A comparison between the homocyclic aromatic metabolic pathways from plant-derived compounds by bacteria and fungi

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Abstract
Aromatic compounds derived from lignin are of great interest for renewable biotechnical applications. They can serve in many industries e.g. as biochemical building blocks for bioplastics or biofuels, or as antioxidants, flavor agents or food preservatives. In nature, lignin is degraded by microorganisms, which results in the release of homocyclic aromatic compounds. Homocyclic aromatic compounds can also be linked to polysaccharides, tannins and even found freely in plant biomass. As these compounds are often toxic to microbes already at low concentrations, they need to be degraded or converted to less toxic forms. Prior to ring cleavage, the plant- and lignin-derived aromatic compounds are converted to seven central ring-fission intermediates, i.e. catechol, protocatechuic acid, hydroxyquinol, hydroquinone, gentisic acid, gallic acid and pyrogallol through complex aromatic metabolic pathways and used as energy source in the tricarboxylic acid cycle. Over the decades, bacterial aromatic metabolism has been described in great detail. However, the studies on fungal aromatic pathways are scattered over different pathways and species, complicating a comprehensive view of fungal aromatic metabolism. In this review, we depicted the similarities and differences of the reported aromatic metabolic pathways in fungi and bacteria. Although both microorganisms share the main conversion routes, many alternative pathways are observed in fungi. Understanding the microbial aromatic metabolic pathways could lead to metabolic engineering for strain improvement and promote valorization of lignin and related aromatic compounds.

Keywords
Aromatic metabolism, fungus, lignin, platform chemicals, plant-derived homocyclic aromatic compounds

Abbreviations

Acar	Aryl carboxylic acid reductase
AroY	Protocatechuate decarboxylase
BadA	Benzoate-CoA ligase
BadDEFG	Benzoate-CoA reductase subunits D, E, F and G
BagI	Gentisate 1,2-dioxygenase
BagL	L-cysteine-dependent maleylpyruvate isomerase
BagK	Fumarylpyruvate hydrolase
BclA	Benzoate-CoA ligase
BenABC	Benzoate 1,2-dioxygenase subunits A, B and C
BenD	Benzoate 1,2-dioxygenase subunit D
BphA	Benzoate 4-monooxygenase
BsdBCD	Phenolic acid decarboxylase subunits B, C and D
BzuA	Benzoate 4-monooxygenase
CalA	Coniferyl alcohol dehydrogenase
CalB	Coniferyl aldehyde dehydrogenase
CatA1	Catechol 1,2-dioxygenase 1
CatA2	Catechol 1,2-dioxygenase 2
CatB	Muconate cycloisomerase
CatC	Muconolactone Delta-isomerase
CatD	3-oxoadipate enol-lactonase 2
CatI	3-oxoadipate CoA-transferase subunit A
CatJ	3-oxoadipate CoA-transferase subunit B
ChqB	Hydroxyquinol 1,2-dioxygenase
CMLE	3-carboxy-*cis,cis*-muconate lactonizing enzyme
CouL	*p*-Hydroxycinnamoyl-CoA synthetase
CouM	*p*-Hydroxycinnamoyl-CoA hydratase
CouN	*p*-Hydroxyphenoxy-β-hydroxyacyl-CoA dehydrogenase
CouO	*p*-Hydroxyphenoxy-β-ketoacyl-CoA hydrolase
CprA	Cytochrome P450 reductase
Cso2	Isoeugenol oxygenase 2
DesA	Syringate *o*-demethylase
DesB	Gallate dioxygenase
DesV	Aldehyde dehydrogenase
DesZ	3-*o*-methylgallate 3,4-dioxygenase
DhbA	2,3-dihydroxybenzoic acid 3,4-dioxygenase
DmpB	Catechol 2,3-dioxygenase
DmpC	2-hydroxymuconic semialdehyde dehydrogenase
DmpD	2-hydroxymuconate semialdehyde hydrolase
DmpE	2-oxopent-4-enoate hydratase
DmpF	Acetaldehyde dehydrogenase
DmpG	4-hydroxy-2-oxovalerate aldolase
DmpH	4-oxalocrotonate decarboxylase
DmpI	2-hydroxymuconate tautomerase
DmpLMNOP	Phenol hydroxylase components L, M, N, O and P
Ech	Enoyl-CoA hydratase/aldolase
EhyA	Eugenol hydroxylase alpha-subunit
EhyB	Eugenol hydroxylase beta-subunit
EugO	Eugenol oxidase
Fcs	Feruloyl-CoA synthase
Fdc1	Ferulic acid decarboxylase

FerA	Feruloyl-CoA synthase
FerB	Enoyl-CoA hydratase/aldolase
Fph1	Fumarylpyruvate dioxygenase
GalA	Gallate dioxygenase
GalB	4-oxalmesaconate hydratase
GalC	4-carboxy-4-hydroxy-2-oxoadipic acid aldolase
GalD	4-oxalomesaconate tautomerase
Gdc	Gallic acid decarboxylase
Gdx1	Gentisate dioxygenase
HbaA	4-hydroxybenzoate-CoA ligase
HbaBCD	4-hydroxybenzoyl-CoA reductase subunits B, C and D
HcaB	Dihydrodiol dehydrogenase
HcaEFCD	3-phenylpropionate/cinnamic acid dioxygenase subunits E, F, C and D
HcrBCD	4-hydroxybenzoyl-CoA reductase subunits B, C and D
Hdq1	Hydroxyquinol dioxygenase
Hdq2	Catechol 1,2-dioxygenase
Hdx1	Hydroxyquinol dioxygenase
HMPHP-SCoA	4-hydroxy-3-methoxyphenyl-β-hydroxypropionyl-CoA
HMPKP-SCoA	4-hydroxy-3-methoxyphenyl-β-ketopropionic acid-CoA
HpaB	4-hydroxyphenylacetate 3-hydroxylase monooxygenase B
HpaC	4-hydroxyphenylacetate 3-hydroxylase oxidoreductase C
HPHP-SCoA	3-hydroxy-3-(*p*-hydroxyphenyl) propyl-CoA
IvaA	Isovanillic acid demethylase
IvaB	Isovanillic acid demethylase reductase
LigAB	Protocatechuate 4,5-dioxygenases alpha chain and beta chain
LigC	4-carboxy-2-hydroxymuconate-6-semialdehyde dehydrogenase
LigI	2-pyrone-4,6-dicarboxylate hydrolase
LigJ	4-oxalmesaconate hydratase
LigK	4-carboxy-4-hydroxy-2-oxoadipate aldolase
LigM	Vanillate/3-*o*-methylgallate *o*-demethylase
LigU	4-oxalomesaconate tautomerase
LinE	Chlorohydroquinone 1,2-dioxygenase
LinF	Maleylacetate reductase
LpdC	Gallate decarboxylase
Mci1	*Cis,cis*-muconate cycloisomerase
MhpB	2,3-dihydroxicinnamic acid 1,2-dioxygenase
Mli1	Muconolactone isomerase
Mnx1	4-hydroxybenzoate 1-hydroxylase
Mnx2	3-hydroxybenzoate 6-hydroxylase
Mnx3	Phenol 2-monooxygenase
MobA	3-hydroxybenzoate-4-monooxygenase
NagG	Salicylate 5-hydroxylase large oxygenase component
NagH	Salicylate 5-hydroxylase, small oxygenase component
NahG	Salicylate hydroxylase (decarboxylating)
Oel1	3-oxoadipate enol-lactonase
Osc1	3-oxoadipate CoA-transferase
Pad	Phenolic acid decarboxylase
Pad1	Flavin prenyltransferase
PadC	Phenolic acid decarboxylase
PcaB	3-carboxy-*cis,cis*-muconate cycloisomerase
PcaC	4-carboxymuconolactone decarboxylase

PcaD	3-oxoadipate enol-lactonase 1
PcaF	Beta-ketoadipyl-CoA thiolase
PcaGH	Protocatechuate 3,4-dioxygenases alpha chain and beta chain
PcaI	3-oxoadipate CoA-transferase subunit A
PcaJ	3-oxoadipate CoA-transferase subunit B
PhgA	*p*-hydroxybenzoyl-CoA hydroxylase
PhgB	Gentisyl-CoA thioesterase
PhgC	*p*-hydroxybenzoyl-CoA ligase
PhhY	Phenol 2-hydroxylase
PobA	4-hydroxybenzoate-3-hydroxylase
PraA	Protocatechuate 2,3-dioxygenase
PraB	2-hydroxymuconate-6-semialdehyde dehydrogenase
PraC	2-hydroxymuconate tautomerase
PraD	4-oxalocrotonate decarboxylase
PraE	2-hydroxypenta-2,4-dienoate hydratase
PraF	4-hydroxy-2-oxovalerate aldolase
PraG	Acetaldehyde dehydrogenase
PraH	5-carboxy-2-hydroxymuconate-6-semialdehyde decarboxylase
PraI	4-hydroxybenzoate-3-hydroxylase
Sam5	4-coumarate 3-hydroxylase
Sdc	Salicylic acid decarboxylase
SdgA	Salicylyl-AMP ligase
SdgB	Salicylyl-CoA synthetase
SdgC	Salicylyl-CoA 5-hydroxylase
SdgD	Gentisate 1,2-dioxygenase
Sdo	Salicylate 1,2-dioxygenase
StyA	Styrene-monooxygenase A
StyB	Styrene-monooxygenase B
StyC	Styrene-oxide isomerase
StyD	Phenylacetaldehyde dehydrogenase
TCA	Tricarboxylic acid cycle
VanA	Vanillate *o*-demethylase oxygenase subunit
VanB	Vanillate *o*-demethylase oxidoreductase
VaO	Vanillyl-alcohol oxidase
VdcC	Vanillate decarboxylase
Vdh	Vanillin dehydrogenase
VerA	Veratric acid *o*-demethylase
VerB	Veratric acid *o*-demethylase oxidoreductase
VprA	Vinylphenol reductase
XlnD	3-hydroxybenzoate 6-hydroxylase
XylE	Catechol 2,3-dioxygenase
XylF	2-hydroxymuconate semialdehyde hydrolase
XylG	2-hydroxymuconic semialdehyde dehydrogenase
XylK	4-hydroxy-2-oxovalerate aldolase
YfmT	Benzaldehyde dehydrogenase

1. Introduction

The growing global human population creates an increasing demand for alternative energy and renewable raw material resources. Lignin is the most complex and one of the most abundant polymers on earth. It consists of the aromatic monolignols coniferyl alcohol, *p*-coumaryl alcohol and sinapyl alcohol that form guaiacyl, *p*-hydroxyphenyl and syringyl (G, H and S) units in lignin (Fig. 1), respectively (Freudenberg, 1965; Humphreys and Chapple, 2002). Thus, it is a rich resource of renewable aromatic compounds that could be used as a basis for biotechnological applications. In plant biomass, aromatic compounds are also found in tannins, linked to polysaccharides and are even found freely (Mäkelä *et al.,* 2015; Mcleod, 1974; Newby *et al.,* 1980). Microbial degradation of lignin results in the release of aromatic compounds, such as ferulic acid and vanillin, which are toxic already at low concentrations for most microorganisms (Adeboye *et al.,* 2014; Friedman *et al.,* 2003; Guiraud *et al.,* 1995; Lima *et al.,* 2017). In order to survive this toxicity, the aromatic compounds need to be degraded or converted to non- or less toxic compounds by the microorganism. This is usually followed by the cleavage of the aromatic ring to eliminate toxicity, resulting in compounds that can be used as a carbon source. Lignin degradation and modification by basidiomycete white-rot and brown-rot fungi has been studied for decades and most of the resulting products are funnelled to the central (ring-fission) intermediates (Mäkelä *et al.*, 2015). Less is known about the role of bacteria in this process, eventhough bacteria that are able to convert or degrade small lignin-derived aromatic compounds have been described previously (Bugg *et al.,* 2011a, Brown and Chang, 2014). Currently, much research is performed in the degradation of small lignin-derived aromatic compounds, especially for the alpha-proteobacterium *Sphingomonas paucimobilis* SYK-6, which was later classified as *Sphingobium* sp. strain SYK-6 (Kamimura *et al.,* 2017; Sonoki *et al.,* 2009).

Plant- and lignin-derived aromatic compounds have great industrial and commercial potential since they can be used for many applications, such as biochemical building blocks for biorefineries, plastics, drugs and cosmetics, and as food additives, such as flavor agents, preservatives or antioxidants (Arif, 2015; Kaur and Chakraborty, 2013; McKenna *et al.,* 2013; Tsuge *et al.,* 2016). The need for plastics increases each year, and plastics derived from renewable aromatic compounds are a sustainable way to supply this increasing demand. Styrene is an example of an aromatic compound, which can be used as a precursor to produce plastics such as acrylonitrile butadiene styrene (ABS), polystyrene and styrene acrylonitrile resin (SAN). Styrene is chemically synthesized from phenylalanine however, in nature styrene can also obtained through the decarboxylation of cinnamic acid (Plumridge *et al.,* 2008, Plumridge *et al.,* 2010, Richard *et al.,* 2015). Another promising industrial niche is the increasing consumer demand for ''naturally'' produced aromatic compounds. For example, vanillin is one of the most important flavor and fragrance compounds in food and cosmetics. Less than 1% of the produced vanillin derives from natural sources, while the majority is produced from guaiacol by chemical synthesis (Gallage and Møller, 2018; Krings and Berger, 1998; Walton *et al.,* 2003). To efficiently produce aromatic compounds such as vanillin or styrene, microorganisms have been genetically modified to produce desired compounds from glucose through the shikimate pathway (Lee and Wendisch, 2017; McKenna and Nielsen, 2011) or through lignin valorization (Barton *et al.,* 2018; Wu *et al.,* 2017).

In the past decades, many studies aimed to identify the pathways, and enzymes involved in the aromatic metabolism of diverse microorganisms have been reported. Recently, aromatic metabolism of filamentous fungi has been reviewed (Mäkelä *et al.,* 2015), but an extensive comparison between fungal and bacterial aromatic metabolism has not been made. At present, only a few fungal enzymes involved in aromatic metabolism have been identified and characterized, whereas more enzymes have been described in bacteria (Tables S1 and S2). A thorough comparison of aromatic metabolism between the two kingdoms will be of great help in identifying new fungal aromatic metabolic enzymes and pathways. This will also greatly expand the potential of lignin and its aromatic compounds in biotechnological applications. This review focuses on the identified aromatic metabolic enzymes and

in particular the similarities and differences of conversion pathways between fungi and bacteria. Due to the current interest in biorefinery of lignin-based aromatics, this review has a special focus on industrially relevant compounds derived from lignin and related non-lignin derived homocyclic aromatic compounds released during plant biomass degradation or found ubiquitously in plants. Only plant-derived homocyclic aromatic metabolic pathways are discussed in this review and not other pathways, such as conversion of xylene and toluene. Aromatic metabolic pathways such as the homogentisate or homoprotocatechuate pathway are not included since these are uncommon pathways and are contributing to the recycling of uncommon compounds. For reviews on conversion of lignin-derived oligomeric aromatic compounds, we suggest the following reviews, Bugg *et al.,* 2011b, Mäkelä *et al.,* 2015 and Kamimura *et al.,* 2017.

2. Aromatic metabolism in bacteria and fungi

Several possible conversion pathways of homocyclic aromatic compounds are described in fungi and bacteria. However, no complete overview of the various aromatic metabolic pathways has been described for a single fungus (Mäkelä *et al.*, 2015). Here, we discuss the pieces of the puzzle that have already emerged from experimental observations in fungi as compared to bacteria. The review is separated into two main parts. The first part (2.1-2.8) describes the conversion pathways of the homocyclic aromatic compounds that are derived from lignin and closely related compounds, which are released during plant biomass degradation or found ubiquitously in plant biomass (Fig. 1). Enzymes involved in these pathways are summarized in Table S1. The second part (2.9) describes the ring cleavage process through the seven central ring-fission intermediates, catechol, protocatechuic acid, hydroxyquinol, hydroquinone, gentisic acid, gallic acid and pyrogallol, and the significance of this conversion for cellular metabolism (Fig. 1). Enzymes involved in these pathways are summarized in tables S1 and S2. It should be noted that some of the referred microorganisms are unable to use aromatic compounds as a sole carbon source. Their detoxicfication mechanisms do not imply ring cleavage and are therefore likely to use a different mechanism.

2.1 Coniferyl alcohol and eugenol metabolic pathways

Coniferyl alcohol is one of the three building blocks found in lignin. The conversion pathway specific to coniferyl alcohol has been characterized in bacteria, but it is not known in fungi (Fig. 2). In the first bacterial pathway, coniferyl alcohol is converted to ferulic acid via the intermediate coniferyl aldehyde. In *Pseudomonas* sp. strain HR199, the step from coniferyl alcohol to coniferyl aldehyde is catalyzed by coniferyl alcohol dehydrogenase (CalA), after which coniferyl aldehyde is converted to ferulic acid by coniferyl aldehyde dehydrogenase (CalB) (Overhage *et al.,* 1999, Overhage *et al.,* 2003). In *Pseudomonas aeruginosa* an alternative pathway was observed, in which coniferyl aldehyde is converted to 5-hydroxyconiferylaldehyde by 4-hydroxyphenylacetate 3-hydroxylase consisting of a monooxygenase (HpaB) and an oxidoreductase (HpaC) component (Chakraborty *et al.,* 2009; Furuya and Kino, 2014). In *P. aeruginosa* and *Burkholderia xenovorans*, HpaBC are also able to convert 4-hydroxyphenylacetate to homoprotocatechuic acid (Chakraborty *et al.,* 2009; Méndez *et al.,* 2011).

The aromatic compound eugenol is of high industrial interest since it can be used for the production of ferulic acid and vanillin. Eugenol is released from Kraft lignin and low sulfonate lignin during 160^{o}C treatment (Varanasi *et al.,* 2013). In addition, high concentrations of eugenol, which is synthesized from coniferyl alcohol, can be extracted from clove oil making it a cheap precursor for the production of ferulic acid and vanillin. In *Pseudomonas* sp. strain OPS1, eugenol is converted to coniferyl alcohol by eugenol hydroxylases EhyA and EhyB (Brandt *et al.,* 2001), while *Rhodococcus* sp. strain RHA1 uses eugenol oxidase (EugO) to catalyze the oxidation of eugenol to coniferyl alcohol (Jin *et al.,* 2007). More recently, EugO was shown to have a broad substrate range as it can also convert the aromatic compounds zingerone, raspberry ketone and 5-indanol (Nguyen *et al.,* 2016). The conversion of eugenol to vanillin through the intermediates coniferyl alcohol, coniferyl aldehyde and ferulic acid was also observed in *Bacillus safensis* (Singh *et al.,* 2018). In addition, *Bacillus cereus* PN42 has been shown

to convert eugenol to *p*-vinyl guaiacol in multiple steps without the intermediate ferulic acid (Kadakol and Kamanavalli, 2010), but the enzymes involved in this conversion have not yet been identified.
In fungi, there have been no pathways described in which coniferyl alcohol is converted. However, the basidiomycete *Pycnoporus cinnabarinus* was reported to be able to reduce ferulic acid to coniferyl aldehyde and coniferyl alcohol (Falconnier *et al.,* 1994). This was also observed for the basidiomycete *Trametes* sp. and was suggested for the ascomycete *Aspergillus japonicus* (Nishida and Fukuzumi, 1978; Milstein *et al.,* 1983). In the yeast *Saccharomyces cerevisiae*, coniferyl aldehyde is directly converted to ferulic acid, but enzymes involved in this conversion are not known (Adeboye *et al.,* 2015). In the ascomycete *Penicillium simplicissimum*, vanillyl-alcohol oxidase (VaO) catalyzes the hydroxylation of eugenol to coniferyl alcohol (de Jong *et al.,* 1992; Van den Heuvel *et al.,* 2002). The physiological substrate of VaO has been proposed to be 4-methoxy(methylphenol) and is the only substrate found so far that induces the production of VaO (Fraaije *et al.,* 1997). The aromatic pathway by which eugenol is converted to *p*-vinyl guaiacol was also observed in the basidiomycete *Schizophyllum commune*, and the ascomycetes *Paecilomyces variotii* and *Fusarium solani* (Ghosh *et al.,* 2005; Nazareth and Mavinkurve, 1986; Rahouti *et al.,* 1989). The enzyme catalyzing this conversion remains unknown in both fungi and bacteria.

