including roots, stems, leaves, flowers, fruits, and seeds. Bacterial endophytes fix nitrogen, solubilize phosphate, produce phytohormones, and shield plants from pathogens, according to early research.

2.2 Research Focus Shifts from Agriculture to Medicine :

Agricultural applications were the main focus of bacterial endophyte research for many years. Researchers investigated their potential applications as biological control agents, plant growth promoters, and environmentally friendly substitutes for chemical pesticides and fertilizers.

Through antimicrobial compounds, endophytic bacteria have been shown to improve nutrient uptake, increase resistance to drought, salinity, and heavy metals, and suppress plant diseases.

Research has shifted toward medical applications since it was found that endophytes produce a large number of bioactive compounds that are either identical to or similar to those produced by their host plants. Researchers started looking at endophytic bacteria as potential sources of pharmaceuticals as the need for new medications to combat inflammation, cancer, diabetes, and antimicrobial resistance grew. The discovery of gene clusters producing useful secondary metabolites was expedited by developments in molecular biology, genome sequencing, metabolomics, and bioinformatics, establishing endophytes as a critical field in natural product chemistry and drug development.

2.3 Important Turning Points in Endophyte-Based Drug Discovery :

When the anticancer medication taxol (paclitaxel) was isolated from the fungal endophyte *Taxomyces andreanae* in 1993, it was a historic finding that demonstrated endophytes could produce important metabolites that were previously believed to be unique to plants. Global interest in endophytes as sustainable substitute sources of bioactive compounds was spurred by this discovery.

Many bacterial endophytes that produce antibiotics, anticancer agents, antioxidants, anti-inflammatory compounds, antiviral metabolites, and enzyme inhibitors were found in later studies. Many therapeutically useful secondary metabolites have been reported to be produced by species from genera like *Streptomyces*, *Bacillus*, *Pseudomonas*, *Burkholderia*, and *Paenibacillus*. Since 2020, advances in synthetic biology, genome mining, metagenomics, metabolomics, and next-generation sequencing have sped up the identification of new natural products and biosynthetic pathways. The importance of endophytic bacteria as potential sources of novel medications for infectious diseases, cancer, metabolic disorders, and chronic illnesses has been emphasized by these technological developments.

Endophytic bacteria are now acknowledged as important microbial resources for long-term drug development. When paired with contemporary biotechnological techniques, their capacity to generate structurally varied bioactive molecules presents new prospects for the development of safe, efficient, and ecologically friendly treatments.

3. Diversity And Ecology :

3.1 Taxonomic Groups Commonly Found in Endophytic Bacteria :

Proteobacteria, Actinobacteria, Firmicutes (Bacillota), and Bacteroidota are the four main phyla of endophytic bacteria. Plant species, tissue type, geographic location, soil conditions, and environmental factors all affect their diversity.

Actinobacteria are significant producers of pharmaceutically valuable secondary metabolites. Antibiotics, anticancer, antifungal, antioxidant, and immunosuppressive compounds are produced by genera like Streptomyces, Micromonospora, Microbacterium, and Nocardia. Particularly well-known for its abundance of bioactive natural products is Streptomyces.

Pseudomonas, Enterobacter, Burkholderia, Rhizobium, and Sphingomonas are examples of proteobacteria. By fixing nitrogen, solubilizing phosphate, producing phytohormones, and controlling pathogens, these bacteria aid in the growth of plants. Antimicrobial, antiviral, and anticancer metabolites are also produced by a number of species.

Bacillus and Paenibacillus are the two main members of the firmicutes (Bacillota). They generate volatile compounds with antibacterial, antifungal, antioxidant, and anti-inflammatory properties as well as lipopeptides, bacteriocins, and enzymes. Their capacity to form endospores improves their ability to survive in hostile environments.

Flavobacterium and Chryseobacterium are examples of Bacteroidota, which are involved in nutrient cycling, organic matter degradation, stress tolerance, and antimicrobial activity.

Pantoea, Serratia, Arthrobacter, Acinetobacter, and Methylobacterium are other common endophytes that also generate useful bioactive metabolites. All things considered, endophytic bacteria are a valuable resource for biotechnology, sustainable agriculture, and the development of novel medicinal drugs due to their extraordinary taxonomic diversity. This version fits about 20 lines in a standard review article format, is succinct, and keeps the main points.

3.2 Environmental Factors and Host Plant Associations Affecting Endophytic Bacterial Diversity :

Environmental factors and the host plant have a significant impact on endophytic bacterial diversity. With particular nutrients, metabolites, and defense compounds that mold its microbial community, every plant species offers a distinct ecological niche. The makeup and quantity of endophytic bacteria are determined by a number of factors, including plant genotype, age, tissue type, and physiological state. By generating phytohormones, fixing nitrogen, solubilizing phosphate, creating siderophores, and shielding plants from infections, these bacteria develop a mutualistic relationship with plants. Because of their intimate relationship to the rhizosphere, roots typically have the highest bacterial diversity.

