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REVIEW ARTICLE

Endophytic fungi—Alternative sources of Pharmacologically Significant Compounds: A Review

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ABSTRACT
Fungal endophytes have been extensively studied due to inherent abilities to produce secondary metabolites which has great pharmacological significance. These fungi alive within ethe plant tissues and do not harm ethe host plant. The have been shown to produce chemicals that have strong antioxidant, anticancer, and antibacterial effects. The ability of endophytic fungus to yield new bioactive chemicals makes them valuable in the field of medicinal chemistry. Recently, researchers shown great interest in ethe isolation and identification of pharmacologically important substances generated from endophytic fungus. The bioactive components in ethe isolated endophytic fungus were determined by spectrum analysis and chromatographic separation. The potential antibacterial activity of ethe chemicals produced from the fungus was further investigated in ethe pharmacological, industrial and agricultural sectors. This review has demonstrated the presence of a broad class of secondary metabolites in endophytic fungal extracts that are similar to host plant extracts.
Keywords: *Antimicrobial, Bioactive compounds, Endophytic fungi, Secondary metabolites*

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INTRODUCTION

An endophyte typically belongs to fungi family that coexists with a plant without appearing to cause any harm[1]. Endophytes are omnipresent and may be found in every type of plant, including stems, leaves, roots, and petioles. Because they keep harmful organisms from invading host plants, endophytes may be advantageous to them [2]. The common name for *Elaeocarpus sphaericus* is Rudraksha. It is a huge, broad-leafed, evergreen tree that grows in Himalayan range of India. [3] The plant rudraksha sometimes referred to as the "king of Herbal Medicine," is applied in conventional medicine to address a range of ailments, including liver illnesses, asthma, hypertension, anxiety, depression, palpitations, nerve pain, epilepsy, and migraines. [4] *Myristica fragrans* is a 5–13 m tall tiny evergreen tree. Which belongs to *Myristicaceae* family and frequently referred to as nutmeg. It has been found to provide several health benefits and is an important herb in Ayurvedic treatment. It has astringent, aromatic, digestive, and appetizer properties.[5] Endophytic fungi (EF) have prevalent source of secondary metabolites (SM) which includes intriguing structures and pharmacological activities. It is commonly recognized that some species of ascomycetes, both sexual and asexual, as well as rarely basidiomycetes and zygomycetes, may live in ethe vascular plant's aerial tissues without showing any symptoms. According to reports, these endophytic fungi mostly occur in conifers [6][7]. A few tropical plants have also been investigated for the existence of endophytes, such as mangroves [8], bananas [9], and palms [10].

THE CULTIVATION AND EXTRACTION OF ENDOPHYTIC FUNGI

Study on EF conducted in Bangladesh which is separated from *Syzygium cumini* plant in Bangladesh to investigate their pharmacological properties and plant constituents [11]. Nearly, 8 fungal isolates were examined through molecular and morphological strategies which includes "*Phyllosticta sp., Fusarium sp., Penicillium sp., Diaporthe sp., and Pestalotiopsis sp."* and preliminary screening revealed that the fungal

and plant extracts contain "anthraquinones, isocoumarins flavonoids and coumarins" [12]. The *Penicillium sp*. fungal extraction demonstrated significant level of free radical scavenging action, nearly as effective as ascorbic acid. Several fungal extracts exhibited cytotoxic activity, suggesting the abundance of biologically active metabolites [13]. The leaf as well as bark extracts presented antifungal and antimicrobial action, while Penicillium sp. and Pestalotiopsis sp. preparations were susceptible to test microorganisms. Present research analysed the pharmacological potential of EF of *Syzygium cumini* in Bangladesh and explores new chemicals derived from these endophytes. The study outcomes discussed the potential pharmaceutical applications EF in bioactive utilisation [14].

ISOLATION, CULTIVATION AND ENDOPHYTIC FUNGI'S ANTIMICROBIAL ACTION

The EF is separated from the medicinal plant Tupistra echinensis Baker in China's Qinling Mountains exhibited diverse antimicrobial properties [15]. Analysis of ITS rDNA sequences identified 371 fungal isolates related to 35 genera across three phyla. Mostly, genera were *Aspergillus, Fusarium, Dactylonectria, and Collectotrichum*. HPLC and UPLC-QTOF MS evaluation revealed two lead compounds with strong antimicrobial activity from strains F8047 and F8075[16]. Metabolites extracted through EF RS-5 is further isolated from Pteris pellucida which showed notable antibacterial effects against *S. aureus* and *A. hydrophila*, and antifungal effects against *Curvularia sp., Fusarium sp.,* and *Cornyespora sp*.

NOVEL ENDOPHYTIC FUNGI BIOACTIVE COMPOUNDS: THEIR BIOLOGICAL CHARACTERISTICS

Endophytic fungus has shown a variety of bioactive metabolites with multiple biological effects, including "antioxidant, antibacterial, anticancer immunosuppressive, anti-inflammatory, antiviral, antiparasitic, antifungal and properties" [17]. Agarwal and associates [18] acknowledged that several investigations have demonstrated that endophytes had defense mechanisms to thwart pathogenic invasion by generating secondary chemicals [19][20][21]. Bioactive metabolites are small organic molecules produced by bacteria, with lower antimicrobial activity compared to other substances with potential antibiotic properties. Endophytes produce antibacterial compounds that belong to different structural classes, including phenols, quinines, terpenoids, peptides, alkaloids, and flavonoids [22]. In Santiniketan, "Endophytic Alternaria alternate" (AE1) was detected in mature, healthy leaf of *Azadirachta indica* plants. The fungal extraction presented impressive antimicrobial effects against different bacteria, including "*Staphylococcus epidermidis* MTCC 2639, Bacillus subtilis MTCC 121, *Pseudomonas aeruginosa* MTCC e741, *Salmonella typhimurium* MTCC 98, Escherichia ecoli MTCC 1667, *Staphylococcus aureus* MTCC 96 and eat MICs" ranging from 300 to 400 µg/mL. In a study conducted in 2000 by Peláez and colleagues, it was found that a promising antifungal triterpene glycoside exhibited inhibitory effects against *Aspergillus esp.* and Candida, with diameters of 19 mm and 30 mm, respectively. [23].

