



Endophytes from ethno-pharmacological plants: Sources of novel antioxidants- A systematic review

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ABSTRACT

Oxidative stress caused by the overproduction of free radicals or radical oxygenated species is recognized today as a major player in the development of several diseases. Emerging shreds of evidence are in favor of antioxidants as a means of controlling the propagation of these radicals or directly inhibiting their formation. Antioxidants can, therefore, be used as drugs to reduce or prevent oxidative stress. Natural sources have and continue to offer opportunities for finding novel and unique chemical structures with antioxidant activities. Endophytic microorganisms living inside plants represent an outstanding source of such active metabolites that can be harnessed and exploited as natural antioxidants. This review of data from the last two decades (2000–2019) provides an overview of the current knowledge on the potential of endophytes to produce metabolites with antioxidant activities. An emphasis is put on metabolites produced by endophytic fungi, bacteria, and actinomycetes isolated from medicinal plants growing in terrestrial and marine habitats. We hope that these findings provide readers with useful information for understanding the potential of endophytes in producing novel antioxidants for pharmaceutical and industrial applications, and therefore motivate scientists to undertake projects that may result in the development of novel natural antioxidant drugs.

1. Introduction

The human body is built-up to defend himself against any loss due to free radicals or radical oxygenated species, generated to fulfil a relevant biological function during the normal aerobic cellular metabolism (Lobo et al., 2010). These reactive species are normally produced within the biological system to modulate diverse cellular activities such as cell survival, stressor responses, and inflammation (Zuo et al., 2015). However, the oxidative stress caused by the imbalance or overproduction of these radicals have been reported to cause deleterious effect on various organs of the body (Brieger et al., 2012), through reactions such as lipid peroxidation and irreversible protein modification that leads to cellular apoptosis (Pisoschi and Pop, 2015; Kumar et al., 2017a). Oxidative stress is recognized today as a major player in the development of diseases such as arthritis, diabetes, dementia, cancer, atherosclerosis, vascular diseases, obesity, osteoporosis, and metabolic syndromes (Pisoschi and Pop, 2015; Liu et al., 2017a; Liguori et al., 2018; Cenini et al., 2019). Moreover, recent studies have reported

evidence supporting the importance of oxidative stress and the detriment of antioxidant defense systems in the pathogenesis, neoangiogenesis, and dissemination of several types of cancer (Oh et al., 2016; Saed et al., 2017). Therefore, understanding and controlling the intracellular levels of reactive species could be the strategy to limit their damage in the body.

Fortunately, emerging shreds of evidence are suggesting that antioxidants can control the autoxidation by interrupting the propagation of free radicals or by directly inhibiting their formation. These antioxidants can, therefore, reduce oxidative stress, improve immune function, and increase healthy longevity (Tan et al., 2018). Indeed, about the ability of natural antioxidants to scavenge the excess of oxidants and convert them into less harmful molecules (Powers and Jackson, 2008), antioxidants are now being looked upon as persuasive therapeutic for diverse oxidative stress-related disorders. Indeed, a review by Gholmian-Dehkordi et al. (2017) showed that antioxidants play a key role in the termination of oxidative chain reactions by eliminating intermediate free radicals. Therefore, antioxidants could be used for therapy against

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free radical-related disorders (Liguori et al., 2018).

Plant products have established a strong reputation over the years as an important source of antioxidants (Uttara et al., 2009; Roleira et al., 2015; Grosso et al., 2018; Swinton et al., 2018). Living inside plant tissues, endophytes are important elements in plant micro-ecosystems. Through a complex and specific microbial host-interaction, endophytes play a very important role in affecting the quality and quantity of metabolites produced by their host plants (Faeth and Fagan, 2002; Hardoim et al., 2008; Jia et al., 2016) and could therefore be implicated in the production of antioxidant compounds by plants. In fact, endophytes particularly endophytic fungi have proven over the years their ability to produce not only their plant-associated metabolites (Stierle et al., 1993; Strobel et al., 1996), but also structurally novel compounds (Tan and Zou, 2001) with outstanding biological activities (Strobel and Daisy, 2003; Rodriguez et al., 2009; Vasundhara et al., 2016). In the quest for novel antioxidant compounds from natural sources aiming to replace their synthetic counterpart, endophytes have been intensively investigated since the discovery of two strong antioxidants from endophytic fungus *Pestalotiopsis macrocarpa*. In the present review, we provided an exhaustive overview of the current knowledge of the potential of endophytes to produce metabolites with antioxidant activities. An emphasis is put on reports of the last two decades (2000–2019) on antioxidant activities of extracts and compounds isolated from endophytes colonizing medicinal plants growing in a diverse habitat including terrestrial, mangrove and marine environments all over the globe. We hope that this review will provide readers with useful information for understanding the potential of endophytes in providing novel antioxidant compounds for pharmaceutical and industrial applications.

1.1. Microorganisms as source of novel antioxidants

The early accounts of utilizing microorganisms as a source of drugs dated from Mayans history where fungi grown on roasted green corn were used as treatment against intestinal sickness (Chrystal et al., 2007). However, the modern breakthrough will come with the discovery of the antibiotic penicillin by Sir Alexander Fleming in 1929 (Fleming, 1929). Ever since microorganisms particularly fungi from diverse habitats have been investigated for drugs which led to interesting discoveries. As far as antioxidants research is concerned, the most interesting discovery reported in early 2000 will mark the beginning of multiple investigations aiming to explore the potential of endophytes, particularly fungi as sources of novel antioxidant metabolites.

1.1.1. Pestacin and isopestacin: catalysts for the research of new antioxidants from endophytes

Antioxidant type compounds are and will continue to be of great interest for industries and many companies marketing products with the ability to protect the human body from the disastrous effect of free radicals and radical oxygenates species. These unstable molecules are known to react with diverse macromolecules in living organisms rendering them unable to function properly causing, therefore, multiple dysfunctions leading to countless diseases observed nowadays (Brewer, 2011; Kumar et al., 2017b; Liguori et al., 2018). Fortunately, it is known for centuries that natural products are an outstanding source of such antioxidant compounds (Anwar et al., 2018). However, the potential of microbial species particularly endophytes to produce strong antioxidants was not widely recognized until the discovery of pestacin (1) and isopestacin (2) (Fig. 1) produced by endophytic fungus *Pestalotiopsis microcarpa* isolated from *Terminalia morobensis*.

Almost two decades ago, Gary Strobel's team in their quest for potential bioactive compounds from endophytic fungi identified extract from *P. microcarpa* exhibiting both antimycosis and antioxidant activities. The bioguided fractionation led to the purification of isopestacin, a new compound with a unique core structure. This compound was tested not only against pathogenic fungal but also for antioxidant activity using various assays. Surprisingly, in addition to its antifungal activity,

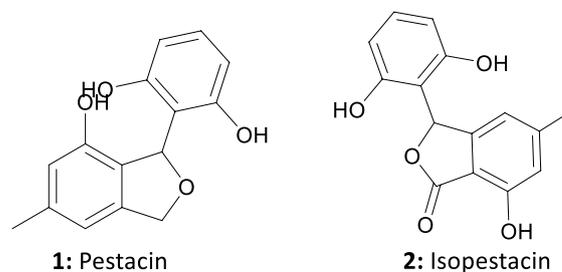


Fig. 1. Structure of Pestacin and Isopestacin produced by *P. microcarpa*.

isopestacin exhibited scavenging activity against both superoxide and hydroxyl free radicals (Strobel et al., 2002). With this achievement at hand and bearing in mind the knowledge that the same fungal can produce dozens of compounds, the same team continued the investigation of *P. microcarpa* and one year later reported the identification of pestacin, a new compound exhibiting both antioxidant and antimycotic activities. More interestingly, this new compound exhibited an astonishing antioxidant activity 11 times greater than the vitamin E derivative Trolox, via the cleavage of an unusually reactive C–H bond and to a lesser extent, O–H abstraction (Harper et al., 2003) making this compound a very attractive antioxidant. The remarkable dual antioxidant and antifungal properties of these two compounds were for the time unprecedented.

Prior to the discovery of pestacin and isopestacin, there has been very little research into the antioxidants derived from endophytes. These discoveries were not only a great motivation for researchers but marked a turning point in the exploration of endophytes for the search of novel antioxidants. Increasingly, scientists have been investigating extracts and compounds from endophytes as potential sources for new antioxidants agents. Consequently, over the past two decades, they have been increasing in several publications reporting the antioxidant activity of metabolites from endophytic fungi, bacteria, and actinomycetes. For instance, our preliminary search in PubMed, Google Scholar and Research gate using key sentences such as "antioxidant activity of endophytes, endophytic fungi, bacteria or actinomycetes; antioxidant metabolites from endophytes, endophytic fungi, bacteria or actinomycetes" gave results summarised in Fig. 2 From this figure, it is obvious that the interest in investigating endophytic microorganisms for novel antioxidant compounds is drastically increasing.

1.1.2. Endophytic fungi as sources of antioxidant metabolites

1.1.2.1. *Endophytic fungi from terrestrial plants.* Terrestrial plant species are a large and important component of the total plant biodiversity (Corlett, 2016). Several of these plants are used as medicines for the treatment of many diseases affecting mankind. Contrary to the previous understanding that only factors such as the genetic background of plants, ecological habitats, and soil nutrients can affect the quality and quantity of crude drugs produced by plants (Pavarini et al., 2012), it is now clear that fungi community hosted by each plant have a very important role in its biology and metabolism (Faeth and Fagan, 2002; Jia et al., 2016). Moreover, research has now proven that these microbial communities are not only highly diverse but also an untapped reservoir for secondary metabolites with outstanding activity including antioxidants. Searching for novel antioxidant compounds, several research groups have been focusing on exploring fungi species isolated from medicinal plants and successful results have been reported. In this section, we are discussing crude extracts and compounds isolated from endophytic fungi associated with diverse medicinal plants and their antioxidant activities.

