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Review

Unveiling the Hidden Allies in the Fight Against Antimicrobial Resistance—Medicinal Plant Endophytes

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Abstract: Medicinal plants have long been a vital source of various natural products in the form of pure compounds or standardized extracts. The World Health Organization estimated that 80% of populations in Africa, Asia, and Latin America rely on traditional medicine for primary health care. In recent decades, endophytic microorganisms living within plants have gained attention for their ability to produce bioactive compounds with significant therapeutic potential. This review explores the diversity of medicinal plant endophytes, focusing on their pharmacological significance, including antimicrobial, anticancer, antidiabetic, and antioxidant properties. Additionally, we discuss the application of nanotechnology and computational tools in enhancing the potency and screening of endophyte-derived metabolites. Despite the promising potential, challenges such as scalability, safety, and commercial viability remain. Future research should prioritize optimizing production, elucidating biosynthetic pathways, and integrating advanced technologies to effectively harness these bioactive compounds for novel drug development.

Keywords: endophyte biodiversity; bioactive compounds; phytotherapy; nanotechnology; antimicrobial resistance

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1. Introduction

The increasing report of antimicrobial resistance among pathogenic microorganisms against valuable drugs is considered a threat to human health. As such, many antimicrobials have become less effective or even ineffective. This has necessitated the need for a more intensified search for novel bioactive compounds for clinical treatment [1]. In recent years, different strategies to salvage the menace of antibiotic resistance have been suggested [2]. One of the recommended approaches involves the combination of other bioactive molecules with failing antimicrobials which could practically restore the intended antimicrobial activity. Secondly, screening indigenous medicinal plants that represent a wealthy source of new antimicrobial agents for bioactive compounds [2].

Plants that possess therapeutic properties or exert beneficial pharmacological effects on humans or animals are referred to as medicinal plants [3]. Historically, medicinal plants are of the utmost importance to man as a cure for different diseases globally [4]. The use of these plants in traditional medicine for healthcare needs is still a common practice, especially in developing countries, probably due to cultural acceptability, accessibility, and affordability. According to the World Health Organization, about 4 billion out of the global population of approximately 6.3 billion humans utilized plant materials for their primary health care (PHC) needs in 2010. It is also acknowledged that roughly 50% of individuals in developed countries consistently utilize complementary and alternative medicine, evidenced by an upsurge in the acceptability of plant-based medicines in recent years [5]. Herbal remedies are now displayed widely in drug stores, health shops, supermarkets, and grocery stores.

The increased acceptability could be attributed to consumers' preference for natural products, the belief that traditional medicines may be more effective with little or no adverse effects, and more [6]. For instance, *Thymus vulgaris*, native to Southern Europe, is widely used in the food and pharmaceutical industries and therapeutic dosages [7]. In South Africa, several plant species including *Siphonochilus aesthiopicus*, *Pelargonium sidoides*, *Sclerocarya birrea*, and others are in use traditionally and in primary health care [8]. Various plant species including *Andrographis paniculata*, *Cinnamon burmanni*, and *Zingiberis officinale* are used traditionally for the treatment of various health issues in Indonesia [9].

It is known that more than 30% of modern medicines are directly or indirectly derived from pharmacologically relevant compounds, abundant in plant metabolites [5]. Nonetheless, extracting secondary metabolites (SMs) from medicinal plants using the traditional approach faces various challenges, such as reliance on seasons, supply-demand gaps, biodiversity depletion, the endangered status of several plant species, environmental and geopolitical instability, and rising expenses. Consequently, research interests in recent years have been redirected to investigating the microbiota of medicinal plants for novel bioactive compounds safe for clinical use to address the concerns of new hypervirulent and multidrug-resistant pathogens and other life-threatening health conditions. Hence, the exploration and bioprospecting of medicinal plants' endophytic microorganisms for novel therapeutic compounds offers a promising alternative.

Microorganisms are ubiquitous and they interact with almost every living and non-living ecological niche like plants, animals, thermal vents, deep sediment rocks, and extreme environments (i.e., marine habitats and deserts) [10]. Microorganisms that live inside the tissues of healthy plants without causing any harm to their host are referred to as endophytic microorganisms [11]. Plant endophytes (i.e., mycorrhizal fungi) have a long history of symbiotic association with plants, as revealed by fossil evidence, and their adaptive capacity has been preserved through the evolutionary history of plants [12]. Nonetheless, reliable evidence describing the presence of non-pathogenic organisms inside plant tissues was first mentioned by De Bary in 1866 [13]. This observation was not explored until microbial interactions with plants were found in modern investigations in the 1930s which led to the understanding of endophytes in plants [14].

Several multidisciplinary research efforts have been deployed to the study of medicinal plant endophytes [15,16]. However, they did not receive much attention until the recent recognition of their ecological and pharmaceutical significance [17]. Since then, endophytes have created immense scientific curiosity about their evolution, ecology, biology, and applications. However, there is no certainty if endophytes are host-specific or systemic within plants [18]. It is noteworthy that plants alone are not the sole producers of their SMs. The bioactive compounds produced by these plants vary greatly based on plant species and their interaction with endophytes in terms of abiotic and biotic stress tolerance and regulation of the synthesis of secondary metabolites [19].

There have been reports that endophytic microorganisms can produce most plant-derived bioactive compounds [20,21]. This could be attributed to the long-held plant–endophyte associations and genetic systems (plasmids/extra-chromosomal materials) that allow the transfer of information between the microbe and the plant partner and vice versa [22]. SMs produced by endophytes are known for strong antioxidant, antimicrobial, antimalaria, and anticancer activities [23–27]. However, the pharmacological relevance of the various SMs produced has not been fully explored considering the increasing report of antimicrobial resistance among pathogenic microorganisms against valuable drugs, which is considered a threat to human health. As such, many antimicrobials have become less effective or even ineffective. This has necessitated the need for a more intensified search for novel bioactive compounds for clinical treatment [1]. This review explored the diversity of endophytes in plants, covering bacteria, actinomycetes, mycoplasma species, algae, and fungi. Furthermore, the pharmacological significance of bioactive compounds produced by endophytes, with a focus on their antibiotic, anticancer, antidiabetic, and antioxidant properties, was explored. Additionally, the synthesis of nanoparticles from endophytic metabolites and the application of computational methods to elucidate the biological function of bioactive metabolites were discussed.

2. Endophytic Microbial Communities: Diversity and Ecological Distributions

Endophytic microbes, including bacteria and fungi, colonize plant tissues without causing harm and are ubiquitous across plant species [28,29]. These diverse communities play crucial roles in plant growth, development, and stress tolerance [30]. Environmental factors like drought, salinity, and pollution influence endophytic populations [31]. Endophytes enhance plant resistance to abiotic and biotic stresses by modulating host functions and producing antioxidants to counteract reactive oxygen species [29]. They also contribute to nutrient cycling, biodegradation, and bioremediation [28]. Recent advancements in sequencing technologies have improved our understanding of endophytic communities, revealing their potential applications in pharmaceuticals, agriculture, and industry [32]. However, the full biotechnological potential of endophytes remains largely unexplored due to limited knowledge of molecular interactions and community dynamics.

2.1. Diversity of Endophytes in Plants

The earth's surface is covered by about 300,000 species of higher plants, and prior studies have shown that each of these species has either one or more endophytic microflora. Despite this, only a few dozen of these plant species have had their endophytic microbial communities examined thus far. Numerous vascular plants have been examined to date for endophytic microbial colonization [10]. Endophytes have been discovered in every plant group, including thallophytes, spermatophytes, hydrophytes, and xerophytes [33–35]. These diverse microbial communities primarily consist of algae, bacteria (including actinomycetes and mycoplasma), and fungi and they play critical roles in plant health and ecology. They have been identified as the most beneficial and diverse group of medicinal plant endophytic microbiota in different regions globally, including rainforests, oceans, mangrove swamps, coastal forests, the Arctic, the Antarctic, and geothermal lands [36–43]. Additionally, endophytes have been isolated from all plants including angiosperms bryophytes, pteridophytes, gymnosperms, and even lichens, from tropical woods, extreme arctic flora, various xeric climates, and boreal forests studied to date [44–50].

