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Alternaria species: endophytic fungi as alternative sources of bioactive compounds

Daniya Eram[1], Manojkumar Arthikala[2], Govindappa Melappa[1] and Gustavo Santoyo[3]

[1]Department of Biotechnology, Dayananda Sagar College of Engineering, Shavige Malleshwara Hills, Kumaraswamy Layout, Bengaluru-560 078, Karnataka, India.
[2]Ciencias Agrogenómicas, Escuela Nacional de Estudios Superiores, León, Universidad Nacional Autónoma de México (UNAM), C.P.-37684, Mexico.
[3]Instituto de Investigaciones Químico-Biológicas, Universidad Michoacana de San Nicolás de Hidalgo, Morelia, Michoacán, Mexico

Correspondig Author e-mail: dravidateja07@gmail.com, drgovindappa-bt@dayanandasagar.edu

Abstract

Fungal endophytes are a rich source of functional metabolites. In particular, the different species of the genus *Alternaria* stand out for their arsenal of metabolites, which have roles as antimicrobial molecules, antioxidants; as well as activities against HIV or cancer or diabetes. This review will highlight on selected aspects of the fungal endophytes of *Alternaria* species: their widespread distribution, and the role of their metabolites with pharmaceutical or agronomical importance. The family plants associated with *Alternaria* species, their bioactive compounds and biological activity to date are examined.

Keywords: Alternaria species; metabolites; antimicrobials; cancer; diabetes; HIV

Riassunto

I funghi endofiti delle piante sono ricche fonti di metaboliti bioattivi. In particolare le specie appartenenti al gen. *Alternaria* producono una serie di molecole ad azione antimicrobica, antiossidante, anti HIV, antitumorale e antidiabetica. Nel presente lavoro vengono esaminate le piante associate alle specie di *Alternaria* e vengono riportati i composti bioattivi prodotti e la loro attività.

Parole chiave: Alternaria spp.; metaboliti; azione antimicrobica; cancro; diabete; HIV

Introduction

Endophytes are the micro-organisms that colonize the inside of the plant parts, without having any negative impact on the host (Arnold *et al*., 2003), and these contribute resistance against both biotic (Breen, 1994; Schulz *et al*., 1999; Dingle and McGee, 2003) and abiotic stresses (Siegel *et al*., 1990; West, 1994). The researchers found endophytic fungi in almost all studied plants and thus it implies an important component of plant micro-ecosystem (Strobel, 2006). In addition, the