Endophytic bacterial communities are also influenced by environmental factors such as soil type, pH, nutrient availability, moisture, temperature, altitude, humidity, and seasonal variations. Specialized endophytes that can produce distinct bioactive metabolites are frequently found in plants growing in stressful environments. Bacterial diversity is also impacted by agricultural practices like pesticide application, fertilizer use, and irrigation. The understanding of these plant-microbe interactions has significantly improved thanks to contemporary methods like metagenomics, next-generation sequencing, and multi-omics. Finding beneficial endophytic bacteria and expanding their uses in biotechnology, sustainable agriculture, and drug development require an understanding of host plant associations and environmental factors.

3.3 Metabolic Exchange and Symbiotic Relationships with Host Plants :

Endophytic bacteria establish mutualistic relationships with host plants by colonizing internal tissues without causing disease. Plants provide a protected habitat and nutrients, while bacteria enhance plant growth, stress tolerance, and disease resistance. These bacteria enter through roots, stomata, lenticels, wounds, or other natural openings and colonize intercellular spaces or vascular tissues.

Endophytic bacteria promote plant growth by fixing nitrogen, solubilizing phosphate, producing siderophores for iron

uptake, and synthesizing phytohormones such as indole-3-acetic acid (IAA), gibberellins, and cytokinins. They also produce ACC deaminase, which lowers ethylene levels and helps plants tolerate drought, salinity, and heavy metal stress.

Plants supply carbohydrates, amino acids, organic acids, vitamins, and phenolic compounds that support bacterial growth. In return, endophytes produce antimicrobial peptides, lipopeptides, enzymes, antioxidants, and volatile organic compounds (VOCs) that improve plant defense and induce systemic resistance against pathogens.

Many endophytic bacteria synthesize bioactive metabolites such as alkaloids, terpenoids, polyketides, non-ribosomal peptides, and phenolic compounds with antibacterial, antifungal, antiviral, anticancer, antioxidant, and anti-inflammatory activities. These metabolites are often similar to those produced by medicinal plants, reflecting long-term co-evolution.

Recent advances in genomics, transcriptomics, metabolomics, and other multi-omics approaches have identified biosynthetic gene clusters responsible for these compounds. Overall, the symbiotic relationship and metabolic exchange between endophytic bacteria and plants play a vital role in plant health and provide valuable resources for biotechnology, sustainable agriculture, and drug discovery.

4. Bio Active Compounds :

4.1 Antibiotics :

Because endophytic bacteria can produce structurally diverse secondary metabolites with broad-spectrum antimicrobial activity, they are acknowledged as a significant source of novel antibiotics. By producing substances that stop harmful microorganisms from growing, these bacteria help the host plant fend off microbial infections. Among the most common genera that produce antibiotic compounds are *Streptomyces*, *Bacillus*, *Pseudomonas*, *Burkholderia*, and *Paenibacillus*. Polyketides, lipopeptides, non-ribosomal peptides, bacteriocins, and other antimicrobial compounds that work against both Gram-positive and Gram-negative bacteria are among their metabolites. Methicillin-resistant *Staphylococcus aureus* (MRSA), *Escherichia coli*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae* are among the multidrug-resistant pathogens that many of these substances effectively combat. The bacterial cell wall and membrane are disrupted, protein and nucleic acid synthesis is inhibited, quorum sensing is interfered with, and biofilm formation is prevented as part of the antibacterial mechanisms. The discovery of new antibiotics has been made easier by recent developments in genome mining, metabolomics, and synthetic biology, which have uncovered many mysterious biosynthetic gene clusters in endophytic bacteria. Endophytic bacteria are thought to be promising resources for creating next-generation antibiotics to fight antimicrobial resistance and emerging infectious diseases because of their distinctive chemical diversity and sustainable production through microbial fermentation.

4.2 Antioxidant Compounds :

Endophytic bacteria are significant producers of antioxidant compounds that shield cells from oxidative stress brought on by free radicals and reactive oxygen species (ROS). These microbes produce peptides, exopolysaccharides, flavonoids, carotenoids, phenolic compounds, and antioxidant enzymes like superoxide dismutase and catalase. Chronic conditions like cancer, diabetes, heart disease, and neurological disorders are all influenced by oxidative stress. As a result, endophytic bacteria's antioxidant metabolites have garnered a lot of interest for use in medicine. Because endophytic bacteria are closely linked to the secondary metabolism of plants, they frequently have higher antioxidant activity when isolated from medicinal plants. These metabolites preserve cellular redox balance, neutralize free radicals, prevent lipid peroxidation, and shield DNA from oxidative damage. Numerous new antioxidant compounds with potential uses in drug development and nutraceuticals have been discovered by recent metabolomic studies. The development of natural antioxidant-based medicines is aided by the capacity to generate these compounds through microbial fermentation, which offers a sustainable

substitute for plant extraction.