Identification of New Bioactive Compounds and their Biological activities

A. Polyketides
a. Chromones
b. α-Pyrones
c. Other Polyketides

B. Alkaloids
a. Cytochalasin
b. Indole Alkaloids
c. Diketopiperazine Derivatives
d. Other Types of Alkaloids

C. Terpenoid
a. Sesquiterpenoids and Their Derivatives
b. Diterpenoids
c. Triterpenoids
d. Meroterpenoids

D. Lactones
E. Anthraquinones, Quinones and Related Glycosides
F. Steroids
G. Other Types of Compounds [24]**.**
A. Polyketides
a. Chromones

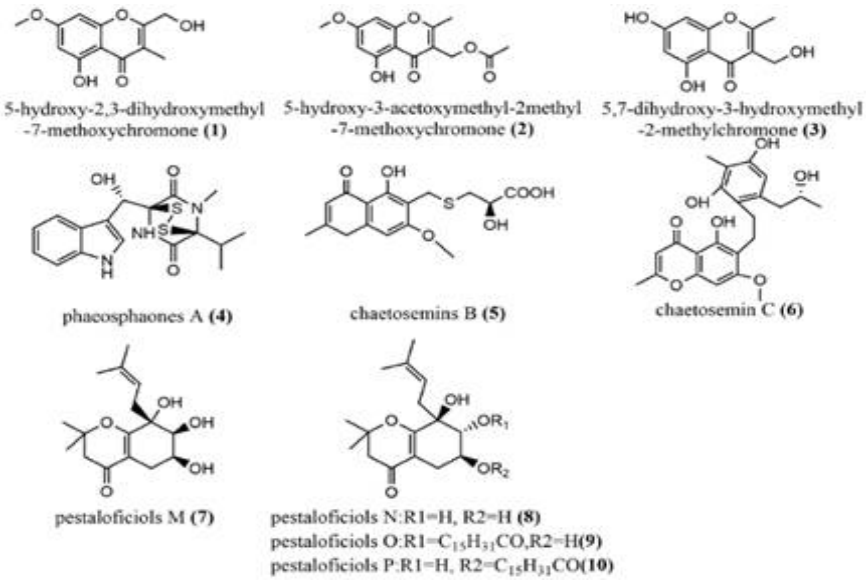

Figure:1 Phaeosphaonesa A 4 and other bioactive compounds

Specifically, to enhance the synthesis of compounds 1, 2, and3 in their designated production sites within the regions. With "minimum inhibitory concentrations" (MIC) of 50µg/mL, 50µg/mL, and 6.25µg/mL, respectively, compounds 1-3 showed significant antibacterial effect against *Fusarium oxysporum*. These results were better than the antimicrobial test results for triomefon, the medication that tested positive (MIC value: 100µg/mL) [25]. Phaeosphaonesa A4 (Figure1) was found in *Phaeosphaeria fuckelii* and has a distinct structure with a β-(oxy) thiotryptophan motif. At a concentration of 100µM, Compound 4 exhibited significant inhibition on mushroom tyrosinase (IC50, 40.4 µM) than kojic acid (IC50, 33.2 µM[26]. Two "fragrant chromones, Chaetosemins B-C 5-6", were discovered in the brown rice cultures of *Chaetomium seminudum*. Compounds 5-7 each had units of "L-cysteine and D-cysteine", respectively. [27]. Compounds 7–8 showed ability to inhibit "HIV-1 repetition in C8166 cells", with EC50 having 56.5µM and 10.5 µM, respectively. Compounds 9–10 presented cytotoxic impact on the human cancer cell line HeLa, with IC50 values of 56.2 µM and 74.9 µM, respectively. "Compound 10 showed significant impact on antifungal responses against "Aspergillus fumigatus" with an IC50 of 7.35µM.

α-Pyrones

Two alpha-pyrone derivatives, named Necrospora eudagawae eudagawanones A-B (11-12), were discovered in a fungus inside oak trees [28]. These substances have unique oxidation units located at the C-2 region. Compound 11 demonstrated considerable antifungal properties against "*Rhodoturula glutinis*", with a MIC of 66 µg/mL. Additional research is required to confirm the limited effectiveness of substances 11 and 12 against different types of fungus and mammalian tissues. This may be attributed to the antimicrobial technique utilized, which included diluting the substances in a series [29]. The" Aspergillus *niger*" MA-132, extracted through "Avicennia marina, synthesized nigerapyrones A-B" (13-14), which exhibited significant antifungal properties against HL60 and A549 tumor cell paths, with IC50 (0.3- 5.41) µM. The user's text is [30]. The "Ficipyrones A-B" (15-16) were obtained from solid extracts of "*Pestalotiopsis fici*." Substance 15 exhibited potent antifungal properties towards "*Gibberella zeae* CGMCC 3.2873", with an IC50(15.9µM).

