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Review

Adaptation of the metabolomics profile of rice after *Pyricularia oryzae* infection

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ABSTRACT

Pyricularia oryzae (*P. oryzae*), one of the most devastating fungal pathogens, is the cause of blast disease in rice. Infection with a blast fungus induces biological responses in the host plant that lead to its survival through the termination or suppression of pathogen growth, and metabolite compounds play vital roles in plant interactions with a wide variety of other organisms. Numerous studies have indicated that rice has a multi-layered plant immune system that includes pre-developed (e.g., cell wall and phytoanticipins), constitutive and inducible (phytoalexins) defence barriers against stresses. Significant progress towards understanding the basis of the molecular mechanisms underlying the defence responses of rice to *P. oryzae* has been achieved. Nonetheless, even though the important metabolites in the responses of rice to pathogens have been identified, their exact mechanisms and their contributions to plant immunity against blast fungi have not been elucidated. The purpose of this review is to summarize and discuss recent advances towards the understanding of the integrated metabolite variations in rice after *P. oryzae* invasion.

1. Introduction

Pyricularia oryzae is a hemibiotrophic fungus that causes blast disease in a wide range of grasses, particularly rice (Azizi et al., 2014). The invasion of a plant with a pathogen induces biological tensions that prevent plant growth and might lead to death. Thus, plants need to survive these biological tensions to attain healthy growth, and sophisticated defence mechanisms for terminating the suppression of pathogen growth are therefore essential for plant growth and survival (Hayashi et al., 2016). Pathogen-associated molecular pattern (PAMP)-triggered immunity and effector-triggered immunity (ETI) are two main innate immunity responses of plants against pathogens. PTI, which confers basal resistance, consists of extracellular surface receptors that are able to identify PAMPs as indicators of common microbial compounds, including fungal chitin. However, ETI is mediated by intracellular receptor molecules containing nucleotide-binding (NB) and leucine rich repeat (LRR) domains encoded by *R* genes (Azizi et al., 2016). In fact, the hypersensitive response (HR) is a defence response regulated by these proteins. These proteins individually recognize the corresponding effector proteins, which are the products of avirulence (*Avr*) genes in the pathogen (Hammond-Kosack and Kanyuka, 2007). The HR, which is a type of planned cell death, can efficiently stop the distribution of pathogens at the initial site of penetration (Heath, 2000; Takahashi et al., 2008) and consists of various responses, and some of these responses involve the production of compounds capable of inhibiting further pathogen attack, including antimicrobial substances, such as phytoalexins, phenol and antioxidants, and molecules that reinforce the cell wall via their precursors (Hayashi et al., 2016; de Pinto et al., 2002; de Ascensao and Dubery, 2003). Abscisic acid (ABA), salicylic acid (SA), ethylene, jasmonic acid (JA), and reactive oxygen

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species (ROS) serve as the main factors that negatively or positively promote these responses (Apel and Hirt, 2004; Fujita et al., 2006).

On the one hand, plants employ elaborate chemical defence mechanisms against pathogen attacks, including metabolic adaptation, and on the other hand, plant pathogens tend to manipulate the host metabolism to break the host defence systems and to supply favourable nutritional conditions. Cereals such as rice use their metabolic arsenal in either local or systemic defence responses, and their chemical responses are greatly adapted to specific pathogens (Balmer et al., 2013). The gene portion of wide metabolic profiles can be approximately detected through analytical chemistry during plant-pathogen interactions (Dunn, 2008; Wolfender et al., 2009). Therefore, highly precise metabolic processes have been established for specific tissues, species and plant-pathogen interactions.

Groups of established compounds are crucial for the identification of novel defence compounds and serve as markers for identifying a plant's protective state. Moreover, these compounds are particularly useful in agronomic management strategies that require relevant markers for crop protection (Obata and Fernie, 2012).

Metabolomics refers to the non-targeted analysis (qualitative and quantitative) of all low-molecular-weight metabolites based on a broad analysis of all metabolite networks in a biological sample and their variations in response to numerous stimuli (Kim et al., 2011). These analyses offer a comprehensive outlook of the biochemical status of an organism or a biological system. Specifically, the metabolome provides a view of the final products of all processes in the cell, including transcriptional, translational and post-translational events, and most notably, it provides evidence regarding the events that occur in the system and describes biochemical phenotypes (Sumner et al., 2003).

The metabolic compounds produced under diverse environmental stimuli might differ among various rice subspecies. For instance, Chen et al. (2014) detected hundreds of metabolites, including *C*-glycosylated flavonoids and phenolamides, and classified these as two major groups of subspecies-specific metabolites involved in different stress regulatory and resistance responses in rice.

Plant-pathogen interactions are very interesting in terms of both biological significance and metabolite productivity. Therefore, these interactions are ideal for further investigation using metabolomics and other -omic techniques. With the exception of some recent publications (Balmer et al., 2013; Du et al., 2011; Allwood et al., 2010), few metabolomics studies of rice-blast disease interactions have been reported. In this review, the variations in the metabolomics profiles of rice during its interaction with *P. oryzae* will be clarified.

2. Metabolite variations involved in plant immunity

Plant immunity involves multiple layers that include pre-developed, constitutive and inducible defence mechanisms (Azizi et al., 2016). Physical pre-developed barriers, such as the cell wall, and pre-developed chemical defences, specifically phytoanticipins, are highly effective defence reactions of plants in response to pathogens (Gonzalez-Lamothe et al., 2009). The constitutive products of secondary metabolism, which are released and stimulated by antimicrobial compounds upon pathogen infection (Piasecka et al., 2015), represent the first layer of the defence mechanism of plants. Many phytoanticipins are involved in the production of saponins, which are secondary metabolites found in different plant species, particularly dicotyledons; however, cereals, with the exception of oats, do not contain saponins (Osbourn, 2003). In addition to pre-developed chemical defences, some antimicrobial compounds are induced only after pathogen infection in plants. These antimicrobial compounds are known as phytoalexins (Hammerschmidt, 1999) and usually exert unspecific inhibitory effects on a wide range of different pathogens, and their induction is controlled by a pathogen-triggered group of enzymes involved in their synthesis.

The compounds that constitute the chemical defence resources of plant cells from different metabolic pathways can be approximately grouped into three main categories (Groβkinsky et al., 2012): alkaloids (such as the indole alkaloid camalexin), which are mostly produced through the citric acid cycle or shikimate pathway, isoprenoids (such as diterpenes), which are created through the methyl erythritol phosphate or acetate-mevalonate pathway, and shikimates (such as flavonoids), which are synthesized via the shikimate pathway.. The synthetized metabolites belonging to these groups and produced by other pathways are well defined based on the plant metabolomes, which reflect the biochemical phenotype in the plant tissues. Such biochemical phenotypes can be summarized qualitatively and quantitatively on a large scale through metabolomics analysis.

Metabolic profiling has recently become a widely used tool for high-throughput research in the field of plant science. Specifically, it has been used for many types of studies, including the screening of diverse species and the analysis of their resistance or responses to herbicides (Schauer and Fernie, 2006). In addition, metabolomics combined with transcriptomics has become an essential tool for the collection of screened crop germplasms during crop breeding programmes (Langridge and Fleury, 2011), and many advances towards an understanding of the stress responses of rice have been achieved using metabolite profiling methods (Table 1).

3. Interplay of rice-*P. oryzae* metabolites during symptom development and infection establishment

Fungal pathogens endeavour to access plant nutrients in order to have the ability to invade, overcome and exploit their host plant (Fisher et al., 2012). A biotrophic fungus (such as powdery mildew) needs living tissue to survive (Spanu, 2012), but necrotrophs (Laluk and Mengiste, 2010) (such as *Botrytis cinerea*) kill their host to obtain nutrients. *Pyricularia oryzae* is a hemibiotrophic fungus (Koeck et al., 2011) that asymptomatically grows within the living cells of plants as a biotroph and then reaches a necrotrophic stage. The rice blast fungus, *P. oryzae*, penetrates its host rice plant using appressoria to establish infection (Martin-Urdiroz et al., 2016). The metabolome profiles of host plants that are susceptible to *P. oryzae* have been analysed by ESI-MS and GC-MS with the aim of identifying a standard pattern of metabolite regulation, and the accumulation of tricarboxylic acid (TCA) intermediates, quinate (through primary changes in the shikimate pathway), phenylalanine, polyamines and the precursors of non-polymerised lignin was observed immediately prior to symptom development (Parker et al., 2009).

Based on the results from various studies, it appears that *P. oryzae* manipulates the metabolic contents of its host plant, including the phenylpropanoid pathway, and restricts the production of lignin in susceptible plants to suppress their defence systems (Tan and Oliver, 2014). Although the pathogen uses different approaches during its biotrophic lifetime to attack the first layer of plant cells or the subsequent cell layers (Parker et al., 2009), plants utilise various mechanisms to defend themselves. For example, a study of the cell wall invertase *GRAIN INCOMPLETE FILLING 1 (GIF1)* found that rice mutants inoculated with *P. oryzae* were hyper-susceptible to blast fungus compared with wild-type rice plants due to a decreased level of sugars and a thinner glume cell wall (Sun et al., 2014). However, compared with the wild-type plants, the overexpression of *GIF1* in inoculated rice plants resulted in the accumulation of higher sugars (glucose, fructose, and sucrose), a thicker cell wall at the infection sites, and the constitutive activation of defence-related genes (Sun et al., 2014), and the metabolic interactions involved in such a finely organized process are difficult to comprehend.

Nevertheless, two different types of metabolic reprogrammings occur during rice-*P. oryzae* interactions (Parker et al., 2009; Jones et al., 2011). First, in susceptible rice varieties, infected leaf tissues showing symptoms become metabolic photosynthetic sinks that contain some amino acids, such as histidine (His), alanine (Ala), cysteine (Cys), tryptophan (Trp) and proline (Pro), and a number of sugars including

Table 1
Investigation of the metabolic compounds induced in rice in response to several biotic and abiotic stresses using analytical methods.

Stress	Plant material	Analytes and metabolite profiling methods	References
Biotic stress	Rice leaves infected with rice brown spot fungi (*Bipolaris oryzae)*	Specialized metabolites; HPLC and LC-MS	Ishihara et al. (2008)
	Rice leaves infected with *P. oryzae*	Malate, polyamines, lignin precursors and other primary metabolites; infusion-MS and GC-MS methods	Parker et al. (2009)
	Rice roots infected with different plant growth-promoting rhizobacteria (PGPR) strains	Secondary metabolite contents; UHPLC-DAD/ESI-QTOF analyses	Valette et al. (2019)
	Suspension-cultured rice cells infected with *P. oryzae*	Metabolite compounds and mostly primary metabolites; gas chromatography coupled to electron impact ionization-time-of- flight-mass spectroscopy (GC/EI–TOF–MS)	Madhavan et al. (2019)
	Rice plants infected with *Rhizoctonia solani*	Mainly secondary metabolites; GC-MS	Ghosh et al. (2017)
	Rice leaves infected with *Xanthomonas oryzae*	Focused on primary metabolites; LC-MS and GC-MS methods	Sana et al. (2010)
	Rice plants inoculated with symbiotic *rhizobacterium*	Specialized metabolites; LC-MS	Chamam et al. (2013)
	Rice infected with *Bipolaris oryzae* and treated with jasmonic acid	13-oxooctadeca-9,11-dienoic acid (13-KODE), 9-oxooctadeca-10,12 dienoic acid (9-KODE); and other secondary metabolites including sakuranetin, naringenin, and serotonin; HPLC and LC-MS/MS analyse	Nishiguchi et al. (2018)
Abiotic stress	Rice plants under salt stress	Mainly primary metabolites; GC-MS	Zuther et al. (2007)
	Rice leaves treated with ozone	Primary metabolites; CE-MS	Cho et al. (2008)
	Developing caryopses under high night temperature	Primary metabolites; CE-MS	Yamakawa and Hakata (2010)
	Rice leaves under drought stress	Primary metabolites; GC-MS	Shu et al. (2011)
	Submerged rice leaves	Mainly primary metabolites; ^{1}H NMR	Barding et al. (2011)
	Rice leaves under drought stress	Mainly primary metabolites; GC-MS	Degenkolbe et al. (2013)
	Aerial parts of rice plants under drought and cold stress	Mainly primary metabolites; GC-MS, CE-MS, and LC-MS	Maruyama et al. (2014)
	Rice transgenic plants under salt stress	Metabolite products of expressed transgene (s) *viz.* inositol and pinitol; GC-MS	Mukherjee et al. (2019)
	Floral organs of rice plants under heat stress	Primary metabolites; GC-MS	Li et al. (2015)
	Rice under OP60 treatment and other oxidative stresses	Serotonin N-acetyltransferase (AA-NAT) (a rate-limiting enzyme for melatonin synthesis); HPLC and mass spectrometry	Moritani et al. (2018)
	Rice leaves under high night temperature	Primary metabolites; GC-MS	Glaubitz et al. (2015)
	Rice under cadmium (Cd) stress	Compounds involved in the melatonin (MLT) biosynthesis pathway including tryptophan (Trp), tryptamine (TAM), 5-hydroxytryptophan (5HTP), serotonin (5HT), *N*-acetylserotonin (NAS), 5-methoxytryptamine (5 MT), and MLT; LC-MS	Ye et al. (2019)
	Rice under salinity stress	Primary and secondary metabolites, including sugars, polyols, amino acids, organic acids, gentisic acid and serotonin and certain purine and chorismic acid derivatives; GC-MS	Gupta and De (2017)
	Rice treated with the herbicide atrazine	Major metabolites, including desmethylatrazine (DMA), desethylatrazine (DEA), desisopropylatrazine (DIA), hydroxyatrazine (HA), hydroxyethylatrazine (HEA) and hydroxyisopropylatrazine (HIA) modified by P450; ultra-performance liquid chromatography-mass spectrometry (UPLC/MS)	Tan et al. (2015)

glucose, malate, fructose and sucrose (Parker et al., 2009; Jones et al., 2011), and these outcomes reflect the biotrophic lifestyle of *P. oryzae*. Conversely, an accumulation of phenolic compounds and phenylpropanoids occurs during the necrotrophic responses of rice plants, and the necrotrophic response kills the plant tissue before the fungus can feed on the host cells. Unlike resistant varieties of rice, susceptible rice plants are unable to strengthen their cell walls due to a lower production of H_2O_2 (Balmer et al., 2013), which causes a deficiency in phenolic cross-linking in the susceptible cells compared with the resistant cells. In addition, during the subsequent stages of infection, the fungus might use the fractioned nutrients in the dying cells as energy sources for its sporulation process (Parker et al., 2009). Furthermore, the combination of compatible and incompatible strains of *P. oryzae* offers an unspoiled prospective approach for metabolic re-programming related to rice defence responses. Major changes in the malate, Ala, Pro, glutamine, cinnamate and sugar contents after blast fungus infection have also been found through MS- and nuclear magnetic resonance (NMR)-based metabolomics (Jones et al., 2011). Moreover, it has been suggested that the high levels of alanine triggered by *P. oryzae* could be responsible for cell death responses that aid *P. oryzae* invasion (Jones et al., 2011). The negation of such reactions might cause incompatible interactions and lead to the protection of rice plants against blast infection. Despite these noteworthy results, further studies are needed to identify the ultimate roles played by primary metabolic compounds in the formation of compatibility.

