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SHORT REVIEW

Biological Potential and Different Pharmaceutical Applications of Bioactive Secondary Metabolites Obtained from Endophytic Fungus

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Abstract

An analysis of the quantity and origins of bioactive agents can show the character of that natural products play in the finding of new therapeutic agents. At least 200,000 naturally occurring metabolites have different bioactive characteristics. Natural product discovery includes isolating, structurally elucidating, and establishing the bio-synthetic pathway of secondary metabolites. Scientists are very interested in this topic because of the structural diversity, complexity, and diverse bioactivities of isolated molecules. Secondary metabolites from marine-derived fungi have also been established to be quite important. The finding of novel species of endophytic fungi and the search for novel anti-fungi substances should continue.

Keywords: Endophyte Fungi, Pharmaceutical Application, Secondary Metabolites

1. Introduction

These anti-property bioactive metabolites are organic compounds formed by fungi, or plants, with no direct evidence of growth and production. Some specific types of secondary metabolites have been limited to an accumulated group of species within the phylogenetic group. Secondary metabolites have frequently been seen to play an important function in shielding the plant against external invading elements, herbicides, and other interspersion motions. For many centuries humans have been using secondary metabolites as various drugs, flavours, dyes, and recreational drugs. Secondary metabolites have always been supportive of their host. They also play an important role in functions such as protection, competition, and species relationships. But it has often been observed that hosts never use secondary bioactive metabolites to survive. Every day, new effective medications are needed to treat malignancies, drug-resistant, fungal infections, developing viruses, and parasitic protozoa diseases.

Natural products have served as the foundation for the bulk of novel medications, and their continuing significance in many cultures traditional health systems has reflected the bioactive qualities of a diverse range of flora[1]. Following the discovery of penicillin from *Penicillium notatum* in 1928, Alexander Fleming first detailed the role of fungi in the production of bioactive compounds. After that, there has been a particular focus on the discovery of natural products from fungi, especially during World War II, with large-scale production of secondary metabolites. They distinguish themselves among common microorganisms as potential sources of natural products by producing huge amounts of bioactive compounds at a sustainable

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and reasonable cost through large-scale cultivation and fermentation of source organisms[2].

Fungi were isolated from soil samples in earlier times. But in the search for new sources of bioactive metabolites especially those that are associated with higher plants and these fungi have been proven to be a probable resource of bioactive metabolites producing a vast category of new bioactive secondary metabolites[3,4]. In recent times, bioprospecting is a term commonly used to clarify the discovery of bioactive metabolites or different organisms of commercial importance from the world's biological community. Endophytic Microorganism support in increase in several plant growth parameters, such as shoot and root length and fresh and dry weight[5].

2. Review of Literature

2.1 Endophytes

The term 'endophytes' includes all those organisms that raise inside plant tissue without any causing symptoms of the disease[5]. Endophytic microorganisms, therefore, may be defined as those microorganisms (mostly fungi and fungi) which spend their lives in the plant tissues generally below the epidermal cell layers without causing any symptoms of disease[6]. By some conditions, endophytes can be parasitic, and pathogenic, which can cause symptomatic infections[7]. When the host is stressed and physiological or ecological factors favor virulence, the symbiosis is considered imbalanced[8,9]. Endophytes of one plant may be a pathogen for another, depending on the balance of pathogenicity and endophytic of the microorganism in the various hosts. When the host-endophyte relationship is disrupted, the pathogenic endophytic fungi is killed by sickness or the plant's defense system. The overall position of the partners, fungi virulence, and host defenses all determine whether the relationship is balanced or imbalanced, with both virulence and defense being changeable and influenced by environmental conditions, nutritional position, and developmental phases of the partners. Therefore, a refined balance of mutualism and commensalism is needed between plant defense responses and the nutrient claim of the endophyte[10] (Figure 1).

It has also often been observed that some endophytes show similarities to phytochemical, rightly the host's competence has changed the field of endophytic biology as well as the importance of producing secondary metabolites of endophytes. Based on different facts, the products obtained from nature are different classes, which have been discovered from a different group of endophytes, they have antimicrobial properties. Even some unusual molecules have been isolated from these endophytes such as Antidiabetic, immunomodulators, insecticidal, herbicidal[11]. Newman and Cragg presented the following statistics from the United States Food and Drug Administration (USFDA) from 1981 (December 34) to January 1981 through December 2014. In which the total number of approved drug entries or medical entries is provided in Figure 2.

