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Endophytic fungi from medicinal plants: a treasure hunt for bioactive metabolites

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Abstract Endophytic fungi are ubiquitous organisms found in the plants, residing intercellular or intracellular, at least for a portion of their lives without causing apparent symptoms of infection. Almost all plants are known to harbor endophytes. The choice of the plant to be used for exploring endophytes for bioactives is important. Therefore, medicinal plants which are known to be used since centuries as an alternative source of medicine, are a valuable source for bioprospecting endophytes. Nevertheless, due to many reasons there is a dire need for novel resources for novel drugs which can be an answer to many deadly diseases. It is in this context that the present review was envisaged. The review reveals the importance of endophytic fungi from medicinal plants as a source of bioactive and chemically novel compounds. The bioactive metabolites produced by endophytic fungi originate from different biosynthetic pathways and belong to diverse structural groups such as terpenoids, steroids, quinones, phenols, coumarins etc. Endophytes therefore, represent a chemical reservoir for new compounds such as, anticancer, immunomodulatory, antioxidant, antiparasitic, antiviral, antitubercular, insecticidal etc. for use in the pharmaceutical and agrochemical industries. Although, efforts have been made to accommodate as many examples as possible but the depth of the subject is so vast that it cannot be covered in one single review. This in itself speaks of the fact that endophytic fungi from medicinal plants is indeed a treasure worth searching. In the present review only some selected examples have been covered.

Keywords Bioactivities · Endophytes · Medicinal plants · New metabolites

Medicinal plants: a source for bioactive metabolites

Since times immemorial medicinal plants have been used as a source of medicine. In ancient texts such as Vedas and Bible, the widespread use of herbal remedies and healthcare preparations has been described. Natural products have been exploited for human use for thousands of years and plants have been the chief source of compounds used for medicine. Use of plants as medicine predates written human history and some of the earliest written records from China, Egypt and Sumeria. Almost all cultures in the world have a body of expertise concerned with the therapeutic properties of local flora. Interaction between different cultures has resulted in the expansion of pharmacopoeia of each group due to adoption of plants used by the others.

In industrialized countries, plants have contributed more than 7,000 compounds to pharmaceutical industry including those used in heart drugs, laxatives,

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anticancer agents, hormones, contraceptives, analgesics, antibiotics, diuretics, etc. The World Health Organization (WHO) defines a medicinal plant as "any plant, which in one or more of its organs, contains substances that can be used for therapeutic purposes or which are precursors for chemo pharmaceutical semi synthesis." This definition distinguishes those plants that are already scientifically tested from those not subjected to a scientific study but are used in the traditional system of medicine. The beneficial effects of the medicinal plants in health care can be well judged from the WHO estimate that around 80 % of the world population uses them in some form or the other (Balick et al. 1996). The people using them are mostly those living in the remote or marginal areas and rural and indigenous people who depend heavily on the natural resources of their surrounding medicine. An ethno biological survey revealed that about 8,000 species of medicinal plants are used as food supplements, medicines, biocides and other phytochemicals.

The ethno-pharmacologists from around the world are fascinated by the fact, that plants are invaluable source of pharmaceutical products (Olalde Rangel 2005). Their usage as traditional health remedies has been reported to have minimal side-effects and is popular among 80 % of the population in Asia, Latin America and Africa (Bibitha et al. 2002; Maghrani et al. 2005).

Importance and need to explore new sources: endophytic fungi

Natural products are naturally derived compounds present as metabolites or byproducts from microorganisms, plants or animals (Strobel and Daisy 2003). They are a continuing source of novel bioactive metabolites, and have profuse impact on modern medicine. About 68 % of antibacterial compounds and 34 % of products used in cancer therapy are either natural products or their derivatives (Newman and Cragg 2007). Natural products derived particularly from medicinal plants have been exploited for human use for thousands of years to make human life easy.

Owing to these facts, there is a need to explore new and useful bioactive compounds to provide assistance and relief in all aspects of human conditions. A new source which can be explored to alleviate the problems faced by mankind is the endophytic fungi. The term endophyte is applied to organisms including fungi which live within plant tissues for all or part of their life cycle and cause no apparent infections (Bacon and White 2000). This definition excludes the mycorrhizal fungi. By definition, an endophytic fungus lives in mycelial form in biological association with living plant at least for some time. Therefore, the minimal requirement before a fungus to be termed as an endophyte should be the demonstration of its hyphae in the living tissue.

Endophytes are synergistic to their host. At times they are known to prevent the host from successfully attacking fungi and pests by producing special substances such as secondary metabolites and in return demanding nutrition (Strobel and Daisy 2003). The array of metabolites and other chemicals synthesized by the endophytes endow the plants with more resistance to nematodes, insects and livestock. Plants inhabited with specific endophytes are often able to grow faster due to the production of phytohormones and become so competitive that they dominate in a particular environment.

The benefit of symbiotic relationship for the endophyte is that the host plant is able to supply the necessary nutrients and compounds required for the endophyte to complete its life cycle. Unlike the host plant, many endophytes are able to survive under quite extreme and inhospitable conditions (Bacon and White 2000). Fungal endophytes have evolved two transmission modes. These are vertical and horizontal transmissions, of which the former transmits the systemic fungus from plant to offspring via host seeds, and the latter operates by sexual or asexual spore transfer (Saikkonen et al. 2004). In a co-evolutionary view, endophytic microbes improve the resistance of the host plant to adversity by the secretion of the bioactive secondary metabolites (Strobel and Daisy 2003). The number of secondary metabolites produced by fungal endophyte is larger than that of any other endophytic microorganism class (Zhang et al. 2006). The search for novel secondary metabolites should be concentrated on those organisms inhabiting unique and exceptional biotopes. Continual metabolic interactions between fungus and plant may enhance the synthesis of secondary metabolites with novel properties (Schulz et al. 2002). This may of course be a consequence of high frequency of isolation of endophytic fungi from plants.

Natural products from fungal endophytes have a broad spectrum of biological activity and can be grouped into several categories including; alkaloids,

steroids, terpenoids, flavonoids, glycosides, xanthones, isocoumarins, quinones, phenyl propanoids, lignans, aliphatic metabolites, lactones etc. (Zhang et al. 2006). Endophytic fungi are a poorly investigated group of microorganisms that represent an abundant and dependable source of bioactive and chemically novel compounds.

Endophytes as a source of bioactive metabolites

Endophytes are the chemical synthesizers inside plants (Owen and Hundley 2004). The secondary metabolites produced by endophytes associated with medicinal plants can be exploited for curing many diseases (Tejesvi et al. 2007). The various natural products produced by endophytic fungi possess unique structures and bioactivities, thus representing a huge reservoir which offers an enormous potential for exploitation in agricultural and industrial areas (Tan and Zou 2001). Attempts have been made to isolate and identify various bioactive metabolites from endophytic fungi. Fermentation of endophytic fungi with potential for bioactive compound production has several advantages, like reproducible and dependable productivity. It can be grown in fermenters to provide inexhaustible supply of bioactive compound and thus can be exploited commercially. Direct changes in the culture conditions can be explored as a method of optimizing various biosynthetic pathways which lead to the production of derivatives and analogues of novel compounds (Strobel et al. 2004). Some of the important categories of bioactive metabolites produced by fungal endophytes of medicinal plants are discussed below (Fig. 1).

Anticancer agents

Endophytic fungi have been studied as a source of anticancer agents since the million dollar drug Taxol (**1**) ($C_{47}H_{51}NO_{14}$) was isolated from the endophytic fungus *Taxomyces andreanae* (Stierle and Strobel 1993). Taxol a diterpenoid (also known as paclitaxel) is a very potent anticancer agent, isolated for the first time, from the bark of the Pacific Yew (*Taxus brevifolia*). The Food and Drug Administration (FDA), USA, hacan be a potentialve proved paclitaxel for the treatment of ovarian and breast cancer (Cremasco et al. 2009). Torreyanic acid (**2**) $C_{38}H_{44}O_{12}$ a quinone dimer, was produced from endophyte *Pestalotiopsis microsporum* isolated from *Torreya taxifolia*. Torreyanic acid is a potent cytotoxic agent and found to be more efficient (5–10 times) in cell lines that are sensitive to protein kinase C agonists; it causes cell death by apoptosis (Lee et al. 1996).