3.1. Alkaloids

Alkaloids are nitrogen-containing compounds with a low molecular weight that are found in approximately 20% of plant species. A large number of alkaloids (∼12,000) play a central role in plant defence against pathogens and herbivores (Wink, 2010; Bennett and Wallsgrove, 1994). In crops, alkaloids constitute a large group of secondary plant substances, and due to their nitrogenous bases, their nitrogen atom(s) are mostly incorporated into a cyclic structure.

The physiological activities of alkaloids are often substantial, and these compounds are therefore used widely in medicine (Harborne, 1998). In the rice industry, the development of high-quality rice varieties with improved levels of bioactive compounds might provide enhanced nutritional value. For example anthocyanin-pigmented rice varieties with antioxidant components (phytochemicals, alkaloids, and phenolic acids) contribute to a reduction in oxidative stress-related diseases, such as blast disease (Chung and Shin, 2007).

Many indole alkaloids, which are a varied group of plant metabolites, are derived from tryptophan (Trp). In the first step of indole alkaloid biosynthesis, tryptamine is generated from the decarboxylation of Trp through a reaction catalysed by Trp decarboxylase (TDC) (Glenn et al., 2011) (Fig. 1).

The overexpression of TDC in tobacco can lead to an accumulation of tryptamine and a reduction in Trp (Guillet et al., 2000). During the clinical biosynthesis of indole alkaloids, two precursors, tryptamine and

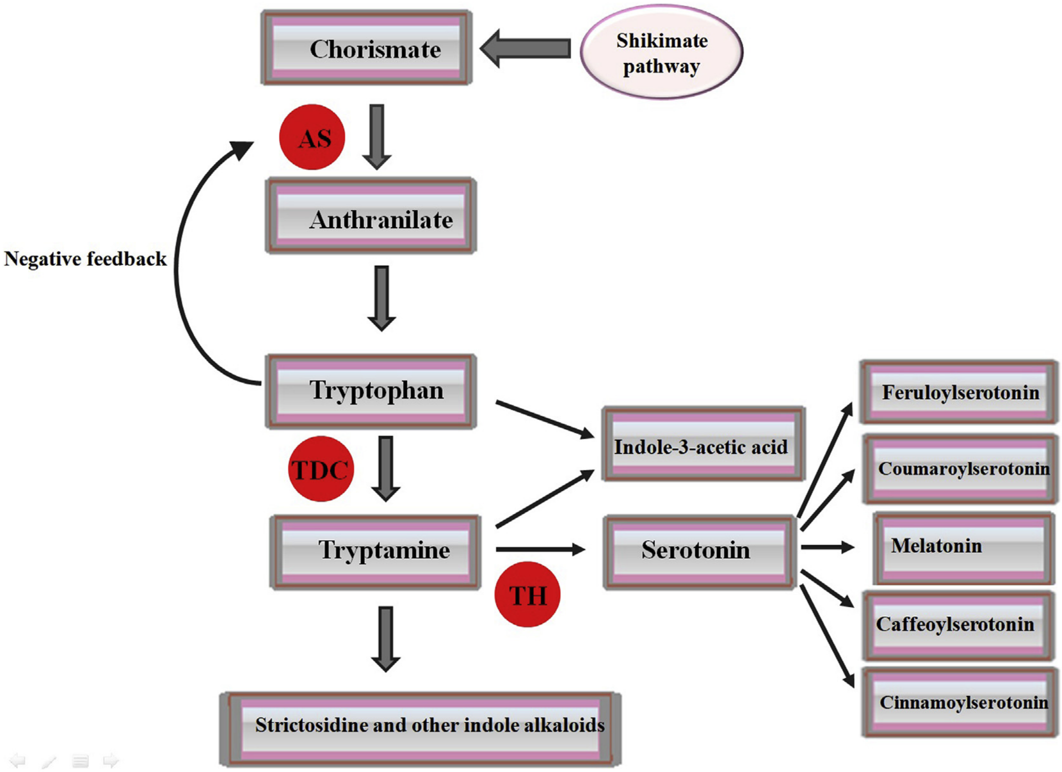

Fig. 1. Biosynthesis of indole alkaloids through the shikimate pathway. AS: anthranilate synthase; TDC: tryptophan decarboxylase; TH: tryptamine 5-hydroxylase; curved arrow: feedback regulation of AS by tryptophan.

secologanin, are essential (Góngora-Castillo et al., 2012). The inhibition of Trp in this biosynthetic pathway affects anthranilate synthase (AS) (Kreps et al., 1996), and the inhibition of AS must be suppressed until the accumulation of Trp is observed. Two AS alpha-subunit genes in rice, *OASA1* and *OASA2*, have been cloned to produce transgenic rice plants. A mutation in *OASA1* produced *OASA1* (N323D), which was named *OASA1D*, and the overexpression of this gene resulted in increased Trp contents in the vegetative organs and seeds of the transgenic rice plants (Tozawa et al., 2001). A metabolic profiling analysis of rice calli containing the *OASA1D* transgene showed trace amounts of indirect derivatives of tryptamine (Wakasa and Ishihara, 2009), and tryptamine and serotonin were detected at the seedling stage (Dubouzet et al., 2007, 2013). Similar results were obtained by Ishihara et al. (2008), who noted that the transcription of *OASA2*, *OASB1* and *OASB2* was elevated. Therefore, a relative inactivity of TDC has been observed in rice, even in the presence of large amounts of its substrates. This hypothesis also suggests that additional Trp might be converted to tryptamine in *OASA1D* transgenic rice plants through the promotion of TDC activity, and the resulting tryptamine could be utilised for the biosynthesis of other indole alkaloids. However, TDC is activated in rice under some physiological conditions, such as blast fungus infection, and the presence of tryptamine in the lesions of a mutant rice line has been confirmed (Ueno et al., 2003). A mono-oxygenase, cytochrome P450, which catalyses the conversion of tryptamine to serotonin, has been found to be a causal gene in this activation (Fujiwara et al., 2010).

In contrast, derivatives of Trp (indole acetic acid and its conjugates) might be produced via tryptamine, which is enhanced in the calli and seeds of transgenic plants overexpressing *OASA1D* (Wakasa et al., 2006).

3.1.1. Serotonin, a scavenger of ROS, inhibits further blast pathogen invasion

Serotonin (5-hydroxy tryptamine), which is derived from tryptophan as a secondary metabolic compound and is easily oxidized (Huether et al., 1997; Kang et al., 2008), plays a role as a scavenger of ROS, and its actions protect non-blast fungus-penetrated leaf tissues. In addition, the biosynthesis pathway for this molecule in plants has been elucidated (Fig. 1). Tryptamine is converted to serotonin by tryptamine 5-hydroxylase, but serotonin is not the end metabolite product of this pathway, and its derivatives, including feruloyl serotonin, coumaroyl serotonin, melatonin, caffeoyl serotonin, and cinnamoyl serotonin, have been found in plants (Kang et al., 2009; Arnao and Hernández-Ruiz, 2006; Dharmawardhana et al., 2013). The serotonin pathway is activated by the defence responses of plants against diseases. Serotonin functions as a physical barrier and confers resistance to brown spot and blast fungus in rice (Ishihara et al., 2008; Fujiwara et al., 2010). Due to the importance of serotonin as an important metabolite in the rice-*P. oryzae* interaction, its roles in lesion browning were considered by Hayashi et al. (2016), who found that serotonin acts as an ROS scavenger to rescue plants by decreasing oxidative damage in the healthy leaf tissue surrounding the blast lesions. Moreover, the deposition of an oxidized form of serotonin has been detected in the HR to lesion browning. *TDC1*, *TDC3* and *SL* are upregulated in the brown rings (halo) of rice leaves infected with a blast fungus, and this upregulation induces an accumulation of serotonin (Hayashi et al., 2016; Kanjanaphachoat et al., 2012). An accumulation of serotonin through the overexpression of *TDC1* has also been observed in the resistance response of rice against *B. oryzae* and senescence (Ishihara et al., 2008; Kang et al., 2009, 2011). Furthermore, the antioxidant activity of serotonin in rice was found to be notably stronger than that of tryptamine (Ishihara et al., 2008; Kang et al., 2009; Gülçin, 2008). Serotonin plays a critical role in the final production of blast lesions due to its antioxidant activity (Hayashi et al., 2016). These results suggest that the accumulation of serotonin through the overexpression of *TDC* genes cannot be a response mechanism specific to halo formation after blast fungus infection but is more than a common physiological response mechanism in rice.

The morphological, physiological and molecular responses of rice to

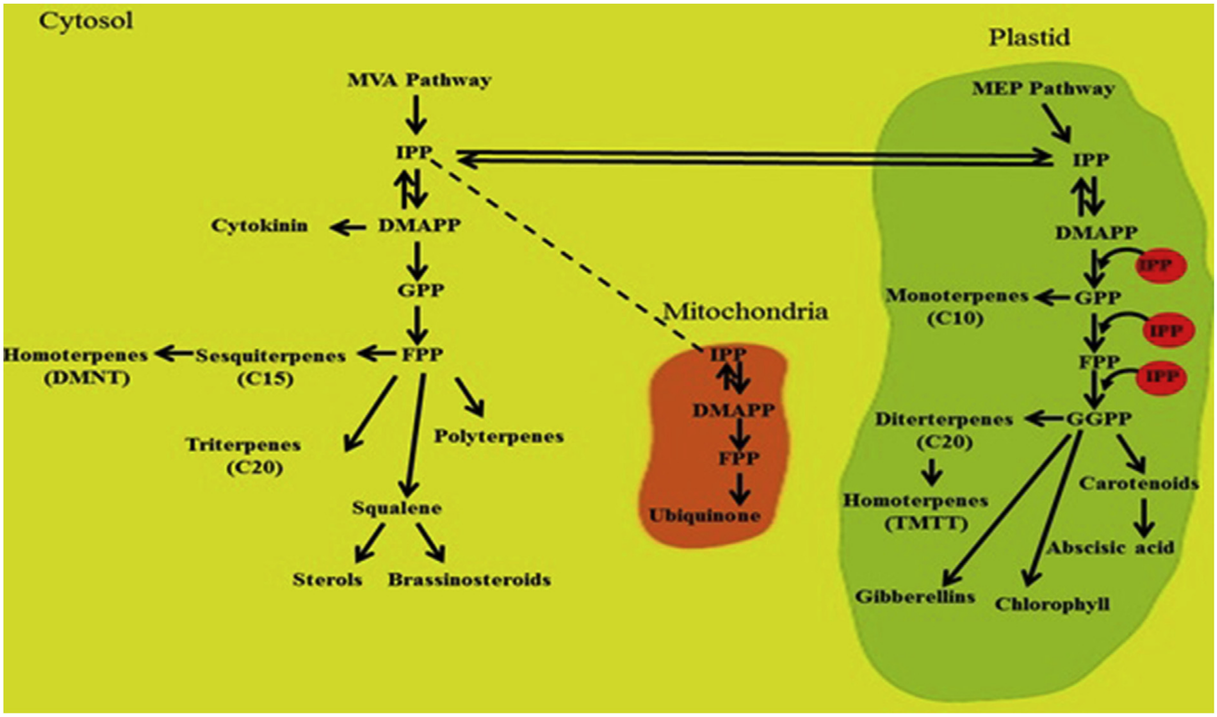

Fig. 2. Isoprenoid biosynthesis in plants. MVA pathway: mevalonate pathway; MEP pathway: methylerythritol phosphate pathway; IPP: isopentenyl diphosphate; DMAPP: dimethylallyl diphosphate; GPP: geranyl diphosphate; FPP: farnesyl diphosphate; GGPP: geranylgeranyl diphosphate.

serotonin have been particularly investigated. For instance, it has been demonstrated that the biosynthesis of serotonin is substantially increased and is closely associated with the endosperm colour (dark brown) in high free lysine (HFL) rice (Yang et al., 2018). This close connection has been confirmed through the over expression of *TDC3*, which is an important enzyme involved in serotonin biosynthesis. In addition, the expression of *TDC* and the activation of the jasmonate signalling pathway are significantly involved in the late phases of endosperm formation in HFL rice, and these effects are consistent with the accumulation of serotonin in and the dark-brown pigmentation of the endosperm (Yang et al., 2018). Furthermore, the induction of serotonin biosynthesis has been observed in rice plants during insect invasion, whereas the suppression of serotonin biosynthesis leads to increased resistance of rice plants to stem borers and planthoppers (Lu et al., 2018).

In plants, serotonin is a precursor to melatonin, and its production is strictly mediated. In rice seedlings, *N*-acetylserotonin (NAS) is rapidly and abundantly converted to serotonin in the presence of *N*-acetylserotonin deacetylase (ASDAC) encoded by *histone deacetylase 10 (HDAC10)* (Lee et al., 2018). In addition, serotonin is converted to *N*-acetyl serotonin through the activation of serotonin *N*-acetyltransferase (SNAT), which is the penult enzyme in the process of melatonin production and encoded by the *SNAT1* and *SNAT2* genes (Hwang and. Back, 2018). In rice, melatonin is involved in skotomorphogenesis by controlling the biosynthesis of brassinosteroids (Hwang and. Back, 2018), whereas melatonin-deficient rice plants illustrate a similar semi dwarf phenotype, regardless of the biosynthesis of brassinosteroid (Lee and Back, 2019). Furthermore, flavonoids inhibit the biosynthesis of melatonin (Hwang and. Back, 2018).

The physiological response processes that occur in response to natural leaf senescence are similar to the responses observed in leaves attacked by pathogens (Buchanan-Wollaston, 1997). Hormonal signalling induced by molecules such as abscisic acid (ABA), jasmonic acid (JA), salicylic acid (SA), and ethylene is involved in leaf senescence (Lim et al., 2007), and the presence of ABA and methanol leads to serotonin accumulation and senescence enhancement in rice leaves. However, SA and JA do not exert any promotional effects on the biosynthesis of serotonin in rice leaf senescence (Kang et al., 2011). A similar hormonal connection was observed in the HR to lesion browning. The expression of genes controlling the biosynthesis of serotonin from chorismate is affected by ABA and JA, whereas only ABA increases the rice browning rate (Hayashi et al., 2016). Therefore, an ABA-dependent antioxidant defence system in serotonin biosynthesis is important in the HR to lesion browning and leaf senescence. Serotonin, due to its role in ROS scavenging, can delay the senescence process, but its accumulation depends on the leaf age (Kang et al., 2009). However, the HR to browning is completed within a few hours after rice infection with *P. oryzae* (Hayashi et al., 2016). Thus, high serotonin accumulation protects rice cells from oxidative damage at the appropriate time after *P. oryzae* infection.

