Bacteriostatic Potential of Melatonin: Therapeutic Standing and Mechanistic Insights

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Diseases caused by pathogenic bacteria in animals (e.g., bacterial pneumonia, meningitis and sepsis) and plants (e.g., bacterial wilt, angular spot and canker) lead to high prevalence and mortality, and decomposition of plant leaves, respectively. Melatonin, an endogenous molecule, is highly pleiotropic, and accumulating evidence supports the notion that melatonin's actions in bacterial infection deserve particular attention. Here, we summarize the antibacterial effects of melatonin *in vitro*, in animals as well as plants, and discuss the potential mechanisms. Melatonin exerts antibacterial activities not only on classic gram-negative and -positive bacteria, but also on members of other bacterial groups, such as *Mycobacterium tuberculosis*. Protective actions against bacterial infections can occur at different levels. Direct actions of melatonin may occur only at very high concentrations, which is at the borderline of practical applicability. However, various indirect functions comprise activation of hosts' defense mechanisms or, in sepsis, attenuation of bacterially induced inflammation. In plants, its antibacterial functions involve the mitogen-activated protein kinase (MAPK) pathway; in animals, protection by melatonin against bacterially induced damage is associated with inhibition or activation of various signaling pathways, including key regulators such as NF-κB, STAT-1, Nrf2, NLRP3 inflammasome, MAPK and TLR-2/4. Moreover, melatonin can reduce formation of reactive oxygen and nitrogen species (ROS, RNS), promote detoxification and protect mitochondrial damage. Altogether, we propose that melatonin could be an effective approach against various pathogenic bacterial infections.

Keywords: melatonin, bacteriostasis, MAPKs, NF-κB, ROS, inflammasome, sepsis

INTRODUCTION

Bacteria include both pathogenic and beneficial species and are universally present in all ecosystems as colonizers of hosts (1). Bacteria can be beneficial in multiple ways, for example, *Lactobacillus* and *Bifidobacterium* species are used for yoghurt production (2, 3), *Lactococcus* species and others in cheese production (4, 5), methane producing bacteria for methane production (6), *Corynebacteria*

for monosodium glutamate formation (7) and *Acetobacter* for vinegar generation (8). Bacteria, being a normal flora can also benefit hosts, such as, *Lactobacillus* species can inhibit inflammation by competing with pathogens or stimulating skin barrier recovery (9). Most, but not all bacteria present in the gut microbiome, which contains slightly more cells than a human body, can be also classified as being beneficial and relevant to health, as far as it possesses a favorable compostion (10). Pathogenic bacteria may cause mild, severe and even life-threatening diseases [e.g., septicemia (11), pneumonia (12) and meningitis (13)]. In terms of accessibility to treatments, the bacterial surface structures are of great importance. These are partially detectable by gram staining (14), according to which they are categorized as gram positive bacteria (GPB), gram negative bacteria (GNB), and others (15, 16). Examples of pathogenic GPB (PGPB) comprise *Staphylococcus aureus* (*S. aureus*) (17), *Streptococcus pneumoniae* (*S. pneumoniae*) (18) and *Bacillus anthracis* (*B. anthracis*) (19). Pathogenic GNB (PGNB) include *Escherichia coli* (*E. coli*) (20), *Helicobacter pylori* (*H. pylori*) (21), *Pseudomonas aeruginosa* (*P. aeruginosa*) (22), *Acinetobacter baumannii* (*A. baumannii)* (23), and *Klebsiella pneumoniae* (*K. pneumoniae*) (24). Another important pathogen, *Mycobacterium tuberculosis* (*M. tuberculosis*) (25) possesses a special waxy coating of its cell wall by mycolic acid, which largely prevents gram staining, although the cell wall structure resembles that of other GPBs and is, thus, devoid of an outer membrane (26). Also in genetic terms, *Mycobacterium* species are GPB-like, but the different surface has consequences to treatment.

Bacterial infections caused by pathogenic bacteria severely threaten public health worldwide (27, 28). Historically, the various antibiotics (e.g., penicillin, tetracycline and their derivatives as well as numerous other similarly acting compounds) usually represent the preferred armory for fighting bacterial infections (29). However, new problems (i.e., antibiotic resistance and residues) occur since the overuse and misuse of antibiotics (30–32); therefore, the development of new antibiotics that can effectively kill pathogenic bacteria and do not give rise to problematic metabolites is a matter of highest urgency. Given that very few compounds are currently under development or approval in the clinical setting, hence, repurposing compounds for novel application may become a productive alternate strategy for the combat against bacterial pathogens.