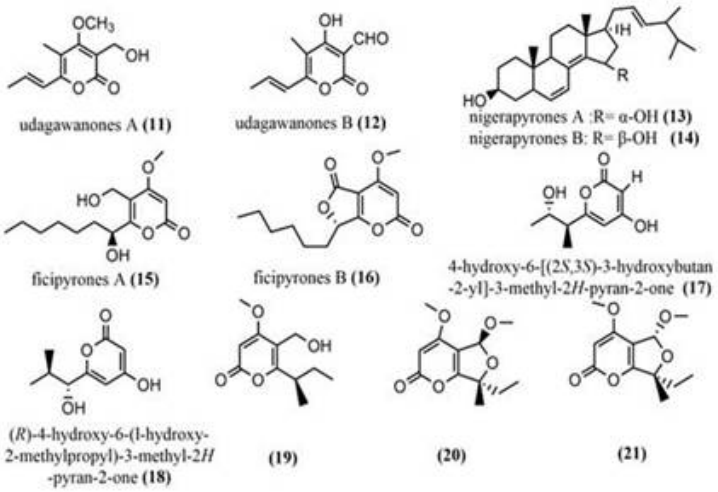

Figure:2 Ficipyrones A-B and other bioactive compounds

Other Polyketides

The EF *Phoma sp*. from marine red algae NTOU4195 yielded "phomaketides A-E (22-26), pseurotins A3 (27), and G (28)". Compound 22 showed significant anti-angiogenic properties (IC50 8.1 μM), and compound 24 inhibited NO in "LPS-induced RAW264.7 cells" (IC50 8.8 μM).[31] Simplicilones A-B (29-30), isolated from *Duguetia staudtii* via Simplicillium sp., were ineffective against "Bacillus subtilis DSM 10 and Staphylococcus aureus DSM" 346 but showed cytotoxicity on the KB3.1 cell line (IC50 1.25 and 2.29 μg/mL).[32] The "*Cladosporium cladosporioides* MA-299" isolated from "*Bruguiera gymnorrhiza*" leaf produced "5R-hydroxyrecifeiolide (31), 5S-hydroxyrecifeiolide (32), and ent-cladospolide F-H" (33-35). The substances demonstrated antibacterial efficacy towards "*Staphylococcus aureus and E-coli*", with minimum inhibitory concentrations interval from 1.0 to 64μg/mL. Compound 33 exhibited a modest level of inhibition against acetylcholinesterase (IC50 40.26μM). *Aspergillus fumigatiaffinis* produced the antibacterial compound palitantin (36), effective against "*Enterococcus faecalis* UW 2689 and *Streptococcus pneumoniae* 25697" (MIC 64 μg/mL).[33-35] Alternaria alternata ZHJG5 in Cercis chinensis leaves yielded bialternacin G (40), (+/-)-50-dehydroxytalaroflavone (38-39), and isotalaroflavone (37). Compound 37 had significant effects against rice blight from *Xanthomonas oryzae* pv. oryza (75.1% protection at 200μg/mL).[36] Peyronetides A-D (41-44) from *Peyronellaea sp.* FT431 showed moderate to mild cytotoxicity on TK10 human kidney cancer and A2780cisR human ovarian tumor tissues (IC50 6.7 to 29μM).[37] Compound 45 showed mild cytotoxic properties on HepG2 and Hela cell lines, with IC50 > 20μM.[38]

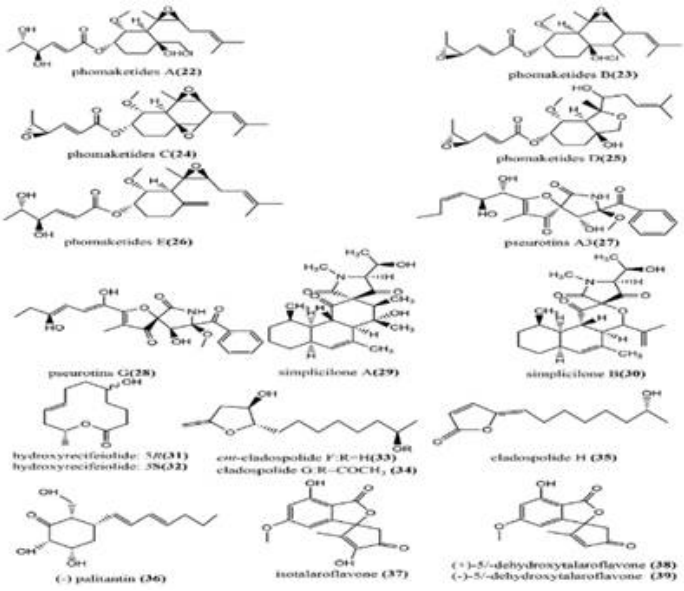

Figure 3 Peyronetides A-D and other bioactive compounds

Alkaloids

Cytochalasin

Phomopsis sp. sh917 brown rice cultures yielded Phomopsisin A-C 46-48 (Figure4) with a methylation-deficient backbone when extracted from "*Isodon eriocalyx* var. laxiflora stems". Compound 46 showed superior performance compared to the "positive control L-NMMA (IC50 value of 42.34 μM) in inhibiting NO production in RAW264.7 cells produced by LPS, with an IC50 value of 32.38eμM" [39]. Compound 46 contained a unique tetracyclic ring structure with a special 2H-isoxazole group. The extremely oxidized cytochalasin alkaloids were discovered and separated from *Chaetomium globosum* TW1-1. These include "7-O-acetylarmochaetoglobin S50 and armochaetoglobins S–Z 49–57" in Figure 4. The impact of each molecule was evaluated on five human tumour cells such as "HL-60, A-549, SMMC-7721, MCF-7, and SW-480" using MTT approach. Compounds 56–57 demonstrated notable cytotoxic effects, with IC50 values falling between 10.45 and 30.42 μM [40]. Furthermore, the MTS technique was employed to assess the cytotoxic effects of "diaporthichalasins D-H 58-62" (Figure 4) on 4 different types of human tumour cell such as "A549, HeLa, HepG2, and MCF-7". The specimens were derived from robust preparations of the EF "*Diaporthe esp*. SC-J0138" that were collected from the leaves of the "fern *Cyclosorus parasiticus*". Compound 58 shown substantial cytotoxic in all tested human tumour cells, while Compounds 59-62 showed specific cytotoxic impacts on several cell types [41]. The EF "*Cytospora chrysosperma* HYQZ-931", which was discovered in "*Hippophae rhamnoides*", produced "cytochrysins A-C 63-65", when grown in rice cells (Figure 4). Compound 63 demonstrated strong antibacterial efficacy against "*Enterococcus faecium*", with a MIC of 25 μg/mL. Compound 65 had strong antibacterial effects against "*Staphylococcus aureus*", MIC (25 μg/mL)[42].

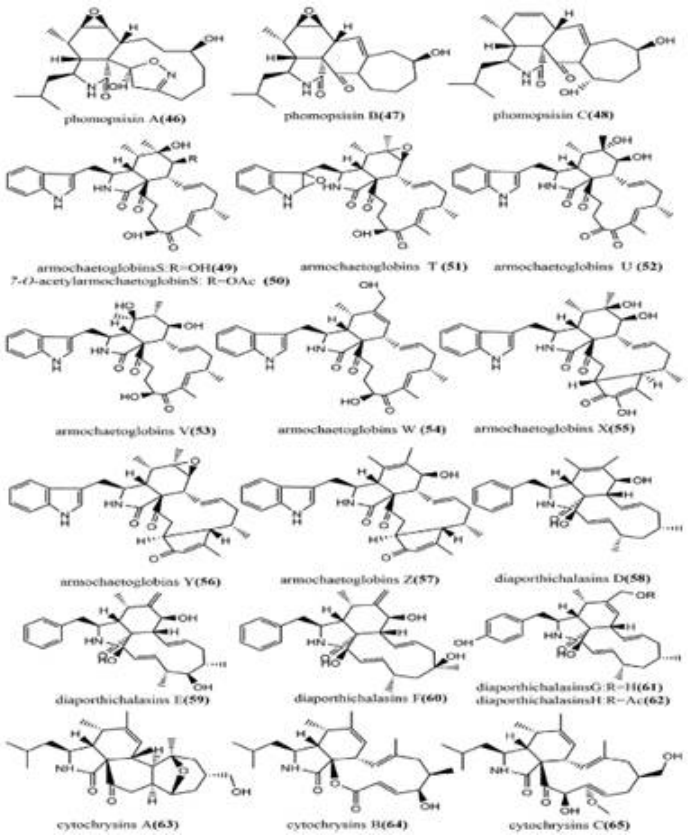

Figure 4 Cytochrysins A-C and other bioactive compounds

Indole Alkaloids

The six "prenylated indole alkaloids (asperthrins A-F, 66-71)" were extracted from the EF *Aspergillus sp*. found in marine environments.[43] Compound 66 showed moderate antibacterial activity (MIC 8μg/mL) and strong anti-inflammatory effects (IC50 1.46 μM) along with compound 69 (IC50 30.5μM).[44] Oxalicine C (72) from *Penicillium chrysogenum* exhibited strong antibacterial activity against *Ralstonia solanacearum* (MIC 8 μg/mL). Scalarane (73) from *Hypomontagnella monticulosa* showed significant cytotoxicity towards "Panc-1, NBT-T2, and HCT116 cancer cell lines"[45] (IC50 0.05-0.75 μg/mL).

