

Review

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Review

An Updated Perspective on the Aromatic Metabolic Pathways of Plant-Derived Heterocyclic Aromatic Compounds in *Aspergillus niger*

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Abstract: Aromatic compounds are vital in both natural and synthetic chemistry, traditionally sourced from non-renewable petrochemicals. However, plant biomass, particularly lignin, offers a renewable alternative source for aromatic compounds. Lignin, a complex polymer in plant cell walls, is the largest renewable source of aromatic compounds, though its degradation remains challenging. Lignin can be chemically degraded through oxidation, acid hydrolysis or solvolysis. Microorganisms, including fungi, offer a sustainable alternative in breaking down lignin into valuable compounds. Fungi possess unique enzymes capable of converting aromatic compounds derived from lignin into biofuels, bioplastics, and chemical building blocks. However, their aromatic metabolic pathways are less studied compared to bacterial systems. Recent advances in genomics, proteomics, and metabolic engineering are helping to reveal these pathways, offering new opportunities to optimize fungi for lignin bioconversion. By manipulating these pathways, researchers aim to enhance lignin valorization, contributing to sustainable biobased industries. This review highlights recent progress in understanding fungal aromatic metabolism, focusing on how *Aspergillus niger* converts plant-derived aromatic compounds into useful products and the versatility of aromatic metabolism within the *Aspergillus* genus. Addressing the current knowledge gaps in fungal pathways could unlock their potential in sustainable technologies, promoting eco-friendly production of biofuels and chemicals from renewable resources.

Keywords: aromatic metabolism; aspergilli; benzoic acids; cinnamic acids; phenolic compounds

1. Introduction

Aromatic compounds play crucial roles in plants and provide structural support (e.g., lignin), defense against herbivores and pathogens (e.g., phenolics), and contribute to pigmentation, fragrance, and flavor, aiding in pollination and protection against environmental stress. Additionally, they are also involved in metabolic processes and allelopathy, helping plants compete and thrive in their ecosystems [1]. Aromatic compounds are also prevalent in everyday life and are found in a wide range of man-made products such as beverages, cosmetics, foods, fuels, lubricants, medicines, paints, and plastics [2]. Most commercial aromatic compounds utilized today are synthesized from base chemicals like benzene, toluene and xylene which are typically extracted from nonrenewable fossil resources. Therefore, developing methods to utilize the wealth of natural aromatic compounds, producing those from renewable sources is essential for sustainable practices and reducing dependence on fossil fuels.

One of the most promising renewable sources for aromatic compounds is the complex plant polymer lignin. Between 15-30% of the dry weight of plant biomass consists of lignin depending on the species. Lignin is mostly built from the aromatic compounds coniferyl alcohol (guaiacyl (G)-units), *p*-coumaryl alcohol (*p*-hydroxyphenyl (H)-units) and sinapyl alcohol (syringyl (S)-units), derived from hydroxycinnamic acids, and the ratios of building blocks used in lignin varies per plant species. Additionally, different building blocks such as caffeoyl alcohol and vanillyl alcohol have

been observed in lignin [3]. Hydroxycinnamic acids such as ferulic acid (3-methoxy-4-hydroxycinnamic acid) and *p*-coumaric acid (*p*-hydroxycinnamic acid) can be linked to complex plant cell wall structures like hemi-cellulose and pectin and have ester linkages with arabinose and galactose [11–13]. Currently, much research is performed in the utilization of lignin through chemical, enzymatic and biotransformation approaches [4–7].

Fungi are able to degrade and metabolize a wide range of monomeric aromatic compounds efficiently but the aromatic metabolic pathways in fungi are poorly studied. Moreover, most existing studies focus on different fungal species, making it challenging to determine which specific pathways are present within a single species. Hence, a complete fungal aromatic metabolic pathway overview is non-existing. In order to fill up the gaps, a comparison between the aromatic metabolic pathways of bacteria, yeast and fungi was made and showed that many pathways are shared between them [8]. Before 2020, the best described aromatic metabolic pathways were from *Aspergillus japonicus* and were obtained by using UV spectra, TLC, GLC and dioxygenase activity [9]. However, this study was before the genome era and no genes were identified. Despite that many fungal genomes are now sequenced and published, the number of identified fungal genes encoding enzymes converting aromatic compounds is remarkably low [8,10]. It was also revealed that unique and unexplored aromatic metabolic pathways exist in fungi.

Recently, multiple genes and enzymes involved in the metabolism of monomeric aromatic compounds, mainly in *Aspergilli* species, have been identified. With the identification of these genes, better predictions and correlations can be made of which metabolic pathways are present in fungi. In this review, the recent advances and insight in the monomeric aromatic metabolic pathways in fungi from the past years, with a main focus on *Aspergillus niger*, are highlighted and discussed.

2. Metabolism of Hydroxycinnamic Acids

The monomeric aromatic compounds ferulic acid (3-methoxy-4-hydroxycinnamic acid) and *p*-coumaric acid (*p*-hydroxycinnamic acid) are hydroxycinnamic acids that are part of complex sugars and are linked to arabinose and galactose residues via ester linkages [11–13]. These linkages are part of the plant cell wall and contribute to the cell wall rigidity and aid in the plants resistance against environmental stress and pathogens. Multiple fungi are able to hydrolyze ester bonds between hydroxycinnamic acids and polysaccharides using feruloyl esterases (Fae's). These enzymes play a crucial role in the degradation on complex plant biomass and it has been shown that Fae's can be used to releases ferulic acid from agricultural waste streams such as wheat bran, maize bran and sugar beet pulp [14–16]. Fae's have been identified and studied in many fungi but mainly in the *Aspergilli*; *Aspergillus niger*, *Aspergillus oryzae* and *Aspergillus nidulans* [17]. At this moment, three Fae's have been identified and characterized in *A. niger* [18–20]. Homologs of feruloyl esterase's have been observed and studied in multiple fungi including *Aspergillus*, *Fusarium*, *Penicillium*, *Pleurotus*, *Trichoderma*, and *Talaromyces* species [17].

Multiple pathways that can convert ferulic acid have been described. *A. oryzae* can release ferulic acid from the cell wall of rice endosperm during brewing processes. After the release, ferulic acid is decarboxylated to 4-vinylguaiacol (Figure 1) [21]. 4-vinylguaiacol can give an undesired flavor in distilled products such as beer, awamori and sake [22–26]. In *Aspergillus luchuensis*, decarboxylation of hydroxycinnamic acids to its vinyl form is catalyzed by phenolic acid decarboxylase (Pad). This conversion was also observed in the *A. niger* diploid strain DAR2 (derived from *A. niger* C28B25). This strain is able to decarboxylate ferulic acid to 4-vinylguaiacol and further to vanillic acid, possibly with vanillin as intermediate (Figure 1) [27]. A close homolog of AIPad is present in *A. niger* (NRRL3_08440) and could be also involved in the decarboxylation of ferulic acid. This pathway has also been observed other fungi such as *Fusarium solani* (Mart.) Sacc., *Colletotrichum gloeosporioides*, *Isaria farinosa* and many yeast species [25,26,28,29] indicating that this pathway is relatively common. Interestingly, the *A. niger* C28B25, the parental strain of DAR2, is degrading ferulic acid to vanillic acid without the non-oxidative decarboxylation step to vinyl-guaiacol indicating that other pathways are present in *A. niger* [27].

Decarboxylation of hydroxycinnamic acid to its vinyl form has been observed in many fungi. In *Saccharomyces cerevisiae*, hydroxycinnamic acids and cinnamic acid are decarboxylated by ferulic acid decarboxylase 1 (Fdc1) and flavin prenyltransferase 1 (Pad1) respectively [30,31]. Homologs of Fdc1 and Pad1 are found in multiple *Aspergillus* species and have been shown to do this catalysis *in vitro* [32,33]. However, deletion of these genes in *A. niger* resulted in abolished growth on cinnamic acid but no phenotypes were observed on the hydroxycinnamic acids; ferulic acid, *p*-coumaric acid and caffeic acid [32]. This gave new indications that these enzymes are involved *in vivo* in cinnamic acid decarboxylation but not hydroxycinnamic acid decarboxylation [32]. In addition this was also supported by transcriptome data, showing that *fdcA* or *padA* are not induced when grown on caffeic acid, ferulic acid or *p*-coumaric acid. Therefore, FdcA of *A. niger* was renamed to cinnamic acid decarboxylase A (CdcA) [32].

