REVIEW

Insight into melatonin-mediated response and signaling in the regulation of plant defense under biotic stress

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Abstract

Key message **Melatonin plays a crucial role in the mitigation of plant biotic stress through induced defense responses and pathogen attenuation. Utilizing the current knowledge of signaling and associated mechanism of this phytoprotectant will be invaluable in sustainable plant disease management.**

Abstract Biotic stress in plants involves complex regulatory networks of various sensory and signaling molecules. In this context, the polyfunctional, ubiquitous-signaling molecule melatonin has shown a regulatory role in biotic stress mitigation in plants. The present review conceptualized the current knowledge concerning the melatonin-mediated activation of the defense signaling network that leads to the resistant or tolerant phenotype of the infected plants. Fundamentals of signaling networks involved in melatonin-induced reactive oxygen species (ROS) or reactive nitrogen species (RNS) scavenging through enzymatic and non-enzymatic antioxidants have also been discussed. Increasing evidence has suggested that melatonin acts upstream of mitogen-activated proteinase kinases in activation of defense-related genes and heat shock proteins that provide immunity against pathogen attack. Besides, the direct application of melatonin on virulent fungi and bacteria showed disrupted spore morphology, destabilization of cell ultrastructure, reduced biofilm formation, and enhanced mortality that led to attenuate disease symptoms on melatonin-treated plants. The transcriptome analysis has revealed the down-regulation of pathogenicity genes, metabolism-related genes, and up-regulation of fungicide susceptibility genes in melatonin-treated pathogens. The activation of melatonin-mediated systemic acquired resistance (SAR) through cross-talk with salicylic acid (SA), jasmonic acid (JA) has been essential for viral disease management. The high endogenous melatonin concentration has also been correlated with the up-regulation of genes involved in pathogen-associated molecular pattern (PAMP)-triggered immunity (PTI) and effector-triggered immunity (ETI). The present review highlights the versatile functions of melatonin towards direct inhibition of pathogen propagule along with active participation in mediating oxidative burst and simulating PTI, ETI and SAR responses. The hormonal cross-talk involving melatonin mediated biotic stress tolerance through defense signaling network suggests its suitability in a sustainable plant protection system.

Keywords Melatonin · Pathogen · Redox network · Propagule · Fungi · Heat shock protein

Introduction

Melatonin (N-acetyl-5-methoxytryptamine) is regarded as a polyfunctional plant master regulator ubiquitously distributed in all living organisms (Arnao and

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Hernández-Ruiz 2019a). This low molecular weight indoleamine compound was initially identified as secretary neurohormone of the pineal gland of vertebrates (Lerner et al. 1958) and subsequently emerged as a vital animal hormone actively involved in the regulation of circadian rhythms, body temperature, appetite, sleep immunological system, seasonal reproduction and tumorigenesis (Arnao and Hernández-Ruiz 2020). The two simultaneous but independent findings of occurrence of melatonin in plants (Dubbels et al. 1995; Hattori et al. 1995) led to the accumulation of a plethora of significant researches regarding, melatonin extraction methodology, quantification and its physiological functions in plants (Liu et al. 2016; Arnao and Hernandez-Ruiz 2020; Tiwari et al. 2020c). The term 'Phytomelatonin" was first used in the year 2004 for plant-derived melatonin and subsequently, the diverse function of endogenous and exogenous phytomelatonin in regulating, plant growth, seed germination, cell respiration, photosynthesis and osmoregulation was established (Reiter et al. 2014; Sharma et al. 2020). Melatonin is reported to be actively involved in rhizogenesis, morphogenesis and caulogenesis (Sharma et al. 2020). Besides, the protective role of melatonin in mitigation of abiotic and biotic stress in plants such as drought (Sharma and Zheng 2019), heat (Ahammed et al. 2019; Buttar et al. 2020), salinity (Altaf et al. 2020b, 2021b), cold (Bajwa et al. 2014; Sharafi et al. 2019), and heavy metal toxicity (Altaf et al. 2020a, 2021a) has established its role as a crucial phytoprotectant. The most striking function of melatonin is scavenging of reactive species viz., reactive oxygen species (ROS) and reactive nitrogen species (RNS) under stress conditions. The hyperaccumulation of these reactive species (ROS and RNS) during stress is reported to have adverse effects such as cell membrane damage, protein and DNA denaturation, lipid peroxidation, carbohydrate oxidation, pigment breakdown and aberrant enzyme activity (Manchester et al. 2015; Moustafa-Farag et al. 2020; Tiwari et al. 2021). Melatonin being a powerful antioxidant scavenges these free radicals and maintain the ionic homeostasis during stress conditions. In addition to ROS scavenging, melatonin activates the inherent antioxidative defense system in plants (Arnao and Hernández-Ruiz 2015). There are several reports of melatonin-mediated up-regulation of genes involved in the biosynthesis of superoxide dismutase (SOD), ascorbate peroxidase (APX), catalase (CAT), glutathione peroxidase (GPX), ascorbic acid (ASA) and glutathione (GSH) during stress conditions (Sun et al. 2019). The up-regulation of genes involved in ASA-GSH cycle which protects the plant under stress is also well established (Tiwari et al. 2020b). The protective nature of phytomelatonin against various abiotic stresses is well recognized and documented however, its effects on biotic tolerance have been less comprehensive and elusive.

Earlier reports suggested that melatonin inhibits viral and fungal infections in animals both directly and indirectly (Vielma et al. 2014; Elmahallawy et al. 2014). During the last decade, some significant findings have reported the role of melatonin indirect inhibition of plant pathogens and induction of systemic acquired resistance in crop plants (Zhang et al. 2017; Zhao et al. 2019b; Chen et al. 2019; Moustafa-Farag et al. 2020). Melatonin has shown high efficacy in protecting plants against viral, fungal and bacterial pathogens along with insects and plant-parasitic nematodes (Moustafa-farag et al. 2020; Vielma et al. 2014). The regulation of plant defense under biotic stress involved defense gene activation, ROS scavenging, cell wall thickening, RNS scavenging and hormonal cross-talk (Shi et al. 2015; Liang et al. 2018; Sharifi and Ryu 2018; Prakash et al. 2019). The higher callose deposition, accumulation of cellulose, galactose, and xylose in melatonin sprayed plants has triggered a series of biochemical defense responses against fungal pathogens (Zhao et al. 2015; Qian et al. 2015). The activation of melatonin-mediated SAR through cross-talk with salicylic acid (SA) and jasmonic acid (JA) has been reported crucial for viral disease management (Zhao et al. 2019b; Chen et al. 2019). The synergistic role of melatonin with serotonin was reported to have induced a defense response in plants (Saremba et al. 2017). However, the molecular mechanism of synergistic interaction has not been explored which needs further investigation.