Puri et al. (2005) isolated the alkaloid Camptothecin (**3**) ($C_{20}H_{16}N2O_4$), a potent anti neoplastic agent from endophytic *Entrophospora infrequens* inhabiting *Nothapodytes foetida*. In order to check the biological activity of this compound, an in vitro cytotoxic assay against human cancer cell lines (A-549 for lung cancer, HEP-2 for liver cancer, OVCAR-5 for ovarian cancer) was performed in comparison to the standard authentic example, resulting in comparable activities (Puri et al. 2005).

Uma et al. (2008) reported the precursors for the two clinically useful anticancer drugs i.e. 9-methoxycamptothecin and 10-hydroxycamptothecin which bring about the synthesis of topotecan (**4**) $C_{23}H_{23}N_3O_5$ and irinotecan. These potent anticancer compounds were extracted from the endophytic *Fusariumsolani* inhabiting *Camptotheca acuminata* (Kusari et al. 2009b). Podophyllotoxin (**5**) ($C_{22}H_{22}O_8$), a non alkaloid lignan and its analogues are clinically relevant mainly due to their antiviral and anticancer activities, further they are the precursors of many other useful anticancer drugs including etoposide (**6**) $C_{29}H_{32}O_{13}$, teniposide (**7**) $C_{32}H_{32}O_{13}S$, etopophos phosphate (**8**) $C_{29}H_{33}O_{16}P$ (Kour et al. 2008). Podophyllotoxin and other related aryl tetralin lignans have also been reported to be produced by another novel endophytic fungus, *Trametes hirsute* with anticancer potential (Puri et al. 2006). Various novel microbial sources of podophyllotoxin include *Aspergillusfumigatus* isolated from *Juniperuscommunis* (Kusari et al. 2009a), *Phialocephala fortinii* isolated from *Podophyllum peltatum* (Eyberger et al. 2006) and *Fusarium oxysporum* isolated from *Juniperus recurva* (Kour et al. 2008).

Ergoflavin (**9**) $C_{30}H_{26}O_{14}$, a novel anticancer agent was isolated from the leaf endophytes of an Indian medicinal plant *Mimusops elengi* belonging to family Sapotaceae. Ergoflavin is a dimeric xanthene linked at position-2, belonging to the ergochrome class of compounds (Deshmukh et al. 2009). Another compound from ergochrome class i.e. secalonic acid D (**10**) ($C_{32}H_{30}O_{14}$) a mycotoxin, isolated from the

mangrove endophytic fungus also exhibits a good cytotoxic activity on HL60 and K562 cells by inducing leukemia cell apoptosis (Zhang et al. 2009).

Wagenaar et al. (2000) studied *Rhinocladiella* sp. inhabiting *Tripterygium wilfordii*, and reported three novel cytochalasins: cytochalasin H (**11**) $C_{30}H_{39}NO_5$, cytochalasin J (**12**) $C_{28}H_{37}NO_4$ and epoxycytochalasin H (**13**) $C_{39}H_{41}NO_5$ alongwith a known compound cytochalasin E (**14**) $C_{28}H_{33}NO_7$. These compounds have been identified as 22-oxa-12-cytochalasins and have antitumor activity. A novel cytotoxic cytochalasan based alkaloid chaetoglobosin U (**15**) along with four known analogues chaetoglobosin C (**16**) $C_{32}H_{36}O_5N_2$, chaetoglobosin F (**17**) $C_{32}H_{38}O_5N_2$, chaetoglobosin E (**18**) $C_{32}H_{38}O_5N_2$ and ponochalasin A, have been produced by the fungal endophyte *Chaetomium globosum* IFB-E019 isolated from *Imperata cylindrica*. Cheatoglobosin U exhibits cytotoxic activity against nasopharyngeal epidermoid tumor KB cell (Ding et al. 2006). Chen et al. (2009) reported *Gliocladicillins* A and B as effective antitumor agents in vitro and in vivo. They induced tumor cell apoptosis and also showed a significant inhibition on proliferation of melanoma B16 cells implanted into immunodeficient mice.

Vincristine (**19**) $C_{46}H_{56}N_4O_{10}$, an alkaloid with cytotoxic activity was isolated from the endophytic mycelia sterilia inhabiting *Catharanthus roseus* (Yang et al. 2004). This drug is mainly used as a chemotherapy regimen in acute lymphoblastic leukemia and nephroblastoma.

Likewise, there are large numbers of anticancer agents produced by fungal endophytes inhabiting different medicinal plants. The reader is suggested to read a latest review by Kharwar et al. (2011) to have an overview of anticancer agents from fungal endophytes. For the sake of convenience, some of the endophytic anticancer metabolites are presented in the form of a table (Table 1).

Antioxidant compounds

Antioxidants are substances that may protect cells from the damage caused by unstable molecules known as free radicals. Free radical mediated reactions are associated with degenerative diseases like cancer, Alzheimer's disease etc. Owing to the fact that only few antioxidants are approved for clinical applications there is a need to search for new and effective antioxidants.

Discovery of pestacin and isopestacin as antioxidant compounds from *Pestalotiopsis microspora* residing in *Terminalia morobensis* led to the exploration of antioxidant potential of this less explored group of fungi. Pestacin (**44**) $C_{15}H_{14}O_4$, 1, 3-dihydro isobenzofuran occurs naturally as a racemic mixture and acts by cleaving an unusual reactive C–H bond and through O–H abstraction to a lesser extent (Harper et al. 2003). Isopestacin (**45**) ($C_{15}H_{12}O_5$) an isobenzofuranone behaves as an antioxidant by scavenging both superoxide and hydroxyl free radicals (Strobel et al. 2002). A new isobenzofuranone derivative 4,6-dihydroxy-5-methoxy-7-methylphthalide alongwith three known compounds: 4,5,6-trihydroxy-7-methyl-1,3-dihydroisobenzofuran; 4,6-dihydroxy-5-methoxy-7-methyl-1,3-dihydroisobenzofuran and 4,5,6-trihydroxy-7-methylphthalide with antioxidative activity were obtained from *Cephalosporium* sp. AL031 endophytic in *Sinarundinaria nitida* (Huang et al. 2012). Graphislactone A was isolated from *Cephalosporium* sp. IFB-E001, an endophytic in *Trachelospermum jasminoides*. The compound was confirmed to have stronger antioxidant activity in vitro as compared to butylated hydroxytoluene and ascorbic acid which were used as positive control (Song et al. 2005).

The natural antioxidant Cajaninstilbene acid (**46**) ($C_{12}H_{22}O_4$) (CSA), 3-hydroxy-4-prenyl-5-methoxystilbene-2-carboxylic acid has been reported from *Fusarium* an endophyte of Pigeon pea, *Cajanus cajan* (Zhao et al. 2012a, b). Similarly, a strong antioxidant activity was exhibited by *Xylaria* sp. isolated from *Ginkgo biloba*. The activity was due to the presence of phenolics and flavonoids (Liu et al. 2007). *Chaetomium* sp. from *Nerium oleander* can be a potential antioxidant resource as the flavonoids and phenolic acid derivatives of this fungus exhibit strong antioxidant activity (Huang et al. 2007).