4.3 Neuroprotective Compounds :

Endophytic bacteria produce several bioactive metabolites with neuroprotective properties that may help prevent or slow the progression of neurodegenerative diseases. These compounds reduce oxidative stress, suppress neuroinflammation, regulate neurotransmitter activity, and inhibit neuronal apoptosis. Secondary metabolites such as phenolics, alkaloids, terpenoids, and peptides have demonstrated protective effects against neuronal damage in experimental studies. Endophytic bacterial metabolites also inhibit the accumulation of toxic protein aggregates associated with Alzheimer's disease and Parkinson's disease while improving mitochondrial function and reducing inflammatory cytokines. Their antioxidant activity further contributes to neuronal survival by limiting ROS-mediated cellular injury. Recent advances in metabolomics and genome mining have accelerated the identification of neuroactive compounds from endophytic microorganisms, highlighting their potential as future therapeutic agents for neurological disorders.

4.4 Anticancer Compounds :

Because endophytic bacteria produce structurally diverse secondary metabolites with strong cytotoxic activity against a variety of cancer cell lines, they are promising sources of anticancer compounds. Alkaloids, polyketides, peptides, terpenoids, quinones, and lipopeptides are significant metabolites. By triggering apoptosis, stopping the cell cycle, inhibiting angiogenesis, and stopping metastasis, these substances stop the growth of tumors. Additionally, some metabolites control signaling pathways like PI3K/Akt, MAPK, and NF- κ B, which prevents the growth of cancer cells. Endophytic bacteria linked to medicinal plants often generate metabolites that resemble those produced by their host plants, providing sustainable substitutes for the synthesis of anticancer drugs. The discovery of new anticancer compounds has been expedited by recent genome mining and synthetic biology techniques, making endophytic bacteria important resources for oncology drug development in the future.

4.5 Antifungal Compounds

In addition to producing a variety of antifungal metabolites that shield host plants from fungal pathogens, endophytic bacteria may be used therapeutically to treat fungal infections in humans. These metabolites include hydrolytic enzymes, antimicrobial peptides, volatile organic compounds, lipopeptides, and bacteriocins. Compounds that can prevent spore germination, disrupt membrane integrity, and inhibit the synthesis of fungal cell walls are produced by species of *Bacillus*, *Pseudomonas*, and *Streptomyces*. *Aspergillus*, *Fusarium*, *Candida*, and other clinically important fungi have been shown to be susceptible to their metabolites. Endophytic bacteria have become important sources of new antifungal agents with distinct mechanisms of action due to the rising incidence of antifungal resistance. The biosynthetic pathways responsible for the production of antifungal metabolites are still being uncovered by modern genomic technologies.

4.6 Anti-inflammatory Compounds :

Bioactive metabolites produced by endophytic bacteria have strong anti-inflammatory qualities that control immune responses and lessen tissue damage brought on by excessive inflammation. These substances suppress inflammatory signaling pathways like NF- κ B and cyclooxygenase (COX) and prevent the synthesis of pro-inflammatory cytokines like TNF- α , IL-1 β , and IL-6. Numerous bacterial metabolites also prevent chronic inflammatory disorders by lowering oxidative stress and nitric oxide production. Because of these functions,

endophytic bacteria are attractive options for creating treatments for inflammatory diseases like asthma, inflammatory bowel disease, and arthritis. Numerous new anti-inflammatory substances with enhanced therapeutic potential have been found thanks to developments in metabolomics.

4.7 Antiviral Compounds:

It is becoming more widely acknowledged that endophytic bacteria are sources of antiviral metabolites that can prevent viral infection in a number of ways. These substances increase host antiviral immunity while interfering with viral attachment, replication, protein synthesis, and genome transcription. Numerous metabolites have demonstrated efficacy against hepatitis viruses, influenza viruses, herpes simplex viruses, and other medically significant viruses. Endophyte-derived metabolites' structural diversity offers chances to find antiviral drugs with unique modes of action that could get past drug resistance. The development of antiviral drugs from endophytic bacteria is still being accelerated by recent developments in high-throughput screening and genome mining.

4.8 Immunomodulatory Compounds:

Numerous metabolites produced by endophytic bacteria control both innate and adaptive immune responses. These include phenolic compounds, peptides, lipopeptides, and polysaccharides that activate lymphocytes, natural killer cells, dendritic cells, and macrophages. Their metabolites enhance immune homeostasis, lessen excessive inflammation, and regulate cytokine production. These immunomodulatory actions may be used in the development of vaccines, autoimmune disorders, infectious diseases, and cancer immunotherapy. Metabolomics and genome-guided methods are being used in ongoing research to find novel immunologically active compounds from endophytic bacteria.