2.2 Secondary Metabolites

All these secondary metabolites such as antitumor agents, pigments, growth hormones, antibiotics, and others, it is not required that they play a substantial part in the plant's growth and development. It is observed that a secondary metabolite, used as a single pure compound or various mixtures, these natural compounds are often seen working when synthetic medicines stop working. Even though the way they work is slow, it works[12]. These secondary metabolites make them stronger as well as synergistic with other treatments, and new effective drugs are needed every day to treat malignancies, drug-resistant fungi, fungal infections, emerging viruses, and parasitic protozoa infections.

Natural products have served as the foundation for the bulk of novel medications, and their continuing significance in many cultures traditional health systems has reflected the bioactive qualities of a diverse range of flora. The importance of microbes to produce bioactive compounds was first reported by Alexander Fleming in 1928, also by Penicillin was discovered in *P. notatum*. Following that, there has been a particular emphasis on the discovery of natural chemicals originating from fungi, particularly during World War II, with large-scale manufacturing of secondary metabolites. Among common microorganisms, they represent themselves as promising sources of natural products that have the advantage of producing large quantities of large-scale culture and fermentation of source organisms yield

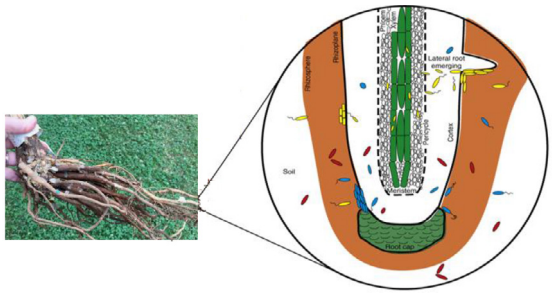


Figure 1. Types of endophytes and their root colonization process. It is the demonstration of the presence of endophytes in most of the tissues of roots like cortex, phloem, rhizoplane[60].

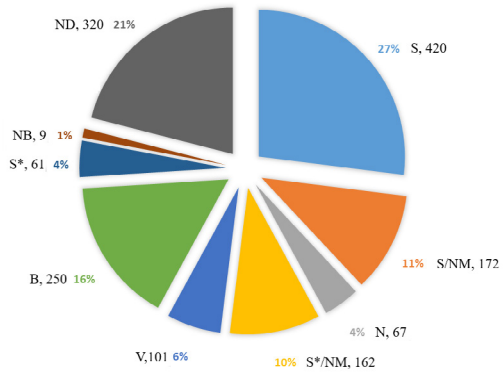


Figure 2. All novel permitted drugs (n=1562) i.e., therapeutic agents or drug entities permitted by the USFDA from the past 34 years (January 1981– December 2014). Here (B) is biological macromolecule, (N) Unaltered natural product, (NB) Botanical drug (defined mixture), (ND) Natural product derivative, (S) Synthetic drug, (S*) Synthetic drug (NP pharmacophore), (S*/NM) Mimic of natural[61].

bioactive chemicals at a sustainable and economical cost[13].

Previously, microorganisms were isolated from soil samples Figure 5. However, in the search for novel sources of bioactive metabolites, fungi, particularly those associated with higher plants, have been proven to be a potential source of bioactive compounds. Table 1, producing a varied category of novel physiologically active secondary metabolites[14,15]. Bioprospecting is a phrase that has recently been coined to describe the finding of bioactive metabolites or other organisms of commercial relevance from the world's biological community.

2.3 Different Antibiotics Production

Despite a large range of antibiotics, we may say that less than 1% of antimicrobial bioactive metabolites agents have medical or economic potential. Penicillin, for example, has a high therapeutic index because it is frequently recognized that it does not harm human cells, although other antibiotics have yet to show such an effect. As more germs become resistant to various antibiotics regularly, it is now critical to develop alternative antibiotics. In addition to research and development in the creation of various novel antibiotics, it has become critical to improve the repackaging and distribution system to retain the efficacy of the currently produced antibiotics. It has been reported on numerous occasions that bioactive metabolites are generated from.