3.2. Isoprenoids, a diverse group of plant secondary metabolites

Isoprenoids are derived from isopentenyl diphosphate (IPP) and dimethylallyl diphosphate (DMAPP) (Sacchettini and Poulter, 1997). The condensing of DMAPP from IPP occurs sequentially to produce the short-chain isoprenoid precursors geranyl diphosphate (GPP), farnesyl diphosphate (FPP), and geranylgeranyl diphosphate (GGPP), and these isoprenoid precursors are cyclized by terpene cyclases and changed by other oxidases to metabolize monoterpenes (C10), sesquiterpenes (C15), and diterpenes (C20). IPP is synthesized through the mevalonate (MVA) (Mayer et al., 1992) and methylerythritol (MEP) pathways (Lichtenthaler, 1996). In plants, GGPP is the main precursor for the production of varied diterpenes and photosynthetic pigments, which are important compounds involved in plant growth, physiology and defence responses against pathogens.

Several of these bioactive cyclic diterpenoids, such as gibberellins, the anticancer compound Taxol, and phytoalexins, such as momilactones (Kasahara et al., 2002; Croteau et al., 2006; Okada et al., 2007), are synthesized via the MEP pathway. The simultaneous expression of several genes involved in the MEP pathway (*OsDXS3*, *OsDXR*, *OsCMS*, *OsCMK*, *OsMCS*, *OsHDS* and *OsHDR*) and the accumulation of their transcriptomes have been observed in elicitor-induced rice cells. Fosmidomycin and 5-ketoclomazone are two chemical inhibitors of 1-deoxy-D-xylulose 5-phosphate synthase (DXS) and 1-deoxy-D-xylulose 5-phosphate reductoisomerase (DXR). Rice cells treated with these compounds exhibit a suppression of the elicitor-induced accumulation of diterpenoids, whereas the treatment of rice cells with mevastatin, which is an inhibitor of the MVA pathway, does not yield similar results (Okada et al., 2007). Therefore, the important regulatory mechanism of isoprenoid biosynthesis in plants involves the efficient production of essential substances for plants (Fig. 2).

3.2.1. Diterpenoids, products of the isoprenoid biosynthesis pathway, and their role in the P. oryzae-rice interaction

The synthesis of phytoalexins in rice plants in response to *P. oryzae* infection was observed over a half century ago (Uehara, 1958). More recently, through an LC-MS analysis of ultraviolet (UV)-irradiated rice leaves, Horie et al. (2016) discovered novel compounds with antifungal activities against *P. oryzae*, including *N*-benzoyl tramine, casbene-type diterpenes, 5-dihydro-*ent*-10-oxodepressin and 5-deoxo-*ent*-10-oxodepressin. These researchers demonstrated that the accumulation of two of these compounds, *N*-benzoyl tryptamine and *N*-cinnamoyl tryptamine, in rice leaves inoculated with *P. oryzae* reached the same level as the accumulation of phytocassanes, which strongly confirms that these two amides are rice phytoalexins.

Various biosynthetic genes (Table 2) and transcription factors, including *OsTGAP1*, a basic leucine zipper (bZIP) transcription factor (Okada et al., 2009), *OsWRKY 45* (Akagi et al., 2014) and basic/helix-loop-helix (bHLH), regulate the production of diterpenoids. The expression of *OsTGAP1* is induced by chitin oligosaccharide, which is a biotic elicitor observed in the leaves of *P. oryzae*-infected rice plants (Okada et al., 2009).

Nevertheless, the involvement of *OsTGAP1* in the inducible accumulation of diterpenoids after rice blast infection remains unclear. It was recently reported that *OsWRKY 45*, which is a transcription factor in the salicylic acid signalling pathway, primes the biosynthesis of diterpenoids (Akagi et al., 2014), but whether *OsWRKY 45* directly and indirectly regulates the expression of DP biosynthesis genes remains unclear. Moreover, the expression of diterpenoid biosynthetic genes and their accumulation were observed through the overexpression of bHLH in rice after blast infection, copper chloride treatment or UV treatment (Yamamura et al., 2015).

In rice, DPs include oryzalexins A-F (Sekido et al., 1986; Kato et al., 1994; Kato et al., 1993; Akatsuka et al., 1983; Akatsuka et al., 1985; KONO et al., 1985; Kono et al., 1984), oryzalexin S (Kodama et al., 1992a), momilactones A and B (Cartwright et al., 1977, 1981), phytocassanes A-E (Koga et al., 1995, 1997) and ent-10-oxodepressin (Inoue et al., 2013).

These diterpenoids are elicited, accumulate and show antibiotic activity in response to *P. oryzae* infection (Fig. 3) (Yamamura et al., 2015; Watanabe et al., 1990, 1992). In contrast, some diterpenoids, such as oryzalic acids, oryzadiones, oryzalides and oryzalide-related compounds, are constitutively produced in rice plants in response to bacterial leaf blight (*Xanthomonas oryzae*) (Kono et al., 1991). Compared with typical phytoalexins, the production and accumulation of some components, such as oryzalide-related compounds, are only moderately induced after *Xanthomonas* infection (Watanabe et al., 1996; VanEtten et al., 1994).

The penetration and growth of blast fungi are suppressed by the exogenous activity of momilactones and ent-10-oxidorepressin (Cartwright et al., 1977; Inoue et al., 2013; Hasegawa et al., 2010). In addition, the activity of phytocassanes inhibits *P. oryzae* spore germination and germ-tube formation in rice (Koga et al., 1997; Umemura et al., 2003).

An accumulation of DPs has also been observed in rice at different developmental stages and in response to environmental stresses. Momilactones were originally extracted from rice husks (Kato et al., 1973) and straw (leaves) at different growth stages (Lee et al., 1999). Furthermore, the accumulation of momilactones and phytocassanes has been detected in and outside rice roots, and the accumulation of these compounds appears to be involved in allelopathic effects, such as the prevention of weed growth in rice paddy fields (Toyomasu et al., 2008, 2014; Xu et al., 2012; Kato-Noguchi, 2004). Chitin elicitor, which is a fungal microbe-associated molecular pattern in rice cells, similarly induces the production of momilactones and phytocassanes (Shimura et al., 2007; Yamada et al., 1993). Momilactones and phytocassanes also accumulate in rice plants after inoculation with compatible and incompatible *P. oryzae* (Yamamura et al., 2015; Hasegawa et al., 2010), and their accumulation has also been observed in rice leaves after treatment with copper chloride ($CuCl_2$), which is an abiotic stress elicitor (Shimizu et al., 2013; Kodama et al., 1988a), and UV irradiation (Kato et al., 1993; Cartwright et al., 1981; Shimizu et al., 2013; Kodama et al., 1988a, 1988b; Horie et al., 2015).

Table 2
Genes involved in the biosynthesis of most diterpenoids in plants.

Genes	Functions	References
COPALYL DIPHOSPHATE SYNTHASE4 (*OsCPS4*)	Biosynthesis of momilactones A and B and oryzalexin S	(Otomo et al., 2004a; Shimura et al., 2007)
KAURENE SYNTHASE-LIKE4 (*OsKSL4*),	Biosynthesis of momilactones A and B	Otomo et al. (2004a)
OsKSL2	A functional ent-beyerene synthase involved in defence mechanisms in rice roots. This enzyme catalyses the cyclization of ent-CDP to ent-beyerene and ent-kaurene as major and minor products, respectively.	Tezuka et al. (2015)
CYTOCHROME P450 MONOOXYGENASE 99A2 and *99A3* (*CYP99A2* and *CYP99A3*)	Biosynthesis of momilactones A and B	(Otomo et al., 2004a, 2004b; Wilderman et al., 2004; Xu et al., 2004; Wang et al., 2011)
MOMILACTONE A SYNTHASE1 (*OsMAS1*)	Biosynthesis of momilactones A and B	(Shimura et al., 2007; Miyamoto et al., 2016)
OsCPS2	Synthesis of phytocassanes A–E and oryzalexins A–F	(Otomo et al., 2004a; Cho et al., 2004; Toyomasu et al., 2008)
OsKSL7	Synthesis of phytocassanes A–E	(Cho et al., 2004; Shimizu et al., 2008)
CYP76M7,8	Synthesis of phytocassanes A–E	Wang et al. (2012a)
CYP71Z6	Synthesis of phytocassanes A–E	Otomo et al. (2004a)
CYP71Z7	Synthesis of phytocassanes A–E	Otomo et al. (2004a)
CYP701A8	Synthesis of phytocassanes A–E	Wang et al. (2012b)
OsKSL8,10	Synthesis of oryzalexins S and A–F	Otomo et al. (2004a)
CYP701A8	Synthesis of oryzalexins A–F	(Otomo et al., 2004a; Wang et al., 2012a, 2012b)
CYP76M5,6,8	Synthesis of oryzalexins A–F	Wang et al. (2012a)
CYP76M8	Biosynthesis of momilactones A	Wang et al. (2012a)

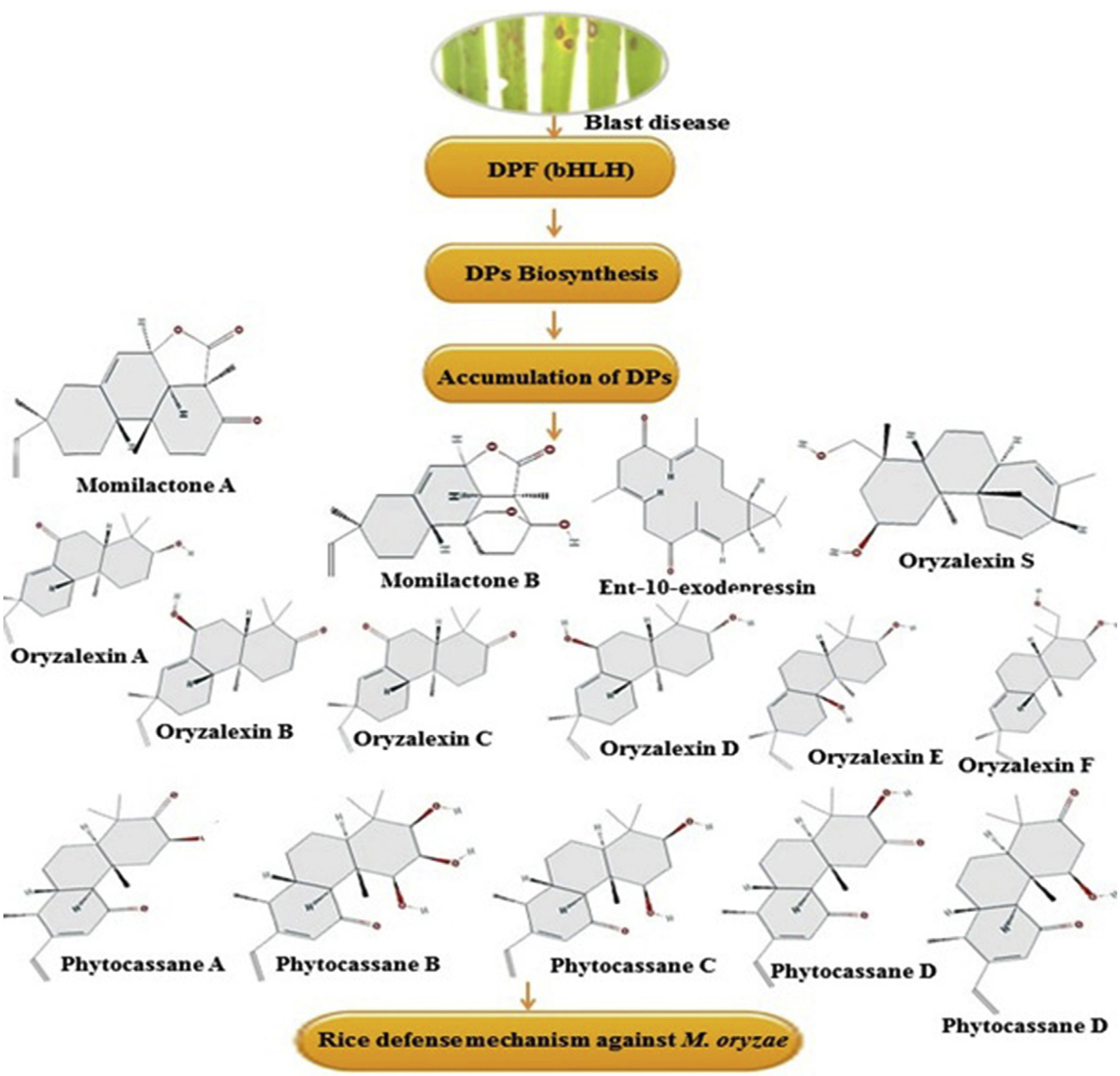

Fig. 3. Diterpenoid phytoalexins (DPs) are involved in the rice defence mechanism in response to blast disease. DPFs: DP factors such as bHLH.

The endogenous level of the plant hormone cytokinin (CK) is increased in rice plants inoculated with *P. oryzae*. CK is able to induce the production of phytoalexins, which are antimicrobial secondary metabolites, in rice, and the induced production of momilactones and phytocassanes (two major DPs) has been detected in both rice cell suspensions and leaves treated with CK. In addition, the CK treatment for 48 and 72 h increases the expression levels of phytoalexin biosynthetic genes, including *OsCPS2, OsCPS4, OsKSL4,* and *OsKSL7* (Ko et al., 2010).

Yamamura et al. (2015) illustrated that a master transcription factor, denoted DP factor, positively modulates the accumulation of DPs through the transcriptional regulation of genes that are involved in DP biosynthesis in rice. In addition, the expression of *COPALYL DIPHOSPHATE SYNTHASE2* (*CPS2*) and *CYTOCHROME P450 MONOOXYGENASE 99A2* (*CYP99A2*), two members of the momilactone and phytocassane biosynthesis pathways, is regulated by this DP factor via activation of their N box regions and promoters. Consequently, these DPs are able to improve the resistance of rice to blast disease through their antifungal activity. However, the expression of *OsDCL1a* increases the susceptibility of rice plants to infection caused by the fungal pathogen *P. oryzae* (Salvador-Guirao et al., 2018). In fact, the activation of *OsDCL1a*, a DICER-like (DCL) ribonuclease, negatively modulates the production of DPs and suppresses the inducible rice defence responses against pathogens. The misregulation of genes involved in ROS detoxification has been observed in rice *dc11a-Ac* mutant plants, which exhibit O_2- accumulation in their leaves and enhanced susceptibility to *P. oryzae* (Salvador-Guirao et al., 2018).

3.3. Sakuranetin, a phenolic phytoalexin, and its role in rice resistance against blast disease

Pathogen attack induces different plant defence responses, including the production of secondary metabolites with antibiotic activity, which are known as phytoalexins (VanEtten et al., 1994; Ahuja et al., 2012). Fifteen phytoalexins, including momilactones A and B, phytocassanes A-E, oryzalexins A-F, oryzalexin S (Kato et al., 1973, 1993, 1994; Akatsuka et al., 1985; Cartwright et al., 1981; Koga et al., 1995, 1997; Yajima and Mori, 2000; Tamogani et al., 1993), and sakuranetin, which is a flavonoid phytoalexin, have been isolated from rice and characterized (Kodama et al., 1992b). Among the mentioned phytoalexins, sakuranetin, a 7-methylated flavanone, is a biologically important compound due to its antimicrobial activity and high accumulation in rice leaves after infection with *P. oryzae* (Kodama et al., 1992b). Compared with the reported role of momilactone A in suppressing blast fungus growth at the site of infection (Hasegawa et al., 2010), limited information regarding the role of sakuranetin in the

Table 3
Antimicrobial activities of sakuranetin in rice against pathogens.