In summary, bacteria have been shown to convert the lignin building block coniferyl alcohol into ferulic acid and 5-hydroxyconiferylaldehyde, while in fungi no conversions of coniferyl alcohol have been observed. Despite that coniferyl alcohol is not a mainstream lignin degradation product, it is likely that fungi can convert coniferyl alcohol since both fungi and bacteria can synthesize coniferyl alcohol from eugenol, and conversion pathways for ferulic acid, a derivative of coniferyl alcohol, have been observed. To determine whether a metabolic system for the conversion of coniferyl alcohol exists in fungi, experimental confirmation is needed. Insufficient information is available about the conversion of coniferyl alcohol in fungi however, in bacteria it appears that the main pathway is towards ferulic acid.

2.2 Ferulic acid metabolic pathways

Ferulic acid is an aromatic compound derived from the monolignol coniferyl alcohol and is released when lignin is degraded by *Bacillus* sp*.*, *Pseudomonas putida* and *Rhodococcus jostii* (Bugg *et al.,* 2011b; Raj *et al.,* 2007). In addition, ferulic acid is also present in polysaccharides, such as xylan and pectin, and can form crosslinks between them and between polysaccharides and lignin through dimerization of ferulic acid (Dilokpimol *et al.,* 2016; Mäkelä *et al.,* 2015). Ferulic acid has diverse pharmaceutical applications because of its antioxidant, anti-inflammatory, and antimicrobial properties (Ou and Kwok, 2004). In food industry, ferulic acid is mainly used as a precursor for vanillin production. The conversion of ferulic acid to vanillin is a well-studied biotransformation and is described in detail for many bacterial species such as *Amycolatopis* sp*., Bacillus subtilis, Pseudomonas fluorescens, P. putida* and *R. jostii* (Achterholt *et al.,* 2000; Chen *et al.,* 2012; Graf *et al.,* 2016; Narbad and Gasson, 1998; Overhage *et al.,* 1999a; Overhage *et al.,* 1999b; Plaggenborg *et al.,* 2003, Plaggenborg *et al.,* 2006). Seven pathways are described for the conversion of ferulic acid in which two result in vanillin (Fig. 3):

1. The conversion of ferulic acid to feruloyl-SCoA by feruloyl-CoA synthase (Fcs, FerA, Atu1416) or *p*-hydroxycinnamoyl-CoA synthetase (CouL) followed by:
    a. Non-β-oxidative decarboxylation in which feruloyl-SCoA is converted to 4-hydroxy-3-methoxyphenyl-β-hydroxypropionyl-CoA (HMPHP-SCoA) and then to vanillin by Enoyl-CoA hydratase/aldolase (Ech, FerB).
    b. β-oxidative decarboxylation in which feruloyl-SCoA is converted to HMPHP-SCoA and then to 4-hydroxy-3-methoxyphenyl-β-ketopropionic acid-CoA (HMPKP-SCoA), before conversion to vanillic acid.
2. The non-oxidative decarboxylation of ferulic acid to *p*-vinyl guaiacol followed by:
    a. Conversion to vanillin catalyzed by an iron-dependent isoeugenol oxygenase (Cso2).

b. Conversion to vanillic acid.
c. Oxidation to *p*-hydroxyphenylethanol.
d. Reduction to 4-ethylguaiacol catalyzed by vinylphenol reductase (VprA).
e. Conversion to guaiacol.

Pathway 1a has been described in the bacteria *Amycolatopsis* sp. ATCC39116, *R. jostii* RHA1, *Streptomyces* sp. strain V-1, *Sphingobium* sp. strain SYK-6, *P. fluorescens* and *P. putida* KT2440 (Gasson *et al.,* 1998; Masai *et al.,* 2002; Otani *et al.,* 2014; Priefert *et al.,* 1999; Yang *et al.,* 2013), and in the yeast *Debaryomyces hansenii* and *Rhodotorula rubra* (Huang *et al.,* 1993; Mathew *et al.,* 2007). Recently, this pathway was also suggested in *Aspergillus luchuensis* (Taira *et al.,* 2018). Pathway 1b was described in *Agrobacterium fabrum* and *R. jostii* (Campillo *et al.,* 2014; Otani *et al.,* 2014). The suggested enzymes CouM, CouN and CouO involved in this pathway are based on transcriptome data (Fig. 3) (Otani *et al.,* 2014). Deletion of the Atu1417, Atu 1415 and Atu1421 in *A. fabrum* resulted in the accumulation of the intermediates (Fig. 3) (Campillo *et al.,* 2014).

Pathway 2a has been observed in *Bacillus coagulans*, *B. cereus*, *B. subtilis, P. fluorescens* and many other bacterial species (Karmakar *et al.,* 2000; Mishra *et al.,* 2013). In *B. subtilis*, a phenolic acid decarboxylase (PadC) catalyzes transformation of ferulic acid, caffeic acid and *p*-coumaric acid, but not cinnamic acid to the *p*-vinyl form (Cavin *et al.,* 1997b, Cavin *et al.,* 1998; Tran *et al.,* 2008). Cinnamic acid lacks the OH group at C4 of the aromatic ring that is present in the other three compounds, suggesting that this is essential for the action of PadC. Close homologs of PadC, for example ferulic acid decarboxylase (Fdc) from *Bacillus pumilus*, are also involved in the decarboxylation of ferulic acid and *p*-coumaric acid. However, the PadC homolog (Pdc) from *Lactobacillus plantarum* was reported to decarboxylate *p*-coumaric acid and caffeic acid, but not ferulic acid (Cavin *et al.,* 1997a; Zago *et al.,* 1995), which suggests differences in substrate specificity despite high sequence homology between these decarboxylases. In the ascomycetes *A. luchuensis* and *Isaria farinosa,* the phenolic acid decarboxylase (Pad) involved in this conversion was characterized (Linke *et al.,* 2017; Maeda *et al.,* 2018). In the yeast *S. cerevisiae*, ferulic acid decarboxylase (Fdc1) together with the flavin prenyltransferase (Pad1) can convert ferulic acid to *p*-vinyl guaiacol (Lin *et al.,* 2015; Mukai *et al.,* 2010), while dihydroferulic acid has been suggested to be a conversion intermediate (Adeboye *et al*., 2015, 2017). Recently, the iron-dependent oxygenase Cso2 catalyzes the conversion of *p*-vinyl guaiacol to vanillin has been identified in the bacteria *Caulobacter segnis* (Fig. 3) (Furuya *et al.,* 2014). Expression of Cso2 together with Fdc of *B. pumilus* in *Escherichia coli* resulted in the conversion of ferulic acid to *p*-vinyl guaiacol and further to vanillin. Pathway 2a has been reported for the filamentous fungi *S. commune*, *P. variotii* and *F. solani*, and the yeasts *Brettanomyces anomalu*s, *D. hansenii* and *S. cerevisiae* (Edlin *et al.,* 1995; Ghosh *et al.,* 2005; Mathew *et al.,* 2007; Nazareth and Mavinkurve, 1986; Rahouti *et al.,* 1989; Tsujiyama and Ueno, 2008). Pathway 2b has been observed in the filamentous ascomycete fungus *Myceliophthora thermophila*, suggesting the conversion of *p*-vinyl guaiacol to vanillic acid instead of vanillin (Topakas *et al.,* 2003). A similar pathway was also described for the diploid ascomycete fungus *Aspergillus niger* DAR2, derived from parasexual crosses with two haploid mutants of *A. niger* C28B25 (Baqueiro-Peña *et al.,* 2010; Montiel-González *et al*., 2002). This pathway was not detected in *A. niger* C28B25 and was suggested to be due to differential regulation of ferulic acid converting enzymes (Baqueiro-Peña *et al.,* 2010). Pathway 2c has been observed in *S. cerevisiae*, in which *p*-vinyl guaiacol was not converted to vanillic acid or vanillin, but instead was suggested to be oxidized to *p*-hydroxyphenylethanol, followed by dehydration to phenethyl alcohol (Adeboye *et al.,* 2015). Pathway 2d has been observed in the several yeasts, such as *Candida* species, *Dekkera bruxellensis, D. anomala* and *Pichia guillermondii* (Suárez *et al.,* 2007). The biological function of the vinylphenol reductase of *D. bruxellensis* has been demonstrated by heterologous expression in *S. cerevisiae* (Romano *et al.,* 2017). Recently, this conversion has been described in *L. plantarum* where it is catalyzed by vinylphenol reductase (VprA) (Santamaria *et al.,* 2018). Pathway 2e has been observed in *S. cerevisiae* in which *p*-vinyl guaiacol is directly converted to

guaiacol (Adeboye *et al.,* 2017). Guaiacol is released from lignin by the bacteria *Aneurinibacillus aneurinilyticus, Bacillus* sp. and *Paenibacillus* sp. (Raj *et al.,* 2007). The conversion of ferulic acid to vanillic acid was observed in the oleaginous yeasts, *Cryptococcus curavatus, Rhodosporium toruloides and Trichosporon guehoae*, however which pathway is used remains unknown (Sànchez i Nogué *et al*., 2018).

Five alternative pathways in which ferulic acid is transformed to different aromatic compounds have been observed (Fig 3):

3. 5-Hydroxylation of ferulic acid to 5-hydroxyferulic acid by HpaBC.
4. 2-Hydroxylation of ferulic acid to 2-hydroxyferulic acid.
5. Demethylation of ferulic acid to caffeic acid.
6. Demethylation of ferulic acid to *p*-coumaric acid.
7. Reduction of ferulic acid to coniferylaldehyde followed by reduction to coniferyl alcohol.

Pathway 3 showed that HpaBC of *P. aeruginosa* can catalyze the conversion of ferulic acid to 5-hydroxyferulic acid (Furuya and Kino, 2014). This pathway has also been observed in the basidiomycete *Lentinula edodes* (Crestini and Sermanni, 1994). In addition, 5-hydroxyferulic acid is further converted to 3,4,5-trihydroxycinnamic acid after which the aromatic ring is cleaved. Pathway 4 has been observed in *L. edodes* in which ferulic acid is converted to 2-hydroxyferulic acid and further to 2,3,4-trihydroxycinnamic acid followed by the cleavage of the aromatic ring (Crestini and Sermanni, 1994). Pathway 5 has been observed in the bacteria *Enterobacter cloacae* and *Streptomyces albogriseolus*, and the ascomycete *Penicillium rubens,* in which ferulic acid is demethylated to caffeic acid and further converted to protocatechuic acid (Buraimoh *et al.,* 2017; Grbić-Galić and La Pat-Polasko, 1985; Tillett and Walker, 1990). The enzymes catalyzing these reactions have not yet been identified. Pathway 6 was suggested in the yeast *S. cerevisiae* (Adeboye *et al.,* 2017). Pathway 7 has been observed in the basidiomycete *P. cinnabarinus,* which reduces ferulic acid to coniferyl aldehyde and coniferyl alcohol (Fig. 2, 3) (Falconnier *et al.,* 1994). The enzymes catalyzing these alternative pathways are not known.

In summary, both bacteria and filamentous fungi are able to produce vanillin from ferulic acid while most yeasts are not known to produce vanillin. This is probably because vanillin has a strong toxic effect on yeast (Shen *et al.,* 2014). At this moment, *D. hansenii* is the only yeast reported to produce vanillin from ferulic acid, but only at low concentrations (Mathew *et al.,* 2007). Nevertheless, yeasts are being used to produce vanillin from dihydroshikimic acid through engineered biosynthetic pathways in which genes from *Podospora pausiceta*, *Nocardia* sp., *E. coli* and *Homo sapiens* are used (Hansen *et al.,* 2009). To avoid the toxicity of vanillin, a glucosylation step was added to produce the less toxic compound vanillin β-D-glucoside resulting in higher vanillin yields. Interestingly, this strategy to avoid toxicity of vanillin was also observed in *A. luchuensis* (Taira *et al.,* 2018). Low tolerance against the toxicity of vanillin is also a major issue in the production of vanillin in microbial production systems (Fleige and Steinbüchel, 2014; Fleige *et al.,* 2016; Fitzgerald *et al.,* 2003, Kaur and Chakraborty, 2013). Another issue is the rapid detoxification of vanillin in their systems. Therefore, many genetic modifications, such as deletions, are needed to increase the metabolic flux and the production of vanillin from eugenol or ferulic acid (Fleige *et al.,* 2016; Gallage and Møller, 2015, Hansen *et al.,* 2009; Kaur and Chakraborty, 2013; Overhage *et al.,* 2003; Priefert *et al.,* 1999; Priefert *et al.,* 2001). From ferulic acid a yield of 19.2 g/l vanillin was obtained while from eugenol around 10 g/l vanillin was obtained (Gallage and Møller, 2015). In the plant *Vanilla planifolia*, ferulic acid is directly converted to vanillin by vanillin synthase (VpVAN) (Gallage *et al.,* 2014), but direct conversion of ferulic acid to vanillin has never been reported for bacteria or fungi. In addition, no homolog of VpVAN was found in fungal genomes, confirming that this conversion is probably not present in fungi. Currently, multiple ferulic acid metabolic pathways have been observed in fungi, but only one enzyme, Pad of *A. luchuensis* and *I. farinosa*, has been characterized (Linke *et al.,* 2017; Maeda *et al.,* 2018). Many observations of the conversion of ferulic acid to vanillic acid through non-β-oxidative decarboxylation

and non-oxidative decarboxylation were made. It is likely that these two pathways are the main ferulic acid metabolic pathways in microorganisms.

2.3 Vanillin, vanillic acid and related metabolic pathways

Degradation of spruce wood lignin by *P. chrysosporium* results in the release of vanillin (Chen *et al*., 1982). Vanillin was also released from kraft lignin by the bacterium *Aeromonas formicans* and from alkaline lignin by the bacterium *Bacillus ligniniphilus* (Gupta *et al.,* 2001; Zhu *et al.,* 2017). Due to the high industrial interest, much research has been performed on the vanillin metabolic pathways in bacteria and fungi. Currently, two pathways are known for the conversion of vanillin (Fig. 4):

1. The oxidation of vanillin to vanillic acid by vanillin dehydrogenase (Vdh) or benzaldehyde dehydrogenase (YfmT).
2. The conversion between vanillin to vanillyl alcohol.

In pathway 1, Vdh catalyzes the conversion of vanillin to vanillic acid through NAD-dependent oxidation (Ding *et al.,* 2015; Fleige *et al*., 2013; Masai *et al.,* 2007b; Priefert *et al.,* 1997). Deletion of *vdh* in *P. fluorescens* resulted in complete loss of ferulic acid utilization (Di Gioia *et al.,* 2011), while overexpression of *fcs* and *ech* (see previous section), and deletion of *vdh* in *Amycolatopsis* sp. ATCC39116 resulted in the accumulation of vanillin (Fleige *et al*., 2016). The deletion of *vdh* in *Corynebacterium glutamicum* revealed delayed growth on vanillin, 3-hydroxybenzaldehyde, *p*-hydroxybenzaldehyde, protocatechuic aldehyde, ferulic acid and caffeic acid, but not on *p*-cresol, cinnamyl aldehyde or syringic aldehyde (Ding *et al.,* 2015). Purified Vdh of *C. glutamicum* biotransformed protocatechuic aldehyde to protocatechuic acid. This was also observed for the vanillin dehydrogenase (Yfmt) of *B. subtilis* 3NA that can catalyze the conversion of vanillin, isovanillin, *p*-hydroxybenzaldehyde, 3-hydroxybenzaldehyde, protocatechualdehyde, ethylvanillin**,** benzaldehyde and salicylaldehyde to the corresponding acids (Graf *et al.,* 2016). Both Vdh and YfmT showed a broad substrate range suggesting an important role of these enzymes in the catabolism of aromatic compounds (Ding *et al.,* 2015; Graf *et al.,* 2016). The conversion of protocatechuic aldehyde to protocatechuic acid has been proposed in the fungus *Aspergillus fumigatus* (Jones *et al.,* 1993). Pathway 2 was described for *Alicyclobacillus acidoterrestris, E. coli* and *Pseudomonas deceptionensis* in which vanillin is converted to vanillyl alcohol (Cai *et al.,* 2015; Kunjapur *et al.,* 2014; Ravi *et al.,* 2018).

Similar to bacteria, two vanillin conversion pathways have been described for fungi. Pathway 1 was reported for several filamentous fungi such as *A. japonicus*, *P. cinnabarinus* and *S. commune*, and the yeasts *Coniochaeta mutabilis, B. anomalus, D. hansenii, Exophiala heteromorpha, Trichosporon oleaginosus* and *Aureobasidium pullulans* (Edlin *et al.,* 1995; Falconnier *et al.,* 1994; Henderson, 1961; Krings *et al.,* 2001; Mathew *et al.,* 2007; Milstein *et al.,* 1983; Stentelaire *et al.,* 2000; Tsujiyama and Ueno, 2008; Yaguchi *et al.,* 2017). Pathway 2 in which vanillyl alcohol is oxidized to vanillin was observed for the filamentous fungi *P. simplicissimum, A. japonicus*, *S. commune* and *Sporotrichum pulverulentum* (an anamorph of *Phanerochaete chrysosporium*), and the yeast *D. hansenii* (Ander *et al.,* 1980; de Jong *et al.,* 1992; Mathew *et al.,* 2007; Milstein *et al.,* 1983; Tsujiyama and Ueno, 2008). In *P. simplicissimum,* VaO is involved in the oxidation of vanillyl alcohol to vanillin (de Jong *et al.,* 1992). VaO is a homolog of EugO from the bacterium *R. jostii* and is also able to catalyze the oxidation of vanillyl alcohol to vanillin, the oxidative demethylation of 4-(methoxymethyl)phenol, the deamination of vanillyl amine, the dehydroxylation of 4-propylphenol, the dehydrogenation of 4-butylphenol and the enantioselective hydroxylation of 4-ethylphenol (Drijfhout *et al.,* 1998; Fraaije *et al.,* 1997; de Jong *et al.,* 1992; Van den Heuvel *et al.,* 2000, 2002). Recently, it was shown that VaO has a broader substrate specificity than EUGO (Ewing *et al.,* 2018). In fungi and yeast, vanillin was observed to be reduced to vanillyl alcohol (Ander *et al.,* 1980; Edlin *et al.,* 1995; Hatakka, 1985; Henderson, 1961; Tsujiyama and Ueno, 2008).

Vanillic acid and isovanillic acid were both released during lignin degradation by the bacteria *A. formicans* and *B. ligniniphilus* and the fungus *P. chrysosporium* (Chen *et al.,* 1982; Gupta *et al.,* 2001; Zhu *et al.,* 2017). Currently, four vanillic acid conversion pathways have been described for bacteria and fungi (Fig. 4):

3. Demethylation of vanillic acid to protocatechuic acid by the vanillate demethylases VanA and VanB, or LigM.
4. Non-oxidative decarboxylation of vanillic acid to guaiacol by the phenolic acid decarboxylase subunits B, C and D (BsdBCD) or vanillate decarboxylase C (VdcC).
5. Oxidative decarboxylation of vanillic acid to methoxy-hydroquinone by vanillate (decarboxylating) hydroxylase and further to hydroxyquinol.
6. Reduction of vanillic acid to vanillin.