Melatonin, which shows a wide distribution within phylogenetically distant organisms from bacteria to humans (33), is synthesized from tryptophan and produced in pineal gland and in numerous other organs of vertebrates (e.g., gut, skin and bone marrow) (34–36). Melatonin is involved in many physiological processes, as summarized comprehensively (37, 38). In particular, this includes growth modulation and reproduction (39), immune regulation (40–43), anti-inflammation (44–47), antioxidative protection (48–51) and antioncogenic action (52, 53). Meanwhile, increasing evidence has accumulated for remarkable antibacterial actions of melatonin, including protection against damage by bacterial infections. For instance, melatonin has been reported to exert antibacterial effects in PGPB and PGNB *in vitro*, concerning *P. aeruginosa*, *A. baumannii* and *S. aureus* (54). Melatonin has also been shown to protect *Arabidopsis* and tobacco against *Pseudomonas syringae pv. tomato DC3000 (Pst DC3000)* (55), suggesting that melatonin reduces biotic stress by bacterial infection in plants. Also in mammals, several reports have demonstrated substantial effects of melatonin in protecting against or alleviating bacterial infections. In mice infected with *S. aureus* and *E. coli*, symptoms were strongly attenuated by melatonin (56). More impressive evidence has been obtained in septic mice treated with cecal ligation and puncture, in which the decisive effects of melatonin were related to inhibition of NO-mediated inflammation in connection with mitochondrial protection (57–59). Efficacy of melatonin was also multiply demonstrated in human sepsis, including that of neonates, which again underlines the excellent tolerability of this agent (60–62). Despite the emerging role of melatonin in fighting against bacterial infections, the protection mechanisms are only evident in the above-mentioned murine studies, plus additional anti-inflammatory effects that have been recently summarized (46, 63). Concerning protection against bacterial infections in plants, promising data have been obtained on the effects of stress-related genes and phytohormones, but still require further elucidation. Of note, with regard to these numerous highly valuable and beneficial organisms, which also represent an immunological quasi-self, one should melatonin not expect to generally act as an anti-bacterial agent. Moreover, various bacteria tested in this regard have been shown to synthesize themselves melatonin, sometimes in relevant quantities (64, 65). Among intestinal bacteria, the formation of melatonin was first described in *Escherichia coli* (66). Bacteria are even regarded as the evolutionary source of melatonin in eukaryotes, in connection with the uptake of α-proteobacteria and cyanobacteria as ancestors of mitochondria and plastids, respectively (67, 68). This has an important consequence for the consideration of melatonin as a bacteria-controlling agent. As many bacteria synthesize this compound or live, at least, in close community with melatonin-producing microbes, one cannot expect anti-bacterial effects at low doses of melatonin to which

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these organisms are exposed anyway under physiological conditions. However, this does not hinder bacteriostatic actions at elevated concentrations and protection of hosts from damage by bacteria or by inflammatory responses induced by bacterial challenges.

In this review, we summarize the findings related to the antibacterial actions of melatonin *in vitro* and *in vivo*. Thereafter, we detailedly discuss the potential mechanisms whereby melatonin influences pathogenic bacteria as well as their deleterious effects on hosts. These concern: 1) *in vitro*: formation and detoxification of free radicals; regulation of bacterial replication by interference with the cell wall and exhaustion of intracellular substrates and micronutrients (e.g., iron); blockade of bacterial glucose and glutamate metabolism as related to bacterial cell division; 2) in plants: upregulation of genes related to phytohormone-dependent defense signaling as well as MAPK signaling; 3) in animals: involvement of multiple signaling pathways (e.g., NF-κB, STAT1 and Nrf2) related to anti-inflammatory and antioxidant control and mitochondrial protection. The review highlights the huge potential of melatonin in counteracting the growing threat of bacterial infections.

THE BASIC PHYSIOLOGY, PATHOPHYSIOLOGY AND CLINICAL SAFETY OF MELATONIN

Melatonin is a methoxyindole, mainly synthesized and secreted by the pineal gland at night under normal light and dark conditions, the main physiological functions of melatonin are related to hormonal properties (69). Melatonin transmits the information "darkness" and contributes to the synchronization of circadian oscillators (70), which is an important physiological sleep regulator in diurnal species including humans (71). In addition, melatonin is involved in numerous other physiological processes, such as regulation of blood pressure (72), glucose (73), and body temperature (74), suppression of oncogenesis (75), immune function (41), oxidative stress and inflammation (76). It is recognized that the "physiological" dose is the same as the peak plasma melatonin level at night, and the difference between the physiological and pharmacological effects of melatonin is not always clear, but is based on the consideration of the dosage rather than the duration of the hormone message (77). Indeed, the secretion of melatonin can be disturbed in the context of many pathophysiological conditions, which may increase the susceptibilities of the diseases (including infectious diseases) as well as increase the severity of symptoms or change the courses and outcomes of the diseases (78).