Some studies have suggested that the diverse environmental factors that determine the microbial community's diversity include drought, low temperature [51], high temperature [52–54], high salinity [55], and extreme circumstances [34,56]. For instance, a highly

diversified fungus endophytic community has been found in the tropics [44]; however, other investigations have shown contrasting outcomes [57,58]. According to Stone et al. [59], the composition and diversity of fungal species in isolated endophytic communities recovered from the host may be influenced by the sample size, isolation medium, sterilization procedures, isolation techniques, and cultural media employed.

The endophytic diversity assessment of medicinal plants is significantly influenced by the season at which the sampling of host tissue from various geographic locations was carried out, the incorporation of different plant parts, the sample size, and the sampling season [56]. Mishra et al. [60] found that the frequency of colonization (FC) of the Indian medicinal plant (*Tinospora cordifolia*) varied significantly depending on the tissue type and season rather than location. Furthermore, endophytes were more prevalent in leaf tissues than in any other parts followed by stem, petiole, and root segments, and the FC was highest during the monsoon, lower in winter, and lowest in the summer. *Guignardia* and *Acremonium* species, for instance, could only be isolated from leaves, but all other species were found in at least two different tissue types. *Penicillium* spp. dominated other isolates, followed by *Colletotrichum* spp., *Cladosporium* spp., *Chaetomium globosum*, *Curvularia* spp., and *Alternaria alternata*. The pattern of FC also aligns with the observed species richness, evenness, and the Shannon–Wiener diversity index, with tissue type and season having the greatest impact on these indices. This indicates that tissue type and season have more impact on the indices than geography.

Recent investigation has highlighted the significance of endophytic communities in various regions globally, including rainforests, oceans, mangrove swamps, coastal forests, the Arctic, the Antarctic, and geothermal lands. For example, studies by Huang et al. [61] and Wang et al. [62] have identified unique endophytic populations in extreme environments such as the Arctic and Antarctic, revealing their potential for novel bioactive compound production. For instance, an investigation by [63] found diverse endophytic communities in tropical rainforests, while studies by Brown et al. [64] and Willing et al. [65] showed significant endophytic diversity in boreal forests and xeric climates. Furthermore, recent advancements in high-throughput sequencing technologies have provided deeper insights into the composition and function of endophytic communities. For instance, studies by Kelliher [66] and Martinez et al. [67] utilized metagenomic and transcriptomic approaches to uncover the metabolic capabilities and ecological roles of endophytes in various plant species.

Endophytes play a significant role in various ecological processes and offer numerous potential applications in biotechnology. Recent studies have demonstrated the potential of endophytes in bioremediation, where they assist in the degradation of pollutants and toxins in the environment [68]. Additionally, endophytes contribute to nutrient cycling by facilitating the breakdown of organic matter and enhancing nutrient availability to plants [69]. In agriculture, endophytes have shown promise in promoting plant growth and increasing crop yields. They achieve this by producing phytohormones such as auxins and gibberellins, which stimulate plant growth [70]. Endophytes also enhance plant resistance to pests and pathogens by producing antimicrobial compounds that inhibit the growth of harmful microorganisms [71].

2.1.1. Endophytic Bacteria

After fungi, the second-most investigated endophytic group is bacteria. Endophytic bacteria are usually found in vascular tissue and intracellular spaces of the plant. According to reports, more than 200 genera and 16 bacterial phyla have been identified as endophytes, with most of these species falling under the actinobacteria, firmicutes, and proteobacteria phyla [72]. Gram-negative and Gram-positive bacteria, including *Acinetobacter*,

Achromobacter, *Agrobacterium*, *Bacillus*, *Brevibacterium*, *Pseudomonas*, *Xanthomonas*, and others, make up endophytic bacteria diversity [73]. Some other groups like *Clavibacter*, *Cellulomonas*, *Curtobacterium*, and *Microbacterium* have been identified using the 16S rRNA gene.

Bacterial endophytes are diverse and have been found to produce a variety of valuable bioactive metabolites similar to those of their host. These substances prove to be a reliable and effective source of therapeutic agents that function as antibacterial and anticancer substances, with 76% of them coming from the single genus, *Streptomyces* [74,75]. As an illustration, endophytic bacteria isolated from the therapeutic plants *Calendula officinalis*, *Matricaria chamomilla*, *Solanum distichum* [76], and *Hypericum perforatum* [77] had outstanding antibacterial and antifungal activity. Celastramycins [78] and kakadumycins [79] are metabolites produced by bacterial endophytes (*Streptomyces* strains) isolated from the wood of *Celastraceae* and *Grevillea pteridifolia* plants, respectively, with antibacterial activities. Other substances with antioxidant properties have been found in endophytes, including phenols, tannins, flavonoids, ascorbic acid, carotene [80], and cajaninstilbene acid [81]. Therefore, the pharmaceutical industry has a lot to gain from studying medicinal plant endophytic bacteria [75]. Other bacterial endophytic groups are listed in Table 1.

2.1.2. Endophytic Actinomycetes

Actinomycetes are prokaryotic microorganisms of the phylum actinobacteria [82,83]. They have mycelium similar to fungi and produce spores [83]. Actinomycetes have historically been thought of as the transitional form between bacteria and fungi [83]. The idea of comparing the similarities between actinomycetes and fungi is largely superficial, though, as most of their characteristics are like those of bacteria. In contrast to bacterial cells, actinomycetes have thin cells with a prokaryotic nucleoid-organized chromosome and a peptidoglycan cell wall. According to Gayathri and Muralikrishnann [84] and Singh and Dubey [85], endophytic actinomycetes can produce a wide range of biological metabolites with distinctive chemical structures that have significant medical value. In the quest for novel bioactive natural compounds, endophytic actinomycetes have gained attention because they produce new drugs with the potential to replace the ones to which pathogenic strains have gradually gained resistance. Actinomycetes as endophytes are popular for unique chemical entities with medicinal significance. There are numerous reports on the production of antimicrobial compounds from different varieties of actinomycetes [86–88]. *Streptomyces* is one of the most commonly isolated genera of endophytic actinomycetes.

Munumbicins (A and B), naphthomycins (A and K), cedarmycin (A and B), clethramycin, coronamycin, kakadumycins, and saadamycin are among the compounds of biological importance identified from *Streptomyces* and endophytic bacterial phyla [13,72,89,90]. Tyrosol from *Emblica officinalis* and paclitaxel recovered from *Kitasatospora* sp. linked with *Taxus baccata* are two other bioactive metabolites derived from actinomycetes, both of which have an inhibitory effect against food-borne pathogens [72,89,91]. Table 1 provides more information on the endophytic bacterial, algal, and actinomycetes endophytes isolated from medicinal plants.

Table 1. Overview of recently isolated endophyte from ethnomedicinal plants and their reported bioactivities.