In pathway 3, demethylation of vanillic acid to protocatechuic acid is catalyzed by VanA and VanB of *Pseudomonas* sp. strain HR199 or LigM of *Sphingobium* sp. strain SYK-6 (Harada *et al.,* 2017; Priefert *et al*., 1997; Rosini *et al.,* 2016). VanAB demethylates vanillic acid through a non-heme iron monooxygenase mechanism, while LigM demethylates vanillic acid through a tetrahydrofolate-dependent mechanism. The homology of Atu1420 to LigM and the deletion of Atu1420, which resulted in the accumulation of vanillic acid, revealed that this mechanism is also present in *A. fabrum* (Campillo *et al.,* 2014). Pathway 3 has also been reported for *Streptomyces* spp. (Sutherland *et al.,* 1981, Sutherland *et al.,* 1983), while pathway 4 has been reported for several bacterial species, such as *B. subtilis*, *Bacillus megaterium*, *Clostridium hydroxybenzoicum, E. coli* and several *Streptomyces* sp. strains (Álvarez-Rodrígues *et al.,* 2003; Cai *et al.,* 2015; Chow *et al.,* 1999; Crawford and Olson, 1978; Lupa *et al.,* 2005, Lupa *et al.,* 2008; Pometto *et al.,* 1981). BsdBCD of *B. subtilis* and VdcC of *Streptomyces* sp. are involved in the non-oxidative decarboxylation of vanillic acid to guaiacol (Chow *et al.,* 1999; van Duy *et al.,* 2007), which can then be further converted to catechol after which the aromatic ring is cleaved (Fig. 4) (Pometto *et al.,* 1981). Pathway 5 has been reported only once in bacteria, suggesting that it is uncommon, and the enzymes of this pathway are unknown (El-Mansi and Anderson 2004). Pathway 6 was observed in *E. coli* expressing an aryl carboxylic acid reductase (Acar) of *Nocardia iowensis,* which catalyzed the conversion of vanillic acid to vanillin (He *et al.,* 2004; Kunjapur *et al.,* 2014).

In fungi, these four pathways have also been described for the biotransformation of vanillic acid. Pathway 3 has been observed for the filamentous fungi *A. japonicus* and *S. commune* (Milstein *et al.,* 1983; Tsujiyama and Ueno, 2008), while pathway 4 was reported for *M. thermophila, P. variotii* and several Aspergilli (Crawford and Olson, 1978; Guiraud *et al.,* 1992). Pathway 5 was observed in many fungi, including *A. niger* and *P. chrysosporium* (Baqueiro-Peña *et al.,* 2010; Guiraud *et al.,* 1992; Kirk and Lorenz, 1973, Rahouti *et al.,* 1989; Yajima *et al.,* 1979). This reaction is also catalyzed by 4-hydroxybenzoate 1-hydroxylase (Mnx1) from *Candida parapsilosis* (van Berkel *et al.,* 1994; Eppink *et al.,* 1997). Pathway 6 is the reduction of vanillic acid to vanillin, which was observed for several filamentous fungi such as *Trichoderma reesei* (Guiraud *et al.,* 1992; Hatakka, 1985). The enzymes involved in these conversions are also unknown.

Veratric acid is a compound similar to vanillic acid and it is derived from veratryl alcohol and veratraldehyde, which are considered as monomeric lignin model compounds (Zapanta and Tien, 1997). Veratric acid is a product of lignin when spruce wood is degraded by *P. chrysosporium* (Chen and Chang, 1982). In the bacterium *Pseudomonas putida*, the ascomycete *P. simplicissimum* and the basidiomycete *P. chrysosporium*, an aromatic pathway in which veratryl alcohol is converted to veratrylaldehyde and further to veratric acid has been observed (de Jong *et al.,* 1990; Leisola *et al.,* 1985; Mohan and Phale, 2017). However, the bacterial and fungal enzymes involved in the conversions

of veratryl alcohol and veratraldehyde have not yet been identified. Two pathways in which veratric acid is converted are described (Fig. 4):

7. Conversion of veratric acid to:
    a. Isovanillic acid through *o*-demethylation catalyzed by VanAB followed by the demethylation to protocatechuic acid catalyzed by isovanillic acid demethylase (IvaA).
    b. Vanillic acid through *p*-demethylation catalyzed by IvaA followed by the *o*-demethylation to protocatechuic acid by VanAB.
8. Reduction of veratric acid to veratrylaldehyde and veratryl alcohol.

Pathway 7a, in which veratric acid is converted to vanillic acid, was observed in *Comamonas testosteroni* BR6020 and *Streptomyces* spp. (Providenti *et al.,* 2006; Sutherland *et al.,* 1981), while pathway 7b was observed in *C. testosteroni* (Providenti *et al.,* 2006). VanA or IvaA demethylates the *meta*- or *para*-methoxy-group of veratric acid, respectively resulting in the formation of isovanillic or vanillic acid. Isovanillic acid and vanillic acid are then converted to protocatechuic acid by IvaA and VanA, respectively. The reductase component IvaB is involved in the reactions of both IvaA and VanA. Recently, the enzymes catalyzing the conversion of veratric acid to vanillic acid in *P. putida* CSV86 have been identified (VerA and VerB; Mohan and Phale, 2017). The main difference in this system is that demethylase VerA uses the reductase VerB, while VanA is using a different reductase.

In fungi, pathway 7, in which veratric acid is converted either to isovanillin or vanillin and further to protocatechuic acid was observed in both *P. simplicissimum* and *P. cinnabarinus* and in the yeast *C. mutabilis* and *A. pullulans* (Fig. 4) (de Jong *et al.,* 1990; Hatakka, 1985; Henderson, 1961). Interestingly, in *A. japonicus* veratric acid was suggested to be directly converted to protocatechuic acid since no intermediates were detected (Milstein *et al.,* 1983). Pathway 8 was observed in the basidiomycete *P. cinnabarinus* (Hatakka, 1985). Fungal enzymes catalyzing these pathways remain unknown.

In summary, vanillic acid, isovanillic acid, veratric acid and vanillin are important G-unit monolignols since these have been detected during lignin degradation (Chen and Chang, 1982; Gupta *et al.,* 2001). Vanillin can be converted by bacteria, filamentous fungi and yeast with two pathways either to vanillic acid or to vanillyl alcohol (Fig. 4). Vanillic acid is converted towards three main compounds (in reducing order): protocatechuic acid, catechol and hydroxyquinol, after which the ring is cleaved as discussed in section 2.9. The pathway towards hydroxyquinol is common for fungi, but uncommon for bacteria (El-Mansi and Anderson 2004). Therefore, it is likely that vanillic acid pathways 3 and 4 are the main pathways in bacteria and yeast while pathway 5 is the main pathway in filamentous fungi. As mentioned before, vanillyl alcohol was oxidized to vanillin in several fungal species, including *A. japonicus, S. commune* and *S. pulverulentum*, and the yeast *D. hansenii* (Ander *et al.,* 1980; Mathew *et al.,* 2007; Tsujiyama and Ueno, 2008). No homolog of VaO were found in the genomes of *A. japonicus, S. commune, Sporotrichum* and *Debaryomyces* (Gygli *et al.,* 2018), indicating that other enzymes are involved in this conversion in these species. An alternative explanation for low frequency of VaO candidates was found in phylogenetic analysis of VaO in fungi and suggested that this gene was possibly obtained from bacteria through horizontal gene transfer (Gygli *et al.,* 2018). Similar to the ferulic acid pathway, multiple vanillic acid pathways have been observed in fungi, but so far, only one fungal enzyme has been characterized.

2.4 Cinnamic acid and related metabolic pathways

Cinnamic acid is one of the key building blocks for lignin synthesis in plants since it can be converted to the three monolignols (Humphreys and Chapple, 2002). Breakdown of kraft lignin by *Bacillus* sp. and *Cupriavidus basilensis* results in the release of cinnamic acid (Raj *et al.,* 2007; Shi *et al.,* 2013). In addition, cinnamic acid also naturally occurs in plants such as *Cinnamomum verum*, and is used as a

flavor agent in cosmetics and pharmaceuticals, and as a precursor for the sweetener aspartame. In fungi and bacteria, four pathways have been described for the conversion of cinnamic acid (Fig. 5):

1. Conversion of cinnamic acid to benzoic acid through:
    a. Non-β-oxidative decarboxylation, in which cinnamic acid is converted to benzaldehyde and then to benzoic acid.
    b. β-oxidative decarboxylation, in which cinnamic acid is converted to cinnamoyl-CoA followed by conversion to β-ketophenylpropionyl-CoA, β-hydroxyphenylpropionyl-CoA, benzoyl-CoA and benzoic acid.
2. Reduction of cinnamic acid to cinnamaldehyde and further to cinnamyl alcohol.
3. Conversion of cinnamic acid to cinnamic acid-dihydrodiol by 3-phenylpropionate/cinnamic acid dioxygenase subunits E, F, C and D (HcaEFCD) and further to 2,3-dihydroxycinnamic acid by the dihydrodiol dehydrogenase (HcaB).
4. Non-oxidative decarboxylation of cinnamic acid to styrene by Fdc1 and Pad1.

Pathway 1 has been observed in *A. japonicus* (Milstein *et al.,* 1983), but it is unknown if the non β-oxidative decarboxylation or the β-oxidative decarboxylation pathway is used (Fig. 5). Bacteria can also transform cinnamic acid through either the non-β-oxidative or the β-oxidative pathway to benzoic acid, as observed for *Alcanivorax borkumensis, Papillibacter cinnamivorans*, *Rhodopseudomonas palutris* and *Streptomyces setonii* (Austin *et al.,* 2015; Defnoun *et al.,* 2000; Dutta and Harayama, 2001; Sutherland *et al.,* 1983). Pathway 1a has been observed in *S. setonii* (Sutherland *et al.,* 1983) while pathway 1b has been observed in *Streptomyces maritimus* (Noda *et al.,* 2012). Enzymes catalyzing these conversions are still unknown. Pathway 2 was described in *A. japonicus* and *S. commune* (Fig. 5) (Milstein *et al.*, 1983; Nimura *et al.,* 2010). In addition, the conversion of cinnamaldehyde through cinnamyl alcohol (Larroy *et al.,* 2002) to hydrocinnamyl alcohol by *S. commune* and the yeast *S. cerevisiae* was reported (Gottardi *et al.,* 2017; Nimura *et al.,* 2010). The overexpression of Acar from *Nocardia* sp. and a phosphopantetheinyl transferase (EntD) from *E. coli* expressed in *S. cerevisiae* also resulted in conversion of cinnamic acid to cinnamaldehyde and further to cinnamyl alcohol by endogenous alcohol dehydrogenases (Gottardi *et al.,* 2017).

Pathway 3 was discovered in *E. coli* (Díaz *et al.,* 1998) and close homologs of the involved enzymes have been also found in the genus *Shigella*. 2,3-dihydroxycinnamic acid is converted by 2,3-dihydroxycinnamic acid 1,2-dioxygenase (MhpB) to 2-hydroxy-6-ketononatrienedioate (Bugg, 1993) and futher converted towards tricarboxylic acid cycle (TCA). This pathway has not been observed in fungi. Pathway 4 is present in filamentous fungi and yeast (Clausen *et al.,* 1994; Milstein *et al.,* 1983; Plumridge *et al.,* 2008; Shimada *et al.,* 1992). The previously mentioned *S. cerevisiae* enzyme involved in converting ferulic acid to *p*-vinyl guaiacol, Fdc1, and its coenzyme Pad1 are essential for the decarboxylation of cinnamic acid to styrene in yeast (Mukai *et al.,* 2010; Richard *et al.,* 2015; Tran *et al.,* 2008). *S. cerevisiae* Fdc1 and Pad1 deletion mutants are unable to convert cinnamic acid. Despite their homology to the bacterial ubiquinone biosynthesis enzymes (UbiX and UbiD), Fdc1 and Pad1 are not involved in ubiquinone biosynthesis in yeast (Mukai *et al.,* 2010). However, it was shown that UbiX could replace Pad1 as a coenzyme for Fdc1 (Lin *et al.,* 2015), which indicates that UbiX and Fdc1 require the same cofactor for enzymatic activation. No direct interaction or complex formation is observed between Fdc1 and Pad1, since Fdc1 is localized in the cytosol while Pad1 is in the mitochondria (Richard *et al.,* 2015). One possible suggestion is that cinnamic acid is converted in two steps. First by Fdc1 and subsequently the formed intermediate passes through the mitochondrial membrane where Pad1 is located but this remains to be proven (Richard *et al.,* 2015). Homologs of Fdc1 and Pad1, ObhA and PadA, were identified in *A. niger* and are involved in the decarboxylation of cinnamic acid and sorbic acid (Plumridge *et al.,* 2010). Deletion of these genes showed decreased tolerance of *A. niger* to the toxicity of cinnamic acid and sorbic acid. The decarboxylation of cinnamic acid to styrene appears to be specific for fungi. The bacterial decarboxylases Pdc, PadC and Fdc are

able to convert ferulic acid, *p*-coumaric acid and caffeic acid, but not cinnamic acid to its *p*-vinyl form (Cavin *et al.,* 1997a; Tran *et al.,* 2008; Zago *et al.,* 1995). Even though bacteria are unable to decarboxylate cinnamic acid, the conversion of styrene was observed in bacteria. This is probably because styrene naturally occurs in plants and soil (Steele *et al*., 1994; Tischler, 2015).

Styrene can be degraded to phenyl-1,2-ethanediol, 2-phenylethanol and benzoic acid by the filamentous basidiomycete *Pleurotus ostreatus* (Braun-Lüllemann *et al.,* 1997). This was also observed for the filamentous basidiomycetes *P. chrysosporium* and *Trametes versicolor,* and the filamentous ascomycete *Daldinia concentrica*, which were able to degrade styrene into 2-phenylethanol, benzoic acid, cyclohexadiene-1,4-dione, butanol and succinic acid (Lee *et al.,* 2006). It was suggested that butanol and succinic acid are the products of ring cleavage. Another pathway for styrene metabolism observed in filamentous fungi is through styrene oxide (2-phenyloxirane), followed by the conversion to styrene glycol, mandelic acid and likely to benzoic acid (Braun-Lüllemann *et al.,* 1997). The yeast *Exophiala jeanselmei* converts styrene to styrene oxide and then to phenylacetaldehyde and phenylacetic acid (Cox *et al.,* 1993). The enzymes involved in these conversions are unknown. The bacteria *P. fluorescens* and *P. putida* can convert styrene to styrene-oxide with the monooxygenases StyA and StyB (Beltrametti *et al.,* 1997; Otto *et al.,* 2004). Styrene-oxide isomerase (StyC) catalyzes the conversion of styrene-oxide to phenylacetaldehyde that is further converted by phenylacetaldehyde dehydrogenase (StyD) to phenylacetate. In *Gordonia rubripertincta*, styrene oxide is further converted through S-glutathionylation to (S)-(1-phenyl-2-hydroxyethyl)-glutathione (Heine *et al.,* 2018). In *P. putida,* phenylacetaldehyde can also be converted to phenylacetic acid and further to phenylacetyl-CoA (Crabo *et al.,* 2017). *Rhodococcus rhodochrous* strain NCIMB 13259 grown on styrene together with 3-fluorocatechol to inhibit catechol dioxygenase activity, accumulated 3-vinylcatechol (Warhurst *et al.,* 1994a, 1994b). It was suggested that styrene *cis*-glycol is the intermediate between styrene and 3-vinylcatechol.

2.5 Benzoic acid, *p*-hydroxybenzoic acid and related metabolic pathways

Benzoic acid is an intermediate aromatic compound of many secondary metabolites and is currently used as a food and beverage preservative. Biodegradation of alkaline lignin by *B. ligniniphilus* results in the release of benzoic acid (Zhu *et al.,* 2017). In bacteria and fungi, five pathways in which benzoic acid is converted are described (Fig. 6):

1. Conversion of benzoic acid to benzoic acid dihydrodiol by the benzoate 1,2-dioxygenase subunits A, B and C (BenABC) while the benzoate 1,2-dioxygenase subunit D (BenD) further catalyzes the reaction of benzoic acid dihydrodiol to catechol.
2. Anaerobic conversion of benzoic acid to benzoyl-SCoA by benzoate-CoA ligase (BadA or BlcA).
3. Reduction of benzoic acid to benzaldehyde by Acar that is further converted to benzyl alcohol.
4. Hydroxylation of benzoic acid to 3-hydroxybenzoic acid followed by:
    a. 6-hydroxylation to gentisic acid by 3-hydroxybenzoate 6-hydroxylase (BagX, XlnD or Mnx2).
    b. *p*-hydroxylation to protocatechuic acid by 3-hydroxybenzoate-4-monooxygenase (MobA).
5. Hydroxylation of benzoic acid to *p*-hydroxybenzoic acid by benzoate 4-monooxygenase (BphA).

Pathway 1 was observed in *Acinetobacter calcoaceticus*, which converts benzoic acid to benzoic acid dihydrodiol and further to catechol (Neidle *et al.,* 1991). In several *Streptomyces* and *Bacillus* species, it has been observed that benzoic acid was slowly converted to catechol (Peng *et al.,* 2003; Sutherland *et al.,* 1981). This slow conversion could be due to the multiple steps required, as was suggested in *Streptomyces* and *Amycolatopsis* species (Grund *et al.,* 1990). It is therefore possible that pathway 1 is also used by *Bacillus* species. Pathway 2 was observed in *Pseudomonas* sp*., Rhodopseudomonas palustris* and *Thauera aromatica* (Austin *et al.,* 2015; Breese and Fuchs; 1998; Gibson *et al.,* 1994), and will be further discussed in the *p*-hydroxybenzoic acid section. Pathway 3 was observed by overexpressing Acar of *N. iowensis* in *E. coli* resulting in the conversion of benzoic acid to benzaldehyde

and further to benzyl alcohol by endogenous enzymes (Kunjapur *et al.,* 2014). The formation of benzyl alcohol was also observed in *Aspergillus flavus* when it was grown on benzoic acid (Palazzolo *et al.,* 2015), indicating that this pathway is also present in nature. Pathway 4a has been described in several Bacilli and *Paenibacillus* sp. strain NyZ101 where conversion of benzoic acid to 3-hydroxybenzoic acid was observed followed by conversion to gentisic acid by 3-hydroxybenzoate 6-monooxygenase (BagX or XlnD) (Crawford, 1975; Liu and Zhou, 2012; Peng *et al.,* 2003). The conversion of 3-hydroxybenzoic acid to gentisic acid is catalyzed by XlnD of *Pseudomonas alcaligenes,* and this conversion was also detected in *Klebsiella pneumoniae* and *R. jostii* (Gao *et al.,* 2005; Jones and Cooper, 1990; Montersino and van Berkel, 2012). Pathway 4b was observed in *C. testosteroni*, which converts benzoic acid to 3-hydroxybenzoic acid and further to protocatechuic acid by MobA (Chang and Zylstra, 2008). MobA also has activity on 3-hydroxyanthranilate, *p*-hydroxybenzoic acid and 2,3-dihydroxybenzoic acid. The mutation of amino acid Val257 to Ala resulted in enhanced activity on phenol, resorcinol and hydroquinone (Chang and Zylstra, 2008). Currently, the enzymes involved in the conversion of benzoic acid to 3-hydroxybenzoic acid are unknown.