The screening of 131 endophytic fungal isolates from different tissues of *B. aristate* was conducted by Sharma et al. (2018). Two fungi *A. flavus* and *A. alternata* exhibiting very good 2,

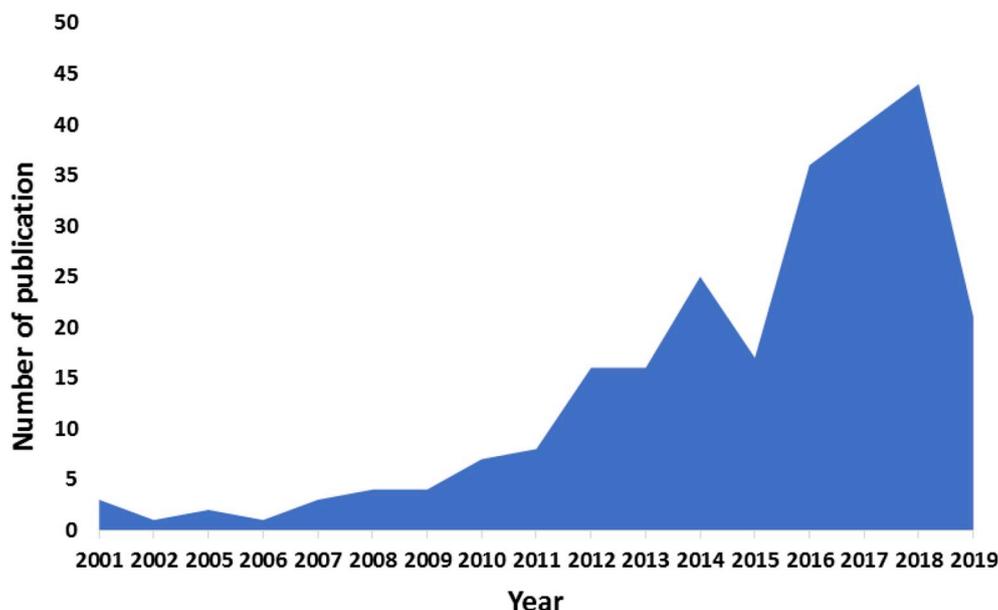


Fig. 2. The significant increase in the number of publications reporting the antioxidant activity of extracts or compounds from endophytes over the last two decades. It is noted that from 2001 till March 2019 (when the data were collected from different databases), the number of publications has significantly increased for more than 14 times. Although this analysis did not include all available literature on the subject, interest in exploring endophytes for new antioxidants is drastically increasing. Of note, even though more than 200 research articles were collected, only those published in peer-reviewed journals with Impact Factor or SCImago Journal Ranking score were considered for this review.

2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging activity with IC_{50} values of 39 and 40 $\mu\text{g}/\text{mL}$ were identified. A similar screening of extracts from 20 endophytic fungi isolated from wheat, showed that 60% were active, exhibiting from 50 to 96% inhibition of the β -carotene/linoleic oxidation. *Penicillium* sp. and *Aspergillus* sp. were identified as the most potent strains (Sadrati et al., 2013). A larger screening of 169 endophytic fungi extracts from a medicinal plant *Aegle marmelos* led to the identification of two endophytes, *A. citrimacularis*, and *C. australiensis* exhibiting good potency (Mani et al., 2015). Extracts from each of the 54 endophytic fungi isolated from *Artemisia lactiflora* were also screened for antioxidant activity using the DPPH scavenging assay. From the results, only two (3.7%) isolates showed potency and isolate *Phomopsis* sp. GYBH42 was the most active (Qian et al., 2014a). From another investigation, forty-four (44) endophytic fungi isolated from the medicinal plant *Curcuma longa* were tested for their antioxidant activity by the radical scavenging assay. Overall, only six isolates showed potency with radical scavenging percentage ranging from 67.76 to 93.58% (Bustanussalam et al., 2015). Similarly, using the DPPH assay, Toghueo et al. (2016) revealed that ethyl acetate extracts from *Diaporthe* sp. (9.929–41.134%), *Fusarium* sp. (8.800–41.107%), *Aspergillus niger* (6.382–38.179%) and *P. chermesinum* (6.741–35.584%) were the most potent among the ten fungi investigated. According to Selim et al. (2013), only extract of *Chaetomium globosum*, an endophyte of *Adiantum capillus* showed potency (99% at 100 $\mu\text{g}/\text{mL}$) among the 99 extracts screened for activity using the DPPH scavenging assay. In a later study, Selim et al. (2016) showed that favourable conditions to produce antioxidant compounds were to culture *C. globosum* in the static condition in potato extract. Conditions that were later applied to grow this fungus and the resulting extract exhibited strong antioxidant activity with IC_{50} of 11.5 $\mu\text{g}/\text{mL}$ (Selim et al., 2018). In another DPPH radical scavenging activity screening of twenty-five endophytic fungi isolated from tissues of *Toona sinensis*, Rahmawati et al. (2016) identified three potent (27.79–81.01%) isolates including *Aspergillus* sp., *Rhizopus* sp., and *Penicillium* sp. Likewise, another *Penicillium* sp. isolated from a medicinal plant *Centella asiatica* was reported to exhibit high antioxidant activity with an IC_{50} value of 54.72 $\mu\text{g}/\text{mL}$ (Devi and Prabakaran, 2014). The investigation of endophyte from *Taxus baccata* also led to the identification of *Fusarium tricinatum* as the most active with IC_{50} of 482 $\mu\text{g}/\text{mL}$ (Vasundhara et al., 2016).

Using various antioxidant model assays, sixty-five crude extracts from 51 endophytic fungi isolated from five *Garcinia* species were screened for antioxidant activity. More than 22% of extracts exhibited

potency with IC_{50} ranging from 40 to 250 $\mu\text{g}/\text{mL}$ (Phongpaichit et al., 2007). Similarly, 49 endophytic fungi isolated from *Scapania verrucosa* were investigated for their *in vitro* antioxidant activities. In primary screening, the 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid) (ABTS) assay was used to select five active fungi (T7, T21, T24, T32, and T38 strains), exhibiting good Trolox equivalent antioxidant capacity (ranging from 997.06 to 1248.10 $\mu\text{mol TE/g}$ extract). Later, the five selected extracts were tested simultaneously for their DPPH and hydroxyl radical scavenging, reducing power, and ferrous ion chelating activities. The results showed that endophytes T24 and T38 have similar scavenging potency against both DPPH-free radicals (93.9 and 88.7%, respectively, at 50 $\mu\text{g}/\text{mL}$) and hydroxyl radicals (97.1 and 89.4%, respectively, at 2 mg/mL). However, only T38 showed ferrous ion chelating ability (Zeng et al., 2011). Antioxidant assays including DPPH, ABTS and reducing power were used to screening 79 endophytic fungi isolated from four medicinal plants. Comparing the activity of extracts from the three assays, *Aspergillus terreus* an endophyte from *Zingiber officinale* was identified as the most potent (Uzma and Chowdappa, 2017). Using both the DPPH and superoxide radical scavenging assays, the endophytic fungal community from *Catharanthus roseus* were screened for antioxidant activities. The results revealed that the extract of *Chaetomium nigricolor* was the most active with respective IC_{50} values of 22 $\mu\text{g}/\text{mL}$ and 65 $\mu\text{g}/\text{mL}$ (Dhayanithy et al., 2019). Using a similar approach, *A. niger*, *A. flavus*, *F. oxysporum* and *F. solani* isolated from *Crotalaria pallida* were reported for their *in vitro* antioxidant activity by ABTS, DPPH and ferric reducing antioxidant power (FRAP) methods (IC_{50} 448.22–2054.63 $\mu\text{g}/\text{mL}$) (Govindappa et al., 2011).

Endophytic fungal strain *Alternaria alternata* AE1 isolated from leaves of *Azadirachta indica* A. Juss was investigated by Chatterjee et al. (2019). The DPPH free radical (IC_{50} 38.0 $\mu\text{g}/\text{mL}$), as well as superoxide radical scavenging (IC_{50} 11.38 $\mu\text{g}/\text{mL}$) activities, suggested that this fungal possess strong antioxidant potential. Another endophyte strain TRF-1, from *Ocimum sanctum* Linn was also found to be a good DPPH free radical (IC_{50} 71.83 $\mu\text{g}/\text{mL}$) and hydroxyl radical (IC_{50} 110.85 $\mu\text{g}/\text{mL}$) scavenger (Shukla et al., 2012). Endophytic fungi isolated from *Tragia involucrata* Linn were investigated using the DPPH scavenging, reducing power, and total antioxidant assays. The results showed that the ethyl acetate extract of *P. citrinum* CGJ-C2 showed the highest antioxidant activity. Moreover, extracts from endophytes *Penicillium citrinum* CGJ-C1, *P. citrinum* CGJ-C2, *Cladosporium* sp. CGJ-D1, and *Cryptendoxyla hypophloia* CGJ-D2 showed moderate DNA protection ability (Danagoudar et al., 2018). Two *Aspergillus* spp., endophytes of *Lycium*

barbarum were the most potent isolates identified among the 11 fungi screened for antioxidant activities using both the hydroxyl radical scavenging and total antioxidant capacity assays (Du and Dai, 2015).

The potential of extracts could be related to their secondary metabolite composition (Srividya et al., 2012). Several studies have related the amount of phenolic compounds contained in endophytic fungi extracts to their antioxidant activities. To demonstrate the correlation between antioxidant capacity of endophytic fungi and their total phenolic and flavonoids contents, Huang et al. (2007) investigated 292 different endophytic fungi isolated from 29 medicinal plants used in China. The results showed that most of the fungi exhibited antioxidant activity in correlation with the total phenolic contents. This led Huang et al. (2007) to hypothesise that phenolic compounds may be the major antioxidant constituents produce by the endophytes investigated. Similarly, extracts from twenty-one endophytic fungi isolated from *Eugenia jambolana* were investigated by Yadav et al. (2014). Extracts from *Chaetomium* sp., *Aspergillus* sp., *Aspergillus peyronelli* and *Aspergillus niger* exhibiting radical scavenging activity ranging from 50 to 80% were the most potent. Further study demonstrated a positive correlation between the amount of phenolic content (58–60 mg/g GAE) in each extract and their activity. Similarly, the total phenolic content (TPC) and antioxidant activity of hydroethanolic extracts of 13 endophytic fungi strain isolated from *Costus spiralis* were investigated and the results also revealed a positive correlation between the activity observed and the total phenol content (Marson Ascêncio, 2014). Another study by Khiralla et al. (2015) revealed that among the extracts from the 21 endophytic fungi isolated from the five Sudanese medicinal plants, *Aspergillus* sp. from *Trigonella foenum-graecum* exhibited the best radical scavenging activity (IC₅₀ 18.0 µg/mL) and the highest total phenolic content (89.9 mg GAE/g).

Likewise, the ethanol extracts from 14 endophytic fungi isolated from different parts of *S. miltiorrhiza* Bge.f.alba were investigated by Li et al. (2015). Two fungi *F. proliferatum* SaR-2 and *A. alternata* SaF-2 were of particular interest because of their stronger antioxidant activities revealed by FRAP (1682.21 and 1659.05 µmol/mg, respectively) and DPPH (90.14% and 83.25%, respectively, at 0.1 mg/mL) assay, along with their quantity of phenol (21.75 and 20.53 GAE/g) and flavonoid (8.27 and 7.36 µg/mg of quercetin equivalent) contents. The ethyl acetate extract of endophytic fungus *Achaetomium* sp., isolated from *Euphorbia hirta* was found to contain 44.02 mg of total phenolic, 54.54 mg of total flavonoid (TFC) and 18.79 mg of tannin. This extract also exhibited potent radical scavenging activity (66.89–87.34%) (Uma Anitha and Mythili, 2017). The ethyl acetate extract of endophytic fungus *Fennellia nivea* NRRL 5504 isolated from *Typhonium divaricatum* Lodd exhibited the highest antioxidant activity and was rich in phenolic compounds (0.544 mg/g) (Sarawaty et al., 2013).