Table 1. List of novel antibiotics produced by endophytic bacteria and their reported

Name of the endophyte	Antibiotics isolated	Reported activities	Source of the Endophyte	Chemical Nature	References
Streptomyces sp. Strain (NRRL -30566)	Kakadumycin	Gram positive and negative bacteria	Greevillea pteridifolia	Peptide with quinoxaline rings	19
Streptomyces sp. strain (NRRL- 30562)	Munumbicin A, B, C and D	Gram positive and negative bacteria	Kennedia nigriscans	Peptide	16,17
Streptomyces sp. GT 2002/1503	Xiamycin A	Anti-HIV	*Bruguiera gymnorrhiza*	Pentacyclic indolosesquiterpine	25
Pseudomonas viridiflava EB 273	Ecomycine B, C	Antifun al	*Lactuca sativa*	Lipopeptides	19
Streptomyces sp. HK 10595	Xiamycin B, Indosespine and Sespenine	Antibacterial	*Kennedelia candel*	Pentacyclic indolosesquiterpine	49

Is *Artemisia annua* capable of manufacturing antimalarial compounds? of concern in the world. *Streptomyces* sp. strains NRRL 30562, an endophyte in *Kennedia nigriscans*, produce broad-spectrum antibiotics. These antibiotics are known as *munumbicins*[16], and depending on the target organism, they have a wide variety of biological activities. *Munumbicins* are active against *Bacillus anthracis* and multidrug-resistant fungi, gram-positive fungi, *Plasmodium falciparum*, and several other drug-resistant pathogens including *Mycobacterium tuberculosis*[17]. Many nonpeptideal fungal metabolites (L-783, 281) have also been identified from endophytic fungi (*Pseudomonas saria* sp.) It was gathered in the Democratic Republic of the Congo's *African bush* near Kinshasa. Some microorganisms (fungi and fungi) also produce immunosuppressive medications; Immunosuppressive medications are currently used to prevent transplant rejection and may be utilized in the future to treat autoimmune illnesses such as rheumatoid arthritis and other insulin-dependent diabetes[18]. Paclitaxel, a highly valuable diterpenoid, may be found in all *Taxus* species around the world.

2.3.1 Ecomycins

The Ecomycins are a type of lipopeptide composed of unique amino acids such as homoserine and -hydroxy aspartic acid. Ecomycins are known to be produced by the endophytic fungi *Pseudomonas viridiflava*[19]. Endophytes are plant-associated fungi such as fluorescent *Pseudomonads*, and *P. viridiflava* strain EB273 produces three antifungal lipopeptides: Ecomycin A, B, and C. The most equivalent of these three drugs is Ecomycin A (in terms of amino acid composition), is an antibiotic syringotoxin that was previously identified[20]. Ecomycin B and C are unique among comparable lipopeptides in that they lack arginine, lysine, ornithine, diaminobutyric acid, and phenylalanine, which are found in compounds such as syringostatins[20,21].

2.3.2 Pseudomycins

Pseudomycins are microbes that produce peptide biochemicals. These peptides are isolated from the pseudomycins liquid media, and the fungi are plant-derived. It is an antifungal peptide linked to lipopeptides that comprises several amino acids including L-diaminobutyric acid, L-chlorothreonine, and together D- and L-hydroxy aspartic acid. *P. syringae* belongs to the *Proteofungi* Phylum's *Pseudomonadaceae* family. The primary peptide in a family of four, pseudomycins A, B, C, and D, pseudomycin A, exhibits extraordinary efficacy against several human diseases[21].

Serine, arginine, hydroxyaspartic acid, diaminobutyric acid, and lysine are among the amino acids included in Pseudoscience A and C. The molecular weight of pseudomycin Dis 2401 Dalton, making it more complicated than pseudomycin A and C. They do, however, appear to be distinct from earlier defined *P. syringae* antimycotics such as syringomycin, syringotoxin, and syringostatins. They are effective against a wide range of pathogenic fungus in humans and plants, including *Candida albicans* and *neoformans*[21]. Munumbicins stimulate the formation of four new categories of bioactive metabolites. Munumbicins A, B, C, and D are antibiotics that have recently been discovered to have a broad spectrum of bioactivity against human or plant pathogenic fungi and fungi, as well as certain *Plasmodium* species. These chemicals were obtained from accumulating fungi.