Immunomodulatory agents

A number of immunomodulatory compounds have been isolated from endophytic fungi. These immunomodulatory compounds are mainly categorized into immunosuppressive and immunoregulatory drugs. Due to the emergence of new diseases particularly autoimmune disorders, need for immunosuppressive drugs in the market have risen considerably. Immunosuppressive

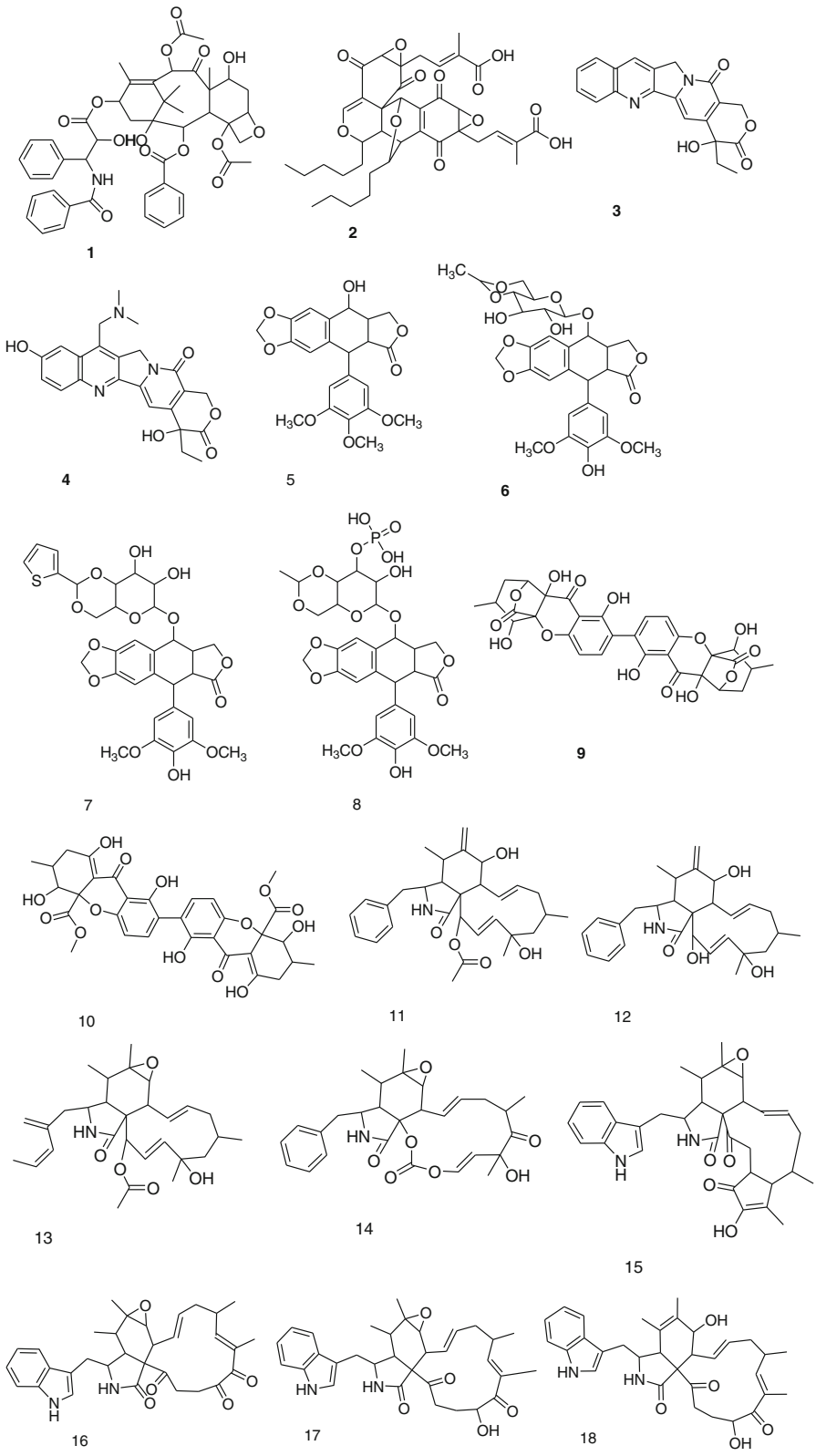
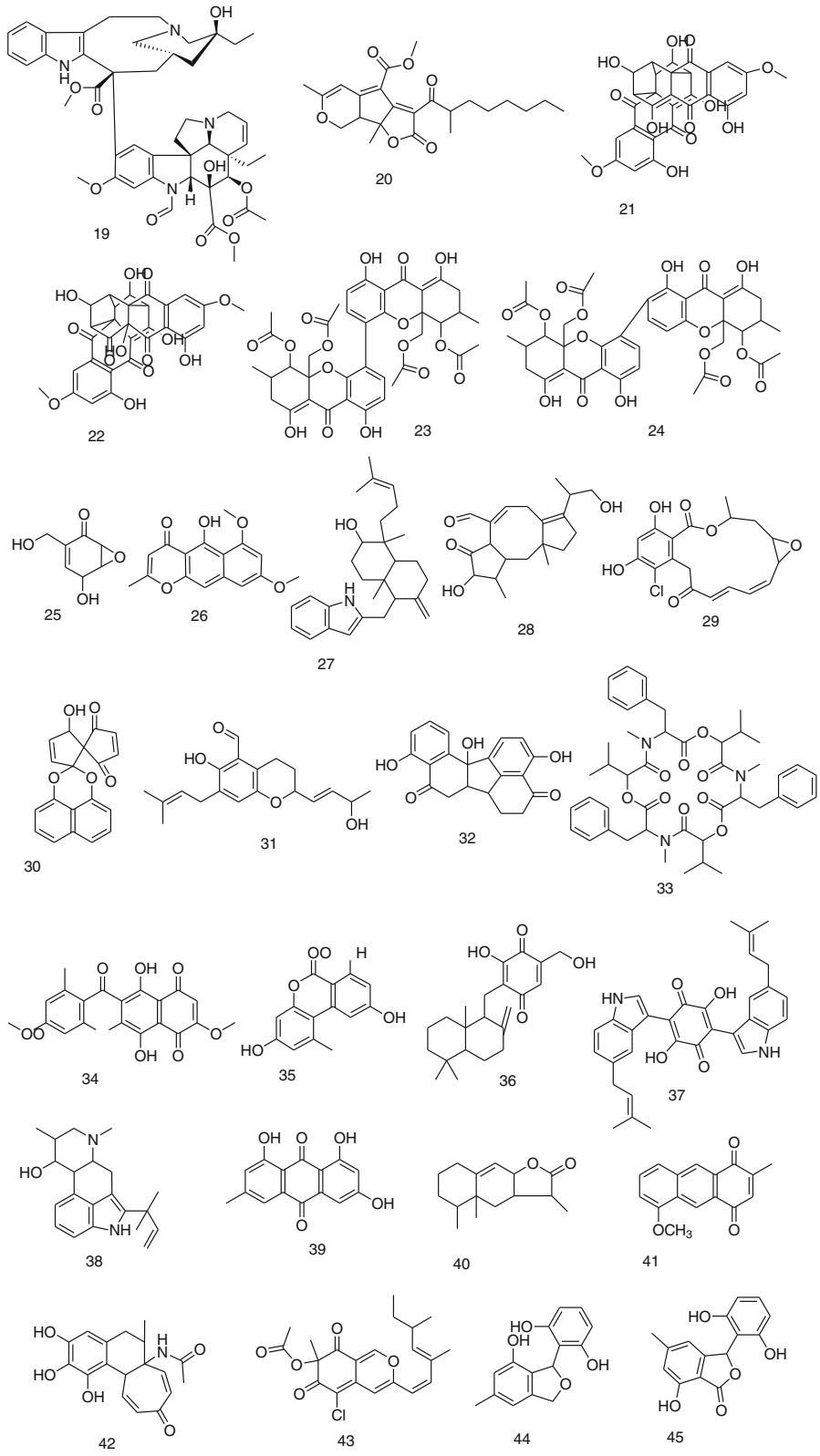