Among the five different solvent extracts prepared from endophytic *Phomopsis liquidambari* strain QH4, isolated from *Artemisia annua*, the methanol extract (200 µg/mL and 4.0 µg/mL) exhibited strong antioxidant capacity in each of the five antioxidant model assays used. That extract was also found to contain the highest phenolic contents (60.07 mg GAE/g dry weight) (Qian et al., 2014b). Likewise, different solvent extracts from *Xylaria* sp. YX-28, an endophyte of *Ginkgo biloba* were investigated. The results indicated that using both the DPPH and the β-carotene–linoleic acid assays, the methanol extract exhibited the strongest antioxidant activity. Further study showed a strong correlation between the total phenolic (54.51 mg GAE/g dry weight) and flavonoid (86.76 mg RE/g dry weight) contents and the activity (Liu et al., 2007). Similarly, methanol extract was also the most potent (66.92%) antioxidant with highest amount of total phenol (400.3 mg of GAE) and flavonoid (295.3 mg of RE/g of extract) content among the different solvent extracts prepared from *Cochliobolus* sp., endophyte isolated from *Aerva lanata* by Shoba and Sathivelu (2018). Seven endophytic fungi isolated from the tissues of *Vitex payos* were investigated by Sibanda et al. (2018). The crude ethyl acetate extract from *Epicoccum nigrum* demonstrated both the highest total phenolic content (2.97 mg GAE/g

dry weight) and total antioxidant capacity (231.23 µM). From another screening of 26 endophytic fungi from roots of Scots pine, extract from *Phialophora lignicola* containing above 46 GAE mg/g of phenolic compounds exhibited high antioxidant potency (FRAP-values (≤228 FeSO₄ µmol/g). This extract was also capable of protecting ARPE-19 cells from oxidative damage (Aapola et al., 2011).

The ethyl acetate extract of *Aspergillus austroafricanus* isolated from *Zingiber officinale* was found to contain 80 µg/mg of phenol and 16.0 µg/mg of flavonoid. This extract also showed significant reducing power (15 µg/mg) as well as total antioxidant activity (82 µg/mg). Besides, a varying degree of activities against DPPH, H₂O₂, and nitric oxide radicals was noted (Danagoudar et al., 2017). Likewise, *Aspergillus nidulans* ST22 and *Aspergillus oryzae* SX10 isolated from *Ginkgo biloba* L. were reported to produce an important amount of phenolic (0.141 and 0.145 mg/mL) and flavonoid compounds (0.0116 and 0.0125 mg/mL) (Qiu et al., 2010) and could therefore exhibit good antioxidant activity. As well, crude extract of *Penicillium frequentans* showed maximum flavonoid (17.48 mg/g) and phenol (288.34 mg/g) content among the seventeen endophytic fungi isolated from *Pinus roxburghii* (Bhardwaj et al., 2015). Extract of endophytic fungus *Cladosporium velox* TN-9S isolated from *T. cordifolia* containing a significant amount of phenolics (730 µg GAE/mL) was also noted to exhibit good antioxidant activity (IC₅₀ 22.5 µg/mL) in DPPH scavenging assay (Singh et al., 2016). The same observation was made with an extract of *Myrothecium* sp. M1-CA-102 isolated from *Calophyllum apetalum* Willd (Ruma et al., 2014). These studies have demonstrated the positive correlation between the antioxidant activities of crude mixtures and their chemical composition. However, although the simple correlation could not be enough to attribute the antioxidant activity of a given crude extract to the phenolic compounds, it is worth mentioning that phenolic compounds are good antioxidants. They can act as hydrogen donors or chelate metal ions such as iron and copper, by inhibiting the oxidation of low-density lipoproteins. These compounds can reduce or inhibit free radicals by the transfer of a hydrogen atom, from its hydroxyl group. In presence of peroxy radicals (ROO●), they act by transferring hydrogen cation from the phenol to the radical, forming a transition state of an H–O bond with one electron which will neutralize the radical (Leopoldini et al., 2004; Brewer, 2011; San Miguel-Chávez, 2017).

From these studies, it is obvious that endophytic fungi extracts contained compounds capable of antioxidant activity. Consequently, a deeper chemical investigation could lead to the identification of potential antioxidant ingredients (Figs. 3 and 4). In this respect, several active compounds have been identified from the metabolome of many endophytic fungi and their antioxidant activity reported. Cajanin-stilbene acid (3), a known antioxidant compound was identified in extracts of *Fusarium solani* ERP-07, *Fusarium oxysporum* ERP-10, and *Fusarium proliferatum* ERP-13, three endophytic fungi isolated from *Cajanus cajan* (L.) Millsp by Zhao et al. (2012). From *Dichotomopilus funicola*, another endophytic fungus from the same tree, Gu et al. (2018) reported the identification of vitexin (4), a DPPH radical scavenger with an IC₅₀ value of 164 µg/mL. The chemical investigation of the ethyl acetate extract (EtOAc) of *Chaetomium globosum* another endophyte of *Cajanus cajan* exhibiting strong antioxidant activities including DPPH radical scavenging (IC₅₀ 6.87 µg/mL), reducing power (IC₅₀ 15.19 µg/mL) and lipid peroxidation (IC₅₀ 16.78 µg/mL) led to identification of apigenin (5), a well-known antioxidant compound (Gao et al., 2012). Similarly, the investigation of extract of *Aspergillus fumigatus* another endophyte of *Cajanus cajan* led to isolation of luteolin (6), an antioxidant compound exhibiting antioxidant activities including DPPH (IC₅₀ 16.38 µg/mL), hydroxyl radical scavenging (IC₅₀ 35.20 µg/mL), reducing power (IC₅₀ 19.69 µg/mL), lipid peroxidation (IC₅₀ 22.64 µg/mL) and XOD inhibition (IC₅₀ 193.24 µg/mL). This compound also significantly increasing the activities of SOD, CAT, and GR in HepG2 cells (Zhao et al., 2014). Another compound, oosporein (7) exhibiting strong DPPH-scavenging activity (IC₅₀ 0.194 mM) was identified in the extract of *Cochliobolus kusanoi*, an endophytic fungus from *Nerium oleander* L.

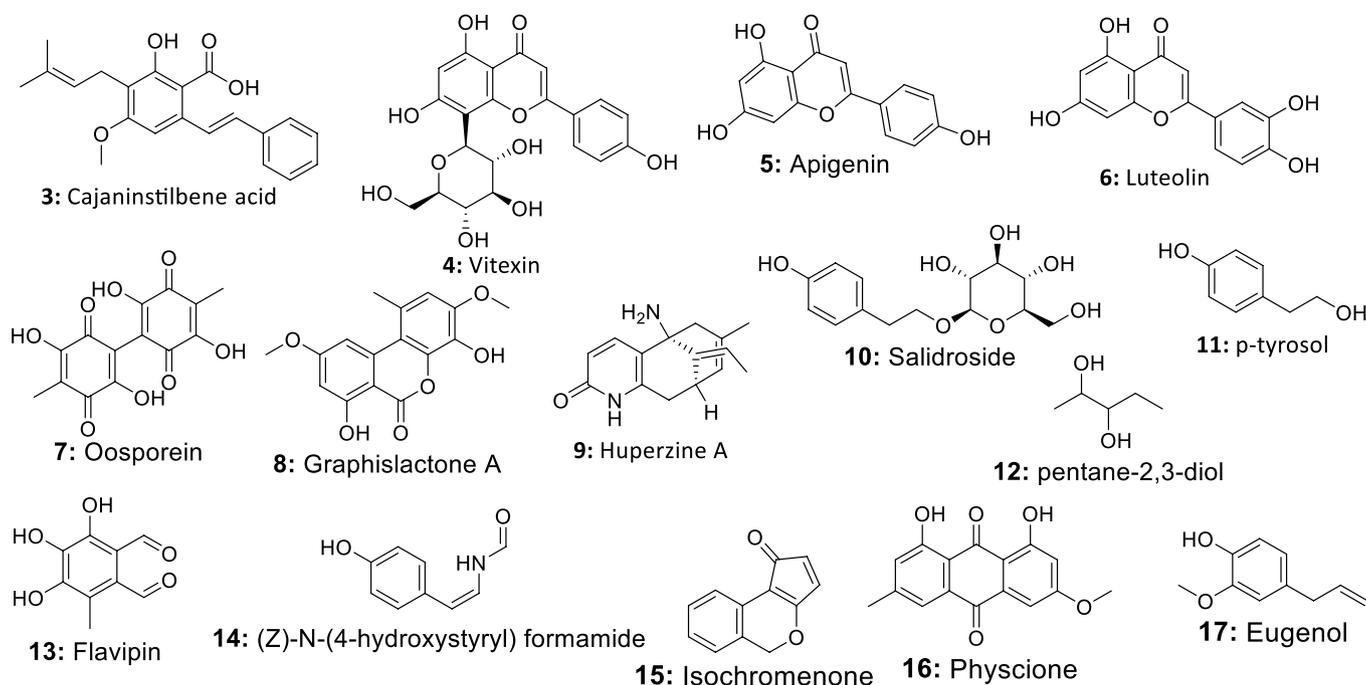


Fig. 3. Selected few well-known natural antioxidants identified from endophytes metabolome.

The structure-activity relationship revealed that the large conjugated system and hydroxyl groups in the chemical structure of oosporein could be responsible for the strong antioxidant activity observed (Alurappa et al., 2018). Similarly, graphis lactone A (8) isolated from an extract of *Cephalosporium* sp. IFB-E001 endophyte of *Trachelospermum jasminoides* was reported to exhibit *in vitro* free radical-scavenging (IC_{50} 2.9 μ g/mL) and antioxidant activities stronger than those of butylated hydroxytoluene and ascorbic acid (Song et al., 2005). Huperzine A (9), an acetylcholine inhibitor with antioxidant activity was also reported from the metabolome of *Trichoderma* species isolated from *Huperzia serrata* (Dong et al., 2014).