This endophyte is mostly fungi found in snake holes. Munumbicins have antifungal properties against a wide variety of gram-positive fungi, including *Staphylococcus aureus*, *Bacillus anthracis, Enterococcus faecalis,* and *Streptococcus pneumonia*. A methicillin-resistant strain of *S. aureus* (MRSA, ATCC 33591) and a vancomycin-resistant strain of *E. faecalis* are also Gram-positive munumbicin-resistant fungal strains (VREF, ATCC 51299). Munumbin B has been demonstrated to be effective in the treatment of numerous medication resistance (MDR), *Mycobacterium tuberculosis* fungi, and an acid-fast bacterium. However, the most unusual finding was that the individual MDR strain of *M. tuberculosis* was sensitive to munumbin B, whereas the drug-susceptible variant of the same bacterium was not. Munumbicins C and D are noteworthy because, in addition to being effective against Gram-positive and negative fungi, they are also effective against *P. falciparum*, the most virulent *Plasmodium* responsible for malaria. Munumbicin D was found to be extra potent than chloroquine, the gold typical antimalarial medication[22]. Furthermore, munumbicins B, C, and D caused no visible lysis of human red blood cells.

2.3.3 Xiamycins

Xiamycins are a kind of Indolosesquiterpene identified from prokaryotes. They are Xiamycin-A and its methyl ester-2, two novel pentacyclic indole sesquiterpenes produced from *Streptomyces* sp. strain GT2002/1503, an endophyte from the mangrove plant *B. gymnorrhiza*[23]. Interestingly, Xiamycin A exhibits selective anti-HIV activity. 03 novel indolo sesquiterpenes, Xiamycin B (1b), Indosespene (2), and Sespenine (3), laterally with the known Xiamycin A (1a) from the culture broth of *Streptomyces sp.* strain HKI0595, a microbial endophyte of the extensive mangrove tree, *Kandelia candel* has been reported by According to their findings, these Xiamycins show moderate to considerable antimicrobial bioactivities against a wide range of fungi and fungi, including methicillin-resistant fungi, vancomycin-resistant *Staphylococcus aureus, Enterococcus faecalis* is a kind of fungi. Kakadumycins is a peptide produced by endophytes (*Streptomyces* NRRL30566) that are isolated by the Grevillea tree (*Grevillea pteridifolia*, Synonym: *Grevillea chrysodendron* R. Br)[17]. Kakadumycin A is chemically associated to echinomycin, an extra *Streptomyces* derived quinoxaline antibiotic, a probable anticancer drug[24,25]. Kakadumycin A possesses anti-fungal properties parallel to Munumbicins and is effective against *P. falciparum*.

2.4 Production of Some Volatile Antibiotics by Endophytes Fungi

Muscodar albus is a novel endophytic fungus isolated from *Cinnamomum zeylanicum* tiny organs (cinnamom tree)[26]. By producing a variety of volatile chemicals, other fungi and fungi are efficiently suppressed and killed by this *Xylariaceae* (non-spore-forming) fungus. Because of the mycofumigation impact of *M. albus*, America will soon phase out and restrict the use of methyl bromide in agriculture. These fungi are currently being used to treat or decontaminate human waste. *Muscodor rosans* have been isolated from trees in Australia's northern area; this plant has been seen to grow twice a year.

This fungus is immediately as effective as *M. albus* at inhibiting and killing test microorganisms in the laboratory[27]. The metabolites of these fungi differ from those of *M. albus* or *M. roseus*. The bioactivity metabolites of *Gliocladium* sp. volatile chemicals are neither as high quality or as extensive as those of *Muscoldor* species[28]. *M. albus* is an endophyte isolated from *C. zeylanicum*. Its endophytes create volatile organic compounds in culture and have a broad range of antifungal action. Scientists hope to identify diverse microorganisms with different cultural and biochemical features that can generate highly active compounds using *M. albus* as an assortment tool. Isolates of *Terminalia prostrata* (*nankana karra*), *Grevillea pterifolia* (fern-leafed grevillea), and *Kennedia nigriscans* have also been studied (snake vine). In bioassays with a variety of test microorganisms, including fungus and fungi, every isolate indicated biological activity, but the variety of activity was large (Table 2).

2.5 Products from Endophytes Fungi as Anticancer Compounds

Many natural anticancer drugs have been found in various plants, microbes, and saltwater sources. It is also employed in several cancer treatments[29]. Numerous secondary metabolites derived from endophytes have recently been studied for their anticancer properties. The following are some examples of how endophytes may affect the development of anticancer medications. Since its discovery, the diterpenoid "Taxol" (also known as paclitaxel in the literature) has gotten more attention and interest than any other innovative drug, most likely because of its unique mechanism of action in comparison to previous anticancer medications[29-30]. These anticancer compounds inhibit cancer cell growth and spread by influencing cell division.