Of note, safety is important when melatonin is considered for clinical treatment. Clinically, 3mg, 6 mg and 10 mg melatonin showed satisfactory safety in patients (79–81). Moreover, there was no side effect of 1g/d melatonin for a month in humans (82). It has been shown that melatonin doses up to 800 mg/kg failed to cause any death in mice and it was impossible to obtain its LD50 (median lethal dose) in rats (83, 84). In study on Amyotrophic lateral sclerosis (ALS) patients, melatonin 300 mg/day was

applied for 2 years and found to be safe (85). However, a trial of long-term controlled melatonin release for the treatment of sleep disorders in children with neurodevelopmental disabilities reported mild adverse effects, including seizures, cold/flu/infection, gastro-intestinal illness, agitation, anxiety and headache (86). In addition, the short- and intermediate-term administration of melatonin produced only minor adverse effects such as agitation, dizziness, headache, nausea and sleepiness in clinical studies on children; in clinical studies on adults, dizziness, paresthesias in the mouth, arms or legs, mild headaches, numbness and dyspnea aggravated; psychomotor impairment, sedation, disorientation, and amnesia in surgical patients; mild headache, increased sleepiness and skin rash in critically ill patients; daytime sleepiness in elderly (87, 88). Moreover, a recent systematic review showed that the most frequently reported melatonin adverse effects were daytime sleepiness (1.66%), dizziness (0.74%), headache (0.74%), other sleep-related adverse events (0.74%), and hypothermia (0.62%); but serious or clinical significance adverse events, including agitation, palpitations, nightmares, mood swings, fatigue, and skin irritation, were very few (89). Therefore, compared to other antibiotics, as a natural small molecule, melatonin is relatively safe with a low risk of side effects. However, the effect and safety of melatonin should be carefully monitored when melatonin is used clinically.

BACTERIOSTATIC ACTIONS OF MELATONIN *IN VITRO* AND THEIR UNDERLYING MECHANISMS

Historically, a great diversity of studies aimed to investigate whether melatonin does possess bacteriostatic actions. Initially, melatonin has only been shown to strongly reduce the lipid levels of the yeast *Candida albicans* (*C. albicans*) (90). Subsequently, one comparative study found that some pineal indoles that share a similar structure with melatonin possess antibacterial activities. For instance, 5-methoxytryptamine (5-MT), which is both a metabolite and precursor of melatonin (65), exhibits antibacterial actions against *S. aureus* and *Bacillus subtilis* (*B. subtilis*), and 6-methoxy-2-benzoxazolinone (6-MBOA) against *Proteus vulgaris* (*P. vulgaris*). However, no corresponding antibacterial effect was observed in the case of melatonin (91). Later, it has been reported that melatonin (31.25~125 mg/mL: 0.13-0.53 mM) is able to suppress the growth of PGPB (e.g., *S. aureus*) and PGNB (e.g., *P. aeruginosa* and *A. baumannii*) by reducing key intracellular substrates *in vitro* (54). Intriguingly, melatonin could also inhibit the growth of the atypical GPB *M. tuberculosis*, while the exact mechanism has not yet been identified (92). In this section, we present further evidence for antibacterial activities of melatonin against PGPBs and PGNBs *in vitro*, and we also discuss the potential mechanisms.

The antimicrobial resistance among GPBs (chiefly *S. aureus*, *Enterococcus faecium*, *Enterococcus faecalis* and *Streptococcus pneumoniae*) has become a serious threat to public health, spurring the development of new compounds against

infections (93, 94). In an early study, melatonin had been shown to moderately inhibit the growth of *S. aureus* (95). This was later also reported for the methicillin-resistant *S. aureus* (MRSA), but this required concentrations in the millimolar range (54). However, another investigation showed that the antibacterial action against *S. aureus* and/or MRSA of flouroquinolones was substantially diminished by melatonin *via* reduction of oxidative stress in the bacterial cells (96). Additional bacteria had been also tested in some studies (54, 95, 96), but melatonin's efficiency against other important PGPBs, such as *Enterococcus faecium*, *Enterococcus faecalis* and *Streptococcus pneumoniae* remains to be demonstrated.

PGNBs are also a major challenge in public health, such as *P. aeruginosa* (97) and *A. baumannii* (98). *P. aeruginosa* is one of the main opportunistic pathogenic bacteria in hospitals (99, 100), which often results in post-operative (101) or post-burn wound infections (102), bacteremia (103) and sepsis (104). Antimicrobial resistance also exists in *P. aeruginosa*, it has been discovered that melatonin has a direct suppressive role in carbapenem-resistant *P. aeruginosa* (54). CBR-4830 (a tricyclic indole analog which shows chemical similarity to melatonin), was supposed to suppress the growth of *P. aeruginosa* (105). *A. baumannii*, is a conditional pathogen (106), which often leads to pneumonia (107), meningitis (108) and bacteremia (109). It causes hospital infection frequently (110) and is often resistant to a variety of antimicrobial agents (111), bringing great difficulties to the clinical treatment. Fortunately, melatonin effectively inhibits the growth of *A. baumannii* (54), suggesting it may be suitable as adjunctive therapy in hospital infection. Similarly, we also found that melatonin could inhibit the growth of enterotoxigenic *Escherichia coli* (ETEC) and *Pasteurella multocida* serotype A strain CQ2 (PmCQ2) (unpublished data). Of note, melatonin was reported to moderately reduce surface hydrophobicity, a characteristic associated with the colonization of mammalian epithelia, inhibiting the adherence of *E.coli*; however, the reduction of surface hydrophobicity in *E. coli* remained at borderline and was only observed at high concentrations (0.2 mM) (112). In contrast, another study by the same group reported that melatonin instead increased cell surface hydrophobicity of *Neisseria meningitidis* (113). Thus, the influence of melatonin on surface hydrophobicity is obviously variable, which would require a convincing explanation, especially as the authors had tried to relate these effects to melatonin's antioxidant properties (112).