Using a panel of assays, 347 endophytic fungi isolated from *R. crenulata*, *R. angusta*, and *R. sachalinensis* were screened for antioxidant activities. An endophytic fungal Rac12 producing salidroside (10) and *p*-tyrosol (11) two well-known antioxidant compounds were identified (Cui et al., 2015). Another compound 2,3-pentanediol (12) with strong antioxidant and anti-aging activities was also identified in the extract of *Fusarium oxysporum*, an endophytic fungus isolated from *Curcuma amada*. This compound also shows the ability to protect *Caenorhabditis elegans* against thermal and oxidative stress (Tiwari et al., 2014). Another screening of 80 endophytes from *Ginkgo biloba*, led to the identification of *Chaetomium globosum* CDW7 producing flavipin (13) a compound with both *in vitro* and *in vivo* antioxidant activities (Ye et al., 2013). Likewise, the screening of extracts from 12 endophytic fungi isolated from riparian plants *Myricaria laxiflora* led to the identification of extract from *Aspergillus fumigatus* SG-17 exhibiting good *in vivo* and *in vitro* antioxidant activity. The chemical analysis led to the identification of (Z)-N-(4-hydroxystyryl) formamide (14), a phenolic compound analog of coumarin (Qin et al., 2019). Similarly, forty-four endophytes isolated from *Zingiber cassumunar* were screened using the DPPH radical scavenging assay. Extract of *Arthrinium* sp. MFLUCC16-1053 was found to be the most potent (IC_{50} 28.47 μ g/mL) and the gas chromatography-mass spectrometry analysis revealed the presence of various antioxidant compounds including β -cyclocitral, cembrene A, laurenan-2-one, sclareol, 2Z,6E-farnesol, cembrene, β -isocembrene and γ -curcumene (Pansanit and Pripdeevech, 2018).

Methanolic extract of *A. fumigatus* hosted in *Bacopa monnieri* was also found to exhibit both ferric reducing and free radical scavenging activities. The chemical analysis led to the isolation of isochromenone (15)

having DPPH (26.93% at 100 μ g/mL) and nitric oxide (45.77% at 10 μ g/mL) radicals scavenging activities (Thakur et al., 2015). Extracts of *Stemphylium lycopersici* BG01 isolated from *Cynanchum auriculatum* was found to possess both DPPH radical (97.9%) and ABTS radical scavenging (50.52%) activities. The chemical analysis led to the identification of phycione (16) as the main component (Li et al., 2017). From the screening of extracts from 11 fungal endophytes isolated from healthy leaves of *Cinnamomum loureiroi*, Tanapichatsakul et al. (2019) recently identified *Neopestalotiopsis* sp. and *Diaporthe* sp., producing eugenol (17), along with myristaldehyde, lauric acid, and caprylic acid four well-known antioxidant compounds. Tanapichatsakul et al. (2017) previously suggested that benzene acetaldehyde, benzyl benzoate, salicylaldehyde, benzoin, and benzyl cinnamate were phenolic compounds responsible for the very good antioxidant activity of extracts from *Diaporthe* sp. MFLUCC16-0682 and *Diaporthe* sp. MFLUCC16-0693 two endophytic fungi isolated from flowers of the medicinal plant *Melodorum fruticosum*. Fifty-three (53) fungal endophytes were isolated from the bulbs of *Fritillaria unibracteata* var. *wabuensis* and screened for antioxidant activities using various assays (DPPH, ABTS, FRAP, TPC, TFC, and TSC). From the potent extracts, several natural antioxidant components including gallic acid, rutin, phlorizin, 2,4-di-tert-butylphenol and 2,6-di-tert-butyl hydroquinone were identified (Pan et al., 2017a).

Two compounds 5-acetoxymethylfuran-3-carboxylic acid (18), and 5-hydroxymethylfuran-3-carboxylic acid (19), exhibiting moderate DPPH scavenging activity (IC_{50} 237 and 435 μ g/mL respectively) were isolated from the extract of *Aspergillus flavus*, endophytic fungal in *Cephalotaxus fortune* by Ma et al. (2016). Another compound exhibiting moderate activity is 18-des-hydroxy Cytochalasin H (20) produced by *Diaporthe phaseolorum*-92C isolated from the roots of *Combretum lanceolatum* (Brissow et al., 2017). Among the fourteen compounds including flavipin (13), epicoccone (21), 3-methoxyepicoccone (22), epicoccolides A (23), and B (24), chaetomugilins A (25) and D (26), chaetoglobosins A (27), B (28), E (29), F (30) and F_{ex} (31), penochalasin F (32) and G (33) isolated from extract of *Chaetomium globosum* endophyte from the seeds of *Panax notoginseng*, compounds 13, 21, 22, 23 and 24 exhibited good DPPH free radical scavenging activity (IC_{50} 3.7–11.6 μ g/mL) while compounds 25–33 were less potent (IC_{50} >100 μ g/mL) (Li et al., 2016a). Seven endophytic fungi were isolated from *E. sylvestris* and investigated for their antioxidant activity. Extract from

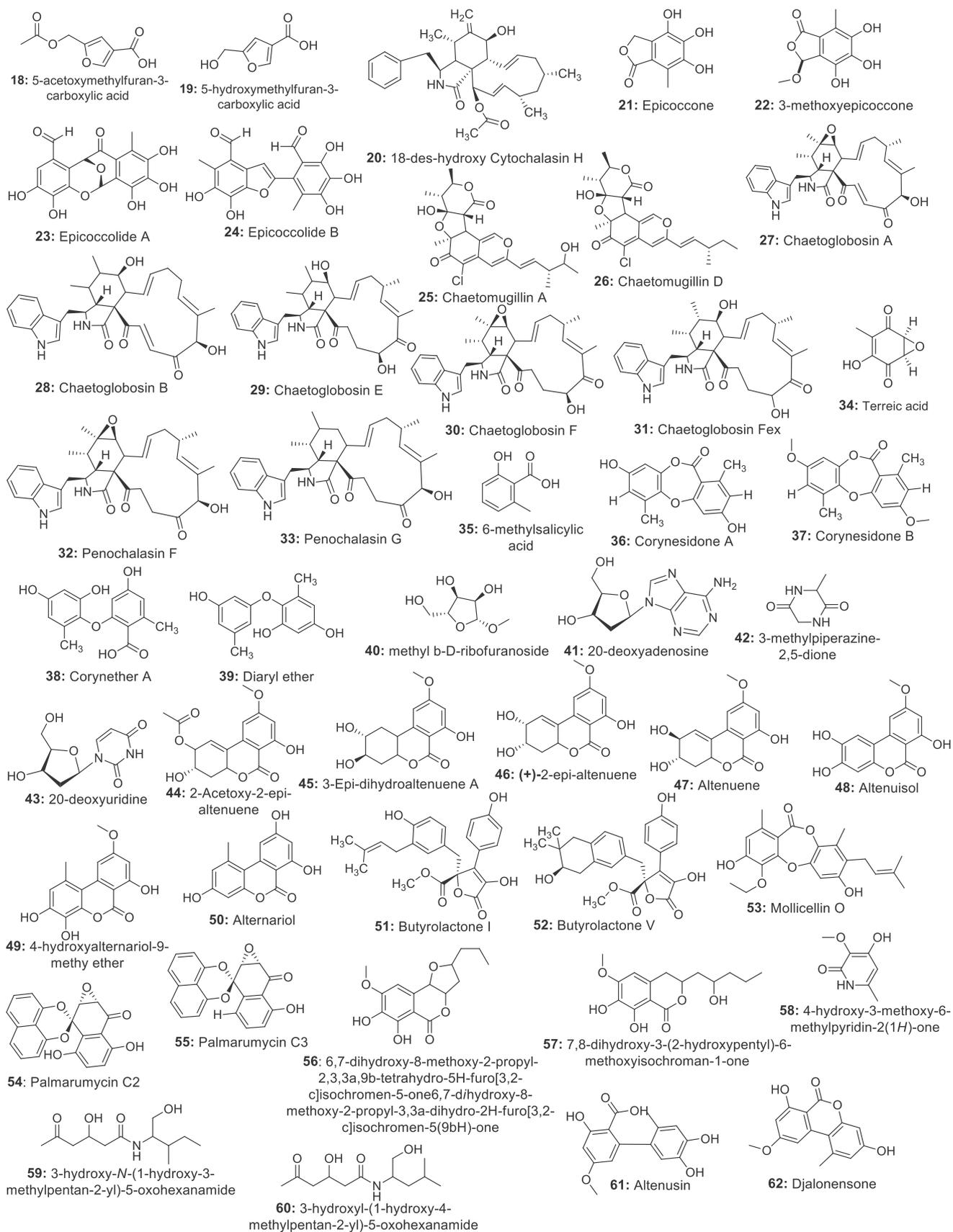


Fig. 4. Novel antioxidant metabolites produced by endophytic fungi from terrestrial habitat.

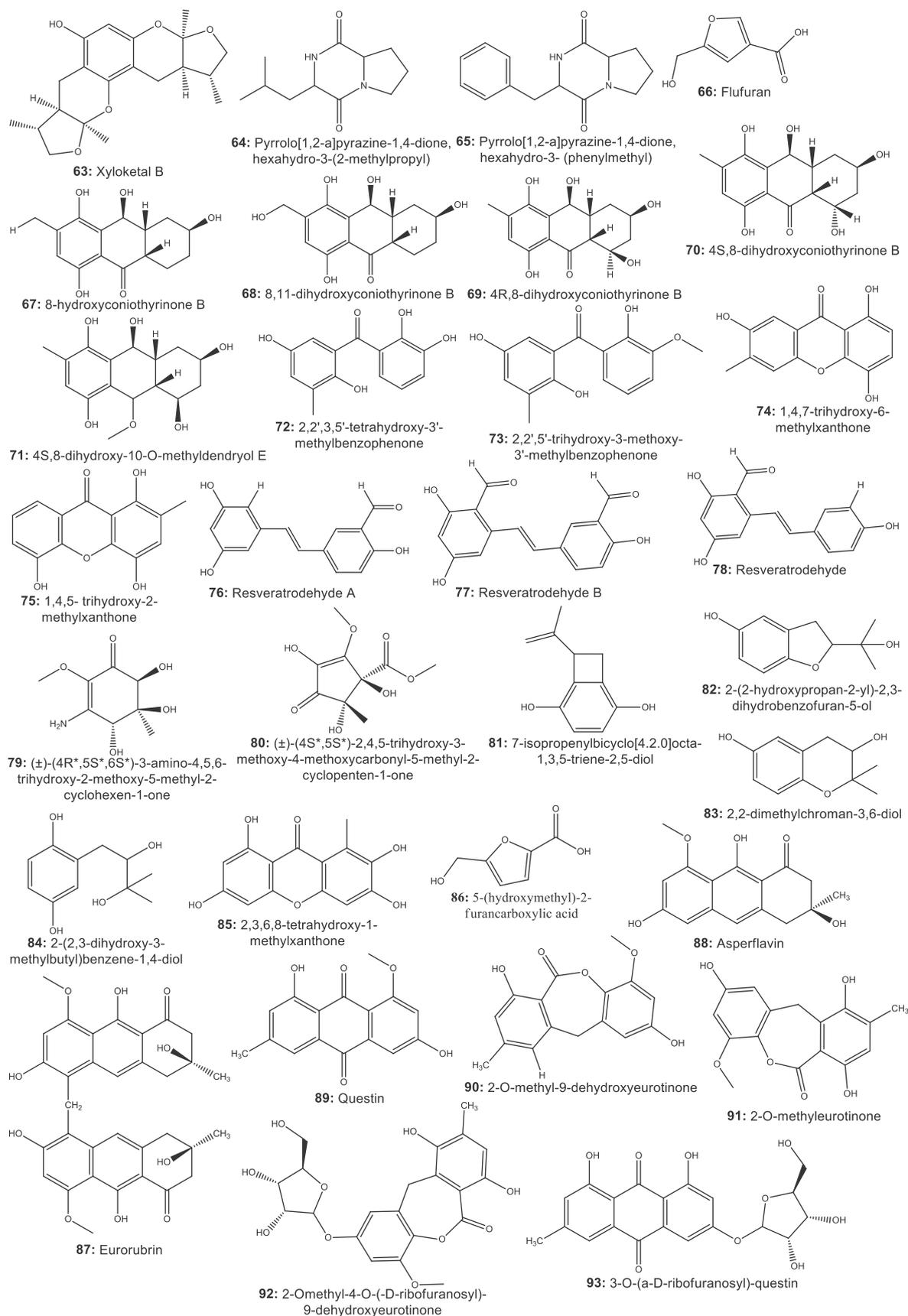


Fig. 5. Antioxidant metabolites produced by endophytic fungi from marine and mangrove habitats.