Fig. 1 Structures of different bioactive compounds isolated from endophytic fungi of medicinal plants: anticancer compounds (**1**–**43**), antioxidant compounds (**44**–**46**), immunomodulatory compounds (**47**–**49**), insecticidal compounds (**50**–**56**), antiparasitic compounds (**57**–**61**), antimicrobial compounds (**62**–**88**), antiviral compounds (**89**–**91**), antitubercular compounds (**92**)

Fig. 1 continued



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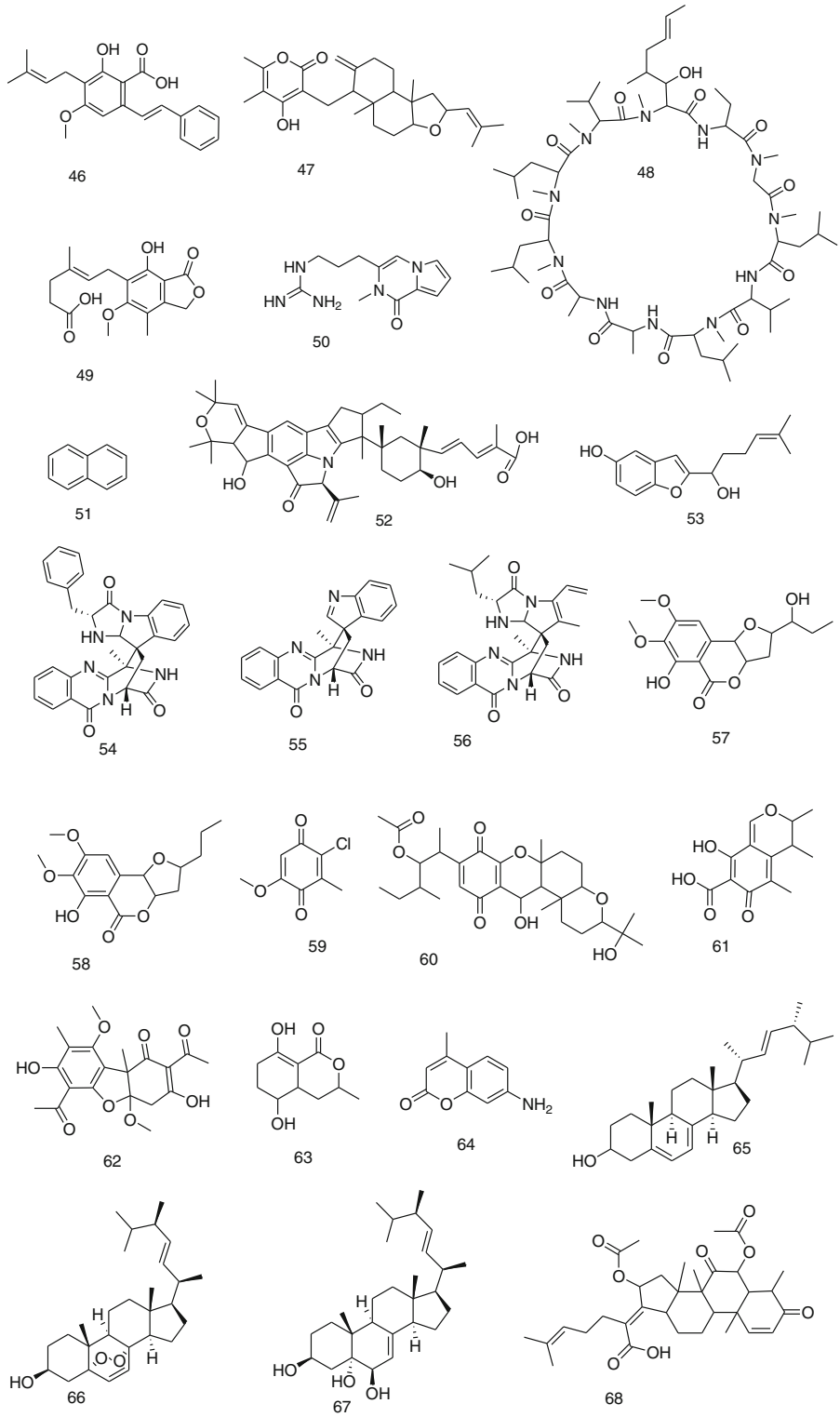

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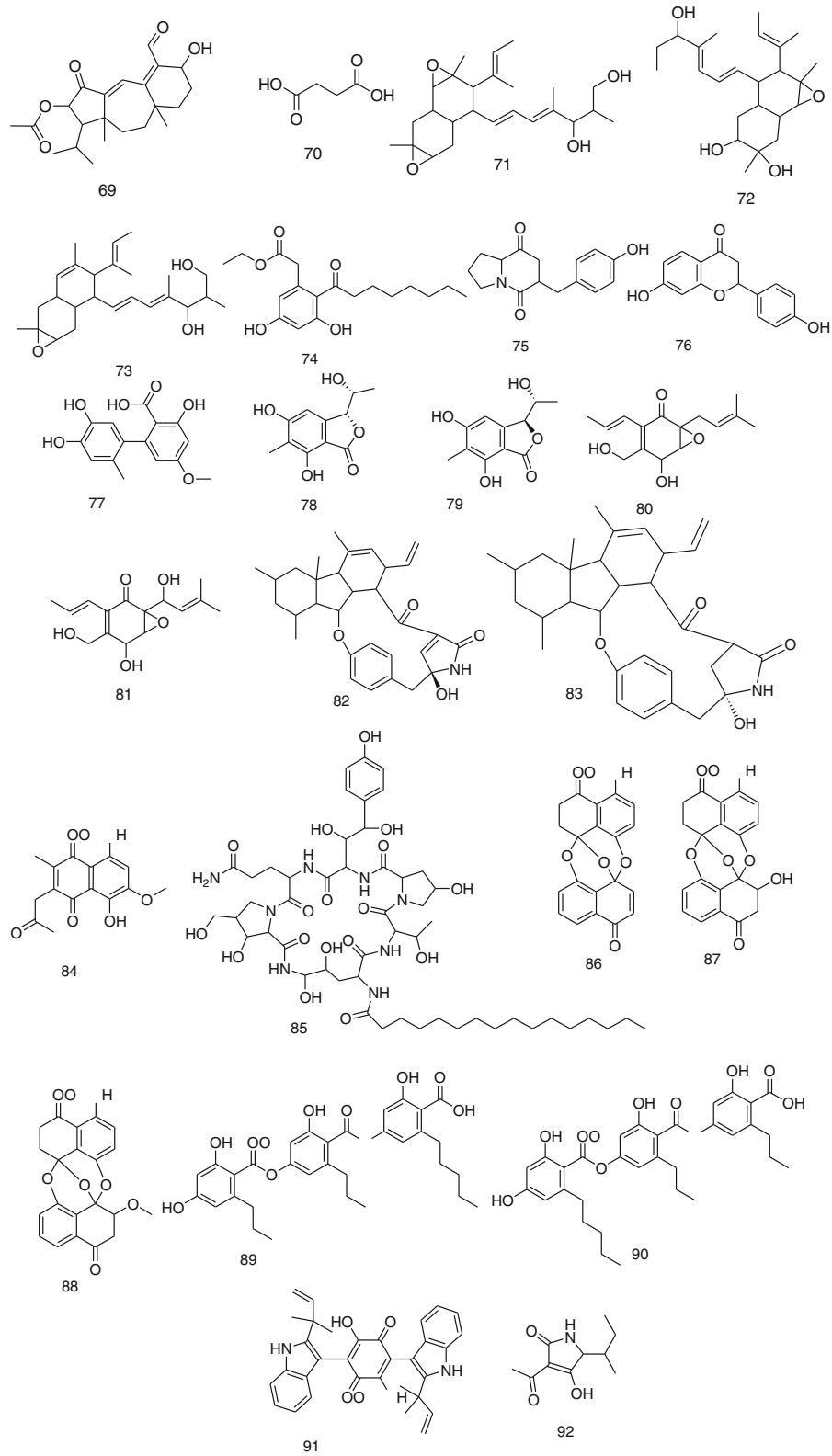

