Cochliobolus, Drechslera, Bipolaris, Curvularia different nomenclature for one potent fungus

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Abstract
Cochliobolus is a Dematiaceous fungi that belong to family: Pleosporaceae. It is known as worldwide pathogen of mostly grasses that caused devastating disease epidemics of important economic food crops as wheat, rice, and maize. Many Cochliobolus species have their asexual states, and consequently synonyms, in either Bipolaris or Curvularia. In this review, highlights were presented on Cochliobolus species as models of fungi rich in therapeutic agents that can be employed in different applications. Moreover, describing the importance and potentials of this fungus in order to encourage for further studies to search, isolate, and purify already known metabolites. Also, screen for, and discover novel metabolites produced by those potent fungi in order to be involved in additional applications.

Keyword: cochliobolus; secondary metabolites; biological activities

Introduction
Natural products represent the significant and important source for discovery of potential novel drugs. The search for novel secondary metabolites is currently focusing on endophytic microorganisms isolated from plants, remote locations, and novel sources. Numerous reports shows that endophytes produce a wide variety of chemical substances, many of which show biological activity [1-3]. There are various uses of the numerous promising secondary metabolites produced by fungal endophytes. The application of microbidual secondary metabolites in various fields of biotechnology has attracted the interests of many researchers. Bioactive compounds have various applications in pharmacology and agriculture [4]. Cochliobolus species are heterothallic fungi that found mainly in soil and organic compost and they are noted for the production of secondary metabolites with vital biological activities [5-8].

The microorganisms such as Cochliobolus may be very interesting for biotechnological production of bioactive substances as medicinally important agents. The endophytic fungus Cochliobolus sp. this fungus possess significant antioxidant, anti-diabetic and anti-inflammatory potentials [9-11].

The previous studies reported that Cochliobolus sp. produce many important secondary metabolites cluding curvularides, anthraquinones, cochliquinones, helminthosporal, helminthosporol, prehelminthosporol as well as various related metabolites. These compounds exhibit many pharmacological importances, due to their antioxidant, antimicrobial as well as antifungal properties. Hence, screening and identification of fungal endophytes s very important as a source for novel natural products. Fascinatingly, it seems that the host–endophytic interaction plays a crucial role in the direction of the endophytes secondary metabolites production [12, 13].

Cochliobolus description and ecology
Endophytes are microorganisms located in internal layers of living plants without being harmful to the plant. There are many remarkable pharmacological agents that are continuously explored and identified from endophytic fungi [14]. It should be mentioned that over 50% of identified bioactive compounds have been isolated from fungal endophytes [15]. Endophytic fungi are the source of many pharmaceutical compounds including those exerting antibacterial, antifungal, anticancer, antitumor, antiviral, and anti-inflammatory activities [16, 17].

Genus Cochliobolus is a fast growing fungus attaining 5.5 cm diameter after 5 days on Czapek’s Agar and Malt Agar. Genus Cochliobolus belong to Phylum Ascomycota; Class: Dothideomycetes; Order: Pleosporales; Family: Pleosporaceae. The genus Cochliobolus (as well as its anamorphic sp. that almost include nearly 55 species (Bipolaris, Curvularia) are found worldwide. These species are weeds pathogens and since the weeds and pathogens are coevolved over long term, these species can be applied as weed herbicides [18]. The taxonomy of Cochliobolus is a little bit confusing due to the frequent changes in nomenclatural that have occurred in the sexual and asexual states of species over the past decades. Cochliobolus ascomata are dark brown to black, unilocular with a globose body and a long or short cylindrical ostiolate neck. Hyaline to brown sterile hyphae and conidiophores often
occur on the ascomata and less so on the neck [19]. Asci are bitunicate, 2-8-spored, cylindrical to obclavate or obclavate cylindrical. Ascospores are filiform and more or less coiled in a helix in the ascus (Figure 1, 2). Most species of Cochliobolus form prothecia (sclerotia) which are sterile without any ascogenous hyphae [20-22]. It is a saprophyte and survives primarily as thick-walled conidia. It can also survive as mycelium in soil or crop debris. The sexual stage is not important in the disease cycle. Primary inoculum includes mycelium from infected seed, conidia in the soil, and conidia on the kernel surface [23]. Cochliobolus species encountered based on conidia different shapes. Conidia straight, conidia curved, conidia wall smooth, conidia curved with 3-distoseptate, conidia wall with tuberculate, conidia with 5-distoseptate and conidia with 6-10-distoseptate.