4.9 Cardioprotective Compounds :

Endophytic bacteria also produce metabolites with cardioprotective properties that help maintain cardiovascular health by reducing oxidative stress, inflammation, and lipid peroxidation. These bioactive compounds improve endothelial function, decrease reactive oxygen species, regulate lipid metabolism, and protect cardiac tissues from ischemic injury. Their antioxidant and anti-inflammatory activities contribute to the prevention of atherosclerosis, hypertension, myocardial infarction, and other cardiovascular diseases. Recent investigations suggest that endophyte-derived metabolites may serve as promising lead compounds for developing safer and more effective cardioprotective drugs. Continued research using metabolomics and synthetic biology is expected to identify additional compounds with therapeutic potential.

5. Therapeutic Applications :

5.1 Anti bacterial activity :

An important global health concern is antimicrobial resistance (AMR), which raises rates of disease, mortality, and medical costs. Because endophytic bacteria produce a variety of secondary metabolites with unique modes of action, they have drawn interest as a promising source of novel antibacterial agents. These bacteria live in healthy plant tissues and produce bioactive compounds that protect their host plants from pathogenic microorganisms. *Bacillus*, *Streptomyces*, *Pseudomonas*, *Paenibacillus*, and *Burkholderia* are important genera of these endophytes. They produce non-ribosomal peptides as well as lipopeptides, polyketides, alkaloids, bacteriocins, and phenazines. Multidrug-resistant (MDR) pathogens such as MRSA, VRE, *Pseudomonas*

aeruginosa, *Acinetobacter baumannii*, *Klebsiella pneumoniae*, and ESBL-producing *Escherichia coli* are effectively combated by these metabolites. Disrupting bacterial cell membranes, preventing peptidoglycan synthesis, interfering with the synthesis of proteins and nucleic acids, inhibiting DNA gyrase and RNA polymerase, preventing biofilm formation, suppressing quorum sensing, and capturing iron through siderophore production are some of the mechanisms by which their antibacterial actions operate. Additionally, some metabolites cause oxidative stress, which destroys bacterial cells. The likelihood of developing resistance is reduced when several antibacterial pathways are combined. Numerous biosynthetic gene clusters responsible for the production of novel antibiotics have been identified thanks to developments in metabolomics and genome mining. In order to effectively combat antimicrobial resistance, endophytic bacteria are regarded as an essential source for the discovery and development of the upcoming generation of antibacterial medications.

5.2 Antifungal action:

An important source of naturally occurring antifungal agents with potential uses in agriculture and medicine is endophytic bacteria. Numerous bioactive substances, including lipopeptides, polyketides, phenazines, siderophores, volatile organic compounds (VOCs), and enzymes that degrade cell components, are produced by these bacteria and effectively inhibit fungal pathogens. Antifungal endophytes are commonly found in the genera *Bacillus*, *Pseudomonas*, *Streptomyces*, *Burkholderia*, and *Paenibacillus*. They have antifungal qualities against medically significant fungi like *Candida albicans*, *Aspergillus fumigatus*, and *Cryptococcus neoformans*, as well as plant pathogens like *Fusarium oxysporum*, *Rhizoctonia solani*, and *Botrytis cinerea*. Fungal cell membrane integrity is compromised, fungal cell walls are broken down by enzymes like chitinase and β -1,3-glucanase, fungal mycelium growth is inhibited, spore germination is prevented, and biofilm formation is stopped, among other antifungal mechanisms. By denying fungi access to iron, these bacteria create siderophores that limit fungal growth and pathogenicity. Furthermore, certain metabolites induce programmed cell death, which is similar to fungal cell apoptosis, and oxidative stress. By initiating plant defense mechanisms through induced systemic resistance (ISR), endophytic bacteria can offer long-lasting protection against fungal infections in addition to their direct antifungal effects. Because of their widespread effectiveness, environmental friendliness, and lower risk of resistance development, endophytic bacterial metabolites are regarded as promising substitutes for synthetic antifungal medications with significant potential for use in pharmaceutical and agricultural applications.

5.3 Antiviral activity :

Because endophytic bacteria produce a variety of secondary metabolites with broad antiviral properties, they are a valuable source of antiviral agents. These microbes produce bioactive substances that can stop many viruses from replicating, such as peptides, alkaloids, polyketides, phenolics, exopolysaccharides, and volatile organic molecules. According to research, these bacteria's metabolites are effective against viruses like the human immunodeficiency virus (HIV), dengue virus, influenza virus, hepatitis B and C virus (HBV, HCV), and herpes simplex virus (HSV). These substances have antiviral properties that include inhibiting viral attachment and entry into host cells, stopping viral genome replication, stopping viral protein synthesis, hindering viral assembly and release, and modifying the host's immune response. In order to prevent viral replication, some of these metabolites specifically target viral enzymes such as RNA-dependent RNA polymerase, protease, and reverse transcriptase. Additionally, their anti-inflammatory and antioxidant properties lessen the harm that viral infections do to cells. By boosting interferon production and stimulating immune cells, endophytic bacteria also improve innate and adaptive immunity, strengthening antiviral defenses even more. They are excellent candidates for creating novel antiviral medications because of their distinct chemical diversity and low toxicity. Endophytic bacteria are anticipated to be crucial in the development of new antiviral therapies, particularly for newly emerging and drug-resistant viral infections, as genomics, metabolomics, and biotechnology continue to advance.