Table 1 Anticancer compounds produced by endophytic fungi isolated from medicinal plants

S. no.	Fungal endophyte	Medicinal plant	Compounds	References
1	*Aspergillus parasiticus*	*Sequoia sempervirens*	SequoiatonesA (**20**) ($C_{23}H_{30}O$)	Stierle et al. (1999)
2	*Cytospora* sp.	*Conocarpus erecta*	CytoskyrinA (**21**) ($C_{30}H_{22}O_{12}$) CytoskyrinB (**22**) ($C_{30}H_{22}O_{13}$)	Brady et al. (2000)
3	*Xylaria* sp., *Phomopsis* sp.	*Licuala spinosa.*, *Tectona grandis*	PhomoxanthoneA (**23**) ($C_{38}H_{38}O_{16}$), PhomoxanthoneB (**24**) ($C_{38}H_{38}O_{16}$)	Isaka et al. (2001)
4	*Apiospora montagnei*	*Polysiphonia violacea*	Epiepoxydon (**25**) ($C_7H_8O_4$)	Klemke et al. (2004)
5	*Aspergillus niger*	*Cynodon dactylon*	RubrofusarinB (**26**) ($C_{16}H_{14}O_5$)	Song et al. (2004)
6	*Emericella nidulans*	*Mediterranean green alga*	EmindoleDA (**27**) ($C_{28}H_{39}NO$)	Kralj et al. (2006)
7	*Periconia atropurpurea*	*Xylopia aromatica*	PericonicinB (**28**) ($C_{20}H_{28}O_4$)	Teles et al. (2006)
8	*Chaetomium chiversii*	*Ephedra fasciculate*	Radicicol (**29**) ($C_{18}H_{17}ClO_6$)	Turbyville et al. (2006)
9	Mycelia sterilia	*Knightia excelsa*	SpiromamakoneA (**30**) ($C_{19}H_{12}O_5$)	van der Sar et al. (2006)
10	*C. globosum*	*Polysiphonia urceolata*	Chaetopyranin (**31**) ($C_{19}H_{24}O_4$)	Wang et al. (2006)
11	*Hypoxylon truncatum*	*Artemisia annua*	Daldinone (**32**) ($C_{20}H_{16}O_5$)	Gu et al. (2007)
12	*F. oxysporum*	*Ephedra fasciculate*	Beauvericin (**33**) ($C_{45}H_{57}N_3O_9$)	Zhan et al. (2007)
13	*F. oxysporum*	*Cylindropuntia echinocarpus*	Bikaverin (**34**) ($C_{20}H_{14}O_8$)	Zhan et al. (2007)
14	*Alternaria* sp.	*Polygonum senegalense*	Alternariol (**35**) ($C_{14}H_{10}O_5$)	Aly et al. (2008)
15	*Phyllosticta spinarum*	*Platycladus orientalis*	Tauranin (**36**) ($C_{22}H_{30}O_4$)	Wijeratne et al. (2008)
16	*Pestalotiopsis photiniae*	*Roystonea regia*	Photinides A–F	Ding et al. (2009)
17	*Chaetomium* sp.	*Salvia officinalis*	Cochliodinol (**37**) ($C_{32}H_{30}N_2O_4$)	Debbab et al. (2009)
18	*A. fumigatus*	*Cynodon dactylon*	9-Deacetoxy fumigaclavine (**38**) ($C_{21}H_{28}N_2O$)	Ge et al. (2009)
19	*Thielavia subthermophila*	*Hypericum perforatum*	Emodin (**39**) ($C_{15}H_{10}O_5$)	Kusari et al. (2009c)
20	*Eutypella* sp.	*Etlingera littoralis*	Eutypellin A	Isaka et al. (2009)
21	*Xylaria* sp.	*Licuala spinosa*	Eremophilanolides (**40**) ($C_{15}H_{22}O_2$)	Isaka et al. (2010)
22	*Halorosellinia* sp. and *Guignardia* sp.	Mangrove	Anthracenedione (**41**) ($C_{16}H_{12}O_3$)	Zhang et al. (2010a, 2010b)

Table 1 continued

S. no.	Fungal endophyte	Medicinal plant	Compounds	References
23	*Aspergillus* sp.	*Gloriosa superba*	6-Methyl-1,2,3-trihydroxy-7, 8-cyclohepta-9,12-diene-11-one-5,6,7,8-tetralene-7-acetamide (**42**) ($C_{18}H_{19}NO_5$)	Budhiraja et al. (2012)
24	*Cephalotheca faveolata*	*Eugenia jambolana*	Sclerotiorin (**43**) ($C_{21}H_{23}ClO_5$)	Giridharan et al. (2012)

drugs are mainly used to prevent allograft rejection in transplant patients, and also to treat autoimmune diseases such as insulin dependent diabetes and rheumatoid arthritis. As a result of this, researchers have mainly focused on the production of these drugs from the alternative source and one of them could be endophytes. An intensive search is going on for more effective agents to deal with immunological disorders related to graft rejection and various other autoimmune diseases. Endophytic fungi could prove a useful source for the production of these drugs because they possess the capacity to produce novel compounds that could be potentially active immunomodulatory substances.

Two important immunosuppressive compounds Subglutinol-A (**47**) ($C_{27}H_{38}O_4$) and Subglutinol-B are non-cytotoxic diterpene pyrones. These compounds were isolated from the fungal endophyte *Fusarium subglutinans*, inhabiting *Tripterygium wilfordii* (Lee et al. 1995). These compounds are non toxic and are very potent in the thymocyte proliferation (TP) assays and mixed lymphocyte reaction (MLR). Another important immunosuppressive drug, cyclosporine-A (**48**) ($C_{62}H_{111}N_{11}O_{12}$) (a fungal metabolite) was 10^4 times more potent in the TP assay and roughly as potent in the MLR assay. Mycophenolic acid (**49**) ($C_{17}H_{20}O_6$) is another potent immunosuppressive fungal metabolite used for the treatment of autoimmune diseases and organ transplantations. This compound has been reported to be produced by *Penicillium*, *Aspergillus*, *Byssochlamys* and *Septoria* species (Bentley 2000; Larsen et al. 2005).

A potent fungus, *Tolypocladium inflatum* has been discovered which produces immunosuppressant cyclosporine (Borel and Kis, 1991). Similarly, Collutelin A, an antimycotic peptide was isolated from *Colletotrichumdematium* inhabiting *Pteromischum* sp. growing in the tropical forests of Costa Rica. It exhibits strong immunosuppressive activity by inhibiting CD4 (+) T cell activation of Interleukin-2 production, whereas the other compound cyclosporin A shows moderate activity in the same experiment (Ren et al. 2008). These examples perfectly depict the current aim of many investigators to seek out rare endophytes from interesting and uncommon hosts and environments.

Insecticidal agents

In order to prevent the ecological damage done by synthetic insecticides, use of safe alternative methods are gaining the pace. Thus, endophytic research continues for the discovery of selective, powerful and safe alternatives. Several endophytes are known to have insecticidal properties. In this field, bioinsecticides have not contributed much but their use in the market is increasing day by day (Demain 2000). Peramine (**50**) ($C_{12}H_{17}NO_5$), a pyrrolopyrazine alkaloid is an insecticidal agent but harmless to mammals. This compound was isolated from endophytic fungi *Neotyphodium coenophialum*, *Neotyphodium lolii*, *Epichole festucae* and *Epichole typhina* present in the stem and leaf of tall fescue, ryegrass and other grasses.

