



Diverse secondary metabolites among *Aspergillus* species

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Abstract

Aspergillus produces several small organic, bioactive natural products called secondary metabolites. These secondary metabolites are of diverse nature in chemical structures and are importantly required during various physiological processes, such as to acquire essential micronutrients, to compete in the environment and hosts, and pathogenicity. *Aspergillus* have a long array of secondary metabolites with diverse biological roles and functional efficiencies. Interestingly, different species of *Aspergillus* have characteristic sets of secondary metabolites. Here, an attempt has been made to make a comprehensive assessment of secondary metabolites among different species of *Aspergillus*.

Index Terms – Secondary metabolites, *Aspergillus*, Fungi, Physicochemical properties.

I. INTRODUCTION

Fungi produces small organic, bioactive natural products called secondary metabolites, which play important roles and regulate various physiological processes under different conditions and stress (1, 2). Fungal secondary metabolites show enormous diversities in its chemical structures and biological activities (3,4), and show broad spectrum of applications in agriculture, food, pharmaceutical industry, and drug discovery including antibiotics (5,6). In general, these secondary metabolites, such as polyketides and terpenoids, are synthesized from the metabolism of common precursor molecule acetyl-CoA. The structural features and functional efficiency of these secondary metabolites are important aspects to understand their biological or pharmacological activities. The characteristic structural and physiochemical features of secondary metabolites are accountable for delivering a variety of characteristics including therapeutic applications, the solubility, and stability of the molecules (7). *Aspergillus* have long array of secondary metabolites which show species specific diversity. In the present study, a comparative assessment of secondary metabolites has been done among different *Aspergillus* species, which are important for their success and survival as opportunistic fungi.

II. Materials and Methods

Extensive literature survey was done to mine the secondary metabolites that are reported from four different species of *Aspergillus*, viz *Aspergillus niger*, *Aspergillus fumigatus*, *Aspergillus nidulans*, and *Aspergillus terreus*. The list of secondary metabolites for these four species were prepared separately and compared together. The basic physicochemical properties of listed secondary metabolites, such as molecular weight, molecular formula, 2-D structures, etc. were calculated and retrieved from standard chemical database 'PubChem' (<https://pubchem.ncbi.nlm.nih.gov/>) (8) by mapping the name of secondary metabolites to chemical identifiers.

III. Results

The *Aspergilli* produces a wide variety of secondary metabolites which have been proved of considerable medical, industrial, agricultural and economic importance. Here we focused to target, evaluate and assess the secondary metabolites that help into success and survival *Aspergillus* as opportunistic fungi. Beside some common molecules, several species-specific secondary metabolites were reported based on the presence of biosynthetic gene cluster in the genome of *Aspergillus* species. Finally, species specific, core secondary metabolites and their basic physicochemical properties were calculated and assembled for four species of *Aspergillus*.

3.1 Core secondary metabolites in *Aspergillus niger*

Aspergillus niger is one of the most common and highly ubiquitous fungal species. *A. niger* produces various secondary metabolites with a broad spectrum of applications in agriculture, food, and pharmaceutical industry (9). Total eight different secondary metabolites have been reported which are specific to *A. niger* and synthesized from core biosynthetic gene clusters (Table 1 & Fig 1).

Table 1. List of secondary metabolites which are synthesized from core biosynthetic genes in *A. niger*.

Sl. No.	Secondary Metabolites	Molecular Formula	Molecular Weight (g/mol)
1	Azanigerone	C ₁₉ H ₂₂ O ₇	362.4
2	Ferrichrome	C ₂₇ H ₄₂ FeN ₉ O ₁₂	739.6
3	Kotanin	C ₂₄ H ₂₂ O ₈	438.4
4	Melanin	C ₁₈ H ₁₀ N ₂ O ₄	318.3
5	Ochratoxin	C ₂₀ H ₁₈ ClNO ₆	403.8
6	Pyranonigrin	C ₁₀ H ₉ NO ₅	223.18
7	Tantalum nitride (TAN)	NTa	194.955
8	Yanuthone	C ₂₈ H ₄₀ O ₈	504.6

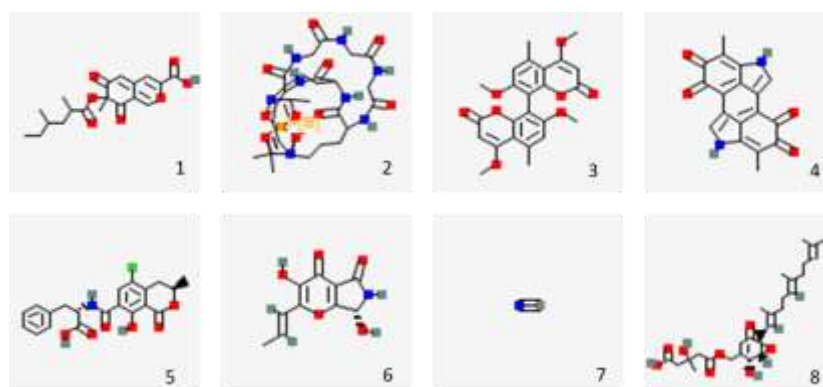


Figure 1. Molecular 2D structure of core secondary metabolites of *A. niger*.