The high endogenous melatonin concentration (1 mM-10 mM) has shown correlation with up-regulation of genes involved in (PAMP)-triggered immunity (PTI) and effector-triggered immunity (ETI) mediated defense in the host against fungal pathogen infection (Mandal et al. 2018). The melatonin-induced activation of transcription factors (*CBF/DREB1s*), defense-gene (pathogenesis-related 1; *PR1*), antimicrobial peptide (plant defensin 1.2; *PDF1*.2) and mitogen-activated protein kinase (*MAPKs*) have been elucidated a regulatory role during a bacterial and fungal infection in *Arabidopsis thaliana* (Shi et al. 2015; Lee and Back 2016). Interestingly, the synergistic effect of melatonin with fungicide was reported in managing the devastating late blight pathogen *Phytophthora infestans* infection in potatoes (Zhang et al. 2017). The combination of melatonin with chemical pesticides might reduce the pesticide load that highlights the significance of this chemical from the perspective of a safe environment (Moustafa-Farag et al. 2020). There are limited reports available on the molecular mechanism of melatonin-mediated biotic stress alleviation and signal transduction mechanism. Previously, it has been reviewed that melatonin mitigates the pathogen infection through an integrative ROS-RNS forward loop (Zhao et al. 2021; Moustafa-Farag et al. 2020) have summarized the antifungal, antiviral and antibacterial potential of melatonin in crop plants. The aim of present review is to highlight the role

of melatonin in mitigation of pathogen infection and mechanistic insights of defense response through regulation of oxidative and antioxidative defense system. The melatonin mediated hormonal cross-talk that leads to the induction of PTI and ETI responses have also been discussed. The recent studies of synergistic interaction of melatonin with chemical pesticides have been discussed which highlight the suitability of this multifunctional phytoprotectant in sustainable plant protection system.

Melatonin biosynthesis in chloroplast and mitochondria and associated signaling

The melatonin is reported to be first synthesized in α-proteobacteria and photosynthetic cyanobacteria (Vivien-Roels and Pévet 1993). As per the endosymbiotic theory, the phagocytosis of these bacteria by primitive eukaryotes resulted in a symbiotic association between the host eukaryotes and ingested bacteria (Zhao et al. 2019a). During the evolutionary process, this ingested α-proteobacteria and cyanobacteria were evolved into mitochondria and chloroplast, respectively. Consequently, these two organelles retained the melatonin biosynthesis ability from their respective progenitors (Zhao et al. 2021). This suggests that all the currently existing living forms which possess mitochondria and chloroplast have retained the ability to synthesize melatonin. There are many reports of melatonin synthesis in mitochondria and chloroplast of several plant species (Zhao et al. 2019a; Hardeland 2019). The melatonin biosynthetic pathways differ considerably in terms of enzymes and stages in animals and plants (Back et al. 2016). However, the amino acid tryptophan is the sole precursor for melatonin biosynthesis in all living forms. The tryptophan is a routine diet supplement for animals but it is continuously synthesized in bacteria, fungi and plants through the shikimic acid pathway by using D-erythrose-4-phosphate, phosphoenolpyruvate, or carbon dioxide as the initial source. The reduction of tryptophan content leads to a significant reduction in melatonin content in animals as compared to plants (Back et al. 2016). The biosynthesis of tryptophan in plants ensures the optimum melatonin level for proving better protection against oxidative stress.

The classical pathways of melatonin biosynthesis consisted of a four-step reaction with six enzymes namely, tryptophan decarboxylase (TDC), tryptophan hydroxylase (TPH), tryptamine 5-hydroxylase (T5H), serotonin N-acetyltransferase (SNAT), N-acetylserotonin methyltransferase (ASMT), and caffeic acid O-methyltransferase (COMT) (Manchester et al. 2015). The first step of melatonin biosynthesis involves decarboxylation and hydroxylation that converts tryptophan into serotonin (Kaur et al. 2015; Back et al. 2016). This step differs across the different taxa as in

plants the decarboxylation reaction leads to the conversion of tryptophan to tryptamine through enzyme TDC followed by serotonin biosynthesis through tryptamine 5-hydroxylase (T5H). In contrast, the hydroxylation of tryptophan occurs first in animals that lead to the formation of 5-hydroxy-tryptophan which is further decarboxylated by aromatic amino acid decarboxylase (AADC) to synthesize serotonin (Back et al. 2016). It implies that serotonin is the key intermediate in melatonin biosynthesis in plants and animals after which two separate biosynthetic pathways have been reported (Tan et al. 2016). N-acetyltransferase (SNAT) and N-acetylserotonin O-methyltransferase (ASMT) catalyze the conversion of serotonin into the final product as melatonin (Lee et al. 2015). The sequential steps of melatonin biosynthesis in plant and animal cells depicting alternative pathways have been illustrated in Fig. 1. It was interesting to examine that SNAT protein which is considered as a rate-limiting enzyme for melatonin biosynthesis, is abundant in mitochondria of animals and chloroplast of the plant (Back et al. 2016). This emphasizes the diverse evolution of biosynthetic enzymes during the process of endosymbiosis. The perspective of the functional evolution of melatonin also corroborates with stress conditions that induced excessive production of reactive species (ROS and RNS) in chloroplast and mitochondria (Zhao et al. 2021). Thereby, the synthesized melatonin in these organelles provides maximum onsite protection through its high scavenging activity (Zhao et al. 2019a, 2021). The evolutionary process also led to the transfer of some genes from chloroplast and mitochondria to the nuclear genome of the host. Recent reports have highlighted that mitochondria and chloroplast are the primary sites of melatonin production and signaling (Manchester et al. 2015; Wang et al. 2017). However, the possibility of its synthesis in the cytosol cannot be ruled out and further studies are required in this aspect. Under normal conditions, the melatonin is maintained at a constant level; however, it is rapidly upregulated during pathogen infection and other unfavourable conditions (Sharma and Zheng 2019; Moustafa-Farag et al. 2020). There are a plethora of available reports which suggest that stress-mediated generation of ROS and RNS can elevate the endogenous melatonin in plant tissue (Arnao and Hernández-Ruiz 2015, 2019b; Shi et al. 2015). An increase in ROS and RNS leads to the up-regulation of melatonin biosynthetic genes in stressed plants that results in higher endogenous melatonin levels (Arnao and Hernández-Ruiz 2015; Reiter et al. 2014; Wei et al. 2018). Apart from the abiotic and biotic stressors, bacterial endophytes have also been reported in elevating the endogenous melatonin levels in plants (Jiao et al. 2016; Ma et al. 2017). The level of endogenous melatonin was enhanced in grape roots by the colonization of *B. amyloliquefaciens* SB-9 which was correlated with the up-regulation of melatonin biosynthetic genes (Jiao et al. 2016). Similarly, another
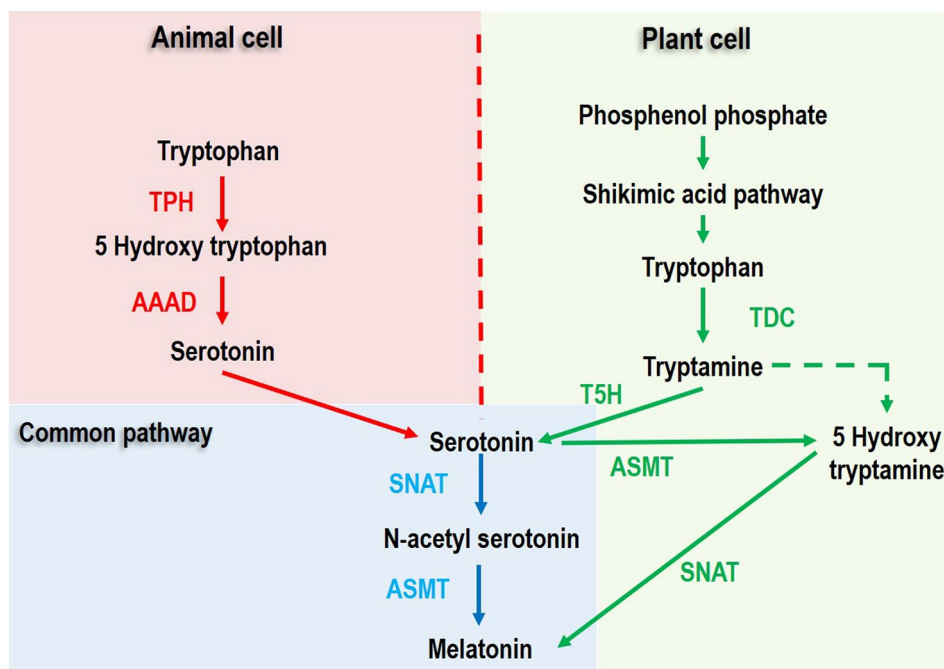
Fig. 1 The conceptual illustration of melatonin biosynthetic pathways in plants and animals. The sole precursor 'tryptophan' is common in plants and animals. In animals, tryptophan is initially hydroxylated to 5-hydroxytryptophan which is then decarboxylated to form serotonin. However, in plants, tryptophan is initially decarboxylated to form tryptamine which is then hydroxylated to form serotonin. Through a common pathway, the 'serotonin' is either acetylated to N-acetylser- otonin followed by melatonin formation. Alternatively, 'serotonin' is methylated to form 5-methoxytryptamine in plants and forms mela- tonin through acetylation. Abbreviation: TDC, tryptophan decarboxy- lase; TPH, tryptophan hydroxylase; T5H, tryptamine 5-hydroxylase; SNAT, serotonin N-acetyltransferase; ASMT, N-acetylserotonin methyltransferase; AAAD, aromatic amino acid decarboxylase