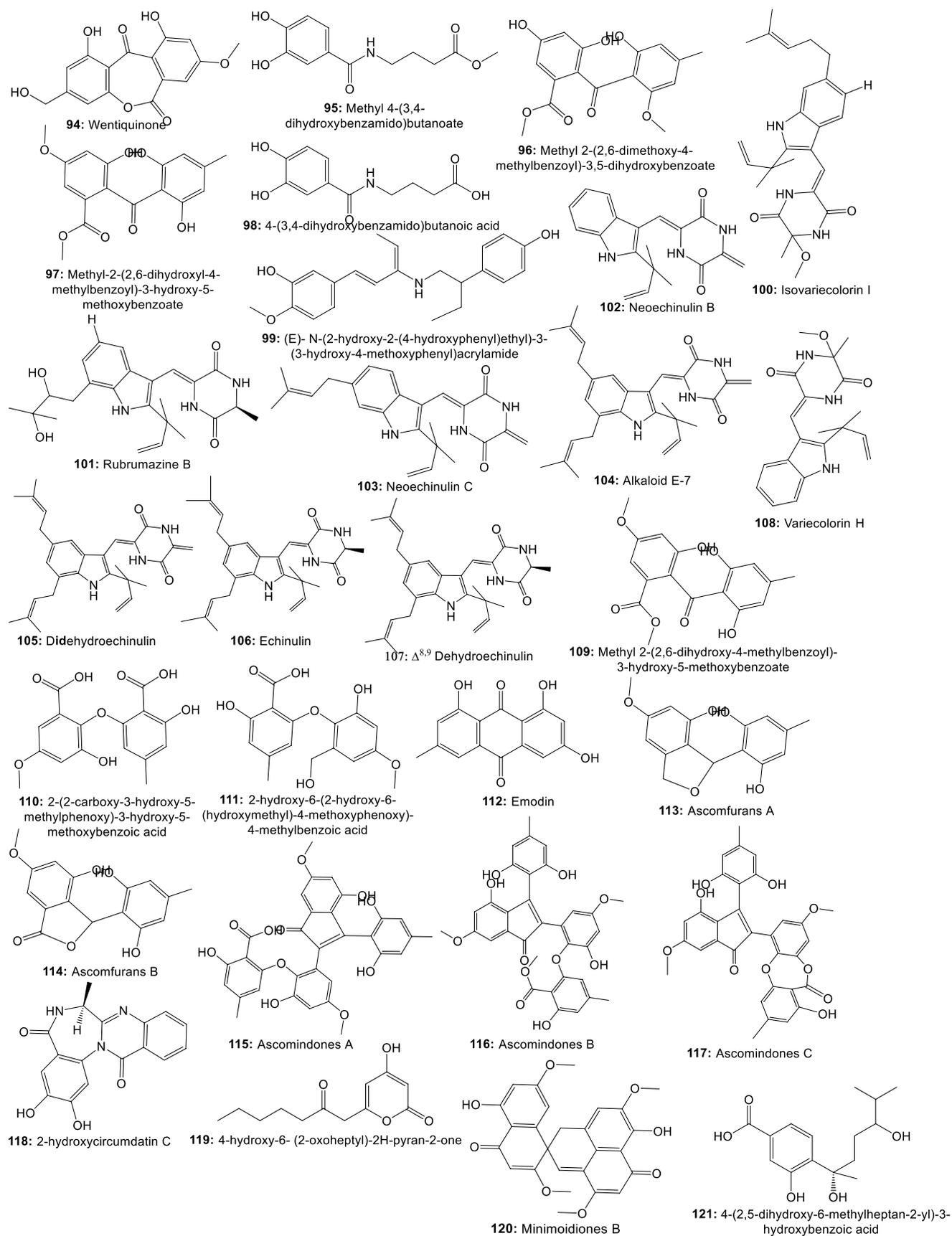


Fig. 5. (continued).

Pseudocercospora sp. ESL 02 showed good antioxidant activity (IC₅₀ 30.54 µg/mL) and the chemical analysis led to the identification of terreic acid (34) and 6-methylsalicylic acid (35) both with DPPH radical scavenging activity with an IC₅₀ value of 0.22 mM and 3.87 mM, respectively. Both compounds also exhibit a good reducing power and β-carotene bleaching capability (Prihantini and Tachibana, 2017). Compounds corynesidone A (36), corynesidone B (37), corynether A (38), and diaryl ether (39) isolated from the extract of endophytic fungus *Corynespora cassicola* L36 were reported for their antioxidant activity using ORAC assay, but only corynesidone B exhibited potent radical scavenging activity (Chomcheon et al., 2009). The DPPH scavenging activity of fourteen fungal endophytes isolated from *Ocimum basilicum* was investigated by Atiphasaworn et al. (2017). The chemical analysis of a crude extract from *Higrospora* sp. MFLUCC16-0605 the most potent (IC₅₀ 15.36 µg/mL) revealed the presence of 5E, 9E farnesyl acetone, columellarin, totarene, laurenan-2-one, and 8S,13-cedranediol as the major compounds. Similarly, using the DPPH scavenging assay, Yuan et al. (2014) showed that compounds adenosine, adenine, methyl β-D-ribofuranoside (40), 20-deoxyadenosine (41), 3-methylpiperazine-2,5-dione (42) and 20-deoxyuridine (43) isolated from the extract of *Penicillium* sp. YY-20 endophytic fungus of *Ginkgo biloba* exhibited activity with IC₅₀ ranging from 2.87 to 100 µg/mL.

Seven compounds including 2-Acetoxy-2-epi-altenuene (44), 3-Epi-dihydroaltenuene A (45), (+)-2-epi-altenuene (46), altenuene (47), altenuisol (48), 4-hydroxyaltenuenol-9-methyl ether (49), and alternariol (50) were isolated from EtOAc extract of *Alternaria* sp. Samif01, an endophytic fungus obtained from *Salvia miltiorrhiza* Bunge and tested for their antioxidant activity. Compounds 45, 48 and 49 displayed promising DPPH and hydroxyl radical scavenging activities with IC₅₀ ranging from 68.3 to 474.5 µM (Tian et al., 2017). Three compounds including terrein (34), butyrolactone I (51), and butyrolactone V (52) were isolated from the ethyl acetate extract of *Aspergillus terreus*-F7, the endophyte of *Hyptis suaveolens* (L.) Poit and exhibited potent DPPH radical scavenging activity (Da Silva, 2017). From the seven compounds isolated from the extract of *Chaetomium* sp. Eef-10, an endophyte isolated from *Eucalyptus exserta*, only mollicellin O (53) displayed weak antioxidant activity with an IC₅₀ value of 71.92 µg/mL (Ouyang et al., 2018).

Palmarumycins C2 (54) and C3 (55), two spirobisnaphthalenes produced by endophytic fungus *Berkleasium* sp. Dzf12 through the chemical elicitation with 1-hexadecene were found to exhibit strong antioxidant activity (Mou et al., 2013). Among the six compounds isolated from endophytic fungus *Colletotrichum* sp., only 6,7-dihydroxy-8-methoxy-2-propyl-2,3,3a,9b-tetrahydro-5H-furo[3,2-c]isochromen-5-one (56) and 7,8-dihydroxy-3-(2-hydroxypentyl)-6-methoxyisochroman-1-one (57) exhibited scavenging activities against DPPH free radical (IC₅₀ values of 23.4 and 16.4 µM, respectively) and superoxide anion radical formation (IC₅₀ values of 52.6 and 4.3 µM, respectively) (Tianpanich et al., 2011). Also, eighteen compounds were isolated from extracts of *Botryosphaeria dothidea* KJ-1, an endophytic fungus of *Melia azedarach* L and tested for antioxidant activity using DPPH assay. New metabolites, 4-hydroxy-3-methoxy-6-methylpyridin-2(1H)-one (58), 3-hydroxy-N-(1-hydroxy-3-methylpentan-2-yl)-5-oxohexanamide (59), and 3-hydroxy-N-(1-hydroxy-4-methylpentan-2-yl)-5-oxohexanamide (60), showed weak activity while, altenusin (61) and djalonensone (62) were the most potent (Xiao et al., 2014).

1.1.2.2. Endophytic fungi from mangrove and marine plants. Today marine microbes because of their wide genetic and biochemical variability have become widely recognized as abundant sources of structurally diverse and biologically active natural products with the potential to be effective drug candidates (Kjer et al., 2010). Many active compounds reported from marine sources are produced by their microbial symbionts. Mangrove endophytic fungi constitute the second-largest ecological group of marine fungi and are reported to produce many chemicals

with novel functions and structures (Cheng et al., 2009; Xing and Guo, 2011). Therefore, these organisms can constitute a great resource for novel antioxidant compounds (Fig. 5). One of the earlier studies reporting the identification of antioxidant compounds from mangrove-derived endophytes was the isolation of five new xyloketal from mangrove fungus *Xylaria* sp. no. 2508 by Lin et al. (2001). Among these compounds, Xyloketal B, besides his DPPH scavenging ability was found to protect mitochondria against oxidative stress. Moreover, xyloketal B (63) also shows the ability to attenuate MPP + -induced intracellular ROS accumulation, loss of mitochondrial membrane potential, restore total GSH level in PC12 cells and protected *C. elegans* from induced dopaminergic neuron degeneration. Suggesting that Xyloketal B can be a promising candidate for novel antioxidant discovery needed to alleviate oxidative stress-related disorders such as neurodegenerative diseases (Lu et al., 2010). Because of these findings, the focus on identifying the antioxidants associated with mangrove endophytic fungi have also increased.