M. tuberculosis, an atypical PGPB whose cell wall is coated by mycolic acid (26), is the main pathogen of tuberculosis (TB) in humans (25, 114) and various mammals (115, 116). In addition to dormancy and persistence, drug resistance is a major obstacle in the treatment of TB (117). Therefore, it is urgent to seek for sensitive anti-TB drugs or methods to enhance the sensibility of existing antimicrobial agents. In the earlier literatures, the protective function of melatonin against *M. tuberculosis* was evaluated with isoniazid *in vitro*, experiments that did not reveal significant growth inhibitions by either isoniazid (0.005 to 0.01 μg/mL) or melatonin (0.26 nM to 2.6 nM) alone, but by a combination of isoniazid (0.005 μg/mL) and melatonin (0.01

mg/mL) (61, 92). Furthermore, the bacteriostatic capacity of melatonin was also reported for *M. tuberculosis* (3×10^7 CFU/mL, 3×10^5 CFU/mL, 3×10^3 CFU/mL) treated with different concentrations of melatonin (0.05, 0.1, 0.2 and 0.4 mg/mL) *in vitro* (118). However, the extent of inhibition was not quantified in that study. Collectively, melatonin can affect pathogenic bacteria in some cases directly (e.g., inhibition of growth and adherence), which has been summarized in **Table 1**. It is likely concluded that the effectiveness of melatonin on pathogenic bacteria is obviously variable, and may depend largely on its working concentrations. Current studies have centered on melatonin's antibacterial activities on GNB, while the bacteriostatic capability of melatonin against other specific bacteria (especially antimicrobial resistant-GNB) is still poorly characterized.

As mentioned above, melatonin could exhibit bacteriostatic action against pathogenic bacteria; however, the potential mechanisms are not fully understood. Actually, there are two main hypotheses about bacteriostatic mechanisms of melatonin *in vitro*. It has been well documented that the growth of bacteria urgently requires metals, particularly free iron (121). Considering that melatonin has a high metal binding capacity, including iron, copper and zinc (122), thus, the addition of melatonin may reduce cytoplasmic availability of metal ions in bacteria to achieve the bacteriostatic effects (**Figure 1A**). Moreover, the membrane of bacteria is imbued with phospholipids (123, 124), and study has shown that melatonin can restrict the absorb of Linoleic acid (LA) used for facilitating cell proliferation (125). Therefore, melatonin may inhibit proliferation of bacteria by blocking the getting of bacterial growth factors (**Figure 1B**). These convincing findings indicate that melatonin inhibits the bacterial growth may through reducing intracellular substrates (54). Interestingly, a recent study declared that melatonin inhibits bacterial growth and proliferation by regulating the expression of genes associated with cell division (**Figure 1C**) and suppressing contents as well as activities of metabolism-related enzymes (**Figure 1D**) (119). These interesting results imply that melatonin could affect bacteria physiological condition by intrinsic molecular mechanisms; however, the experimental validation is still needed. Of note, our recent findings also demonstrated that melatonin exerts antibacterial activity against GNB (e.g., *Klebsiella*, *Pasteurella multocida* and *Pseudomonas aeruginosa*) through specifically inhibiting the activity of bacterial citrate synthase (**Figure 1E**), and the combination of colistin with melatonin enhances bacterial outer membrane permeability, oxidative damage and inhibits the effect of efflux pumps (**Figure 1F**) (126).
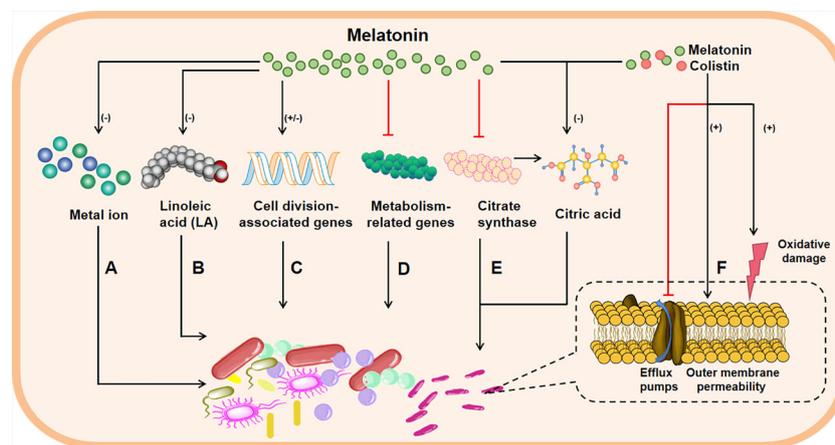
BACTERIOSTATIC ACTIONS OF MELATONIN *IN VIVO* AND THEIR UNDERLYING MECHANISMS

Melatonin not only has antibacterial effect *in vitro*, but also plays a significant role in the clinical prevention and treatment of

TABLE 1 | The antibacterial action of melatonin *in vitro* on different bacteria.