endophyte *Pseudomonas fluorescens* RG11 enhanced the melatonin content in different grape cultivars. It is necessary to explore the possible underlying mechanism at the level of transcriptional and post-transcriptional modification of melatonin biosynthetic genes during endophyte colonization and pathogen infection. It is also equally important to under- stand the mechanism of action of this signaling molecule on pathogen propagule as well as on host defense network. The further sections elaborate on the aforementioned findings during host plant and pathogen interactions.

Melatonin affecting plant-pathogen interaction

In animal science, melatonin is well accepted as the therapeutic endogenous regulator of diseases through its immunomodulatory, antioxidant, neuroprotective and autophagy-mediated functions during viral and bacterial infections (Vielma et al. 2014; Elmahallawy et al. 2014). There are significant reports of direct inhibition of fungal pathogen through melatonin treatment in a concentration- dependent manner. A recent study by Zhang et al. (2017) demonstrated that exogenous treatment of melatonin (0,

1, 3, 6, 8, 10 mM) attenuated late blight disease in potato through reduced mycelial growth and deformation of cell ultrastructure of pathogen *Phytophthora infestans*. The transcriptome analysis revealed that the genes governing pathogen virulence, fungicide resistance and stress tol- erance were downregulated with melatonin application which resulted in a reduced infection on potato plants (Zhang et al. 2017). Likewise, a 100 μM concentration of phytomelatonin significantly reduced 76 and 71% of myce- lial growth in phytopathogenic fungi (*Colletotrichum gloe- osporioides* and *Colletotrichum acutatum*) which cause severe anthracnose in pepper; *Capsicum annum* (Ali et al. 2021). Melatonin has shown its efficacy against several other devastating fungal pathogens viz., *Diplocarpon mali* in apple (Yin et al. 2013), *Fusarium oxyspoum* in banana (Wei et al. 2017), *Botrytis cineraria* in tomato (Liu et al. 2019) and *Podosphaera xanthii* in cucurbits (Mandal et al. 2018).

Plant viruses are a constant threat in the crop produc- tion system as there is no direct cure available to curb these pathogens (Kumar et al. 2021; Lal et al. 2021). The alter- native way of virus management is through host-mediated defense and vector control. In this context, melatonin has recently merged as a vital phytoprotectant against plant viral

diseases. Treatment of melatonin (100 µM) through root irrigation has resulted in reduced titer of *Tobacco mosaic virus* in *Nicotiana glutinosa* and *Solanum lycopersicum* (Zhao et al. 2019b). The reduced viral load in melatonin-treated plants was positively correlated with higher expression of *PR1* and *PR5* genes that lead to SAR. A similar report on the *Apple stem grooving virus* revealed that the addition of melatonin to the prolifereding media completely eradicated the virus from previously infected explants of apples (Chen et al. 2019). This emphasizes the utilization of melatonin as a supplement to the tissue culture media during the process of generating virus-free plants. Several other reports of melatonin-mediated plant virus mitigation and associated molecular or biochemical mechanism of resistance were summarized in Table 1. The bactericidal ability of melatonin is also well documented against gram-negative and gram-positive multidrug-resistant bacteria *Pseudomonas aeruginosa, Staphylococcus aureus*, and *Acinetobacter baumannii* (Wei et al. 2018; Chen et al. 2018). The mechanism of antibacterial activity was mainly reported as cAMP and Ca^{2+} regulation, destabilization of the bacterial cell wall and intracellular substrates reduction. The direct inhibitory action of melatonin (200 µg mL^{-1}) has been reported on rice phytopathogenic bacteria *X. oryzae* pv. *oryzae* and *X. oryzae* pv. *oryzicola* which causes bacterial leaf streak and bacterial leaf blight (Chen et al. 2018). Likewise, the bacterial blight disease resistance in Cassava has been correlated with higher expression of transcriptional activators of melatonin (*MeRAV2* and *MeRAV1*) genes (Wei et al. 2018) (Table 2). The devastating citrus greening disease has also been attenuated by the application of melatonin in the affected plants (Ghosh et al. 2018). In model plant *A. thaliana*, the disease resistance against *Pseudomonas syringe tabaci* (DC3000) was correlated with melatonin-mediated cell wall strengthening and callose depositing factors (Shi et al. 2015).

Insect pests are the most notorious biotic stressors in the global crop production system. They cause both direct and indirect loss to the plant through feeding as well as transmission of viral and bacterial pathogens (Dhaliwal et al. 2015). There are a significant number of reports of melatonin biosynthesis and regulation in insect pests affecting their circadian oscillations, feeding behavior, fecundity, photoperiodism, moulting, and reproduction. A study by Saremba et al. (2017) demonstrated the role of melatonin as a plant signal chemical in resistant American elm (*Ulmus americana* Planch) infested with bark beetle (*Scolytus multistriatus*). However, the molecular and regulator mechanism was unexplored in this aspect and needs further exploration. The psyllid vector (*Daphrina citri*) responsible for the spread of devastating citrus greening disease (Huanglongbing) has been shown to bear low bacterial titer after melatonin supplementation (Nehela and Killiny 2018). This highlights the positive role of melatonin in minimizing the vector-driven spread of citrus greening in sweet oranges. There is no direct report on the effect of melatonin on insect pest management in plants. However, it can be speculated that like any other stress the antioxidative defense may also be observed against the insect pest and virus vectors. There is a plethora of unanswered questions and unexplored mechanisms underlying in melatonin-mediated alleviation of viral, fungal and bacterial plant pathogens. The study involving the control of virus vectors through melatonin is completely lacking. In succeeding sections, we have attempted to summarize and illustrate the defense mechanism associated with this single regulatory chemical and how these mechanisms are interlinked.