Asperlenines A-C (74-76) from *Aspergillus lentulus* demonstrated medium to low antibacterial activity against "*Xanthomonas oryzae* pv. Oryzicola" (MIC 25-100 µg/mL). All compounds were evaluated against five agricultural diseases using the broth microdilution method [46]

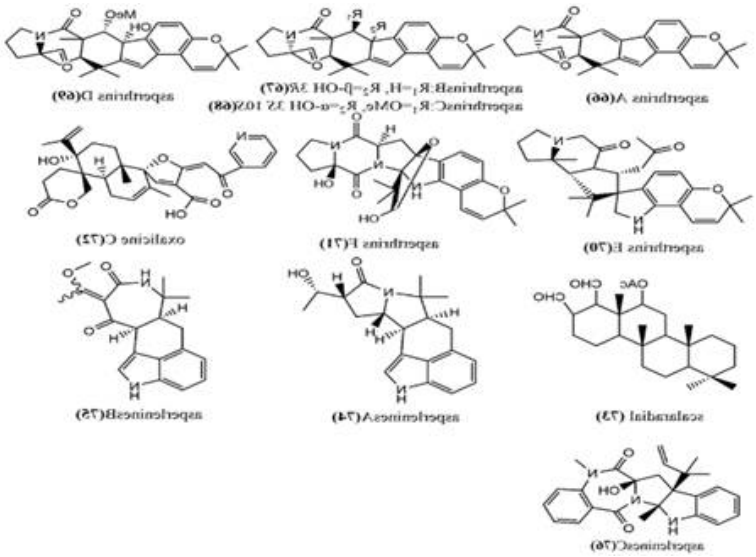

Figure 5 Bioactive compounds

Diketopiperazine Derivatives

Phaeosphaones D (77), a thiodiketopiperazine alkaloid from *Phaeosphaeria fuckelii* in *Phlomis umbrosa*, exhibited stronger mushroom tyrosinase inhibition (IC50 33.2 µM) [47] compared to kojic acid (IC50 40.4 µM). *Paecilomyces variotii* EN-291 microalgae yielded varioloids A-B (78-79), showing significant antifungal activity against *Fusarium graminearum* (MIC 8µg/mL and 4µg/mL)[48]. The "Aspergiamides A–F" (80–85) from *Aspergillus sp*. demonstrated moderate to strong α-glucosidase inhibition, with compounds 80 and 81 having IC50 (18.2µM and 40.7µM) respectively, but no significant effect on PTP1B[49]. *Penicillium brocae* MA-231 produced penicibrocazines A–E (86–90), with potent antibacterial efficacy against "*Staphylococcus aureus* (MIC 0.25 to 32µg/mL). Spirobrocazines A–C (91–93)" from the same fungus showed slight antibacterial effects on "*Aeromonas hydrophilia* and *Vibrio harveyi*" (MIC 16 to 64 µg/mL)[50].

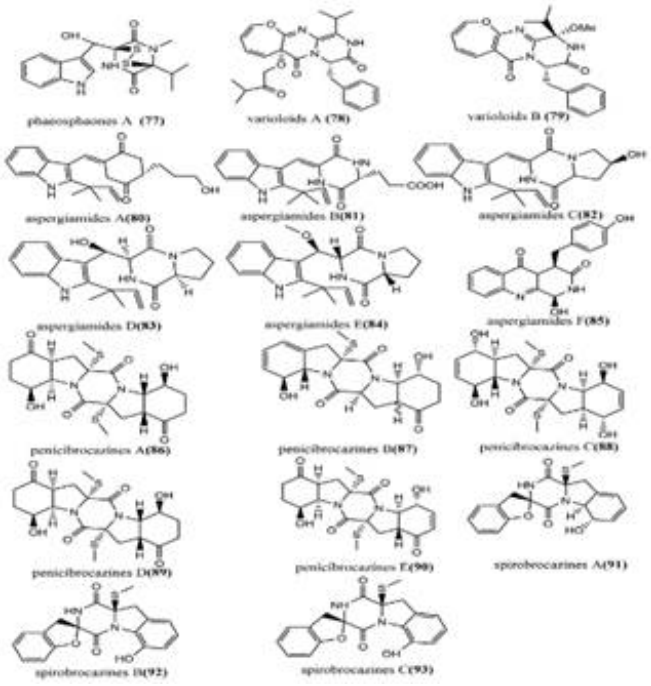

Figure 5 Bioactive compounds

Other Types of Alkaloids

Penicillium vinaceum X1, an EF from Crocus sativus corms, produced the alkaloid compound 94, which showed slight cytotoxic effects on "A549, LOVO, and MCF-7[51] human carcinoma cell lines (IC50 values: 76.83, 68.08, and 40.55μg/mL, respectively)". *Acanthodendrilla* sp. from a sponge yielded "bromotyrosine alkaloids S-Acanthodendrilline (95) and R-Acanthodendrilline" (96). Compound 95 was three times more effective against H292 cells than compound 96, with IC50 values of 58.5μM and 173.5μM, respectively.[52] *Penicillium sumatrense* from Garcinia multiflora leaves produced citridones E–G (97–99), showing moderate to poor antibacterial activity against "Pseudomonas aeruginosa, Staphylococcus aureus, and E-coli" (MIC 32-128μg/mL)[53]. The "New isoprenylisoindole alkaloids, diaporisoindoles A-B" (100–101) were extracted from "*Diaporthe sp*. isolated and the mangrove plant (*Excoecaria agallocha*)". Compound 100 exhibited potent suppression of "Mycobacterium TB protein-tyrosine phosphatase B", with an IC50 value of 4.2μM [54].