Endophyte Class	Medicinal Plant	Endophyte	Bioactive Metabolite	Test Pathogen	Solvent	Activity	References
Bacteria	*Cordia dichotoma* L.	*B. thuringiensis*	Eicosane, heneicosane, hexadecane, tetradecane, tetrapentacontane, trichlorooctadecyl, and 2,4-di-tert-butylphenol.	*S. aureus*, *E. coli*, *Bacillus subtilis*, *P. aeruginosa*, *Klebsiella pneumonia*, and *S. typhi*	Ethyl acetate	Antibacterial	[92]
	Urtica dioica L.	*B. cereus*	Polyphenol compounds (caffeic acid, chlorogenic acid) and fatty acid esters (hexadecenoic, heptadecanoic, and octadecanoic acids)	*P. aeruginosa*, *E. coli*, *Mucor racemosus*, and *Phanerochaete chrysosporium*	Hexane	Antimicrobial	[21]
	Alectra sessiliflora	*Bacillus* sp. strain AS_4, *Lysinibacillus* sp. strain AS_1, and *Peribacillus* sp. strain AS_2	Tridecane, hexadecane, tetracosane, and ergotaman-3′,6′,18-trione,9,10-dihydro-12′-hydroxy-2′-methyl-5′-(phenylmethyl)-, benzyl 2-coumaranone, and octacosane	*B. cereus*, *E. coli*, *K. pneumoniae*, *K. oxytoca*, *Mycobacterium smegmatis*, *P. aeruginosa*, *S. aureus*, *S. saprophyticus*, *S. epidermidis*, *Veillonella parvula*, and *Enterococcus faecium*	Ethyl acetate	Antimicrobial, anticancer (0.25–16 mg/mL)	[93]
	Origanum vulgare L.	*Arthrobacter* sp. OVS8	Volatile organic compounds	*P. aeruinosa*, *S. aureus*, *K. pneumonia*, *S. epidermidis*	-	Antagonistic	[94]
Actinomycetes	Pharmaceutical plants from different sites at Xishuangbanna, tropical rainforest, Yunnan province China	*Streptomyces* sp.	-	*S. aureus*, *S. epidermidis*, *E. coli*, *Klebsiella pneumoniae*, and *C. albicans*	-	Antitumor and antimicrobial	[86]
	Camella sinensis var. *assamica*	*Brevibacterium celere*	-	*Staphylococuss epidermidis*, *Shigella flexneri*, *E. coli*, and *Bacillus cereus*	Ethyl acetate	Antibacterial and immunomodulatory activity	[87]
Algae	Macroalgae	*Colaconema. formosnum*	Phycobiliproteins (phycoerythrin, phycocyanin, and allophycocyanin)	-	-	Antibacterial, anticancer, antidiabetes, anti-inflammation, antioxidants, anti-obesity, neuroprotective activity	[95]

2.1.3. Endophytic Mycoplasma Species

Mycoplasma is a unique bacteria genus with over 100 different species lacking cell walls. Members of this genus are well-known human and animal parasites causing a wide range of symptoms and infections [96]. Additionally, they are common members of the intestinal bacterial flora of fishes and abalones (marine snails) where they may partake in nutrient supply to their host [97–99]. However, there have been reports of mycoplasma species as plant endophytes [91]. Some red algae, including *Bryopsis pennata*, *B. hypnoides*, and *Arcobacter*, have symbiotic relationships with endophytic mycoplasma species, and various biological activities of *Bryopsis* sp. have been documented [100].

Several studies have described mycoplasma species as part of the microbial community composition within the cytoplasm of *Bryopsis* species [99,101,102]. For instance, Rao et al. reported that kahalalide K, a cyclic depsipeptide isolated from *Bryopsis* sp., was found in the collection of *Elysia rufescens* (sea slug), and the production of this metabolite could potentially come from the association of microbes with molluscs and algae [103]. Despite the existing studies that identify mycoplasma species as plant endophytes, there is a noticeable gap in the literature regarding reports on the isolation, antimicrobial, and pharmacological activity of the secondary metabolites produced by mycoplasmas against foodborne pathogens and other pathogenic microbial and non-microbial infections. Further studies in this direction are required to isolate and unveil the therapeutic relevance of mycoplasma species.

2.1.4. Endophytic Algae

Algae are a group of photosynthetic eukaryotic organisms comprising dinoflagellates, diatoms, and macrophytes (brown, green, and red algae). These groups play a pivotal role as producers in oceans and marine food chains [104]. Macroalgae, also known as seaweeds, have gained attention in various industries due to their potential as a novel food source with nutritional benefits and as a source of high-value therapeutic compounds for use in medicine. Like other plants, algae produce a wide range of amazing secondary metabolites synthesized at the end of the growth phase or probably because of metabolic changes induced by environmental stressors. These metabolites (carotenoids, phycobiliprotein pigments, phenolic compounds, polysaccharides, and unsaturated fatty acids) are rich in naturally occurring bioactive compounds with antibacterial, antifungal, antiviral, anti-inflammatory, antioxidant, hypercholesterolemia, hypolipidemic, and antitumorogenic effects [104–106].

Microalgae and endophytic algae represent a largely untapped reservoir of natural products with vast potential applications. These algal-derived metabolites have diverse uses and can provide a consistent and sustainable source of natural compounds [104,107]. A few studies have described the isolation and pharmacological prospects of endophytic algae from medicinal plants. The isolation of endophytic filamentous red algae *Colaconema formosnum* sp. nov. from economically important macroalgae in Taiwan was described in a previous study [108]. Another study observed a significant increase in phycobiliprotein (phycoerythrin, phycocyanin, and allophycocyanin) production during fermentation of *C. formosnum* together with *Pseudoalteromonas haloplanktis* to enhance metabolite production by *C. formosnum* [95]. Phycobiliproteins are high-valued natural products known for antibacterial, anticancer, antidiabetes, anti-inflammation, antioxidants, anti-obesity, neuroprotective activity, growth, and immunity improvement in humans [109]. Trémouillaux-Guiller et al. reported endophytic algae (*Coccomyxa* sp.) from medicinal plant *Ginkgon biloba* [110]. However, information about metabolite production by the endophyte was not documented.

Other studies described the parasitic association of endophytic algae with their hosts. The occurrence of three pathogenic endophytic algae (*Acrochaete heteroclada* Correa,

A. operculata and *Nielson* sp. nov.) within red algae (*Chondrus crispus* Stackh) was documented [111]. Likewise, pathogenic algal endophytes [(*Audouinella porphyrae* (Drew)] and *A. vaga*) growing in *Porphyra* and *Pterosiphonia* were described, respectively [112]. In addition, the algal endophyte *Colaconema daviesii* was isolated from the thali of edible seaweed *Chondracanthus chamissoi* in Chile, and it was observed that the filaments of *C. daviesii* were able to grow and reproduce independently of *C. chamissoi* [113]. Gao et al. investigated the percentage of *Chondrus ocellatus* infected by green endophytic algae in Korea [114]. Furthermore, the semi-endophytic coralline algae *Lithopyllum cuneatum* from coral reefs of the Caribbean Sea (Belize) was reported [115]. However, the limited information on the pharmacological significance of endophytic algae necessitates more focused and intensified research efforts to unveil the potential of endophytic algae as a viable source of safer and more effective bioactive metabolites. By exploring the potential of endophytic algae, researchers may discover safer and more effective bioactive metabolites, unlocking new possibilities in the pharmaceutical industry.

2.1.5. Endophytic Fungi

Fungi are heterotrophic organisms with several forms of life cycles including mutualistic, antagonistic, or neutral symbiotic association with a wide range of autotrophic microorganisms [116]. Based on taxonomic and evolutionary relationships, plant hosts, ecological activities, phylogenetic relationships, and life cycles, endophytic fungi have been classified into two major groups (clavicipitaceous and non-clavicipitaceous endophytes) [117,118]. The clavicipitaceous (Ascomycota; Hypocreales) endophytes (class 1 fungal endophytes) are commonly found in cool and warm seasonal grasses, rushes, and sedges. For instance, *Claviceps* spp., *Epichloe* spp., and *Balansia* spp. Have a constrained range of hosts and comprise phylogenetically related fungal endophyte species [119].