Recently, it has been shown that *A. niger* degrades the hydroxycinnamic acids; caffeic acid, ferulic acid, *p*-coumaric acid and *m*-coumaric acid through the peroxisomal CoA-dependent beta-oxidative metabolic pathway resulting in the formation of protocatechuic acid (3,4-dihydroxybenzoic acid), vanillic acid (4-hydroxy-3-methoxybenzoic acid), *p*-hydroxybenzoic acid and *m*-hydroxybenzoic acid, respectively (Figure 1) [34]. Also, dihydrocaffeic acid (3-(3,4-dihydroxyphenyl)propanoic acid) and phloretic acid (3-(4-hydroxyphenyl)propanoic acid) are degraded through this pathway [34]. The CoA-dependent beta-oxidative metabolic pathway is well-known for the degradation of fatty acids but was not previously known to be involved in the degradation of hydroxycinnamic acids. Interestingly, also in plants it has been shown that hydroxycinnamic acid can be degraded through this pathway [35]. Multiple genes involved in the degradation of hydroxycinnamic acids in *A. niger* were identified using whole genome transcriptome data [34].

In *A. niger*, the first step of the CoA-dependent beta-oxidative metabolic pathway is catalyzed by the hydroxycinnamate-CoA synthase (HscA), and deletion of it results in strongly reduced growth on hydroxycinnamic acids but appears not to be required for fatty acid degradation [34]. The second and third step of this pathway is catalyzed by fatty acid oxidase A (FoxA) and is was identified in multiple fungal species to be involved in the fatty acid degradation [34,36–41]. The fourth step is catalyzed by 3-ketoacyl-CoA thiolase (KatA) (Figure 1). Deletion of these related genes resulted in clear phenotypes on several hydroxycinnamic acids, however growth was not abolished on ferulic acid or *p*-coumaric acid indicating that another pathway, functional redundancy or alternative genes are present in *A. niger* [34]. The final step of the CoA-dependent oxidative pathway is proposed to be catalyzed by a thioesterase. Four thioesterases (TheA, TheB, TheC and TheD) have been identified and individual deletion of these genes did not result in reduced growth on ferulic acid, *p*-coumaric acid and caffeic acid. Deletion of *theB* results in growth reduction on *m*-coumaric acid but the growth recovers over time and it was suggested that there is functional redundancy in the final step. The redundancy of the thioesterases could be further studied by making a quadruple deletion of the genes and analyze the growth on hydroxycinnamic acids. Interestingly, deletion of the CoA-dependent beta-oxidative genes did not result in reduce growth on sinapic acid (3,5-dimethoxy-4-hydroxycinnamic acid) or cinnamic acid indicating that they are degraded through other pathway(s) in *A. niger*.

In *A. niger*, *o*-coumaric acid (2-hydroxycinnamic acid) can be converted to 4-hydroxycoumarin but it appears not to be further degraded [42]. In *A. fumigatus*, melilotic acid (3-(2-hydroxyphenyl)propanoic acid) is converted through esterification to *o*-coumaric acid and further to 4-hydroxycoumarin and dicoumarol [43,44]. Interestingly, a CoA-dependent beta-oxidative pathway was suggested for the conversion of *o*-coumaric acid to 4-hydroxycoumarin with *o*-coumaryl-SCoA, *o*-hydroxyphenyl- β -hydroxypropionyl-SCoA, *o*-hydroxyphenyl- β -ketopropionic acid-SCoA as intermediates [44]. As mentioned before, in *A. niger* dihydrocaffeic acid (3-(3,4-dihydroxyphenyl)propanoic acid) and phloretic acid (3-(4-hydroxyphenyl)propanoic acid) are converted through the CoA-dependent beta-oxidative pathway and it is possible that both

compounds are esterified to caffeic acid and *p*-coumaric acid, respectively. However, the involved genes of this pathway still need to be identified.

An alternative metabolic pathway for the metabolism of hydroxycinnamic acid is a CoA-independent non-oxidative pathway which has been observed in *A. flavus* [45]. *p*-coumaric acid is converted to β -hydroxy-(*p*-hydroxyphenyl)propionic acid and *p*-hydroxybenzoylacetate followed by a conversion to *p*-hydroxybenzoic acid. In *A. luchuensis*, it is proposed that ferulic acid is converted to vanillin through a CoA-dependent non-oxidative pathway having feruloyl-CoA and 4-hydroxy-3-methoxyphenyl- β -hydroxypropionyl-CoA (HMPKP-SCoA) as intermediate [24]. In *A. brasiliensis* ATCC 16404, the 2' position of the aliphatic chain of ferulic acid is methoxylated to (E)-3-(4-hydroxy-3-methoxyphenyl)-2-methoxyacrylic acid [46].