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endophytes impart resistance against plant pathogens and herbivores and they are also able to produce known or unknown pharmaceutical and agricultural important bioactive compounds. Most of endophytic organism bioactive compounds act as plant defence molecules and some of them are using to treat various human diseases (Owen and Hundley, 2004). Endophytic fungi from *Muscador albus* of rainforest plant are able to produce fumigant agent against stored grain pests (Strobel, 2006; Strobel *et al*., 2001). The endophytic fungi are able to produce many antimicrobial metabolites, such as colletotric acid (Zou *et al*., 2000) and griseofulvin (Park et al., 2005) reported from *Alternaria* species ubiquitous fungal genus including saprobic, endophytic and pathogenic species. *Alternaria* species are associated with a wide variety of substrates including seeds, plants, agricultural products, animals, soil and the atmosphere. Pathogenic species of *Alternaria* pose variety of phytopathological problems which results in yield losses in a wide range of crop plants. Several taxa are also important postharvest pathogens, causative agents of phaeohyphomycosis in immuno-compromised patients or airborne allergens. von Esenbeck (1816) originally described *Alternaria*, based on *A. tenuis* as the only species. Characteristics of the genus included the production of dark-coloured phaeodictyospores in chains, and a beak of tapering apical cells. von Keissler (1912) synonymised both *A. tenuis* and *Torula alternata* (Fries, 1832) with *Alternaria alternata*, due to ambiguities in Nees's description of *A. tenuis*. Two additional genera, *Stemphylium* (Wallroth, 1833) and *Ulocladium* (Preuss, 1851) were subsequently described for phaeodictyosporichyphomycetes, further complicating the taxonomic resolution in this group of fungi. Several re-descriptions and revised criteria of these genera (Saccardo, 1886; Elliot 1917; Wiltshire, 1933, 1938; Joly, 1964) resulted in a growing number of new species. Results of a lifetime study on *Alternaria* taxonomy based on morphological characteristics were summarised by Simmons (2007), in which 275 *Alternaria* species were recognised. One species was transferred to the genus *Prathoda* and three new genera, *Alternariaster*, *Chalastospora* and *Teretispora* were segregated from genus *Alternaria*. Molecular studies revealed multiple non-monophyletic genera within the *Alternaria* complex and *Alternaria* species clades, however based on morpholigical characteristics it do not correlate to species-groups (de Hoog and Horré, 2002; Pryor and Bigelow, 2003; Hong *et al*., 2005; Inderbitzin *et al*., 2006; Pryor *et al*. 2009; Runa *et al*., 2009; Lawrence *et al*., 2012). The *A. alternata*, *A. brassicicola*, *A. infectoria*, *A. porri* and *A. radicina* species groups were strongly supported by these studies and two new species-groups, *A. sonchi* (Hong *et al*., 2005) and *A. alternantherae* (Lawrence *et al*., 2012) and two new genera, *Crivellia* (Inderbitzin *et al*., 2006), *Undifilum* (Pryor *et al*., 2009) were described. The latest molecular revision of *Alternaria* (Lawrence *et al*., 2012) introduced two new species groups, *A. panax* and *A. gypsophilae*, and elevated eight species-groups to sections within *Alternaria*. The sexual phylogenetic *Alternaria* lineage, the *A. infectoria* species-group, did not get the status of section, in contrast to the eight asexual phylogenetic lineages in *Alternaria*. The *Alternaria* complex currently comprises the genera *Alternaria*, *Chalastospora* (Simmons, 2007), *Crivellia*, *Embellisia*, *Nimbya*, *Stemphylium*, *Ulocladium*, *Undifilum* and the recently described *Sinomyces* together with eight sections of *Alternaria* and the *A. infectoria* species-group. The present review focused on endophytic fungi, *Alternaria* species, their phytochemicals, biological activity and their plant hosts in detail.

Spreading family

Details of endophytic *Alternaria* species, hosts, natural compounds are represented in table 1. Their biological activities are briefly explained in figure 1. Endophytic fungi, *Alternaria* species been found in various plant species belonging to different families. *Alternaria* species in *Taxus cuspidata, T. yunnanensis* and *T. chinensis var. mairei* belonging to the *Taxaceae* family produce taxol, cladosporol

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and paclitaxel which mainly exhibit anti-cancer/ anti-tumour properties (Vasundhara *et al*., 2016; Chen *et al*., 2009; Strobel *et al*., 1996; Kim and Ford, 1999; Tian *et al*., 2006; Zhou *et al*., 2007; Guo *et al*., 2009; Wu *et al*., 2011). Li and co-workers (2016a) obtained 940 isolates from different tissues of *Zanthoxylum bungeanum* and were grouped into 93 morphotypes, 43 species, and 23 genera. Potent antioxidant and antimicrobial activity was observed with extract of *A. alternata*, isolated from bark of *Aegle marmelos* (Mani *et al*., 2015; Selvi and Balagengatharathilagam, 2014) and *Phellodendron amurense* (Duan, 2009) belonging to *Rutaceae* family.

Alternaria alternata (isolated from *Eugenia jambolana*) extract exhibited strong antibacterial property against MDR (Multi-Drug Resistance) (Yadav *et al*., 2016). *Salvia miltiorrhiza* (Tian *et al*., 2017; Lou *et al*., 2016), *Salvia przewalskii* (Wang *et al*., 2014) and *Ocimum sanctum* (Chowdhary and Kaushik, 2015) of *Lamiaceae* family have exhibited *Alternaria* species and it showed anti-bacterial and anti-phytopathogenic property.

Alternaria tenuissima was reported from bark of *Erythrophleum fordii* (Fang *et al*., 2012) able to produce cyclopeptides, and also from leaves of *Acacia magnum* produce alternariol monomethyl ether and α, β- dehydrocurvularin. These biomolecules has been reported to have inhibitory effect on *Magnaporthe grisea* appressorium development (Jeon *et al*., 2010).