Naphthalene (**51**) ($C_{10}H_8$), that has insect repellent activity, was produced by fungus *Muscodor vitigenus* which was isolated from a liana (*Paullina paullinoides*) (Daisy et al. 2002a, b). Naphthalene is an active ingredient in common mothballs and is widely used as an insect repellant. As an insect deterrent, *M. vitigenus* shows promising preliminary results and has also exhibited a potent insect repellency against *Cephus cinctus* (wheat stem sawfly) (Daisy et al. 2002a, b).

Nodulisporic acid (**52**) ($C_{43}H_{55}NO_6$) (novel indole diterpene), is an insecticidal agent isolated from *Nodulisporium* sp. endophytic in *Bontia daphnoides*.

This compound showed insecticidal activity against the larvae of the blowfly. As an insecticidal agent, it works by activating glutamate-gated chloride channels (Demain 2000). Two more new insecticidal compounds namely 5-hydroxy-2-(1′-hydroxy-5′-methyl-4′-hexenyl) benzofuran (**53**) ($C_{15}H_{18}O_3$) and 5-hydroxy-2-(1′-oxo-5′-methyl-4′-hexenyl) benzofuran have been isolated from an unidentified endophytic fungus of *Gaultheria procumbens*. Both these compounds showed toxic effect on spruce budworm, but the latter shows toxic effects also on the larvae of spruce budworm (Findlay et al. 1997). Fabio et al. (2005) reported few more new insecticidal compounds that have been isolated from the fungal endophyte *Eupenicillium* sp. inhabiting the host plant *Murrayapaniculata*. These compounds include Alantryphenone (**54**) ($C_{30}H_{25}N_5O_3$), Alantrypinene (**55**) ($C_{21}H_{16}N_4O_2$) and Alantryleunone (**56**) ($C_{27}H_{27}N_5O_3$) (Fabio et al. 2005). Two fungal endophytes *Claviceps-purpurea* and *Clavicepschaetomium* isolated from *Achnatheruminebrians* in China possess significant insecticidal activity against *Aphis gossypii* (cotton aphis). This study can provide a newer biological resource to explore novel microbial insecticides (Zhang et al. 2010a, b).

Antiparasitic compounds

A parasitic disease is an infectious disease caused or transmitted by a parasite. These parasitic infections are caused by two main types of organisms protozoa and helminths. Malaria, a tropical disease caused by protozoan parasites of the genus *Plasmodium*, has been a real concern for centuries and is now extended to more than 40 % of the world's population. *Plasmodium falciparum*, the most prevalent species across the globe, may cause cerebral malaria that is often fatal (Robert et al. 2001). Antimalarial drugs have been proved to be the precious and cost effective public health resource. Like all drugs for infectious diseases, they have a limited useful life and eventually need replacing due to emergence of multidrug resistance. So, endophytes would be acting as a source of novel antimalarial drugs and thus make a huge impact on the health and economic situation of people and communities affected by malaria.

Phomopsis archeri an endophytic fungus of *Vanilla albindia* (Blume) produces aromatic sesquiterpenes-phomoarcherins A–C which show antimalarial activity against *P. falciparum* (Hemtasin et al. 2011). Another *Phomopsis* sp. produced two novel xanthone dimers Phomoxanthones A (**23**) and B (**24**) ($C_{38}H_{38}O_{16}$), exhibiting significant antimalarial activity (Isaka et al. 2001). 11-hydroxymonocerin (**57**) ($C_{16}H_{20}O_7$) a new analogue of monocerin (**58**) ($C_{16}H_{20}O_6$), alongwith 12-hydroxymonocerin were isolated from *Exserohilum rostratum* inhabiting *Stemona* sp. displaying activity against multidrug resistant strains of *P. falciparum* (Sappapan et al. 2008). Tansuwan et al. (2007) also reported inhibition of *P. falciparum* by two novel benzoquinone metabolites 2-chloro-5-methoxy-3-methylcyclohexa-2,5-diene-1,4-dione (**59**) ($C_8H_7ClO_3$) and xylariaquinone A produced by *Xylaria* sp. *Leishmania* and *Trypanosome* are other parasitic protozoans responsible for causing leshmaniasis and tryponamiasis which cause high morbidity and mortality to humans. Currently the drugs used to treat these infections are either toxic or sometimes ineffective. So, novel sources for treating these types of infections would be beneficial for mankind. The discovery of new drugs from endophytes reinforces their role as an important source of compounds with potential to enter the field of drug development against these infections. The active compounds against *Leshmania* viz. cochlioquinone A (**60**) ($C_{30}H_{44}O_8$) and isocochlioquinone A with EC50 values of 1.7 and 4.1 mM, respectively were obtained from *Cochliobolus* sp. (UFMGCB-555) from *Piptadenia adiantoides* (Campos et al. 2008). A polyketide citrinin (**61**) ($C_{13}H_{14}O_5$) was produced by *Penicillium janthinellium* an endophytic fungus from *Melia azedarach* inhibiting 100 % Leishmania growth after 48 h at a concentration of 40 μg/ml (Marinho et al. 2005). Martinez-Luis et al. (2012), reported different compounds from different endophytic fungi with good anti leishmanial activities. Bioassay directed fractionation of organic extracts of *Edenia* sp. endophytic in *Petrea volubilis* also led to the isolation of the antileishmanial compounds preussomerin EG1, palmarumycin CP2, palmarumycin CP17, palmarumycin CP18, CJ-12,37, palmarumycin CP19 and 5-methylochracin which inhibited the growth of *Leishmania donovani*. Preussomerin EG1 was the most active substance and inhibited growth of *L. donovani* with potency similar to that of amphotericin B (Martinez-Luis et al. 2009). *Aspergillus* sp. strain F1544 produced five compounds pseurotin A, 14-norpseurotin A, FD-838, pseurotin D and fumoquinone with anti leishmanial activity (Martinez-Luis et al. 2012).

A new endophytic fungus *Mycosphaerella* sp. associated with *Psychotria horizontalis* afforded cercosporin which on acetylation produced a new analogue of cercosporin. Both these compounds exhibited high potency against *L. donovani*, *Trypanosoma cruzi* and *P.falciparum* (Moreno et al. 2011). A new compound determined as 3,4-dimethyl-2-(4′-hydroxy-3′,5′-dimethoxyphenyl)-5-methoxy-tetrahydrofuran was obtained on biotransforming tetrahydrofuran lignan, (−)-grandisin, by *Phomopsis* sp., residing within *Viguiera arenaria*. The compound displayed trypanocidal activity against the parasite *T. cruzi*, the causative agent of Chagas's disease (Verza et al. 2009).

Antimicrobial compounds

Antimicrobial agents are low molecular-weight organic natural substances produced by microorganisms that are active at low concentrations against other microorganisms (Guo et al. 2000). Endophytic *Phoma* sp. isolated from different medicinal plants has been reported to be a promising source of antimicrobial compounds. A new α-tetralone derivative (3S)-3,6,7-trihydroxy-α-tetralone together with cercosporamide, β-sitosterol and trichodermin was reported to be produced by *Phoma* sp. endophytic in *Arisaema erubescens*. These isolated compounds exhibited antifungal and antibacterial activity against pathogenic fungi *Fusarium oxysporum*, *Rhizoctonia solani*, *Colletotrichum gloeosporioides* and *Magnaporthe oryzae* as well as against two plant pathogenic bacteria *Xanthomonas campestris* and *Xanthomonas oryzae* (Wang et al. 2012). Similarly, *Phoma* sp. endophytic in *Saurauia scaberrinae* is known to produce Phomodione(**62**) ($C_{20}H_{22}O_8$) [(4aS*,9bR*)-2,6-diacetyl-7-hydroxy-4a,9-dimethoxy-8,9b-dimethyl-4a.9b-dihydrodibenzo[b,d]furan-1,3(2H,4H)-dione], an usnic acid derivative. Phomodione was found to be effective at a minimum inhibitory concentration of 1.6 μg/ml against *Staphylococcusaureus* (Hoffman et al. 2008). Santiago et al. (2012), investigated endophytic *Phoma* sp. of *Cinnamomum mollissimum* for the bioactivity of its metabolites. A polyketide compound 5-hydroxyramulosin (**63**) ($C_{10}H_{14}O_4$) inhibiting fungal pathogen *Aspergillus niger* was reported.