Predominant endophytic fungi *Aspergillus flavus* from four different mangrove plant species were investigated for antioxidant activities using a large panel of assays. Extracts from these fungi exhibited very good antioxidant activity. Also, the high amount of phenolic and flavonoid compounds in extract of *Aspergillus flavus*, an endophyte from leaves of *Excoecaria agallocha* was also noted (Ravindran et al., 2012). Similarly, the ethyl acetate extract of *Cladosporium cladosporioides* isolated from *Sargassum wightii* exhibited antioxidant activity and was found to contain a significant amount of phenolic compounds (Hulikere et al., 2016). Extract from another endophytic fungus *Epicoccum* sp., isolated from the marine alga *Fucus vesiculosus* was also found to exhibit potent antioxidant activity. The analysis led to the identification of epicoccone (21), a potent antioxidant compound (Abdel-Lateff et al., 2003a). Extract from the endophytic fungus *Mortierella alpina* strain ITA1-CCMA 952 isolated from the Antarctic plant *Schistidium antarctici* demonstrated strong antioxidant activity with the IC₅₀ value of 48.7 µg/mL. The GC-MS analysis revealed the presence of compounds such as Pyrrolo[1,2-a]pyrazine-1,4-dione, hexahydro-3-(2-methylpropyl) (64) and Pyrrolo[1,2-a]pyrazine-1,4-dione, hexahydro-3-(phenylmethyl) (65) (Melo et al., 2013). The antioxidant screening of 46 extracts from endophytic fungal from *R. stylosa* and *R. mucronata* using DPPH and ABTS assays, led to identification of several active extracts among which extracts from endophytic strains *Cytospora rhizophorae* HHL55 and *Seiridium ceratosporum* HHL38 isolated from *R. stylosa* were the most potent with IC₅₀ values of 0.33 mg/mL and 0.37 mg/mL, respectively. Moreover, another potent strain *Pestalotiopsis* sp., showed the ability to produce flufuran (66), a compound exhibiting DPPH and ABTS radicals scavenging activities with IC₅₀ values of 34.85 and 9.75 µg/mL (Zhou et al., 2018).

The investigation of extract of *Talaromyces islandicus* EN-501, an endophyte of *Laurencia okamurai* led to identification of 8-hydroxyconiothyronine B (67), 8,11-dihydroxyconiothyronine B (68), 4R, 8-dihydroxyconiothyronine B (69), 4S, 8-dihydroxyconiothyronine B (70), and 4S, 8-dihydroxy-10-O-methyl dendryol E (71) displaying DPPH radical scavenging activity with IC₅₀ values ranging from 12 to 52 µM (Li et al., 2016b). The same endophyte was also found to produce four other compounds including 2,2',3,5'-tetrahydroxy-3'-methylbenzophenone (72), 2,2',5'-trihydroxy-3-methoxy-3'-methylbenzophenone (73), 1,4,7-trihydroxy-6-methylxanthone (74), 1,4,5-trihydroxy-2-methylxanthone (75) exhibiting potent DPPH and ABTS radical scavenging activities with IC₅₀ values ranging from 0.58 to 6.92 µg/mL (Li et al., 2016c). Similarly, the mangrove endophytic fungus *Alternaria* sp. R6 was reported to produce compounds resveratroldehydes A-C (76-78) exhibiting moderate antioxidant activity (Wang et al., 2014) and further investigation of this fungal species by Wang et al. (2015) led to the identification of four new compounds. Two were inactive while, (±)-(4R*,5S*,6S*)-3-amino-4,5,6-trihydroxy-2-methoxy-5-methyl-2-cyclohexen-1-one (79), and (±)-(4S*,5S*)-2,4,5-trihydroxy-3-methoxy-4-methoxycarbonyl-5-methyl-2-cyclopenten-1-one (80), exhibited potent ABTS

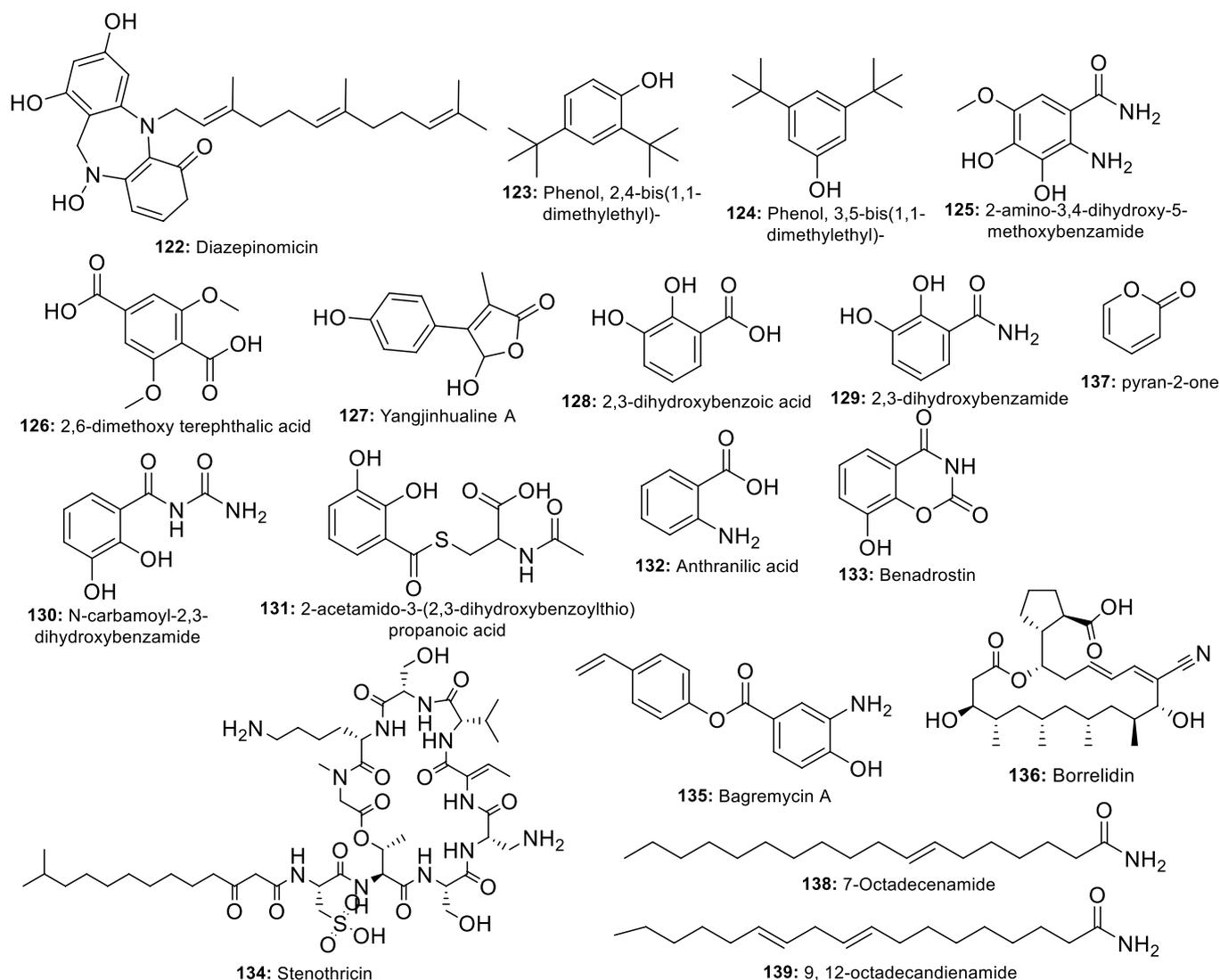


Fig. 6. Antioxidant compounds from bacteria and actinomycetes endophytes.

scavenging activity with IC_{50} values of 8.19 and 16.09 μ M, respectively. The investigation of extract from *Acremonium* sp., isolated from *Cladostephus spongus* by Abdel-Latteff et al. (2002) led to identification of 7-isopropenylbicyclo[4.2.0]octa-1,3,5-triene-2,5-diol (81), 2-(1-hydroxy-1-methyl)-2,3-dihydrobenzofuran-5-ol (82), 2,2-dimethylchroman-3,6-diol (83), and 2-(3-dihydroxy-3-methylbutyl)benzene-1,4-diol (84) with significant DPPH radical scavenging activity (at 25 μ g/mL), and ability to inhibit peroxidation of linolenic acid (at 37 μ g/mL). In a similar investigation, Abdel-Latteff et al. (2003b) identified two DPPH radical scavenging compounds 2,3,6,8-tetrahydroxy-1-methylxanthone (85) and 5-(hydroxymethyl)-2-furanocarboxylic acid (86) from the extract of *Wardomyces anomalus*, endophyte of *Enteromorpha* sp.

Another endophyte *Eurotium rubrum* from the marine mangrove plant *Hibiscus tiliaceus* was also reported to produce seven compounds including eurorubrin (87), asperflavin (88), questin (89), 2-O-methyl-9-dehydroxyeurotinone (90), 2-O-methyleurotinone (91), 2-O-methyl-4-O-(α -D-ribofuranosyl)-9-dehydroxyeurotinone (92), and 3-O-(α -D-ribofuranosyl)-questin (93) all exhibiting DPPH radical scavenging activity (Dong-Li et al., 2009). Likewise, the eight compounds including wentiquinone C (94), methyl 4-(3,4-dihydroxybenzamido)butanoate (95), methyl 2-(2,6-dimethoxy-4-methylbenzoyl)-3,5-dihydroxybenzoate (96), methyl-2-(2,6-dihydroxyl-4-methylbenzoyl)-3-hydroxy-5-methoxybenzoate (97),

4-(3,4-dihydroxybenzamido)butanoic acid (98), (E)-N-(2-hydroxy-2-(4-hydroxyphenyl)ethyl)-3-(3-hydroxy-4-methoxyphenyl)acrylamide (99), and physcione (16), 5-O-methylsulochine (3), isolated from extract of endophytic fungus *Aspergillus wentii* EN-48 demonstrated good DPPH radical scavenging activities with IC_{50} values ranging from 5.2 to 99.4 μ g/mL (Li et al., 2014).