Alternaria brassicola isolated from *Malus halliana* (*Rosaceae*) producing alternariol, alternariol 9-methyl ether, altechromone A, herbarin A, cerevisterol, 3β, 5α- 22E, 24R)-3,5-dihydroxyergosta-7,22-dien-6-one and 3β, 5α-dihydroxy- (22E,24R)-ergosta-5,8,22-trien-7-one are antimicrobial agents (Guo *et al*., 2009). A phenylpropene known as eugenol was identified in *Alternaria* species isolated from *Rosa damacaena* (Rosaceae) (Kaul *et al*., 2008). Anti-insecticidal podophyllotoxin was noticed in extract of *Alternaria* species isolated from *Sabina vulgaris* (*Cupressaceae*) (Lu *et al*., 2006).

The *Alternaria* species was isolated from root of marine semi-mangrove plant, *Myoporum bontioides* (*Scrophulariaceae*) able to produce cyclohexenone, cyclopentenone and xanthone and were reported to be a strong antioxidant and antimicrobial agents (Wang *et al*., 2014). Antibacterial agent altenusin was noticed in the extract of *Alternaria* species, endophytic fungi of *Sonneratia alba* (*Lythraceae*) (Kjer *et al*., 2009).

Endophyte, *Alternaria* species was also isolated from *Ginkgo biloba* of *Ginkoaceae* (Qin *et al*., 2009) and extracts showed strong antifungal activity (Xiao *et al*., 2013). *Alternaria* species isolated from phloem of *Catharanthus roseus* (*Apocynaceae*) had the ability to produce vinblastine (Zhang *et al*., 1998). Podophyllotoxin was identified from *Alternaria neesex* of *Sinopodophyllum hexandrum* (*Berberidaceae*) (Li, 2007; Cao *et al*., 2007; Yang *et al*., 2003) and also from *Alternaria* species obtained from *Sabina vulgaris* (Lu *et al*., 2006). Paclitaxel was isolated from *Alternaria* species (*Taxus cuspidata*), *Alternaria* species (*Ginkgo biloba*), *Alternaria alternata* (*Taxus chinensis* var *mairei*) (Strobel *et al*., 1996; Kim *et al*., 1999; Tian *et al*., 2006).

The endophytic *Alternaria* species were also reported from *Quercus emoryi* of *Fagaceae* (Bashyal *et al*., 2014), *Tabebuia argentea* of *Bignoniaceae* (Channabasava and Govindappa, 2014), *Viscum album* of *Santalaceae* (Govindappa *et al*., 2015), *Trixis vauthieri* of *Asteraceae* (Cota *et al*., 2008), *Ficus carica* of *Moraceae* (Feng and Ma, 2010), *Denderonephthya hemprichi* of *Nephtheidaceae* (Shaaban *et al*., 2012), *Polygonum senegalense* of *Polygonaceae* (Aly *et al*., 2008), *Azadirachta indica* of *Meliaceae* (Taware and Rajurkar, 2015), *Aegiceras corniculatum* of *Primulaceae* (Huang *et al*., 2011), *Laurencia* species of *Rhodomelaceae* (Gao *et al*., 2009), *Paeonia delavayi* of *Paeoniaceae* (Wu *et al*., 2011), *Maytenus hookeri* of *Celastraceae* (Yuan *et al*., 2008), *Tylophora indica* of *Apocynaceae* (Kumar *et al*., 2011) and *Vitis vinifera* of *Vitaceae* family (Shi *et al*., 2012).