Pathogens		Antimicrobial activity	References
Fungus	*P. oryzae*	Prevention of germ tube and mycelia growth	(Park et al., 2014; Sekido and Akatsuka, 1987)
	R. solani	Prevention of mycelia growth	Park et al. (2014)
	B. oryzae	Prevention of mycelia growth	Park et al. (2014)
Bacteria	*B. glumae*	Prevention of cell growth	Park et al. (2014)
	X. oryzae pv. oryzae	Prevention of cell growth	Park et al. (2014)
	X. oryzae pv. oryzicola	Prevention of cell growth	Park et al. (2014)

prevention of *P. oryzae* growth and penetration at the infection site in rice has been reported. Thus, determining whether sakuranetin plays any role in the suppression of fungal growth after blast infection is important. More recent studies have revealed that sakuranetin strongly inhibits *P. oryzae* germ-tube growth even more potently than DPs. In addition, the inhibitory effects of sakuranetin on the growth of blast fungus mycelia are reportedly greater than those of the diterpenoid oryzalexin D (Park et al., 2014; Sekido and Akatsuka, 1987). In addition to its anti-*P. oryzae* activity, sakuranetin shows antimicrobial activity against different fungi and pathogens in rice (Park et al., 2014) (Table 3).

The anti-inflammatory activity of sakuranetin reportedly occurs through the inhibition of 5-lipoxygenase. The enzyme 5-lipoxygenase is involved in arachidonic acid metabolism in animal cells (Zhang et al., 2006) and exhibits anti-mutagenic (Miyazawa et al., 2003) and anti-*Helicobacter pylori* (Zhang et al., 2008) activity by suppressing β-hydroxyacyl-acyl carrier protein dehydratase, as well as antileishmanial and antitrypanosomal activities (Grecco et al., 2012). Sakuranetin can be used as a plant antibiotic and for the induction of diabetes by sensitizing adipocytes to insulin (Saito et al., 2008). Sakuranetin, as an aglycone, was first identified from the cortex layer of cherry tree bark (Asahina, 1908) and was later identified in rice and other plants, such as *Artemisia campestris* and *Prunus* spp. (Baxter et al., 1998). However, sakuranetin is not synthesized in healthy rice leaves, and its biosynthesis is induced by biotic (such as *P. oryzae*) (Dillon et al., 1997) and abiotic stresses (such as $CuCl_2$ treatment) (Rakwal et al., 1996).

The simultaneous activation of the shikimate, aryl monoamine and phenylpropanoid pathways is essential for the biosynthesis of phenolic phytoalexins in rice (Fig. 4), and the expression of the genes involved in these pathways is induced by biotic and abiotic stresses (Parker et al., 2009). The shikimate and phenylpropanoid pathways produce aromatic L-amino acids and phenolic acid moieties, respectively, in phenylamides and sakuranetin (Cho and Lee, 2015), and phenolic acid-CoAs serve as intermediates and are connected to aryl monoamines to form sakuranetin and phenylamide phytoalexins (Cho and Lee, 2015). The precursor for sakuranetin biosynthesis is naringenin, which is a common precursor of flavonoids obtained through the activation of S-adenosyl-L-methionine (SAM)-dependent naringenin 7-O-methyltransferase (NOMT) (Rakwal et al., 1996; Shimizu et al., 2012a). Naringenin is transformed from a naringenin chalcone through the action of chalconeisomerase, which is also an intermediate biosynthetic compound obtained from an isoflavone and a wide range of flavones (Shimizu et al., 2012a). Thus, NOMT is the main factor involved in the biosynthesis of sakuranetin through a common flavonoid biosynthetic pathway. The *OsNOMT* gene encoding NOMT in rice was identified by Shimizu et al. (2012b) in *oscomt1* rice mutants under *in vivo* conditions. These researchers discovered that *Os12g0240900* encodes a protein with kinetic properties similar to those of OsNOMT and is expressed during treatment with jasmonic acid prior to sakuranetin accumulation in rice leaves. More recently, Ogawa et al. (2017) confirmed that activation of the *OsNOMT* promoter is significantly affected by OsMYC2, which serves as a jasmonic acid-inducible basic helix-loop-helix transcription factor, and two of its collaborators, OsMYC2-like protein 1 and 2 (OsMYL1 and OsMYL2, respectively). In fact, the production of sakuranetin as a result of the transactivation activity of OsMYC2 is enhanced by OsMYL1 and OsMYL2.

Jasmonic acid and its derivatives are key regulators of a plant's immune system, particularly in the defence responses to pathogens (Pieterse et al., 2012). Methyl jasmonate (MJ) affects the production of enzymes such as TDC, which catalyses the creation of terpene indole alkaloids through responsible genes (Dubouzet et al., 2013). TDC influences MJ and the derived tryptamine products, and the elimination of TDC might improve the stress tolerance of rice. Tryptamine derivatives, such as serotonin and its hydroxycinnamic acid amides, accumulate in rice leaves after fungal infection (Ishihara et al., 2011), which indicates that these compounds might be involved in the rice defence system. Furthermore, two jasmonate-deficient allene oxide cyclase mutants, *cpm2* and *hebiba*, have been recognized to be susceptible to *P. oryzae* (Riemann et al., 2013). By using of *osjar1 Tos 17* mutant, Shimizu et al. (2013) found that *OSJAR1* contributes mostly to stress-induced JA-Ile production. The researchers found that the mutant was unable to express JA-related genes or produce phytoalexin during treatment with jasmonic acid and was susceptible to rice blast fungus. Additionally, these researchers have reported that endogenous JA-Ile (the *OSJAR1* product) is essential for production of the flavonoids phytoalexin and sakuranetin but is not necessary for diterpenoid phytoalexins (DP) production in response to treatment with heavy metals and *P. oryzae*. Therefore, JA-Ile production has important impacts on the defence responses of rice to environmental stresses through the induction of sakuranetin production.

In addition, rice osjar12 mutants appear to be more susceptible to blast fungus than wild-type plants (Shimizu et al., 2013), which indicates that JA-Ile (the JAR1 product) mediates the defence responses of both rice and Arabidopsis against blast fungus.

3.4. Phenylamides, a new phenolic phytoalexin, and their roles in P. oryzae challenge

It was previously believed that sakuranetin is the only flavonoid that forms part of the phenolic group of phytoalexins in rice, but recent findings suggest that various phenylamides, which are amine-conjugated phenolic compounds with antimicrobial activity, are also involved in the defence responses of rice plants against pathogens and abiotic stresses such as UV radiation (Ishihara et al., 2008, 2011; Park et al., 2013, 2014). The synthesis of several phenylamides, including N-feruloylserotonin (FerSer), N-feruloyltyramine (FerTrp) and N-p-coumaroylserotonin (CouSer), is induced by the presence of bacterial and fungal pathogens (such as *P. oryzae*) to preserve the antimicrobial activities of these compounds in rice (Ishihara et al., 2008, 2011). This induction demonstrates the direct inhibitory effects of phenylamides on pathogen invasion and suggests that phenylamides play important roles due to the presence of phytoalexins, phenolic phytoalexins and sakuranetin in rice.

Plants respond to pathogen attack through reinforcement of the cell wall and the deposition of different biopolymers (i.e., callose and lignin) into the cell wall. Phenylamides also help rice plants resist diseases and allelopathy through reinforcement of the cell wall and exert direct toxic effects against the pathogens (Cho and Lee, 2015).

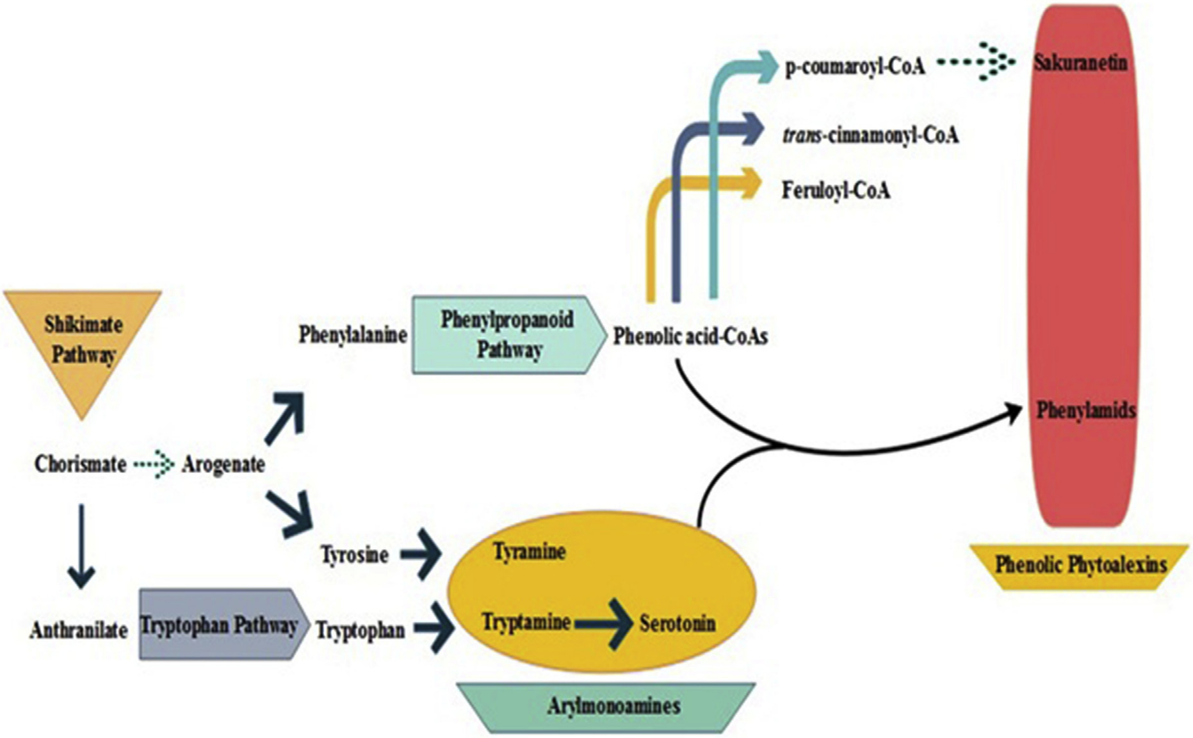

Fig. 4. Metabolic pathways involved in phenolic phytoalexin biosynthesis in rice. The dashed arrows show multiple enzymatic steps.

Table 4
Phenolic phytoalexin biosynthesis-related genes induced in rice leaves in response to *P. oryzae.*

Gene	Product	Pathway	References
OsPAL6 (*Os02g41680*)	PAL	Phenylpropanoid pathway	Duan et al. (2014)
OsPAL1 (*Os02g41630*)	PAL	Phenylpropanoid pathway	(Park et al., 2013; Duan et al., 2014)
OsPAL8 (*Os02g41650*)	PAL	Phenylpropanoid pathway	(Park et al., 2013; Duan et al., 2014)
OsPAL4 (*Os02g41680*)	PAL	Phenylpropanoid pathway	Tonnessen et al. (2015)
PAL07 (*Os04g43800*),	PAL	Phenylpropanoid pathway	Giberti et al. (2012)
PAL04 (*Os05g35290*)	PAL	Phenylpropanoid pathway	Giberti et al. (2012)
OsASA2 (*Os03g15780*)	ASα	Tryptophan pathway	(Ishihara et al., 2008; Tozawa et al., 2001; Dharmawardhana et al., 2013)
OsASB1 (*Os04g38950*),	ASβ	Tryptophan pathway	(Ishihara et al., 2008; Tozawa et al., 2001; Dharmawardhana et al., 2013)
OsASB2 (*Os03g50880*)	ASβ	Tryptophan pathway	(Ishihara et al., 2008; Tozawa et al., 2001; Dharmawardhana et al., 2013)
Os03g03450	APT	Tryptophan pathway	Dharmawardhana et al. (2013)
Os02g16630	PAI	Tryptophan pathway	Dharmawardhana et al. (2013)
TSA (*Os07g08430*)	TSα	Tryptophan pathway	Dharmawardhana et al. (2013)
TSB1 (*Os08g04180*)	TSβ	Tryptophan pathway	Dharmawardhana et al. (2013)
Os08g04540	AADC	Phenylamide biosynthesis	Kang et al. (2007)
SL (*Os12g16720*)	T5H	Phenylamide biosynthesis	Fujiwara et al. (2010)

The plant phenolic compounds, including lignins, flavonoids and soluble phenolics, are derived from L-phenylalanine (Phe) via the phenylpropanoid pathway and are induced by the expression of the genes involved in this pathway (Table 4) (Dixon and Paiva, 1995; Winkel-Shirley, 2002; Vogt, 2010; Naoumkina et al., 2010).

Phenylalanine ammonia lyase (PAL) transforms Phe to trans-cinnamate, and this product is later converted into different phenylalanine metabolites (Edreva et al., 2007). As a result, the actions of phenylpropanoid pathway enzymes, which include p-coumarate 3-hydroxylase (C3H), cinnamate 4-hydroxylase (C4H), 4-coumarate: CoA ligase (4CL) and caffeate O-methyltransferase (COMT), are essential (Vogt, 2010). The upregulation of four putative *OMT* genes, including *Os11g19840*, *Os09g17560*, *Os08g06100* and *Os04g01470*, in rice in response to UV treatment has also been reported (Park et al., 2013).

This upregulation occurs prior to the accumulation of sakuranetin and phenylamide phytoalexins, which further supports their potential involvement in the biosynthesis of phenolic phytoalexins in rice (Park et al., 2013). The phenylpropanoid metabolites are used to produce sakuranetin and phenolic moieties in phenylamide phytoalexins (Park et al., 2013; Vogt, 2010; Edreva et al., 2007; Bassard et al., 2010; Jeandet et al., 2014). A large family of *PAL* genes plays a main role in the biosynthesis of defence-relevant compounds such as hormone salicylic and phenolic compounds, and 11 members of this family (*OsPALs*) have been identified in rice (Park et al., 2013; Duan et al., 2014; Kawahara et al., 2013). A mutation in *OsPAL6* increases the susceptibility of rice roots to invasion by blast fungi, and sakuranetin production is suppressed in the infected mutant rice roots (Duan et al., 2014). These results show the importance of the phenylpropanoid pathway in the biosynthesis of sakuranetin and resistance to blast disease. Previous studies have revealed that the phenylamide tryptamine is produced in response to *B. oryzae* infection in rice and that compound is deposited in the cell wall at the lesion site (Ishihara et al., 2008, 2011). Morimoto et al. (2018) studied the phenylamide contents of rice leaves after infection with *Xanthomonas oryzae* and *Cochliobolus miyabeanus* and found that the production of benzoyl tryptamine, feruloyl agmatine, benzoyl serotonin, and cinnamoyl and feruloyl putrescines as well as p-coumaroyl-, cinnamoyl-, feruloyl-, and benzoyl tyramines was induced after infection by these two pathogens. These researchers realized that phenylamide accumulation in rice plants in response to the two pathogens differs depending on the available hormones (e.g., jasmonic acid, salicylic acid, 6-benzylaminopurine, and ethephone) and other factors and considered phenylamides with antimicrobial activity as phytoalexins.