Taxol has been proven by the FDA (Food and Medicine Administration) to be an essential drug for breast, ovarian, and lung cancer treatment[31]. Taxol ($C_{47}H_{51}NO_{14}$) was discovered in the bark of *Taxus* trees (*Taxus brevifolia),* which is now its most common source[32]. Tax-producing plants meet seldom and produce a large amount of taxol. As a result, its market price is relatively high. Furthermore, in the context of environmental deterioration, the utilization of plant sources as an exceptional option has limited the availability of this medicine due to damaging yew tree collection[33]. After a long period, a research report on Taxol's qualities was published. Taxol-producing endophyte *Taxomyces andreanae* isolation has developed an alternate way of getting a low-cost and widely available product via microorganism fermentation[34]. Following that, Taxol

Table 2. List of some volatile antibiotics produce by endophyte microbes

Compounds	Biological activity	Endophytic bacteria	References
Bacillomycin	Antifungal, Hemolytic	*B. subtilis, B. amyloliquefaciens*	59
Nystatin	Anti-fungal	*Streptomyces noursei*	60
KB425796-A	Anti-fungal	*Paenibacillus* sp. 530603	61
Bacilysocin	Anti-fungal	*B. subtilis* 168	62
Ecomycin	Anti-fungal	*Pseudomonas viridiflava*	19
Harmaomycin	Antibacterial	*Streptomyces* sp.	63
Munumbicin	Antibacterial	*Streptomyces* NRRL 30562	16
Tetracyclin	Antibacterial	Streptomyces remosus and S. aureofaciens	64
Bacteriocins	Antibacterial	B. subtilis	65
Amicoumacin	Antibacterial, anti-inflammatory	*B. subtilis*	66
Treponemycin	Anti-tuberculous	*Streptomyces* strain MS-6-6	67
Camptothecine	Anti-cancer	*Lysinibacillus* sp. and *B. cereus*	68
Androprostamines	Anti-prostate cancer	*Streptomyces* sp. MK932-CF8	69
Doxorubicin	Treatment of Breast cancers and tumors	*Streptomyces* sp.	70
Indolocarbazoles	Anti-cancer	*Streptomyces* sp.	38
Anthracyclin	Antitumor	*Streptomyces* sp. YIM66403	2
Monensin	Prevent coccidiosis	*Streptomyces cinnamonensis*	3
Daptomycin	Bacterial infections of skin and underlying tissues	*Streptomyces roseoporous*	4
Saadamycin	Anti-dermatophyte	*Streptomyces* sp. Hedaya48	71
b-exotoxin	Insecticidal	*B. thuringiensis*	72
Strepturidin	Immunotherapy	*Strepturidin Streptomyces albus* DSM 40763	73
Xiamycin	Anti-HIV activity	*Streptomyces* sp.	49

was discovered in a variety of fungal endophyte genera that were either connected or not with yews, including *Wollemia nobilis*[35], *Taxodium distichum*[36], *Bartalinia robillardoide*[30], *Pestalotiopsis terminaliae*. If we are talking about another anti-cancer medicine, it is the alkaloids "Camptothecin" ($C_{20}H_{16}N_{2O4}$), a powerful anti-neoplastic agent discovered in the wood of *Camptotheca acuminata* Decaisne (*Nyssaceae)* in China[37]. Camptothecin and 10-hydroxycamptothecin are two major forerunners of the anticancer drugs irinotecan and topotecan. Unaltered Camptothecin is less commonly used in medical science due to constraints such as low solubility and high toxicity in aqueous solvents[38]. As a result, methods for isolating, separating, and producing Camptothecin and its equivalents from new endophytic fungal sources must be developed. Microbial products and its two derivatives (9-methoxy camptothecin and 10 hydroxy camptothecin) are previously reported. Which has been used in the treatment of various diseases in the medical field and will continue to happen in the future. Because it is a natural product that has a less adverse effects on health (Figure 3).

There have been several reports describing additional camptothecin (or equivalents) generating endophytes microorganisms[39,40]. Endophytes have since been involved in various studies aimed at developing novel ways for new medication discovery. "Ergoflavin" ($C_{30}H_{26}O_{14}$), a dimeric xanthene was characterized as a novel synthesized anticancer drug obtained from an endophytic microbe thriving on the leaves of a traditional Indian medicinal plant[41].