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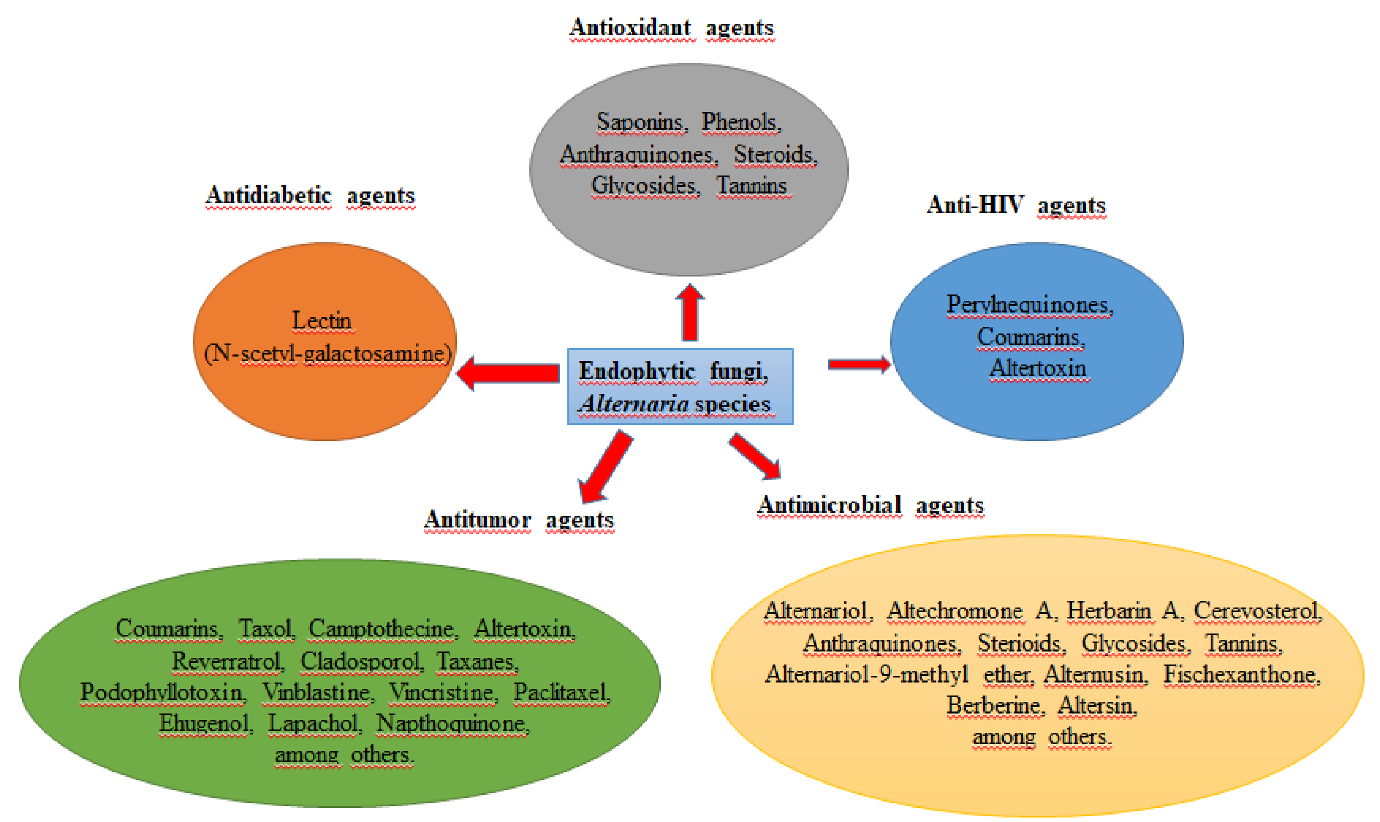

Fig. 1. Important phytochemicals from endophytic fungi, *Alternaria* species and their biological activity
Fig. 1. Importanti prodotti fitochimici da specie di *Alternaria* e loro attività biologica.

Antimicrobial molecules

Alternaria species or *A. alternata* from *Camptotheca acuminata* (Ding *et al.*, 2006), *Achyranthus aspera, Adhatoda zeylanica, Aegle marmelos, Leucas aspera, Azadirachta indica* (Selvi and Balagengatharathilagam, 2014), *A. raphami* from *Vitax negundo* (Monali *et al.*, 2013), *A.tenussima* from *Ricinus communis* (Sandhu *et al.*, 2014a) were the promising antibacterial compounds against different pathogenic bacterial species.