Germination of conidia takes place in presence of susceptible hosts and initiate primary infection on the coleoptile, or primary roots. Before penetration, appressoria and dome-shaped infection cushions are formed. Infection pegs form underneath infection cushions and appressoria. Tissue disintegration come as the final step after development of infection from epidermis to cortex then endodermis. Spreading of conidia is causing the progress in colonization of infected plant parts [24].

**Figure 1.** Cochliobolus Sp. On Potato Dextrose Agar (cited in: www.ipmimages.org)

**Figure 2.** Cochliobolus sp. with different shapes and septate conidia. On Potato Dextrose Agar (cited in: www.sen.wikipedia.org and www.forestryimages.org).

**Cochliobolus** *secondary metabolites*

Species of Cochliobolus Drechsler [25] and its anamorphs Bipolaris [20] as well as Curvularia [26, 27] are worldwide pathogens of most grasses. There are a lot of secondary metabolites produced by strains of Cochliobolus and its anamorph. Cochliobolus carbonum produced TOXEp Novel as protein Regulation of cyclic peptide biosynthesis [28], EXG1p novel exo-β1,3-glucanase Cell wall degradation. *Cochliobolus spicifer* which produced spiciferone as AGamma-pyrones as plant growth inhibitor [29] and 6-Chlorodehydrocurvularin [30]. *Cochliobolus miyabeanus* produced Cochlioquinones A, B compound as new metabolites with p-quinoind nature [31]. *Cochliobolus sativus* which produced 9-Hydroxyprehelminthosporol compound which as Anti-viral property [32]. Cochliobolus sp. produced Isocochlioquinone and Cochlioquinone A which as ALeishmanicidal activity [33].

Mycotoxin production by Cochliobolus (Bipolaris species) may or may not be host-specific [19]. HS toxin (a peptide and a secondary amine) produced by Cochliobolus victoriae, HC toxin (a polypeptide) produced by Cochliobolus carbonum race 1, and T toxin produced by Cochliobolus hetero-strophus are examples of host-specific toxins. Ophiobolins (terpinoid) produced by Cochliobolus miyabeanus and carbotoxin produced by Cochliobolus carbonum are examples of non-host-specific toxins [19]. Other mycotoxin are Bipolaroxin, Sorokinianin, Carbotoxine, Victorin and Ophiobolin which produced by Cochliobolus.
The filamentous fungi *Cochliobolus sorokiniana* efficiently produces the biotransformation of α-bisabolol (Figure, 3) to bisabolol-oxide B. α-Bisabolol is economically significant due to its delicate characteristic floral odor and its anti-inflammatory and antiseptic biological activities. Therefore, it is being widely employed in the pharmaceutical industry.

Potent antifouling activity is observed in some newly isolated resorcylic acid lactones found in the fungus *Cochliobolus lunatus* derived from the gorgonian *Dichotella gemmacea*. Thus obtained were cochliomycins A–C (Figure, 4). Only cochliomycin A shows potent activity against *Balanus amphitrite*.

**Some biological activities of Cochliobolus metabolites**

![Chemical structures](image)

Apart from being a worldwide pathogens of mostly grasses (Poaceae) and important food crops such as rice, wheat and maize [26], *Cochliobolus* exhibit different activities that can be useful for plants. For example, *Cochliobolus* can be used as a biochemical modulator to alleviate salinity stress in okra plants [34, 35]. Chloromonilinic acids C and D extracted from *Cochliobolus australiensis* showed toxic effect to buffelgrass in a seedling elongation bioassay, with significantly delayed germination and dramatically reduced radicle growth, especially at a concentration of $5 \times 10^{-3} \text{M}$ [36].