3.2 Core secondary metabolites in *Aspergillus fumigatus*

Aspergillus fumigatus is an airborne saprophytic fungus that plays important role in the recycling of environmental carbon and nitrogen (10). It causes severe, usually fatal invasive infections in hosts which are immunocompromised (11). *A. fumigatus* produces large number of secondary metabolites which may be ordered into 24 different biosynthetic families (12). Out of these, following are the core secondary metabolites which are specific to *A. fumigatus*.

Table 2. List of secondary metabolites which are synthesized from core biosynthetic genes in *A. fumigatus*.

Sl. No.	Secondary Metabolites	Molecular Formula	Molecular Weight (g/mol)
1	Endocrocin	C ₁₆ H ₁₀ O ₇	314.25
2	Ferricrocin	C ₂₈ H ₅₀ FeN ₉ O ₁₃ ⁺³	776.6
3	Fumagillin	C ₂₆ H ₃₄ O ₇	458.5
4	Fumicycline	C ₂₄ H ₂₄ O ₇	424.4
5	Fumigaclavine C	C ₂₃ H ₃₀ N ₂ O ₂	366.5
6	Fusarinine C	C ₃₃ H ₅₄ N ₆ O ₁₂	726.8
7	Gliotoxin	C ₁₃ H ₁₄ N ₂ O ₄ S ₂	326.4
8	Helvolic acid	C ₃₃ H ₄₄ O ₈	568.7
9	Hexadehydroastechrome	C ₆₀ H ₆₆ FeN ₉ O ₉ ⁺³	1113.1
10	Neosartoricin	C ₂₆ H ₂₈ O ₉	484.5
11	Pseurotin	C ₂₂ H ₂₅ NO ₈	431.4
12	Pyripyropene	C ₃₂ H ₃₉ NO ₁₀	597.7
13	Trypacidin	C ₁₈ H ₁₆ O ₇	344.3
14	YWA1	C ₁₄ H ₁₂ O ₆	276.24