Bacteria	Dosage	Time	Effects	Ref.
Carbapenem-resistant *P. aeruginosa*	31.25 or 125 µg/mL (0.13 or 0.53 mM)	24 or 48 h	Inhibition of carbapenem-resistant *P. aeruginosa* growth	(54)
Carbapenem-resistant *A. baumannii*	31.25 or125 µg/mL (0.13 or 0.53 mM)	24 or 48h	Inhibition of crbapenem-resistant *A. baumannii* growth	(54)
Methicillin-resistant *S. aureus*	125 or 250 µg/mL (0.53 or 1.07 mM)	24 or 48h	Inhibition of methicillin-resistant *S. aureus* growth	(54)
S. aureus ATCC 29123	125 or 250 µg/mL (0.53 or 1.07 mM)	24 or 48h	Inhibition of *S. aureus* (ATCC 29123) growth	(54)
P. aeruginosa ATCC 27853	125 or 250 µg/mL (0.53 or 1.07 mM)	24 or 48h	Inhibition of *P.aeruginosa* (ATCC 27853) growth	(54)
M. tuberculosis H37Rv	26.0 nM 0.01 to 10 mM	unknown	Inhibition of *M. tuberculosis* H37Rv growth. The antibacterial efficacy of melatonin with isoniazid increased at least a threefold	(92)
M. tuberculosis bovis BCG	0.13 to 10 mM	unknown	Inhibitin of *M. bovis* BCG growth	(92)
Multidrug-resistant *M. tuberculosis* (TBRI 40 and TBRI 204)	0.01 to 10 mM	unknown	Inhibition of multidrug-resistant *M. tuberculosis* (TBRI 40 and TBRI 204) growth	(92)
Xanthomonas oryzae pv. Oryzae (Xoo)	200 µg/mL	12, 21 or 24 h	Inhibition of Xoo proliferation, motility and biofilm formation. Alteration of Xoo cells length. Downregulation of mRNA expression of genes involved in cell division, carbohydrate metabolism and amino acid metabolism	(119)
Xanthomonas oryzae pv. Oryzicola Xoc)	200 µg/mL	24 h	Inhibition of Xoc growth, the motility and biofilm formation. Reduction of mRNA expression of genes related to toxin and cell division	(120)

P. aeruginosa, Pseudomonas aeruginosa; A. baumannii, Acinetobacter baumannii; S. aureus, Staphylococcus aureus; M. tuberculosis, Mycobacterium tuberculosis; B. anthracis, Bacillus anthracis.

FIGURE 1 | The possible bacteriostatic mechanisms of melatonin *in vitro*. Melatonin inhibits the growth of bacteria through these avenues: reducing cytoplasmic availability of metal ion **(A)**; interfering cell wall formation, for example, melatonin restricts the absorb of Linoleic acid (LA), which makes up the cell wall, thus limiting cell proliferation **(B)**; melatonin can also regulate the expressions of genes associated with cell division **(C)** or suppress the content and activity of metabolism-related enzymes **(D)** to inhibit bacterial growth and proliferation; melatonin resists against Gram-negative bacteria through inhibiting bacterial citrate synthase and reducing the synthesis of citric acid **(E)**, besides, when melatonin is combination with colistin, bacterial outer membrane permeability and oxidative damage are enhanced, and the effect of efflux pumps is inhibited **(F)**, leading to increased bacteria damage. Note: minus in parentheses represents decrease; plus in parentheses represents increase; and the red line represents inhibition; the black arrow indicates activation.

bacterial infections *in vivo* (61). The inhibitory effects of melatonin *in vivo* includes both on PGPB [e.g., *S. aureus* (56) and *S. pneumoniae* (127)] and PGNB [e.g., *E.coli* (128), *H. Pylori* (129) and *K. pneumonia* (130)]. For example, in many GNB-infected animal models (e.g., sepsis), melatonin has a favorable effect in improving survival rates, ameliorating tissue damage and reducing levels of pro-inflammation mediators (e.g., TNF-α

and IFN-γ), and increasing levels of anti-inflammation mediators (e.g., IL-10) (131, 132). Notably, various signaling have been described to shape bacterial infection *in vivo* by melatonin, including NF-κB, Nrf2, NLRP3 and ROS pathways. In this section, firstly, we present the evidence from studies that have used melatonin to resist bacterial infections *in vivo*. Subsequently, we illustrate the possible mechanisms.