The Hypocreales is a lineage of well-known plant endophytes that produce bioactive compounds, whereas the non-clavicipitaceous (NC) endophytes are highly diverse and have been recovered from nearly all plant species (including non-vascular plants, ferns and allies, grasses, conifers, and angiosperms) from temperate and tropical regions and are restricted to the Ascomycota or Basidiomycota. Rodriguez et al. further classified NC-endophytes into three classes based on the pattern of host colonization, the method of transmission between hosts, ecological importance, and the diversity of the endophytic community within the host [119]. Classes 2, 3, and 4 of the NC fungal endophyte species have a wider host range. Among these, class 2 is known to colonize both the phyllosphere and the rhizosphere, whilst classes 3 and 4 are restricted to plant tissues above the ground and roots [119]. The diversity of class 3 endophytes within a host plant or tissue can be exceedingly high (e.g., >20 species observed from a single tropical leaf [120]), while the diversity of class 2 endophytes in individual host plants is generally rather limited [121].

Some of the most widely used antibiotics and anticancer medications are produced by endophytic fungi. Javanicin was produced by the endophytic fungus (*Chloridium* sp.) of the neem medicinal plant [122] and the anticancer drug (Taxol) from the endophytic fungi *Taxomyces andreanae* [123]. In addition, Penicillenols, obtained from *Penicillium* species are cytotoxic to several cell lines. Several foodborne pathogens have been reported to be susceptible to clavatol (*Torreya mairei*), javanicin (*Chloridium* sp.), jesterone (*Pestalotiopsis jesteri*), and sordaricin (*Fusarium* sp.). In addition, pestacin isolated from *Pestalotiopsis microspore* exhibits remarkable antioxidant properties [13,124,125]. Similarly, fungal endophytes are known to be the source of many immunosuppressive, anticancer, antidiabetic, and insecticidal compounds [13,126,127]. Table 2 summarizes the antimicrobial activities of endophytic fungi isolated from medicinal plants.

Table 2. Antimicrobial activities of endophytic fungi isolated from medicinal plants.

Medicinal Plant	Endophyte	Bioactive Metabolite	Test Pathogen	Solvent	Activity	References
Andrographis paniculata (Green Chiretta)	*Cochliobolus* sp. APS1	-	*Bacillus cereus*, *B. subtilis*, *Proteus. mirabilis*, *P. aeruginosa*, *Escherichia coli*, *Shigella flexneri*, Vancomycin-Resistant *Staphylococcus aureus* (VRSA), and Methicillin-Resistant *Staphylococcus aureus* (MRSA)	Ethyl acetate	Anti-biofilm, antilarval potency, and Cidal antibacterial (MIC and MBC values range: 15.62–125 µg/mL and 62.5–125 µg/mL, respectively). Larvicidal effect against Dengue-vector *Aedes aegypti*	[23]
Dillenia indica	*Aspergillus flavus*, *A. niger*, and *A. fumigatus*	Dodecane, 2-isopropyl-5-methyl-1-heptanol, and 2-ethylhexyl ester, 1-octanol	*B. subtilis*, *E. coli*, and *S. aureus*	Ethyl acetate	6.0–14.0 µg/mL	[128]
Psidium guajava L. (leaves)	*Alternaria tenuissima* PE2	Several natural bioactive compounds	*Listeria monocytogenes*, *B. subtilis*, *S. aureus*, *S. epidermidis*, *Salmonella typhimurium*	Ethyl acetate	MIC and MBC values (~500 µg/mL ~800 µg/mL, respectively)	[129]
Gynura procumbens (Sambung Nyawa)	*Colletotrichum gloeosporiodes Macrophomina phaseolina*, *Mycoleptodiscus indicus*, *Phomopsis* sp., and *Diaporthe hongkongensis*	A plethora of bioactive metabolites including isoelemicin, terpinel, eucalyptol, oleic acid, β-pinene, γ-terpinine, 4-carene, octadecanoic acid, caryophyllene, aromadendrene, and globulol.	*E. coli*, *P. aeruginosa*, *S. typhi*, *S. aureus*, and MRSA	Ethyl acetate and methanol	Antibacterial—MIC and MBC (5000 µg/mL)	[130]
Vernonia anthelmintica	*Ovatospora senegalensis*, *Chaetomium globusum*, *A. calidoustus*, *A. keveii*, and *A. terreus*	9,12-octadecadienoic acid (Z, Z)	*E. coli*, *S. aureus*, and *Candida albicans*	Ethyl acetate	Antimicrobial anticancer and cytotoxic (MIC: 62.5–250 µg/mL)	[131]
Rumex nervous, *Pulicaria crispa*, and *Withania somnifera*	*Aspergillus flavipes*, *Fusarium clamydosporum*, *Penicillium commune*, and *P. glaucoroseum*	Antioxidants Phenols: catechol, cinnamic acid, *p*-OH benzoic, ferulic, and protocatechulic acids Flavonoids: acacetin, apigenin, chrysin, and epicatectin, luteolin, rutin, quercetin.	*B. subtilis*, *E. coli*, *C. albicans*, *C. glabrata*, *K. pneumonia*, and *S. aureus*	Ethyl acetate	Weak antimicrobial and cytotoxic effects and cancer activity	[24]

Table 2. *Cont.*

Medicinal Plant	Endophyte	Bioactive Metabolite	Test Pathogen	Solvent	Activity	References
Dillenia indica L.	*Fomitopsis meliae*, *Colletotrichum gloeosporioides*, *Nigrospora sphaerica*, *Chaetomium globosum*, *Schizophyllum commune*, *Fomes meliae*, *Fusarium oxysporum*, *Xylaria longipes*	A plethora of bioactive compounds including benzaldehyde, 4-(1-methylethyl)-, dodecane, ethyl 2-thiopheneacetate, griseofulvin, hexadecane, octadecane, tetradecane	*E. coli*, *P. aeruginosa*, *B. subtilis*, and *S. aureus*	Ethyl acetate and methanol	Antibacterial (zones of inhibition: 0–29 mm)	[132]
Scheleichera oleosa (Lour.) Merr	*Arcopilus cupreus*	Caffeic acid, citric acid, isofraxidin, and quercetin	*E. coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *P. syringae*, *S. enterica*, *S. typhi*, *Enterococcus faecalis*, *S. aureus*, and *Xanthomonas campestris*	Ethyl acetate	Antimicrobial and antioxidant activities	[133]
Lycium shawii	*Neurospora crassa*	-	*P. aeruginosa*, *E. coli*, *Klebsiella pneumonia*, *S. aureus*, *Aspergillus niger*, and *Candida albicans*	Ethyl acetate	Antimicrobial and wound healing	[134]
Aloe vera	*Preussia africana*	-	-	-	Antioxidant	[135]
	Talaromyces purpureogenus	Polysaccharides TEPS1 and TEPS2	-	-	Antioxidant and wound healing	[136]
Digitaria bicornis	*Penicillium citrinum*	benzophenone, caffeic acid, cannabidol, ergosterol, α-eleostearic acid, oleamide, sclerotiorin, and solanine	-	Ethyl acetate	Antioxidant	[137]
Artemisia annua	*Aspergillus terreus*	Coumarins, phenolics, and polyketide	-	Ethyl acetate	Antioxidant	[138]
Plants from *Brazilians pampa* and Atlantic Forest biomes	*Botryosphaeria dothidea*	bis(2-methylpropyl) ester, Hexahydropyrrolizin-3-one, and 6-bis(2-methylpropyl)-2.5-piperazinedione	-	Ethyl acetate	Antioxidant	[139]
Psidium guajava and *Newbouldia leavis*	*Fusarium* sp. and *Cladosporium* sp.	Citrinin, citreohybridinol, cyclopenin, p-hydrobenzoic acid, nakijinol, nidulanin, and protocatechuic acid	-	Ethyl acetate	Antioxidant and immunomodulatory	[140]

Nearly all plant parts, including the petiole, flower, twig, seed, leaf, stem, bark, and root, have been reported to harbour fungal endophytes. The age of the host plant itself has an impact on the endophytic variety in the host plant [56,141,142]. Woody plants typically have a wider variety of endophytes than grasses, which has resulted in lesser host specificity for endophytes [56]. However, endophytes of many woody plants are expected to be quite specific at the host-species level [56]. The most commonly documented fungal endophytes are the *Ascomycotina*, followed by *Basidomycotina* and *Zygomycotina* [143].