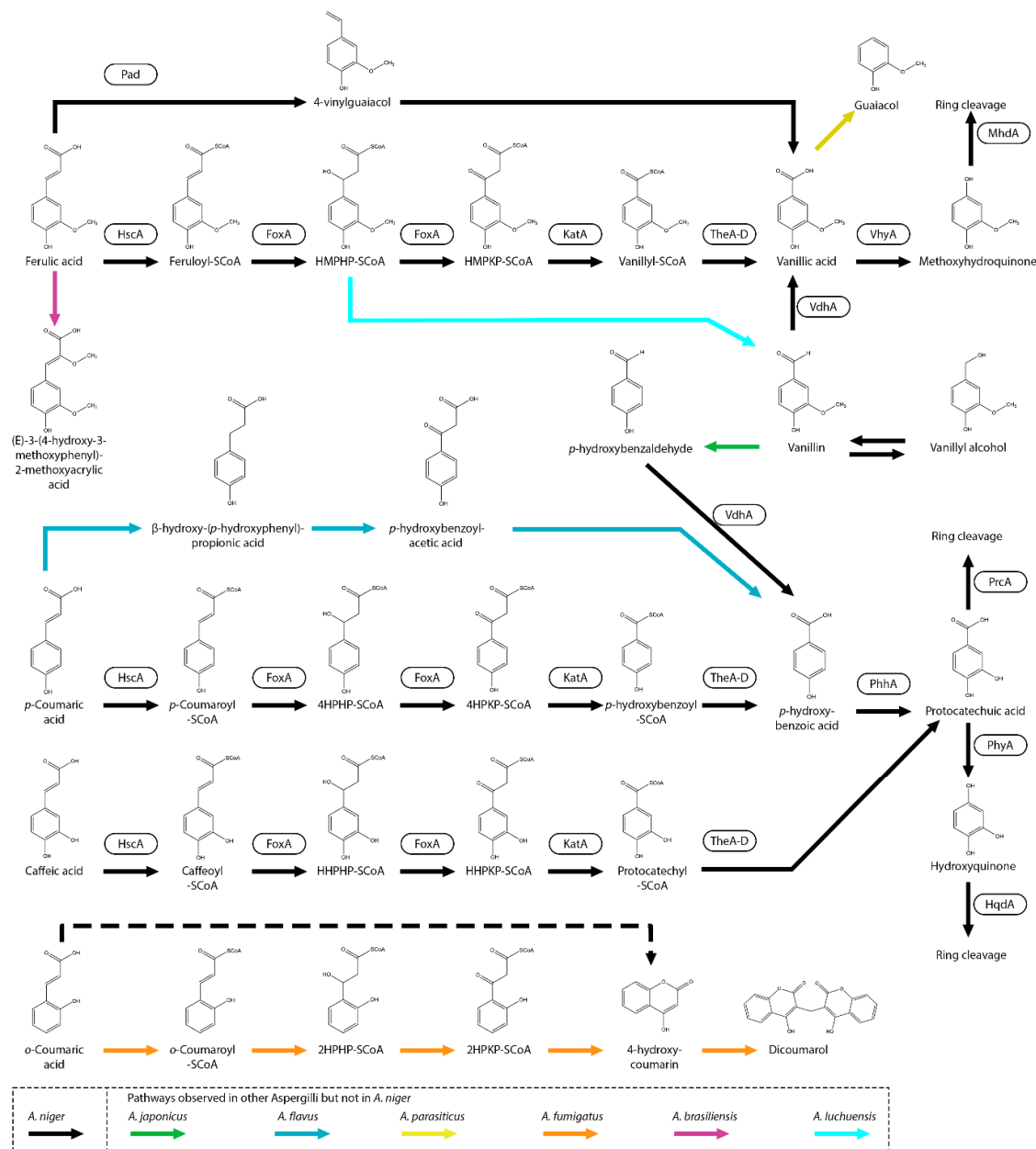


Figure 1. Metabolic pathway of the hydroxycinnamic acids, ferulic acid, *p*-coumaric acid and caffeic acid in *A. niger*. Pathways observed in *A. niger* are marked with black arrows. Unidentified pathways in *A. niger* are marked with dashed arrows. Boxes near an arrow represents identified enzymes catalyzing the reactions. Pathways that were not observed in *A. niger* but in other *Aspergilli* are marked with blue (*A. flavus*), green (*A.*

japonicus) yellow (*A. parasiticus*), orange (*A. fumigatus*), cyan (*A. luchuensis*) and purple (*A. brasiliensis*) arrows. HMPKP-SCoA, 4-hydroxy-3-methoxyphenyl- β -hydroxypropionyl-CoA; HMPKP-SCoA, 4-hydroxy-3-methoxyphenyl- β -ketopropionic acid-CoA; 4HPKP-SCoA, 4-hydroxyphenyl- β -hydroxypropionyl-CoA; 4HPKP-SCoA, 4-hydroxyphenyl- β -ketopropionic acid-CoA; HHPKP-SCoA, 3,4-dihydroxyphenyl- β -hydroxypropionyl-CoA; HHPKP-SCoA, 3,4-dihydroxyphenyl- β -ketopropionic acid-CoA.

3. Metabolism of Cinnamic Acid

The decarboxylation of cinnamic acid has been observed in multiple *Aspergilli* and *Trichoderma* species including *A. niger*, *A. japonicus*, *A. flavus*, *A. oryzae*, *A. wentii*, *T. reesei*, *T. viride*, *T. koningii* but also *Penicillium* species and the yeast *S. cerevisiae* [9,30,32,47–49]. As mentioned before, *A. niger* decarboxylates cinnamic acid to styrene by CdcA and PadA (Figure 2). Both genes are also involved in the degradation of sorbic acid and are regulated by the sorbic acid regulator A (SdrA) [30,32,50]. Interestingly, all three genes are clustered on the genome of many *Aspergilli* and a strong correlation was found in *Aspergilli* species between the ability to grow on cinnamic acid and sorbic acid and this gene cluster [32]. For example, *A. nidulans* is unable to grow on cinnamic acid due to a mutation resulting in a truncated *padA*.

In *A. japonicus* and *A. niger*, cinnamic acid can also be converted to benzoic acid [9,32,51]. Deletion of benzoate-4-monooxygenase (*bphA*), *p*-hydroxy-*m*-hydroxylase (*phhA*), protocatechuate 3,4-dioxygenase (*prcA*) or the combination protocatechuate hydroxylase (*phyA*)/*prcA* or hydroxyquinol 1,2-dioxygenase (*hqdA*)/*prcA* in *A. niger* results in reduced growth on cinnamic acid indicating that it is converted towards benzoic acid [51,52]. In addition, *A. niger* $\Delta prcA \Delta phyA$ transformant grown on cinnamic acid and cinnamyl alcohol resulted in accumulation of protocatechuic acid [51]. Currently, it remains unknown whether styrene is an intermediate of this conversion pathway or that an alternative cinnamic acid metabolic pathway is present in *A. niger*. However, in other fungi cinnamic acid pathways towards benzoic acid and *p*-hydroxybenzoic acid have been observed. In *Phomopsis liquidambari*, it is suggested that cinnamic acid is decarboxylated to styrene followed by the conversion to benzaldehyde and benzoic acid by a putative laccase [53]. In the yeast *Yarrowia lipolytica* OKYL029, cinnamic acid is hydroxylated to *p*-coumaric acid and further converted to *p*-hydroxybenzoic acid [54]. Deletion of a cytochrome P450 sharing homology with trans-cinnamate 4-monooxygenases (YALI1_B28430g, TCM1) resulted in a blockage of *p*-coumaric acid formation however cinnamic acid was still converted through an unknown pathway. The conversion of cinnamic acid to *p*-coumaric acid was also suggested in *A. japonicus* [9] and observed in *A. niger* [42]. However, in the latter also melilotic acid (3-(2-hydroxyphenyl)propanoic acid), *o*-coumaric acid and *p*-hydroxybenzoic acid were also detected (Figure 2) [42].

In several fungi other alternative cinnamic acid metabolic pathways have been observed. In *Neurospora crassa* and *Mucor* sp. JX23, cinnamic acid is converted towards acetophenone [55,56]. In *A. japonicus* and *Schizophyllum commune*, cinnamic acid can be reduced to cinnamaldehyde and cinnamyl alcohol [9,57]. The genes encoding these enzymes still remains to be identified.

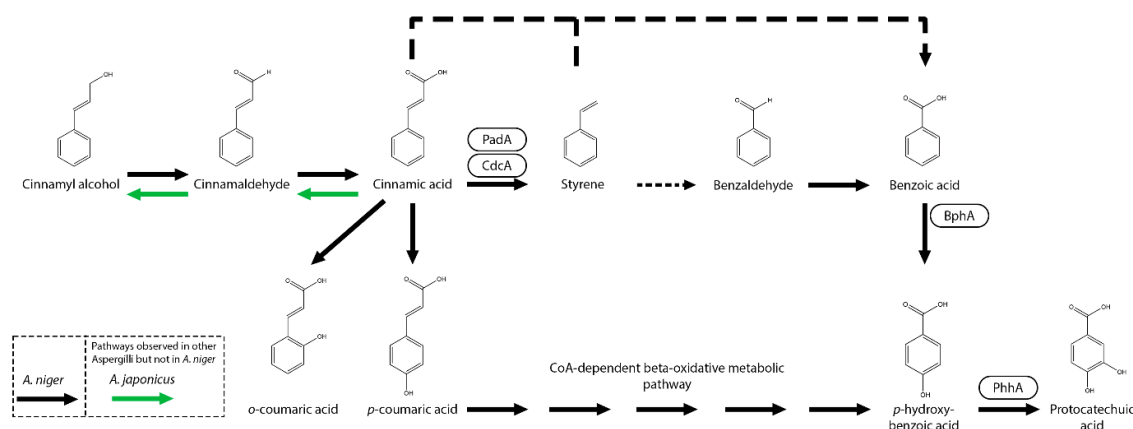


Figure 2. Cinnamic acid metabolic pathway of *A. niger*. Boxes near an arrow represents the enzymes catalyzing the reactions. Suggested pathways are marked with dashed arrows. Pathways that were not observed in *A. niger* but in other *Aspergilli* are marked with green (*A. japonicus*) arrows.

4. Metabolism of Benzoic Acid and Related Aromatic Compounds

In fungi, multiple aromatic compounds are metabolized and funneled towards protocatechuic acid [8,51]. In *A. niger*, all *p*-hydroxyphenyl and 3,4-dihydroxyphenyl units, which are derived from H-unit monolignol, are converted towards protocatechuic acid, indicating that this pathway plays an important role in the degradation of hydroxylated aromatic compounds in fungi.