Although several studies have investigated phenylamide phytoalexins, such as N-cinnamoyl triptamine (CinTrp) and CouSer (which exert antimicrobial, anti-inflammatory and antiatherogenic effects), more research is needed to clearly understand their biological roles and biosynthetic pathways in rice.

3.5. Fusion of arylmonoamine biosynthesis with phenolic acid-CoAs

Phenylamides are also known as hydroxycinnamic acid amides or phenylamides, which are the hydroxycinnamoyl acylated derivates of the mono-, di- and tri-phenolic acids coumaric, caffeic, and ferulic acids, respectively. These compounds are also substitutions of polyamines, including putrescine, spermidine, agmatine, tryptamine, and serotonin, or arylmonoamines, such as tyramine, octopamine, and anthranilate (Edreva et al., 2007; Bassard et al., 2010; Bienz et al., 2005).

In the flavonoid and phenylamide biosynthesis pathways, the branch points, which include phenolic acid-CoAs such as feruloyl-CoA and p-coumaroyl-CoA serve as activated intermediates (Cho and Lee, 2015). The ligation of CoA to phenolic acids is catalysed by *OsCLs*, and five different *OsCLs* (*OsCL1-5*) involved in lignin and phenolic metabolism have been identified in rice (Gui et al., 2011). The specific expression of *Os4CL2* and its role in flavonoid biosynthesis in response to UV irradiation have been demonstrated (Sun et al., 2013). Phenylamides are produced through the conjugation of arylamines and phenolic acids (Park et al., 2013; Edreva et al., 2007; Bassard et al., 2010) (Fig. 4). Tyramine, tryptamine and serotonin are aryl monoamines found in rice phenylamide phytoalexins (Fig. 4) (Ishihara et al., 2008, 2011; Park et al., 2013, 2014). Tryptamine and tyramine are derivatives of L-tryptophan (Trp) and Tyr, respectively. The biosynthesis of Tyr, which typically shares the phenylalanine biosynthesis pathway, is induced in rice leaves under UV treatment (Park et al., 2013; Tzin and Galili, 2010), and activation of the Trp biosynthesis pathway from chorismate has been observed in rice infected with *B. oryzae* and *P. oryzae* (Ishihara et al., 2008). AS is responsible for the conversion of chorismate to anthranilate (Tzin and Galili, 2010), and four genes (*OsASA1*, *OsASA2*, *OsASB1* and *OsASB2*) in the rice genome have been found to encode AS. The infection of rice leaves by phytopathogens, such as *P. oryzae*, *B. oryzae* and *Xoo*, and chitin elicitor treatment result in the induction of *OsASA2* (*Os03g15780*) and thereby increases in the intermediates of the Trp biosynthesis pathway (Ishihara et al., 2008; Tozawa et al., 2001; Dharmawardhana et al., 2013). Furthermore, the expression of both *OsASB1* and *OsASB2* is induced in rice via UV treatment and pathogen infection (Ishihara et al., 2008; Tozawa et al., 2001; Dharmawardhana et al., 2013), and induced expression of *OsASB2* has also been observed in the rice mutant spotted leaf 5 (spl5), which shows improved resistance to pathogens (Jin et al., 2015). In the next step of the pathway, anthranilate is converted to Trp through the serial action of a group of enzymes, including phosphoribosyl transferase (APT), phosphoanthranilate isomerase (PAI), indole-3-glycerol phosphate synthase (IGPS), and Trp synthase (TS) (Tzin and Galili, 2010). The expression of *APT* (*Os03g03450*) and *PAI* (*Os02g16630*) has been detected in response to a pathogen attack (Dharmawardhana et al., 2013), and the expression of the *IGPS* gene is induced in rice leaves by UV treatment and in the spl5 rice mutant (Jin et al., 2015). The TS enzyme is categorized into two subunits, TSα and TSβ, and the expression levels of *TSA* (*Os07g08430*) and its encoded protein (TSα) are increased in rice leaves after UV treatment and pathogen attack and in the spl5 rice mutant (Dharmawardhana et al., 2013; Jin et al., 2015; Du et al., 2011). Induced expression of *TSB1* (*Os08g04180*) and *TSB2* (*Os06g42560*) has been observed in rice leaves treated with UV, and *TSB1* expression is also detected in rice leaves under pathogen attack (Dharmawardhana et al., 2013). Two members of the aromatic AA decarboxylase (AADC) family, namely, Trp decarboxylase (TDC) and Tyr decarboxylase (TYDC), convert Trp and tyrosine to their corresponding aryl monoamines (tryptamine and tyramine, respectively) (Facchini et al., 2000). Furthermore, induced activity of TDC has been observed in Sekiguchi lesion (*sl*) mutant rice infected with *P. oryzae* (Ueno et al., 2003). The levels of tryptamine and serotonin are also increased in transgenic rice plants overexpressing the *AADC* gene (*Os08g04540*) (Kang et al., 2007). Tryptamine is converted to serotonin (5-hydroxytryptamine) through the action of tryptamine 5-hydroxylase (T5H) (Fujiwara et al., 2010; Dharmawardhana et al., 2013), and the accumulation of tryptamine leads to expression of the *SL* gene (*Os12g16720*), which encodes the cytochrome P450 monooxygenase T5H, as observed in the *sl* rice mutant rice in response to chitin treatment and *P. oryzae* infection (Fujiwara et al., 2010). This induced expression of the *SL* gene has also been observed in rice leaves after UV and cadmium treatment (Byeon et al., 2015).

These results indicate that T5H, as a product of the *SL* gene, plays a major role in the biosynthesis of serotonin in the responses of plants to these stresses. Phenylamides are produced through the conjugation of arylmonoamines with phenolic acid-CoAs, and phenolic acid-CoAs are catalysed by the activation of acyltransferases, such as BAHD acyltransferase and tyramine: N-hydroxycinnamol transferase-like enzymes (Bassard et al., 2010; D'Auria, 2006; Peng et al., 2016). However, there is little information regarding the definitive roles of the acyltransferases involved in phenylamide phytoalexin biosynthesis in rice. Several loci have been identified in rice leaves (22 loci) and seeds (16 loci) that affect phenolamides production (Peng et al., 2016). These researchers also found eight BAHD *N*-acyl transferases, including four aromatic amine *N*-acyltransferases located on chromosome 5, that play diverse roles in rice plants (Peng et al., 2016). In addition, previous studies have confirmed that the genetic differences observed in phenolamides are partly determined by allelic variations in the expression of the *BAHD* genes responsible for their biosynthesis in specific rice tissues. Furthermore, two bifunctional tryptamine/tyramine *N*-acyltransferases, tryptamine hydroxycinnamoyl transferase 1/2 (Os-THT1/2) and tryptamine benzoyl transferase 1/2 (Os-TBT1/2), are specific for agmatine and have not been characterized as particularity determinants for BAHD transferases in other plants. Therefore, it is understood that BAHD transferases have the flexibility to acquire new acyl acceptor particularities and are conserved in monocots, particularly Gramineae (Peng et al., 2016).

4. Conclusion

The studies on genetic improvements in crops conducted over the past few decades have mainly focused on crop yield. Thus, functional genomics and the recognition of stress-related genes that improve crop yield without inducing a reduction or loss in the nutritional value of the crop will become increasingly important over the next half century. Progress in metabolomics could also aid improvements in the resistance of plants to biotic and abiotic stresses. These advances could challenge plant geneticists, breeders, biochemists, biologists, pathologists and bioinformaticians to enhance plant resistance and subsequently contribute to global food security.

Extensive metabolomic profiles, including knowledge of the shikimate, flavonoid, phenylpropanoid, fatty acid, and terpenoid pathways, are available for cereals and plant-fungal pathogen interactions, such as maize-*Ustilagomaydis*/*C. graminicola* and barley-*Fusarium* head blight. In fact, the importance of secondary metabolites in plant survival under environmental stress is due to the diversities in their structures and functions. It is anticipated that the development of novel strategies will improve our knowledge of the metabolite changes that occur during various plant-pathogen interactions. Advancements in techniques (such as cell culture) and biotechnological tools (such as the production of transgenic cells/tissues to manipulate biosynthetic pathways) help researchers create a framework for identifying and analysing structures and regulatory pathways that lead to secondary metabolite production. For instance, information about the type, accumulation and location of flavonoids has not been precisely obtained for cereal grains under stress conditions. Therefore, biotechnological advancements along with improvements in genome sequencing, genome editing and microarray technology could lead to the discovery of novel genes and regulatory mechanisms that would complete the profiles of metabolites, including flavonoids, in cereal crops, particularly rice. These advancements would also help researchers obtain a better understanding of the origins of secondary metabolites, which would allow the production of commercially acceptable levels of these metabolites and ultimately their potential use for pathogen control.

However, metabolomics studies have various limitations, including the inability to analyse the complete metabolome of a plant. It has been estimated that plants have more than 200,000 metabolites (Trethewey, 2004; Saito and Matsuda, 2010), but only a limited number of these diverse compounds have been identified. Therefore, despite the availability of public MS databases (such as KNApSAck3, KEGG4 or BRENDA5), new strategies are needed to create an information database that would further our cellular- and molecular-level understanding of the synthesis pathways of bioactive secondary metabolites involved in plant defence responses against pathogens.

The limitations associated with the simultaneous analysis of a wide range of metabolites are another drawback of this type of study. For instance, high levels of sugars might interfere with flavonoid detection (Sumner et al., 2003). In addition, metabolite profiling techniques have to be regularly modified based on the compounds of interest. For example, the analysis of oligosaccharides through LC/MS faces some difficulties (Sumner et al., 2003), and the use of inoculated plant materials could pose particular challenges to the methodology that would require specific approaches (Allwood et al., 2011).

The key roles of the metabolites involved in the rice-*P. oryzae* interaction, namely, sugars and amino acids, are highlighted in the current review. The prominent potential of rice metabolites, such as momilactone A and sakuranetin, in pathogen (*Pyricularia oryzae* and *Xanthomonas oryzae*) resistance shows the potential of targeting metabolic pathways as part of transgenic strategies for rice. Therefore, the recognition of the effects of specific metabolic compounds on resistance and the manipulation of their biosynthetic pathways appear to be potential high-yield strategies for transgenic crops.

Our knowledge of these strategies was recently updated. It is well known that phytoalexins are typically diterpenoids, but recent studies showed that phenolic compounds such as phytoalexins, which comprise a variety of phenylamides and sakuranetin, are the main factors involved in rice disease resistance. Moreover, these phenolic phytoalexins play roles in the defence mechanisms of rice against biotic and abiotic stresses by strengthening the cell wall, scavenging ROS and exhibiting allelopathic characteristics. Furthermore, rice phytoalexins show a variety of beneficial health characteristics; for example, sakuranetin exhibits antibiotic activity against *Helicobacter pylori* and can protect against allergy, and phenylamide phytoalexins, such as CinTrp and CouSer, exhibit antimicrobial activity against bacteria as well as anti-inflammatory and antiatherogenic properties. Therefore, understanding the precise biological and biosynthetic roles of phenolic phytoalexins in rice is necessary, and the application of metabolomics combined with other -omics technologies (such as genomics, transcriptomics and proteomics) within a system biology framework will allow researchers to obtain a comprehensive understanding of the rice-*P. oryzae* interaction.

Author contributions

PA, MO, MMH and MS were responsible for the conception of the study, the drafting of the manuscript and the design of the required figures. MYR, MMH and ST made critical revisions to the manuscript.

Declaration of competing interest

The authors declare that they have no competing interests.

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References

Ahuja, I., Kissen, R., Bones, A.M., 2012. Phytoalexins in defense against pathogens. Trends Plant Sci. 17, 73–90.

Akagi, A., Fukushima, S., Okada, K., Jiang, C.-J., Yoshida, R., Nakayama, A., Shimono, M., Sugano, S., Yamane, H., Takatsuji, H., 2014. WRKY45-dependent priming of diterpenoid phytoalexin biosynthesis in rice and the role of cytokinin in triggering the reaction. Plant Mol. Biol. 86, 171–183.

Akatsuka, T., Kodama, O., Kato, H., Kono, Y., Takeuchi, S., 1983. 3-Hydroxy-7-oxo-sandaraco-pimaradiene (oryzalexin A), a new phytoalexin isolated from rice blast leaves. Agric. Biol. Chem. 47, 445–447.

Akatsuka, T., Kodama, O., Sekido, H., Kono, Y., Takeuchi, S., 1985. Novel phytoalexins (oryzalexins A, B and C) isolated from rice blast leaves infected with *Pyricularia oryzae*. Part I: isolation, characterization and biological activities of oryzalexins Part II: structural studies of oryzalexins. Agric. Biol. Chem. 49, 1689–1701.

Allwood, J.W., Clarke, A., Goodacre, R., Mur, L.A., 2010. Dual metabolomics: a novel approach to understanding plant-pathogen interactions. Phytochemistry 71, 590–597.

Allwood, J.W., Heald, J., Lloyd, A.J., Goodacre, R., Mur, L.A., 2011. Separating the inseparable: the metabolomic analysis of plant–pathogen interactions. In: Plant Metabolomics. Springer, pp. 31–49.

Apel, K., Hirt, H., 2004. Reactive oxygen species: metabolism, oxidative stress, and signal transduction. Annu. Rev. Plant Biol. 55, 373–399.

Arnao, M.B., Hernández-Ruiz, J., 2006. The physiological function of melatonin in plants. Plant Signal. Behav. 1, 89–95.

Asahina, Y., 1908. Ueber das Sakuranin, ein neues Glykosid der Rinde von Prunus Pseudo-Cerasus Lindl. var. Sieboldi Maxim. Arch. Pharm. 246, 259–272.

Azizi, P., Rafii, M.Y., Abdullah, S.N.A., Nejat, N., Maziah, M., Hanafi, M.M., Latif, M.A., Sahebi, M., 2014. Toward understanding of rice innate immunity against *Magnaporthe oryzae*. Crit. Rev. Biotechnol. 1–10.

Azizi, P., Rafii, M., Abdullah, S., Nejat, N., Maziah, M., Hanafi, M., Latif, M., Sahebi, M., 2016. Toward understanding of rice innate immunity against *Magnaporthe oryzae*. Crit. Rev. Biotechnol. 36, 165–174.

Balmer, D., Flors, V., Glauser, G., Mauch-Mani, B., 2013. Metabolomics of cereals under biotic stress: current knowledge and techniques. Front. Plant Sci. 4.

Barding Jr., G.A., Fukao, T., Béni, S., Bailey-Serres, J., Larive, C.K., 2011. Differential metabolic regulation governed by the rice *SUB1A* gene during submergence stress and identification of alanylglycine by 1H NMR spectroscopy. J. Proteome Res. 11, 320–330.

Bassard, J.-E., Ullmann, P., Bernier, F., Werck-Reichhart, D., 2010. Phenolamides: bridging polyamines to the phenolic metabolism. Phytochemistry 71, 1808–1824.

Baxter, H., Harborne, J.B., Moss, G.P., 1998. Phytochemical Dictionary: a Handbook of Bioactive Compounds from Plants. CRC press.

Bennett, R.N., Wallsgrove, R.M., 1994. Secondary metabolites in plant defence mechanisms. New Phytol. 127, 617–633.