Pathways 1, 2, 3 and 4 have not been observed in filamentous fungi or yeast except for the conversion of 3-hydroxybenzoic acid by the filamentous fungi *P. chrysosporium* and *A. japonicus* (Fig. 6). In these fungi, 3-hydroxybenzoic acid is converted to protocatechuic acid and/or catechol, which is a part of the 3-oxoadipate pathway (Matsuzaki and Wariishi, 2005; Milstein *et al.,* 1983; Sugumaran *et al.,* 1973). In contrast, in the yeast *C. parapsilosis,* 3-hydroxybenzoic acid is converted to gentisic acid by the 3-hydroxybenzoate 6-hydroxylase (Mnx2) (Holesova *et al.,* 2011). Pathway 5 was observed in fungi and not in bacteria. In *A. niger*, this reaction is catalyzed by BphA that acts together with a cytochrome P450 reductase (CprA), whereas in *A. nidulans* the corresponding enzymes are benzoate 4-monooxygenase (BzuA) and an uncharacterized reductase (AN0595, homolog of CprA) (Fraser *et al.,* 2002; Martins *et al.,* 2015; van der Brink *et al.,* 1996; van Gorcom *et al.,* 1990). This conversion by a cytochrome P450 monooxygenase was also reported for *Cochliobolus lunatus*, *P. chrysosporium* and the yeast *Rhodotorula minuta* (Fukuda *et al.,* 1996; Korošec *et al.,* 2014; Lah *et al.,* 2011; Matsuzaki and Wariishi, 2005).

Breakdown of kraft lignin by the bacterium *A. formicans* and the fungus *P. chrysosporium* results in the release of *p*-hydroxybenzoic acid (Chen and Chang, 1982; Gupta *et al.,* 2001). In bacteria and fungi, six pathways for *p*-hydroxybenzoic acid conversion have been described (Fig. 7):

6. Hydroxylation of *p*-hydroxybenzoic acid to protocatechuic acid by 3-hydroxybenzoate-4-hydroxylase (PobA or PraI).
7. Decarboxylation of *p*-hydroxybenzoic acid to phenol by BsdBCD and further to catechol by HpaBC or by the phenol hydroxylase components L, M, N, O and P (DmpLMNOP).
8. Conversion of *p*-hydroxybenzoic acid to gentisic acid through:
    a. Conversion to *p*-hydroxybenzoyl-CoA by *p*-hydroxybenzoyl-CoA ligase (PhgC) followed by the conversion to gentisyl-CoA by *p*-hydroxybenzoyl-CoA hydroxylase (PhgA) and gentisic acid by gentisyl-CoA thioesterase (PhgB).
    b. Conversion to salicylic acid followed by the conversion to gentisic acid.
9. Anaerobic conversion of *p*-hydroxybenzoic acid to *p*-hydroxybenzoyl-CoA by 4-hydroxybenzoate-CoA ligase (HbaA) and then to benzoyl-CoA by 4-hydroxybenzoyl-CoA reductase subunits B, C and D (HbaBCD or HrcBCD).
10. Conversion of *p*-hydroxybenzoic acid to phenylacetic acid followed by conversion to tyrosol and benzenethanol.
11. Decarboxylation of o-hydroxybenzoic acid to hydroquinone by Mnx1 and further to hydroxyquinol by phenol 2-monooxygenase (Mnx3).

Pathway 6 was observed in the bacteria *P. aeruginosa, P. desmolytica, P. fluorescens, P. putida* and *Paenibacillus* sp. (Entsch *et al*., 1988; Howell *et al.,* 1972; Hosokawa and Stanier, 1966; Kasai *et al.,* 2009), and the filamentous fungi *A. flavus, A. niger, A. nidulans, C. lunatus, S. commune* and several Penicillia, and the yeast *T. oleaginosus* (Halsall *et al.,* 1969; Iyayi and Dart, 1982; Lah *et al.,* 2011; Martins *et al.,* 2015; Yaguchi *et al.,* 2017). Currently, many bacterial sequences for 3-hydroxybenzoate-4-hydroxylase have been annotated (Westphal *et al*., 2018).

The fungal enzymes involved in this conversion are unknown, but in *A. nidulans,* a monooxygenase and NADPH flavin reductase have been suggested to catalyze this reaction (Martins *et al.,* 2015). In *C. lunatus*, CYP53A15, the ortholog of BphA, with its reductase partners CPR1 and CPR2 catalyzes both steps of the *p*-hydroxybenzoic acid to protocatechuic acid pathway (Lah *et al.,* 2011). Pathway 7 has been observed in *B. subtilis* (Lupa *et al.,* 2005, 2008). In *E. coli, Rhodococcus opacus, Pseudomonas* sp. CF600 and *P. aeruginosa,* phenol is converted to catechol and is catalyzed by HpaBC or DmpLMNOP (Furuya and Kino, 2014; Powlowski and Shingler, 1994; Xun and Sandvik, 2000; van Duy *et al.,* 2007; Yoneda *et al.,* 2016). The ring cleavage of catechol is further discussed in section 2.9.1. The conversion of *p*-hydroxybenzoic acid to phenol has not been described for fungi, but the conversion of phenol to catechol was observed in *Candida albicans* and *Trichosporon cutaneum* (Gérecová *et al*., 2015; Kälin *et al.,* 1992). The phenol hydroxylase PhhY of *T. cutaneum* catalyzes this reaction (Kälin *et al.,* 1992).
Pathway 8 has been observed in several Bacilli and suggested to be a direct conversion (Peng *et al.,* 2003). In principle, this conversion can be catalyzed by one enzyme through an intramolecular migration (NIH shift) of the carboxyl group, however it was never demonstrated for *p*-hydroxybenzoic acid. Pathway 8a was recently demonstrated in the bacterium *Brevibacillus laterosporus* that *p*-hydroxybenzoic acid converted to gentisic acid involving the three enzymes, *p*-hydroxybenzoyl-CoA ligase, *p*-hydroxybenzoyl-CoA hydroxylase and gentisyl-CoA thioesterase (Zhao *et al.,* 2018). Pathway 8b was suggested in *Rhizobium* sp. (Muthukumar *et al.,* 1982). It was also suggested that salicylic acid could be the intermediate between *p*-hydroxybenzoic acid and catechol (Seo *et al.,* 2009). The enzymes involved in this pathway have not been identified. The salicylic acid pathway is further discussed in section 2.7.

Pathway 9 has been described in *R. palustris* and *T. aromatica* and continues through the benzoyl-CoA pathway to 1,5-diene-cyclohexanoyl-CoA and 1-ene-cyclohexanoyl, both catalyzed by benzoate-CoA reductase subunits D, E, F and G (BadDEFG) (Austin *et al.,* 2015; Breese and Fuchs, 1998). Deletion of BadE resulted in the accumulation of benzoic acid when *R. palustris* was grown on ammonia fibre expansion (AFEX)-pretreated cornstover hydrolysate. The deletion of HbaB resulted in the accumulation of *p*-hydroxybenzoic acid but did not block the benzoyl pathway. Pathway 10 has been observed in *S. cerevisiae* in which *p*-hydroxybenzoic acid is converted to phenylacetic acid followed by the conversion to tyrosol and benzenethanol (Adeboye *et al.,* 2017). Pathway 11 has been described in the yeast *C. parapsilosis* (Eppink *et al.,* 1997, 2000; Holesova *et al.,* 2011). In the fungi *A. fumigatus*, hydroquinone is converted to hydroxyquinol (Jones *et al.,* 1994). Hydroxyquinol is further processed through ring cleavage, which is discussed in section 2.9.3. Mnx1 is also able to catalyze the conversion of protocatechuic acid to hydroxyquinol (Anderson and Dagley, 1980; Eppink *et al.,* 1997; Holesova *et al.,* 2011).

Currently, only one pathway was described for the conversion of benzoic acid by filamentous fungi, whereas several pathways have been described for bacteria excluding the conversion of benzoic acid to *p*-hydroxybenzoic acid (Fig. 6, 7). It is likely that bacteria prefer the conversion of benzoic acid to 3-hydroxybenzoic acid or benzoic acid to benzoic acid dihydrodiol, while fungi prefer the conversion to *p*-hydroxybenzoic acid. However, bacteria are able to convert *p*-hydroxybenzoic acid, probably through the *p*-coumaric acid pathway in which *p*-hydroxybenzoic acid is the conversion product as discussed in section 2.6. Because of many observations in filamentous fungi, this indicates that the hydroxylation of benzoic acid to *p*-hydroxybenzoic acid continued to protocatechuic acid is the main

metabolic pathway. For bacteria, it is likely that either pathway 1 or 4 is the main benzoic acid metabolic pathway.

2.6 *p*-Coumaric acid metabolic pathways

p-Coumaric acid is released during lignin breakdown by the bacteria *A. formicans*, *C. basilensis* and *R. toruloides* (Gupta *et al.,* 2001; Shi *et al.,* 2013; Yaegashi *et al.,* 2017). In addition, *p*-coumaric acid, similar to ferulic acid, can be linked to polysaccharides (Mäkelä *et al.,* 2015). Lignin synthesis in plants converts cinnamic acid to *p*-coumaric acid (Humphreys and Chapple, 2002). *p*-Coumaric acid, a derivative from the monolignol *p*-coumaryl alcohol, has antioxidant and antimicrobial properties (Pei *et al.,* 2016). In the filamentous fungi *A. flavus*, the monolignol *p*-coumaryl alcohol is converted to *p*-coumaryl aldehyde followed by conversion to *p*-coumaric acid (Iyayi and Dart, 1982). Five pathways are described for bacteria and fungi, in which *p*-coumaric acid is mainly converted to *p*-hydroxybenzoic acid or caffeic acid through (Fig. 8):

1. Non-oxidative decarboxylation in which *p*-coumaric acid is converted to *p*-vinylphenol by PadC, Fdc1 or Pad and is followed by;
    a. The conversion to *p*-hydroxybenzaldehyde and then to *p*-hydroxybenzoic acid by YfmT.
    b. The reduction to 4-ethylphenol by VprA
2. Conversion of *p*-coumaric acid to *p*-coumaryl-CoA by Fcs or CouL followed by:
    a. CoA-dependent β-oxidation to 3-hydroxy-3-(*p*-hydroxyphenyl) propyl-CoA (HPHP-SCoA) and then to *p*-hydroxybenzaldehyde, both catalyzed by Ech.
    b. CoA-dependent non-β-oxidation in which *p*-coumaric acid is first converted to *p*-coumaryl-SCoA by Fcs and then to *p*-hydroxybenzaldehyde and *p*-hydroxybenzoic acid by YfmT.
3. Conversion of *p*-coumaric acid to β-hydroxy-(*p*-hydroxyphenyl)-propionic acid followed by (*p*-hydroxybenzoyl)-acetic acid and *p*-hydroxybenzoic acid.
4. Conversion of *p*-coumaric acid to 3-(*p*-hydroxyphenyl)-propionic acid followed by 3-(*p*-hydroxyphenyl)-propyl aldehyde to 3-(*p*-hydroxyphenyl)-propanol and to *p*-hydroxybenzoic acid.
5. Hydroxylation of *p*-coumaric acid to caffeic acid by HpaBC or 4-coumarate 3-hydroxylase (Sam5).

Pathway 1a was observed for several *Bacillus* species (Jung *et al.,* 2013; Torres and Rosazza *et al.,* 2001;). It has been proposed that *p*-vinylphenol is converted to *p*-hydroxybenzaldehyde and then to *p*-hydroxybenzoic acid (Monisha *et al.,* 2017). In fungi, this pathway was described for *P. variotii* and *F. solani* (Nazareth and Mavinkurve, 1986; Sachan *et al.,* 2006). The pathway was also reported for *S. commune*, but *p*-vinylphenol was not detected (Sachan *et al.,* 2010). Fdc1 of *S. cerevisiae* and Pad of *A. luchuensis* and *I. farinosa* can catalyze the conversion of *p*-coumaric acid to *p*-vinylphenol (Linke *et al.,* 2017; Maeda *et al.,* 2018; Mukai *et al.,* 2010). Pathway 1b has been observed in the wine spoilage yeasts of the genera *Brettanomyces* and *Dekkera* (Suárez *et al.,* 2007). Recently, this pathway has also been observed in the bacterium *L. plantarum* where it is catalyzed by VprA (Santamaría *et al.,* 2018). In the bacterium *P. putidia*, *p*-vinylethyl is further converted to hydroquinone through the intermediates 1-(4-hydroxyphenyl)ethanol, 4-hydroxyacetophenone and 4-hydroxyphenylacetate, respectively (Darby *et al.,* 1987). Hydroquinone is further processed through ring cleavage (see section 2.9.3). The same pathway has also been suggested for *A. fumigatus* which further hydroxylates hydroquinone to hydroxyquinol (Jones *et al.,* 1994), even though the conversion of *p*-vinylphenol to *p*-ethylphenol was not observed. Pathway 2 was observed in *P. putida, R. jostii* and *R. palustris* (Austin *et al.,* 2015; Hirakawa *et al.,* 2012; Otani *et al.,* 2014; Ravi *et al.,* 2017). While *R. palustris* uses both pathways, only pathway 2b was observed in *P. putida* (Austin *et al.,* 2015; Hirakawa *et al.,* 2012; Ravi *et al.,* 2017). The conversion of *p*-hydroxybenzaldehyde is catalyzed by Yfmt and is probably also catalyzed by Vdh since the deletion of Vdh in *C. glutamicum* resulted in reduced growth on *p*-hydroxybenzaldehyde (Ding *et al.,* 2015; Jung *et al.,* 2016; Graf *et al.,* 2016 Ravi *et al.,* 2017). In *S. setonii, p*-coumaric acid is converted to *p*-hydroxybenzaldehyde, followed by the conversion to *p*-hydroxybenzoic acid, but it is unclear if one of the CoA-dependent pathways is used (Sutherland *et al.,*

1983). *Bacillus* sp. strain B1, *P. deceptionensis* and *S. caeruleus* are able to convert *p*-coumaric acid to *p*-hydroxybenzoic acid, but it is not known if the described or an alternative pathway is used (Peng *et al.,* 2003; Ravi *et al.,* 2018; Sachan *et al.,* 2005). Pathway 3 was only observed in the fungus *A. flavus* (Iyayi and Dart, 1982), but the enzymes catalyzing this pathway remain unknown. Pathway 4 has also been described for filamentous fungi. The basidiomycete *P. cinnabarinus* converts *p*-coumaric acid to 3-(*p*-hydroxyphenyl)-propanoic acid and then to *p*-hydroxybenzoic acid or 3-(*p*-hydroxyphenyl)-propanol (Alvarado *et al.,* 2001), while in *S. commune,* β-hydroxy-(*p*-hydroxyphenyl)-propionic acid has been suggested to be first converted to 3-(*p*-hydroxyphenyl)-propyl aldehyde and 3-(*p*-hydroxyphenyl)-propanol before it is converted to *p*-hydroxybenzoic acid (Nimura *et al.,* 2010). Interestingly, the *Bacillus* sp. strain B1 can convert 3-(*p*-hydroxyphenyl)-propanoic acid to *p*-coumaric acid, and it has been suggested that it is followed by conversion to *p*-hydroxybenzoic acid (Peng *et al.,* 2003). Pathway 5 was observed in bacteria and is catalyzed by HpaBC of *P. fluorescens* and Sam5 of *Saccharothrix espanaensis* (Furuya and Kino, 2014; Heo *et al.,* 2017). Comparison of these protein sequences to all available fungal genomes by BlastP (www.ncbi.nlm.nih.gov) results in a few hits with low homology indicating that these enzymes are unique for bacteria. However, the transformation of *p*-coumaric acid to caffeic acid is observed for the basidiomycete *P. cinnabarinus* and the ascomycetes *Gliocladium deliquescens* and several Aspergilli (Alvarado *et al.,* 2003; Torres and Rosazza, 2001), indicating that this transformation is probably catalyzed by different enzymes in fungi.

Multiple conversion pathways of *p*-coumaric acid in bacteria and filamentous fungi towards *p*-hydroxybenzoic acid have been described (Fig. 8). However, in yeast the conversion of *p*-coumaric acid to *p*-hydroxybenzoic acid has not been observed (Adeboye *et al.,* 2015). Despite the many observations of *p*-coumaric acid being converted to *p*-hydroxybenzoic acid in filamentous fungi, no enzymes have been characterized. Because of many observations, it is possible that the non-oxidative decarboxylation of *p*-coumaric acid is likely the main metabolic pathway of microorganisms.

2.7 Salicylic acid metabolic pathway

Salicylic acid can be converted through *p*-hydroxybenzoic acid (Fig. 7), which can be derived from the monolignols *p*-coumaryl alcohol and *p*-coumaric acid (Fig. 8). Salicylic acid is an important aromatic compound, because it has activity against bacterial plant pathogens and an important role in the signaling cascade of the plant immune system (Shah, 2003; Vernooij *et al.,* 1994). In addition, In the pharmaceutical industry, salicylic acid is used as a peeling agent to treat various skin disorders such as acne, melasma and psoriasis (Arif, 2015). In bacteria and fungi, the metabolism of salicylic acid is well studied and six pathways have been described (Fig. 9):

1. Conversion of salicylic acid towards catechol through:
    a. Direct conversion to catechol by salicylate hydroxylase (NahG).
    b. Hydroxylation of salicylic acid to 2,3-dihyroxybenzoic acid and further to catechol by salicylic acid decarboxylase (Sdc).
2. Conversion of salicylic acid to gentisic acid by the salicylate 5-hydroxylase components NagG and NagH.
3. Decarboxylation of salicylic acid to phenol by BsdBCD or Sdc.
4. Conversion of salicylic acid to salicylyl-AMP by salicylyl-AMP ligase (SdgA).
5. Extradiol cleavage of salicylic acid to 2-oxohepta-3,5-dienedioic acid by salicylate 1,2-dioxygenase (Sdo).
6. Reduction of salicylic acid to salicylicaldehyde and further to salicyl alcohol.

Pathway 1a has been observed in *P. putida, Amycolatopsis* spp. and *Streptomyces* spp., where salicylic acid is converted to catechol (Grund *et al.,* 1990). The reaction is catalyzed by NahG of *P. putida* (Grund *et al.,* 1990; Katagiri *et al.*, 1965; Suzuki *et al.,* 1991). In the filamentous fungi *Sclerotinia sclerotiorum* and several Aspergilli, salicylic acid pathway 1a and 1b have been reported (Kuswandi and Roberts,

1992; Martins *et al.,* 2015; Milstein *et al.,* 1983; Penn and Daniel, 2013). Both pathways have also been observed in the yeasts *Trichosporon cutaneum* and *T. moniliiforme* (Anderson and Dagley, 1980; Kirimura *et al.,* 2010). Sdc of *T. moniliiforme* and 2,3-dihydroxybenzoate decarboxylase of *A. niger* have been shown to catalyze the decarboxylation of 2,3-dihydroxybenzoic acid to catechol (Kirimura *et al.,* 2010; Santha *et al.,* 1995). In addition, Sdc can also convert 2,4-dihydroxybenzoic acid to resorcinol. In *Pseudomonas reinekei, P. putida* and *P. fluorescens,* extradiol cleavage of 2,3 dihydroxybenzoic acid has been observed, which is catalyzed by the 2,3-dihydroxybenzoic acid 3,4-dioxygenase DhbA (Marín *et al.,* 2012). Pathway 2 has been observed in *Ralstonia* sp. and is catalyzed by NagG and NagH to gentisic acid, after which the aromatic ring is cleaved (Fuenmayor *et al.,* 1998; Zhou *et al.,* 2001). This pathway was also suggested in *Streptomyces umbrinus* (Grund *et al.,* 1990), but has not been observed in fungi.

Pathway 3 is observed in the bacterium *B. subtilis* catalyzed by BsdBCD and in the yeast *T. moniliiforme* catalyzed by Sdc (Fig. 9) (Kirimura *et al.,* 2010; Lupa *et al.,* 2008). This pathway has also not been observed in filamentous fungi. In pathway 4, *Streptomyces* sp. strain WA46 converts salicylic acid to salicylyl-AMP by salicylyl-AMP ligase (SdgA) (Ishiyama *et al.,* 2004). Subsequently, salicylyl-AMP is converted to salicylyl-SCoA by SdgA and/or salicylyl-CoA synthetase (SdgB) and then to gentisate-SCoA by salicylyl-CoA 5-hydroxylase (SdgC), followed by conversion to gentisic acid. Pathway 5 has been observed in *Pseudaminobacter salicylatoxidans,* revealing an extradiol ring cleavage of salicylic acid catalyzed by salicylate 1,2-dioxygenase (Sdo) (Hintner *et al.,* 2001; Matera *et al.,* 2008). Pathway 6 has been observed in the ascomycete *Neurospora crassa* (Bachman *et al.,* 1960). The enzymes catalyzing these conversions remain unidentified. This pathway has not been observed in bacteria.

