Allergen, pathogen, or biotechnological tool? The dematiaceous fungi Alternaria what’s for it and what’s on it?

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Abstract
Fungi are rich sources of biologically active natural compounds, which are used in the manufacturing of a wide range of clinically important drugs. Alternaria is a fungal genus that belongs to family Pleosporaceae, and has been known as a promising secondary metabolites producer. However the same fungus showed a harmful pathogenicity against different plants causing crops economical losses, and is a common allergen in humans, growing indoors and causing hay fever or hypersensitivity reactions. Alternaria is a multicultural fungal genus widely distributing in soil and organic matter. It includes saprophytic, endophytic and pathogenic species. This review aims to briefly summarize the structurally different metabolites produced by Alternaria fungi, as well as their occurrences, biological activities and functions.

Keywords: alternaria; biological activities; phytotoxins; endophytic fungi; secondary metabolites

Introduction
Fungi generally and endophytic ones specifically represent future factories and potent biotechnological tools for production of bioactive natural substances, which could extend healthy life of humanity [1]. Fungi play important role in human life such as in agriculture, food industry, medicine, textiles, bioremediation, natural cycling, as bio-fertilizer and in many other ways. Fungi are ubiquitous on earth and represent essential components of many ecosystems where they are involved in many vital processes [2]. Fungi are promising sources for a wide variety of vital metabolites such as alkaloids, flavonoids, phenols, steroids and terpenoids [3-5]. Fungi capacity to synthesize variety of new bioactive metabolites forced researchers to explore these avenues [6]. Fungi are promising sources for such compounds due to their ability to produce assortment of secondary metabolites that could be, if truly investigated, the solution for currently serious problems. Alternaria is one of the pioneer fungi in this field with proven potent ability as promising biotechnological tool to produce industrially, and biologically diverse metabolites [7, 8]. Fungi are well known biotechnological tools that have various applications in the fields of industry. Thanks to their ability to produce set of prestigious enzymes that is eco-friendly and can replace harmful chemicals used in those industries [9, 10].

Alternaria sp. description and ecology

The genus Alternaria comprises a group of fungi in the family Pleosporaceae (Pleosporales, Dothideomycetes, Ascomycota). The genus Alternaria was established in 1817 with Alternaria alternata as a type isolate. Alternaria belongs to the family Dematiaceae and commonly exists as a saprophyte deriving energy through cellulolytic activity [11]. Generally, Alternaria species are inhabitants of soil or decaying (plant based) organic matter. However, some members of this genus are opportunistic pathogens and cause diseases in economically important plants such as ornamentals, vegetables like broccoli, cauliflower, tomatoes citrus, apples, and oil crops. Alternaria fungi, belonging to the Dematiaceae of the Hyphomycetes in the fungi Imperfecti, have a widespread distribution in nature [11, 12]. Almost any kind of substrate can support these saprophytic species: from flour to leather, from bottled water to textiles. It can grow on food, clothes, materials, goods and paper. As a facultative pathogen it can be found in a variety of cultures, crops and manufactured products [13].

Alternaria genus is currently divided into 26 sections. Alternaria section contains most of the small-spored Alternaria species with concatenated conidia, including important plant, human and postharvest pathogens. Alternaria have been mostly described based on morphology and / or host-specificity, yet molecular variation between them is minimal. Conidiophores of majority of the species of Alternaria produce asexual spores (conidia) measuring between 160-200 μm long. Under in vitro conditions, sporulation occurs at a temperature range of 8-24 °C,
where mature spores occur after 14-24h. Optimum temperatures are between 16 and 24 °C where sporulation time ranges from 12 to 14h [14]. Moisture in the presence of rain, dew or high humidity are essential for infection and a minimum of 9-18h are required for majority of the species [11, 14]. Continuous moisture of 24h or longer practically guarantees infection [15]. Relative humidity of 91.5% (at 20 °C) or higher will result in the production of large numbers of mature spores in 24h [16].

Alternaria is a common fungal genus that causes pre- and postharvest damage to agricultural products, including cereal grains, fruits, and vegetables. In addition to spoiling a wide variety of foods. Several Alternaria species are able to produce secondary metabolites considered as both phytotoxins, which play an important role in the pathogenesis of plants, and mycotoxins [17-19]. At least 268 metabolites from Alternaria fungi have been reported in the past few decades. They mainly include nitrogen-containing metabolites, steroids, terpenoids, pyranones, quinones, and phenolics [20-22].