5.4 Anti cancer activity :

Endophytic bacteria have garnered significant interest as a rich source of novel anticancer compounds due to their ability to produce a range of bioactive secondary metabolites. These metabolites, which include polyketides, peptides, alkaloids, phenazines, exopolysaccharides, terpenoids, and enzyme inhibitors, have potent cytotoxic effects on cancer cells. Endophytic bacteria belonging to the genera *Streptomyces*, *Bacillus*, *Pseudomonas*, *Micromonospora*, and *Burkholderia* have shown significant anticancer potential. Their metabolites exhibit activity against a variety of cancers, including breast, lung, colon, liver, cervical, prostate, and leukemia. Among the anticancer mechanisms are apoptosis (programmed cell death), cell cycle arrest, angiogenesis inhibition, tumor cell proliferation suppression, metastasis prevention, and modulation of signaling pathways such as PI3K/Akt, MAPK, and NF- κ B. Furthermore, certain metabolites increase intracellular reactive oxygen species (ROS), which results in oxidative stress and specifically kills cancer cells while posing minimal risk to healthy cells. Furthermore, some endophytic bacterial compounds enhance the effectiveness of conventional chemotherapy by helping tumor cells overcome multidrug resistance. New anticancer metabolites from endophytic bacteria have been found more quickly thanks to developments in synthetic biology, metabolomics, and genome mining. Therefore, these microorganisms provide a viable and sustainable source for the development of safer and more effective anticancer drugs.

5.5 Anti diabetic activity :

Endophytic Bacteria's Antidiabetic Properties Endophytic bacteria are increasingly acknowledged as a significant source of bioactive substances with potent anti-diabetic properties. These bacteria generate secondary metabolites that support metabolic health and help control blood glucose levels, including phenolic compounds, flavonoids, alkaloids, peptides, polysaccharides, and terpenoids. Endophytic bacteria from genera like *Bacillus*, *Streptomyces*, *Pseudomonas*, and *Enterobacter* have demonstrated promising antidiabetic properties in experimental investigations. Their metabolites function by blocking the enzymes that break down carbohydrates, such as α -amylase and α -glucosidase. This reduces the intestinal absorption of glucose and improves the regulation of blood sugar spikes after meals. Additionally, some of these substances increase insulin sensitivity, promote glucose uptake by bodily tissues, and stimulate insulin secretion from pancreatic β -cells. Furthermore, these bacteria produce antioxidant metabolites that lower oxidative stress and shield pancreatic β -cells from reactive oxygen species (ROS) damage. By lowering pro-inflammatory cytokines like TNF- α and IL-6, which are known to contribute to insulin resistance, they also have anti-inflammatory effects. Additionally, these bacterial metabolites help control lipid metabolism, lower hyperlipidemia, and enhance overall metabolic balance, all of which can lower the risk of diabetes-related complications. Metabolites from endophytic bacteria are considered promising candidates for the development of new antidiabetic drugs because of their low toxicity, natural origin, and capacity to target multiple pathways. To turn these discoveries into successful treatments, more metabolomics, genomics, and clinical trial research is necessary.

Anti inflammatory activity

Natural substances with potent anti-inflammatory qualities and significant therapeutic potential can be found in endophytic bacteria. Alkaloids, polyketides, peptides, phenolic compounds, flavonoids, and exopolysaccharides are among the many bioactive metabolites produced by these bacteria that have functions in controlling inflammation. In both lab and in vivo studies, genera such as *Bacillus*, *Streptomyces*, *Pseudomonas*, and *Burkholderia* have demonstrated notable anti-inflammatory effects. Pro-inflammatory cytokines like interleukin-1 β (IL-1 β), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF- α) are lowered by their metabolites.

Additionally, they block important inflammatory signaling pathways, such as mitogen-activated protein kinase (MAPK) and nuclear factor-kappa B (NF- κ B). These substances also inhibit the production of prostaglandins and nitric oxide by suppressing the enzymes cyclooxygenase (COX-2) and inducible nitric oxide synthase (iNOS). These bacterial metabolites' antioxidant properties also aid in reducing oxidative stress linked to persistent inflammation. These metabolites have the potential to treat inflammatory diseases like rheumatoid arthritis, inflammatory bowel disease, asthma, and cardiovascular disorders by controlling immune cell functions and limiting excessive inflammatory responses. Endophytic bacterial metabolites are promising candidates for the development of safer anti-inflammatory drugs due to their natural source, multiple modes of action, and reduced toxicity. Nevertheless, additional pharmacological and clinical studies are required to validate their therapeutic efficacy.