Melatonin-mediated antioxidative plant defense under biotic stress

Like any other stressful condition, the pathogen infection leads to altered redox homeostasis through a series of plant cellular responses (Zhao et al. 2021). The altered redox homeostasis results in excessive production of ROS (singlet oxygen;^{1} O_2, superoxide anion; O_2^- and hydrogen peroxide; H_2O_2) and RNS (nitric oxide; NO, and alkoxyl radical; RO) which are mainly responsible for 'oxidative burst' that is a ubiquitous plant defense and signaling response under stress. There is a considerable difference in how reactive species mediate the activation of defense response under abiotic and biotic stress conditions. Under abiotic stress, the excessive ROS/RNS generation may lead to irreversible damage to the lipid, proteins and nucleic acids of cells. To mitigate this adversity the inherent enzymatic and non-enzymatic antioxidant system of plants come into play (Tiwari et al. 2020c). However, during biotic stress conditions, the defense regulation is completely different. The early recognition response against pathogen attack aims to restrict the pathogen propagule at the site of its entry through onsite programmed cell death (PCD) that leads to a phenomenon called 'hypersensitive response' (Zhao et al. 2021). An oxidative burst is necessary for the activation of local and systemic defense response during the initial phase of pathogen infection. It implies that the ROS scavenging is delayed in the initial phase of pathogen infection and the associated scavenging enzymes are down-regulated to accumulate more ROS for PCD which restricts the pathogen at the point of infection (Zhao et al. 2021). However, during the later stage of infection when the hypersensitive response curbs the pathogen infection the excessive ROS and RNS needs to be neutralized through the onset of an antioxidative defense mechanism. Melatonin being a strong antioxidant scavenges the excess ROS and RNS and indirectly activates the non-enzymatic [ascorbic acid (AsA), α-tocopherols, glutathione (GSH), carotenoids, and phenolic compounds] and enzymatic[superoxide dismutase (SOD), guaiacol

Table 1 Melatonin-mediated mitigation of fungal, viral and bacterial diseases

Pathogen	Host	Melatonin application (Concentration)	Mechanism	References
Fungal pathogens				
Phytophthora infestans	Potato (*Solanum tuberosum*)	Spray on leaves and tuber slices (10 mM)	Disruption of mycelia and spores, increase fungicide susceptibility	Zhang et al. (2017)
Podosphaera xanthii and *Phytophthora capsici*	Cucurbit (*Citrullus lanatus*)	Leaf treatment (100 μm)	Regulation of PTI and ETI	Mandal et al. (2018)
Pseudoperonospora cubensis	Cucumber (*Cucumis sativus*)	Leaf treatment (100 μm)	Activation in antioxidant genes	Sun et al. (2019)
Fusarium oxysporum	Banana (*Musa acuminate*)	Root and leaf spray (100 μm)	Regulating the expression of heat shock proteins	Wei et al. (2017)
Diplocarpon mali	Apple (*Malus prunifolia*)	Root spray (50–500 μm)	ROS scavenging and activation of defence genes	Yin et al. (2013)
Botrytis cinerea *Rhizopus stolonifer*	Strawberry (*Fragaria ananassa*)	Leaf treatment (100 μm)	Maintain intracellular H_2O_2	Aghdam and Fard (2017) Liu et al. (2019)
Verticillium dahliae	Cotton (*Gossypium spp.*)	Foliar treatments (10 μM)	Enhanced resistance and promoted lignin and gossypol accumulation	Li et al. (2019)
Bacterial pathogens				
Pseudomonas syringae	*Arabidopsis thaliana* *Nicotiana benthamiana*	Foliar spray (10 μM)	Up-regulation of defense gene *PR1*, *PR5* and plant defensin	Lee et al. (2014)
Pseudomonas syringae	*Arabidopsis thaliana*	Foliar spray (10 μM)	Activation of defence through SA and ET signalling	Qian et al. (2015)
Pseudomonas syringae	*Arabidopsis thaliana*	Added to the culture media (20 μM)	NO-mediated defense signalling	Shi et al. (2015)
Pseudomonas syringae	*Arabidopsis thaliana*	Added to the culture media (50 μM)	Cell wall strengthening and callose deposition	Zhao et al. (2015)
Pseudomonas syringae	*Arabidopsis thaliana*	Foliar spray (1 μM)	Activation of *MAPK* cascade	Lee and Back (2017)
Xanthomonas oryzae pv. *oryzae*	Rice (*Arabidopsis thaliana*)	Foliar spray (100 μM)	Down-regulation of bacterial virulence genes and metabolic genes	Chen et al. (2018)
Xanthomonas axonopodis pv *manihotis*	Cassava (*Manihot esculenta*)	Melatonin deficient mutants	Activation of transcription factors for disease resistance	Wei et al. (2018)
Viral pathogens				
Alfalfa mosaic virus (AMV)	Eggplant (*Solanum melongena*)	Foliar spray (100 μM)	Reduction of hydrogen peroxide, superoxide anions, hydroxyl radicals, and malondialdehyde	El-Abhar et al. (2021)
Tobacco mosaic virus (TMV)	Tomato (*Solanum lycopersicum*)	Applied to Roots (100 μM)	Elevated *PR1* and *PR5* expressions	Zhao et al. (2019b)
Rice stripe virus	Rice (*Oryza sativa*)	Foliar spray (10 μM)	Up-regulation of resistance related transcription factors *OsPR1b* and *OsWRKY45*	
Apple stem grooving virus (ASGV)	Apple (*Malus domestica*)	Addition to nutrient media (15 μM)	Virus eradication from infected shoots (mechanism unidentified)	Moustafa-Farag et al. (2019)

SA salicylic acid, *PR1* and *PR5* plant resistance genes 1 and 5, *ET* ethylene, *MAPK* mitogen-activated protein kinase, *NO* nitric oxide

Table 2 Hormonal cross-talk in melatonin-mediated biotic stress regulation

Hormone	Plant Name	Pathogen	Molecular mechanism	Reference
Salicylic acid (SA)	*Arabidopsis thaliana*	*Pseudomonas syringae* Tomato (DC3000)	Activation of defense related genes	Shi et al. (2015), Zhao et al. (2015)
	Tobacco (*Nicotiana tabaccum*)	*Tobacco mosaic virus*	Up-regulation of *PR1* and *PR 5* defense genes	Zhao et al. (2019b)
Jasmonic acid	Tomato (*Solanum lycopersicum*)	*Botrytis cineraria*	Up-regulation *AOC*, *LoxD* and *PI II* Down regulation *SlMYC2* and *JZD 1*	Sharma et al. (2020)
Indole acetic acid (IAA)	Banana (*Musa paradisica*)	*Fusarium oxysporum cubense*	Heat shock protein (*HSP90*) mediated induced defense	Wei et al. (2017)
	Apple (*Malus prunifolia*)	*Apple stem grooving virus* (ASGV)	Not investigated	Chen et al. (2019)
Ethylene	Cassava (*Manihot esculenta*)	*Xanthomonas axonopodis pv. manihotis*	Regulation of *RAV* transcription factors	Ding et al. (2019)
	Cucumber (*Cucumis sativus*)	*Podosphaera xanthii*	Up-regulation of ethylene biosynthetic genes	Weeda et al. (2014)

SA, salicylic acid; JA, jasmonic acid; ET, ethylene; TF, transcription factor; *HSP*, heat shock proteins; *AOC*, allene oxide cyclase; *LOD*, lipoxygenase; *JZD*, *JASMONATE ZIM DOMAIN 1*; *PR1* and *PR5*, pathogenesis related protein 1,5

peroxidase (POD), catalase (CAT), glutathione peroxidases (GPX), glutathione S-transferase (GST), dehydroascorbate reductase (DHAR), glutathione reductase (GR), and ascorbate peroxidase (APX)] antioxidant system under biotic stress (Moustafa-Farag et al. 2020). ROS and RNS signaling act in harmony during pathogen intrusion that leads to activation of genes associated with stress response and hormonal signaling. Interestingly, there are reports of a simultaneous increase in melatonin, ROS and RNS during pathogen infection (Arnao and Hernández-Ruiz 2019a; Zhao et al. 2021). Moreover, melatonin enhances the H_2O_2 and RNS levels which in turn enhance melatonin content and this crosstalk regulates the defense response during biotic stress (Arnao and Hernández-Ruiz 2019a; Zhao et al. 2021).