2.2. Environmental Influences on Endophytic Microbial Communities

2.2.1. Seasonal and Abiotic Stress

Environmental factors such as drought, temperature extremes, and salinity significantly influence the diversity and composition of endophytic communities. Studies by Zhang et al. [144] and Chen et al. [145] have demonstrated that drought conditions can alter the microbial community structure within plant tissues, leading to an increase in drought-tolerant endophytes. Similarly, research by Ji-Won Kim et al. [146] and Lee et al. [147] has shown that temperature extremes and high salinity can shape endophytic diversity, promoting the prevalence of stress-tolerant species.

Endophytic communities are subject to changes due to seasonal variations and environmental stressors. For instance, in *Kalidium schrenkianum*, a perennial halophyte, the diversity of bacterial communities in roots was higher in summer and autumn, while fungal diversity peaked in spring. This indicates that seasonality is a significant determinant of microbial community composition, particularly in roots, and that stochastic processes largely shape these communities under radiation stress [148]. Similarly, in desert ecosystems, root endophytic communities are differentially regulated by stochastic processes and functional traits during dry and wet seasons, with certain bacterial and fungal taxa showing increased prevalence in response to seasonal transitions [149].

2.2.2. Geographic and Environmental Gradients

Geographic and environmental gradients also play a critical role in shaping endophytic communities. In Heuchera species across North America, host phylogeny significantly influenced bacterial communities, while geographic distance was a key predictor for fungal community composition. Environmental factors such as aridity and precipitation affected fungal diversity, highlighting the importance of abiotic conditions in structuring microbial communities [150,151]. In Hawaiian landscapes, temperature and rainfall were strongly correlated with the diversity and composition of foliar endophytic fungi, suggesting that broad-scale environmental controls are crucial in structuring microbial diversity [152].

2.2.3. Salinity and Soil Conditions

Salinity acts as an environmental filter for endophytic communities in halophytes like Salicornia europaea, where distinct bacterial and fungal communities were observed at sites with different salinization histories. The bacterial community influenced the fungal one, indicating a complex interaction between these microbial groups under varying salinity conditions [153]. In coastal dune ecosystems, abiotic environmental filtering significantly affected below-ground fungal communities, while above-ground communities were more influenced by host species and geographic distance [154].

2.3. Community Structure and Host Interactions

2.3.1. Host Plant Influence

The structure of endophytic communities is also determined by the host plant species and the specific ecological niches they provide. In transgenic and non-transgenic poplar trees, the bacterial and fungal community structures were influenced more by environ-

mental conditions and plant tissue types than by transgenic events, with each plant tissue representing a unique ecological niche [62]. Similarly, in argan trees, site-specific profiles of endophytic communities were observed, with environmental factors playing a significant role in shaping these communities [155].

2.3.2. Functional Traits and Plant Adaptation

Endophytic microbes contribute to plant adaptation by promoting growth and enhancing stress resistance. They engage in mutualistic interactions with host plants, aiding in nutrient acquisition and providing resistance against pathogens. These interactions are crucial for plant health and can be leveraged for sustainable agricultural practices [156].

3. Pharmacological Significance of Bioactive Compounds Produced by Medicinal Plant Endophytes

Endophytic microorganisms have become an interesting subject for research due to their potential therapeutic benefits. They have been reported to produce a diverse range of bioactive secondary metabolites which exhibit potent antimicrobial activity against pathogenic microorganisms [157–159]. The functional groups of the metabolites produced have been described and they include alkaloids, steroids, saponins, benzopyranones, phenolic acids, chinones, flavonoids, tannins, quinones, tetralones, terpenoids, xanthones, and others [13,160].

3.1. Mechanism of Actions of Endophytic Bioactive Compounds

The mechanisms of action of endophytic bioactive compounds are diverse and impactful, particularly in antimicrobial, antifungal, anticancer, and plant growth promotion activities (Figure 1). Bioactive compounds derived from endophytic fungi and plants exhibit various biological effects that can be harnessed for therapeutic applications.

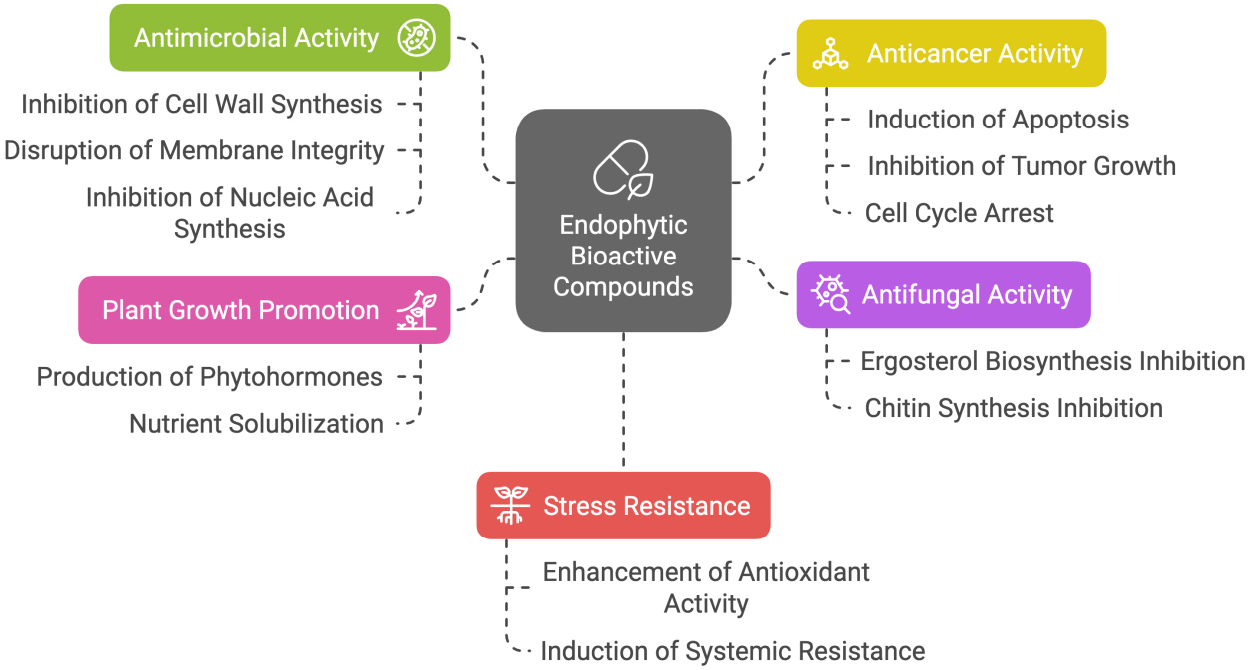

Figure 1. The mechanisms of action of endophytic bioactive compounds.

These compounds have shown the capacity to inhibit the growth and multiplication of various pathogenic microbes by different mechanisms, including disruption of the cell membrane, enzyme inhibition, and interference with DNA replication. Recent studies

have shown that endophytic microorganisms isolated from medicinal plants produced metabolites with promising antimicrobial activity against pathogenic microorganisms, including bacteria, fungi, viruses, and protozoans [22,87,92,131]. In terms of antimicrobial activity, endophytic compounds can inhibit cell wall synthesis by disrupting peptidoglycan synthesis, which leads to bacterial cell lysis [161]. They can also disrupt membrane integrity by integrating into microbial membranes, causing leakage and cell death [162]. Additionally, some compounds inhibit nucleic acid synthesis, preventing microbial replication by hindering DNA or RNA synthesis [163].

For antifungal activity, many endophytic compounds target ergosterol, increasing fungal membrane permeability. Others disrupt chitin synthesis, weakening fungal cell walls and leading to cell lysis [70].