Salicylic acid can be produced from *p*-hydroxybenzoic acid in bacteria (Fig. 7), whereas in fungi no pathway leads to the production of salicylic acid. The reason to have a salicylic acid metabolic pathway can be explained by the fact that salicylic acid is an important signaling compound in disease resistance in plants and the conversion of salicylic acid is a strategy to suppress the corresponding plant defenses (Loake and Grant, 2007). In addition, salicylic acid can be found freely in plants and functions as an important plant hormone involved in many developmental processes (Jayakannan *et al.,* 2015; Klessig *et al.,* 2016). In filamentous fungi, the enzymes involved in the salicylic acid metabolic pathways are mostly unknown, but suggestions have been made (Martins *et al.,* 2015). Salicylic acid is converted to catechol in fungi and bacteria or to gentisic acid in bacteria after which the ring is cleaved. Due to many observations, it is likely that pathway 1a to catechol is the main salicylic acid metabolic pathway in microorganisms.

2.8 Sinapic acid, syringic acid and related compounds

Less is known about the aromatic metabolic pathways of sinapic acid, a derivative of the monolignol sinapyl alcohol. Sinapic acid was observed to form a dehydrodimer and sinapate-ferulate heterodimers and therefore has a role in cross-linking polysaccharides in cereal grains (Bunzel *et al.,* 2003). No release of sinapic acid during lignin degradation was detected, but the related compound syringic acid was identified (Gupta *et al.,* 2001). In the fungus *P. variotii*, sinapic acid is converted to syringaldehyde followed by conversion to syringic acid (Mukherjee *et al.,* 2006). The conversion of syringaldehyde to syringic acid has been observed in many ascomycete soil fungi (Henderson and Farmer, 1955). It is unclear, whether this is a direct conversion or that a β-oxidative decarboxylation, a non-β-oxidative decarboxylation or a non-oxidative decarboxylation pathway is used. A similar pathway has been observed in the yeast *Rhodotorula glutinis*, but the intermediate syringaldehyde was not observed (Gupta *et al.,* 1986). Since no syringaldehyde was detected, it is likely that this yeast is using a non-oxidative decarboxylation pathway forming *p*-vinylsyringol as intermediate. However, this intermediate was also not detected. In the yeast *Brettanomyces,* sinapic acid is degraded to *p*-vinylsyringol and *p*-ethylsyringol, but the conversion to syringic acid was not observed (Heresztyn, 1986). Up to now, no sinapic acid conversions have been detected in bacteria. However, *Sphingobium*

sp. strain SYK-6 converts syringaldehyde to syringic acid by the aldehyde dehydrogenase DesV (Kamimura *et al.,* 2017). This conversion was also observed in *B. subtilis* and is catalysed by YfmT (Graf *et al.,* 2016). Currently, four syringic acid metabolic pathways have been described (Fig. 10):

1. Demethylation of syringic acid to 3-*o*-methylgallic acid (5-hydroxyvanillic acid) by syringate *o*-demethylase (DesA) followed by:
   a. Demethylation of 3-*o*-methylgallic acid to gallic acid by LigM.
   b. Intradiol ring cleavage of 3-*o*-methylgallic acid to 2-pyrone-4,6-dicarboxylic acid by the 3-*o*-methylgallate 3,4-dioxygenase (DesZ).
2. Methylation of syringic acid to 3,4,5-trimethoxybenzoic acid.
3. Decarboxylation and hydroxylation of syringic acid to 2,6-dimethoxy-1,4-hydroquinone followed by the conversion to 2,6-dimethoxy-1,4-benzoquinone.
4. Decarboxylation of syringic acid to 2,6-dimethoxyphenol.

Pathway 1 has been observed in the bacteria *Sphingobium* sp. strain SYK-6 and *P. putida* (Donnelly and Dagley, 1980, Masai *et al.,* 2004), the filamentous fungi *P. variotii, P. chrysosporium* and *S. pulverulentum* (Eriksson *et al.,* 1984; Higuchi, 1986; Mukherjee *et al.,* 2006) and the yeast *R. glutinis* (Gupta *et al.,* 1986). Pathway 1a is the most described conversion and is well studied in the bacterium *Sphingobium* sp. strain SYK-6 in which it is catalyzed by LigM (Abe *et al.,* 2005; Harada *et al.,* 2017). This pathway has also been observed in the yeast *R. glutinis* (Mukherjee *et al.,* 2006). The formation of gallic acid was suggested in *S. pulverulentum,* altrough no gallic acid was observed (Eriksson *et al.,* 1984). Pathway 1b has been described in the bacterium *Sphingobium* sp. strain SYK-6 (Kasai *et al.,* 2007). Pathway 2 has been observed in the fungi *S. pulverulentum, Petriellidium boydii* and *Phialophora mutabilis* (Eriksson *et al.,* 1984). 3,4,5-Trimethoxybenzoic acid is further demethylated towards 3-hydroxy-4,5-methoxybenzoic acid followed by another demethylation to 3-*o*-methyl gallic acid. In *P. putida* and *Eubacterium limosum*, 3,4,5-trimethoxybenzoic acid is oxidized to syringic acid (Cocaign *et al.,* 1991; Donnelly and Dagley, 1980). Pathway 3 has been observed in the fungus *P. ostreatus* and the yeast *R. glutinis* (Gupta *et al.,* 1986; Shin, 1995), while pathway 4 has been described for the fungus *P. ostreatus* and is catalysed by an extracellular peroxidase (Shin, 1995). No fungal enzymes have been characterized for these pathways.

Gallic acid is the observed conversion product of pathways 1a and 2, and the aromatic ring can be cleaved (discussed in section 2.9.5). The direct conversion of gallic acid to pyrogallol was observed in the bacteria *Entrobacter* spp., *Klebsiella aerogenes, Pelobacter acidigallici* and *L. plantarum,* and is catalyzed by the gallate decarboxylase (LpdC) (Brune and Schink, 1992; Grant and Patel, 1969; Jiménez *et al.,* 2013; Sonia *et al.,* 2017). This conversion has also been observed in the fungus *A. oryzea* and in the yeast *Arxula adeninivorans* (Guo *et al.,* 2014; Meier *et al.,* 2017). *A. adeninivorans* converts gallic acid to pyrogallol (trihydroxybenzene) by gallic acid decarboxylase (Gdc) followed by an intradiol cleavage (Meier *et al.,* 2017). Two additional gallic acid conversions were reported in *A. oryzea* and *R. glutinis* resulting in the formation of progallin A and methyl gallate which can be converted to pyrogallol (Guo *et al.,* 2014; Gupta *et al.,* 1986).

Despite the low amount of observations, it appears that in microorganisms, the main syringic acid metabolic pathway is the conversion to 3-*o*-methylgallic acid followed by the demethylation to gallic acid. Nevertheless, more research is needed in order to fully understand the metabolic pathway and to discover possible alternative pathways such as the CoA-dependent β-oxidation and CoA-dependent non-β-oxidation of sinapic acid.

2.9 Ring cleavage of aromatic compounds

The ring cleavage pathways are very important for microorganism to detoxify aromatic compounds and to use these as a carbon source (Vaillancourt *et al.,* 2006). The cleaved ring is then converted in

multiple steps to pyruvate, fumarate, succinate, oxaloacetate or acetyl-CoA and finally entering the TCA cycle. Prior to entering ring cleavage pathways, most aromatic compounds are converted to seven central ring-fission intermediates, i.e. catechol, protocatechuic acid, hydroxyquinol, hydroquinone, gentisic acid, gallic acid and pyrogallol (Fig. 11). In this section, we discuss the ring cleavage pathways through the seven central ring-fission intermediates. Since ring cleavage pathways are quite conserved and currently only intradiol cleavage is observed in fungi, we summarized their differences and similarities in Table S3 and in section 2.10.

2.9.1 Catechol ring cleavage

Catechol derives from several aromatic compounds such as benzoic, salicylic and vanillic acids, which are derived from coniferyl and *p*-coumaryl alcohols (Fig. 4, 6, 9). Catechol is one of the many industrial and commercially interesting aromatic compounds, which can be used as a precursor for artificial flavors and fragrances, and which also has antimicrobial activity (Kocaçalışkan *et al.,* 2006). In bacteria, there are two pathways for the cleavage of catechol (Fig. 11). In the intradiol cleavage (*ortho*-cleavage) pathway, the catechol 1,2-dioxygenase 1 and 2 (CatA1 and CatA2) of *Acinetobacter iwoffii* cleave the catechol forming *cis,cis*-muconic acid (Kim *et al.,* 1997)**.** Interestingly, *cis,cis*-muconic acid is a platform chemical used as a precursor for bioplastics (Curran *et al.,* 2013; Sun *et al.,* 2013; Xie *et al.,* 2014). Deletion of these dioxygenases resulted in accumulation of catechol. Neither CatA1 nor CatA2 has activity on protocatechuic acid. *Cis,cis*-muconic acid is further converted to muconolactone and then to 3-oxoadipate enol-lactone by the *P. putida* muconate cycloisomerase 1 (CatB) and muconolactone Delta-isomerase (CatC), respectively (Ornston, 1966, Parsek *et al.,* 1992). 3-Oxoadipate enol-lactone is further converted to 3-oxoadipate by CatD. 3-oxoadipate is converted 3-oxoadipate-SCoA which is converted to acetyl-CoA and succinate before entering the TCA cycle. The enzymes 3-oxoadipate CoA-transferase subunit A and B (CatI and CatJ or PcaI and PcaJ) of *P. putida* and β-ketoadipyl-CoA thiolase (PcaF) of *Pseudomonas knackmussii* catalyze these conversions (Kaschabek *et al.,* 2002). This pathway was also observed in *R. opacus* and candidate enzymes were identified with transcriptome analysis (Yoneda *et al.,* 2016).

The extradiol cleavage (*meta*-cleavage) pathway, in which catechol is converted to 2-oxoadipate, has been observed for several *Pseudomonas* species (Cao *et al.,* 2008; Hamzah and Al-Baharna, 1994; Kukor and Olsen, 1991). The first step is the conversion of catechol to 2-hydroxymuconate semialdehyde by catechol 2,3-dioxygenase (XylE in *P. putidia*) or by metapyrocatechase (DmpB in *Pseudomonas* sp. strain CF600) (Shingler *et al.,* 1992; Shu *et al.,* 1995). 2-hydroxymuconate semialdehyde is then converted to 2-oxopent-4-enoate and formate by 2-hydroxymuconate semialdehyde hydrolase (DmpD) or XylF in *P. putida* (Duggleby and Williams, 1986; Shingler *et al.,* 1992). An additional pathway was observed in which 2-hydroxymuconate semialdehyde is converted to 2-hydroxymuconate by 2-hydroxymuconic semialdehyde dehydrogenase (DmpC) or XylG in *P. putida*, then to 4-oxalocrotonate (keto form) by 2-hydroxymuconate tautomerase (DmpI), and finally to 2-oxopent-4-enoate by 4-oxalocrotonate decarboxylase (DmpH) (Duggleby and Williams, 1986; Inoue *et al.,* 1995; Shingler *et al.,* 1992). 2-Oxopent-4-enoate is then converted to 4-hydroxy-2-oxovalerate by 2-oxopent-4-enoate hydratase (DmpE), and further to pyruvate and acetaldehyde by 4-hydroxy-2-oxovalerate aldolase (DmpG) or XylK in *P. putida* (Duggleby and Williams, 1986; Shingler *et al.,* 1992). Acetaldehyde is further converted to acetyl-CoA by acetaldehyde dehydrogenase (DmpF) (Shingler *et al.,* 1992).

In fungi, the intradiol cleavage pathway cleaves catechol to *cis,cis*-muconic acid, followed by the conversion to muconolactone (Fig. 11). The yeast *C. albicans* uses the catechol 1,2-dioxygenase (Hqd2) to cleave the aromatic ring of catechol (Tsai and Li, 2007). This enzyme is substrate specific and has no activity towards hydroxyquinol and catechol-related compounds. Transcriptome data of *A. nidulans* revealed induction of a catechol 1,2-dioxygenase (AN4532) during growth on salicylic acid (Martins *et al.,* 2015). *Cis,cis*-muconic acid is converted to muconolactone, catalysed by *cis,cis*-

muconate cycloisomerase. Deletion of AN3895, encoding for an *cis,cis*-muconate cycloisomerase, in *A. nidulans*, resulted in accumulation of *cis,cis*-muconic acid (Martins *et al.,* 2015). Muconolactone is further converted by muconolactone isomerase. Deletion of AN4061, encoding for a muconolactone isomerase, in *A. nidulans,* resulted in accumulation of muconolactone when grown on salicylic acid (Martins *et al.,* 2015). Muconolactone is further converted to 3-oxoadipate-enol lactone by 3-oxoadipate enol-lactone hydrolase, encoded by AN4531. Deletion of AN4531 in *A. nidulans* resulted in accumulation of 3-oxoadipate-enol lactone. 3-oxoadipate-enol lactone is converted to 3-oxoadipate by and 3-oxoadipate-SCoA by 3-oxoadipate CoA-transferase (Osc1) and further to acetyl-CoA and succinate that enters the TCA cycle. Based on homology of AN3895, AN4061 and AN4531 and gene expression data of *C. albicans,* putative *cis,cis*-muconate cycloisomerase (Mci1), muconolactone isomerase (Mli1) and 3-oxoadipate enol-lactone hydrolase (Oel1) were suggested (Gérecová *et al.,* 2015).

2.9.2 Protocatechuic acid ring cleavage

Protocatechuic acid derives from the aromatic compounds *p*-hydroxybenzoic acid and vanillic acid, the conversion products of *p*-coumaric acid and ferulic acid, respectively (Fig. 4, 7). Protocatechuic acid is the second aromatic compound where most aromatic pathways end**.** In bacteria, the aromatic ring of protocatechuic acid can be cleaved at the 2,3-, 3,4- and 4,5-side (Fig. 11). The most observed pathway in this group is the protocatechuic acid intradiol (3,4-) cleavage pathway, by which the ring of protocatechuic acid is cleaved to form 3-carboxy-*cis*,*cis*-muconic acid (Harwood and Parales, 1996). This cleavage is catalyzed by protocatechuate 3,4-dioxygenases (PcaGH) of *P. putida* (Harwood *et al.,* 1994). 3-Carboxy-*cis,cis*-muconic acid is converted to *γ*-carboxymuconolactone by 3-carboxy-*cis,cis*-muconate cycloisomerase (PcaB), which is converted to 3-oxoadipate enol-lactone by 4-carboxymuconolactone decarboxylase (PcaC) (Buchan *et al.,* 2000). Subsequently, 3-oxoadipate enol-lactone is converted to 3-oxoadipate by 3-oxoadipate enol-lactonase 1 (PcaD) and is further converted to 3-oxodipate-SCoA by PcaF.

Two protocatechuic acid extradiol cleavage pathways are observed in bacteria. The 4,5-cleavage pathway is observed in *Sphingobium* sp. strain SYK-6 converts protocatechuic acid to 4-carboxy-2-hydroxymuconate-6-semialdehyde by the protocatechuate 4,5-dioxygenase (LigAB), and is further converted through a non-enzymatic reaction to its intramolecular hemiacetal form (Masai *et al.,* 2007a). This compound is hydrated to 2-pyrone-4,6-dicarboxylate by 4-carboxy-2-hydroxymuconate-6-semialdehyde dehydrogenase (LigC) (Masai *et al.,* 2000). Interestingly, 2-pyrone-4,6-dicarboxylate is also the 4,5-cleavage product of gallic acid revealing a connection between the ring cleavage pathway of protocatechuic acid and gallic acid (Dennis *et al.,* 1973). 2-Pyrone-4,6-dicarboxylate is further converted to 4-oxalomesaconate (enol form) by 2-pyrone-4,6-dicarboxylate hydrolase (LigI) (Masai *et al.,* 2007a). 4-oxalomesaconate (enol form) can be converted to either its keto form by the putative 4-oxalomesaconate tautomerase (LigU or GalD) or to 4-carboxy-4-hydroxy-2-oxoadipate by 4-oxalomesaconate hydratase (LigJ or GalB) (Hara *et al.,* 2000, 2003; Hogancamp and Raushel, 2018; Hogancamp *et al.,* 2018; Nogales *et al.,* 2005; Kamimura and Masai, 2014). 4-Carboxy-4-hydroxy-2-oxoadipate is cleaved by 4-carboxy-4-hydroxy-2-oxoadipate aldolase (LigK or GalC) to form oxaloacetate and pyruvate (Hara *et al.,* 2003; Masai *et al.,* 2007a; Nogales *et al.,* 2005; 2011). An alternative pathway has been described for *Pseudomonas testosteroni* in which 4-carboxy-2-hydroxymuconate-6-semialdehyde is converted to 4-hydroxy-4-methyl-2-oxoglutarate and then to two pyruvate units by a 4-hydroxy-4-methyl-2-oxoglutarate aldolase (Dennis *et al.,* 1973). The enzymes of this alternative pathway are not characterized.

The second extradiol pathway cleaves protocatechuic acid at the 2,3 side. This pathway has been described for *Paenibacillus* sp. in which protocatechuate 2,3-dioxygenase (PraA) cleaves protocatechuic acid to form 5-carboxy-2-hydroxymuconate-6-semialdehyde (Crawford *et al*., 1979, Kasai *et al.,* 2009). This compound is decarboxylated by 5-carboxy-2-hydroxymuconate-6-

semialdehyde decarboxylase (PraH) to 2-hydroxymuconate-6-semialdehyde, followed by the conversion to 2-hydroxymuconate by 2-hydroxymuconate-6-semialdehyde dehydrogenase (PraB). 2-Hydroxymuconate dehydrogenase (PraC) catalyzes the conversion of 2-hydroxymuconate to 4-oxalocrotonate which is followed by the formation of 2-hydroxypenta-2,4-dienoate catalyzed by 4-oxalocrotonate decarboxylase (PraD). Thereafter, 2-hydroxypenta-2,4-dienoate is converted to 4-hydroxy-2-oxovalerate by 2-hydroxypenta-2,4-dienoate hydratase (PraE), which is converted by 4-hydroxy-2-oxovalerate aldolase (PraF) to pyruvic acid and acetaldehyde. The latter compound is converted to acetyl-SCoA by acetaldehyde dehydrogenase (PraG). An alternative pathway was observed in *K. pneumoniae* in which protocatechuic acid is converted to catechol by protocatechuate decarboxylase (AroY) and further converted through the catechol pathway (Sonoki *et al.,* 2014).