Extracts of *Alternaria* species isolates of *Tephrosia purpurea* (Luo *et al.*, 2015) and *Opuntia humifusa* (Silva-Hughes, 2015), *A. alternata* from *Suaeda martiana, Sueada monoica* (Kalyanasundaram *et al.*, 2015), *A. solani* from *Heptacdium miconioides* (Wang *et al.*, 2016), *Altrnaria* species had shown strong antifungal activity against plant pathogens. The *Alternaria* species of *Garcinia* plant exhibited antiviral activity (Wiyakrutta *et al.*, 2004; Phongpaichit *et al.*, 2007). *Alternaria* species from *Mllotus philippinensis* (Gangwar *et al.*, 2015), *Loranthus* (Govindappa *et al.*, 2011), *Artemissia* species (Cosoveanu *et al.*, 2016) extract showed strong antimicrobial activity.

Antioxidant molecules

Oxidative stress has been identified as the root cause of the development and progression of several diseases. Supplementation of exogenous antioxidants or boosting endogenous antioxidant defences of the body is a promising way of combating the undesirable effects of reactive oxygen species (ROS) induced oxidative damage. Many medicinal plants contain large amounts of antioxidants other than vitamin C, E and carotenoids (Javanmardi *et al.*, 2003). Antioxidants are molecules that can delay or

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prevent an oxidative reaction (Velioglu *et al.*, 1998) catalysed by free radicals. This antioxidant effect is mainly due to the presence of phenolic components such as flavonoids (Pietta *et al.*, 1998), phenolic acids and phenolic diterpenes (Shahidi *et al.*, 1992). Antioxidants such as Butylated Hydroxy-Anisol (BHA), Butylated Hydroxy-Toluene (BHT) protect plants against oxidative assault (Dziezak, 1986) either by binding to metallic ions, eliminating free radicals or by decomposing peroxides (Matook, 2005). Despite the availability of synthetic antioxidants, present research seeks at discovering new natural antioxidant compounds that may play a role in oxidative stress related disorders (Agbor *et al.*, 2005). Epidemiological studies (Urquiaga and Leighton, 2000; Halliwell, 1994) have showed that decreases in the incidence of chronic diseases in some populations were related to the consumption of fruits and vegetables. Antioxidants such as saponins, phenolic compounds, anthraquinones, steroids, cardiac glycosides and tannins are produced by endophytic *Alternaria* species found in *Aegle marmelos* (Selvi and Balagengatharathilagam, 2014) and Dibenzo-α-pyrones (1–7) in *Salvia miltiorrhiza* Bunge (Tian *et al.*, 2017). The crude extracts of *A. alternata* from *Coffea arabica* (Fernandes *et al.*, 2009), *Alternaria* species from *Mussaenda luteola* (Gunasekharan *et al.*, 2017) showed strong antioxidant activity.

Anti-diabetic molecules

In humans, diabetes mellitus is considered as one of the five leading causes of death in the world (Joseph and Jini, 2011). Diabetes mellitus is a major global health concerning with a projected rise in prevalence from 171 million in 2000 to 366 million in 2030 (Shaw *et al.*, 2010). It is a syndrome of disordered metabolism, usually due to a combination of hereditary and environmental causes, resulting in abnormally high blood sugar levels (hyperglycemia) (Patel *et al.*, 2012). Being a major degenerative disease, diabetes is found in all parts of the world and increasing rapidly and thus it is the third most lethal disease of mankind (Ogbonnia *et al.*, 2008). It is the most common endocrine disorder, affecting 16 million individuals in the United States alone and as many as 200 million individuals worldwide. Diabetes has been a clinical model for general medicine (Sharma *et al.*, 2012). Complementary and alternative medicine involves the use of herbs and other dietary supplements as alternatives to mainstream western medical treatment. A recent study has estimated that up to 30% of patients with diabetes mellitus use complementary and alternative medicine (Raman *et al.*, 2012). *Alternaria* species can be an excellent source for production of anti-diabetic molecules. Lectin (N-acetyl-Galactosamine) produced by endophytic *Alternaria* species of *Viscum album* been characterized to process has anti-diabetic properties (Govindappa *et al.*, 2015). In another study, *Alternaria* species from *Phyllanthus emblica* fruits (Singh *et al.*, 2017) and *Morus alba* (Zheng *et al.*, 2014) exhibited strong inhibitory effect on diabetic enzymes.