One of the aromatic compound that is converted to protocatechuic acid is benzoic acid (benzene carboxylic acid), a commonly used food preservative with anti-microbial properties [58,59]. In multiple *Aspergillus* species, benzoic acid can be hydroxylated by benzoate-4-monooxygenase (BphA) to *p*-hydroxybenzoic acid [9,52,60–64]. This pathway is continued by conversion of *p*-hydroxybenzoic acid to protocatechuic acid catalyzed by PhhA, with further conversion to 3-carboxy-*cis,cis*-muconic acid by PrcA [52,63]. Interestingly, deletion of *prcA* in *A. niger* did not abolish growth on protocatechuic acid, indicating that an alternative pathway is present. Protocatechuic acid can also be converted to hydroxyquinol (1,2,4-trihydroxybenzene) by protocatechuate hydroxylase (PhyA) and is further converted by hydroxyquinol 1,2-dioxygenase (HqdA) [51,52]. Deletion of *phyA* did not result in growth reduction on protocatechuic acid, revealing that this metabolic pathway may have a minor role in protocatechuic acid metabolism, as also observed in *A. nidulans* [65]. In *A. niger*, benzoic acid can also be hydroxylated to *m*-hydroxybenzoic acid and further to protocatechuic acid [66]. BphA is not able to *meta*-hydroxylate benzoic acid to *m*-hydroxybenzoic acid [67] while deletion of *bphA* results in severely reduced growth on benzoic acid [52]. Therefore, conversion of benzoic acid to *m*-hydroxybenzoic acid is likely to be a minor pathway in *A. niger*.

With this knowledge, an *A. niger* cell factory was constructed that can accumulate protocatechuic acid from benzoic acid, benzaldehyde, benzyl alcohol, *p*-anisic acid, *p*-anisaldehyde, *p*-anisyl alcohol, *p*-hydroxybenzoic acid, *p*-hydroxybenzaldehyde, *p*-hydroxybenzyl alcohol, *m*-hydroxybenzoic acid, protocatechuic aldehyde, *p*-coumaric acid, caffeic acid, cinnamic acid and cinnamyl alcohol [51]. However, accumulation of protocatechuic acid was not observed on ferulic acid, vanillin, veratric acid, *p*-cresol, or anethole indicating that these are converted through alternative pathways. This study contributed greatly to mapping out which aromatic compounds are ultimately converted into protocatechuic acid (Figure 3).

Several aromatic compounds were not tested for protocatechuic acid accumulation with the *A. niger* cell factory [51], but were observed in other studies to be converted to protocatechuic acid. In *A. niger*, the chlorinated derivatives 2-chlorobenzoate and 3-chlorobenzoate are both observed to be converted to *p*-hydroxybenzoic acid and further to protocatechuic acid [68]. Mandelic acid is also converted to protocatechuic acid with benzoyl formate, benzaldehyde, benzoic acid and *p*-hydroxybenzoic acid as intermediate [69]. The polyethylene terephthalate (PET) derived compounds;

dimethyl-terephthalate, monomethyl-terephthalate and terephthalate are all suggested to be converted into protocatechuic acid [70]. In *A. flavus*, conversion of *p*-coumaryl alcohol to *p*-coumaric aldehyde followed by conversion to *p*-coumaric acid followed by the conversion to *p*-hydroxybenzoic acid and protocatechuic acid was observed [45]. Interestingly, *A. japonicus* can convert veratric acid into protocatechuic acid [9] but in *A. niger* converted to vanillic acid [71]. *Aspergillus fumigatus* is able to degrade *p*-cresol which is suggested to subsequently be converted *p*-hydroxybenzyl alcohol followed by *p*-hydroxybenzaldehyde, *p*-hydroxybenzoic acid and finally to protocatechuic acid [72]. In another suggested pathway, *p*-cresol is converted to 4-methylcatechol, (3,4-dihydroxybenzyl alcohol), protocatechualdehyde and protocatechuic acid which is then converted by *prcA* to 3-oxoadipate. No evidence was found in *A. niger* that *p*-cresol is converted through these pathways (Lubbers and de Vries, 2021). In *A. japonicus*, *p*-anisic acid can also be reduced to the corresponding aldehyde and alcohol form [9] but was not observed in *A. niger* [51]. In *Aspergillus sojae*, protocatechuic acid is decarboxylated to catechol [64].

Despite the fact that most *meta*- and *para*-hydroxylated benzoic acids are converted towards protocatechuic acid, several exceptions have been observed (Figure 3). *A. flavus* and *A. niger* are also able to reduce benzoic acid to benzyl alcohol possibly with benzaldehyde as intermediate [73,74].

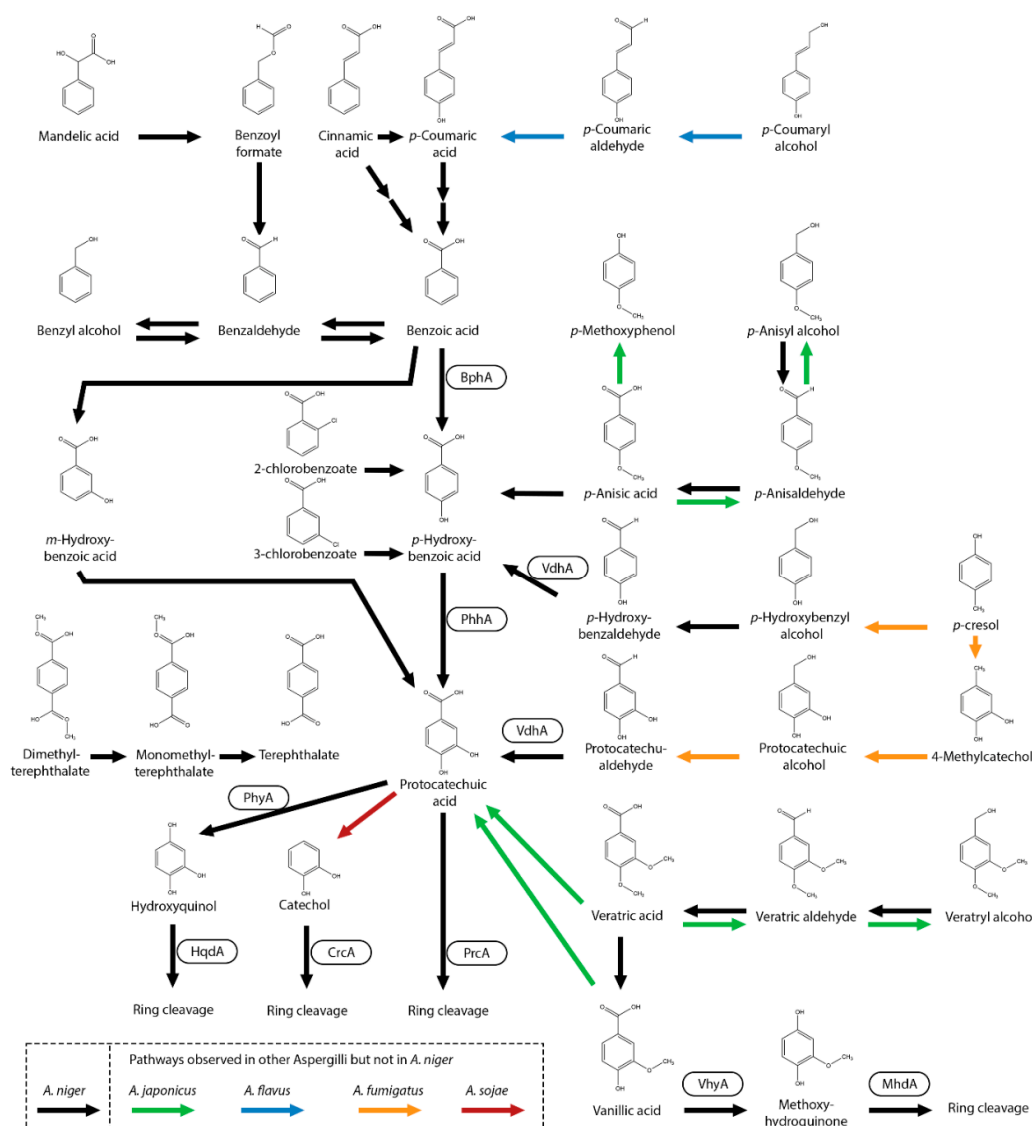


Figure 3. Benzoic acid and related compounds metabolic pathway of *A. niger*. Black arrow represent observed *A. niger* metabolic pathways and boxes near an arrow represents the enzymes catalyzing the reactions. Pathways that were not observed in *A. niger* but in other *Aspergilli* are marked with green (*A. japonicus*), blue (*A. flavus*), orange (*A. fumigatus*) or red (*A. sojae*) arrows.