Apart from antimicrobial properties, endophytes also produce bioactive metabolites with various other therapeutic potentials including anticancer, anti-inflammatory, antidiabetic, antioxidant, immunosuppressive, and immunomodulatory activities. These compounds have shown promising results in preclinical studies and have the potential to be developed into novel therapeutic agents for the treatment of various diseases [22,140,164–166].

When it comes to anticancer activity, certain endophytic compounds induce apoptosis, triggering programmed cell death in cancer cells. These compounds may also inhibit tumour growth by preventing angiogenesis, which is essential for tumour development. Some metabolites interfere with the cell cycle, preventing cancer cell proliferation [167,168].

Endophytic compounds also play a role in plant growth promotion by synthesizing growth-promoting hormones like auxins and gibberellins [169].

While the therapeutic potential of endophytic compounds is significant, challenges such as variability in bioactive compound efficacy and the need for extensive clinical trials remain. This highlights the importance of continuing research to fully understand and optimize these natural products for practical applications.

3.2. Antibiotic Compounds of Medicinal Plant Endophytes

Low-molecular-weight natural organic products produced by microorganisms that are active at low concentrations against other microorganisms are referred to as "antibiotics" [25]. Previous studies have reported many endophytic microorganisms from medicinal plants producing natural metabolites with potent antimicrobial properties against human pathogens including viruses, bacteria, fungi, and protozoans [24,86,92,130].

Some of the natural compounds including alkaloids (alkaloid aziridine, 1-2-aminoethyl); isoelemicin, eucalyptol, oleic acid, terpenes (terpineol, terpinene); aromadendrene, globulol, flavonoids (luteolin, rutin, quercetin); phenolic antioxidants (catechol, cinnamic acid, *p*-OH benzoic, ferulic and protocatechuic acids); antioxidant flavonoids (acacetin, apigenin, chrysin and epicatechin); polyphenol compounds (caffeic acid, chlorogenic acid); benzyl benzoate, 2-coumaranone, alkanes (dodecane, hexadecane, tetradecane, eicosane and octacosane); alcohols (1-octanol, 4-methylethyl); fatty acids and fatty acid esters (hexadecenoic, heptadecanoic, octadecanoic acids, hexadecane, methyl ester); and aromatic compounds (benzaldehyde, 2,4-di-tert-butylphenol, ethers (ethyl 2-thiophene acetate) have been produced by medicinal plant endophytes [21,23,93,94,128,129,131]. These natural metabolites serve as lead compounds for many synthetic drugs.

Ecomycins, kakadumycins, munumbicins, pseudomycins, hypericin, podophyllotoxin, and cytonic acids A and B are examples of novel antibiotics in use that were produced by bacterial and fungal endophytes isolated from medicinal plants. These antibiotics have proven antibacterial, antimalarial, antifungal, and antiviral properties [22,170,171]. Novel compounds with strong antimicrobial properties, such as actinoallolides, trehangelins, and

spoxamicins, which are produced by actinomycetes, have been documented. While they exhibit promising pharmacological properties in preclinical studies, there is limited information available on their development into commercial pharmaceutical products [172–175]. The antimicrobial activities of some medicinal plants reported in previous studies are summarized in Tables 1 and 2.

3.3. Antioxidant Properties

To adapt to the ever-changing environmental conditions, plants have developed a vast array of active substances, including several antioxidants. These compounds are known to effectively scavenge free radicals, protect cells from oxidative stress, delay ageing, and are relevant in various health conditions [176,177]. Endophyte-derived antioxidants may find applications in preventing and managing oxidative damage-related diseases. Medicinal plant endophytes are known producers of these compounds. For instance, Caicedo et al. documented that the purified extracts of the endophytic fungus *Fusarium oxysporium* isolated from the leaves of *Otoba gracilipes* showed high antioxidant potential (51.5% scavenging effect) to inactivate free radical DPPH (2,2-diphenyl-1-picryhydrayl) [178] and a 71.5% inhibition of DPPH radicals by the secondary metabolites produced by *Fusarium* sp. isolated from Gall Rust Sengon Plants (*Falcataria moluccana*) [179]. Another study also showed that the bioactive secondary metabolites produced by medicinal plant endophytes obtained from the botanical garden at the Madurai Kamaraj University, Tamil Nadu, India showed promising antioxidant properties in vitro [180].

Other pharmacologically significant secondary metabolites from medicinal plant endophytes with potential applications as parasitic agents and anti-inflammatories, some with potential applications for immunological disorders, cardiovascular diseases, wound healing, pain management, metabolic disorders, and drug delivery, have been investigated [133,140,181].

3.4. Anticancer Compounds

According to the WHO, cancer is the second leading cause of death, globally accounting for an estimated one in six deaths (9.6 million) in 2018. The burden is still rising with a tremendous impact on individuals, families, communities, and health systems. In the past decades, many anticancer drugs have been synthesized and successfully deployed therapeutically. As previously mentioned, Paclitaxel (Taxol), a highly functionalized diterpenoid, is generally found in the taxa of yew species. It is one of the best-known anticancer drugs to date and the first billion-dollar anticancer drug. This outstanding example of natural product isolation comes from the *Taxus wallachia* tree [182]. Furthermore, this same compound (taxol) and other related compounds were produced by the endophytic fungus *Taxomyces andreanae* isolated from *Taxus* plant species such as *Taxus brevifolia* [123]. These compounds may inhibit tumour cell growth, induce apoptosis, or inhibit angiogenesis, offering potential solutions in cancer therapy. For instance, a selectively cytotoxic quinone dimer (torreyanic acid), in several cancer cell line experiments, demonstrated 5–10 times more potency with sensitivity to protein kinase C agonist, causing cell death by apoptosis [25,183].

Many researchers have unveiled other taxol-producing endophytes isolated from medicinal plants including *Aspergillus oryzae*, *Botryodiplodia theobromae*, and *Seimatoantlerium terpuiense* isolated from *Tarenna asiatica*, *Morinda citrifolia*, and *Maguireothamus specious* [165,166,184–186]. Due to the successes of research advancements in this direction, several anticancer drugs with proven efficacy against benign or malignant cancer cells such as camptothecin, vinblastine, and vincristine have been successfully developed from medicinal plant metabolites [22]. The discovery of these bioactive ingredients and their

derivatives in plants has spurred more research interest in endophytes as potential sources of similar bioactive compounds for anticancer drug development.

3.5. Antidiabetic Compounds

Diabetes mellitus is a condition at the cellular level characterized by hyperglycemia resulting from insulin resistance or lack of it. Based on estimation, about 366 million people may become diabetic by 2030 globally [187]. In most cases, diabetes management strategies primarily involve the use of insulin and some other synthetic antidiabetic substances such as biguanides, glinides sulfonylureas, etc. Considerable successes have been achieved in managing diabetes with these strategies; however, newer approaches are required to overcome the limitations of existing compounds. Endophytic microorganisms have yielded compounds with potential antidiabetic properties. These compounds may help improve insulin sensitivity and regulate blood sugar levels. Akshatha et al. observed that endophytic actinomycetes (*Streptomyces* sp. and *Streptomyces longisporoflavus*) isolated from the stem of antidiabetic medicinal plants (*Leucas ciliata* and *Rauwolfia densiflora*) significantly inhibited alpha-amylase and promoted glucose uptake in the porcine hemidiaphragm, respectively demonstrating their potential antidiabetic activities [26].

Additionally, Shao et al. reported the antidiabetic activity of novel galactomannan (homogeneous exopolysaccharide named PJ1-1) produced by the fungus *Penicillum janthinellum* in vivo which exhibited strong hypoglycemic activity in vitro, as demonstrated by its inhibition of α-glucosidase [27]. The compound also substantially lowered blood glucose levels and improved glucose tolerance in mice with type II diabetes induced by a high-fat diet and streptozotocin. This compound has the potential to be developed as a novel antidiabetic agent for clinical use. A recent in silico study identified potent α-amylase inhibitors for the therapeutic management of diabetes from endophyte *Streptomyces longisporoflavus*, isolated from the antidiabetic plant *Leucas ciliate* [164].