**Figure 3. Some important structures compounds produced by Cochliobolus sorokiniana.**
On the other hand, Cochliobolus species have well known potency in the field of microbial biotransformation of compounds generally, and steroidal compounds in particular [37, 38]. Furthermore, Cochliobolus species have shown promising various biological activities. Metabolites originated from Cochliobolus exerted antileishmanial activities against Leishmania and Trypanosoma. It was reported that the crude extract of Cochliobolus sp. (UFMGCB-555) at 20 µg/m concentration could kill 90% of the amastigote-like forms of Leishmania amazonensis and inhibit by 100% Ellman's reagent reduction in the trypanothione reductase (TryR) assay, which demonstrated that the chromatographic fractionation of that Cochliobolus sp. extract was a promising drug target for Trypanosoma cruzi. The metabolites, Cochlioquinone A and Isocochlioquinone A were identified as the enzyme inhibitors responsible for the antileishmanial activities [33], [39, 40]. Cochliobolus metabolites showed also promising anticancer activities. Radicinin isolated from Cochliobolus geniculatus WR12 exhibited high cytotoxic activity against T47D cells recording IC₅₀ of 25.01 ppm [41]. The same compound showed also anti-MRSA activity with minimum inhibitory concentration (MIC) of 125 µg/disc against tested MRSA [42]. Dendryphiellin I isolated from the marine derived Cochliobolus lunatus SCSIO41401 showed cytotoxic activity against three renal cancer cell lines (ACHN, 786-O, and OS-RC-2), a human liver cancer cell line (HepG-2), and a human gastric cancer cell line (SGC7901) (IC₅₀ 1.4 to 5.9 and antibacterial activities against three bacterial species (MIC 1.5 to 13 µg/mL). Another metabolite, (dendryphiellin J), was extracted from the same fungus and showed cytotoxicity against ACHN and HepG-2 cells with IC₅₀ values of 3.1 and 5.9 µM, respectively [42].

**Cochliobolus in biological control**

Cochliobolus species and its asexual states have been isolated as saprobes from different dead wood plants. Also Cochliobolus can be found in association with many species of Poaceae such as bamboo and also other host plants. For example, Curvularia lunata is a frequently recorded saprove of bamboo clumps [43-45].

Using fungi as biological control agents is a rapidly growing area of research with implication for plant productivity, animal and human health, and food production [46]. Weeds are an economic restraint to agricultural production [47]. Biological control of weeds by using plant pathogens has gained acceptance as a practical, safe, environmentally beneficial weed management method applicable to agroecosystems. The use of mycoherbicides is important in the move towards organic farming and the reduction in the use of chemical herbicides.

Many Cochliobolus and its anamorphic species (Bipolaris and Curvularia) are pathogens of weeds and can successfully be applied as weed herbicides. Some examples of research that shows Bipolaris and Curvularia can be used as potential mycoherbicides. The pathogens may have evolved biochemical mechanisms to kill the weed host [18]. Bipolaris sp. were tested as a potential herbicide agent against serrated tussock in Australia [48]. The biological control of weeds has generally been limited by the slow development of effective, broader spectrum biological control agents [49, 50], and more effective biocontrol agents need to be developed.

Curvularides, cochlioquinones, anthroquinones and some novel proteins involved in cyclic peptide regulation and cell wall degradation have been reported from Cochliobolus strains. These compounds may have important medicinal values, such as anti-fungal properties, and thus have the potential to be used in medical science [12].
Conclusion

Fungi are promising sources for such compounds due to their ability to produce a variety of secondary metabolites that could be, if truly investigated, the solution for currently serious problems. Every study conducted on Cochliobolus resulted in discovery of new metabolites or pointing to a possible application, which made Cochliobolus species potential source of pharmaceuticals and attracted attention for further investigations of their medical properties.

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