5.6 Anti oxidant activity :

It is well known that endophytic bacteria are a rich source of naturally occurring antioxidants that protect cells from oxidative stress and free radical damage. These microbes produce a variety of bioactive compounds with strong antioxidant properties, including phenolic compounds, flavonoids, carotenoids, alkaloids, peptides, polysaccharides, and exopolysaccharides. Endophytic bacteria belonging to the genera *Bacillus*, *Streptomyces*, *Pseudomonas*, *Enterobacter*, and *Paenibacillus* have demonstrated notable antioxidant activity. Their metabolites protect lipids, proteins, and DNA from oxidative damage by effectively scavenging reactive oxygen species (ROS) and reactive nitrogen species (RNS). Furthermore, they boost the activity of endogenous antioxidant enzymes like glutathione peroxidase (GPx), catalase (CAT), and superoxide dismutase (SOD), which are critical for maintaining cellular redox balance. Additionally, these compounds protect cell membranes from oxidative damage and reduce lipid peroxidation. These bacterial metabolites' antioxidant activity helps prevent neurodegenerative illnesses like Parkinson's and Alzheimer's disease as well as chronic diseases like cancer, diabetes, and cardiovascular problems. They also improve immunity and postpone cellular aging by lowering oxidative stress. Antioxidants derived from endophytic bacteria have garnered significant attention for pharmaceutical, nutraceutical, and biomedical applications because of their natural origin, high efficacy, and low toxicity. New antioxidant compounds with therapeutic potential are anticipated to be discovered through ongoing metabolomics and biotechnology research.

5.7 Neuroprotective :

It is becoming more widely acknowledged that endophytic bacteria are an important source of neuroprotective agents that can be used to prevent and treat neurodegenerative diseases. They produce a wide range of bioactive metabolites with significant neuroprotective effects, such as alkaloids, phenolic compounds, flavonoids, peptides, terpenoids, and exopolysaccharides. Neuronal cells can be shielded from oxidative stress and inflammation by bacteria belonging to genera like *Bacillus*, *Streptomyces*, *Pseudomonas*, and *Burkholderia*. Their metabolites prevent oxidative damage to neurons by lowering the generation of reactive oxygen species (ROS). Additionally, they prevent neuroinflammation by controlling the NF- κ B signaling pathway and inhibiting pro-inflammatory cytokines like TNF- α , IL-1 β , and IL-6. Acetylcholinesterase (AChE) is inhibited by some of these substances, which increases acetylcholine levels and improves cognitive function, particularly in Alzheimer's disease. These bacterial metabolites also aid in maintaining neurotransmitter balance, lowering neuronal apoptosis, and promoting mitochondrial function. Neurodegenerative diseases such as Alzheimer's, Parkinson's, Huntington's, and amyotrophic lateral sclerosis (ALS) may be slowed down by these actions. These metabolites are promising candidates for the creation of novel neuroprotective medications due to their anti-inflammatory, anti-apoptotic, and antioxidant characteristics. Endophytic bacteria are anticipated to produce novel therapeutic molecules for the

treatment of neurological disorders as metabolomics, genomics, and biotechnology continue to progress.

6. Bio Technological Approaches:

6.1. Genome Mining and Metagenomics :

Genome mining and metagenomics have revolutionized the search for bioactive compounds from endophytic bacteria by making it possible to identify novel biosynthetic gene clusters (BGCs) without exclusively depending on conventional culture-based methods. In order to identify the genes that produce secondary metabolites like polyketides (PKS), non-ribosomal peptides (NRPS), bacteriocins, terpenoids, and ribosomally synthesized and post-translationally modified peptides (RiPPs), genome mining entails the analysis of entire genome sequences. Additionally,

this technique reveals silent or cryptic gene clusters that are normally not expressed in a lab setting. By directly sequencing DNA taken from plant tissues, metagenomics enhances genome mining by enabling the study of endophytic microorganisms that are both culturable and unculturable. The prediction and annotation of biosynthetic pathways are made easier by the combination of bioinformatics tools such as antiSMASH, BAGEL, and PRISM with high-throughput sequencing technologies. These methods have expedited the discovery of new compounds produced by endophytic bacteria that have antibacterial, antifungal, antiviral, and anticancer properties. Furthermore, genome mining facilitates comparative genomics to identify distinct metabolic capacities among various endophytes. A thorough understanding of the biosynthesis and control of metabolites can be obtained by combining metagenomics with transcriptomics, proteomics, and metabolomics. As a result, genome mining and metagenomics have emerged as key biotechnological techniques in drug discovery, offering an effective way to investigate the enormous and hitherto unexplored biosynthetic potential of endophytic bacteria and hasten the creation of novel therapeutic agents.