Figure 1. Alternaria sp. with different shapes and septate conidia. On Potato Dextrose Agar, isolated and identified by Dr. Waill Elkhateeb (Photographs was taken by Dr. Waill A. Elkhateeb, Locality: National Research Center of Egypt).

Alternaria sp. secondary metabolites and their biological activities

Fungi are known to produce a vast array of secondary metabolites that are gaining importance for their biotechnological applications. Microbial secondary metabolites have contributed immensely in the development of a variety of medicines, namely antibiotics, metabolic inhibitors, immunomodulatory agents, antioxidants and anticancer agents [23]. Endophytism in the past decade has further opened avenues of exploration and exploitation of new chemical entities produced during the plant-microbe interaction for pharmaceutical as well as agricultural applications [23]. Alternaria is a genus belonging to ascomycete and generally comprise of members which cause agricultural spoilage, involved in decay and decomposition and some exist as opportunistic human pathogens. The genus is a prolific producer of secondary metabolites, which are finding applications in the agrochemical as well as pharmaceutical industry [23]. More than 300 metabolites of fungi of the genera Alternaria have been reported in the last few decades; some of them display phytotoxic, antibiotic, antifungal, and antiprotozoal activity [24, 25].

Members of the genus Alternaria are known to produce a wide range of phytotoxic secondary metabolites which affect a large number of plants on which the fungus is found [26]. These phytotoxins include alternariol, alternariol monomethyl ether (AME), altenuene, altenuic acid, tenuazonic acid (TA), tentoxin, alternaric acid, AKtoxin and AAL-taxon and posses a broad range of biological and metabolic effects [27, 28]. The metabolites produced by Alternaria exhibit a wide variety of biological activities ranging from phytotoxic, cytotoxic, and antimicrobial activities. Owing to possess such diverse properties, the metabolites of Alternaria have drawn the attention of many chemists, pharmacologists, and plant pathologists to consider them as tools in research programs as well as in application studies [29, 30]. Alternaria alternata is the most common species and one of the most frequently occurring species of genus Alternaria which is of particular interest because it produces a number of harmful secondary metabolites. Some of the secondary metabolites produced by Alternaria alternata include alternariol, alternariol monomethyl ether, altenuene, tentoxin, tenuazonic acid and many more [17, 18, 31, 32].

Biological Activities and Functions

Alternaria metabolites have varied chemical properties. Some of them act as phytotoxins to plants or as mycotoxins to humans and animals. They have been examined to have a variety of biological activities and functions, which mainly include the effects on plants, cytotoxic and antimicrobial activities [11, 12].

Effect on plants

Plant pathogenic Alternaria species can affect cereals, vegetables and fruit crops in the field and during storage. Alternaria fungi contamination is responsible for some of the world’s most devastating plant diseases, causing serious reduction of crop yields and considerable economic losses. The metabolites from plant pathogenic fungi are usually toxic to plants and are called phytotoxins. They were further divided into host-specific and host non-specific toxins. The host-specific toxins (HSTs) are toxic only to host plants of the fungus that produces the toxin [33]. Another definite ion seems to be more acceptable that the host-specific toxins are toxic to plants that host the pathogen, but have lower Phytotoxicity on non-host plants [34, 35]. Most HSTs are considered to
be pathogenicity factors, which the fungi producing them require to invade tissue and induce disease [36]. All isolates of the pathogen that produce an HST are pathogenic to the specific host.

Interactions between Alternaria species and cruciferous plants were studied in detail by the Pedras group [35]. Nectrocthy phytopathogens such as A. alternata and A. brassicicola are known to synthetize phytotoxins that damage plant tissues and facilitate colonization, while in response to pathogen attack crucifers biosynthesize phytoanticipins and phytoalexins. Phytoalexins are secondary metabolites produced de novo by plants in response to diverse forms of stress including microbial infection, UV irradiation, and heavy metal salts, whereas phytoanticipins are constitutive defenses whose concentrations can increase upon stress [37]. To the detriment of cruciferous plants, the phytopathogens can overcome phytoanticipins and phytoalexins by producing detoxifying enzymes. For example, the phytoalexin brassinin was detoxified into 3-indolylmethanamine and N′-acetyl-3-indolylmethanamine by the pathogen A. brassicicola [38]. Very interestingly, cruciferous plants (Brassica napus and Sinapis alba) can convert host-specific toxins destruxin B and homodestruxin B into less phytotoxic hydrodestruxin B and hydroxyhomodestruxin B, respectively [39, 40].