The investigation of extract from *Eurotium cristatum* EN-220, an endophytic fungus obtained from the marine alga *Sargassum thumbergii* led to identification of 13 compounds among which nine including isovaricolorin I (100), rubrumazine B (101), neoehinulin B (102), neoehinulin C (103), alkaloid E-7 (104), didehydroehinulin (105), ehinulin (106), dehydroehinulin (107), and varicolorin H (108) exhibited DPPH radical scavenging activity with IC_{50} value ranging from 6.4 to 28.5 μ g/mL (Du et al., 2017). Similarly, the study of extract from mangrove-derived fungus *Ascomycota* sp. SK2YWS-L led to the identification of compounds, methyl 2-(2,6-dihydroxy-4-methylbenzoyl)-3-hydroxy-5-methoxybenzoate (109), 2-(2-carboxy-3-hydroxy-5-methylphenoxy)-3-hydroxy-5-methoxybenzoic acid (110), 2-hydroxy-6-(2-hydroxy-6-(hydroxymethyl)-4-methoxyphenoxy)-4-methylbenzoic acid (111), emodin (112), ascomfurans A-B (113–114), and ascomindones A-C (115–117) exhibiting significant antioxidant effects, with compound 115 being the most potent (IC_{50} 18.1 μ M) (Tan et al.,

2016). 2-hydroxycircumdatin C (118), a novel benzodiazepine with good antioxidant activity (IC_{50} 9.9 μ M) was isolated from *A. ochraceus* endophyte of *S. kjellmanianum* by Cui et al. (2009). Two compounds, 4-hydroxy-6-(2-oxoheptyl)-2H-pyran-2-one (119) and minimoidones B (120) were isolated from the liken-derived endophytic fungi *Preussia* sp. and compound 120 showed strong antioxidant activity (IC_{50} 3.0 μ g/mL) (Paudel et al., 2018). Likewise, among the twelve compounds isolated from *Aspergillus* sp. xy02 endophyte of *Xylocarpus moluccensis*, only 4-(2,5-dihydroxy-6-methylheptan-2-yl)-3-hydroxybenzoic acid (121) showed moderate DPPH radical scavenging activity with an IC_{50} of 72.1 μ M (Wang et al., 2018). All the six compounds including phomopsidone A, excelsione, 7-methoxy-4,26-methyl-3-oxo-1,3-dihydroisobenzofuran-4-carboxylic acid, diaporthelactone, 7-hydroxy-4,6-dimethyl-3H-isobenzofuran-1-one, and 7-methoxy-4,6-dimethyl-3H-isobenzofuran-1-one isolated from the mangrove endophytic fungus *Phomopsis* sp.

exhibited weak antioxidant activity (Zhang et al., 2014). While the five compounds isolated from mangrove endophytic fungus *Pleosporales* sp. SK7 did not show any potency even at the highest concentration of 100 μ g/mL (Wen et al., 2019).

1.1.3. Antioxidants from bacteria and actinomycetes endophytes

Endophytic bacteria and actinomycetes are also been considered as an important source of diverse natural products with a wide range of activities (Ryan et al., 2008; Qin et al., 2011) and can constitute a source for new antioxidant compounds. Indeed, dozens of studies have reported the antioxidant activities of extracts and compounds (Fig. 6) from bacteria and actinomycetes endophytes isolated from medicinal plants and will constitute the focus of the present section.

Twenty-nine bacterial endophytes isolated from *Aloe vera* were screened for their antioxidant activity using DPPH assay. The results

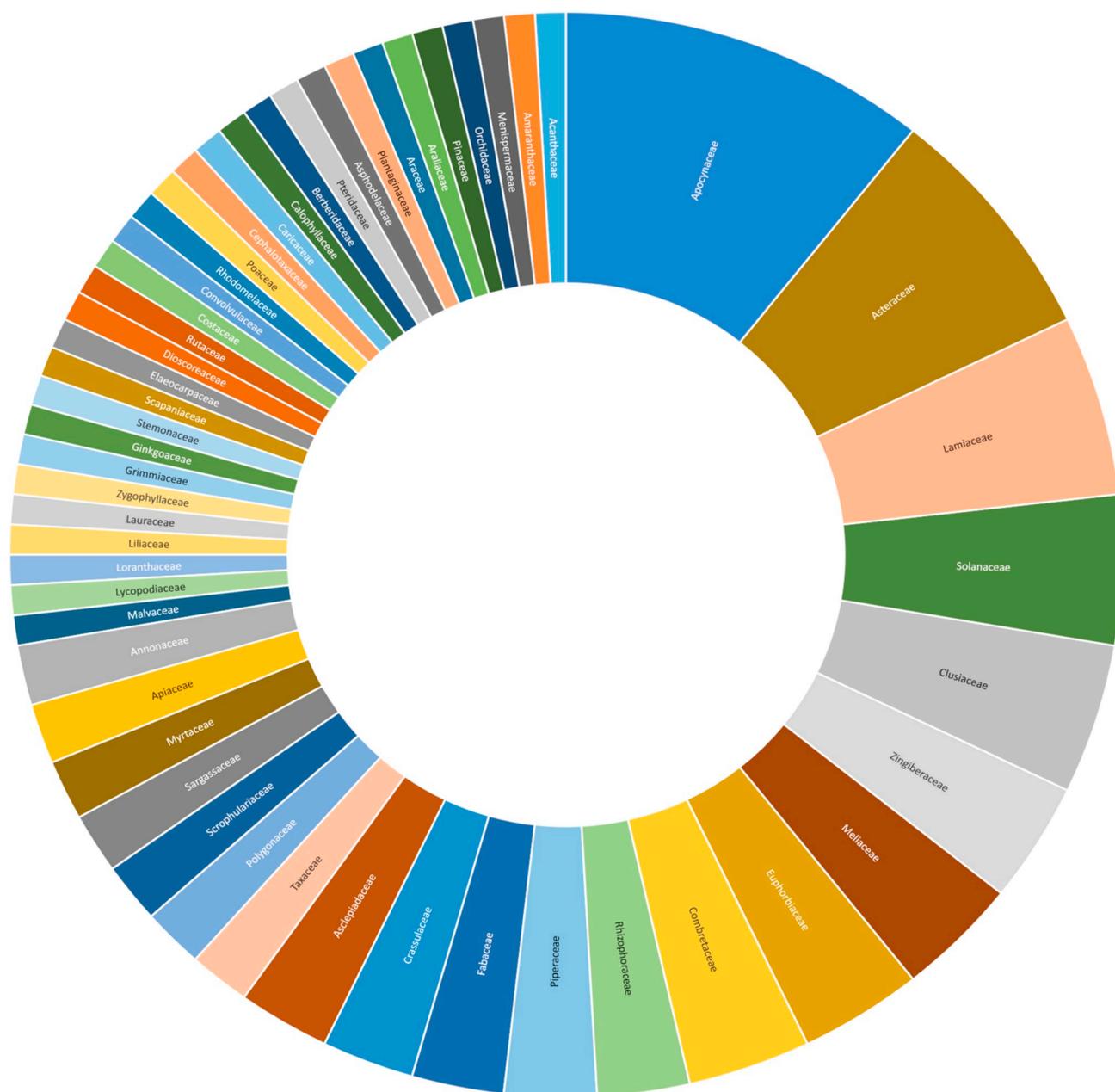


Fig. 7. Families of medicinal plants sampled for the bioprospecting endophytes for novel antioxidant compounds. Among the 52 families of plants represented, species belonging to Apocynaceae (12), Asteraceae (8), Lamiaceae (6) and Clusiaceae (5) were the most investigated. Overall, medicinal plants from these families are well-known for a wide range of biological and pharmacological activities. To name but few, they are used traditionally as immune-stimulatory, hypoglycemic, anti-inflammatory, cardioprotective, hepatoprotective, neuroprotective, antibacterial, anticancer, antimalarial, antiviral and antioxidant.

showed that 80% of endophytes extracts exhibited scavenging activity with the more potent (75–88%) being *Pseudomonas hibiscicola*, *Macroccoccus caseolyticus*, *Enterobacter ludwigii*, *Bacillus anthracis* (Akinsanya et al., 2015). Similarly, endophytes isolated from papaya fruits were reported to exhibit free radical scavenging activity and another *Bacillus* sp. PE-LR-3 was the most active isolate (Krishnan et al., 2012). Using a panel of antioxidant assays, endophytic bacteria isolated from *Fagonia indica* were investigated for their antioxidant activity. The results showed that the quantity of phenolic compounds varies among all the bacterial extracts. *Bacillus subtilis* had the highest phenolic contents 243 µg/mg of GAE while, *Stenotrophomonas maltophilia* in addition of having the high flavonoids contents (15.9 µg/mg quercetin equivalents), exhibited the best total antioxidant capacity (37.6 µg/mg of extract), reducing power (206 µg/mg of extract) as well as the best DPPH free radical scavenging activity (IC₅₀ 98.7 µg/mL) (Rahman et al., 2017). Using the DPPH scavenging assay, extract of the endophytic bacteria, *Lactobacillus* sp. was found to possess strong activity with an IC₅₀ value of 35 µg/mL (Swarnalatha et al., 2015).

The investigation of marine sponge-associated strain *Microspora* sp. RV115 led to the purification of diazepinomicin (122). Using the ferric reducing antioxidant power (FRAP) assay, diazepinomicin showed strong antioxidant potential. This compound also demonstrated a good protective ability against the genomic damage induced by the hydrogen peroxide in human kidney (HK-2) and human promyelocytic (HL-60) cell lines (Abdelmohsen et al., 2012). Different solvent extracts of an endophytic *Acinetobacter baumannii* were investigated for their antioxidant activities using a panel of assays. All the extracts exhibited antioxidant activity and the GC-MS revealed the presence of a total of 74 compounds among which two phenolic compounds, namely, phenol, 2,4-bis(1,1-dimethylethyl)- (123) and phenol, 3,5-bis(1,1-dimethylethyl)- (124) were identified (Monowar et al., 2019).

The ethyl acetate extract of endophytic actinomycetes isolated from the roots of *Catharanthus roseus* was found to be a good free radical scavenger of four radicals including hydroxyl, hydrogen peroxide, nitric oxide and DPPH (Jasmine and Agastian, 2013). The chemical investigation of this extract could lead to the purification of potent compounds with radical scavenging activity. An endophytic actinomycete, *Streptomyces* sp. loyola UGC isolated from *Datura stramonium* L. was investigated by Christudas et al. (2013). The results showed that methanolic extract shows scavenging activity against DPPH radicals (IC₅₀ 435.31 µg/mL), hydroxyl radical (IC₅₀ 350.21 µg/mL), nitric oxide (IC₅₀ 800.12 µg/mL), superoxide anion radical (IC₅₀ 220.31 µg/mL), as well as high reducing power. That extract also showed a strong ability to limit the effect of lipid peroxidation in rat liver. These results demonstrate that this extract possess a wide antioxidant spectrum and could offer an opportunity for new discovery. Another endophytic actinobacterium, *Streptomyces hydrogenans* isolated from leaves of *Aloe vera* was reported to exhibit good free radical-scavenging activity with an IC₅₀ value of 5.58 µg/mL. This extract also possesses a high amount of phenolic (15.41 µg GAE/mg extract) and flavonoid (11.41 µg QE/mg extract) contents (Nafis et al., 2018). Four other endophytic *Streptomyces* sp. were also reported by Passari et al. (2017) to exhibit DPPH radical scavenging activity with an IC₅₀ value of 43.2 µg/mL. Likewise, Zhong et al. (2011) reported the DPPH radical scavenging activity (IC₅₀ 842.18 µg/mL) of the extract of endophytic *Streptomyces* sp. strain Eri12 isolated from *Rhizoma curcumae*. In a similar investigation, Wang et al. (2016) showed that ethyl acetate extracts of endophytic *Streptomyces* sp. A01916 isolated from *Polygonum cuspidatum* possess good antioxidant properties. From these investigations, we may postulate that endophytic *Streptomyces* spp. can produce potent antioxidant compounds. In fact, from the extract of another endophytic *Streptomyces* sp. YIM67086 isolated from *Dysophylla stellate*, Yang et al. (2015) reported the identification of five compounds and the DPPH assay revealed that 2-amino-3, 4-dihydroxy-5-methoxybenzamide (125) was potent with IC₅₀ value at 68.6 µg/mL. The investigation of another endophyte *Streptomyces* sp.