6.2. Synthetic Biology for Pathway Engineering :

A potent technique to increase the synthesis and discovery of medicinal compounds derived from endophytic bacteria is synthetic biology. In order to increase the quantity and diversity of useful secondary metabolites, this strategy entails creating, modifying, and reconstructing microbial biosynthetic pathways. Genetic engineering techniques can be used to activate biosynthetic gene clusters (BGCs) that are either weakly expressed or silent in many endophytic bacteria. Modifying regulatory genes, optimizing precursor availability, and introducing heterologous biosynthetic pathways into appropriate microbial hosts like *Escherichia coli* and *Streptomyces* species are all made possible by pathway engineering. To boost metabolite production, cutting-edge techniques like CRISPR-Cas genome editing, promoter engineering, ribosome engineering, and metabolic pathway optimization are frequently used. Antibiotics, anticancer agents, immunomodulators, and other valuable natural products that are difficult to obtain through traditional fermentation processes have been made possible by synthetic biology. Novel derivatives with improved biological efficacy and decreased toxicity can be produced by reconstructing entire biosynthetic pathways. Combining genome mining, metabolomics, and synthetic biology provides an effective way to find previously unreachable natural products. As a result, pathway engineering is a particularly promising method for turning endophytic bacteria into microbial cell factories that are optimized for large-scale industrial production and sustainable drug discovery.

6.3. Fermentation Optimization and Scale up :

Strategies for fermentation optimization and scale-up are essential for the commercial production of bioactive

compounds derived from endophytic bacteria. Low metabolite yields frequently impede the industrial application of endophytic bacteria, despite the fact that many of them show considerable therapeutic potential. By adjusting fermentation parameters like temperature, pH, carbon and nitrogen sources, oxygen levels, agitation speed, incubation time, and precursor addition, it is possible to increase the production of secondary metabolites. To find the ideal growth conditions, statistical techniques like response surface methodology (RSM), design of experiments (DoE), and one-factor-at-a-time (OFAT) are commonly used. Submerged fermentation (SmF) and fed-batch fermentation are examples of advanced fermentation techniques that provide better control over microbial growth and metabolite output. Crucial elements like dissolved oxygen, nutrient supply, and metabolic regulation are closely watched throughout the scale-up process, from lab flasks to industrial bioreactors. Metabolic engineering and immobilized cell systems further improve productivity and culture stability. Fermentation techniques are combined with downstream procedures like extraction, purification, and formulation to produce high-quality bioactive compounds. Large-scale production of enzymes, antibiotics, anticancer drugs, and other medicinal compounds derived from endophytic bacteria is made possible by successful scale-up. Therefore, turning laboratory results into pharmaceutical products that can be sold commercially requires optimized fermentation technology.

6.4 Co culture Techniques to Activate silent Biosynthetic Gene Clusters :

In order to activate silent biosynthetic gene clusters (BGCs) in endophytic bacteria and aid in the discovery of novel bioactive compounds, co-culture techniques have emerged as a novel biotechnological approach. In their natural habitat, microorganisms use chemical communication to signal or compete with nearby species and control the synthesis of secondary metabolites. However, under typical laboratory conditions, a large number of biosynthetic pathways remain dormant. Researchers can mimic these natural ecological interactions by co-cultivating endophytic bacteria with other microbes, which causes previously silent genes to express themselves. Through mechanisms like nutrient competition, quorum sensing, and stress responses, this process promotes the production of antibiotics, antifungals, anticancer agents, and a variety of secondary metabolites. Numerous structurally diverse natural products have been discovered as a result of co-culture systems involving *Streptomyces*, *Bacillus*, *Pseudomonas*, and fungal endophytes. Newly activated metabolites can be found using sophisticated methods like mixed fermentation, microbial community engineering, and metabolomics-guided screening. Co-culture allows for a more thorough comprehension of the regulatory networks that govern BGC activation when paired with transcriptomic analysis and genome mining. This approach gets around the drawbacks of conventional monoculture fermentation and increases the chemical diversity of metabolites from endophytic bacteria. As a result, co-culture technology is a potent way to uncover latent biosynthetic potential and hasten the creation of new pharmaceutical compounds.

7. Challenges And Limitations :

7.1. Challenges in Growing Specific Endophytes :

The challenge of isolating and cultivating numerous endophyte species in lab settings is one of the main challenges in researching endophytic bacteria for therapeutic purposes. Due to their heavy reliance on the particular environment of their host plants, particular nutritional requirements, and interactions with other microbes, many of these microorganisms are either impossible or extremely difficult to cultivate. The complete diversity of endophytic communities is frequently not captured by conventional cultivation methods, which results in the loss of potentially important sources of novel bioactive compounds. Advanced techniques like metagenomics, single-cell sequencing, and genome-based analyses are being developed to get around this. By

using these methods, scientists can investigate these hidden microbial populations without the need for cultivation, which makes it possible to identify biosynthetic gene clusters and predict new therapeutic compounds from endophytes that were previously unreachable.