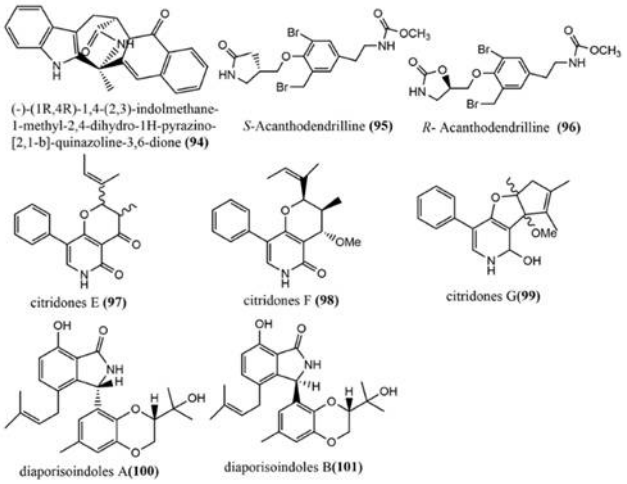

Figure 6: Bioactive compounds of other types of alkaloids

Terpenoids

Sesquiterpenoids and their Derivatives

The EF *Diaporthe sp.* from mangrove *Rhizophora stylosa* synthesized 1-methoxypestabacillin B (107), [55] which, while non-virucidal against HIV and influenza A, may serve as a foundation for potent antiviral compounds. Rhizoperemophilanes A-N (102–115) from *Rhizopycnis vagum* showed selective cytotoxicity, with compound 115 being notably effective against "NCI-H1650 and BGC823 cell lines (IC50: 15.8 μM and 48.2 μM, respectively)"[56] and compounds 106-107 and 113-114 displaying significant phytotoxic effects on rice seedlings. Trichoderma sp. extracted from *Paeonia delavayi* stems yielded trichoderic acid (116) and 2β-hydroxytrichoacorenol (117), with moderate to poor antibacterial properties against "E-coli and *Shigella sonnei*" (MIC: 50-175 μg/mL). Fusarium proliferatum from Chlorophytum comosum roots produced α-pinene sesquiterpenes (118-119) with slight antibacterial effects against MRSA and other bacteria (MIC > 100 μg/mL).[57] The EF "*Aspergillus sydowii* from marine red algae produced (7S, 8S)-8-hydroxysydowic acid (120)", a potent DPPH radical scavenger (IC50: 113.5 μmol/L). *Ulocladium sp*. yielded ophiobolins P–T (121–125), showing moderate antibacterial activity (MIC: 15.6-62.5 μM) and significant cytotoxicity against HepG2 cells (IC50: 0.24 μM).[58][59] *Trichoderma virens* from *Artemisia argyi* roots produced trichocarotins I-M (126-130), exhibiting strong antibacterial effects against E. coli (MIC: 0.5-16μg/mL).[60]

Diterpenoids

Cultures of the EF *Diaporthe sp*. derived from mangroves. QYM12 produced diaporpenoid A 131, a ring diterpene with a tricyclic ring structure that is fused in a 5/10/5 arrangement (Figure 10). The extract was prepared with MeOH. Compound 131 displayed impressive anti-inflammatory properties in the RAW264.7 murine macrophage cell line by inhibiting the generation of NO induced by LPS, with an IC50 of 21.5μM. compound called libertellenone M 132, a diterpene of the pimarane type, was found in the marine endophytic fungus Phomopsis sp. S12 [61] remains unchanged. Compound 132 effectively suppressed the "mRNA expression of pro-inflammatory cytokines IL1β and IL-18 in colon tissue". Furthermore, it significantly decreased the splitting of pro-caspase1 and hindered the movement of NF-κB to the nucleus in macrophages, with the extent of these effects being dependent on the dosage. Administering different intravenous dosages of compound 132 (10 or 20 mg/kg) reduced the severity of

symptoms in a rat model of acute colitis caused by 3% "dextran sulphate sodium". Compound 132, a powerful inhibitor of NLRP3 inflammatory vesicles, is regarded as a potentially efficacious novel treatment for acute colitis e[62]. The EF Phomopsis sp. was shown to contain three distinct "epimarane diterpenoids: pedinophyllol K 133, pedinophyllol L 134, and libertellenone T 135". The OSMAC approach was used to elucidate the attributes of S12 culture. Additionally, compounds 133-134 showed anti-inflammatory properties comparable to compound 135, especially in suppressing IL-6 [63]. Two "Botryosphaerins G-H 136-137, tetranorlabdane diterpenoids" were separated through "ethyl acetate" extract of "Botryosphaeria sp. P483". *Huperzia serrata* Trev, also known as Thunb, was a plant that induced isolation. The antifungal properties of these substances were valuated using the disc diffusion method against *Fusarium solani, Pyricularia oryzae*, and *Gaeumannomyces graminis*. Compound 137 displayed significant antifungal efficacy with a 9 mm inhibitory zone diameter at a dosage of 100 µg/disk. The positive control carbendazim showed inhibitory zone diameters ranging from 15 to 18 mm. Compounds 136–137 were tested for their ability to kill "*Panagrellus redivivus* and *Caenorhabditis elegans*" as well as their antifungal properties. At a concentration of 400 mg/L for 24 hours, they demonstrated moderate nematicidal effects with mortality rates of 30% and 28%[64]. At a concentration of 1.5 µM, Sphaeropsidin A 138, an isopimarane diterpene, hindered the movement of "MDA-MB-231 cells" by 50% and displayed strong preference for five human cancer cell lines. It was obtained from the EF *Smardaea sp.* AZ0432 is a strain of Ceratodon purpureus [65].Substance 139, obtained from Pestalotiopsis adusta cultures isolated from Clerodendrum canescens stems, showed modest cytotoxicity against HL-60 tumor cells with an IC50 of 12.54µM[65]. Asperolides A-C 141-143, new tetranorlabdane diterpenoids found in the *Aspergillus wentii* EN-48 maine brown alga extract, showed moderate cytotoxicity against seven human cancer cell lines with IC50 values ≤ 10µM[66].