When it comes to another chemical, "Secalonic acid D" ($C_{32}H_{30}O_{14}$), a mycotoxin belonging to the ergochrome class, is well known for its anticancer properties. It was derived from mangrove endophytic microorganisms and demonstrated great cytotoxicity on K-562 and HL-60 cell lines by causing apoptosis in leukemia cell lines[42]. "Phenyl propanoids" are

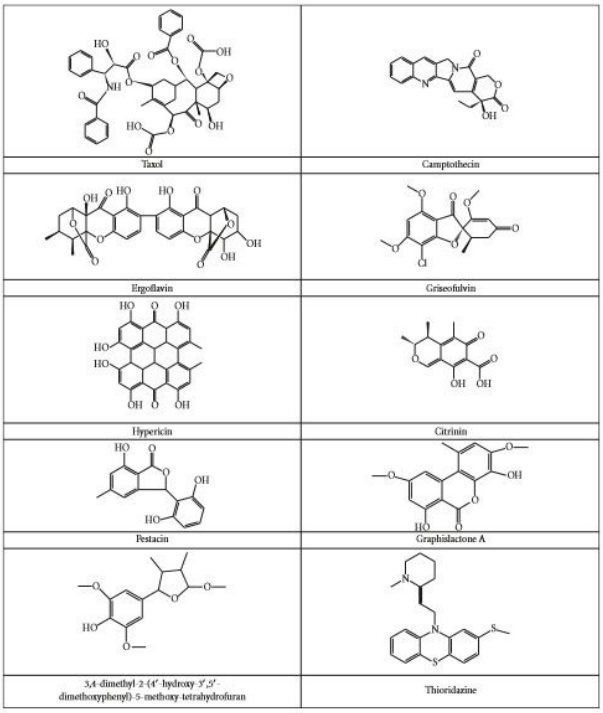


Figure 3. Selected natural bioactive metabolites with their chemical structure from endophytic microorganism.

gaining popularity in medicine due to their antifungil, anticancer, antioxidant, immunosuppressive, and anti-inflammatory activities.

Even though phenyl propanoids are among the most abundant bioactive metabolites produced by fungi, the paper demonstrates the creation of a substance that has been medically characterized in many reports. Endophytes of *Penicillium brasilianum* were discovered in the root of the *Melia azedarach* plant. Furthermore, this endophyte increases the production of phenyl propanoid amides[43]. Similarly, 02 monolignol glucosides, syringing, and coniferin, which are not only produced by plants but also manufactured by microorganisms, were detected as chemical indicators during the formation of fungal-plant interactions by endophytic *Xylariaceae species*. Koshino and colleagues isolated two phenyl propanoids and lignin from *Epichloe typhina* stromata on *Phleum pretence*[44].

Lignans are many forms of anticancer mediators that are generated as secondary metabolites by the shikimic acid system and serve various biological activities, making many lines of research attractive. Despite having only two phenyl propane units (C6-C3) in their molecular backbone, lignans have a wide structure and variety. "Podophyllotoxin" ($C_{22}H_{22}O_8$) and because of their cytotoxicity and antiviral properties, its analogs are clinically beneficial, and they are appreciated as the precursor to valuable anticancer drugs such as *teniposide*, *etoposide,* and *etoposide*[45]. Although many tetralin lignans, for example, podophyllotoxin, are naturally important and generated by *Podophyllum sp.,* alternate sources have been investigated to avoid endangered plants.

Trametes hirsuta, a novel fungal endophyte, has been discovered to produce podophyllotoxin and other aryltetralin lignans that have anticancer and antifungal properties[46]. Endophytic fungi such as *Aspergillus fumigatus* Fresenius isolated from *Juniperus communis* L. Horstmann[45], *Phialocephala fortinii* isolated from *Podophyllum peltatum*[47], and *Fusarium oxysporum* isolated from *Juniperus recurva*. Lastly, talk about some different types of the anti-cancer compound that is obtained from endophytes microbes. such as "cytoskyrins", "phomoxanthones A" and "B"[48], "photinides A-F"[49], "rubrofusarin B"[50], and "(+) epiepoxydon[51] (Figure 4).