5. Metabolism of Guaiacyl Units and Related Aromatic Compounds

Guaiacyl units, a key building block of lignin in gymnosperms (softwoods), feature a methoxy group at the *meta*-position and a hydroxyl group at the *para* position on their aromatic ring (Figure 4). Coniferyl alcohol, ferulic acid, guaiacol, vanillic acid and vanillin are all guaiacyl units. As mentioned previously, in *A. niger* ferulic acid is converted to vanillic acid through the CoA-dependent beta-oxidative metabolic pathway. Recently, the gene and enzyme, vanillate hydroxylase A (VhyA), involved in the conversion of vanillic acid to methoxyhydroquinone was identified [71]. This pathway was also observed in *A. flavus*, *Paecilomyces variotii* and *Sporotrichum pulverulentum* [73,75,76]. Methoxyhydroquinone is further processed through ring cleavage by methoxyhydroquinone 1,2-dioxygenase (MhdA) [71]. Deletion of *vhyA* in *A. niger* showed that, when grown on coniferyl alcohol, ferulic acid, vanillin, vanillyl alcohol, veratryl alcohol, veratric aldehyde or veratric acid, the fungus converts these substrates into vanillic acid, which subsequently accumulates due to the deletion of *vhyA* [71].

In *A. niger*, vanillin is converted to vanillic acid by vanillin dehydrogenase (VdhA) (Figure 4). Deletion of *vdhA* abolished growth on vanillin and vanillin did not accumulate in the $\Delta vdhA$ mutant when grown on ferulic acid or coniferyl alcohol, indicating that ferulic acid is not degraded to vanillin in *A. niger*. It has been shown in *A. niger* and *A. japonicus* that vanillin can also be reduced to vanillyl alcohol [9,71]. In *A. luchuensis*, vanillin is converted to vanillic acid but is also converted vanillin-glucoside [24]. *Aspergillus carbonarius* and several *Trichoderma* species have been observed to produce vanillin from vanillic acid while none of the other tested *Aspergillus* and *Penicillium* species were not able to do this conversion and indicates that they are lacking a vanillate reductase [77]. Demethylation of vanillin to *p*-hydroxybenzaldehyde was observed in *A. japonicus* [9].

Other pathways have been observed in fungi in which vanillic acid is decarboxylated to guaiacol, protocatechuic acid, vanillin or/and vanillyl alcohol [77]. Interestingly, *A. flavus*, *A. niger* and *A. nidulans* are only able to convert vanillic acid to methoxyhydroquinone while multiple *Aspergillus* and *Penicillium* species are able to convert vanillic acid to methoxyhydroquinone but also to protocatechuic acid or guaiacol.

In *A. japonicus*, it was suggested that veratric acid is demethylated to vanillic acid followed by an additional demethylation to protocatechuic acid (Figure 4) [9]. Conversion of vanillic acid to protocatechuic acid has also been reported in *F. solani* [28]. In *A. niger*, veratric acid, veratric aldehyde and veratryl alcohol are converted to vanillic acid but the conversion towards protocatechuic acid was not observed [51,71]. The gene encoding veratric acid demethylase remains to be identified. As observed with other aromatic acids, reduction to its aldehyde and alcohol form has been observed, both *A. flavus* and *A. japonicus* are able to reduce veratric acid towards veratric aldehyde and veratryl alcohol [9,73].

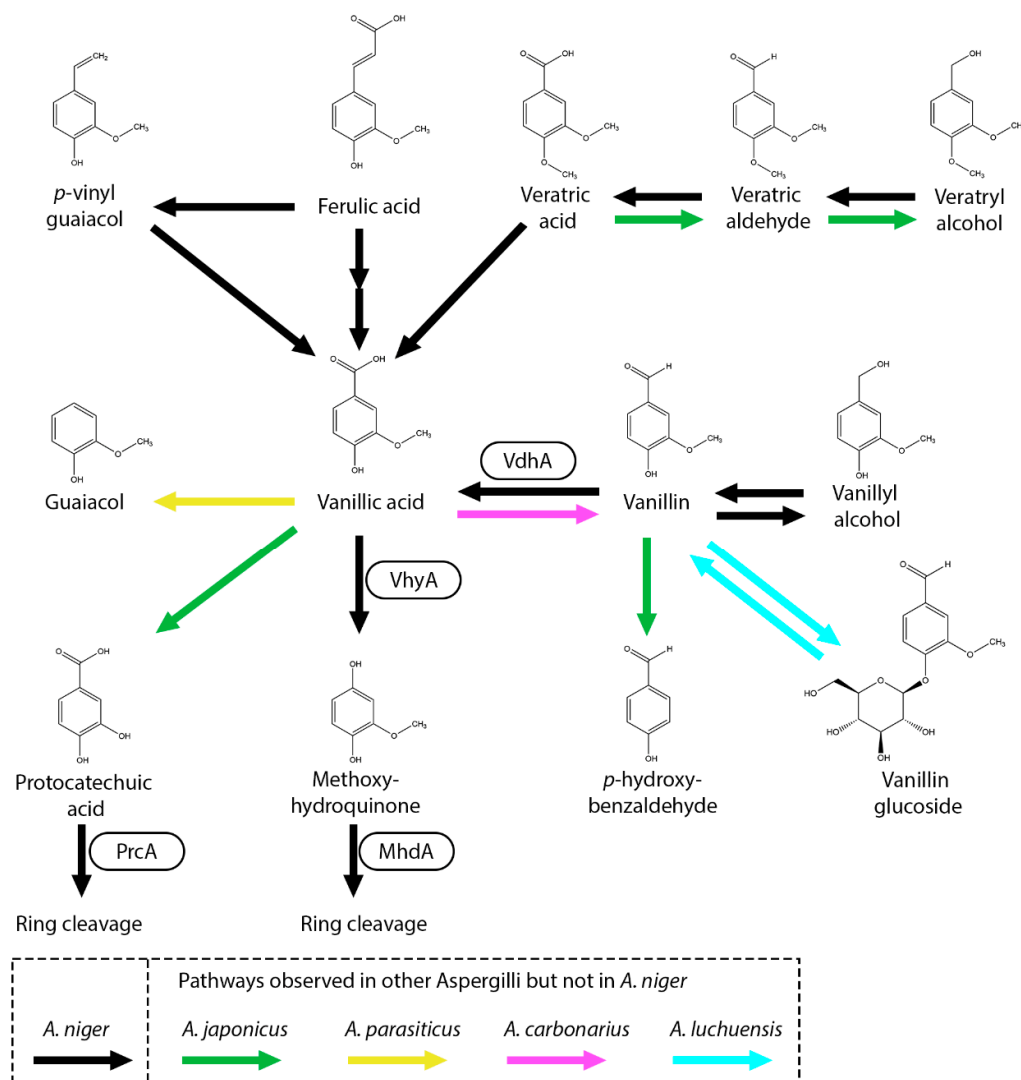


Figure 4. Vanillic acid and related compounds metabolic pathway of *A. niger*. Black arrow represents pathways observed in *A. niger*. Boxes near an arrow represents the enzymes catalyzing the reactions. Pathways that were not observed in *A. niger* but in other *Aspergilli* are marked with green (*A. japonicus*), pink (*A. carbonarius*), Cyan (*A. luchuensis*) and yellow (*A. parasiticus*) arrows.