S. aureus always causes many serious infections in human (133, 134). Virtually, melatonin not only inhibits the growth of *S. aureus in vitro*, but also has significant defensive effects against *S. aureus*-induced infection *in vivo*. For example, melatonin reduces lipid peroxidation (LPO), catalase (CAT), neutrophil recruitment, and TNF-α, IFN-γ, IL-6, iNOS, COX-2 and C-reactive protein (CRP), while increases superoxide dismutase (SOD) and glutathione (GSH) in animals infected by *S. aureus* (5×10^6 CFU/mL) (56). The pathogenicity of *S. pneumoniae* is second only to *S. aureus* in pyogenic cocci (135), which triggers major lobe pneumonia (136), meningitis (137), bronchitis (138). Fortunately, it has found that melatonin has a certain inhibitory effect on the infection of *S. pneumonia* (95). These aforementioned findings indicate that melatonin can target GPB to alleviate infections *in vivo*. However, it has been shown that melatonin therapy fails to reduce neuronal injury in *S. pneumoniae*-infected rabbit model, the possible reason may due to the 12 h delay in the administration of melatonin after the infection (139).

Historically, *E. coli* has been regarded as an integral part of the normal intestinal flora (140), and was considered to be non-pathogenic bacteria (141). Nevertheless, as the research moves along, some special serotypes of *E. coli* [e.g., ETEC (142), enterohemorrhagic *E. coli* (EHEC) (143) and enteropathogenic *E. coli* (EPEC) (144)] are shown to be pathogenic to humans and animals (especially infants and young animals) (145), causing severe diarrhea (146) and sepsis (147). Some studies have found that melatonin has a bacteriostatic effect in the animals infected by *E. coli*, for instance, melatonin reduces LPO, CAT, neutrophil recruitment, and TNF-α, IFN-γ, IL-6, iNOS, COX-2 and CRP, while increases SOD and GSH in animals infected by *E. coli* (2.5×10^7 CFU/mL) (56, 148). *H. Pylori* is the only microbial species known to survive in the human stomach (149) to induce gastritis (150), gastrointestinal hemorrhage (151) and gastric lymphoma (152). It has been revealed that *H. Pylori* infection inhibits gastric mucosal melatonin synthesizing enzymes [e.g., arylalkylamine-N-acetyltransferase (AANAT) and N-acetylserotonin O-methyltransferase (ASMT)] expression (153). Interestingly, melatonin facilitates *H. pylori* eradication in patients with gastroduodenal ulcer by omeprazole treatment (154–156), indicating melatonin can be used as an adjuvant clinical drug against *H. Pylori* infection. Furthermore, *K. pneumonia* is also a member of PGNB, isolated from the sputum of patients with pneumonia (157), mainly leads to pneumonia (158), septicemia (159) or bacteremia (160), meningitis (161) and peritonitis (162). An experimental study showed that the supply of 100 mg/kg of melatonin can reduce pro-inflammatory cytokines, inhibit microglial activation, and counteract neurocognitive damage in *K. pneumoniae*-infected rats (130). Likewise, we also found that melatonin can inhibit macrophage-mediated excessive inflammatory responses in *Pasteurella multocida* (PmCQ2)-infected mice (unpublished data). Of note, like GPB *S. pneumoniae*, the effect of melatonin on inactivated *Pasteurella multocida* (P52 strain) vaccine-mediated immune responses is time-dependent evidenced by exogenous melatonin administration at 4 h post vaccination augments immune responses in rats in comparison to 16 h post vaccination (163, 164).

Notably, melatonin has been demonstrated to increase survival rates and improve organ function in several sepsis models (165, 166). The oxidative imbalance is one of the characteristics of sepsis (167), and mitochondria play key roles in regulating sepsis-related redox dysregulation (168). Mechanistically, melatonin can alleviate sepsis symptoms by preventing mitochondria dysfunction *via* ROS/RNS scavenging (169) and many other pathways (e.g., intra-mitochondrial SIRT3 and MAPK/ERK pathway) (170–176). Inflammation is essential for the host to resist infection by pathogenic bacteria, however, excessive inflammation is another characteristic of the initial stage of sepsis, leading to organ dysfunction and eventually death (177, 178).

Melatonin as a signal molecule of stress can be induced by the pathogenic (but not the beneficial) bacteria invasion and the increased melatonin level in hosts can improve the protective effects or tolerance to the bacteria (179). In addition to inhibiting pathogenic bacteria, melatonin has a beneficial effect on intestinal flora (180, 181). For example, melatonin reprogramming of gut microbiota improves lipid dysmetabolism to prevent obesity in mice (182–185). Moreover, melatonin contributes to reshape gut microbiota to alleviate neuroinflammation and metabolic disorder in DSS-induced depression rats (186). Furthermore, melatonin ameliorates ochratoxin A-induced liver inflammation, oxidative stress and mitophagy involving in intestinal microbiota in mice (187). Altogether, as summarize in **Table 2**, melatonin may function as a novel compound to resist pathogenic bacterial infections *in vivo*. However, the defensive effects of melatonin against pathogenic bacteria are likely dose- and/or time-dependent.