A series of studies performed on *A. thaliana* revealed that melatonin application elevated the ROS and RNS levels during *Pseudomonas syringae* tomato (DC3000) infection (Lee et al. 2014, 2015; Shi et al. 2015). Melatonin-mediated ROS generation acts as a signal molecule for elevated defense response against bacterial infection. Likewise, elevated ROS generation was observed through exogenous melatonin treatment during the infection of fungus *Botrytis cineraria* in strawberry and *Diplocarpon mali* in apple. Pretreatment of 100 μM melatonin triggered H_2O_2 accumulation strawberry fruits that were associated with higher SOD activity and lower CATand APX activities during fungus attack (Aghdam and Fard 2017). Subsequently, enhanced H_2O_2 accumulation resulted in higher activity of phenylalanine ammonia-lyase (PAL) enzyme, higher total phenol content and 2,2-diphenyl-1-picrylhydrazyl (DPPH) scavenging. During fungal infection, melatonin acts as a secondary messenger of defense signaling (Shi et al. 2015). Additionally, melatonin played a

significant role in preventing the decay of tomato fruits due to the fungus *Botrytis cinerea*, by regulating cellular H_2O_2 levels and enhanced antioxidant enzyme activities (Liu et al. 2019). The melatonin pretreatment (100 μM) shown a substantial increase in antioxidant enzymes such as POD, SOD, and APX in the infected tomatoes as compared to healthy ones. Likewise, the downy mildew disease in cucumber was successfully managed using melatonin treatment (Sun et al. 2019). The foliar spray of 100 μM melatonin reduced the disease index and severity which was correlated with higher activity of antioxidant enzymes SOD, CAT, APX, and POD. This was further confirmed with enhanced expression of associated genes. Further, it was observed that melatonin pretreatment lowered the malondialdehyde (MDA) content in downy mildew affected plants that ultimately leads to membrane integrity, reduced electrolyte leakage and disease-resistant phenotype (Sun et al. 2019). The antioxidant activity has also been observed in virus-infected plants. The exogenous melatonin sprayed on *Alfalfa mosaic virus* (AMV) infected eggplants ameliorated the viral infection, which was possible through reduced oxidative damage, and H_2O_2, superoxide anions, hydroxyl radicals, and MDA.

The other significant key regulators of osmotic balance in plants are soluble protein and proline which play a significant role in their resistance to stress conditions (Abdel et al. 2011; Meng et al. 2014). The stress induced soluble proteins can defend the cell membrane disruption and maintain the osmotic pressure both inside and outside of the cell, thereby relieving the damage associated with adverse conditions and pathogen infection (Vielma et al. 2014). In downy mildew affected cucumber plants, the melatonin treatment enhanced the soluble protein content significantly which

provided stability to the plant cells (Sun et al. 2019). The proline content was also reported to be higher in melatonin sprayed plants which provided a valuable role in maintaining the stability of protein structures and scavenging free radicals during pathogen attack (Sun et al. 2019). There are several other reports on a similar aspect of melatonin-mediated regulation of antioxidative systems in the plants during pathogen infection (Arnao and Hernández-Ruiz 2015; Dhole and Shelat 2018). But there are still some unanswered questions regarding the ROS and RNS regulation during the initial and later phases of infection. The role of melatonin in regulating the oxidative burst against biotrophic and necrotrophic pathogens is still not clear.

Melatonin activates the defense-related genes

To further investigate the mechanism of melatonin-mediated biotic stress tolerance, the involvement of melatonin biosynthesis and metabolism related genes, plant defense related genes, pathogenesis associated genes and transcription factors are summarized in this section. There are several reports of overexpression or down-regulation of melatonin biosynthetic genes that were correlated with mitigating abiotic and biotic stress in plants (Sharma and Zheng 2019; Zhan et al. 2019; Moustafa-Farag et al. 2020; Mandal et al. 2018) reported that watermelon plantlets transformed with melatonin biosynthetic gene *SNAT* showed resistance against powdery mildew and *Phytopathora capsici* infection as compared to non-transgenic plants. The relative expression of *SlSNAT1* and melatonin content was remarkably induced in tomato during fungal infection which indicated the role of melatonin in defense response. Subsequently, the expression of defense-related genes such as chitinase (*CHI*), glucanase (*GLU*), polyphenol oxidase (*PPO*), and phenyl ammonia lyase (*PAL*) was also noted high in melatonin treated plants during fungal infection (Ali et al. 2021). The primary defense enzyme CHI and GLU respectively belong to the *PR3* and *PR2* families and play vital roles in the disruption of fungal cell walls. Ubiquitously occurring PPO catalyzes the oxidation of phenolic compounds to form quinines that possess antibiotic and cytotoxic activities against pathogens (Tiwari et al. 2020a). PAL is a crucial enzyme in the phenylpropanoid pathway and indirectly plays a crucial role in plant disease resistance. Previous studies have highlighted the positive role of these enzymes in plant defense responses against pathogen infection which can be used as markers for plant innate immunity (Aghdam and Fard 2017). Sun et al. (2018) found that the expression of genes for *PAL* and *PPO* were higher after fungus inoculation, and pretreatment of melatonin further increased the associated enzyme activities. Moreover, melatonin up-regulated the expression of *PR1*

in treated plants that resulted in induced defense response (Fig. 2).

The melatonin-induced antibacterial mechanism against phytopathogenic bacteria was characterized by higher expression of defense genes such as plant defensin 1.2 (*PDF1.2*), *PR1* and *PR5* in plants. Similar findings of higher expression of *PDF 1.2* in melatonin treated tobacco and Arabidopsis plants have also been reported during bacterial infection. Similarly, the local lesion assay of the *Tobacco mosaic virus* (TMV) in *Nicotiana glutinosa* and systemic infection in *Solanum lycopersicum* was ameliorated with exogenous melatonin application (Zhao et al. 2019b). The major mechanism of viral resistance was evaluated as up-regulation of defense-related genes such as *PR1* and *PR5* in the treated plants. There are several other similar reports of induction of defense genes after melatonin treatment in virus and bacterial infected plants (Zhao et al. 2019b; Chen et al. 2019).

Recently, Ali et al. (2020) observed that the chitinase gene (*CaChiIII2*) improved resistance against anthracnose disease in pepper and *Arabidopsis*. Additionally, the transcript level of *CaChiIII2* was considerably enhanced after treatment with 100 μM melatonin on plants infected with anthracnose causing fungus. The study highlighted the positive role of melatonin in the regulation of chitinase gene-mediated defense response in fungus-infected pepper plants. Besides, the transcript level of other defense-related genes, such as *PR1* and *PO1* was reported to be higher in melatonin pretreated pepper plants.