6. Conversion of Syringyl Units

While syringyl units, in combination with guaiacyl units, are the predominant building blocks of lignin in hardwoods, the degradation of syringyl units by fungi remains less understood. Syringyl units such as sinapyl alcohol, sinapic acid, syringic acid and syringic aldehyde, feature two methoxy groups at both *meta* positions and a hydroxyl group at the *para* position on their aromatic ring (Figure 5). It is observed that *A. niger* can degrade sinapic acid (3,5-dimethoxy-4-hydroxycinnamic acid) and syringic acid (3,5-dimethoxy-4-hydroxybenzoic acid) (Lubbers *et al.*, unpublished data). However, it remains unknown how these are degraded. Sinapic acid is not degraded through the CoA-dependent beta oxidative pathway since deletion of *hcsA*, *foxA*, or *katA* did not result in any growth phenotype [34]. No other new studies have become available concerning the degradation of syringyl units by *Aspergilli* and therefore the metabolic pathways remains unknown.

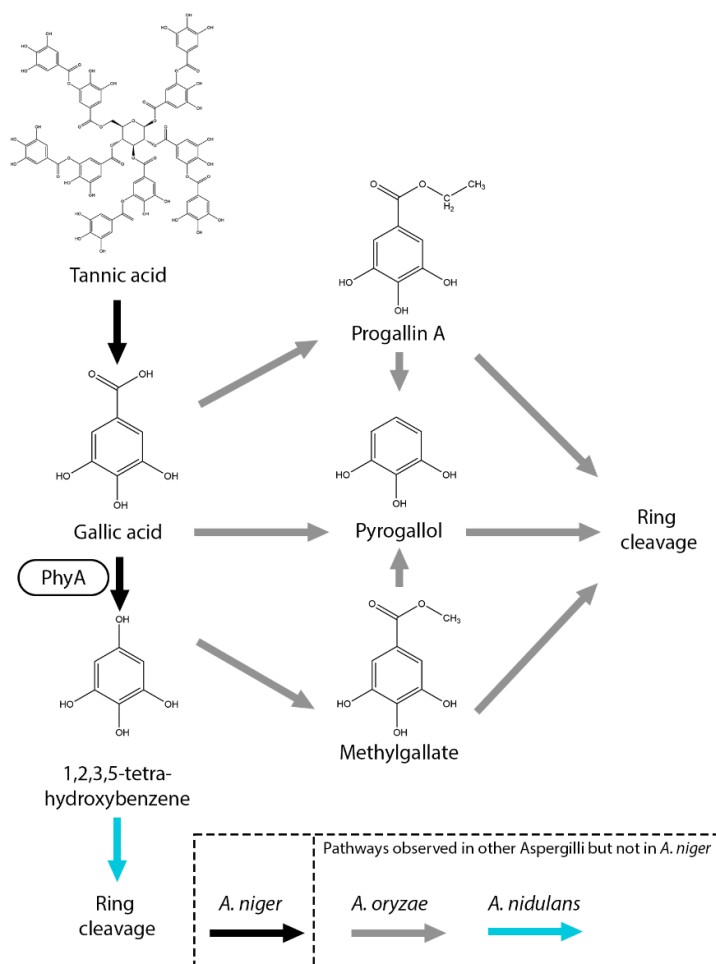


Figure 5. Gallic acid and related compounds metabolic pathway of *A. niger*. Black arrow represents pathways observed in *A. niger*. Boxes near an arrow represents the enzymes catalyzing the reactions. Pathways that were not observed in *A. niger* but in other *Aspergilli* are marked with gray (*A. oryzae*) and light blue (*A. nidulans*) arrows.

7. Gallic Acid Metabolic Pathways

Gallic acid (3,4,5-trihydroxybenzoic acid) is a commonly observed metabolite in the degradation of syringyl units [8] and is part of the polymeric aromatic compound tannic acid. It has been shown that many *Aspergillus* species can release gallic acid from tannic acid using tannases [78–80]. Gallic acid has anti-oxidative and antimicrobial properties and is applied in cosmetic, food and beverage, agricultural and pharmaceutical industry [81].

Currently, not many gallic acid metabolic pathways have been observed in fungi [8]. In *A. oryzae*, gallic acid is converted to pyrogallol (1,2,3-trihydroxybenzene), progallin A (ethyl 3,4,5-trihydroxybenzoate) and methyl gallate (Figure 5) [82]. It was suggested that these compounds were further processed by a ring opening reaction. In *A. niger* and *A. nidulans*, gallic acid is converted into 1,2,3,5-tetrahydroxybenzene, catalyzed by PhyA [65,83]. Deletion of 17 putative dioxygenase genes, including *prcA*, *hqdA*, and *crcA*, did not impair growth on gallic acid, suggesting that gallic acid is metabolized through an alternative pathway [83]. In *A. nidulans*, it has been proposed that 1,2,3,5-tetrahydroxybenzene is further converted to 5-hydroxydienelactone by a DUF3500 containing protein (AN10530) functioning as a putative dioxygenase [65]. Homologs of this gene are present in *A. niger* and remain to be studied.

8. Salicylic Acid Metabolic Pathways

Salicylic acid (2-hydroxybenzoic acid) is a well-known signaling molecule in plants and is involved in the defense against pathogens [84]. Currently, not many different fungal salicylic acid metabolic pathways have been elucidated. The most observed conversion is the hydroxylation of the carboxylic group of salicylic acid resulting in the formation of catechol (1,2-dihydroxybenzene). This conversion is catalyzed by the salicylic acid hydroxylase (ShyA) [85]. This conversion was observed in several aspergilli including *A. niger*, *A. japonicus*, *A. nidulans* and *A. terreus* but also in other fungi such as *Epichloë festucae* and *Sclerotinia sclerotiorum* (Figure 6) [9,63,85–88]. Alternatively, it has been proposed in *A. nidulans* and *Fusarium graminearum* that salicylic acid can also be hydroxylated to 2,3-dihydroxybenzoic acid (*o*-pyrocatechuic acid) [63,89] followed by a decarboxylation step to catechol catalyzed by 2,3-dihydroxybenzoic acid decarboxylase (DhbA) [85,90,91]. In *A. niger*, no evidence was found for the hydroxylation of salicylic acid to 2,3-dihydroxybenzoic acid since the deletion of *shyA* resulted in abolished growth on salicylic acid and deletion of *dhbA* did not result in reduced growth on salicylic acid [85]. Deletion of catechol 1,2-dioxygenase (CrcA) revealed that salicylic acid, 2,3-dihydroxybenzoic acid and catechol are converted towards *cis,cis*-muconic acid. *Cis,cis*-muconic acid is an interesting compound since it is a valuable chemical building block that can be used for polymer and drug production [92]. In *A. fumigatus*, phenol can be *ortho*-hydroxylated to catechol and *cis,cis*-muconic acid but also *para*-hydroxylated to hydroquinone (1,4-dihydroxybenzene) and hydroxyquinol [72].

Recently, an additional salicylic metabolic pathway was observed in *A. terreus* in which salicylic acid is hydroxylated to gentisic acid (2,5-dihydroxybenzoic acid) (Figure 6) [86]. Gentisic acid is further converted to maleylpyruvate by a putative gentisate 1,2-dioxygenase (ATEG_06714). In *N. crassa*, salicylic acid can also be reduced to salicylic aldehyde and salicyl alcohol [93]. Those pathways had not been observed in *Aspergilli*.

