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Epicoccum Species as Potent Factories for the Production of Compounds of Industrial, Medical, and Biological Control Applications

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ABSTRACT

Epicoccum is an endophytic fungus famous for its application in the biocontrol of numerous phytopathogenic fungi. Moreover, *Epicoccum* Sp. are known for their capability of producing various biologically active compounds with medical applications as antioxidant, antimicrobial, and anticancer agents. In addition to pigments formation and their industrial application. The aim of this review is to highlight the diversity of compounds produced by *Epicoccum* sp. and pointing out their medical, bio-control, and industrial applications.

Keywords: *Epicoccum*; Biological Control; Biotechnology; Secondary Metabolites

Introduction

Discovering new applications for currently known bioactive metabolites and/ or exploring novel biologically active metabolites are of critical need nowadays due to the current increasing dilemma of microbial resistance to available and used antibiotics and therapeutic agents, beside the emergence of new life threatening diseases. These problems have encouraged scientists to look for unconventional sources in order to find novel compounds. Fungi are promising sources for a wide variety of vital metabolites such as alkaloids, flavonoids, phenols, steroids and terpenoids [1-3]. Fungi capacity to synthesize variety of new bioactive metabolites forced researchers to explore these avenues. *Epicoccum* is an ascomycotic, endophytic fungus that is commonly isolated from different sources in moderate frequencies [4-6]. *E. nigrum* is famous for its successful applications in the bio-control of many phyto-pathogens [7-13], also for its ability to produce diverse classes of chemically, structurally, and biologically diverse secondary metabolites [13-17]. The aim of this review is to provide information about secondary metabolites of *Epicoccum* and their promising and current applications. Highlighting the importance of rich sources of biologically active compounds can contribute in encouraging searching for novel sources of potent compounds to face current needs for antimicrobial agents to overcome microbial antibiotic resistance, and to discover drugs for existing life-threating diseases.

Secondary Metabolites of *Epicoccum* Species

Epicoccum Sp. produces variety of secondary metabolites such as polyketides, polyketide hybrids, diketopiperazines, Siderophores, Carotenoid, and others (Table 1). Majority of these compounds exert promising biological activities such as antioxidant, antimicrobial, anticancer, in addition to potential industrial applications of pigments produced from *E. nigrum* as a likely safe, nontoxic, and non-pathogenic fungus. Among the important biologically active compounds produced by *Epicoccum* spp., the anticancer drug, taxol [18]. Also, epicocconone which is known commercially as fluorophore and is used in cell staining and in gel electrophoresis for protein detection [19,20], D8646-2-6 which is a telomerase inhibitor [21,22], in addition to many potential factories for silver nano-particles production such as Orsellinic acid and Curvularin.

Table 1: some secondary metabolites produced by Epicoccum species and their biotechnological applications.

Compound	Type	Applications	References
Orsellinic acid	Polyketides	potential factory for silver nano-particles production	Mohamed [23]; Abdel-Hafez et al. [24]
Flavipin	Polyketides	Antifungal, antioomycete, antialgal, anti-nematode, and yellow pigment	Bamford et al. [25]; Burge et al. [26]; Brown et al. [27]; Madrigal et al. [28]
Epicoccine	Polyketides	Antioxidant	Ishikawa et al. [29]; Lee et al. [30]; Kemami Wangun et al. [31]; El Amrani et al. [32]
Epicoccones A and B	Polyketides	Antioxidant, and brown pigment	Abdel-lateff et al. [33]; Kemami et al. [31]; El Amrani et al. [32], Lee et al. [30]
3-methoxy epicoccone	Polyketides	Anticancer, yellow pigment	El Amrani et al. [32]
3-methoxy epicoccone B	Polyketides	Anticancer, yellow pigment	El Amrani et al. [32]
2,3,4-trihydroxy-6-(methoxymethyl)-5-methylbenzaldehyde	Polyketides	Anticancer, brown pigment	El Amrani et al. [32]
Mellein	Polyketides	Antibacterial, antifungal, antialgal and antiworm	Cabras et al. [34]; da Silva Ara ujo et al. [35]; Herzner et al. [36]; Ramos et al. [37]; Wang et al. [38]
4-hydroxy mellein	Polyketides	Antioxidant	Abdel-Lateff et al. [33]
5-hydroxy mullein	Polyketides	Antioxidant	Abdel-Lateff et al. [33]
7-methoxy-4-oxo-chroman-5-carboxy acid methyl ester	Polyketides	Pale yellow pigment	Lee et al. [30]
1,3-dihydro-5-methoxy-7-methyl isobenzofuran	Polyketides	Light brown pigment	Lee et al. [30]
Epicoccalone	Polyketides	Inhibit Serine protease α-chymotrypsin, and yellow pigment	Kemami Wangun et al. [31]
Epicolactone	Polyketides	Antibacterial, antifungal and antioomycete	da Silva Araujo et al. [35]; Talontsi et al. [39]
Epicocconigrones A and B	Polyketides	Anticancer	El Amrani et al. [32]
Epicocconone	Polyketides	Pigment of high orange-red fluorescent in the presence of proteins	Bell and Karuso [19]
Epicoccolide A and B	Polyketides	Antifungal and antioomycete	Talontsi et al. [39]; El Amrani et al. [32]
Acetosellin	Polyketides	Yellow pigment	Talontsi et al. [39]
Quinizarin	Polyketides	Red pigment	Dzoyem et al. [40]
Orevactaene	Polyketides	Orange	Shu et al. [14]
Epipyridone	polyketide-nonribosomal peptide hybrid	Antibacterial, and red pigment	Kemami Wangun and Hertweck [41]; Li et al. [42]
Epicoccamide A, B, C, and D	polyketide-nonribosomal peptide hybrid	Anticancer	Wright et al. [43]; Wangun et al. [44]
Epicoccarines A and B	polyketide-nonribosomal peptide hybrid	Antibacterial, and red pigment	Kemami Wangun and Hertweck [41]; Li et al. [42]
Preaustinoid A	polyketide-nonribosomal peptide hybrid	Antibacterial	Perveen et al. [17]
Epicoccin A	Diketopiperazines	Antibacterial	Zhang et al. [45]; Guo et al. [46]; Wang et al. [47]
Epicoccin E	Diketopiperazines	Anti-inflammatory	Zhang et al. [45]; Guo et al. [46]; Wang et al. [47]
Epicoccin G	Diketopiperazines	Inhibit replication of HIV-1	Zhang et al. [45]; Guo et al. [46]; Wang et al. [47]
Epicoccin H	Diketopiperazines	Inhibit replication of HIV-1	Zhang et al. [45]; Guo et al. [46]; Wang et al. [47]