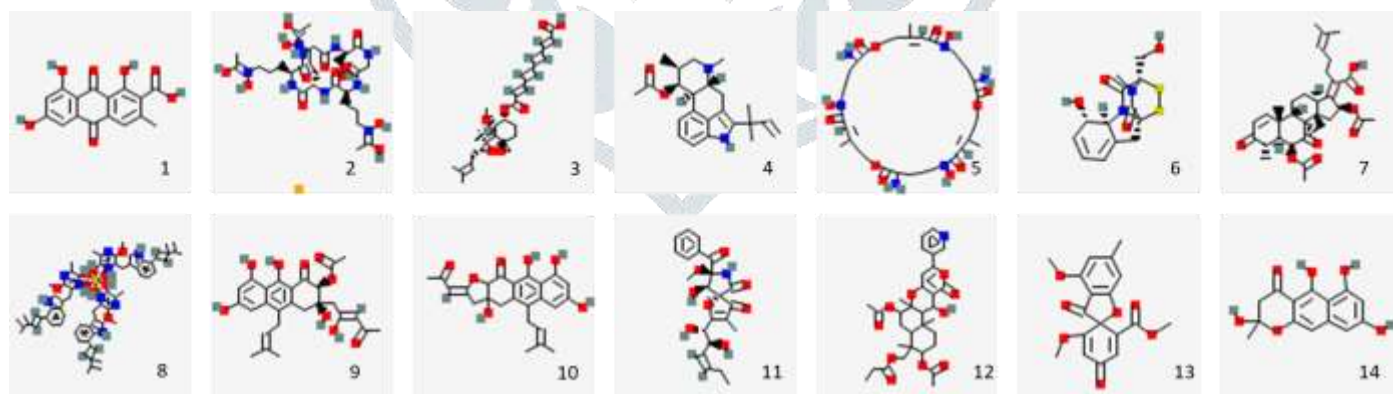


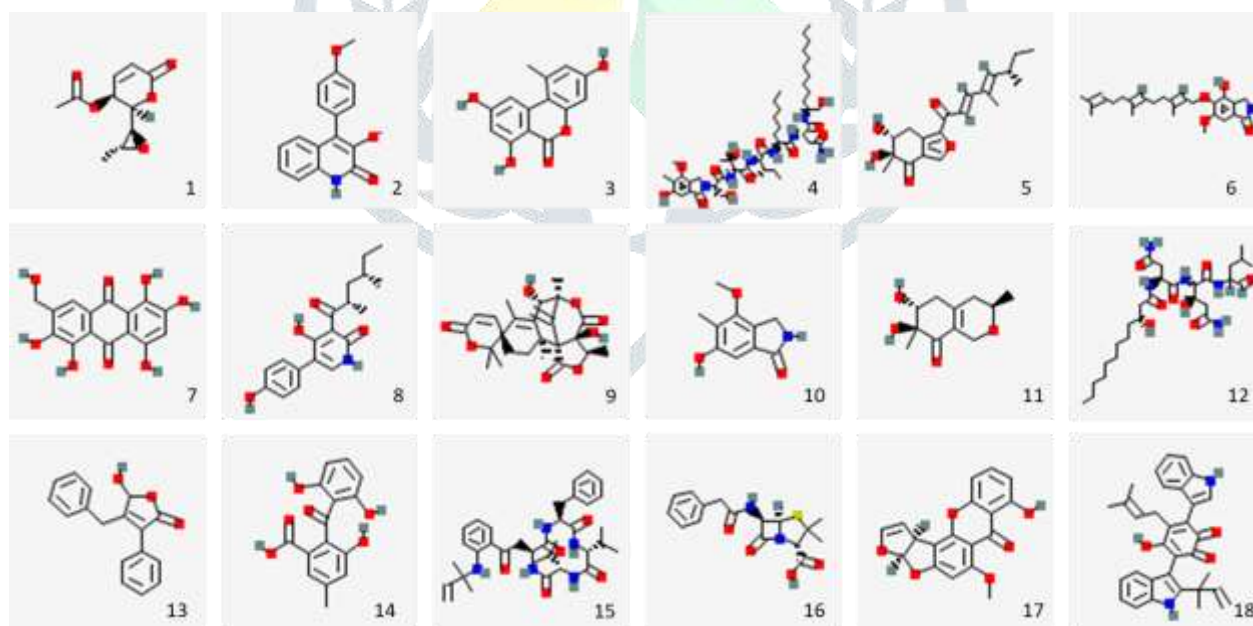
Figure 2. Molecular 2D structure of core secondary metabolites of *A. fumigatus*.

3.3 Core secondary metabolites in *Aspergillus nidulans*

Aspergillus nidulans has been used as workhorse to understand fungal genetics (13). However, much is not known about the natural diversity of secondary metabolites in *A. nidulans*. Genetics work in *A. nidulans* has proven its importance for the discovery and manipulation of genes associated with secondary metabolism in fungi (14). Total eighteen different secondary metabolites are specific to *A. nidulans* and are synthesized from core biosynthetic gene clusters.

Table 3. List of secondary metabolites which are synthesized from core biosynthetic genes in *A. nidulans*.

Sl. No.	Secondary Metabolites	Molecular Formula	Molecular Weight (g/mol)
1	Asperlin	C ₁₀ H ₁₂ O ₅	212.2
2	Methoxyviridicatin	C ₁₆ H ₁₂ NO ₃ ⁻	266.27
3	Alternariol	C ₁₄ H ₁₀ O ₅	258.23
4	Aspercryptin	C ₄₇ H ₇₉ N ₇ O ₁₂	934.2
5	Asperfuranone	C ₁₉ H ₂₄ O ₅	332.4
6	Aspernidine	C ₂₄ H ₃₃ NO ₄	399.5
7	Asperthecin	C ₁₅ H ₁₀ O ₈	318.23
8	Aspyridone	C ₁₉ H ₂₃ NO ₄	329.4
9	Austinol	C ₂₅ H ₃₀ O ₈	458.5
10	Cichorine	C ₁₀ H ₁₁ NO ₃	193.2
11	Felinone	C ₁₁ H ₁₆ O ₄	212.24
12	Fellutamide	C ₂₇ H ₄₉ N ₅ O ₈	571.7
13	Microperfuranone	C ₁₇ H ₁₄ O ₃	266.29
14	Monodictyphenone	C ₁₅ H ₁₂ O ₆	288.25
15	Nidulanin	C ₃₄ H ₄₅ N ₅ O ₅	603.8
16	Penicillin	C ₁₆ H ₁₈ N ₂ O ₄ S	334.4
17	Sterigmatocystin	C ₁₈ H ₁₂ O ₆	324.3
18	Terrequinone	C ₃₂ H ₃₀ N ₂ O ₃	490.6

Figure 3. Molecular 2D structure of core secondary metabolites of *A. nidulans*.