In fungi, the intradiol cleavage pathway is observed in which protocatechuic acid is cleaved to form 3-carboxy-*cis,cis*-muconic acid (Harwood and Parales, 1996; Mazur *et al.,* 1994). Transcriptome data of *A. nidulans* revealed induction of a protocatechuate 3,4-dioxygenase (AN8566) during growth on benzoic acid (Martins *et al.,* 2015). After ring cleavage, 3-carboxy-*cis,cis*-muconic acid is converted to β-carboxymuconolactone and is catalyzed by 3-carboxy-*cis,cis*-muconate lactonizing enzyme (CLME) of *N. crassa* (Kajander *et al.,* 2002). In *A. nidulans*, the gene assigned to this conversion is AN1151 encoding for carboxy-*cis,cis*-muconate cyclase, deletion of AN1151 resulted in the accumulation of 3-carboxy-*cis,cis*-muconic acid and abolished growth of *A. nidulans* on benzoic acid (Martins *et al.,* 2015). 3-Carboxymuconolactone is converted to 3-oxoadipate and 3-oxoadipate-SCoA and is further converted to acetyl-CoA and succinate that enters the TCA cycle. In *A. nidulans*, the gene AN5232 encoding for 3-carboxymuconolactone hydrolase is predicted to catalyze this conversion. Deletion of AN5232 resulted in abolished growth of *A. nidulans* on benzoic acid and the accumulation of 3-carboxymuconolactone acid (Martins *et al.,* 2015), indicating that this fungus has no alternative pathway for this compound. In yeasts, no protocatechuic acid ring cleavage pathways were observed, but protocatechuic acid is converted to catechol by the yeast *A. adeninivorans* and is catalyzed by Gdc (Meier *et al.,* 2017). Another pathway has been described in the yeasts *T. cutaneum* and *C. parapsilosis* in which protocatechuic acid is converted to hydroxyquinol by Mnx1 (Anderson and Dagley, 1980; Eppink *et al.,* 1997; Holesova *et al.,* 2011).

2.9.3. Hydroxyquinol and hydroquinone ring cleavage

Hydroxyquinol derives from several aromatic compounds such as *p*-hydroxybenzoic and vanillic acids, which are derived from ferulic acid and *p*-coumaric acid (Fig. 4, 7). In bacteria, two hydroxyquinol ring cleavage pathways have been described (Fig. 11). The first pathway converts hydroxyquinol through intradiol ring cleavage to maleylacetate (Chapman and Ribbons, 1976; Daubaras *et al.,* 1996). In *Nocardioides simplex*, this conversion is catalyzed by hydroxyquinol 1,2-dioxygenase (ChqB) (Travkin *et al.,* 2006). Maleylacetate is then converted to 3-oxoadipate by maleylacetate reductase (LinF), after which it is converted to 3-oxoadipate-SCoA and further to acetyl-CoA and succinate that enters the TCA cycle (Endo *et al.,* 2005).

The second pathway converts hydroxyquinol through extradiol cleavage at the 4,5-side to form 2,4-dihydroxymuconic semialdehyde (Chapman and Ribbons, 1976). 2,4-dihydroxymuconic semialdehyde is further converted to acetylpyruvate and formate. Finally, acetylpyruvate is converted to acetate and pyruvate and they are introduced to the TCA cycle. The enzymes catalyzing these reactions are unknown. In the filamentous fungus *S. pulverulentum* (*P. chrysosporium*), and the yeasts *C. parapsilosis* and *C. albicans,* the intradiol ring cleavage of hydroxyquinol to maleylacetate is observed (Buswell and Eriksson, 1979; Eppink *et al.,* 2000; Gérecová *et al.,* 2015; Rieble *et al.,* 1994). In *C. parapsilosis,* this conversion is catalyzed by the hydroxyquinol dioxygenase 1 (Hdx1) (Holesova *et al.,* 2011). Maleyacetate is further converted to 3-oxoadipate and 3-oxoadipate-SCoA.

Hydroquinone derives from the aromatic compounds 4-hydroxyphenylacetate and *p*-hydroxybenzoic acid (Fig 7, 8). In the bacteria *P. putida, P. fluorescens* ACB and *Sphingobium* sp. strain SYK-6, hydroquinone is converted through extradiol cleavage to 4-hydroxymuconic semialdehyde and is catalyzed by the chlorohydroquinone 1,2-dioxygenase (LinE or HapCD) (Darby *et al.,* 1987; Endo *et al.,* 2005; Miyauchi *et al.,* 1999; Moonen *et al.,* 2008a, 2008b). In *P. fluorescens* ACB, hydroquinone is converted by hydroquinone dioxygenase (HapCD) to 4-hydroxymuconic semialdehyde and further degraded through maleylacetate to 3-oxoadipate (Moonen *et al.,* 2008a, 2008b). The conversion of 4-hydroxymuconic semialdehyde to maleyacetate was suggested to be catalyzed by 4-hydroxymuconic semialdehyde dehydrogenase (HapE). The reduction of maleylacetate to 3-oxoadipate was suggested to be catalyzed by maleylacetate reductase (HapF). In filamentous fungi and yeast, no ring cleavage of hydroquinone was observed instead it is hydroxylated to hydroxyquinol (Jones *et al.,* 1994; Holesova *et al.,* 2011). In the yeast *C. parapsilosis*, this conversion is catalyzed by Mnx3 (Eppink *et al.,* 2000).

2.9.4. Gentisic acid ring cleavage

Gentisic acid is a conversion product of 3-hydroxybenzoic acid, *p*-hydroxybenzoic acid and salicylic acid (Fig. 6, 7, 9). In the bacteria *B. laterosporus*, *Bacillus* spp., *Peanibacillus* sp. and *Stryptomyces* spp., gentisic acid is converted through extradiol ring cleavage to maleylpyruvate catalyzed by the gentisate 1,2-dioxygenase (SdgD or BagI) (Fig. 11) (Clark and Buswell, 1979; Ishiyama *et al.,* 2004; Liu and Zhou *et al.,* 2012; Sutherland *et al.,* 1981; Zhao *et al.,* 2018). Maleylpyruvate is then further converted to fumarylpyruvate by L-cysteine-dependent maleylpyruvate isomerase (BagL) that is further hydrolyzed by fumarylpyruvate hydrolase (BagK) into fumarate and pyruvate that enter the TCA cycle (Evans, 1963; Liu and Zhou *et al.,* 2012). Another pathway was observed in which maleylpyruvate was hydrolyzed by a GSH-independent maleylpyruvate hydrolase to maleic acid and pyruvate (Hopper and Chapman, 1971).

In the yeast *C. parapsilosis,* gentisate dioxygenase (Gdx1) catalyzes the cleavage of the aromatic ring of gentisic acid to maleylpyruvate (Holesova *et al.,* 2011). Maleylpyruvate is converted to fumarylpyruvate that is split into fumarate and pyruvate by fumarylpyruvate dioxygenase 1 (Fph1). Interestingly, in the yeast *Trichosporon cutaneum*, gentisic acid is converted to hydroxyquinol (Anderson and Dagley, 1980). Trace amounts of catechol were detected when *S. sclerotiorum* was grown in glucose supplemented with gentisic acid indicating that gentisic acid is converted to catechol (Penn and Daniel, 2013).

2.9.5 Gallic acid and pyrogallol ring cleavage

Gallic acid and pyrogallol are the central intermediates of the sinapic acid and syringic acid metabolic pathways (Fig. 10, 11). In the bacteria *Sphingobium* sp. strain SYK-6*, P. testosteroni* and *P. putida*, gallic acid is converted through intradiol ring cleavage to 4-oxalomesaconate (keto form) catalyzed by the gallate dioxygenase DesB or GalA (Dennis *et al.,* 1973; Kasai *et al.,* 2005; Nogales *et al.,* 2005; Tack *et al.,* 1972). This pathway has also been suggested for the fungi *A. oryzea, A. flavus* and *A. japonicus* (Guo *et al.,* 2014; Gurujeyalakshmi and Mahadevan, 1987; Milstein *et al.,* 1983). From 4-oxalomesaconate the pathway continues as described for the protocatechuic acid 4,5-cleavage pathway.

In the yeast *A. adeninivorans*, pyrogallol is converted to 2-hydroxymuconic acid (Meier *et al.,* 2017) and the pathway continues as described in the catechol extradiol ring cleavage pathway (Fig. 11). This pathway has also been suggested for the fungus *A. oryzea* (Guo *et al.,* 2014).

2.10 Discussion

All aromatic metabolic pathways described in this review are summarized in Table S3. Various aromatic metabolic pathways have been described for different species. The reason why so many different aromatic metabolic strategies are observed in nature is currently unknown. However, one

can speculate that the natural habitat of a microorganism has a major influence on which metabolic pathways are present or activated. Many factors can influence which pathway is present, such as substrate availability, anaerobic or aerobic conditions, and co-factor availability. This will result in selection of the most beneficial pathway for that habitat. In addition, many species have two or more metabolic pathways to convert one single aromatic compound, which indicates that these pathways can have different activators. Most aromatic metabolic pathways have been observed in bacteria, fungi and yeasts (Table S3) however, several pathways were only observed in either bacteria, fungi or yeasts. It appears that most of the unique pathways were observed in bacteria, but this is likely due to the larger amount of research that is performed on these microorganisms. There are also many shared metabolic pathways, such as those presented in the ferulic acid and vanillin pathways (sections 2.2 and 2.3) in which most pathways are observed in both bacteria and fungi. The ferulic acid metabolic pathway is important for many microorganisms due to the interaction of ferulic acid with polysaccharides such as xylan and pectin (Mäkelä *et al.*, 2015), which could explain the overlap between ferulic acid metabolic pathways of bacteria and fungi. However, several pathways also appear to be unique for fungi and yeasts. The decarboxylation of cinnamic acid to styrene (Fig. 5) and the *para*-hydroxylation of benzoic acid to *p*-hydroxybenzoic acid (Fig. 6, 7) have not been observed in bacteria (Table S3). Also between ascomycete and basidiomycete fungi differences were observed. For example, pathways 3 and 4 (section 2.6) in which *p*-coumaric acid is converted to *p*-hydroxybenzoic acid through β-hydroxy-(*p*-hydroxyphenyl)-propionic acid and 3-(*p*-hydroxyphenyl)-propionic acid, and the ferulic acid hydroxylation converting it to 2-hydroxyferulic acid or 5-hydroxyferulic acid were only observed in basidiomycetes. This indicates that many different metabolic strategies exist to convert aromatic compounds, which could be a reason for the efficient lignin degradation of basidiomycetes.

Due to the lack of data in fungi, it is not feasible to suggest the main aromatic metabolic pathways for all the mentioned aromatic metabolic pathways. However, several similar strategies were observed for different aromatic compounds. For example, non-oxidative decarboxylation has been observed for ferulic acid, *p*-coumaric acid and sinapic acid and so it is possible to be the main pathway for ferulic acid and *p*-coumaric acid in microorganisms. In most aromatic pathways, the aliphatic chain is first modified from the alcohol towards the aldehyde form, after which they are converted to their acidic form. This was observed for many aromatic alcohols such as coniferyl alcohol, *p*-coumaryl alcohol, benzyl alcohol and vanillyl alcohol (Fig. 2, 3, 6, 8). Thereafter, the compounds are modified through decarboxylation forming *p*-hydroxybenzoic acid, vanillic acid and syringic acid, which are the key compounds of the aromatic metabolic pathways (Fig. 3, 7, 6, 10). All major pathways are funnelled to seven central ring-fission intermediates (Fig. 1, 11). Aromatic compounds derived from the G and H subunits of lignin are converted to protocatechuic acid, catechol, hydroxyquinol or gentisic acid, while aromatic compounds derived from the S subunit are converted to gallic acid and pyrogallol. Two catechol ring cleaving pathways have been described. The intradiol cleavage pathway has been well studied in bacteria, while in fungi the enzymes are identified but need to be further characterized. Currently, much research is focused on the production of *cis,cis*-muconic acid, the cleavage product of catechol, which can be used as precursor for the production of bioplastics such as nylon and polyethylene terephthalate (Becker *et al.,* 2018; Brückner *et al.,* 2018; Curran *et al.,* 2013; Sun *et al.,* 2013; Xie *et al.,* 2014). The increased focus makes it of great interest to study these pathways further in filamentous fungi. The extradiol cleavage pathway of catechol has not been reported for fungi or yeast. Three protocatechuic acid ring cleavage pathways have been described. The intradiol ring cleavage pathway was observed in bacteria and filamentous fungi, which one major difference was observed. Bacteria convert 3-carboxy-*cis,cis*-muconic acid to γ-carboxymuconolactone and further to 3-oxoadipate enol-lactone and 3-oxoadipate while filamentous fungi convert 3-carboxy-*cis,cis*-muconic acid to β-carboxymuconolactone and further to 3-oxoadipate. In yeasts, the ring cleavage has so far been observed for catechol and hydroxyquinol, but not for protocatechuic acid, which instead may be decarboxylated or hydroxylated to form catechol or hydroxyquinol, respectively, prior

the cleavage (Anderson and Dagley, 1980; Holesova *et al.,* 2011; Meier *et al.,* 2017). The decarboxylation of protocatechuic acid to catechol was also observed in bacteria (Sonoki *et al.,* 2014). Two hydroxyquinol ring cleavage pathways have been described. In the intradiol ring cleavage pathway, bacteria and fungi seem to share similar mechanism. An extradiol ring cleavage of hydroxyquinol has not been observed for fungi. Currently, only one gentisic acid ring cleavage pathway has been described for bacteria and yeasts, whereas no pathway has been observed in filamentous fungi. The cleavage of pyrogallol and gallic acid result in an overlap between the extradiol cleavage of catechol and the 2,3 extradiol cleavage of protocatechuic acid revealing that parts of these pathways are present in fungi. Alternative ring cleavage pathways have been observed on several aromatic compounds such as 2,3-dihydroxybenzoic acid, 2,3,4-trihydroxycinnamic acid and 3,4,5-trihydroxycinnamic acid cleavage pathway however these are observed sporadically (Crestini and Sermanni, 1994; Marín *et al.,* 2012). It was suggested that intradiol ring cleavage pathways are the main mechanism found in bacteria (Bugg *et al.,* 2011b). This is presumably the same in filamentous fungi as no extradiol ring cleaving pathway has been reported for these seven central ring-fission intermediates thus far. The cleavage of pyrogallol and gallic acid result in an overlap between the extradiol cleavage of catechol and the 2,3 extradiol cleavage of protocatechuic acid indicating that parts of these pathways are present in fungi.

Most bacterial aromatic metabolic enzymes have been characterized, while only a few of these enzymes are characterized in fungi and yeasts (Tables S1 and S2). Most bacterial genes encoding a set of related enzymes, such as *cat*, *dmp*, *gal*, *pca*, etc. (Tables S1, S2), are clustered on the genome. While currently only a few enzymes are characterized in fungi and yeasts, it appears that these are scattered over the genome. Several BLAST searches using amino acid sequences of bacterial enzymes to find potential homologs in fungi and yeast were performed. These have not been shown in the review since they resulted in no suitable (<25% identity) homologs making them unlikely to be related to the catalytic function. Homology between bacterial and fungal enzymes is low, making it difficult to identify these enzymes in fungi. However, the increasing number of fungal genomes, transcriptomes and proteomes will aid in the identification and characterization of fungal aromatic metabolic enzymes.

3. Conclusions

This review compares the similarities and differences in aromatic metabolic pathways, as well as unique aromatic metabolic pathways in bacteria, filamentous fungi and yeasts. In addition, it sheds light on the missing puzzles in particular for the fungal pathways. Understanding the aromatic metabolic pathways can reveal for example, how pathogens evade or suppress the plant defense system and cause diseases. More importantly, discovery of novel aromatic modifying enzymes is of great interest for the valorization of lignin and compounds derived from it. This will offer great opportunities for innovations to produce valuable compounds for many industries, e.g. food, plastics, cosmetics and pharmaceutical industries.

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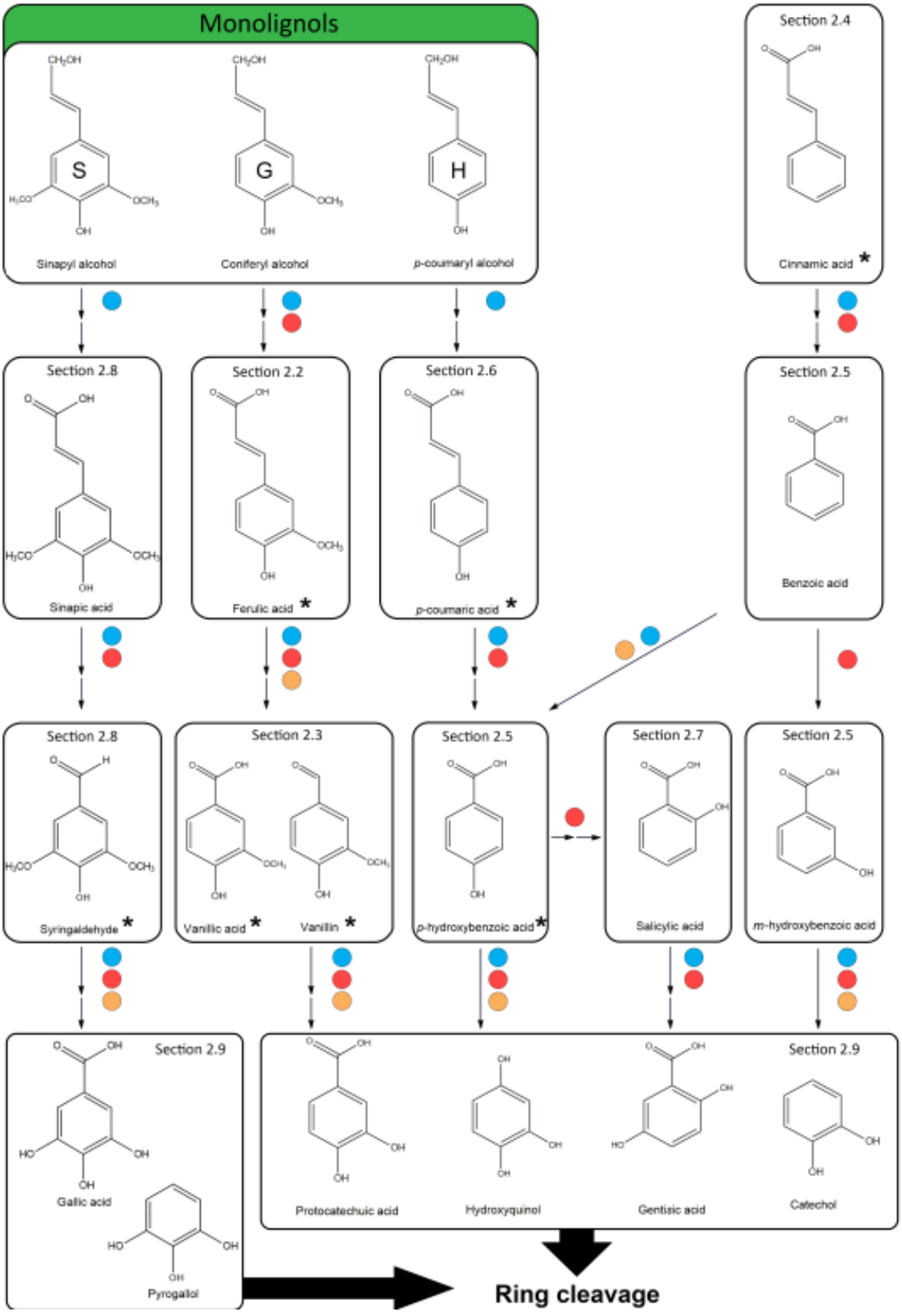

Figure 1. Roadmap of the main aromatic metabolic pathways in bacteria, fungi and yeast. Arrows indicate in which species these aromatic metabolic pathways are observed. Species are marked with a red dot for bacteria, blue for fungi and orange for yeast. Aromatic compounds marked with an asterisk are released during lignin degradation.