Sesquiterpenes, diterpenoids and triterpenoids are the major terpenoids produced by endophytic fungi and possess antimicrobial activity. A terpenoid compound with known antibacterial activity was obtained from the ethyl acetate fraction of *Phomopsis* sp. an endophyte of *Plumeria acutifolia* Poiret plant (Nithya and Muthumary 2010). Similarly, Silva et al. (2006), reported *Phomopis cassiae*, isolated from *Cassia spectabilis* to produce five cadinane sesquiterpenes 3,9,12-trihydroxycalamenenes; 3,12-dihydroxycalamenene; 3,12-dihydroxycadalene and 3,11,12-trihydroxycadalene. Among them 3,11,12-trihydroxycadalene was the most active compound with antifungal activity. Ethyl acetate extract of *Xylaria* sp. isolated from *Piper aduncum* also produced two new presilphiperfolane sesquiterpenes with antifungal activity (Silva et al. 2010). Liu et al. (2008) reported *Xylaria* sp. YX-28 from *Ginkgo biloba* producing 7-amino-4-methylcoumarin (**64**) ($C_{10}H_9NO_2$) which showed antibacterial and antifungal activity against many pathogenic organisms. Endophytic *Chaetomium globosum* was also reported to be isolated from *G.biloba* and was found to be a source of chaetomugilin D, chaetomugilin A, and chaetoglobosins C. The compounds were derivative of chlorinated azaphilone and displayed significant activity against *Artemia salina* and *Mucor miehei* (Qin et al. 2009). One terpenoid along with three steroidal compounds was obtained from an endophytic fungus *Pichia guillermondii* Ppf9 from *Paris polyphylla* var. *yunnanensis*. The compounds were identified as ergosta-5,7,22-trienol (**65**) ($C_{28}H_{44}O$), 5α,8α-epidioxyergosta-6,22-dien-3β-ol (**66**) ($C_{28}H_{44}O_3$), ergosta-7,22-dien-3β,5α,6β-triol (**67**) ($C_{28}H_{46}O_3$) and helvolic acid (**68**) ($C_{32}H_{44}O_8$). Among them helvoic acid exhibited the strongest antibacterial activity (Zhao et al. 2010). The novel diterpenoid guanacastepene (**69**) ($C_{20}H_{30}O_5$) antibiotic was isolated from an unidentified endophytic fungus (Brady et al. 2001).

A broad diversity of endophytic fungi exists in the rhizome of *Paris polyphylla* var. *yunnanensis* a medicinal plant used in traditional Chinese medicine. *Gliomastix murorum* Ppf8 from this plant yielded two antimicrobial metabolites by bioassay-guided fractionation. By means of physicochemical and spectrometric analysis, they were identified as ergosta-5,7,22-trien-3-ol and 2,3-dihydro-5-hydroxy-α,α-dimethyl-2-benzofuranmethanol (Zhao et al. 2012a, b). Another endophytic fungus that was isolated from the rhizome of this plant was *Fusarium* sp. *Ppf4*. Two sterols and one fatty acid was obtained by bioassay-guided fractionation from the light petroleum extract of this fungus. The compounds were elucidated as 5alpha,

8alpha-epidioxyergosta-6,22-dien-3beta-ol,ergosta-8(**9**),22-dien-3beta,5alpha,6beta,7alpha-tetraol and butanedioic acid (**70**) ($C_4H_6O_4$) having antimicrobial activity (Huang et al. 2009a, b). Another endophytic *Fusarium* sp. produced novel antifungal antibiotic fusarielin A (**71**) ($C_{25}H_{38}O_4$) and three related compounds, fusarielin B (**72**) ($C_{20}H_{40}O_5$), fusarielin C (**73**) ($C_{25}H_{38}O_3$) and D (Kobayashi et al. 1995). *F. solani* from *Taxus baccata* showed antibacterial as well as antifungal activity. The compounds responsible for this activity were identified as 1-tetradecene, 8-octadecanone, 8-pentadecanone, octylcyclohexane and 10-nonadecanone (Tayung et al. 2011).

The mangrove endophytic fungus, *Phomopsis* sp. *ZSUH76* produced three new metabolites Phomopsin A, B, C and known cytosporone B (**74**) ($C_{18}H_{26}O_5$) and cytosporone C. The latter possessed antifungal activity against *Candida albicans* and *F. oxysporum* (Huang et al. 2008). *Acrostic hum arena* harbored *Penicillium* sp. 0935030 which produced compounds identified as cyclo (pro-Thr), cyclo (pro-Tyr) (**75**) ($C_{15}H_{17}NO_3$) and liquiritigenin (**76**) ($C_{15}H_{12}O_4$) exhibiting antibacterial activity against *S. aureus* and methicillin-resistant *S. aureus* (Cui et al. 2008). The two new compounds xanalteric acids I and II displayed weak antibiotic activity against multidrug-resistant S. *aureus* and Altenusin (**77**) ($C_{15}H_{14}O_6$) exhibited broad antimicrobial activity against several additional multidrug-resistant bacterial and fungal strains. These antimicrobial compounds were isolated from the extracts of *Alternaria* sp. inhabiting mangrove plant, *Sonneratia alba* (Kjer et al. 2009).

Li et al. (2012) reported two new alkaloids, 12β-hydroxy-13α-methoxyverruculogen TR-2 and 3-hydroxyfumiquinazoline A alongwith other known compounds and isolated them from *A. fumigatus* LN-4 endophytic in *Melia azedarach* which exhibited antifungal activity. Two new metabolites asperfumoid and asperfumin alongwith other known compounds were isolated from *Aspergillus fumigatus* CY018 an endophyte of *Cynodon dactylon*. The active metabolites inhibited *Candida albicans* (Liu et al. 2004).

Three new chlorinated benzophenone derivatives pestalachlorides A–C inhibiting *A. fumigatus* and five new cyclohexanone derivatives Pestalofones A–E displaying significant activities against plant pathogens have been isolated from *Pestalotiopsis adusta* and *Pestalotiopsis fici*, respectively (Li et al. 2008a, b, Liu et al. 2009). Other species of the same genus *Pestalotiopsis foedan* afforded two new isobenzofuranones Pestaphthalides A, B (**78**, **79**) ($C_{11}H_{12}O_5$) and reduced spiro azaphilone derivative Pestafolide A with antifungal activity (Ding et al. 2007). *Pestalotiopsis jesteri* from *Fragraea bodenii* produced jesterone (**80**) ($C_{15}H_{20}O_4$) and hydroxy-jesterone (**81**) ($C_{15}H_{20}O_5$) which are novel cyclohexenone epoxides displaying activity against plant pathogens (Li and Strobel 2000).

Acremonium zeae endophytic in maize displayed significant antifungal activity against *Aspergillus flavus*, *Fusarium verticollioides* and antibacterial activity against most gram positive bacteria including drug resistant strain. The metabolites accounting for this activity were two newly reported antibiotics pyrrocidines A (**82**) ($C_{31}H_{37}NO_4$) and B (**83**) ($C_{31}H_{39}NO_4$) (Wicklow et al. 2005). Colletotric acid, a metabolite of *Colletotrichum gloeosporioides*, an endophytic fungus in *Artemisia mongolica*, displays antimicrobial activity against bacteria as well as against *Helminthsporium sativum* (Zou et al. 2000).