Notably, the mechanisms whereby melatonin exerts bacteriostatic action *in vivo* are tightly associated with the immune responses, for example, during polymicrobial infection, melatonin treatment could promote the development of the neutrophil extracellular trap (NET), whereas inhibits the phagocytic activities of neutrophils (188). Indeed, mounting evidences suggest that melatonin always exerts its physiological effects *via* its receptors (e.g., MT1 and MT2). It has been discovered that melatonin is able to improve the survival rate of polymicrobial sepsis of mice through MT1 and MT2 receptor (**Figure 2A**) (189). Melatonin also alleviates acute lung injury induced by LPS *via* inhibiting the activation of NLRP3 inflammasome (**Figure 2B**) (190). Melatonin could dose-dependently reduce pro-inflammatory cytokine TNF-α, IL-6 and IL-8, increase anti-inflammatory cytokine IL-10 and improve survival, which are associated with p38MAPK and NF-κB signaling pathway (173, 191–195) (**Figure 2C**). Moreover, melatonin could block LPS (which is from *P. intermedia*)-induced activation of NF-κB signaling (**Figure 2D**) and STAT1 pathway (**Figure 2E**), thereby inhibiting the production of inflammatory mediators (e.g., NO and IL-6) (196, 197). Likewise, it has found that melatonin can reduce pro-inflammatory mediators [e.g., IL-1β, IL-6, NO and granulocyte-monocyte colony-stimulating factor (GM-CSF)], while increase anti-inflammatory cytokine (e.g., IL-10) by

TABLE 2 | The antibacterial action of melatonin *in vivo* infected with different bacteria.

Bacteria	Dosage	Time	Effects	Ref.
S. aureus	10 mg/kg	At 17:00, 17:30, 18:00	Reducing expression of LPO, CAT, iNOS, COX-2 and production of TNF-α, IFN-γ, IL-6, CRP, increasing the production SOD and GSH	(56)
S. pneumoniae	2 mg/mL	40 h	Suppressing bacterial growth at a high concentration	(95)
E. coli	10 mg/kg or 1nM	At 17:00, 17:30 and 18:00 or 70 s	Reducing expression of LPO, CAT, iNOS, COX-2 and production of TNF-α, IFN-γ, IL-6, CRP, increasing the production SOD and GSH	(56, 148)
H. Pylori	5 mg or 3 mg	21 days	Increasing efficacy of *H. pylori* elimination, Accelerating duodenal ulcer recovery	(154–156)
K. pneumonia	100 mg/kg	24 h	Counteracting neurocognitive damage inhibiting microglial activation, and reducing pro-inflammatory cytokine levels	(130)
Pasteurella multocida (P52)	100mg/kg	4 h	Exogenous melatonin at 4 h post vaccination augments immune responses in rats.	(163)
Pasteurella multocida (PmCQ2)	30 mg/kg, 60 mg/kg, 120mg/kg	12 h, 16 h, 24 h, 32 h	Inhibiting macrophage-mediated excessive inflammatory responses	Unpublished

S. aureus, Staphylococcus aureus; S. pneumonia, Streptococcus pneumonia; E. coli, Escherichia coli; H. Pylori, Helicobacter Pylori; K. pneumonia, Klebsiella pneumonia; LPO, lipid peroxidation; CAT, catalase; iNOS, inducible nitric oxide synthase, CRP, C-reactive protein; SOD, superoxide dismutase; GSH, glutathione.
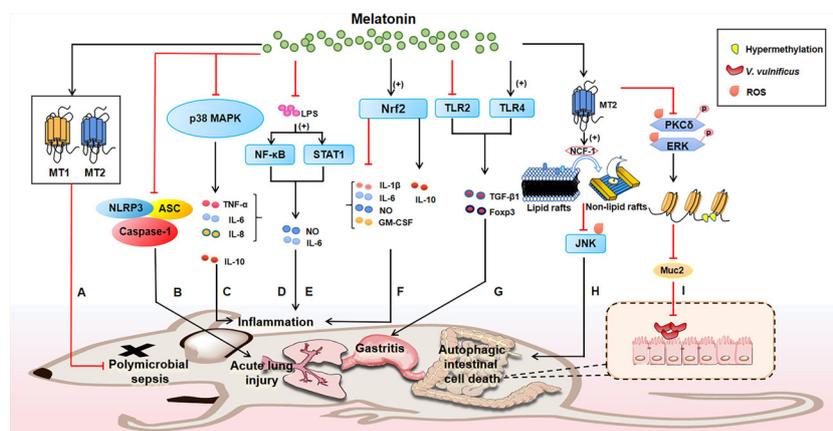
FIGURE 2 | The bacteriostatic mechanisms of melatonin in animals. Melatonin receptors (e.g., MT1 and MT2) play a great role in mediating the functions of melatonin. Melatonin reduces polymicrobial sepsis through MT1 and MT2, thus improving the survival rate of mice **(A)**; notably, the mechanisms whereby melatonin exerts bacteriostatic action *in vivo* are tightly associated with the immune responses, for instance, melatonin inhibits NLRP3 inflammasome to alleviate acute lung injury **(B)**; melatonin reduces pro-inflammatory cytokines, increases anti-inflammatory cytokines and improves survival through p38MAPK signaling pathway **(C)**; melatonin blocks LPS-induced activation of NF-κB **(D)** and STAT1 **(E)**, thus inhibiting the production of inflammatory factors to modulate inflammation. Likewise, suppression of inflammation also occurs when melatonin activates Nrf2, evidenced by reduced pro-inflammatory mediators (e.g., IL-1β, IL-6, NO and GM-CSF) and increased anti-inflammatory cytokine (e.g., IL-10) **(F)**; melatonin treatment can target TLR to alleviate *H. pylori*-induced gastritis by promoting TLR4 and inhibiting TLR2 to regulate TGF-β1 and Foxp3 expression **(G)**; of note, melatonin could be a therapeutic alternative agent to fight bacterial infections due to its antioxidant function. For example, melatonin signaling *via* MT2 promotes NCF-1 recruitment from lipid rafts to non-lipid rafts to block the ROS-mediated JNK pathway, preventing autophagic intestinal cell death **(H)**; moreover, MT2 signaling inhibits the ROS-mediated phosphorylation of PKCδ and ERK to reduce region-specific hypermethylation in the Muc2 promoter, combating *V. vulnificus* infection **(I)**. Note: plus in parentheses represents increase; and the red line represents inhibition; the black arrow indicates activation.