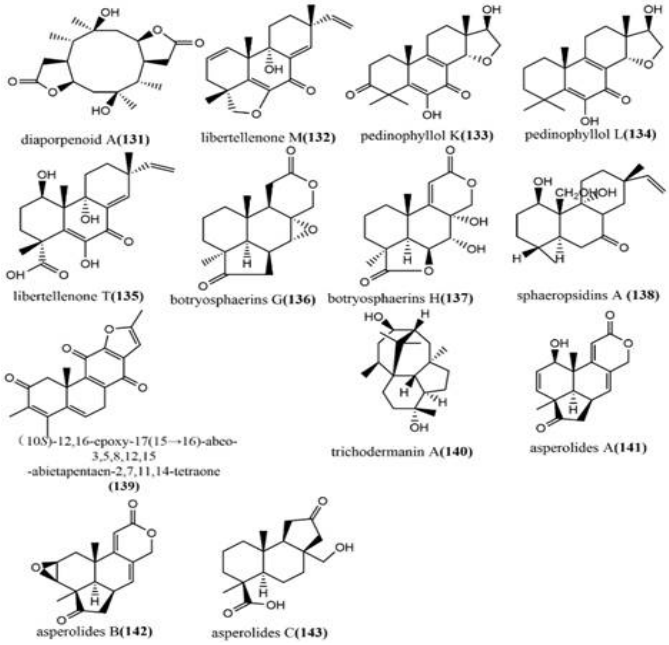

Figure 7: Diterpenoids and other types of Bioactive compounds

Triterpenoids

The 24-homo-30-nor-cycloartane triterpenoid 154 (Figure 11) was obtained from the endophytic fungus *Mycoleptodiscus indicus* FT1137. Little effect against the human ovarian tumour cell line A2780[67] was observed at a concentration of 20µg/mL. From Scleroderma UFSMSc1, Eucalyptus grandis cultures yielded three "Lanostane-type triterpenes: lanosta-8,23-dien-3β,25-diol 146" (Figure11) and "sclerodols A–B 144–145" (Figure 11). The agar diffusion approach was employed to analyse their antifungal effects on *Candida albicans* and *Candida parapsolosis*. Compounds 144–146 exhibit mild to weak antifungal effectiveness with MIC values ranging from 12.5 to 50µg/mL. Their ability to inhibit "selenocysteine methyltransferase" (SMT) activity facilitated the antifungal actions of these substances against *Candida albicans* [68]. Acremonium pilosum F47, an EF obtained from the stem of *Mahonia fortunei*, synthesized fusidic acid 147 (Figure 11). It showed strong antibacterial activity when examined against "*S. aureus* ATCC 6538 and B. subtilis ATCC 9372". In order for Compound 147 to exhibit antibacterial effects, the C-

16 hydroxyl group must be acetylated [69]. Two recently discovered "glometenoid A–B" 148–149 (Figure 11) triterpenoids were found in the "ethyl acetate" extract of the EF Glomerella sp. F00244 that prospers among mason pines. Compounds 148–149 were experimented on to determine their cytotoxic impact on the HeLa human ovarian tumour cell line through the MTT assay. Compound 148 exhibited a mild cytotoxic impact, demonstrating a 21% inhibition at a dosage of 10 μM [70]. Nine highly oxygenated schitriterpenoids, such as 7β-schinalactone C 158 and cadhenrischinins A–H 150–157 (Figure e8), were isolated from Penicillium sp. SWUKD4.1850 remains unchanged. Compounds 154–157 exhibit a distinct 3-one–2-oxabicyclo [1,2,3]–octane structure. The MTT test was used to study the cytotoxicity of each drug on HepG2 tumor cells. The compounds displayed slight cytotoxic effects, as evidenced by their IC50 values, varying between 14.3 and 40μM. Two "tetracyclic triterpenoids"(TT) called integrateacide E 159 (Figure 11) and "isointegracide E 160" were obtained from the "mycelia of Hypoxylon sp. 6269". Compound 159 showed a slight ability to inhibit HIV-1 integrase, with an IC50 measurement of 31.63 μM [71]. The TT H–J 161–163 (Figure 10) were derived from the roots of Mentha longifolia L. (Labiatae) by the endophytic fungus *Fusarium sp*. These integracides were later examined for their effectiveness in inhibiting the growth of *L. donovani* promastigotes. Compound 161 demonstrated a notable "antileishmanial effect with an IC50 of 4.75μM, surpassing the IC50 value of 6.35μM for pentamidine, the positive control" [72].

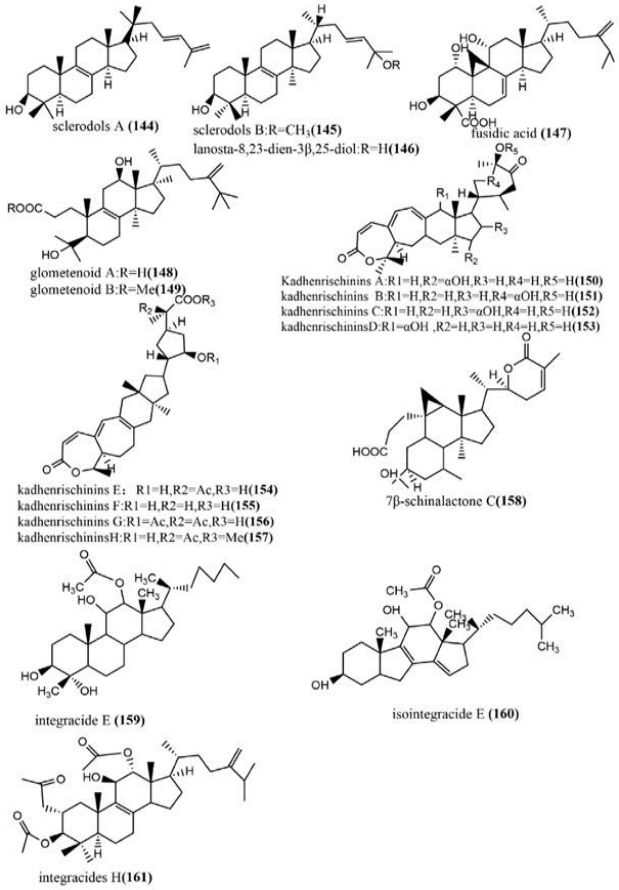

Figure 8 schitriterpenoids -7β-schinalactone and others

Tetracyclic triterpenoids, also known as integracides F–G 164–165 (Figure 11), were found in the EF Fusarium sp. derived from "Mentha longifolia L. (Labiatae)". Compounds 164–165 were tested for their anti-leishmanial and cytotoxic effects on "BT-549 and SKOV-3 cells", and also on "Leishmania donovani promastigotes". Compounds 164–165 exhibited significant cytotoxicity against "SKOV-3 and BT-549 cell lines", showing IC50 values between 0.16 to 1.97 μg/mL and 0.12 to 1.76 μg/mL, respectively. (The IC50 value for pentamidine, which served as the positive control, was noted to be e2.1 μg/mL.) Compounds 164-165 exhibited potent antileishmanial effects on L. donovani promastigotes, with IC50 values of 3.74 μg/mL and 2.53 μg/mL, respectively[73].