7.2 Low yield of metabolites :

Although endophytic bacteria generate a variety of pharmacologically valuable secondary metabolites, their use in commercial settings is frequently limited because of their frequently very low production quantities. Numerous gene clusters involved in biosynthesis are either dormant or only manifest under particular environmental circumstances. Metabolite production is affected by changes in temperature, pH, nutrient availability, culture conditions, and host plant-related factors. Among the methods being employed to boost metabolite yields are growth media optimization, elicitor addition, metabolic engineering, genome mining, and synthetic biology. However, consistently achieving economically viable production levels is a significant barrier to industrial-scale development.

7.3 Regulatory and ethical considerations :

There are many ethical and regulatory obstacles to overcome when developing pharmaceutical products from metabolites made by endophytic bacteria. Throughout the commercialization process, concerns about biosafety, intellectual property rights, genetic resource ownership, and fair benefit-sharing must be addressed. International agreements like the Nagoya Protocol on Access and Benefit Sharing must be followed when collecting endophytes from medicinal plants. Before these metabolites are approved for therapeutic use, thorough assessments of toxicity, pharmacokinetics, quality control, and clinical safety are also required. To ensure sustainable drug discovery and development, ethical management of microbial resources and proper documentation are essential.

7.4 The necessity of sophisticated screening techniques :

In order to identify valuable bioactive molecules derived from endophytic bacteria, sophisticated and highly effective screening techniques must be used. Conventional screening methods frequently fail to identify compounds that function through novel mechanisms because they are labor-intensive and time-consuming. The process of finding and characterizing therapeutic compounds is significantly improved by cutting-edge techniques like high-throughput screening, metabolomics, proteomics, transcriptomics, artificial intelligence, and bioinformatics-based predictive modeling. The discovery of novel antibiotics, anticancer drugs, and immunomodulatory compounds is greatly accelerated by combining these cutting-edge technologies..4 Need for advanced screening methods :

8. Future Prospectives:

8.1 Incorporation of Artificial Intelligence (AI) and Machine Learning (ML) in Drug Development :

By facilitating quick analysis of intricate biological datasets, AI and ML are transforming the identification of bioactive compounds from endophytic bacteria. Molecular structures, biological activities, toxicity profiles, and drug-target interactions can all be predicted by AI algorithms. The time, cost, and failure rates associated with traditional drug discovery can be decreased by using machine learning models that combine genomic and

metabolomic data to identify promising biosynthetic gene clusters and rank new drug candidates.

8.2 Prospects for Personalized Medicine :

Endophytic bacterial metabolites have the potential to be used in personalized medicine by enabling the development of targeted treatments based on a person's genetic, metabolic, and disease-related traits. Treatment effectiveness can be increased and side effects can be reduced by screening and optimizing bioactive compounds to match patient-specific requirements.

Innovative treatments for cancer, infectious diseases, metabolic disorders, and inflammatory conditions may result from the integration of microbial metabolites with precision medicine.

8.3 Integration of Multi-Omics Technologies :

A comprehensive understanding of endophytic bacterial systems can be obtained by combining genomics, transcriptomics, proteomics, metabolomics, and bioinformatics. Multi-omics techniques assist in mapping metabolite production networks, identifying silent biosynthetic pathways, and clarifying the mechanisms underlying therapeutic effects. The development of novel antibiotics, anticancer medications, and other pharmaceuticals is improved by this integrated data analysis.

8.4 Nanotechnology in Drug Formulation and Delivery :

The genetic engineering of endophytic bacteria to increase the production of useful metabolites has been revolutionized by genome editing tools, especially CRISPR-Cas systems. CRISPR makes it possible to precisely alter biosynthetic gene clusters, activate dormant pathways, eliminate competing pathways, and optimize metabolic flux in the direction of desired compounds. Endophytic bacteria can be transformed into effective biofactories for the manufacture of drugs using these technologies.

8.5 Precision Fermentation :

The delivery and efficacy of bioactive compounds from endophytic bacteria can be improved with the use of nanotechnology. Drug stability, solubility, targeted delivery, and bioavailability can all be improved by nanoformulations, such as liposomes, nanoparticles, and nano-carriers. Improved therapeutic outcomes and decreased toxicity could result from combining microbial metabolites with nanotechnology.

9. Conclusion :

The enormous therapeutic potential of endophytic bacteria is set to be unlocked by future developments combining AI, multi-omics integration, genome editing, CRISPR, nanotechnology, and precision fermentation. Novel drug discovery, optimization, and commercialization will be enhanced by these complementary strategies. Transforming endophytic bacterial metabolites into safe and effective therapeutic agents will require effective cross-disciplinary collaboration.

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