YIM66017 isolated from *Alpinia oxyphylla* Miq led to the identification of four other compounds among which 2,6-dimethoxy terephthalic acid (126) and yangjinhualine A (127), exhibited DPPH radical-scavenging activities with IC₅₀ of 4.61 and 57.12 µg/mL, respectively (Zhou et al., 2014). Further investigation of *Streptomyces* spp. could, therefore, be an opportunity for discoveries.

Sugiyama and Hirota (2009) reported the identification of compounds, 2,3-dihydroxybenzoic acid (128), 2,3-dihydroxybenzamide (129), N-carbamoyl-2,3-dihydroxybenzamide (130), 2-acetamido-3-(2,3-dihydroxybenzoylthio) propanoic acid (131), anthranilic acid (132) and benadrostin (133) from a marine-derived actinobacterium. These compounds were found to exhibit DPPH radical scavenging activity with an IC₅₀ value ranging from 10.3 to 1801.8 µM. In another study, extracts from *Nocardia caishijiensis* SORS64b and *Pseudonocardia carboxydivorans* AGLS2 isolated respectively from *Sonchus oleraceus* and *Ageratum conyzoides* were investigated. The DPPH assay showed that both extracts were potent with IC₅₀s value of 0.552 and 0.670 µg/mL respectively. Moreover, the chemical analysis revealed the presence of stenothricin (134) and bagremycin A (135) in the extract of *N. caishijiensis* while, borrelidin (136), 2-pyrone (137), 7-Octadecenamamide (138), and 9, 12-octadecandienamide (139) were found in *P. carboxydivorans*'s extract (Tanvir et al., 2016).

1.1.4. Endophytes exopolysaccharide and nanoparticles as potent antioxidant agents

Exopolysaccharides (EPSs) are carbohydrates with high-molecular-weight reported for their wide range of bioactivities (Chen et al., 2016). In recent years, endophytes (bacteria and fungi) have been reported as an exceptional source of new exopolysaccharides. In fact, several researchers (Chen et al., 2010, 2011; Li et al., 2011, 2012; Liu et al., 2009, 2012; Liu et al., 2010b; Mahapatra and Banerjee, 2013a; Zheng et al., 2016) have successfully reported the antioxidant activity of exopolysaccharides produced by endophytes and their findings were recently summarised in a review by Liu et al. (2017b). Later that year, Pan et al. (2017b) reported the isolation of two exopolysaccharides, 6WBY3EPS-3 (Mw 17.41 × 10⁶ Da) and 6WBY3EPS-4 (Mw 8.84 × 10⁵ Da) from *Fusarium redolens* 6WBY3, endophytic fungal isolated from *Fritillaria unibracteata* var. wabuensis. The structural characterization showed that 6WBY3EPS-3 was composed of mannose, glucose, and galactose (molar ratio of 8.16:4.96:10.00), while 6WBY3EPS-4 was composed of mannose, rhamnose, glucose, and galactose (molar ratio of 8.08:1.71:6.32:10.00). From the activity point of view, 6WBY3EPS-3 and 6WBY3EPS-4 exhibited weak DPPH radical scavenging ability, a moderate ABTS radical scavenging activity and iron-chelating ability. Following their investigation of endophytes from the same plant species, Pan et al. (2018) reported the purification of two other water-soluble EPSs, named A14EPS-1 and A14EPS-2 from *Fusarium* sp. A14. The two EPS, A14EPS-1 and A14EPS-2 also exhibiting moderate antioxidant activity. In a more recent study, Wang et al. (2019) purified one EPS from *A. tenuissima* F1 endophyte of *Angelica sinensis*. That EPS (Mwt of 3.246 × 10⁴ Da) composed of D-galacturonic acid, rhamnose, D-mannose, glucose, and D-galactose in the ratio of 0.45:3.02:3.25:1.0:0.95 exhibited very strong scavenging activity. This finding suggest that this ESP may be a good antioxidant agent. Moreover, further investigations of the potential of endophytes exopolysaccharides are needed for the development of more natural antioxidant drugs.

Green synthesized NPs play significant roles in medicines, clinical and *in vitro* diagnostic applications. They possess outstanding properties owing to their small sizes, large surface areas with free dangling bonds and higher reactivity. Therefore, the development of eco-friendly and reliable technology for the synthesis of these nanoparticles has attracted considerable interest in nanotechnology (Hussain et al., 2015). Extracts from microorganisms have been identified as the eco-friendly means for the synthesis of bioactive nanoparticles. Indeed, in addition to producing bioactive metabolites, increasing pieces of evidence are suggesting that crude extracts from endophytes can be used to synthesize

nanoparticles (NPs) exhibiting antioxidant activity. [Netala et al. \(2016\)](#) reported the DPPH (IC₅₀ 76.95 µg/mL) and H₂O₂ (IC₅₀ 94.95 µg/mL) radicals scavenging activities of AgNPs nanoparticles synthesized from an extract of *Pestalotiopsis microspore* isolated from the leaves of *Gymnema sylvestre*. In a recent study, [Popli et al. \(2018\)](#) reported the synthesis of silver nanoparticles using the aqueous extract of *Cladosporium* species, an endophytic fungal isolated from the healthy leaf of *Loranthus micranthus*. This nanoparticle also exhibited good antioxidant activity. These studies are confirming that endophytes can also be harness as a tool for the synthesis of green nanoparticles for a very wide range of applications including pharmaceuticals.

2. Methods: brief overview

2.1. Ethnopharmacological plants used in this study

From the results of the present investigation, it appears that more than 1000 endophytes isolated from over 100 medicinal plants, belonging to over 50 different families of plants ([Fig. 7](#); S1) have been investigated for their antioxidant potential. All the plants investigated have been selected for their ethnobotanical history due to their usage by indigenous peoples (in collected areas) for the management of several diseases including oxidative stress-related disorders. Moreover, for many of these medicinal plants, studies reporting their pharmacological properties including antioxidant activity are available (data not shown). In addition to their medicinal properties, several of these plants were collected in unusual environments such as mangrove, marine, mountain, high-density forests, deserts, cities, even the Antarctic region. It was also noted that plants were collected in varied seasons including winter, summer, dry seasons, rainy seasons, etc. Given that the type of interaction between endophyte and the host plant is dictated by location of host, the season, and the host species himself ([Jia et al., 2016](#)), the difference in term of antioxidant activities and crude metabolites composition observed between endophytes from different species, between the same species isolated from different hosts, or endophytes from the same host growing in the different environment observed from this studies can be easily understood.

Overall, parameters such as the history, location, and environment of the plant species agree very well with the rationale of plant collection for the bioprospecting of endophytes as proposed by [Strobel and Daisy \(2003\)](#). Indeed, it is now accepted that the healing powers of the botanical source, could be related to the endophyte community inhabiting the plant. This has been the driving force supporting the investigation of medicinal plant-derived endophytes for the search of novel bioactive compounds. These strategies applied to select the plant's species used in investigations mentioned in the present review can likely explain the successful identification of dozens of active compounds already reported.

2.2. Methods used to screen extracts and compounds for antioxidant activities

Methods used in the screening of crude mixture or compounds for their antioxidant properties are varied. From our investigation, it appears that more than dozens of different assays have been used to evaluate the potential of metabolites from endophytes to exhibit antioxidant activity. A number of chemical assays including 2,2-diphenyl-1-picrylhydrazyl (DPPH), 2,2-azobis (2-methylpropionamide) (AAPH), 2,2'-Azino-bis(3-Ethylbenzothiazoline-6-Sulfonic Acid) (ABTS), oxygen radical absorbance capacity (ORAC), Hydroxyl (HO[•]), Hydrogen peroxide (H₂O₂), superoxide, Nitric oxide (NO), and reducing power were used. The DPPH was the most frequently used assay in almost all the articles investigated. Indeed, this essay offers the first insight into the potential antioxidant property of a given sample and therefore constitutes a good starting point to define potential antioxidant compounds or extracts.

We also found that assays used to measure the activity at the molecular and cellular level using both food and biological model systems were used to evaluate the activity of several extracts and compounds. These methods included lipid peroxidation, superoxide dismutase, β-Carotene-linoleic acid, xanthine oxidase (XOD) inhibition, DNA damage protection, SOD, CAT and GR activities in HepG2 cells, glutathione peroxidase activity, oxidized glutathione level, activity of the superoxide dismutase. In addition to these assays, the quantity of phenolic compounds in crude extracts was determined using assays such as the total phenolic and flavonoids content and finally, several statistical tools were also used to study the correlation between the amount of compounds and the activity observed in several studies. In general, these antioxidants assays need no introduction as they are very well-known and intensively well documented ([Prior et al., 2005](#); [Litescu et al., 2010](#); [Zhong and Shahidi, 2015](#)).

3. Conclusion and perspectives

The antioxidant activities of endophytes from medicinal plants have been investigated and interesting results are reported. Although an impressive number of medicinal plants (112) collected from diverse habitats and growing in different environment conditions have already been investigated, this represents only a negligible fraction (0.03%) of the total number of plant species that exist on the earth (nearly 300,000). Moreover, only a few numbers of these plants were intensively investigated relative to their endophytic content. This highlights the opportunity to find interesting endophytic microorganisms among myriads of plants in different settings and ecosystems, capable of producing novel and highly potent antioxidants, needed to counteract oxidative stress-related disorders.

Indeed, the current review has shown that a very large number of endophytes have already been investigated for their capacity to produce antioxidants. Over 100 active compounds produced by a wide diversity of endophytes exhibiting a varying degree of potency have been characterized from their crude extracts. However, this study also revealed a great number of endophytes were investigated only at the crude extract level. Although many studies correlated the activity with their chemical composition, a deeper chemical investigation is still needed to identify potential antioxidant ingredients. Overall, it has become clear from our investigation that endophytes associated with ethnomedicinal plants are great sources of natural antioxidant metabolites and that more investigation of these microorganisms could lead to the discovery of novel and more potent natural antioxidants.

Declaration of competing interest

The authors declare that they are no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.bcab.2019.101430>.

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