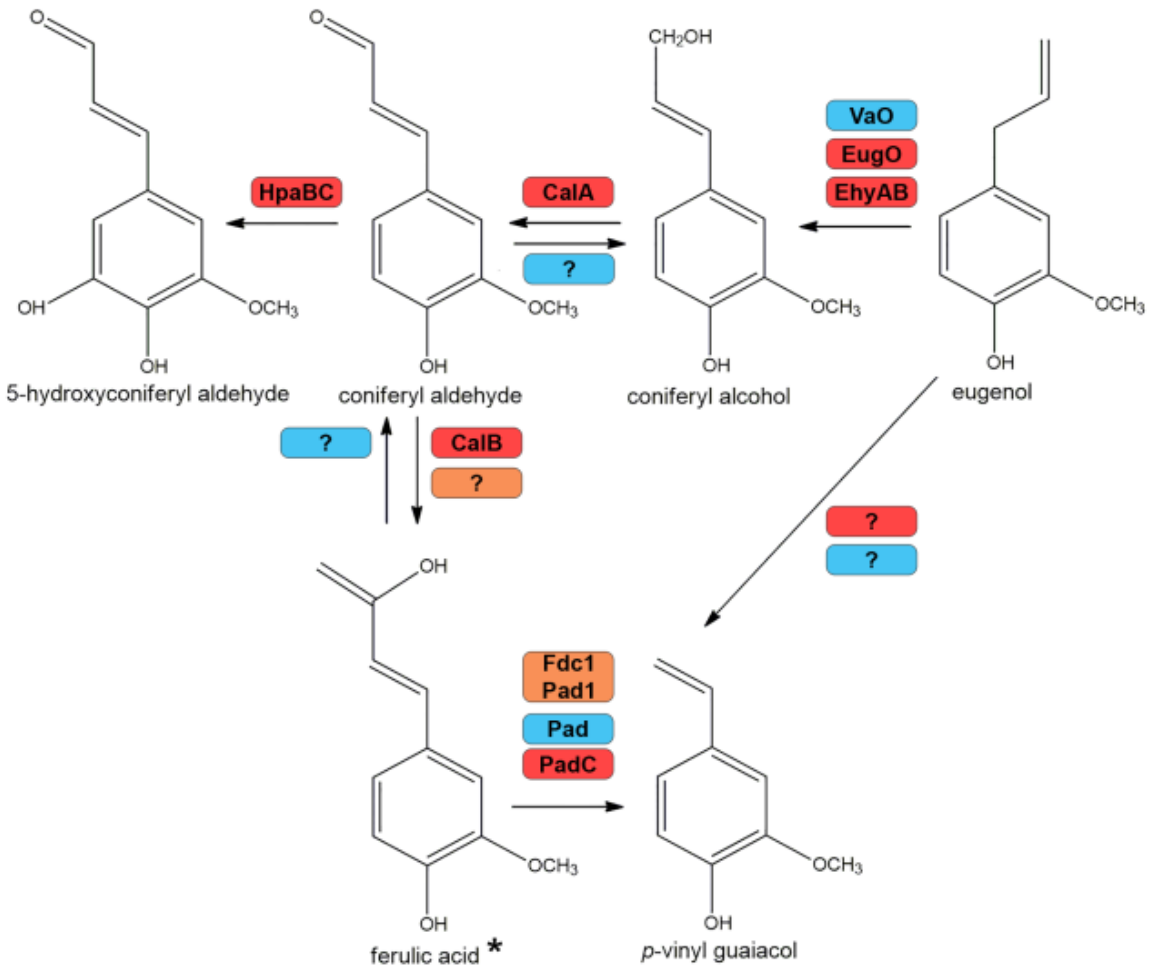

Figure 2. Bacterial, fungal and yeast aromatic metabolic pathways of coniferyl alcohol, eugenol and related aromatic compounds. The aromatic converting enzymes of bacteria (red), filamentous fungi (blue) and yeast (orange) are boxed next to the corresponding pathway. Question marks indicate that the enzyme is not identified. Aromatic compounds marked with an asterisk are released during lignin degradation.

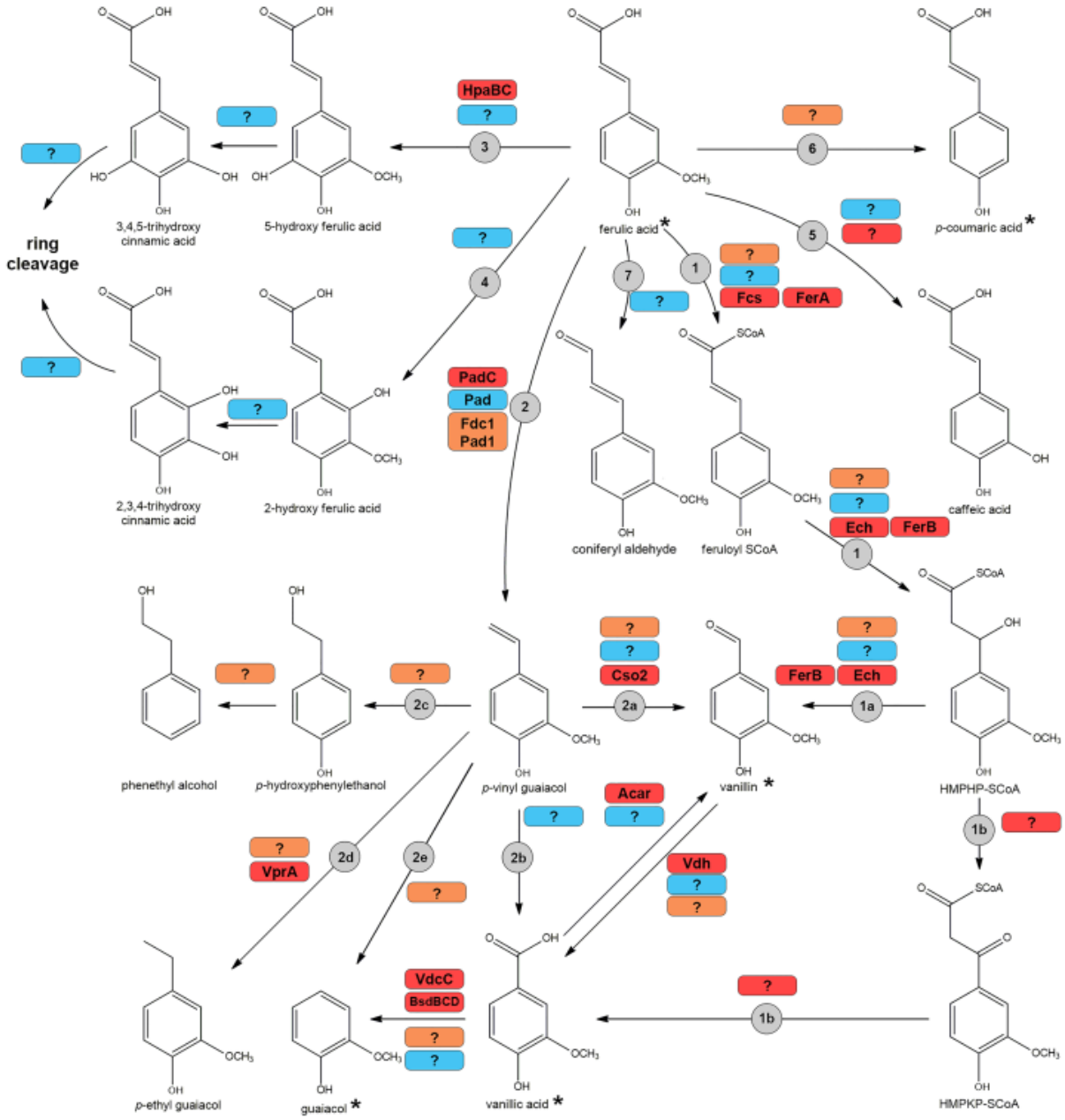

Figure 3. Bacterial, fungal and yeast aromatic metabolic pathways of ferulic acid and related aromatic compounds. The aromatic converting enzymes of bacteria (red), filamentous fungi (blue) and yeast (orange) are boxed next to the corresponding pathway. Question marks indicate that the enzyme is not identified. Pathway numbers corresponds with the numbers given in section 2.2. Aromatic compounds marked with an asterisk are released during lignin degradation.

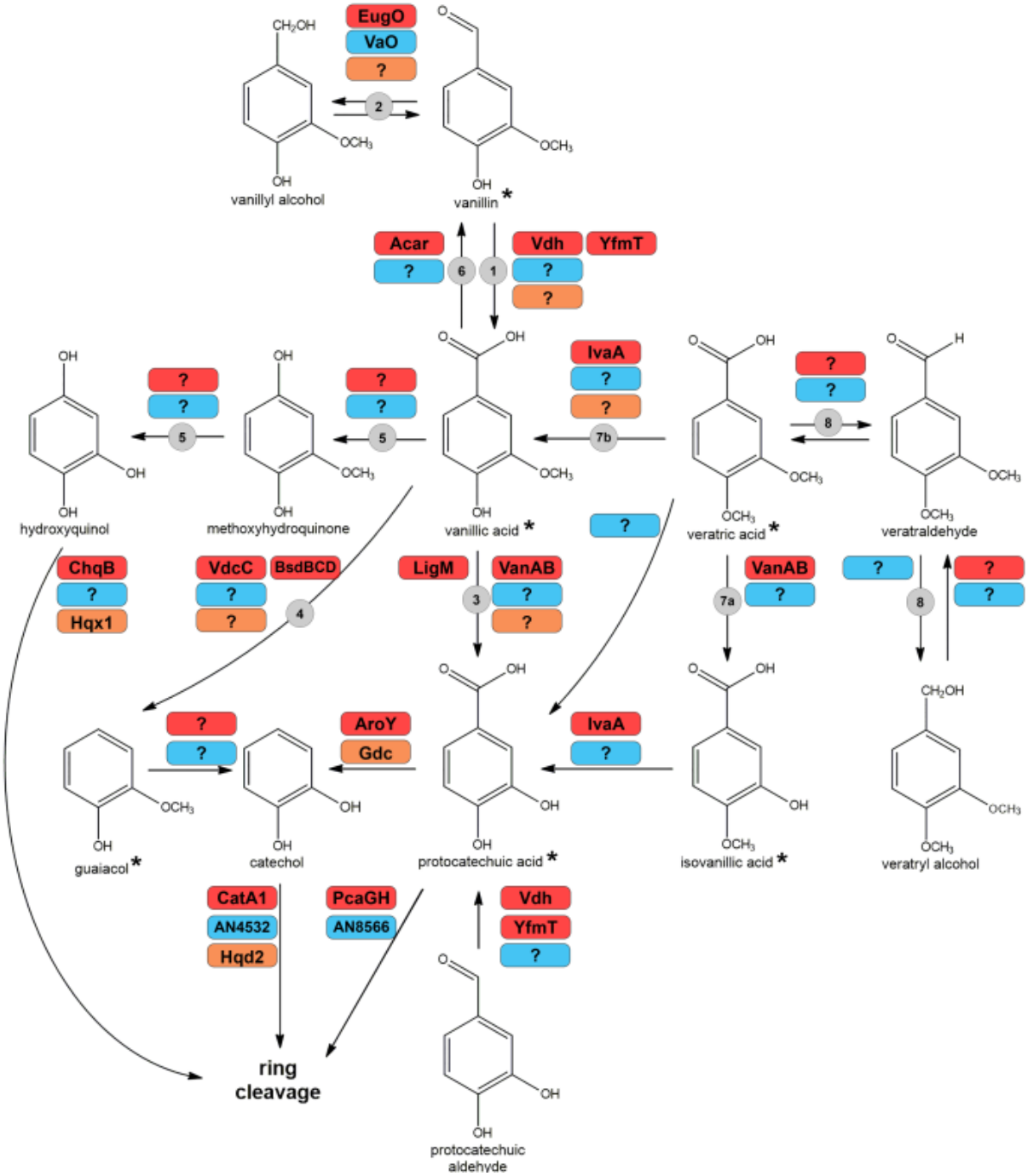

Figure 4. Bacterial, fungal and yeast aromatic metabolic pathways of vanillin, vanillic acid and related aromatic compounds. The aromatic converting enzymes of bacteria (red), filamentous fungi (blue) and yeast (orange) are boxed next to the corresponding pathway. Question marks indicate that the enzyme is not identified. Pathway numbers corresponds with the numbers given in section 2.3. Aromatic compounds marked with an asterisk are released during lignin degradation.

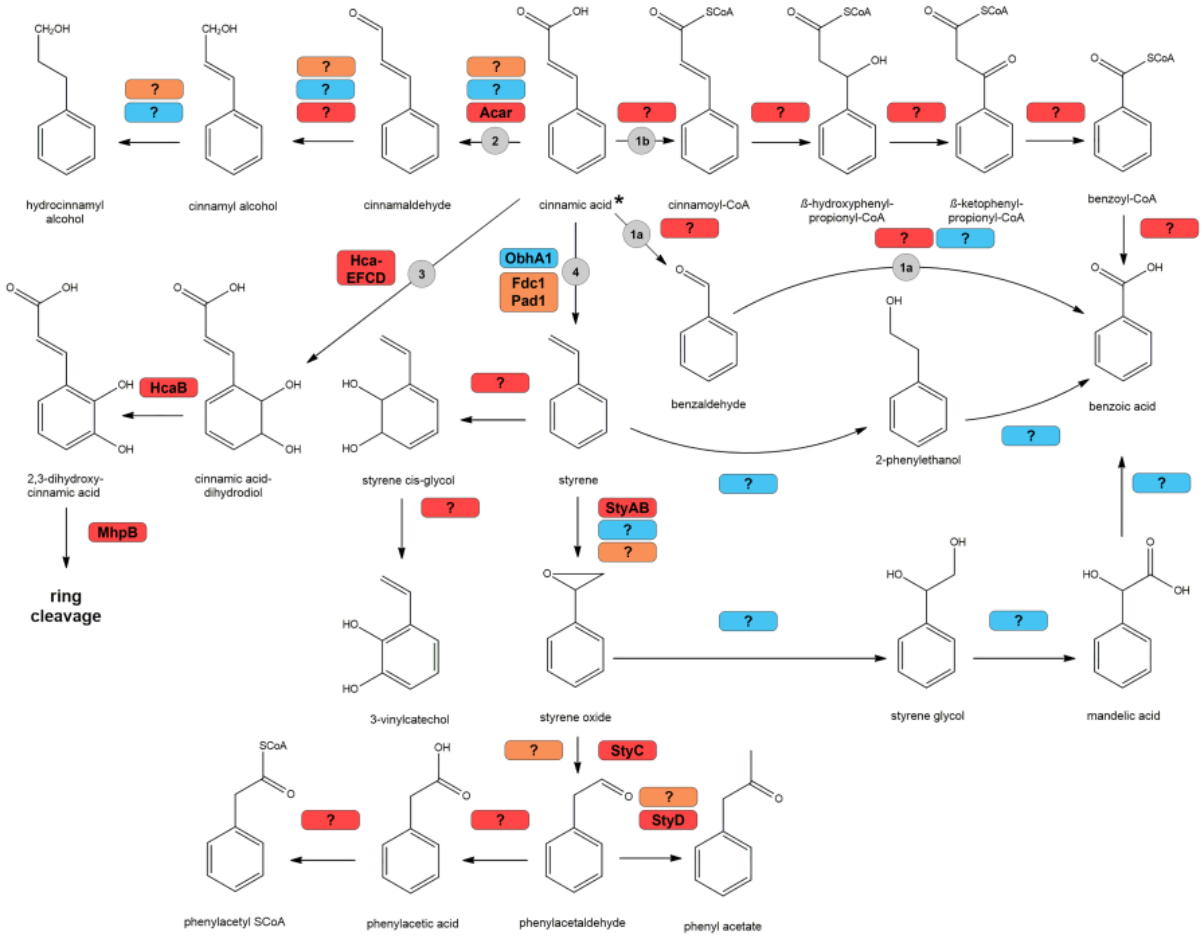

Figure 5. Bacterial, fungal and yeast metabolic pathways of cinnamic acid and related aromatic compounds. The aromatic converting enzymes of bacteria (red), filamentous fungi (blue) and yeast (orange) are boxed next to the corresponding pathway. Question marks indicate that the enzyme is not identified. Pathway numbers corresponds with the number given in section 2.4. Aromatic compounds marked with an asterisk are released during lignin degradation.

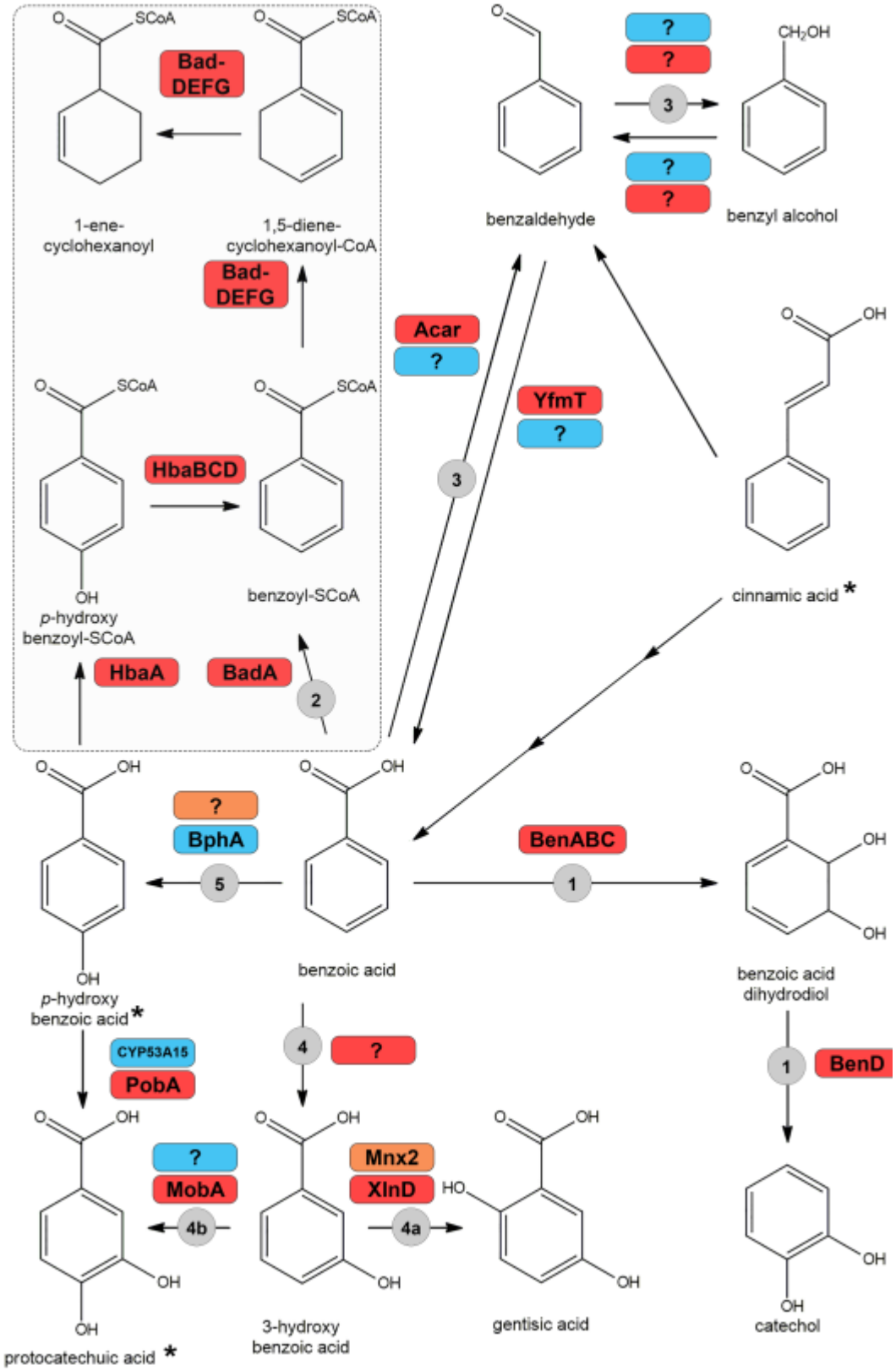

Figure 6. Bacterial, fungal and yeast aromatic metabolic pathways of benzoic acid and related aromatic compounds. The aromatic converting enzymes of bacteria (red), filamentous fungi (blue) and yeast (orange) are boxed next to the corresponding pathway. Question marks indicate that the enzyme is not identified. Pathway numbers corresponds with the numbers given in section 2.5. Compounds within the dashed box are obtained through anaerobic conversion. Aromatic compounds marked with an asterisk are released during lignin degradation.