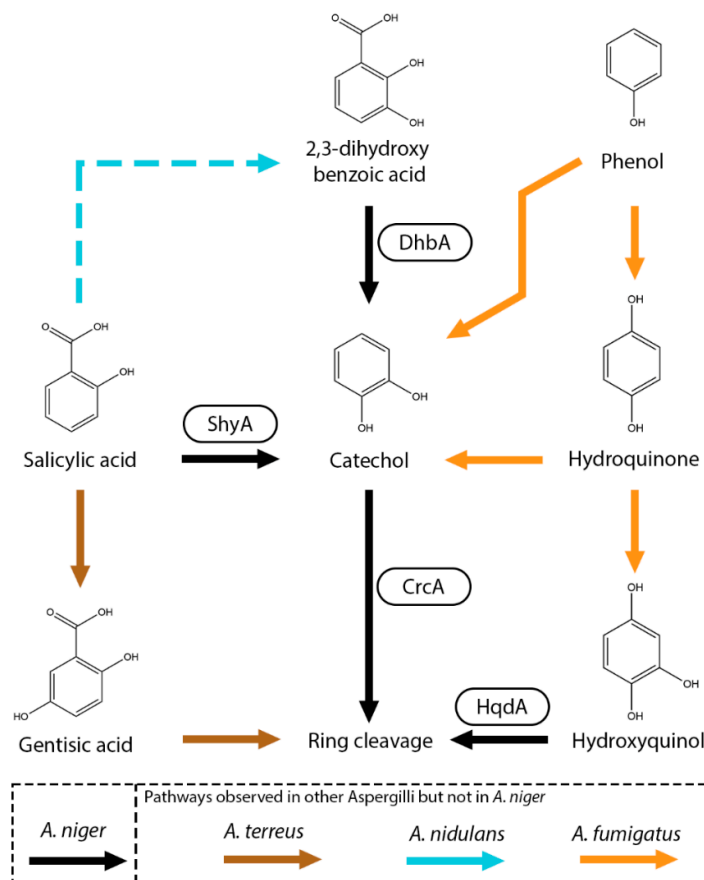


Figure 6. Salicylic acid metabolic pathway of *A. niger*. Boxes near an arrow represents the enzymes catalyzing the reactions. Suggested pathways are marked with dashed arrows. Pathways that were not observed in *A. niger* but in other Aspergilli are marked with brown (*A. terreus*), orange (*A. fumigatus*) or light blue (*A. nidulans*) arrows.

9. Ring Cleavage Pathways

The cleavage of the aromatic ring is a critical step in the detoxification and utilization of aromatic compounds as a carbon source. In fungi, most aromatic compounds are mainly converted towards catechol, hydroxyquinol, gallic acid, gentisic acid, protocatechuic acid or pyrogallol. These aromatic compounds are targeted by dioxygenases that catalyze the ring cleavage. The cleaved compounds are converted in multiple steps to acetyl-CoA, fumarate, oxaloacetate, pyruvate, or succinate and enter the TCA cycle [8,94]. In fungi, most aromatic compounds are cleaved by intradiol dioxygenases and uses non-heme Fe(III) to cleave the aromatic nucleus *ortho* to the hydroxyl substituents [95]. Extradiol dioxygenases using non-heme Fe(II) or other divalent metal ions to cleave the aromatic nucleus *meta* to the hydroxyl substituents, are less common in fungi [8].

Recently, multiple intradiol dioxygenases have been described in *A. niger*. Currently, four dioxygenases have been studied i.e. the catechol 1,2-dioxygenase (CrcA), hydroxyquinol 1,2-dioxygenase (HqdA), protocatechuic 3,4-dioxygenase (PrcA) and NRRL3_05330, a putative hydroxyquinol 1,2-dioxygenase [51,52,85,96]. Also, a methoxyhydroquinone 1,2-dioxygenase (MhdA) was identified which shares similarities with homogentisate 1,2-dioxygenases [71]. The role of NRRL3_05330 remains unknown since deletion did not result in any clear phenotype [85].

Protocatechuic acid is one of the main intermediates in the degradation of hydroxy phenolic compounds. It has been shown for several Aspergilli, that the aromatic ring of protocatechuic acid is cleaved into 3-carboxy-*cis,cis*-muconic acid and further converted through the β -ketoadipate pathway to acetyl-CoA and succinyl-CoA [63,94]. Several genes in this pathway were identified in *A. nidulans* and deletion of these genes resulted in reduced growth on protocatechuic acid [63]. More recently, the β -ketoadipate pathway has been further studied in *A. niger* resulting in the identification of four enzymes (3-carboxy-*cis,cis*-muconate cyclase (CmcA; NRRL3_02586), 3-carboxymuconolactone hydrolase/decarboxylase (ChdA; NRRL3_01409), β -ketoadipate:succinyl-CoA transferase (KstA; NRRL3_01886) and β -ketoadipyl-CoA thiolase (KctA; NRRL3_01526)) [94]. In addition, an essential protein (NRRL3_00837) was found involved in the β -ketoadipate pathway but its function remains unknown [94].

In *A. nidulans* and *A. niger*, catechol is cleaved by CrcA into *cis,cis*-muconic acid with subsequent conversion towards 3-oxoadipate. In *A. nidulans*, several genes involved in the degradation of catechol have been identified with whole-genome transcriptomics and proteomics [63]. Deletion of AN3895 (muconate isomerase), AN4061 (muconolactone isomerase), AN4531 (3-oxoadipate enol-lactone hydrolase) results in the formation of *cis,cis*-muconic acid, muconolactone and 3-oxoadipate enol-lactone, respectively, when grown on salicylic acid. Homologs of these genes were also identified in *A. niger* with whole-genome transcriptomics and were strongly induced by salicylic acid [85].

10. Regulation of Aromatic Pathways

Transcriptional regulators are important for the regulation of metabolic pathways in fungi. Many transcription factors involved in the regulation of sugar metabolic pathways have been described [97]. However, only a few transcriptional regulators involved in the regulation of metabolic pathways for aromatic compounds have been identified. Recently, a regulator/repressor (TanR/TanX) complex is involved in the regulation of gallic acid metabolic genes has been identified [83]. Deletion of *tanR* resulted in abolished growth on gallic acid and tannic acid indicating that this transcription factor regulates genes involved in the regulation of genes involved in the degradation of gallic acid and tannic acid. Whole-genome transcriptomic data of *A. niger* Δ *tanX* grown on fructose, revealed

that *phyA* is 2300 times more expressed than the parental strain. As mentioned above, cinnamic/sorbic acid metabolic pathway genes *cdcA* and *padA* are regulated by SdrA. More recently, it was shown that the weak acid regulator A and B (WarA and WarB) also play a role in the degradation of cinnamic acid and sorbic acid, however the exact role of WarA and WarB needs to be further studied [98].

Fatty acid regulator A (FarA) has a role in the degradation of fatty acids [99,100] but also hydroxycinnamic acids in *A. niger* [101]. Deletion of *farA* results in reduced growth on *p*-coumaric acid and abolished growth on ferulic acid and caffeic acid and the fatty acids valeric acid and oleic acid. A new far-like protein (FarD) was identified and deletion of it results in abolished growth on caffeic acid and ferulic acid and reduce growth on *p*-coumaric acid and *p*-hydroxybenzoic acid. Deletion of *farA* in *A. nidulans* results in reduced expression of *foxA* [99], which is also important for the degradation of hydroxycinnamic acids [34]. A putative FarA binding site has been observed in the promoter of *hscA* [101]. The exact role of FarA in the degradation of aromatic compounds need to be studied further but it is highly likely that it regulates multiple genes involved in the CoA-dependent beta-oxidative metabolic pathway.

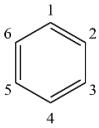
Recently, it was observed that the regulator FarB has a role in the degradation of benzoic acid, vanillic acid and the short fatty acid valeric acid, but not on *p*-coumaric acid, caffeic acid, protocatechuic acid or *p*-hydroxybenzoic acid [101]. It is possible that FarB is regulating *bphA* since no phenotypes are not observed on *p*-hydroxybenzoic acid and protocatechuic acid. Currently, it is remains unknown which genes are regulated by FarB.