The transcriptomic analysis targeting the direct effect of melatonin on pathogen gene expression revealed that the virulence genes were down-regulated after melatonin treatment in *Phytophthora infestans* (Zhang et al. 2017). Differentially expressed genes (DEGs) related to amino acid metabolism of late blight causing fungus *P. infestans* were adversely affected by melatonin application. The disconcertion of amino acid metabolism leads to spore mortality and cell death. Subsequently, the fungicide susceptibility genes were upregulated that lead to attenuated disease phenotype in melatonin treated potato plants. The melatonin showed synergistic interaction with other fungicides in managing late blight disease in potato. Similarly, the black shank disease of potato caused by oomycete pathogen was managed with synergistic interaction of melatonin and ethylicin (Zhang et al. 2018a). The treatment combination of melatonin and ethylicin induced the expression of genes associated with the apoptosis-inducing factor and caused dysfunction of virulence-related genes on the pathogen. Chen et al. (2018) performed a global gene expression analysis in melatonin treated bacterial strain (*Xanthomonas oryzae oryzae* PXO99) in rice and reported the downregulation of genes associated with cell division, catalytic activity, metal-binding activity, carbohydrate and amino acid metabolism.
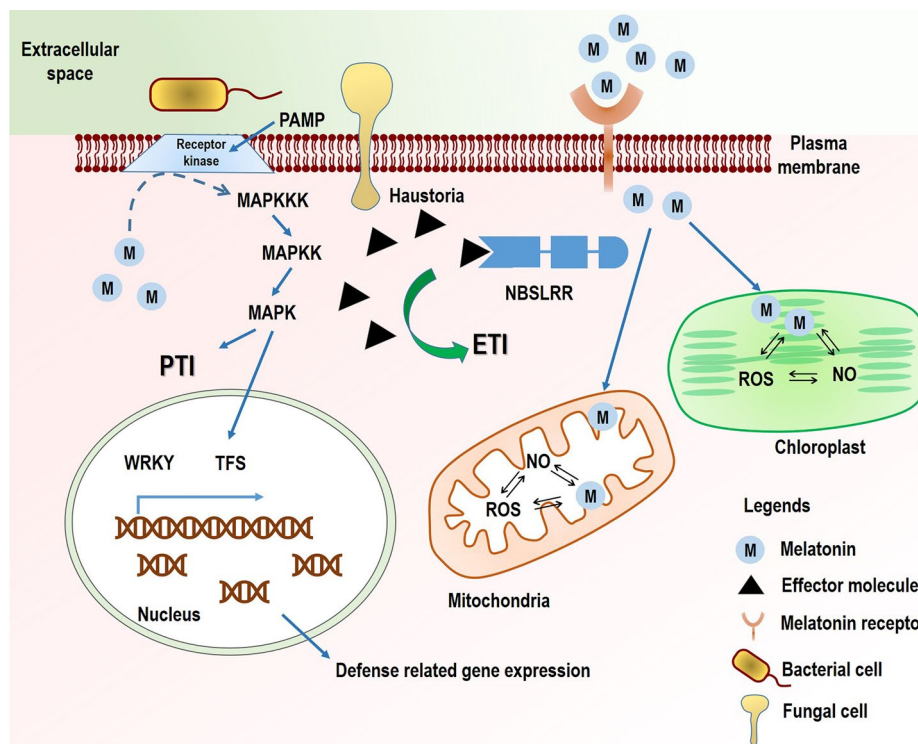
Fig. 2 Model illustrating the melatonin induced defense signaling in plants under biotic stress. The initial infection of pathogen or exogenous melatonin application leads to the synthesis and accumulation of high endogenous melatonin in chloroplast and mitochondria. The melatonin induced activation of MAPK cascades leads to the initial PTI response and activation of defense related genes in the nucleus. Alternatively, endogenous melatonin modulates the R genes mediated immunity in plants against pathogen infection. Abbreviation: ROS, reactive oxygen species; PAMPs, pathogen-associated molecular patterns; MAPK, Mitogen-activated protein kinase; PTI, PAMP-triggered immunity; ETI, effector triggered immunity; NBSLRR, Nucleotide binding site leucine rich repeats; NO, nitric oxide Dotted arrows represent the hypothetical pathway

The role of transcription factors is critical in regulating plant developmental processes as well as abiotic and biotic stress-related defense responses (Weeda et al. 2014). Melatonin may regulate the expression of transcription factors for resistance response in plants. A virus-induced gene silencing (VIGS) mediated knockout of transcription factor *MeRAV1* and *MeRAV2 of* apetala2/ethylene response factor (AP2/*ERF*) gene family in cassava, demonstrated its positive role in mitigating bacterial blight disease through modulation of melatonin biosynthetic genes. Similarly, exogenous melatonin enhanced the transcription of C-repeat binding factors (*CBFs*)/drought response element-binding 1 factors (*DREB1s*) that improves the disease resistance of *Arabidopsis* against bacterial infection (Shi et al. 2015). In another experiment, the role of heat shock proteins (*HSP90s*) was established in melatonin-induced resistance in *Fusarium oxysporum cubence* infected banana plants. The resistance response in melatonin treated banana plants against *Fusarium* wilt was lost after co-treatment with HSP inhibitor geldanamycin (Wei et al. 2017). The role of heat-shock proteins (*HSP70s*) of fungus *P. infestans* conferred opposite results. Zhao et al. (2017) reported the down regulation of *HSP70s* of fungus *P. infestans* after melatonin treatment under *in vitro* conditions resulted in reduced virulence of the fungus in potato.

A recent study by Li et al. (2019) showed the role of melatonin in delivering better tolerance to the cotton plants against *Verticillium dahlia*. The transcriptomics analysis showed the increased expression of genes of gossypol biosynthesis, phenylpropanoid and mevalonate (MVA) pathways after exogenous melatonin spray on fungus-infected plants. Silencing the melatonin biosynthesis genes *GhSNAT1* and *GhCOMT* conceded cotton resistance, with minimized lignin and gossypol levels after *V. dahliae* inoculation. The level of melatonin content also varied in resistant and susceptible cotton cultivars (Li et al. 2019). The melatonin-induced regulation of lignin and gossypol biosynthesis in deploying broad-spectrum resistance in cotton paved a path for exploring similar possibilities in other crops too. A unified model of melatonin-mediated induced defense response has been illustrated in Fig. 3.
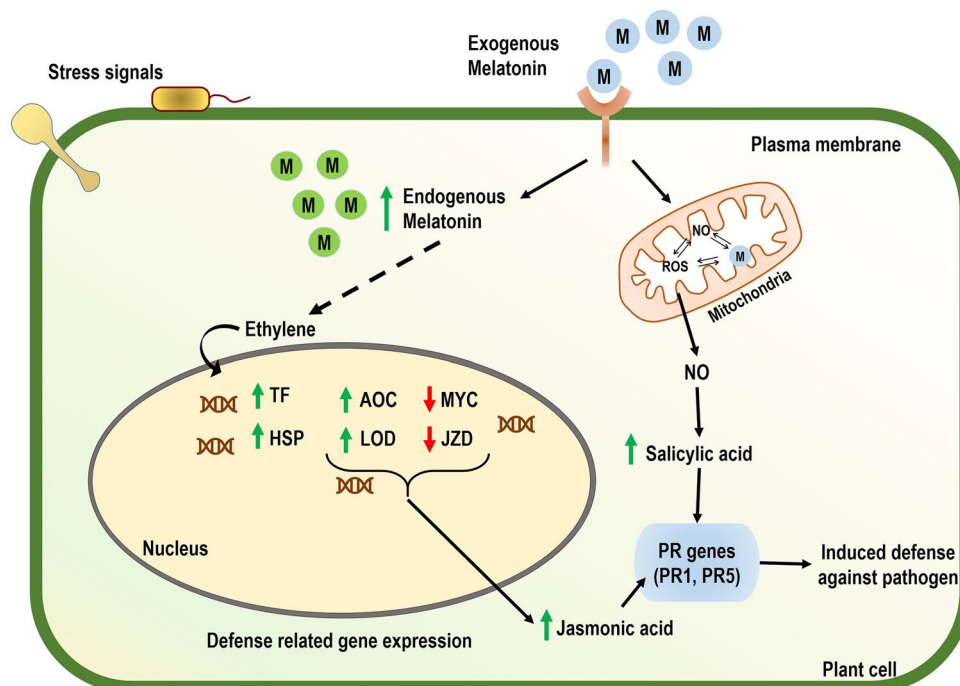
Fig. 3 A conceptual model depicting melatonin cross-talk with phytohormones (JA, SA, ethylene) to regulate the plant defense. Melatonin treatment enhances the methyl jasmonate (MeJA) content and the expression of JA biosynthesis-related gene AOC and LoxD. Moreover, the expression of SlMYC2 and JASMONATE ZIM DOMAIN 1 (negative regulator in JA signaling pathway) is down-regulated. Melatonin induced NO accumulation in mitochondria enhances the SA concentration during infection. The JA and SA independently induce the expression of PR genes that activates the plant defense. The melatonin mediated activation of ethylene is unknown but melatonin treatment enhances the ethylene concentration in infected plants and which in turn activates the defense related gene expression. Abbreviation: NO, nitric oxide; SA, salicylic acid; JA, jasmonic acid; ET, ethylene; TF, transcription factor; HSP, heat shock proteins; AOC, allene oxide cyclase; LOxD, lipoxygenase; JZD, JAS-MONATE ZIM DOMAIN 1; PR1 and PR5, pathogenesis-related protein 1,5. Dotted arrows represent the hypothetical pathway. The green upside arrow represents up-regulation whereas the red downside arrow represents down-regulation