**Cytoxic Activity**

Some Alternaria metabolites have been screened to show cytotoxic activity. They were thought as the potential sources for possible cancer chemopreventive agents. Porritoxin was examined to have anti-tumor-promoting activity [41]. Three amides, AI-77-B, AI-77-F andSIg17-1-4, from a marine fungus A. tenuis Sig17-1 exhibited cytotoxic activity. AI-77-B exhibited the cytotoxic activity on human malignant A375-S2 and human cervical cancer [41].

Of Alternaria dibenzopyranones, alternariol was the most active metabolite to have cytotoxic activity on L5178Y mouse lymphoma cells [42, 43], as well as to have inhibitory activity on protein kinase and mammalian cells [57]. Rubrofusarin B from Alternaria alternata was toxic on L5178Y mouse lymphoma cells (3',3'-4'-7'-methoxy-α,β-dihydroxypyrano[3,2-b]pyrrole-6-one-5) with MICs of 1.56–12.50 μg/mL [56]. Herbarin A and altechrome A from A. brassicicola ML-P08 showed antimicrobial activity on Trichophyton rubrum, Candida albicans, Apergillus niger, Bacillus subtilis, Pseudomonas fluorescens with MICs ranged from 1.8 to 62.5 μg/mL [57]. Rubrofusarin B from A. alternativele showed antifungal activity on Candida albicans [58]. Some antraquinone metabolites, e.g., macrosporin, hydroxybostycin, altersolanol A, altersolanol B, altersolanol C, altersolanol G, and allopurinol C from A. solani and Alternaria sp. showed antibacterial activity on Bacillus subtilis, Escherichia coli, Micrococcus luteus, Pseudomonas aeruginosa, Staphylococcus albus, Staphylococcus aureus, Vibrio parahemolyticus [36]. Two perylenequinones alternerylenol and dihydroaltererylenol from Alternaria sp. had antifungal activity on Valsa ceratoperma. Alternusin and porric acid D from Alternaria sp. showed inhibitory activity against Staphylococcus aureus with MICs of 100 μg/mL and 25 μg/mL, respectively. (4S)-α,β-Dihydrocurvalarin from Alternaria sp. showed inhibitory activity on appressorium formation of Magnaporthe oryzae, and antibacterial activity on Proteus vulgaris and Salmonella typhimurium with MICs as 25 μg/mL [33].

Chatterjee et al., [22], reported that Alternaria alternata AE1 exhibited excellent antimicrobial activity especially against both Gram positive and Gram negative bacteria and also showed cidal mode of action. The organism was able to produce a number of antimicrobial compounds in the extracellular broth. The extract of AE1 has exerted adverse effect on central carbohydrate metabolism of pathogenic bacteria. Besides, the EA extract of AE1 exhibited very strong free radical scavenging activity [22].

Helvolic acid from Alternaria sp. FL25, an endophytic fungus in Ficus carica, showed the strong antifungal activity on all tested phytopathogenic fungi (Alternaria alternata, A. brassicicae, Botrytis cinerea, Colletotrichum gloeosporioides, Fusarium graminearum, F. oxysporum, F. oxysporum, F. oxysporum, Phytophthora capsici, Valsa mali) with MICs of 1.56–12.50 μg/mL [56]. Herbarin A and altechrome A from A. brassicicola ML-P08 showed antimicrobial activity on Trichophyton rubrum, Candida albicans, Apergillus niger, Bacillus subtilis, Pseudomonas fluorescens with MICs ranged from 1.8 to 62.5 μg/mL [57]. Rubrofusarin B from A. alternata showed antifungal activity on Candida albicans [58]. Some antraquinone metabolites, e.g., macrosporin, hydroxybostycin, altersolanol A, altersolanol B, aldersolanol C, altersolanol G, and allopurinol C from A. solani and Alternaria sp. showed antibacterial activity on Bacillus subtilis, Escherichia coli, Micrococcus luteus, Pseudomonas aeruginosa, Staphylococcus albus, Staphylococcus aureus, Vibrio parahemolyticus [36]. Two perylenequinones alternerylenol and dihydroaltererylenol from Alternaria sp. had antifungal activity on Valsa ceratoperma. Alternusin and porric acid D from Alternaria sp. showed inhibitory activity against Staphylococcus aureus with MICs of 100 μg/mL and 25 μg/mL, respectively. (4S)-α,β-Dihydrocurvalarin from Alternaria sp. showed inhibitory activity on appressorium formation of Magnaporthe oryzae, and antibacterial activity on Proteus vulgaris and Salmonella typhimurium with MICs as 25 μg/mL [33].