Bienz, S., Bisegger, P., Guggisberg, A., Hesse, M., 2005. Polyamine alkaloids. Nat. Prod. Rep. 22, 647–658.

Buchanan-Wollaston, V., 1997. The molecular biology of leaf senescence. JExB 48, 181–199.

Byeon, Y., Lee, H.Y., Hwang, O.J., Lee, H.J., Lee, K., Back, K., 2015. Coordinated regulation of melatonin synthesis and degradation genes in rice leaves in response to cadmium treatment. J. Pineal Res. 58, 470–478.

Cartwright, D., Langcake, P., Pryce, R., Leworthy, D., 1977. Chemical activation of host defence mechanisms as a basis for crop protection. Nature 267, 511–513.

Cartwright, D.W., Langcake, P., Pryce, R.J., Leworthy, D.P., Ride, J.P., 1981. Isolation and characterization of two phytoalexins from rice as momilactones A and B. Phytochemistry 20, 535–537.

Chamam, A., Sanguin, H., Bellvert, F., Meiffren, G., Comte, G., Wisniewski-Dyé, F., Bertrand, C., Prigent-Combaret, C., 2013. Plant secondary metabolite profiling evidences strain-dependent effect in the Azospirillum–*Oryza sativa* association. Phytochemistry 87, 65–77.

Chen, W., Gao, Y., Xie, W., Gong, L., Lu, K., Wang, W., Li, Y., Liu, X., Zhang, H., Dong, H., 2014. Genome-wide association analyses provide genetic and biochemical insights into natural variation in rice metabolism. Nat. Genet. 46, 714–721.

Cho, M.-H., Lee, S.-W., 2015. Phenolic phytoalexins in rice: biological functions and biosynthesis. Int. J. Mol. Sci. 16, 29120–29133.

Cho, E.M., Okada, A., Kenmoku, H., Otomo, K., Toyomasu, T., Mitsuhashi, W., Sassa, T., Yajima, A., Yabuta, G., Mori, K., 2004. Molecular cloning and characterization of a cDNA encoding ent-cassa-12, 15-diene synthase, a putative diterpenoid phytoalexin biosynthetic enzyme, from suspension-cultured rice cells treated with a chitin elicitor. PlJ 37, 1–8.

Cho, K., Shibato, J., Agrawal, G.K., Jung, Y.-H., Kubo, A., Jwa, N.-S., Tamogami, S., Satoh, K., Kikuchi, S., Higashi, T., 2008. Integrated transcriptomics, proteomics, and metabolomics analyses to survey ozone responses in the leaves of rice seedling. J. Proteome Res. 7, 2980–2998.

Chung, H.S., Shin, J.C., 2007. Characterization of antioxidant alkaloids and phenolic acids from anthocyanin-pigmented rice (*Oryza sativa* cv. Heugjinjubyeo). Food Chem. 104, 1670–1677.

Croteau, R., Ketchum, R.E., Long, R.M., Kaspera, R., Wildung, M.R., 2006. Taxol biosynthesis and molecular genetics. Phytochem. Rev. 5, 75–97.

de Ascensao, A.R., Dubery, I.A., 2003. Soluble and wall-bound phenolics and phenolic polymers in *Musa acuminata* roots exposed to elicitors from *Fusarium oxysporum* f. sp. *cubense*. Phytochemistry 63, 679–686.

de Pinto, M.C., Tommasi, F., De Gara, L., 2002. Changes in the antioxidant systems as part of the signaling pathway responsible for the programmed cell death activated by nitric oxide and reactive oxygen species in tobacco Bright-Yellow 2 cells. Plant Physiol. 130, 698–708.

Degenkolbe, T., Do, P.T., Kopka, J., Zuther, E., Hincha, D.K., Köhl, K.I., 2013. Identification of drought tolerance markers in a diverse population of rice cultivars by expression and metabolite profiling. PLoS One 8, e63637.

Dharmawardhana, P., Ren, L., Amarasinghe, V., Monaco, M., Thomason, J., Ravenscroft, D., McCouch, S., Ware, D., Jaiswal, P., 2013. A genome scale metabolic network for rice and accompanying analysis of tryptophan, auxin and serotonin biosynthesis regulation under biotic stress. Rice 6, 15.

Dillon, V.M., Overton, J., Grayer, R.J., Harborne, J.B., 1997. Differences in phytoalexin response among rice cultivars of different resistance to blast. Phytochemistry 44, 599–603.

Dixon, R.A., Paiva, N.L., 1995. Stress-induced phenylpropanoid metabolism. Plant Cell 7, 1085.

Du, H., Liang, Y., Pei, K., Ma, K., 2011. UV radiation-responsive proteins in rice leaves: a proteomic analysis. PCPhy 52, 306–316.

Du Fall, L.A., Solomon, P.S., 2011. Role of cereal secondary metabolites involved in mediating the outcome of plant-pathogen interactions. Metabolites 1, 64–78.

Duan, L., Liu, H., Li, X., Xiao, J., Wang, S., 2014. Multiple phytohormones and phytoalexins are involved in disease resistance to *Magnaporthe oryzae* invaded from roots in rice. Physiol. Plant. 152, 486–500.

Dubouzet, J.G., Ishihara, A., Matsuda, F., Miyagawa, H., Iwata, H., Wakasa, K., 2007. Integrated metabolomic and transcriptomic analyses of high-tryptophan rice expressing a mutant anthranilate synthase alpha subunit. JExB 58, 3309–3321.

Dubouzet, J.G., Matsuda, F., Ishihara, A., Miyagawa, H., Wakasa, K., 2013. Production of indole alkaloids by metabolic engineering of the tryptophan pathway in rice. Plant Biotechnol. J. 11, 1103–1111.

Dunn, W.B., 2008. Current trends and future requirements for the mass spectrometric investigation of microbial, mammalian and plant metabolomes. PhBio 5, 011001.

D'Auria, J.C., 2006. Acyltransferases in plants: a good time to be BAHD. Curr. Opin. Plant Biol. 9, 331–340.

Edreva, A., Velikova, V., Tsonev, T., 2007. Phenylamides in plants. Russ. J. Plant Physiol. 54, 287–301.

Facchini, P.J., Huber-Allanach, K.L., Tari, L.W., 2000. Plant aromatic L-amino acid decarboxylases: evolution, biochemistry, regulation, and metabolic engineering applications. Phytochemistry 54, 121–138.

Fisher, M.C., Henk, D.A., Briggs, C.J., Brownstein, J.S., Madoff, L.C., McCraw, S.L., Gurr, S.J., 2012. Emerging fungal threats to animal, plant and ecosystem health. Nature 484, 186–194.

Fujita, M., Fujita, Y., Noutoshi, Y., Takahashi, F., Narusaka, Y., Yamaguchi-Shinozaki, K., Shinozaki, K., 2006. Crosstalk between abiotic and biotic stress responses: a current view from the points of convergence in the stress signaling networks. Curr. Opin. Plant Biol. 9, 436–442.

Fujiwara, T., Maisonneuve, S., Isshiki, M., Mizutani, M., Chen, L., Wong, H.L., Kawasaki, T., Shimamoto, K., 2010. Sekiguchi lesion gene encodes a cytochrome P450 monooxygenase that catalyzes conversion of tryptamine to serotonin in rice. J. Biol. Chem. 285, 11308–11313.

Ghosh, S., Kanwar, P., Jha, G., 2017. Alterations in rice chloroplast integrity, photosynthesis and metabolome associated with pathogenesis of *Rhizoctonia solani*. Sci. Rep. 7, 41610.

Giberti, S., Bertea, C.M., Narayana, R., Maffei, M.E., Forlani, G., 2012. Two phenylalanine ammonia lyase isoforms are involved in the elicitor-induced response of rice to the fungal pathogen *Magnaporthe oryzae*. J. Plant Physiol. 169, 249–254.

Glaubitz, U., Erban, A., Kopka, J., Hincha, D.K., Zuther, E., 2015. High Night Temperature Strongly Impacts TCA Cycle, Amino Acid and Polyamine Biosynthetic Pathways in Rice in a Sensitivity-dependent Manner. JExB., erv352.

Glenn, W.S., Nims, E., O'Connor, S.E., 2011. Reengineering a tryptophan halogenase to preferentially chlorinate a direct alkaloid precursor. J. Am. Chem. Soc. 133, 19346–19349.

Góngora-Castillo, E., Childs, K.L., Fedewa, G., Hamilton, J.P., Liscombe, D.K., Magallanes-Lundback, M., Mandadi, K.K., Nims, E., Runguphan, W., Vaillancourt, B., 2012. Development of transcriptomic resources for interrogating the biosynthesis of monoterpene indole alkaloids in medicinal plant species. PLoS One 7, e52506.

Gonzalez-Lamothe, R., Mitchell, G., Gattuso, M., Diarra, M.S., Malouin, F.o., Bouarab, K., 2009. Plant antimicrobial agents and their effects on plant and human pathogens. Int. J. Mol. Sci. 10, 3400–3419.

Grecco, S.d.S., Reimão, J.Q., Tempone, A.G., Sartorelli, P., Cunha, R.L., Romoff, P., Ferreira, M.J., Fávero, O.A., Lago, J.H.G., 2012. In vitro antileishmanial and antitrypanosomal activities of flavanones from *Baccharis retusa* DC.(Asteraceae). Exp. Parasitol. 130, 141–145.

Großkinsky, D.K., van der Graaff, E., Roitsch, T., 2012. Phytoalexin transgenics in crop protection—fairy tale with a happy end? Plant Sci. 195, 54–70.

Gui, J., Shen, J., Li, L., 2011. Functional characterization of evolutionarily divergent 4-coumarate: coenzyme A ligases in rice. Plant Physiol. 157, 574–586.

Guillet, G., Poupart, J., Basurco, J., De Luca, V., 2000. Expression of tryptophan decarboxylase and tyrosine decarboxylase genes in tobacco results in altered biochemical and physiological phenotypes. Plant Physiol. 122, 933–944.

Gülçin, I., 2008. Measurement of antioxidant ability of melatonin and serotonin by the DMPD and CUPRAC methods as trolox equivalent. J. Enzym. Inhib. Med. Chem. 23, 871–876.

Gupta, P., De, B., 2017. Metabolomics analysis of rice responses to salinity stress revealed elevation of serotonin, and gentisic acid levels in leaves of tolerant varieties. Plant Signal. Behav. 12, e1335845.

Hammerschmidt, R., 1999. Phytoalexins: what have we learned after 60 years? Annu. Rev. Phytopathol. 37, 285–306.

Hammond-Kosack, K.E., Kanyuka, K., 2007. Resistance Genes (*R* Genes) in Plants. ELS.

Harborne, A., 1998. Phytochemical Methods a Guide to Modern Techniques of Plant Analysis. Springer Science & Business Media.

Hasegawa, M., Mitsuhara, I., Seo, S., Imai, T., Koga, J., Okada, K., Yamane, H., Ohashi, Y., 2010. Phytoalexin accumulation in the interaction between rice and the blast fungus. Mol. Plant Microbe Interact. 23, 1000–1011.

Hayashi, K., Fujita, Y., Ashizawa, T., Suzuki, F., Nagamura, Y., Hayano-Saito, Y., 2016. Serotonin attenuates biotic stress and leads to lesion browning caused by a hypersensitive response to *Magnaporthe oryzae* penetration in rice. PlJ 85, 46–56.

Heath, M.l.C., 2000. Hypersensitive response-related death. In: Programmed Cell Death in Higher Plants. Springer, pp. 77–90.

Horie, K., Inoue, Y., Sakai, M., Yao, Q., Tanimoto, Y., Koga, J., Toshima, H., Hasegawa, M., 2015. Identification of UV-induced diterpenes including a new diterpene phytoalexin, phytocassane F, from rice leaves by complementary GC/MS and LC/MS approaches. J. Agric. Food Chem. 63, 4050–4059.

Horie, K., Sakai, K., Okugi, M., Toshima, H., Hasegawa, M., 2016. Ultraviolet-induced amides and casbene diterpenoids from rice leaves. Phytochem. Lett. 15, 57–62.

Huether, G., Fettkötter, I., Keilhoff, G., Wolf, G., 1997. Serotonin acts as a radical scavenger and is oxidized to a dimer during the respiratory burst of activated microglia. J. Neurochem. 69, 2096–2101.

Hwang, O.J., Back, K., 2018. Melatonin is involved in skotomorphogenesis by regulating brassinosteroid biosynthesis in rice plants. J. Pineal Res. 65, e12495.

Inoue, Y., Sakai, M., Yao, Q., Tanimoto, Y., Toshima, H., Hasegawa, M., 2013. Identification of a novel casbane-type diterpene phytoalexin, ent-10-oxodepressin, from rice leaves. Biosc. Biotech. Biochem. 77, 760–765.

Ishihara, A., Hashimoto, Y., Tanaka, C., Dubouzet, J.G., Nakao, T., Matsuda, F., Nishioka, T., Miyagawa, H., Wakasa, K., 2008. The tryptophan pathway is involved in the defense responses of rice against pathogenic infection via serotonin production. PlJ 54, 481–495.

Ishihara, A., Nakao, T., Mashimo, Y., Murai, M., Ichimaru, N., Tanaka, C., Nakajima, H., Wakasa, K., Miyagawa, H., 2011. Probing the role of tryptophan-derived secondary metabolism in defense responses against *Bipolaris oryzae* infection in rice leaves by a suicide substrate of tryptophan decarboxylase. Phytochemistry 72, 7–13.

Jeandet, P., Hébrard, C., Deville, M.-A., Cordelier, S., Dorey, S., Aziz, A., Crouzet, J., 2014. Deciphering the role of phytoalexins in plant-microorganism interactions and human health. Molecules 19, 18033–18056.

Jin, B., Zhou, X., Jiang, B., Gu, Z., Zhang, P., Qian, Q., Chen, X., Ma, B., 2015. Transcriptome profiling of the *spl5* mutant reveals that *SPL5* has a negative role in the biosynthesis of serotonin for rice disease resistance. Rice 8, 1.

Jones, O.A., Maguire, M.L., Griffin, J.L., Jung, Y.-H., Shibato, J., Rakwal, R., Agrawal, G.K., Jwa, N.-S., 2011. Using metabolic profiling to assess plant-pathogen interactions: an example using rice (*Oryza sativa*) and the blast pathogen *Magnaporthe grisea*. Eur. J. Plant Pathol. 129, 539–554.

Kang, S., Kang, K., Lee, K., Back, K., 2007. Characterization of rice tryptophan decarboxylases and their direct involvement in serotonin biosynthesis in transgenic rice. Planta 227, 263–272.

Kang, K., Kang, S., Lee, K., Park, M., Back, K., 2008. Enzymatic features of serotonin biosynthetic enzymes and serotonin biosynthesis in plants. Plant Signal. Behav. 3, 389–390.

Kang, K., Kim, Y.-S., Park, S., Back, K., 2009. Senescence-induced serotonin biosynthesis and its role in delaying senescence in rice leaves. Plant Physiol. 150, 1380–1393.