Melatonin-mediated MAPKs cascade activation in defense

Among the most well-studied signaling networks the *MAPK* cascades are critical signal transduction modules that actively participate in drought, cold, salinity, heat stress and pathogen infection (Lee and Back 2016). These *MAPK* cascades are ubiquitous in plants, animals and other eukaryotes. The cascade comprises three sequential protein kinases, beginning from *MAPKKK* at the upstream followed by *MAPKK*, and then *MAPK* at the extremity. Any external signal which is perceived by receptors on the plasma membrane further leads to a phosphorylated *MAPKKK* which further phosphorylates *MAPKK* and in the end, the *MAPK* is phosphorylated via *MAPKK* (Lee and Back 2017). This series of phosphorylation leads to the activation of several downstream transcription factors, which in turn regulates an array of plant growth and developmental function including adaptation to stressors (Dong et al. 2015). There are several reports which suggest a pivotal role of these MAPKs in plant immunity against pathogen infection. For instance, challenge inoculation of *Arabidopsis* plants with *flg22* peptide (a bacterial elicitor), activated various *MAPKs* (*MPK3* and *MPK6*) that activate *flg22* signal transduction network with *MAP-KKK1-MKK4/5-MPK3/*6 (Lee and Back 2016). Similarly, the *hrp* genes of plant pathogenic bacteria involved in hypersensitive response also activate the *MAPKs* signaling during plant immunity. Zhang et al. (2018b) demonstrated that knockout of SlMPAK3 leads to compromised disease resistance in tomato against *Botrytis cineraria* infection.

When much attention has been paid to melatonin as a signaling molecule in innate plant defense, the association of *MAPKs* cascade with melatonin cannot be neglected. Intriguingly, an *Arabidopsis* ortholog of *MPK6* (salicylic acid-induced protein kinase) was highly induced in tobacco leaves in response to melatonin (Lee and Back 2016). Treatment of melatonin reduced inflammation due to a virulent bacteria *Pseudomonas syringae tomato* DC 3000 through activation of *MPK6* in *Arabidopsis*. To investigate the regulatory role of melatonin in *MAPK* activation, Lee and Back (2016) treated *Arabidopsis* and tobacco leaves with melatonin and examined MAPK activation using

antiphospho- p44/42 *MAPK* (*Erk1*/2) monoclonal antibody. During pathogen infection, *MPK3* and *MPK6* were rapidly activated by 1 μM melatonin treatment in both *Arabidopsis* and tobacco. Moreover, the G-protein uncoupling was not involved in *MAPK* activation *via* melatonin which indicates that plants have evolved some novel melatonin receptors which need further investigations. Melatonin-mediated stimulation of MAP kinase cascade reaction (*MAPKKK3/OXI1-MAPKK4/5/7/9-MAPK3/6*), secondarily activates the transcription of the *ICS1* (isochorismate synthase 1) gene responsible for SA synthesis that leads to systemic resistance response in *Arabidopsis*. Up to a lesser extent, 2-hydroxymelatonin and N-acetyl serotonin have also been reported to activate *MAPKs* to mitigate biological stress (Lee and Back 2016). Convincingly, melatonin acts as a signaling molecule upstream of *MAPK* cascade and further research on upstream *MAPKKKs* and identification of melatonin receptors will shed more light on the mechanism of melatonin-mediated stress regulations (Fig. 2).

Regulation of PTI and ETI response

During the course of evolution, the consistent interaction of plant and pathogen has resulted in the evolution of diverse mechanisms of pathogen recognition, interception and defense in host plants (Mandal et al. 2018). The first line of defense after pathogen perception is PAMP-triggered immunity (PTI) and when a virulent pathogen breaches the barrier of PTI the effector-triggered immunity (ETI) comes into action (Liu et al. 2021). This two-layer of defense mechanism works in synchrony to alleviate the pathogen attack (Fig. 2). There are several reports for phytohormones and signaling molecules that activate the PTI and ETI response in plants during pathogen infection (Moustafa-Farag et al. 2020; Tiwari et al. 2020c). However, the direct role of melatonin in stimulating PTI and ETI is not well explored. To our knowledge, there is a single study that sheds some light on melatonin-mediated induction of immunity. Mandal et al. (2018) studied the effect of melatonin spray in alleviating powdery mildew infection in watermelon. They demonstrated the positive role of melatonin in boosting plant resistance through enhancing the expressions of genes involved in PTI and ETI response in watermelon. The transcriptomic analysis revealed that there were twenty-seven up-regulated genes which were either involved in constitutive defense or initial priming for melatonin-induced resistance response. Overexpression of melatonin biosynthetic gene resulted in higher expression of resistance proteins of *TIR-NBS-LRR* and *CC-NBS-LRR* category. Some of these genes include *WRKY* transcription factors, *LRR*-receptor-like kinases, a subtilisin-like serine protease, glutathione S-transferase serine /threonine kinase which are the active component of

PTI and ETI responses. There is a huge underlying gap in functional analysis of genes involved in melatonin-mediated defense signaling and their contribution to enhanced endogenous melatonin levels in plants. The exhaustive investigation and research in this aspect may lead to the development of novel crops with better plant disease resistance.