Meroterpenoids

Guignardones P–S 166–169 were sourced from cultures of "*Guignardia mangiferae* A348" (Figure 12). Compounds 166–169 were experimented on to determine their cytotoxic impact on three different human cancer cell lines ("SF-268,MCF-7, and NCI-H460") through the MTT. It was reported that Compounds 167 and 169 exhibited slight cytotoxicity against MCF-7 cell lines, with IC50 (83.7 to 92.1) μM [74].

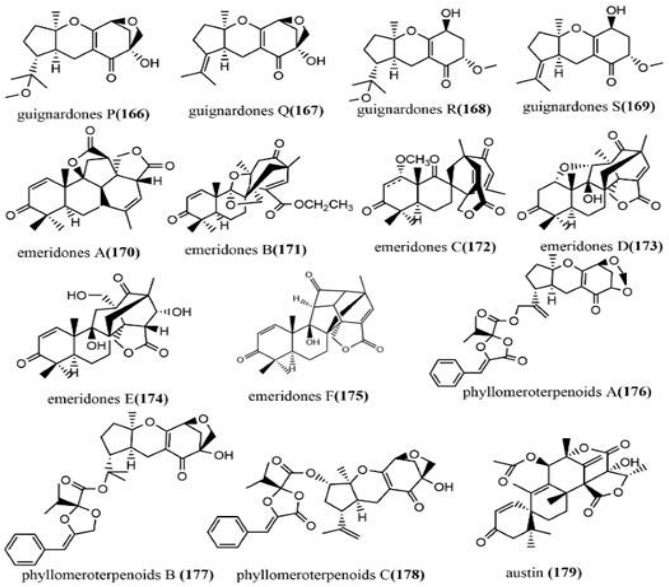

Figure 9 Meroterpenoids

Emeridones A-F 170-175 (Figure 9), derived from *Emericella sp*., are six meroterpenoids based on 3, 5-demethylorsellinic acid. Cultures of TJ29. Compound 171 consists of two parts: "2,6 dioxabicycloe[2.2.1] heptane and a spiro [bicycle [3.2.2] nonane-2,1′-cyclohexane]. The MTT test was used to evaluate the cytotoxic impacts of each drug on five human cancer cell lines (HL-60, SMMC7721, A549, MCF-7, and SW-480)". The cell lines showed mild toxic effects from compounds 172, 173, and 175 [75]. Compounds A–C 176–178 known as phyllomeroterpenoids were isolated from the raw extract of *Phyllosticta* sp. fermentation broth J13-2–12Y. Compounds e175–176 showed decent antibacterial effects with MIC levels varying from 32 to 128 μg/mL against "*Staphylococcus aureus* 209P, Candida aureus 209P, and Candida albicans FIM709" [76]. Austin 179 (Figure 9) showed significant trypanocidal effect against T. cruzi at 100 μg/mL, with an IC50 value of 36.6 μM. This portion was taken from the co-cultures of "*Talaromyces purpurogenus* H4 and Phanerochaete sp. H2". Restate the following passage using the same source language while preserving the word count [77].

Lactones

The bacterium "*Talaromyces assiutensis* JTY2", which was discovered in "Ceriops tagal leaves", synthesized Helicascolide F 180 (depicted in Figure 10). Study assessed the harmful effects of Compound 180 on 3 kinds of human tumor cells ("HeLa, MCF-7, and A549") by using the MTT test. Compound 180 had a mild hazardous impact on all tested cell lines, with an IC50 value ranging from 14.1 to 38.6μM [78]. Two "beta-lactones, namely polonicin A and B 181-182" (Figure 10), were extracted from brown rice cultivation of the EF "*Penicillium polonicum*" found in the fruit of "*Camptotheca acuminata*". Compound 181 exhibited 1.8 times more effective glucose absorption than the control at a conc. of 30μg/mL in the L6 rat skeletal myoblast cell line. The impact of Compound 182 on the movement of GLUT4 was analyzed using "fluorescent protein IRAP-mOrange", a protein that is consistently produced in L6 cells. It demonstrated a 2.1-fold rise in fluorescence intensity on L6 cell surfaces when compared to control samples that were not treated [79]. Chaetocuprum 183, a spirodilactone compound, was produced by cultivating Wild Anemopsis californica's endophytic fungus *Chaetomium cupreum* in New Mexico, USA (Figure 11). A MIC value of 50μg/mL for Compound 183 showed a moderate antibacterial effect on S. aureus [80]. The phytotoxic compound 184, a bicyclic lactone with the molecular structure ("3aS,6aR)-4,5-dimethyl-3,3a,6,6a- -2H-cyclopenta[b]furan-2-one" was separated from the fermentation "broth of *Xylaria curta* 92092022". Compound 184 was tested for its impact on lettuce seedlings and its ability to combat four "pathogens (*Pseudomonas aeruginosa* ATCC 15442, *Staphylococcus aureus* NBRC 13276,

Aspergillus clavatus F318a, and *Candida albicans* ATCC 2019)". Compound 184 possessed a unique fusion mechanism involving 5 rings, each with a rating of 5. Compound 184 exhibited modest antibacterial activity against "Pseudomonas aeruginosa ATCC 15442 and Staphylococcus aureus NBRC 13276" at a conc. of 10μg/disk, yielding in inhibitory region diameters of 13 mm and 12 mm, respectively. Further, compound 184 demonstrated 50% suppression on lettuce roots measuring 1.6 ± 0.3 cm when present at a concentration of 25μg mL −1. The control group, on the other hand, had lettuce roots measuring 3.2 ± 0.5 cm. Compound 184, at a conc. of 200μg mL −1, significantly hindered the sprouting of lettuce seeds, resulting in a 90% reduction [81].Lasiodiplactone A 185 is synthesized by *Lasiodiplodia theobromae*, an endophytic fungus found in mangroves. It has a distinct tetracyclic structure of RAL 12, with pyran and furan rings. Compound 185 displayed impressive anti-inflammatory properties by effectively blocking NO production in RAW 264.7 cells stimulated by LPS, with an IC50 value of 23.5μM. In comparison to indomethacin, which has an IC50 of 26.3 μM, the positive control showed greater resilience. Additionally, compound 185 displayed a higher IC50 value of 29.4 μM for inhibiting α-glucosidase activity compared to the widely used drug acarbose (IC50 = 36.7 μM) [82]. In vitro, an anti-epimastigote test was utilized to evaluate the anti-trypanosomal effects of (+)-"phomalactone" 186 (Figure 13), "hydroxypestalopyrone" 187 (Figure 13), and "pestalopyrone" 188 (Figure 13) extracted from *Aspergillus pseudonomiae* J1 endophytic fungus cells. Compounds 186–188 exhibited varying levels of effectiveness against trypanosomes, with IC50 values of 88.33μM, 580.19μM, and 0.86μM respectively, indicating moderate to poor activity.