Furthermore, the antidiabetic drug (Diosgenin) with proven efficacy against diabetes Mellitus produced from medicinal plant endophytic SMs has been documented [22,188]. In addition, this compound has been reported for anticancer, arthritis, inflammation, asthma, thrombotic, cardiovascular diseases, and immune system-modulating activity. This valuable compound is also used as a starting material for steroidal drug preparation in the pharmaceutical industry. Other compounds such as Rohitukine have been reported for potent anticancer, anti-inflammatory, and immune-modulatory activities, while Huperzine A is known for anti-Alzheimer's disease activity [22]. However, advances in biotechnology and microbiology could eventually harness endophytes as viable producers of diosgenin and other potential antidiabetic compounds, providing an innovative and sustainable approach to obtaining these important compounds. Further research activities are required to isolate and optimize endophytes to produce antidiabetic compounds.

4. Boosting Metabolite Efficacy Through Endophyte-Derived Nanoparticle Synthesis

An approach that involves the use of nanoparticles with a size range of 1–100 nm is referred to as nanotechnology. Nanotechnology is a recent technology that finds application for utilization in many fields such as biology, medicine (drug delivery and diagnosis), pharmacy chemistry, physics, sensing, electronics, and manufacturing [189]. There are different categories of nanoparticles such as carbon, ceramic, metal polymeric-based nanoparticles, et cetera. Based on shapes and structures, different categories such as nanoshapes, nanocubes, nanorods, nanobranches, nanoflowers, nanocages, nanoshells, nano-bipyramides, nanowires, and nanomaterials have been identified, and they appear to be the most stable nanoparticles [189–191].

Nanoparticle synthesis using microorganisms is an important branch in nanotechnology and the organic nanoparticles consist of polymeric or lipid-like compounds which range in size between 10 nm and 1 µm in diameter. The synthesis is performed by different biological, chemical and physical methods. The biological method (using microorganisms, plants, and seaweeds) is cost-effective, ecologically friendly, non-toxic, and easier for large-scale production compared with the physical and chemical methods [17,192]. Organic nanoparticles are relatively biodegradable and do not remain in the environment for a long time [193]. The morphological characterization of nanoparticles from microorganisms is performed by wavelength (ranging from 200 to 800 nm) using a scanning/transmission electron microscope, whereas the chemical structure and functional group are characterized using the X-ray diffraction method and Fourier transform infrared spectroscopy, respectively [17]. SMs from microorganisms such as bacteria, fungi, and algae have been used for the synthesis of therapeutically valuable nanoparticles due to their ability to reduce metals into nano sizes and reduce overdependence on plants [194].

In the past decade, the search for nanomedicine has revealed well-established techniques for novel material synthesis. Endophytes demonstrated the capacity to be used for the synthesis of different novel, organic, therapeutically important nanoparticles. In this interest, different nanoparticles (such as copper (Cu), nickel (Ni), gold (Au), titanium (Ti), silver, zinc (Zn), and platinum (Pt)) with effective antimicrobial activities based on their chemical properties, morphology, and size have been produced and they are applicable in the pharmaceutical industries [17,189]. A recent investigation revealed that nanoparticles synthesized from endophytes have various characteristics including antimicrobial, anticancer, antioxidant, bactericidal activity, et cetera, and they are considered valuable substances against notorious antibiotic-resistant pathogens [17,195].

Syed et al. described the biological activities of AgNPs synthesized from the culture supernatants of an endophytic bacterial endophyte isolated from *Euphorbia hirta* L., demonstrating effective bactericidal activity against a panel of bacteria including *Pseudomonas aeruginosa*, *E. coli*, *Staph. aureus*, *B. subtilis*, and *Klebsiella pneumonia* [196]. Furthermore, the in vitro antimicrobial, antioxidant, and antidiabetic potential of AgNPs of an endophytic fungus (*Phyllostica capitalensis* Henn) isolated from the leaves of *Annona muricata* was observed in a previous study [197]. Nanoparticles synthesized from endophytes are more stable due to their affinity to encapsulate active molecules as protein conjugates and biomolecules, liposomes, vehicles for DNA delivery, and copolymer micelles [198,199]. Some popular organic nanoparticles including micelles, ferritin, dendrimers, and liposomes that showed characteristic biodegradability and non-toxicity have been documented [189]. For instance, liposomes and micelles also known as nanocapsules have hollow cores and are more sensitive to electromagnetic (light) and thermal (heat) radiation [200]. With these unique properties, they are considered an ideal alternative for drug delivery. Their stability, drug-carrying capacity, and delivery systems determine their effectiveness and the field where they can be applied [189]. Hence, endophyte nanoparticle biosynthesis is considered a novel strategy with tremendous potential in the formulation of drugs [201].

5. Computational Strategies for Endophytic Metabolite Interactions

The study of how two or more molecular structures, such as a drug, enzyme, or protein, fit together is known as molecular docking. Docking in simple terms is a molecular modelling method used to forecast the interactions between enzymes (proteins) and ligands (small molecules). The dynamics of a protein are mostly determined by its capacity to interact with smaller molecules to form supramolecular complexes, which can either promote or impede an enzyme's biological activity. Molecular docking provides insights into the interplay between a ligand and a receptor molecule [202,203]. Finding the correct

lead compound is crucial to success in the difficult process of drug discovery. The Tufts Centre for the Study of Drug Development estimated in 2016 that the cost of developing a new medication has risen by over 145% in the previous ten years [204]. Furthermore, the success percentage of medications receiving approval from the US Food and Drug Administration (FDA) has declined to 12%, despite a decrease in the average time to get a drug to clinical trials [204].

Computer-aided drug design (CADD) has contributed to a decrease in both the expenses and duration of drug discovery by accelerating experimental research geared toward the search for ideal molecules. High-throughput screening (HTS) is an expensive and time-consuming experimental process. Within CADD, methods like virtual screening (VS) and molecular docking have offered a useful alternative [205]. It has been demonstrated that by computationally screening vast libraries of compounds that either have complementarity toward target structures (structure-based screening) or similarity toward known inhibitors (ligand-based screening), it is possible to efficiently identify highly focused subsets from which actives can subsequently be experimentally confirmed [206]. Creating these "educated guesses" has yielded numerous lead compounds thus far.

It is known that many clinical candidates and commercially available drugs, including zanamivir, imatinib, erdafitinib, and nelfinavir, were found or improved with the use of computational studies [205,207,208], while a significant number of unpublished examples in corporate collections can only be speculated [205]. The process of predicting the ideal location, orientation, and conformation of a drug candidate when bound to a protein makes lead optimization easier in the future. It is easier to logically design modifications to optimize the protein-ligand interaction, boost activity, and prevent modifications that can cause protein-ligand clashes when one is aware of the precise location and mode of binding of a ligand [205].

6. Strategies Against Drug-Resistant Microorganisms

The global rise of antimicrobial resistance (AMR) has underscored the urgent need for novel approaches to combat drug-resistant microorganisms. Among the promising alternatives, plant-derived antimicrobials, particularly those derived from endophytes, have garnered significant attention. Endophytes are microorganisms that reside within plant tissues without causing harm, and they are known to produce bioactive compounds with antimicrobial properties. These compounds can inhibit the growth of various pathogens, offering a novel source of antibiotics in the face of diminishing returns from traditional antimicrobial drug development [209–211]. In addition to endophytes, plant secondary metabolites such as polyphenols, alkaloids, and tannins have shown potential in overcoming multidrug resistance. These metabolites may act either as direct antimicrobials or as resistance modifiers, further enhancing their utility against resistant pathogens [212,213].