Hormonal cross-talk involving melatonin in systemic acquired resistance

Melatonin is a significant regulator of gene expression concerning phytohormones such as 3-acetic acid (IAA), abscisic acid (ABA), cytokinins (CKs), gibberellins (GA), ethylene (ET) and brassinosteroids (BRs) (Vleesschauwer et al. 2014). There is enough supporting evidence of cross-talk of melatonin with phytohormones (ABA, IAA, GA, ET) in the regulation of plant growth, physiology and adaptation of abiotic stresses such as heat (Wei et al. 2017), drought (Chinnusamy et al. 2010; Demirel et al. 2020), cold (Ding et al. 2017), salinity (Fleta-Soriano et al. 2017) and metal toxicity (Yu et al. 2018). Phytohormones are also well identified in regulating disease defense signaling networks (Zulfiqar and Ashraf 2021). For example, SA provides plant resistance against biotrophic and hemibiotrophic pathogens. Likewise, JA and ET in combination or individually induces resistance against necrotrophic pathogens (Bari and Jones 2009). Moreover, ABA has also been demonstrated to participate in the defense against fungus and bacterial infections. The studies highlighting the crosstalk of melatonin with plant hormones during pathogen infection are limited and mainly focused on JA and SA signaling which plays a crucial role in induced defense response (Weeda et al. 2014; Zhang et al. 2018b). However, there are several indirect effects of melatonin-phytohormone crosstalk which help the plants to cope with the pathogen attack (Fig. 3). A series of investigations on *Arabidopsis* plants artificially inoculated with virulent bacteria elucidated that exogenous melatonin application induced SA mediated induced defense in plants (Shi et al. 2015; Zhao et al. 2015). Another study involving same host pathogen combination suggested the role of melatonin as a secondary messenger in proving immunity in plants through SA dependent pathway. The local lesion assay based infection of TMV in tobacco elucidated that melatonin treatment minimized the viral load via activation of SA mediated plant defense genes (Zhao et al. 2019b). There are several other studies depicting the genetic interaction of melatonin and SA in biotic stress adaptations (Lee et al. 2014; Lee and Back 2016).

On the other hand, JA enhances the resistance against necrotrophic pathogens which cause great damage through toxins and cell wall degrading enzymes. In this context,

the post-harvest decay in tomato caused by the necrotrophic fungus *Botrytis cineraria* was shown to be minimized with melatonin treatment and this resistance was correlated with the activated JA signaling pathway (Liu et al. 2019). The study highlighted that melatonin treatment increased methyl jasmonate (MeJA) content and the expression of JA biosynthesis-related gene *AOC* (allene oxide cyclase), *LoxD* (lipoxygenase) and *PI II* (proteinase inhibitor II) were up-regulated. Moreover, the expression of *SlMYC2* and *JASMONATE ZIM DOMAIN 1* (negative regulator in JA signaling pathway) was down-regulated (Fig. 3). Altogether, melatonin and JA signaling actively provided the required resistance against fungus attack. Previously, it was also suggested that melatonin promotes JA accumulation in banana (Wei et al. 2017). As per the transcriptome analysis in *Arabidopsis*, most JA pathways related genes were up-regulated by the application of 1 mM melatonin. Moreover, there has been a report that knockout of *SlMAPK3* reduced the ability of tomato plants to defense against *B. cinerea* where *SlMAPK3* mutant showed down-regulation of JA-signaling pathway-related genes (Zhang et al. 2018b).

Melatonin has been suggested to possess auxin-like activity in the regulation of plant growth and defense response. Under abiotic stress such as drought, it has been observed that melatonin enhanced endogenous IAA levels to withstand the stress conditions. Likewise, during *Fusarium* wilt infection of banana plants, the cross-talk of melatonin with IAA was observed in the regulation of heat-shock proteins (*HSP90s*) (Wei et al. 2017). Besides, the eradication of the *Apple stem grooving virus* (ASGV) through the addition of melatonin in the shoot proliferating media indicated the potential cross-talk with IAA. The plants developed on a proliferation medium containing 15 μM melatonin showed the highest concentration of endogenous IAA along with the lowest virus titer (Chen et al. 2019). There is a need for further investigations to establish the exact interaction mechanism of different phytohormones during pathogen infection.

The stomatal opening is the prime entry point for the majority of fungal and bacterial pathogens. As a basal defense mechanism, the plants synthesize the stress hormone ABA during pathogen infection (Arnao and Hernández-Ruiz 2019b). The ABA modulates the regulation of defence-related genes and simultaneously controls the stomata aperture opening and closing that confers the resistance against invading pathogens (Kou et al. 2021). Previously, it has been reported that melatonin negatively regulates the ABA biosynthesis that in turn provides drought tolerance in apple (Wang et al. 2013). Although there are no direct reports it can be speculated that melatonin-mediated ABA metabolism and stomatal regulation might be involved in restricting pathogen invasion in plants.

The commonly designated ripening hormone ET also plays a crucial role in regulating stress responses including plant disease resistance (Bari and Jones 2009; Zhou and Cai 2021). The cross-talk of melatonin with ethylene is well explored under abiotic stress such as drought (Tiwari et al. 2020b). However, this aspect is not well studied in biotic stress regulation. It was reported that most of the genes associated with ET signaling were up-regulated under the influence of melatonin treatment in *Arabidopsis* (Weeda et al. 2014). Similarly, the melatonin treated powdery mildew affected watermelon plants shown up-regulation of ET signaling genes in resistant cultivars. Furthermore, the suppression of pathogen-responsive genes was observed in ethylene insensitive 2 (*ein2*) knockout mutant of *Arabidopsis* plants (Lee et al. 2014). ET response factor encoding gene *RAV* was reported to be critical in the melatonin-induced immune response against cassava bacterial blight disease (Wei et al. 2018). Additionally, the three-way interaction of melatonin with ET and SA has been observed through studies obtained from npr1, *ein2* and *mpk6 Arabidopsis* mutants that resulted in reduced bacterial multiplication. Altogether, there is a synergistic interaction in melatonin and ET signaling in imparting the pathogenesis gene-mediated defense response to the infected plants. The conceptual model depicting the hormonal cross-talk in induced defense response is depicted in Fig. 3.

Conclusion and future perspectives

The ubiquitous multifunction of melatonin from unicellular endosymbionts to higher living forms has been exhaustively explored during the past 50 years. Although the science of melatonin in plants is relatively new and there are accumulating shreds of evidence of its diverse role starting from seed germination to senescence and providing adaptive immunity in biotic and abiotic stress conditions. The center of the redox network is primarily controlled by melatonin that corroborates several cellular, biochemical and molecular responses. The powerful antioxidant nature of melatonin regulates the ROS and RNS levels during the initial and later phases of pathogen infection. The studies highlighting antifungal and antibacterial actions of melatonin are intriguing. Melatonin may directly inhibit the mycelial and spore growth and at the molecular level, it neutralizes the virulence proteins and toxins. The finding regarding its synergistic action with other fungicides emphasizes its potential as an antifungal, antibacterial chemical that can be integrated with a disease management schedule along with other pesticides. This will reduce the pesticide burden and minimize the chemical pollution of soil. Melatonin has shown its indirect role in virus eradication and reducing virus titer and it may be used in the generation of virus-free tissue

culture plants by incorporation in proliferation media. The melatonin-mediated activation of PTI and ETI responses also emphasizes its importance in biotic stress management.

Despite recent progress, there are still many unanswered questions in the melatonin signaling network and resultant actions. The finding on plant melatonin receptor is elusive and unexplored which will shed some light on melatonin-ROS/RNS complete signaling mechanism and other disease resistance pathways. The molecular mechanism of melatonin cross-talk with other phytohormones in ameliorating pathogen infection is not well studied. The mechanism of virus eradication from the tissue cultured plants and reduction of virus titer by exogenous melatonin application is still unknown. Looking ahead, the genetic transformation of plants with melatonin biosynthetic genes to improve endogenous melatonin levels should be performed with the aim of enhanced biotic stress tolerance and better plant growth.

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Declarations

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval No human subjects were used in the writing of the manuscripts.

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