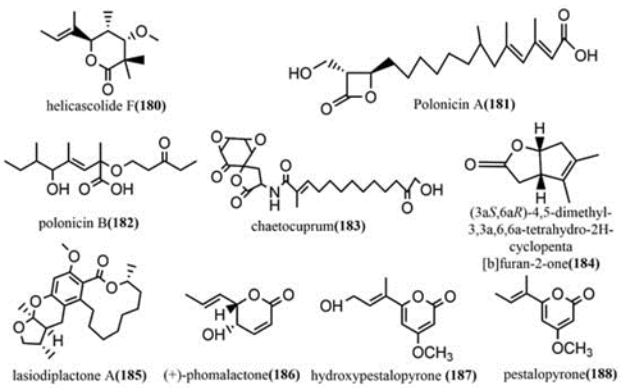

Figure10 Helicascolide F 180 and others

HPLC for Compound Analysis and Screening of metabolites from endophytic fungi

Carolina Santiago and colleagues used ethyl acetate to extract fungal components from a broth culture, followed by HPLC analysis. Cytotoxic effects on P388 murine leukemic cells and the antimicrobial activities of the fractions were tested. Mass spectrometry, capillary NMR, and the AntiMarin database identified three compounds: "4-hydroxymellein, 1-(2,6-dihydroxyphenyl) ethanone, and 4-hydroxy-6-methoxy-3-methyl-3,4 -dihydro-1H- isochromen-1-one"[83] Endophytic fungi from plant leaves were tested for antimicrobial effect using agar well diffusion. HPLC determination was performed using "Dionex P580 system with a Eurospher-10 C18 column and a linear gradient of nanopure water and methanol". Fungal extracts were dissolved in methanol for analysis, and absorption peaks were detected at 235 nm.[84][85]. Ethyl acetate extracts of fungal metabolites, obtained through solid-state fermentation on rice medium, exhibited antifungal and antibacterial properties with MIC values between 0.0625 and 1 mg/mL.[86][87] Secondary metabolites were generated via liquid culture fermentation, and an active component with a molecular weight of 906.4474 g/mol and a retention time of 26.6 minutes was purified using HPLC and LCMS.[88] Between 1997 and 1999, fungal species from plants in Hong Kong were identified, revealing 205 fungal species. The diversity was higher in substrates with robust, highly sclerenchymatic structures. *Cucurbita maxima* had the fewest endophytes, while *Abutilon indicum* stems had 14, and *Cuscuta reflexa* stems yielded 40 different fungi, with a 37% overlap in endophyte assemblages between Abutilon indicum and its parasite.[89]

Key Insights, Emerging Prospects, and Challenges of Endophytic fungi

Endophytes have garnered increasing attention in recent times due to their advantageous impacts on the synthesis of new metabolites that hold significant therapeutic value. Well-known metabolites such as vincristine from *Fusarium oxysporum,* Endophytic fungi are the source of "azadirachtin A and B from *Eupenicillium parvum, taxol* from *Taxomyces andreanae*, and quinine from Phomopsis sp." The increasing importance of endophyte secondary metabolites is mostly due to their diverse range of applications,

which include immunosuppressive medications, industrial applications, and pharmaceuticals. Out of 22,500 chemicals generated from microbes, Fungi provided the most (38%) of the bioactive metabolites that were collected, including antibiotics [90]. Recently, the process of finding new drugs has been hindered by the poor rate of antibiotic development and the rise in AMR. Endophytic fungi further adopt the phenomena of "balanced antagonism" with potential existing microorganisms, balancing their virulence and plant defense. [91]. The synthesis of taxol by Paraconiothyrium SSM001 to combat host infections is a crucial illustration of this phenomena [92]. One example of this is their ability to decrease β-glucan-triggered immunity in a variety of plants [93].

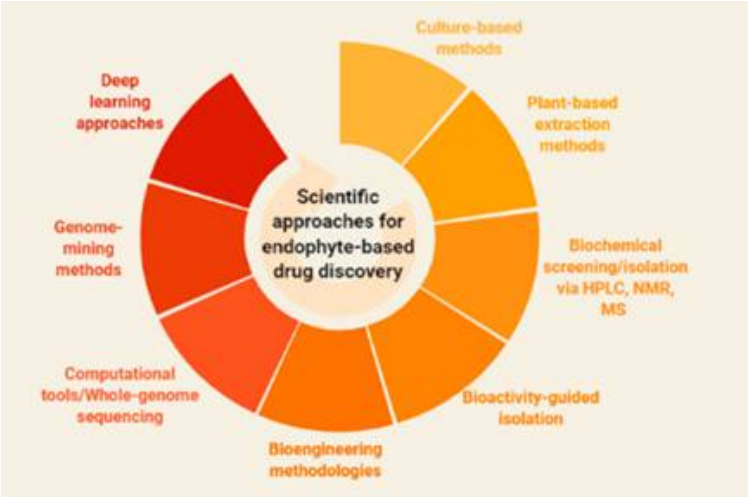

Figure 11: Scientific approaches for endophytic based drug discovery

Utilizing plant-associated endophytes as a biological source for drug development presents a number of difficulties, despite the fact that they have established an appealing "biosynthetic platform" for the synthesis of new bioactive compounds. For instance, the majority of secondary metabolite pathways are suppressed, and a thorough understanding of metabolic networks and processes is necessary. [94][95]. Powerful, low-throughput techniques have been vital to the identification of natural products from endophytes in recent decades [96].

CONCLUSION

Scientists studying pharmaceutical chemistry are now concentrating on creating novel, low-toxic, effective, and safe medications produced using natural resources. With the need for new compounds to be extracted increasing exponentially and quickly in the future, endophytic fungi could offer sustainable supplies of novel bioactive molecules with potential applications in medicine. We can find new, valuable chemicals faster because of recent studies on the synthesis of plant metabolites by endophytic fungi, as well as improvements in structural identification procedures, isolation, extraction and, fermentation culture. The greatest substitute for utilizing pharmacologically bioactive substances in the creation of medications for both human and animal usage might be endophytic fungus.

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