11. Future Perspectives; Strategies for Studying and Identifying Aromatic Metabolic Pathways in Filamentous Fungi

The aromatic metabolic pathways of filamentous fungi belonging to the *Aspergillus* family have been better studied compared to other fungal species. However, still many aromatic pathways are have gaps or are unstudied. In addition, many of the enzymes involved in these pathways remain to be identified.

To study aromatic metabolic pathways in fungi, deletion of the ring cleaving dioxygenases is a straight forward approach, as these enzymes play critical roles in the metabolic pathway and deleting them causes severe phenotypes on aromatic compounds (Table 1) [8,65,71,83]. In *A. niger*, deletion of *prcA* gave clear phenotypes on many aromatic compounds related to the H-unit, while deletion of *hqdA* alone did not result in any phenotypes on the tested aromatic compounds [52]. However, the combined deletion of *prcA* and *hqdA* resulted in more severe phenotypes and even revealed the existence of an alternative pathway in *A. niger*. Deletion of *mhdA*, revealed that aromatic compound related to the G-unit are degraded to methoxyhydroquinone [71]. This pathway is important to created aromatic compounds such as vanillin and vanillic acid. Deletion of *crcA*, revealed that salicylic acid, 2,3-dihydroxybenzoic acid are degraded to catechol and that there is no alternative enzyme or pathway present in *A. niger* [85]. It appears that in *A. niger*, *ortho*-hydroxylated benzoic acids are converted to catechol, while *meta*- and *para*-hydroxylated benzoic acids are converted to protocatechuic acid, and hydroxyquinol. *Meta*-methoxylated compounds such as ferulic acid, vanillic acid and veratric acid are converted to methoxyhydroquinone.

Table 1. Phenotypes observed of *A. niger* dioxygenase deletion transformants on aromatic compounds.

													
Aromatic compound	1	2	3	4	5	6	$\Delta prcA$ [46,47,78]	$\Delta hqdA$ [46,47,78]	$\Delta prcA/hqdA$ [46,47]	$\Delta crcA$ [78]	$\Delta mhdA$ [71]	$\Delta 5330$ [78]	$\Delta 17$ [83]
H-unit related compounds													
Cinnamic acid	CH=CHC=OOH	H	H	H	H	H	++	-	++	-	-	-	n.d.

<i>p</i> -coumaric acid	CH=CHC=OOH	H	H	OH	H	H	+	-	++	-	-	-	++
Caffeic acid	CH=CHC=OOH	H	OH	OH	H	H	+	-	++	-	-	-	++
Benzaldehyde	CH=O	H	H	H	H	H	++	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Benzoic acid	C=OOH	H	H	H	H	H	++	-	++	n.d.	-	n.d.	n.d.
Benzyl alcohol	CH ₂ OH	H	H	H	H	H	++	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
<i>p</i> -hydroxybenzoic acid	C=OOH	H	H	OH	H	H	++	-	++	n.d.	-	n.d.	++
<i>p</i> -hydroxybenzaldehyde	CH=O	H	H	OH	H	H	++	-	++	n.d.	n.d.	n.d.	n.d.
<i>m</i> -hydroxybenzoic acid	C=OOH	H	OH	H	H	H	++	n.d.	n.d.	n.d.	-	n.d.	n.d.
Protocatechuic acid	C=OOH	H	OH	OH	H	H	+	-	++	-	-	-	++
Protocatechuic aldehyde	CH=O	H	OH	OH	H	H	+	-	++	n.d.	-	n.d.	n.d.
<i>p</i> -Anisic acid	C=OOH	H	H	OCH ₃	H	H	++	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
<i>p</i> -Anisyl alcohol	CH ₂ OH	H	H	OCH ₃	H	H	++	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
G-unit related compounds													
Coniferyl alcohol	CH=CHC=OOH	H	OCH ₃	OH	H	H	n.d.	n.d.	n.d.	n.d.	++	n.d.	n.d.
Ferulic acid	CH=CHC=OOH	H	OCH ₃	OH	H	H	-	-	-	-	++	-	-
Vanillic acid	C=OOH	H	OCH ₃	OH	H	H	-	-	-	n.d.	++	n.d.	-
Vanillin	CH=O	H	OCH ₃	OH	H	H	n.d.	n.d.	n.d.	n.d.	++	n.d.	n.d.
Vanillyl alcohol	CH ₂ OH	H	OCH ₃	OH	H	H	n.d.	n.d.	n.d.	n.d.	++	n.d.	n.d.
Veratric acid	C=OOH	H	OCH ₃	OCH ₃	H	H	-	n.d.	n.d.	n.d.	+	n.d.	n.d.
S-unit related compounds													
Gallic acid	C=OOH	H	OH	OH	OH	H	-	-	-	n.d.	n.d.	n.d.	-
Others													
Salicylic acid	C=OOH	OH	H	H	H	H	-	-	n.d.	++	n.d.	-	++
2,3-dihydroxybenzoic acid	C=OOH	OH	OH	H	H	H	-	-	n.d.	++	n.d.	-	n.d.
Catechol	OH	OH	H	H	H	H	-	-	-	++	n.d.	-	++
Gentisic acid	C=OOH	OH	H	H	OH	H	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	-

- no phenotype; + phenotype; ++ strong phenotype; n.d. not determined.

For the identification of genes encoding aromatic compound converting enzymes, whole genome transcriptomics is a strong tool that can aid in the identification of genes after exposure to aromatic compounds. Currently, most genes involved in the aromatic metabolism of *A. niger* and *A. nidulans* were identified using this approach [34,52,63,65,71,83,86]. In *A. niger*, a short exposure of 2h to an aromatic compound can results in a strong induction of aromatic compound metabolic genes. For example, salicylic acid metabolic genes; *shyA*, *dhbA* and *crcA*, are strongly upregulated by salicylic acid and by not *p*-hydroxyphenyl or guaiacylic aromatic compounds such as benzoic acid or *p*-coumaric acid, ferulic acid or vanillic acid. Similar observations were made for *vhyA* and *mhdA*, that are strongly induced by guaiacylic aromatic compounds while the CoA-dependent β-oxidative genes *hcsA*, *foxA*, *katA*, *theA*, *theB*, *theC* and *theD* are strongly induced by hydroxycinnamic acids. This demonstrated that these genes are not only rapidly upregulated but also induced by specific aromatic compounds.

12. Conclusions

In this review, we highlight recent advances in understanding aromatic metabolism in *Aspergillus niger*. It is important to note that *Aspergillus* species, in general, possess a remarkable diversity of aromatic metabolic pathways, reflecting their adaptability to different environmental conditions and substrates. Given the already substantial versatility observed in *Aspergillus* species, it is anticipated that even greater metabolic diversity will be uncovered when studying basidiomycetes, which are known for their complex and highly specialized systems for degrading aromatic compounds such as lignin.

Further exploration of fungal aromatic metabolism will not only enhance biotechnological production but also uncover new opportunities for bio-based solutions in pharmaceuticals, food, and fragrance industries. Currently, research is primarily focused on the production of aromatic compounds such as vanillin, gallic acid, catechol, and protocatechuic acid using microorganisms, given their widespread applications across various industries [81,102–104]. Advances in metabolic engineering, synthetic biology, and systems biology will enable the optimization of fungal strains for higher yields and broader compound diversity. Additionally, a deeper understanding of regulatory networks and enzyme mechanisms involved in aromatic biosynthesis could lead to innovative bioprocesses, reducing reliance on petrochemical-based production and promoting sustainability. As research continues to uncover novel and expand fungal aromatic metabolic pathways, the potential for industrial applications will continue to expand, reinforcing fungi as valuable cell factories for aromatic compounds.

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