Anti-HIV molecules

Since the first cases of AIDS were identified in 1981 in the United States. AIDS has become the largest and most devastating public health pandemic of our time, and has infected nearly 70 million people and left 25 million dead, and around the world, the number of people living with HIV is about 36.7 million. Combination therapy of anti-HIV drugs now available has improved the quality of life and life-span of HIV/AIDS patients. Emergence of HIV drug resistance, side effects and the need for long-term antiretro-viral treatment are the main causes for the failure of anti-retroviral therapy (ART). Continuous development of new anti-HIV agents, targets and therapy appear to be inevitable. In some countries, traditional medicine is used to meet primary health care needs and to treat AIDS patients (Harnett *et al.*, 2005). Natural products are the most consistently successful source in drug discovery, and may offer more opportunities to find anti-HIV drugs or lead compounds. Many compounds with an

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anti-HIV-1 effect have been screened out from natural products and discovered to inhibit HIV at nearly all stages of the viral life cycle (Wang *et al*., 2004). They include alkaloids, sulphated polysaccharides, polyphenolics, flavonoids, coumarins, phenolic, tannins, triterpenes, lectins, phloroglucinols, lactones, iridoids, depsidones, O-caffeoyl derivatives, lignans, ribosome-inactivating proteins, saponins, xanthones, naph-thadianthrones, photosensitisers, phosholipids, quinines and peptides (Ng *et al*., 1997; Vlietinck *et al*., 1998; Yang *et al*., 2001). Natural products provide a large reservoir for screening anti-HIV agents with novel structure and anti-viral mechanisms because of their structural diversity. A variety of natural products have been found to inhibit unique enzymes and proteins crucial to the life cycle of HIV, including efficient intervention with the reverse transcription process, virus entry, integrase and protease (De Clercq, 2000; Cos *et al*., 2004). But the mechanism of anti-HIV activity of many more natural products is still unknown.

People living with HIV/AIDS often choose traditional or complementary and alternative medicine to complement or replace conventional treatment. The presence of multi-drug or even multiclass resistance in HIV also warrants the need to explore additional means to combat HIV and provide further justifications for the need of alternative and complementary medicines in the treatment of HIV/ AIDS. Most of the traditional systems of medicine in India include some form of 'medicinal plant', herbs or natural plant products. It is therefore not surprising that the activity of these traditional medicines against HIV can be scientifically analysed to deduce the role of natural plant products in their anti-HIV activities. A number of medicinal plants have been reported to have anti-HIV properties (Fritts *et al*., 2008). Over the past two decades, substantial progress has been made in research on the natural products possessing anti-HIV activity. A variety of secondary metabolites obtained from natural origin showed moderate to good anti-HIV activity.

Endophytes present in various plants can also be a potential source for production of anti-HIV molecules (Singh *et al*., 2005). Altertoxins produced by *A. tenussima* shows a significant anti-HIV activity (Bashyal *et al*., 2014; Wellensiek *et al*., 2013). Partially purified coumarin extracts of *Alternaria* species from *Calophyllum inophyllum*) have inhibited the HIV-1 replicating proteins significantly (Govindappa *et al*., 2015). Perylnequinones isolated from *A. tenussima* of *Quercus emoryi* have shown potent HIV-1 inhibitors (Hudson *et al*., 1997).

Anti-microbial molecules

Endophytes, microorganism that reside in the tissue of living plants, are relatively understudied and potential source of novel natural products for exploitation in medicine, agriculture and industries (Sandhu *et al*., 2014b). The resistance of pathogenic microorganisms to drugs and antibiotics has become a major challenge in the health sector leading to reduction in drug effectiveness and economic wastage. This challenge has once again stirred up a need in scientific research and the discovery of new more effective antimicrobial metabolites becoming a major research interest. In recent years, the isolation of endophytic fungi and screening of antimicrobial activity has gained more attention (Strobel, 2003).