3.4 Core secondary metabolites in *Aspergillus terreus*

Aspergillus terreus is a popular and well-known producer of lovastatin, a cholesterol-lowering drug (15). Besides these, *A. terreus* also produces other SMs, including terreulactones, 11- α hydroprogesterone (antitumor compounds), quadrone (antibiotic terrecyclic acid A), and terpeptin (a cell cycle inhibitor) (16). *A. terreus* is also as an effective agent for the bioremediation of heavy metals. Followings are the list of core secondary metabolites which are specific to *A. terreus*.

Table 4. List of secondary metabolites which are synthesized from core biosynthetic genes in *A. terreus*.

Sl. No.	Secondary Metabolites	Molecular Formula	Molecular Weight (g/mol)
1	Acetylaranotin	C ₂₂ H ₂₀ N ₂ O ₈ S ₂	504.5
2	Asperfuranone	C ₁₉ H ₂₄ O ₅	332.4
3	Asperphenamate	C ₃₂ H ₃₀ N ₂ O ₄	506.6
4	Aspterric acid	C ₁₅ H ₂₂ O ₄	266.33
5	Asterelenin	C ₂₅ H ₂₅ N ₃ O ₄	431.5
6	Citreoviridin	C ₂₃ H ₃₀ O ₆	402.5
7	Geodin	C ₁₇ H ₁₂ Cl ₂ O ₇	399.2
8	Isoflavipucine	C ₁₂ H ₁₅ NO ₄	237.25
9	Lovastatin	C ₂₄ H ₃₆ O ₅	404.5
10	Phenguignardic acid	C ₁₈ H ₁₄ O ₅	310.3
11	Terreic acid	C ₇ H ₆ O ₄	154.12
12	Terretonin	C ₂₆ H ₃₂ O ₉	488.5

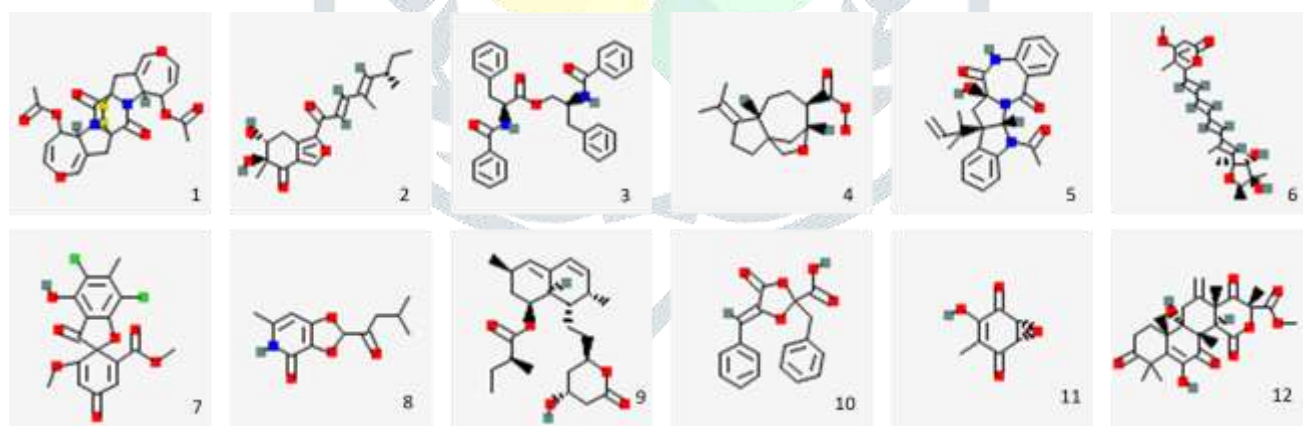


Figure 4. Molecular 2D structure of core secondary metabolites of *A. terreus*.

IV. Discussion and Conclusion

Aspergillus produces diverse secondary metabolites having bioactive potentials that make them as potential drug candidates. Significant effort has been done to activate secondary metabolite biosynthetic genes which offers a promising source for new drug discovery. In the post-genomic era, genome sequencing and whole genome analyses made it possible to link secondary metabolites to their biosynthetic gene clusters. Genetic identification and characterization of secondary metabolites biosynthetic gene clusters have been worked out for different species *Aspergillus*. The comparative assessment suggest that diverse secondary metabolites are

synthesized by biosynthetic gene clusters of four different species of *Aspergillus*, viz. *A. niger*, *A. fumigatus*, *A. nidulans* and *A. terreus*, which are specific to respective species. However, a thorough and deep analyses of genomes by using combination of approaches, including the use of heterologous expression, gene knockout techniques, overexpression of pathway-specific regulators, and growth in various conditions along with the collaborative effort will help into the characterization of the *Aspergillus* secondary metabolome.

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