Antibacterial naphthaquinone Javanicin (**84**) ($C_{15}H_{14}O_6$) exhibiting activity against *Pseudomonas* sp. was isolated from *Chloridium* sp. an endophyte of Neem (Kharwar et al. 2008). A new antifungal agent, cryptocandin was produced by endophytic *Cryptosporiopsis* cf. *quercina*. Cryptocandin (**85**) ($C_{15}H_{82}N_8O_{17}$) possessed antifungal activity against *C. albicans*, and *Trichophytonrubrum*. It also showed inhibitory activity against a number of plant-pathogenic fungi including *Sclerotinia sclerotiorum* and *Botrytis cinerea* (Strobel et al. 1999). A novel endophytic fungus *Edenia gomezpompae* was isolated from the leaves of *Callicarpa acuminata*. This endophyte resulted in the isolation of four napthaquinone spiroketals and palmarumycin. The structures of the compounds were elucidated as Preussomerin EG1 (**86**) ($C_{20}H_{12}O_6$), EG2 (**87**) ($C_{20}H_{14}O_7$), EG3 (**88**) ($C_{21}H_{16}O_7$). The compounds were tested against phytopathogens. All spiroketals possessed significant activity against all phytopathogens (Macias-Rubalcava et al. 2008).

Antiviral compounds

The discovery of the potential of endophytes for the production of antiviral compounds is still in its infancy. There are only limited number of compounds reported as antiviral agents from endophytes. However, the fewer compounds that have already been isolated have been reported to show promising results

and thereby provide an alternative means of antiviral drug production. The main limitation to antiviral compound discovery is most probably related to the absence of antiviral screening system in most of the compound discovery programs.

Two novel compounds cytonic acid A (**89**) ($C_{32}H_{36}O_{10}$) and B (**90**) ($C_{32}H_{36}O_{10}$) have been isolated from *Cytonaema* sp. These compounds are reported to be the novel human cytomegalovirus protease inhibitors and their structure was elucidated by mass spectrometry and NMR methods as *p*-tridepside isomers (Guo et al. 2000). Singh et al. (2004) reported Hinnuliquinone (**91**) ($C_{32}H_{30}N_2O_4$), a potent inhibitor of the HIV-1 protease antiviral compound, from the endophytic fungi inhabiting the leaves of Oak trees (*Quercus coccifera*). Four new compounds have been isolated from *Pullularia* sp. BCC 8613. Structural elucidation of these compounds was done by mass spectrometry and NMR spectroscopic analysis. The compounds isolated were Pullularins A–D (86) (cyclohexadepsipeptides). Out of these compounds, Pullularin A exhibited activities against the herpes simplex virus type-1 and also against the malaria parasite *Plasmodium falciparum* K1 (Isaka et al. 2007). Li et al. (2008a, b) isolated an important antiviral compound Pestalotheol-C from the fungal endophyte *Pestalotiopsistheae* of an unidentified tree on Jianfeng Mountain, China. The isolated compound showed anti-HIV properties.

Antitubercular compounds

The World Health Organization (WHO) estimated that currently 50 million people are infected and 1500 people die each hour from tuberculosis worldwide. After emergence and spread of *Mycobacterium tuberculosis* resistant strains to multiple drugs, the search for new anti mycobacterial agents is timely. The globe recognized medicinal plants as repository for fungal endophytes with metabolites containing novel molecular structure and biologically active compounds against various human pathogenic diseases for potential use in modern medicine. Endophytic fungi from *Garcinia* sp. are good source for exploring the possibility of new anti mycobacterial drugs. Phomoxanthone A and B isolated from the endophytic fungus *Phomopsis* sp. from *Garcinia* sp. in Thailand exhibits significant activity against *M. tuberculosis* (Isaka et al. 2001). *Phomopsis* sp. isolated from *Garcinia dulcis*, produced new metabolites as Phomoenamide and Phomonitroester inhibiting *M. tuberculosis* (Rukachaisirikul et al. 2008). Tenuazonic acid (**92**) ($C_{10}H_{15}NO_3$) was isolated by bioassay guided fractionation of dichloromethane extract of *Alternaria alternata*. It was found to be active against *Mycobacterium tuberculosis* at MIC of 250 μg/ml concentrations (Sonaimuthu et al. 2011). *Diaporthe* sp. isolated from *Pandanus amaryllifolius* leaves produced two new benzopyranones diaportheone A and B. Both compounds inhibited the growth of virulent strains of *Mycobacterium tuberculosis* (Bungihan et al. 2011).

Conclusions

Endophytes have proven to be a rich source of novel natural compounds with a wide-spectrum of biological activities and a high level of structural diversity. Bioactive natural compounds produced by endophytes have shown promising potential and usefulness in safety and human health concerns. Taking advantage of modern biotechnology such as genetic engineering, metabolic technology and microbial fermentation process, we can better understand and manipulate this important microorganism resource, and make it more beneficial for the mankind.

Discovering new chemical compounds from natural products is very important for formulating new drugs. Endophytic fungi have recently received more attention as they can sometimes produce bioactive compounds analogous to their hosts. We can say that the endophytic fungi could be a reliable source for pharmaceutically and industrially important compounds that can be used in the treatment of various life threatening diseases along with various industrial applications. Many novel and valuable bioactive compounds with antimicrobial, insecticidal, immunomodulatory, antiviral, anticancer activities have been successfully obtained from the endophytic fungi. Perusal of literature reveals that endophytic *Phomopsis* spp. from different medicinal plants alone is a storehouse of a number of biologically active metabolites (Table 2). Thus, we can conclude that the endophytic fungi are a novel and important microbial resource for producing bioactive compounds and has attracted attention of many researchers' on their theoretical study as well as their potential applications. Plethora of bioactive metabolites produced by endophytic fungi

Table 2 Bioactive compounds produced by endophytic *Phomopsis* sp. inhabiting different medicinal plants

S. no.	Endophytic *Phomopsis* sp.	Medicinal plant	Compound	Activity	References
1	*Phomopsis* sp.	–	PhomoxanthonesA and B	Antimalarial Anti-tubercular Anticancer	Isaka et al. (2001)
2	*Phomopsis longicolla*	*Dicerandra frutescens*	Dicerandrol A	Anticancer	Wagenaar and Clardy (2001)
3	*Phomopsis phaseoli*	*Betula pendula*	3-Hydroxypropionic acid	Nematicidal	Schwarz et al. (2004)
4	*Phomopsis* sp.	*Erythrina cristagalli*	Phomol	Antifungal Antibacterial Antiinflammatory Weakly cytotoxic	Weber et al. (2004)
5	*Phomopsis* spp.	*Erythrina cristagalli*	Mevinic acid	Antiinflammatory	Weber et al. (2004)
6	*P. cassiae*	*C. spectabilis*	3,11,12-trihydroxycadalene	Antifungal activity	Silva et al. (2006)
7	*Phomopsis* sp. PSU-D15	*G. dulcis*	Phomoenamide, Phomonitroester	Anti–tubercular	Rukachaisirikul et al. (2008)
8	*Phomopsis* sp.	Mangrove	Phomopsin A, B,C Cytosporone B	Antifungal	Huang et al. (2008)
9	*Phomopsis* sp.	*Excoecaria agallocha*	2-(7′-Hydroxyoxooctyl)-3-hydroxy-5-methoxybenzene acetic acid ethyl ester	Anticancer	Huang et al. (2009a, 2009b)
10	*Phomopsis* sp	*Viguiera arenaria*	3,4-dimethyl-2-(4′-hydroxy-3′, 5′-dimethoxyphenyl)-5-methoxy-tetrahydrofuran	Trypanocidal	Verza et al. (2009)
11	*Phomopsis* sp.	*Plumeria acutifolia* (Poiret)	Terpenoids	Antibacterial	Nithya and Muthumary (2010)
12	*Phomopsis* sp.	*Musa acuminata*	Oblongolide Y	Anticancer	Bunyapaiboonsri et al. (2010)
13	*P. archeri*	*V. albindia*	Phomoarcherins A–C	Antimalarial	Hemtasin et al. (2011)

inhabiting the unique niche i.e. plants are indeed a hidden treasure worth exploring.

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