The increase in the resistance of drugs by infectious pathogens as well as undesirable effects of certain antimicrobial agents indicates that there is an urgent need for novel and effective bioactive compounds with fresh modes of action which is what this study is aimed at achieving stated that during the last 20 years (Strobel, 2006; Porras-Alfaro and Bayman, 2011). It has been observed that much of the wealth of microbial biodiversity with novel biochemistry and secondary metabolite production resides in plant tissues. The endophytes of these plants, especially the *Alternaria* species produce a wide range of anti-microbial compounds.

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Fischexanthone, an anti-fungal compound, is produced by endophytic *Alternaria* from root tissues of *Myoporum bontioides* (Li *et al*., 2016b). Strong anti-fungal activity was observed in *Ficus carica* due to the production of helvolic acid by the endophytic *Alternaria* (Feng and Ma, 2010). Cyclo-[L-Leu-trans-4-hydroxy-L-Pro-], Cyclo-(L- Phe-trans-4-hydroxy-L-Pro-), and Musetti *et al*. (2007) have produced Cyclo-(L-Ala-trans-4-hydroxy-L-Pro) in broth culture of the grapevine also exhibits anti-fungal activity. Xanalteric acids I and II produced in *Somneratia alba* exhibits weak anti-bacterial activity against multidrug-resistant *Staphylococcus aureus* (Kjer *et al*., 2009). Solanapyrones P–R (1–3), solanapyrones (4–6) and benzopyrones (7–9) produced in the root tissues of a Chinese herbal medicinal plant *Salvia przewalskii* also exhibits anti-bacterial activity (Xiao *et al*., 2014). Apart from these dibenzo-α-pyrones produced in *Salvia miltiorrhiza* (Danshan) due to endophytic *Alternaria* also shows anti-bacterial activity (Tian *et al*., 2017).
Altersin produced by *Alternaria* shows broad anti-microbial activity (Hellwig *et al.*, 2002; Fernandes *et al*., 2009). Alternusin produced by endophytic *Alternaria* species of *Sonneratia alba* exhibits anti-microbial activity against several additional multidrug-resistant bacterial and fungal strains (Kjer *et al*., 2009). Alternariol 9-methyl ether (AME) in *Salvia miltiorrhiza* (Lou *et al*., 2016); berberine in *Phellodendron amurense* (Duan, 2009); saponins, phenolic compounds, anthraquinones, steroids, cardiac glycosides and tannins in *Aegle marmelos* (Selvi and Balagengatharathilagam, 2014); pyrophen, rubrofusarin B, fonsecin, fonsecin B aurasperone A, aurasperone B, aurasperone C , and aurasperone F in *Denderonephthya hemprichi* (Shaaban *et al*., 2012); 7-epi-8-hydroxyaltertoxin I and 6-epi-stemphytriol, stemphyperylenol and altertoxin I in *Laurencia* sp. (Gao *et al*., 2009); alternariol, alternariol 9-methyl ether, altechromone A, herbarin A, cerevisterol, 3β,5α-dihydroxy-(22E,24R)-ergosta-7,22-dien-6-one and 3β-hydroxy-(22E,24R)-ergosta-5,8,22-trien-7-one in *Mallus haliana* (Guo *et al*., 2009); alternariol, djalonensone, cerebroside B, cerebroside C, (2S, 3S, 4R, 2' R) -(2'-hydroxytetracosanoylamino) octadecane-1,3,4-triol, and mannitol in *Paeonia delavayi* (Wu *et al*., 2011) were reported to process anti-microbial activity. Gunasekharan *et al*. (2017), Srinivasan *et al*. (2015) have reported that *Alternaria* species extracts have inhibited the activity of pathogenic bacteria. Two new antimicrobial compounds, 10-oxo-10H-phenaleno[1,2,3-de] chromene-2-carboxylic acids, xanalteric acids I and II and 11 known secondary metabolites were obtained from *Alternaria* species extract (*Sonneratia alba*) and they are strong antibacterial compounds (Kjer *et al*., 2009). The potent antifungal activity was observed from *Alternaria* species extract isolated from *Clerodendrum inerme* (Gong *et al*., 2015).