7. Safety, Efficacy, and Commercial Viability of Endophyte Therapies

Endophyte-derived antimicrobials hold substantial promise due to their natural origin and potent efficacy against a wide range of pathogens [211,213]. However, for these therapies to be viable alternatives to traditional antibiotics, concerns regarding their safety and commercial scalability need to be addressed. The mechanisms of action and potential side effects of endophyte-derived compounds must be thoroughly investigated to ensure their safe application in humans. Moreover, for widespread adoption, the commercial production of these compounds must be optimized, including overcoming challenges related to yield enhancement and cost-effectiveness. Recent advances in synthetic biology and biotechnology offer promising solutions for improving the production and purification of these bioactive compounds [209,210,214]. Despite these hurdles, the potential of endo-

phytes to provide sustainable alternatives to conventional antibiotics remains significant, especially as the urgency of finding new antimicrobials grows.

8. Economic Challenges of Alternative Therapies

While endophyte-based therapies and other alternative approaches to combat AMR offer considerable promise, their development and commercialization face substantial economic challenges. These include the high cost of research and development, which is exacerbated by the need for extensive clinical trials to ensure safety and efficacy before approval. Additionally, in low- and middle-income countries (LMICs), limited resources for research and healthcare infrastructure further complicate the widespread adoption of these therapies [212]. Moreover, the financial barriers related to competition with established antibiotics and the complexities of scaling production are considerable obstacles to the commercialization of endophyte-based therapies [212,215]. Addressing these challenges will require sustained investment in both scientific research and local infrastructure to ensure that alternative therapies can be developed in a cost-effective and accessible manner.

9. One Health Approach

The One Health approach is an integrated framework that emphasizes the interconnectedness of human, animal, and environmental health. This holistic perspective is crucial for understanding the spread of antimicrobial resistance, which can be influenced by the overuse of antibiotics in both human and veterinary medicine, as well as by environmental contamination [216]. The One Health approach promotes collaborative efforts across sectors to reduce the misuse of antibiotics, implement sustainable agricultural practices, and develop antimicrobial stewardship programs [209,215,217]. By focusing on the broader environmental and ecological factors contributing to AMR, this approach offers a comprehensive strategy for mitigating the spread of resistant strains and fostering long-term solutions to the AMR crisis [218].

10. Role of Policymakers and Regulatory Bodies

Policymakers and regulatory bodies play a pivotal role in advancing the development and adoption of endophyte-derived antimicrobials. They can facilitate the necessary research and development by providing funding, establishing research grants, and creating policies that incentivize the exploration of natural products as alternative therapies. Regulatory bodies, in turn, must develop frameworks to ensure the safe and ethical use of endophyte-derived compounds, ensuring that these therapies meet rigorous standards of safety and efficacy before being integrated into healthcare systems [219,220]. By fostering collaboration between researchers, the pharmaceutical industry, and healthcare providers, policymakers can help promote the adoption of novel antimicrobials that address the growing threat of AMR.

11. Geographical Perspective of Antibiotic Resistance

Antibiotic resistance is a global issue, but its impact varies significantly by region [161]. In Africa, the challenge of multidrug-resistant pathogens is exacerbated by limited healthcare infrastructure, inadequate surveillance, and widespread antibiotic misuse in both human healthcare and agriculture [213]. Despite these challenges, Africa is home to a rich diversity of medicinal plants, many of which have bioactive compounds with potential antimicrobial properties. The exploration of endophytes within these plants offers an exciting opportunity to develop new antimicrobial therapies tailored to the region's unique needs [213]. However, unlocking the full potential of endophytes in Africa requires

addressing key barriers, including limited research capacity, insufficient funding, and the lack of adequate infrastructure to support the development of these novel therapies.

Endophytes and Antibiotic Resistance in Africa

Antibiotic resistance in Africa is a pressing concern, and the continent faces unique challenges in combating drug-resistant pathogens. The widespread use of antibiotics in both human and veterinary medicine, combined with limited regulatory oversight, has contributed to the rapid emergence of resistant strains [181,213]. Furthermore, Africa's healthcare systems are often under-resourced, which impedes the ability to address the growing burden of multidrug-resistant infections effectively. In this context, endophytes, which are microorganisms that live within the tissues of plants, offer a promising alternative. These endophytes produce a variety of bioactive compounds that have been shown to possess antimicrobial activity against drug-resistant pathogens, including those responsible for diseases such as tuberculosis, malaria, and HIV [213]. The rich biodiversity of African medicinal plants provides a unique opportunity to identify novel endophytes with antimicrobial properties that could serve as the basis for new therapies. Studies have shown that Indigenous plants, often used in traditional medicine, harbour endophytes with promising bioactive compounds that may provide effective solutions to combat resistance [211]. However, the implementation of endophyte-based therapies in Africa faces significant challenges, such as limited research infrastructure, lack of funding, and insufficient capacity to conduct large-scale clinical trials. To overcome these barriers, it is essential to foster collaborations between local researchers, international organizations, and policymakers to build research capacity and ensure that the benefits of endophyte-based therapies are realized. Moreover, the integration of endophytes into Africa's healthcare systems requires addressing the economic challenges associated with drug development and ensuring that these therapies are accessible and affordable for the population. This could involve utilizing local resources to cultivate and produce endophyte-based treatments, thereby reducing costs and promoting sustainable development. The role of international partnerships and funding agencies will also be crucial in supporting research initiatives and providing the necessary resources for the successful commercialization of endophyte-derived antimicrobials in Africa [213,214].

12. Limitations in the Study of Endophytes

Certainly, while endophytes hold immense promise, several limitations hinder their use and study. Understanding the diverse interactions between endophytes and their host plants is challenging. These relationships can vary greatly depending on the host, environmental factors, and the specific endophytic species involved, making it difficult to generalize findings. While promising bioactive compounds are found within endophytes, scaling up production for commercial use can be challenging and costly, affecting their viability in large-scale applications. For instance, the paucity of information identified in this study on the isolation and metabolite production by endophytic algal and mycoplasma bacterial species can be attributed to several factors. Historically, more attention has been given to endophytic fungi and bacteria within plants compared to algae and mycoplasma species. This bias in research focus has resulted in limited exploration and documentation of these endophytic groups.

Endophytic algae and mycoplasma are often more challenging to isolate compared to other endophytes due to their microscopic nature, complex associations with host plants, diverse habitats within plant tissues, and lack of adequate understanding of the biology and ecology of endophytic algae compared to other microorganisms. This lack of understanding makes it harder to identify and study these organisms effectively and hinders research

efforts. Techniques and methodologies specific to isolating and studying these endophytic species might be less developed or less accessible compared to those available for other types of endophytes, contributing to the paucity of information. Furthermore, endophytic algae and mycoplasma might have been underestimated in their potential contributions to metabolite production and their role in plant health. This underestimation could have led to less research interest in this area. Efforts to address these gaps in research, including advancements in isolation techniques, increased awareness of the importance of endophytic algae and mycoplasma, and targeted studies focusing on their metabolite production and potential applications, could help alleviate the paucity of information and enrich the body of knowledge in this field.

13. Conclusions and Future Perspectives

The exploration of endophytic microorganisms residing within medicinal plants has unveiled a treasure trove of bioactive compounds with immense therapeutic potential. These metabolites exhibit diverse biological activities, including antimicrobial, antioxidant, anticancer, and anti-inflammatory properties, among others. The future of bioactive metabolites from medicinal plant endophytes is brimming with possibilities. Further research should focus on elucidating the biosynthetic pathways of these compounds, optimizing their production through fermentation or biotechnological methods, and exploring their potential synergistic effects. Additionally, efforts to enhance extraction techniques and scale up production are crucial to facilitate their commercial viability. Integration of advanced technologies like metabolomics and genomics will enable a deeper understanding of these compounds, accelerating their translation from lab to market. Collaborations between academia, industry, and traditional medicine practitioners can foster a comprehensive approach toward harnessing these bioactive metabolites for novel drug development and therapeutic interventions. Harnessing these compounds can revolutionize drug discovery, providing novel candidates for the treatment of various ailments and preventing the biodiversity depletion of endangered plant species.

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