Kang, K., Park, S., Natsagdorj, U., Kim, Y.S., Back, K., 2011. Methanol is an endogenous elicitor molecule for the synthesis of tryptophan and tryptophan-derived secondary metabolites upon senescence of detached rice leaves. PlJ 66, 247–257.

Kanjanaphachoat, P., Wei, B.-Y., Lo, S.-F., Wang, I.-W., Wang, C.-S., Yu, S.-M., Yen, M.-L., Chiu, S.-H., Lai, C.-C., Chen, L.-J., 2012. Serotonin accumulation in transgenic rice by over-expressing tryptophan decarboxlyase results in a dark brown phenotype and stunted growth. Plant Mol. Biol. 78, 525–543.

Kasahara, H., Hanada, A., Kuzuyama, T., Takagi, M., Kamiya, Y., Yamaguchi, S., 2002. Contribution of the mevalonate and methylerythritol phosphate pathways to the biosynthesis of gibberellins in Arabidopsis. J. Biol. Chem. 277, 45188–45194.

Kato, T., Kabuto, C., Sasaki, N., Tsunagawa, M., Aizawa, H., Fujita, K., Kato, Y., Kitahara, Y., Takahashi, N., 1973. Momilactones, growth inhibitors from rice, *Oryza sativa* L. Tetrahedron Lett. 14, 3861–3864.

Kato, H., Kodama, O., Akatsuka, T., 1993. Oryzalexin E, a diterpene phytoalexin from UV-irradiated rice leaves. Phytochemistry 33, 79–81.

Kato, H., Kodama, O., Akatsuka, T., 1994. Oryzalexin F, a diterpene phytoalexin from UV-irradiated rice leaves. Phytochemistry 36, 299–301.

Kato-Noguchi, H., 2004. Allelopathic substance in rice root exudates: rediscovery of momilactone B as an allelochemical. J. Plant Physiol. 161, 271–276.

Kawahara, Y., de la Bastide, M., Hamilton, J.P., Kanamori, H., McCombie, W.R., Ouyang, S., Schwartz, D.C., Tanaka, T., Wu, J., Zhou, S., 2013. Improvement of the *Oryza sativa* Nipponbare reference genome using next generation sequence and optical map data. Rice 6, 1.

Kim, H.K., Choi, Y.H., Verpoorte, R., 2011. NMR-based plant metabolomics: where do we stand, where do we go? Trends Biotechnol. 29, 267–275.

Ko, K.-W., Okada, K., Koga, J., Jikumaru, Y., Nojiri, H., Yamane, H., 2010. Effects of cytokinin on production of diterpenoid phytoalexins in rice. J. Pestic. Sci. 35, 412–418.

Kodama, O., Yamada, H., Yamamoto, A., Takemoto, T., Akatsuka, T., 1988a. Induction of phytoalexins with heavy metal ions in rice leaves. J. Pestic. Sci. 13, 615–617.

Kodama, O., Suzuki, T., Miyakawa, J., Akatsuka, T., 1988b. Ultraviolet-induced accumulation of phytoalexins in rice leaves. Agric. Biol. Chem. 52, 2469–2473.

Kodama, O., Xin Li, W., Tamogami, S., Akatsuka, T., 1992a. Oryzalexin S, a novel stemarane-type diterpene rice phytoalexin. Biosc. Biotech. Biochem. 56, 1002–1003.

Kodama, O., Miyakawa, J., Akatsuka, T., Kiyosawa, S., 1992b. Sakuranetin, a flavanone phytoalexin from ultraviolet-irradiated rice leaves. Phytochemistry 31, 3807–3809.

Koeck, M., Hardham, A.R., Dodds, P.N., 2011. The role of effectors of biotrophic and hemibiotrophic fungi in infection. Cell Microbiol. 13, 1849–1857.

Koga, J., Shimura, M., Oshima, K., Ogawa, N., Yamauchi, T., Ogasawara, N., 1995. Phytocassanes A, B, C and D, novel diterpene phytoalexins from rice, Oryza sativa L. Tetrahedron 51, 7907–7918.

Koga, J., Ogawa, N., Yamauchi, T., Kikuchi, M., Ogasawara, N., Shimura, M., 1997. Functional moiety for the antifungal activity of phytocassane E, a diterpene phytoalexin from rice. Phytochemistry 44, 249–253.

Kono, Y., Takeuchi, S., Kodama, O., Akatsuka, T., 1984. Absolute configuration of oryzalexin A and structures of its related phytoalexins isolated from rice blast leaves infected with *Pyricularia oryzae*. Agric. Biol. Chem. 48, 253–255.

KONO, Y., TAKEUCHI, S., KODAMA, O., SEKIDO, H., AKATSUKA, T., 1985. Novel phytoalexins (oryzalexins A, B and C) isolated from rice blast leaves infected with *Pyricularia oryzae*. Part II: structural studies of oryzalexins. Agric. Biol. Chem. 49, 1695–1701.

Kono, Y., Uzawa, J., Kobayashi, K., Suzuki, Y., Uramoto, M., Sakurai, A., Watanabe, M., Teraoka, T., Hosokawa, D., Watanabe, M., 1991. Structures of oryzalides A and B, and oryzalic acid A, a group of novel antimicrobial diterpenes, isolated from healthy leaves of a bacterial leaf blight-resistant cultivar of rice plant. Agric. Biol. Chem. 55, 803–811.

Kreps, J.A., Ponappa, T., Dong, W., Town, C.D., 1996. Molecular basis of [alpha]-methyltryptophan resistance in amt-1, a mutant of Arabidopsis thaliana with altered tryptophan metabolism. Plant Physiol. 110, 1159–1165.

Laluk, K., Mengiste, T., 2010. Necrotroph attacks on plants: wanton destruction or covert extortion? Arabidopsis Book, e0136.

Langridge, P., Fleury, D., 2011. Making the most of 'omics' for crop breeding. Trends Biotechnol. 29, 33–40.

Lee, K., Back, K., 2019. Melatonin-deficient rice plants show a common semidwarf phenotype either dependent or independent of brassinosteroid biosynthesis. J. Pineal Res. 66, e12537.

Lee, C.W., Yoneyama, K., Takeuchi, Y., Konnai, M., Tamogami, S., Kodama, O., 1999. Momilactones A and B in rice straw harvested at different growth stages. Biosc. Biotech. Biochem. 63, 1318–1320.

Lee, K., Lee, H.Y., Back, K., 2018. Rice histone deacetylase 10 and Arabidopsis histone deacetylase 14 genes encode N-acetylserotonin deacetylase, which catalyzes conversion of N-acetylserotonin into serotonin, a reverse reaction for melatonin biosynthesis in plants. J. Pineal Res. 64, e12460.

Li, X., Lawas, L.M., Malo, R., Glaubitz, U., Erban, A., Mauleon, R., Heuer, S., Zuther, E., Kopka, J., Hincha, D.K., 2015. Metabolic and transcriptomic signatures of rice floral organs reveal sugar starvation as a factor in reproductive failure under heat and drought stress. Plant Cell Environ. 38, 2171–2192.

Lichtenthaler, H.K., 1996. Vegetation stress: an introduction to the stress concept in plants. J. Plant Physiol. 148, 4–14.

Lim, P.O., Kim, H.J., Gil Nam, H., 2007. Leaf senescence. Annu. Rev. Plant Biol. 58, 115–136.

Lu, H.-p., Luo, T., Fu, H.-w., Wang, L., Tan, Y.-y., Huang, J.-z., Wang, Q., Ye, G.-y., Gatehouse, A.M., Lou, Y.-g., 2018. Resistance of rice to insect pests mediated by suppression of serotonin biosynthesis. Nat. Plants 4, 338.

Madhavan, S., Paranidharan, V., Erban, A., Al-Sadi, A., Kopka, J., Velazhahan, R., 2019. The metabolic response of suspension-cultured cells from blast-resistant and-susceptible rice (*Oryza sativa* L.) genotypes to a *Pyricularia oryzae* elicitor. Indian Phytopathol. 1–8.

Martin-Urdiroz, M., Oses-Ruiz, M., Ryder, L.S., Talbot, N.J., 2016. Investigating the biology of plant infection by the rice blast fungus *Magnaporthe oryzae*. Fungal Genet. Biol. 90, 61–68.

Maruyama, K., Urano, K., Yoshiwara, K., Morishita, Y., Sakurai, N., Suzuki, H., Kojima, M., Sakakibara, H., Shibata, D., Saito, K., 2014. Integrated analysis of the effects of cold and dehydration on rice metabolites, phytohormones, and gene transcripts. Plant Physiol. 164, 1759–1771.

Mayer, M.P., Hahn, F.M., Stillman, D.J., Poulter, C.D., 1992. Disruption and mapping of IDI1, the gene for isopentenyl diphosphate isomerase in Saccharomyces cerevisiae. Yeast 8, 743–748.

Miyamoto, K., Fujita, M., Shenton, M.R., Akashi, S., Sugawara, C., Sakai, A., Horie, K., Hasegawa, M., Kawaide, H., Mitsuhashi, W., 2016. Evolutionary trajectory of phytoalexin biosynthetic gene clusters in rice. PlJ 87, 293–304.

Miyazawa, M., Kinoshita, H., Okuno, Y., 2003. Antimutagenic activity of sakuranetin from Prunus jamasakura. J. Food Sci. 68, 52–56.

Morimoto, N., Ueno, K., Teraishi, M., Okumoto, Y., Mori, N., Ishihara, A., 2018. Induced phenylamide accumulation in response to pathogen infection and hormone treatment in rice (*Oryza sativa*). Biosci. Biotechnol. Biochem. 82, 407–416.

Moritani, C., Kawakami, K., Fujita, A., Kawakami, K., Shimoda, H., Hatanaka, T., Tsuboi, S., 2018. Isolation of activating factors of serotonin N-acetyltransferase from rice peptides. J. Funct. Foods. 41, 148–154.

Mukherjee, R., Mukherjee, A., Bandyopadhyay, S., Mukherjee, S., Sengupta, S., Ray, S., Majumder, A.L., 2019. Selective manipulation of the inositol metabolic pathway for induction of salt-tolerance in indica rice variety. Sci. Rep. 9, 5358.

Naoumkina, M.A., Zhao, Q., Gallego-Giraldo, L., Dai, X., Zhao, P.X., Dixon, R.A., 2010. Genome-wide analysis of phenylpropanoid defence pathways. Mol. Plant Pathol. 11, 829–846.

Nishiguchi, S., Murata, K., Ube, N., Ueno, K., Tebayashi, S.-i., Teraishi, M., Okumoto, Y., Mori, N., Ishihara, A., 2018. Accumulation of 9-and 13-KODEs in response to jasmonic acid treatment and pathogenic infection in rice. J. Pestic. Sci. D18–D022.

Obata, T., Fernie, A.R., 2012. The use of metabolomics to dissect plant responses to abiotic stresses. Cell. Mol. Life Sci. 69, 3225–3243.

Ogawa, S., Miyamoto, K., Nemoto, K., Sawasaki, T., Yamane, H., Nojiri, H., Okada, K., 2017. OsMYC2, an essential factor for JA-inductive sakuranetin production in rice, interacts with MYC2-like proteins that enhance its transactivation ability. Sci. Rep. 7, 40175.

Okada, A., Shimizu, T., Okada, K., Kuzuyama, T., Koga, J., Shibuya, N., Nojiri, H., Yamane, H., 2007. Elicitor induced activation of the methylerythritol phosphate pathway toward phytoalexins biosynthesis in rice. Plant Mol. Biol. 65, 177–187.

Okada, A., Okada, K., Miyamoto, K., Koga, J., Shibuya, N., Nojiri, H., Yamane, H., 2009. OsTGAP1, a bZIP transcription factor, coordinately regulates the inductive production of diterpenoid phytoalexins in rice. J. Biol. Chem. 284, 26510–26518.

Osbourn, A.E., 2003. Saponins in cereals. Phytochemistry 62, 1–4.

Otomo, K., Kanno, Y., Motegi, A., Kenmoku, H., Yamane, H., Mitsuhashi, W., Oikawa, H., Toshima, H., Itoh, H., Matsuoka, M., 2004a. Diterpene cyclases responsible for the biosynthesis of phytoalexins, momilactones A, B, and oryzalexins A–F in rice. Biosci. Biotechnol. Biochem. 68, 2001–2006.

Otomo, K., Kenmoku, H., Oikawa, H., König, W.A., Toshima, H., Mitsuhashi, W., Yamane, H., Sassa, T., Toyomasu, T., 2004b. Biological functions of ent-and syn-copalyl diphosphate synthases in rice: key enzymes for the branch point of gibberellin and phytoalexin biosynthesis. PlJ 39, 886–893.

Park, H.L., Lee, S.-W., Jung, K.-H., Hahn, T.-R., Cho, M.-H., 2013. Transcriptomic analysis of UV-treated rice leaves reveals UV-induced phytoalexin biosynthetic pathways and their regulatory networks in rice. Phytochemistry 96, 57–71.

Park, H.L., Yoo, Y., Hahn, T.-R., Bhoo, S.H., Lee, S.-W., Cho, M.-H., 2014. Antimicrobial activity of UV-induced phenylamides from rice leaves. Molecules 19, 18139–18151.

Parker, D., Beckmann, M., Zubair, H., Enot, D.P., Caracuel-Rios, Z., Overy, D.P., Snowdon, S., Talbot, N.J., Draper, J., 2009. Metabolomic analysis reveals a common pattern of metabolic re-programming during invasion of three host plant species by *Magnaporthe grisea*. PlJ 59, 723–737.

Peng, M., Gao, Y., Chen, W., Wang, W., Shen, S., Shi, J., Wang, C., Zhang, Y., Zou, L., Wang, S., 2016. Evolutionarily Distinct BAHD N-Acyltransferases Are Responsible for Natural Variation of Aromatic Amine Conjugates in Rice. The Plant Cell Online. 00265.02016.

Piasecka, A., Jedrzejczak-Rey, N., Bednarek, P., 2015. Secondary metabolites in plant innate immunity: conserved function of divergent chemicals. New Phytol. 206, 948–964.

Pieterse, C.M., Van der Does, D., Zamioudis, C., Leon-Reyes, A., Van Wees, S.C., 2012. Hormonal modulation of plant immunity. Annu. Rev. Cell Dev. Biol. 28, 489–521.

Rakwal, R., Hasegawa, M., Kodama, O., 1996. A methyltransferase for synthesis of the flavanone phytoalexin sakuranetin in rice leaves. BBRC (Biochem. Biophys. Res. Commun.) 222, 732–735.

Riemann, M., Haga, K., Shimizu, T., Okada, K., Ando, S., Mochizuki, S., Nishizawa, Y., Yamanouchi, U., Nick, P., Yano, M., 2013. Identification of rice Allene Oxide Cyclase mutants and the function of jasmonate for defence against *Magnaporthe oryzae*. PlJ 74, 226–238.

Sacchettini, J.C., Poulter, C.D., 1997. Creating isoprenoid diversity. Sci 277, 1788–1789.

Saito, K., Matsuda, F., 2010. Metabolomics for functional genomics, systems biology, and biotechnology. Annu. Rev. Plant Biol. 61, 463–489.