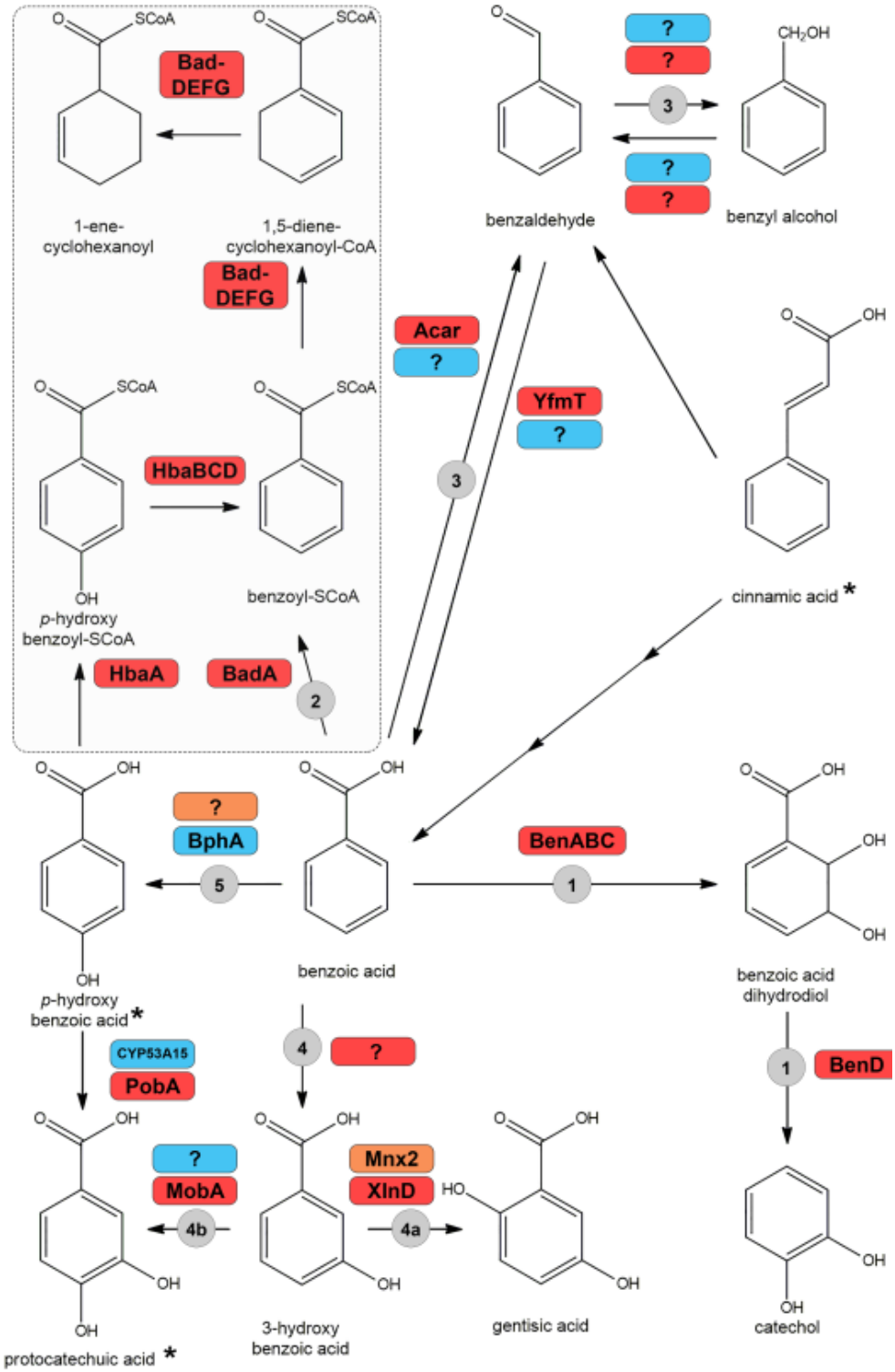

Figure 7. Bacterial, fungal and yeast aromatic metabolic pathways *p*-hydroxybenzoic acid and related aromatic compounds. The aromatic converting enzymes of bacteria (red), filamentous fungi (blue) and yeast (orange) are boxed next to the corresponding pathway. Question marks indicate that the enzyme is not identified. Pathway numbers corresponds with the numbers given in section 2.5. Compounds within the dashed box are obtained through anaerobic conversion. Aromatic compounds marked with an asterisk are released during lignin degradation.

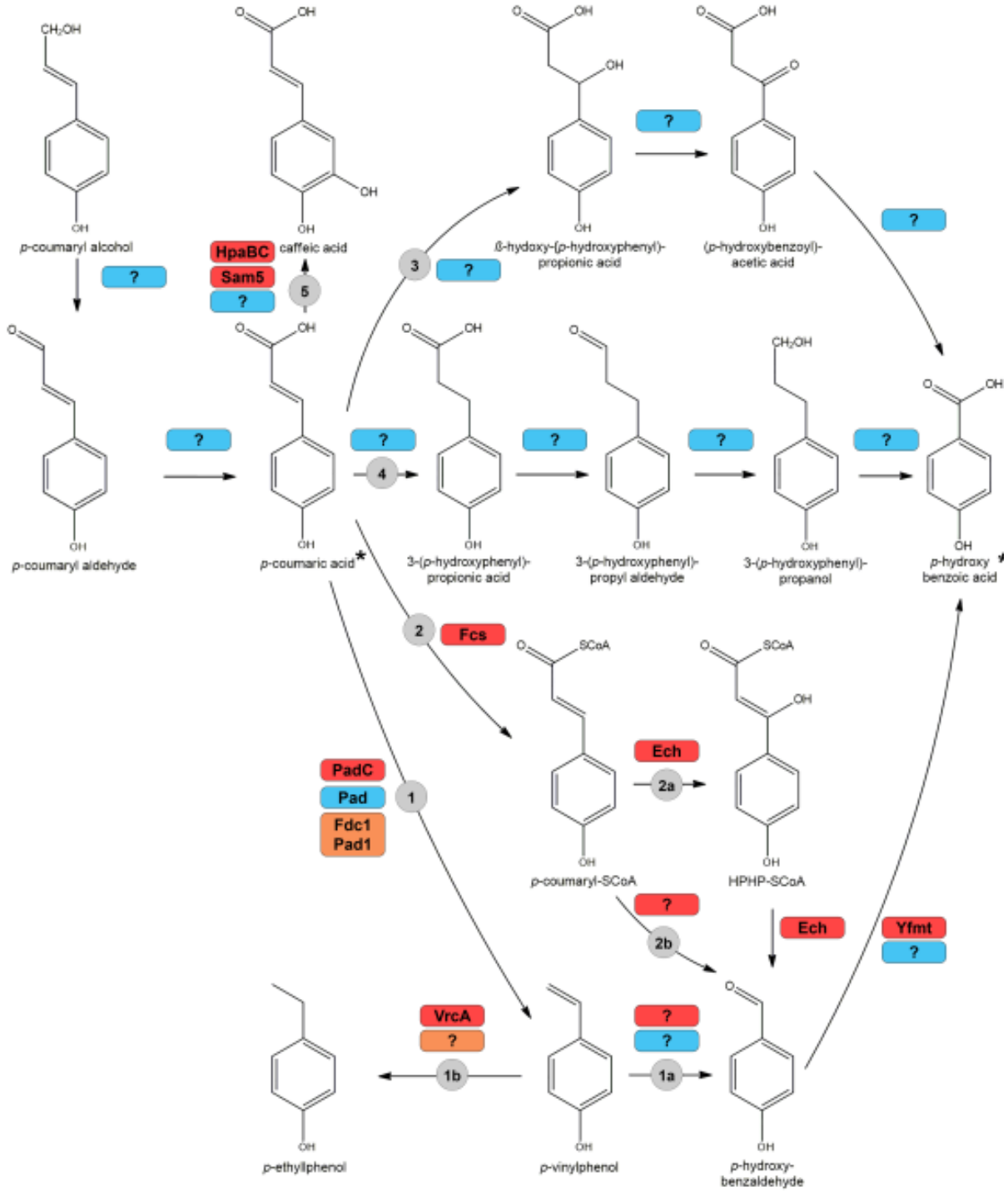

Figure 8. Bacterial, fungal and yeast aromatic metabolic pathways of *p*-coumaric acid and related aromatic compounds. The aromatic converting enzymes of bacteria (red), filamentous fungi (blue) and yeast (orange) are boxed next to the corresponding pathway. Question marks indicate that the enzyme is not identified. Pathway numbers corresponds with the numbers given in section 2.6. Aromatic compounds marked with an asterisk are released during lignin degradation.

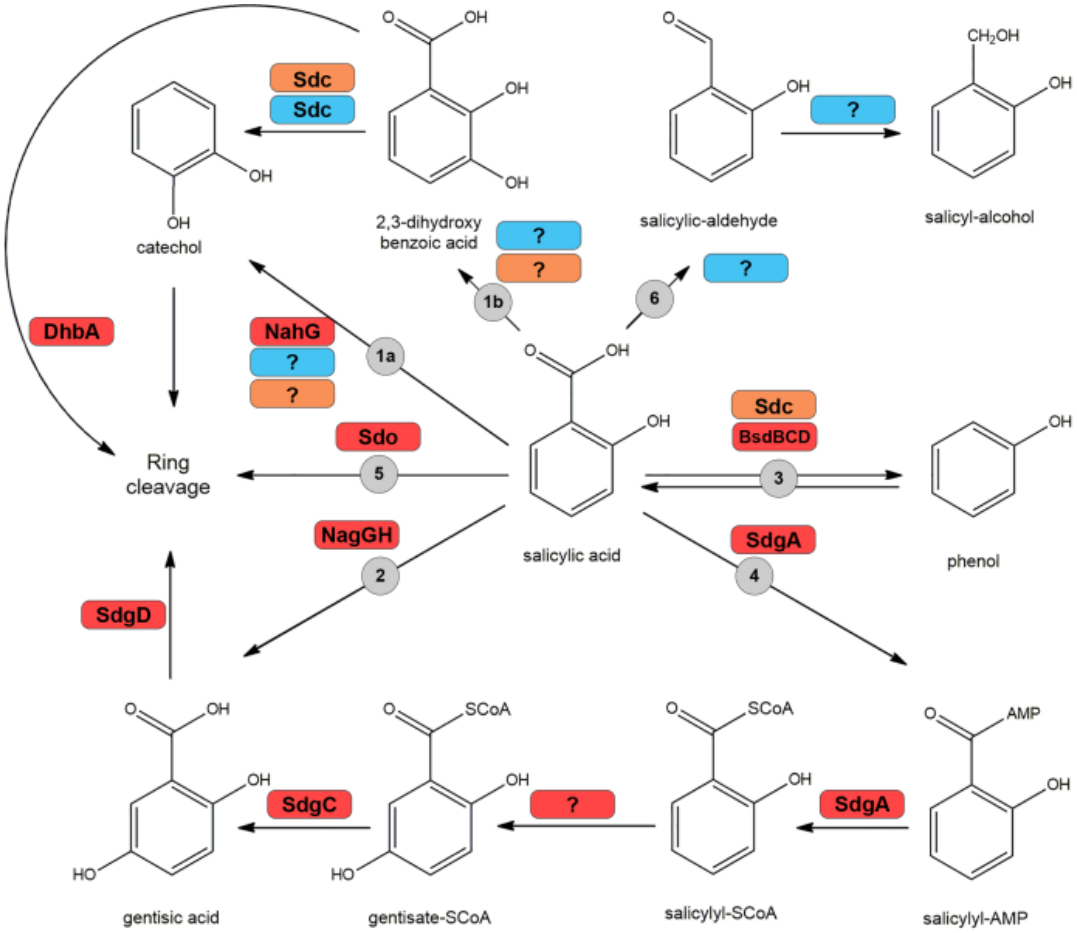

Figure 9. Bacterial, fungal and yeast aromatic metabolic pathways of salicylic acid. The aromatic converting enzymes of bacteria (red), filamentous fungi (blue) and yeast (orange) are boxed next to the corresponding pathway. Question marks indicate that the enzyme is not identified. Pathway numbers corresponds with the numbers given in section 2.7. Aromatic compounds marked with an asterisk are released during lignin degradation.

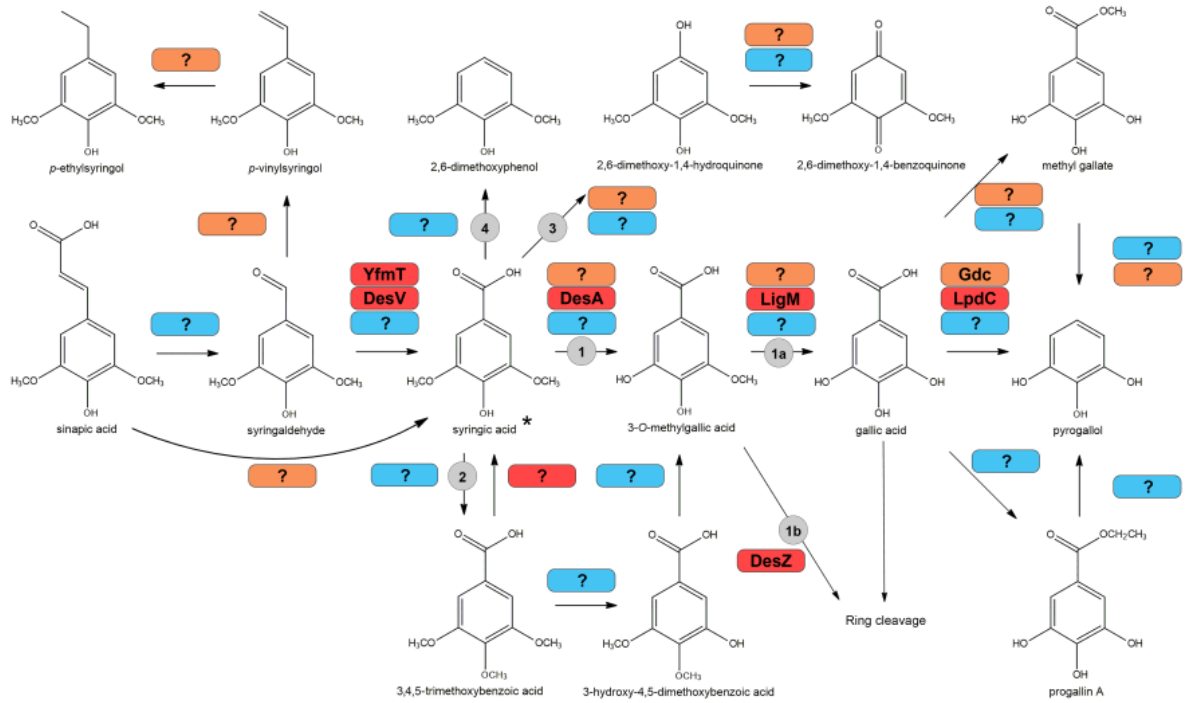

Figure 10. Bacterial, fungal and yeast aromatic metabolic pathways of sinapic acid, syringic acid and related aromatic compounds. The aromatic converting enzymes of bacteria (red), filamentous fungi (blue) and yeast (orange) are boxed next to the corresponding pathway. Question marks indicate that the enzyme is not identified. Pathway numbers corresponds with the numbers given in section 2.8. Aromatic compounds marked with an asterisk are released during lignin degradation.

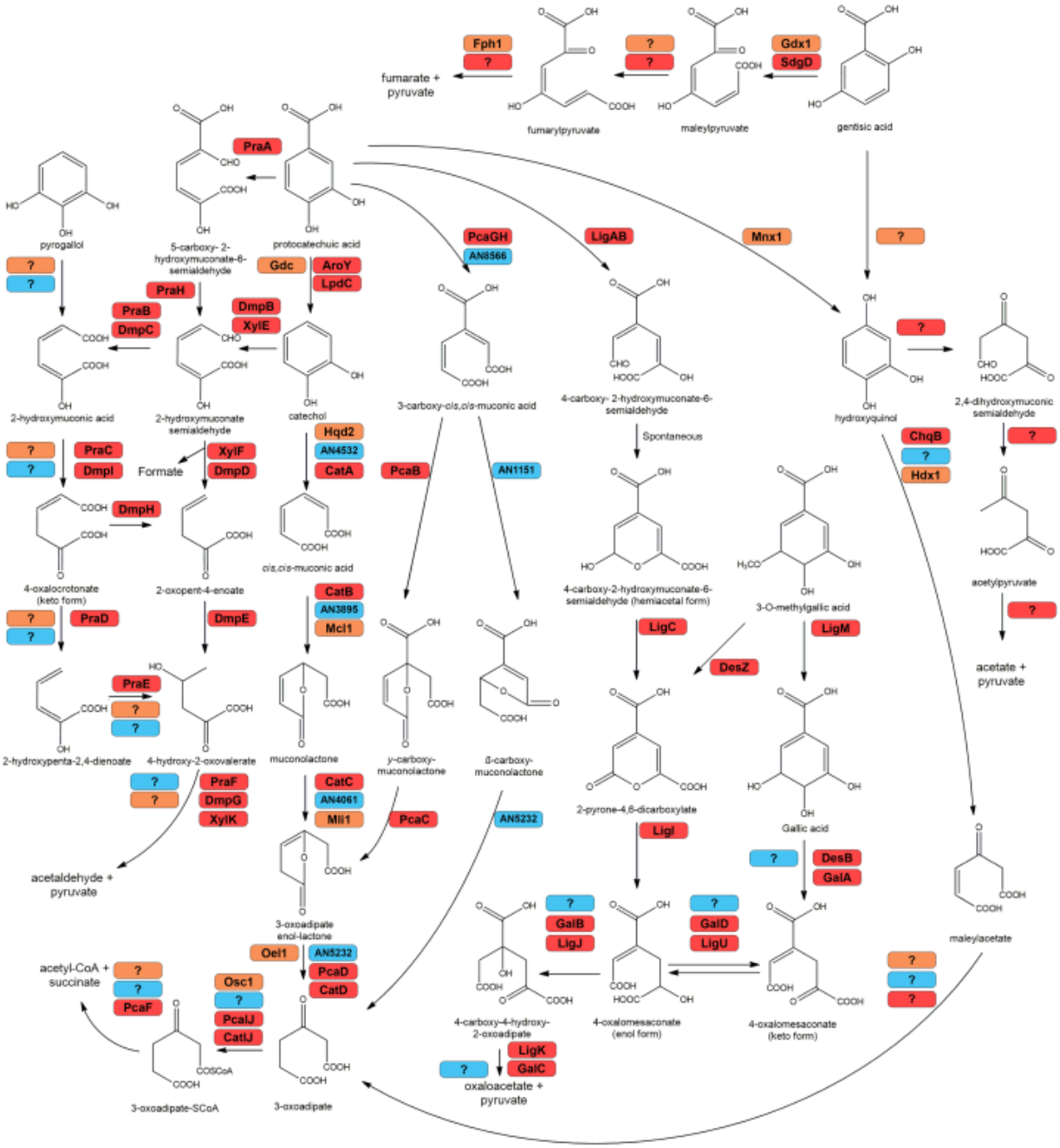

Figure 11. Bacterial, fungal and yeast aromatic ring cleavage pathways. The aromatic converting enzymes of bacteria (red), filamentous fungi (blue) and yeast (orange) are boxed next to the corresponding pathway. Question marks indicate that the enzyme is not identified.