Anti-cancer molecules

Cancer is considered one of the most common causes of human mortality worldwide. Progress made in cancer therapy has not been sufficient to a significantly lower annual death rate from most tumor types, and there is an urgent need for new strategies in cancer control (Mesnah *et al*., 1987). For centuries, people have been using plants for their therapeutic values. Today 85000 plants have been documented for therapeutic use globally (Liu and Wang, 2008). The World Health Organization (WHO) estimates that almost 75% of World's population has therapeutic experience with herbal drugs. Cancer is one of the most widespread diseases in humans and presently there is a considerable scientific discovery of new anticancer agents from natural products (Kasabana and Hemini, 1998). The potential of using the natural products as anticancer drugs was recognized in 1950's by U.S. Natural Cancer Institute (NCI) since 1950 major contributions have taken for the discovery of naturally occurring anticancer drugs (Cragg and Newman, 2005).
In this sense, altertoxin IV showed significant anticancer activity was isolated from endophytic fungi *Alternaria* species of *Broussonetia papyrifera* (Zhang *et al*., 2016). Taxol is producing by *Alternaria*

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species of *Salacia oblonga* (Roopa *et al*., 2015), *Taxus cuspidata* (Strobel *et al*., 1996), *Ginkgo biloba* (Kim *et al*., 1999), *Corylus avellena* (Michalczyk *et al*., 2014; Soliman and Raizada, 2013) and paclitataxel from *Alternaria tenuissima* (Ismaiel *et al*., 2017). Taxanes was isolated from *Alternaria* species of *Taxus baccata* (Staniek *et al*., 2010). *Alternaria* species have ability to produce paclitaxel or its analogues (Zhao *et al*., 2012; Chandra, 2012). Camptothecine (CPT) and its analogues 9-methoxycmptothecine (MCPT) and 10-hydroxycamptothecine (HCPT) produced by *Alternaria alternata* from *Miquelia dentata* (Shweta *et al*., 2013). Anticancer agent, coumarins were reported from *Alternaria* species which colinize *Crotalaria pallida* (Umashankar *et al*., 2015), lapachol from *Alternaria* species and *A. alternata* (Sadananda *et al*., 2011; Channabasava and Govindappa, 2014), podophyllotoxin from *Alternaria* species (*S. hexandrum*). Vinblastine and vincristine were produced from *Alternaria* species isolated from *Catharanthus roseus* (Guo and Kunming, 1998). Kaul *et al*. (2008) have reported the eugenol produced by *Alternaria* species of rose. Reveratrol isolated from *Alternaria* species of *Vitis vinifera*, *Vitis quinquangularis*, *Polygonum cuspidatum* (Shi *et al*., 2012) and cytotoxic compounds were isolated from *Alternaria* species of *Polygonum senegalense* (Aly *et al*., 2008).
Alternariol metabolite from *Alternaria* species of *Polygonum senegalense* (Aly *et al*., 2008), *Salvia miltiorrhiza* (Lou *et al*., 2016) exhibit anti-cancer activity. *Alternaria alternata* (*Cissus quadrangularis, Asclepias curassavica*) extract had shown strong cytotoxicity activity (Tenguria and Firodiya, 2016).

Discussion and future research

Alternaria species are an abundant source of bioactive molecules, with promising roles to fight against pathogenic microbes or human diseases, such as diabetes, HIV and cancer. However, it is suggested that the work done in the future include a step to take a step forward to apply all these promising metabolites. It is known that the regulations in each country of the world are different for the clinical application of new compounds, but undoubtedly, researchers from each region should make an effort to achieve this goal for the benefit of humanity.
Likewise, attention is needed within the basic research on different compounds that produce the endophytic fungi, *Alternaria* species and to identify environmental aspects that regulate their production, as well as their effectiveness when applied. The aspects of resistance in antimicrobial compounds are also an area, requires a continuous research, because new resistance mechanisms arise with new drugs. Large scale commercial productions of such biomolecules using biotechnological tools are also in urgent used. Therefore, it is a potential area for investigation and pharmaceutical applications.

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Table 1. in supplementary file.