2.6 Products from Endophytes Fungi as Antimicrobial Compounds

Antibiotic metabolites are low molecular weight organic natural compounds produced by microbes that are active against other microorganisms at low concentrations. Pathogens can build a robust immune mechanism in resistance to invasive germs by creating secondary metabolites, according to the theory[52]. To date, flavonoids, steroids, phenols, peptides, quinones, alkaloids, and terpenoids are among the antimicrobial compounds extracted from endophytes that have been studied[53].

The development of novel anti-fungal metabolites by endophytes is an important substitute for tackling escalating levels of drug resistance in plant and human diseases, a scarcity of effective antibiotics against various fungal species, and a scarcity of novel antimicrobial compounds in development, maybe because of the comparatively low returns on investment[50-53].

The anti-microbial chemical is not only utilized as a treatment but is also used to prevent food spoilage fungi to preserve the food, making it a global concern in the food chain. This has occurred, and it is becoming

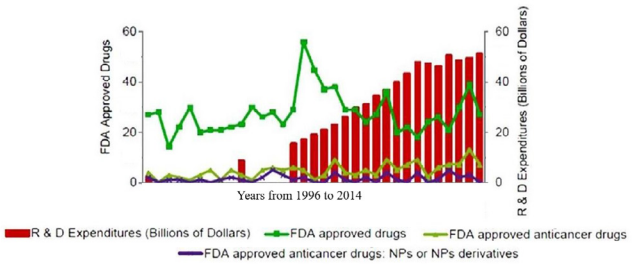


Figure 4. Different bioactive metabolites produced in different years. Source of data obtained and modified from: (1) Pharmaceutical research and Manufacturers of America[62].

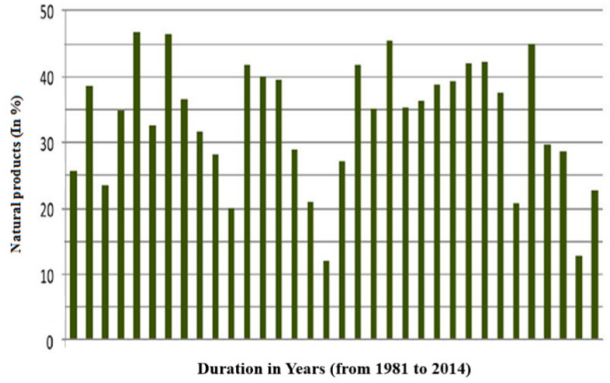


Figure 5. Percentage of Natural products (N) i.e., therapeutic agents or drug entities approved by the USFDA from the past 34 years (January 1981– December 2014)[62].

more often by the day[54]. The bioactive metabolite described as "7-amino-4-methyl coumarin" was produced from culture extracts of the endophytic fungi *Xylaria* sp. YX-28 isolated from *Ginkgo biloba*[55]. The chemical exhibited broad-spectrum inhibitory efficacy against a diverse array of food-borne and food-spoiled fungi, including *E. coli, S. typhia, A. niger, S. aureus, A. hydrophila, Yersinia* sp., *V. anguillarum, Shigella* sp., *V. parahaemolyticus, C. albicans, P. expansum*[56].

3. Conclusion

The identification of numerous bioactive metabolites that are effective against infections. Our findings from a review of the literature indicate that endophytic fungi have the potential to manufacture a variety of antimicrobial medications, as many new bioactive metabolites have been discovered because of this research. These findings reinforce the growing body of evidence that endophytic microorganisms create bioactive compounds, they are not only involved in the host-endophyte connection but also have various therapeutic uses, in agricultural, and nutraceutical industries. According to a study of the literature, endophytic fungi are a key store of numerous secondary metabolites.

As a result, the capability of plants to acclimatize to stressful circumstances, as well as the important and valuable role of endophytes fungi against pathogens (infection by environmental conditions), can be recognized, and because they continue to be an important proven source of pharmaceutical importance as well as secondary metabolites, broad studies of various endophytes fungi are expected to become an important component of bacteriology. Furthermore, according to rapidly developing evidence, a considerable number of medications are created naturally through the interaction of endophytes and endophytes with their hosts[57]. Most of the researchers attention is naturally drawn to the subject of natural products daily[58].

But there are several difficulties in identifying and isolating bioactive metabolites like complexity of natural sources, low concentration, structural diversity, instability, complex extraction and purification processes, bioactivity testing, scale-up challenges, interference from other compounds, and limited availability of reference standards. Despite the various competition provided by different approaches of new drug discovery, bioactive metabolites are still delivering suitable information on emerging new medicinal lead compounds.

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