Saito, T., Abe, D., Sekiya, K., 2008. Sakuranetin induces adipogenesis of 3T3-L1 cells through enhanced expression of PPARγ2. BBRC (Biochem. Biophys. Res. Commun.) 372, 835–839.

Salvador-Guirao, R., Baldrich, P., Tomiyama, S., Hsing, Y.-I., Okada, K., San Segundo, B., 2018. *OsDCL1a* activation impairs phytoalexin biosynthesis and compromises disease resistance in rice. Ann. Bot.

Sana, T.R., Fischer, S., Wohlgemuth, G., Katrekar, A., Jung, K.-h., Ronald, P.C., Fiehn, O., 2010. Metabolomic and transcriptomic analysis of the rice response to the bacterial blight pathogen *Xanthomonas oryzae* pv. oryzae. Metabolomics 6, 451–465.

Schauer, N., Fernie, A.R., 2006. Plant metabolomics: towards biological function and mechanism. Trends Plant Sci. 11, 508–516.

Sekido, H., Akatsuka, T., 1987. Mode of action of oryzalexin D against *Pyricularia oryzae*. Agric. Biol. Chem. 51, 1967–1971.

Sekido, H., Endo, T., Suga, R., Kodama, O., Akatsuka, T., Kono, Y., Takeuchi, S., 1986. Oryzalexin D (3, 7-dihydroxy-(+)-sandaracopimaradiene), a new phytoalexin isolated from blast-infected rice leaves. J. Pestic. Sci. 11, 369–372.

Shimizu, T., Jikumaru, Y., Okada, A., Okada, K., Koga, J., Umemura, K., Minami, E., Shibuya, N., Hasegawa, M., Kodama, O., 2008. Effects of a bile acid elicitor, cholic acid, on the biosynthesis of diterpenoid phytoalexins in suspension-cultured rice cells. Phytochemistry 69, 973–981.

Shimizu, T., Lin, F., Hasegawa, M., Nojiri, H., Yamane, H., Okada, K., 2012a. The potential bioproduction of the pharmaceutical agent sakuranetin, a flavonoid phytoalexin in rice. Bioengineered 3, 352–357.

Shimizu, T., Lin, F., Hasegawa, M., Okada, K., Nojiri, H., Yamane, H., 2012b. Purification and identification of naringenin 7-O-methyltransferase, a key enzyme in biosynthesis of flavonoid phytoalexin sakuranetin in rice. J. Biol. Chem. 287, 19315–19325.

Shimizu, T., Miyamoto, K., Miyamoto, K., Minami, E., Nishizawa, Y., Iino, M., Nojiri, H., Yamane, H., Okada, K., 2013. *OsJAR1* contributes mainly to biosynthesis of the stress-induced jasmonoyl-isoleucine involved in defense responses in rice. Biosci. Biotechnol. Biochem. 77, 1556–1564.

Shimura, K., Okada, A., Okada, K., Jikumaru, Y., Ko, K.-W., Toyomasu, T., Sassa, T., Hasegawa, M., Kodama, O., Shibuya, N., 2007. Identification of a biosynthetic gene cluster in rice for momilactones. J. Biol. Chem. 282, 34013–34018.

Shu, L., Lou, Q., Ma, C., Ding, W., Zhou, J., Wu, J., Feng, F., Lu, X., Luo, L., Xu, G., 2011. Genetic, proteomic and metabolic analysis of the regulation of energy storage in rice seedlings in response to drought. Proteomics 11, 4122–4138.

Spanu, P.D., 2012. The genomics of obligate (and nonobligate) biotrophs. Annu. Rev. Phytopathol. 50, 91–109.

Sumner, L.W., Mendes, P., Dixon, R.A., 2003. Plant metabolomics: large-scale phytochemistry in the functional genomics era. Phytochemistry 62, 817–836.

Sun, H., Li, Y., Feng, S., Zou, W., Guo, K., Fan, C., Peng, L., 2013. Analysis of five rice 4-coumarate: coenzyme A ligase enzyme activity and stress response for potential roles in lignin and flavonoid biosynthesis in rice. Biochem. Biophys. Res. Commun. 430, 1151–1156.

Sun, L., Yang, D.l., Kong, Y., Chen, Y., Li, X.Z., Zeng, L.J., Li, Q., Wang, E.T., He, Z.H., 2014. Sugar homeostasis mediated by cell wall invertase *GRAIN INCOMPLETE FILLING 1 (GIF1)* plays a role in pre-existing and induced defence in rice. Mol. Plant Pathol. 15, 161–173.

Takahashi, H., Matsumura, H., Kawai-Yamada, M., Uchimiya, H., 2008. The cell death factor, cell wall elicitor of rice blast fungus (*Magnaporthe grisea*) causes metabolic alterations including GABA shunt in rice cultured cells. Plant Signal. Behav. 3, 945–953.

Tamogani, S., Mitani, M., Kodama, O., Akatsuka, T., 1993. Oryzalexin S structure: a new stemarane-type rice plant phytoalexin and its biogenesis. Tetrahedron 49, 2025–2032.

Tan, K.-C., Oliver, R.P., 2014. 12 metabolomics and proteomics to dissect fungal phytopathogenicity. In: Fungal Genomics. Springer, pp. 301–319.

Tan, L.R., Lu, Y.C., Zhang, J.J., Luo, F., Yang, H., 2015. A collection of *cytochrome P450 monooxygenase* genes involved in modification and detoxification of herbicide atrazine in rice (*Oryza sativa*) plants. Ecotoxicol. Environ. Saf. 119, 25–34.

Tezuka, D., Ito, A., Mitsuhashi, W., Toyomasu, T., Imai, R., 2015. The rice *ent-KAURENE SYNTHASE LIKE 2* encodes a functional ent-beyerene synthase. BBRC (Biochem. Biophys. Res. Commun.) 460, 766–771.

Tonnessen, B.W., Manosalva, P., Lang, J.M., Baraoidan, M., Bordeos, A., Mauleon, R., Oard, J., Hulbert, S., Leung, H., Leach, J.E., 2015. Rice phenylalanine ammonia-lyase gene *OsPAL4* is associated with broad spectrum disease resistance. Plant Mol. Biol. 87, 273–286.

Toyomasu, T., Kagahara, T., Okada, K., Koga, J., Hasegawa, M., Mitsuhashi, W., Sassa, T., Yamane, H., 2008. Diterpene phytoalexins are biosynthesized in and exuded from the roots of rice seedlings. Biosci. Biotechnol. Biochem. 72, 562–567.

Toyomasu, T., Usui, M., Sugawara, C., Otomo, K., Hirose, Y., Miyao, A., Hirochika, H., Okada, K., Shimizu, T., Koga, J., 2014. Reverse-genetic approach to verify physiological roles of rice phytoalexins: characterization of a knockdown mutant of OsCPS4 phytoalexin biosynthetic gene in rice. Physiol. Plant. 150, 55–62.

Tozawa, Y., Hasegawa, H., Terakawa, T., Wakasa, K., 2001. Characterization of rice anthranilate synthase α-subunit genes *OASA1* and *OASA2*. Tryptophan accumulation in transgenic rice expressing a feedback-insensitive mutant of *OASA1*. Plant Physiol. 126, 1493–1506.

Trethewey, R.N., 2004. Metabolite profiling as an aid to metabolic engineering in plants. Curr. Opin. Plant Biol. 7, 196–201.

Tzin, V., Galili, G., 2010. New insights into the shikimate and aromatic amino acids biosynthesis pathways in plants. Mol. Plant 3, 956–972.

Uehara, K., 1958. On the production of phytoalexin by the host plant as a result of interaction between rice plant and the blast fungus (*Piricularia oryzae* Cav.). Ann. Phytopathol. Soc. Jpn. 23, 127–130.

Ueno, M., Shibata, H., Kihara, J., Honda, Y., Arase, S., 2003. Increased tryptophan decarboxylase and monoamine oxidase activities induce Sekiguchi lesion formation in rice infected with *Magnaporthe grisea*. PlJ 36, 215–228.

Umemura, K., Ogawa, N., Shimura, M., Koga, J., Usami, H., Kono, T., 2003. Possible role of phytocassane, rice phytoalexin, in disease resistance of rice against the blast fungus Magnaporthe grisea. Biosci. Biotechnol. Biochem. 67, 899–902.

Valette, M., Rey, M., Gerin, F., Comte, G., Wisniewski-Dyé, F., 2019. A common metabolomic signature is observed upon inoculation of rice roots with various rhizobacteria. J. Integr. Plant Biol.

VanEtten, H.D., Mansfield, J.W., Bailey, J.A., Farmer, E.E., 1994. Two classes of plant antibiotics: phytoalexins versus" Phytoanticipins. The Plant Cell 6, 1191.

Vogt, T., 2010. Phenylpropanoid biosynthesis. Mol. Plant 3, 2–20.

Wakasa, K., Ishihara, A., 2009. Metabolic engineering of the tryptophan and phenylalanine biosynthetic pathways in rice. Plant Biotechnol. 26, 523–533.

Wakasa, K., Hasegawa, H., Nemoto, H., Matsuda, F., Miyazawa, H., Tozawa, Y., Morino, K., Komatsu, A., Yamada, T., Terakawa, T., 2006. High-level tryptophan accumulation in seeds of transgenic rice and its limited effects on agronomic traits and seed metabolite profile. JExB 57, 3069–3078.

Wang, Q., Hillwig, M.L., Peters, R.J., 2011. CYP99A3: functional identification of a diterpene oxidase from the momilactone biosynthetic gene cluster in rice. PlJ 65, 87–95.

Wang, Q., Hillwig, M.L., Okada, K., Yamazaki, K., Wu, Y., Swaminathan, S., Yamane, H., Peters, R.J., 2012a. Characterization of CYP76M5–8 indicates metabolic plasticity within a plant biosynthetic gene cluster. J. Biol. Chem. 287, 6159–6168.

Wang, Q., Hillwig, M.L., Wu, Y., Peters, R.J., 2012b. CYP701A8: a rice ent-kaurene oxidase paralog diverted to more specialized diterpenoid metabolism. Plant Physiol. 158, 1418–1425.

Watanabe, M., Sakai, Y., Teraoka, T., Abe, H., Kono, Y., Uzawa, J., Kobayashi, K., Suzuki, Y., Sakurai, A., 1990. Novel C19-kaurane type of diterpene (oryzalide A), a new antimicrobial compound isolated from healthy leaves of a bacterial leaf blight-resistant cultivar of rice plant. Agric. Biol. Chem. 54, 1103–1105.

Watanabe, M., Kono, Y., Watanabe, M., Uzawa, J., Teraoka, T., Hosokawa, D., Suzuki, Y., Sakurai, A., Teraguchi, M., 1992. Structures of oryzalic acid B and three related compounds, a group of novel antibacterial diterpenes, isolated from leaves of a bacterial leaf blight-resistant cultivar of rice. Biosc. Biotech. Biochem. 56, 113–117.

Watanabe, M., Kono, Y., Esumi, Y., Teraoka, T., Hosokawa, D., Suzuki, Y., Sakurai, A., Watanabe, M., 1996. Studies on a quantitative analysis of oryzalides and oryzalic acids in rice plants by GC-SIM. Biosc. Biotech. Biochem. 60, 1460–1463.

Wilderman, P.R., Xu, M., Jin, Y., Coates, R.M., Peters, R.J., 2004. Identification of syn-pimara-7, 15-diene synthase reveals functional clustering of terpene synthases involved in rice phytoalexin/allelochemical biosynthesis. Plant Physiol. 135, 2098–2105.

Wink, M., 2010. In: Introduction, Annual Plant Reviews Volume 39: Functions and Biotechnology of Plant Secondary Metabolites, second ed. pp. 1–20.

Winkel-Shirley, B., 2002. Biosynthesis of flavonoids and effects of stress. Curr. Opin. Plant Biol. 5, 218–223.

Wolfender, J.-L., Glauser, G.t., Boccard, J., Rudaz, S., 2009. MS-based plant metabolomic approaches for biomarker discovery. Nat. Prod. Commun. 4, 1417–1430.

Xu, M., Hillwig, M.L., Prisic, S., Coates, R.M., Peters, R.J., 2004. Functional identification of rice syn-copalyl diphosphate synthase and its role in initiating biosynthesis of diterpenoid phytoalexin/allelopathic natural products. PlJ 39, 309–318.

Xu, M., Galhano, R., Wiemann, P., Bueno, E., Tiernan, M., Wu, W., Chung, I.M., Gershenzon, J., Tudzynski, B., Sesma, A., 2012. Genetic evidence for natural product-mediated plant–plant allelopathy in rice (*Oryza sativa*). New Phytol. 193, 570–575.

Yajima, A., Mori, K., 2000. Synthesis and absolute configuration of (−)-Phytocassane D, a diterpene phytoalexin isolated from the rice plant, Oryza sativa. Eur. J. Org. Chem. 2000, 4079–4091.

Yamada, A., Shibuya, N., Kodama, O., Akatsuka, T., 1993. Induction of phytoalexin formation in suspension-cultured rice cells by N-acetyl-chitooligosaccharides. Biosci. Biotechnol. Biochem. 57, 405–409.

Yamakawa, H., Hakata, M., 2010. Atlas of rice grain filling-related metabolism under high temperature: joint analysis of metabolome and transcriptome demonstrated inhibition of starch accumulation and induction of amino acid accumulation. PCPhy 51, 795–809.

Yamamura, C., Mizutani, E., Okada, K., Nakagawa, H., Fukushima, S., Tanaka, A., Maeda, S., Kamakura, T., Yamane, H., Takatsuji, H., 2015. Diterpenoid phytoalexin factor, a bHLH transcription factor, plays a central role in the biosynthesis of diterpenoid phytoalexins in rice. Plant J. 84, 1100–1113.

Yang, Q.-Q., Zhao, D.-S., Zhang, C.-Q., Wu, H.-Y., Li, Q.-F., Gu, M.-H., Sun, S.S.-M., Liu, Q.-Q., 2018. A connection between lysine and serotonin metabolism in rice endosperm. Plant Physiol. 176, 1965–1980.

Ye, T., Yin, X., Yu, L., Zheng, S.J., Cai, W.J., Wu, Y., Feng, Y.Q., 2019. Metabolic analysis of the melatonin biosynthesis pathway using chemical labeling coupled with liquid chromatography-mass spectrometry. J. Pineal Res. 66, e12531.

Zhang, X., Hung, T.M., Phuong, P.T., Ngoc, T.M., Min, B.-S., Song, K.-S., Seong, Y.H., Bae, K., 2006. Anti-inflammatory activity of flavonoids from Populus davidiana. Arch. Pharm. Res. 29, 1102–1108.

Zhang, L., Kong, Y., Wu, D., Zhang, H., Wu, J., Chen, J., Ding, J., Hu, L., Jiang, H., Shen, X., 2008. Three flavonoids targeting the β-hydroxyacyl-acyl carrier protein dehydratase from Helicobacter pylori: crystal structure characterization with enzymatic inhibition assay. Protein Sci. 17, 1971–1978.

Zuther, E., Koehl, K., Kopka, J., 2007. Comparative metabolome analysis of the salt response in breeding cultivars of rice. In: Advances in Molecular Breeding toward Drought and Salt Tolerant Crops. Springer, pp. 285–315.