Ghosh et al., [19], reported that Endophytic fungi Alternaria sp. LR4 isolated from Rauvolfia serpentina showed very good antibacterial activities against Gram-positive pathogenic bacterial strains. It can produce at least two different antibacterial compounds with cidal mode of action. In addition, it also showed antioxidant and anticancerous properties. Therefore, Alternaria sp. LR4 could be a very good source of bioactive compounds or in development of new drugs [19].

**Antimicrobial Activity**

Three diketopiperazine dipetides namely cyclo-[L-Leu-trans-4-hydroxy-L-Pro-], cyclo-[L-Phe-trans-4-hydroxy-L-Pro-], and cyclo-[L-Ala-trans-4-hydroxy-L-Pro] extracted from broth culture of the grapevine endophyte Alternaria alternata showed effectiveness by inhibiting sporulation of the pathogen Plasmodiophora viticola at concentrations of 10−3, 10−4, 10−5 and 10−6 mol/L. This indicated that endophytic fungus A. alternata can be used as biocontrol agent to control fungal disease in grapevine cultivation [52]. Cyclo-(Phe-Ser-) from Alternaria sp. FL25 showed antifungal activity on Fusarium graminearum, F. oxysporum, F. cucumarum, F. oxysporum, Phytophthora capsici, Colletotrichum gloeosporioides with MICs from 6.25 to 25.00 μg/mL [53]. Tenuazonic acid was found to be an active compound in A. alternata against Mycobacterium tuberculosis H37Rv with MIC value of 250 μg/mL. This compound was thought as a promising ant tubercular principle [54]. Other nitrogen-containing metabolites with antimicrobial activity included alternesrin, pyrophein, tenuazocin acid and brassicicolin A [38, 55].

Usama et al., [17], reported that Alternaria alternata showing a high level inhibition of HCV protease (IC50 14.0 μg/mL) was selected for further investigation on its secondary metabolites. The fungus was identified by its morphology and 18S rDNA. Bioassay guided fractionation of the EtOAc extract of Alternaria alternata culture broth revealed 5
metabolites; alternariol9methyl ether 3Osulphate, alternariol9methyl ether, alternariol, maculosin and maculosin5. These secondary metabolites act as phytotoxins which are either host specific or nonspecific. In addition, some compounds have antibacterial, anti-viral, cytotoxic or insecticidal effects [18]. Alternariol and alternariol - 9-methyl ether were isolated from the ethyl acetate extract of Alternaria alternata PGL-3. The ethyl acetate extracts of Alternaria alternata PGL-3, showed the most potent inhibition of HCV NS3/4A protease with IC50 17.0 [59].

From many previous work indicate that some species of micromycetes belonging to the genus Alternaria are able to produce metabolites with insecticidal activity. Thus, fungi of the genus Alternaria, similar to many soil endophytic and phytopathogenic micromycetes, were able to produce phytotoxins, antibiotics, and insecticidal metabolites [60-62].

Conclusion

Secondary metabolites from the endophytic fungi will be a cheap source for medical, agriculture and other industries. It is sure that the research on endophytic fungi will lead to isolate more novel compounds. This review demonstrate the chemistry and bioactivities of secondary metabolites from the fungal genus Alternaria. A comprehensive investigation of secondary metabolites produced by Alternaria sp. must be carried out for a better understanding of the chemical interactions between Alternaria sp. and its host plants. Many previous research reported that, several metabolites including brassicicolin A, diterpenoids, polyketides, siderophores, alternariol, alternariol methyl ester, tentoxin, tenuazonic acid, altetroxin I, altetroxin II and other were produced by different Alternaria species. Secondary metabolic pathways of Alternaria sp. are strongly dependent on culture conditions, specifically nitrogen sources, ferric ion and temperature. The potential of fungi of the genus Alternaria as producers of biological active compounds remains very high. Secondary metabolites isolated from endophytic genus Alternaria using different culture method like common culture. These compounds have a variety of unique structures, the difference in structure leads to various biological activities of these compounds. Some of these metabolites display significant antimicrobial effects, cytotoxic activities, antioxidant activities and other biological activities, which indicate that they have potential to be agents to treat some diseases.

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