Epicoccin J	Diketopiperazines	Anti-inflammatory	Zhang et al. [45]; Guo et al. [46]; Wang et al. [47]
Epicoccin M	Diketopiperazines	Anti-inflammatory	Zhang et al. [45]; Guo et al. [46]; Wang et al. [47]
Epicoccin S	Diketopiperazines	Anti-inflammatory	Zhang et al. [45]; Guo et al. [46]; Wang et al. [47]
Diphenylalazines A, and B	Diketopiperazines	Inhibit replication of HIV-1	Guo et al. [46]
Epicorazine A, and B	Diketopiperazines	Antibacterial	Baute et al. [48]; Brown et al. [27]
Pimarane diterpene 1	Diterpene	Antitumor	Xia et al. [49]
Pimarane diterpene 2	Diterpene	Antitumor	Xia et al. [49]
Diaporthin B	Diterpene	Antitumor and Antibacterial	Xia et al. [49]
Isopimarane diterpene	Diterpene	Inhibition of α-glucosidase	Xia et al. [49]
11-deoxydiaporthein A	Diterpene	Inhibition of α-glucosidase	Xia et al. [49]
Iso-D8646-2-6	Pyronepolyene C-glucoside	NF-kB inhibition and anti-influenza A viral (H1N1)	Kanai et al. [21]; Peng et al. [22]; Li et al. [42]
D8646-2-6	Pyronepolyene C-glucoside	Inhibition of telomerase and anti-influenza A viral (H1N1)	Kanai et al. [21]; Peng et al. [22]; Li et al. [42]
β-Carotene	Carotenoid	Antioxidant, and yellow pigment	Foppen and Gribanovski Sassu [50]
γ-Carotene	Carotenoid	Antioxidant, and orange pigment	Foppen and Gribanovski Sassu [50]
Rhodoxanthin	Carotenoid	Antioxidant, and red pigment	Foppen and Gribanovski Sassu [50]
Torularhodin	Carotenoid	Antioxidant, and violet pigment	Foppen and Gribanovski Sassu [50]
Taxol	Diterpene	Anticancer	Somjaipeng et al. [18]
Acetyl Sumiki's acid	Furan carboxylic acid	Antibacterial	Abdel-Lateff et al. [33]
2-furoic acid	Furan carboxylic acid	Antibacterial	Abdel-Lateff et al. [33]
Sumiki's acid	Furan carboxylic acid	Antibacterial	Abdel-Lateff et al. [33]
Ferricrocin	Siderophore	Antitumor	Frederick et al. [51]
Beauvericin	Depsipeptide	Antibacterial, antioxidant insecticidal, antiviral and cytotoxic activities	Dzoyem et al. [40]
Curvularin	macrolide	potential factory for silver nano-particles production	Mohamed [23]; Abdel-Hafez et al. [24]

Epicoccum Spp. As Biocontrol Agents

Epicoccum spp. have proven to be a potent biocontrol agents against many phytopathgenic fungi, specially Botrytis cinerea waxflower [23], Claviceps africana in sorghum [24], Pythium spp. infecting cotton [9], Rhizoctonia solani infecting potato plants [25], and Sclerotinia sclerotiorum in sunflower [26], Phytophthora infestans [27], phytoplasma in apple trees [28] and Monilinia spp. in peaches and nectarines [29-33] and against other plant pathogenic fungi [10,11,34,35].The action mechanisms exhibited by *E. nigrum* as a biocontrol agent varies from reducing host stem disease severity index, and growing along the fungal pathogen hyphae and inducing its lysis [36], or through causing degradation of the pathogen protoplast, malformation in its hyphae, and leakage of cytoplasm [37]. The polyketide, Flavipin, produced by many *Epicoccum* Sp is the reason causing growth inhibition of numerous phytopathogenic fungi [25,28,38-41]. On the other hand, Epicolactone isolated from *E. nigrum* has antifungal activity and can induce root growth [42-57]. All those studies support using *Epicoccum* species in different host plants as a safe biological control agent and encourage deep investigations for further understanding of the physiological and molecular aspects of this interaction [57-62].

Conclusion

Emerging of microbial resistance, spread of life-threatening diseases, and biological control of pathogens destroying economically important crops, are serious problems that encourage scientists to search for unconventional sources for novel compounds with biological activities. 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. *Epicoccum* is one of the pioneer fungi in this field with proven potent ability as promising biotechnological tool to produce industrially, and biologically diverse metabolites.

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