activating Nrf2 pathway (**Figure 2F**) (198). Actually, melatonin treatment can also alleviate *H. pylori*-induced gastritis through regulating TGF-β1 and Foxp3 expression *via* the suppression of TLR2 and activation of TLR4 (**Figure 2G**) (129), although the molecular target of melatonin in the TLR signaling warrants further investigation.

Moreover, it should be noted that melatonin could be a therapeutic alternative agent to fight bacterial infections due to its antioxidant function. Intriguingly, melatonin inhibits apoptotic cell dealth in colonic epithelial cells induced by *Vibrio vulnificus* VvhA *via* MT2 (199). Mechanistically, melatonin signaling *via* MT2 stimulates NCF-1 recruitment

into non-lipid rafts from lipid rafts to block the ROS-mediated JNK pathway, preventing rVvhA-induced apoptosis and autophagic intestinal cell death (**Figure 2H**). Similarly, melatonin treatment maintains the expression level of Muc2 in the intestine of *V. vulnificus*-infected mouse. Mechanistically, melatonin inhibits the ROS-mediated phosphorylation of PKCδ and ERK responsible for region-specific hypermethylation in the Muc2 promoter *via* MT2 receptor, restoring the level of Muc2 production in intestinal epithelial cells to resist *V. vulnificus* infection (**Figure 2I**) (200).

Collectively, melatonin could exert its bacteriostatic action *in vivo* by various potential mechanisms, including NF-κB, STAT1, Nrf2, TLR2/4, and ROS signaling (**Figure 2**). These aforementioned findings may provide promising strategies for controlling many diseases of public health importance. It should not be neglected that melatonin has a significant antibacterial effect *in vitro*; thus, whether the powerful effect of melatonin *in vivo* is also directly inhibiting bacterial growth remains further exploration.

BACTERIOSTATIC ACTIONS OF MELATONIN IN PLANTS AND THEIR UNDERLYING MECHANISMS

In addition to the significant bacteriostatic functions of melatonin *in vitro* and in animals, melatonin also exerts

similar function against pathogenic bacterial infections in plants (201, 202). It has found that melatonin treatment inhibits the growth, motility and capsule formation of the bacterium *Xanthomonas oryzae pv. oryzae* (Xoo) (119), which leads to bacterial blight in rice (203, 204). Melatonin increases the resistance to *Verticillium dahlia* in cotton by regulating lignin and gossypol biosynthesis (205), although the molecular mechanisms are still not available. Authentically, it has been demonstrated that Serotonin N-acetyltransferase (SNAT)-deficient *Arabidopsis* shows lower melatonin levels and exhibits susceptibility to pathogen infection (206). Conformably, melatonin can trigger defense responses against *Pst* DC3000 infection in *Arabidopsis* and/or tobacco (55, 207, 208). Mechanistically, melatonin-induced rise of NO that favors in the expression of salicylic acid (SA)-related genes (e.g., *AtEDS1*, *AtPAD4*, *AtPR1*, *AtPR2* and *AtPR5*), conferring improved disease resistance against *Pst* DC3000 infection in *Arabidopsis* (**Figure 3**); however, the beneficial effects of melatonin could be jeopardized by using a NO scavenger (cPTIO) and/or lost in NO-deficient mutants of *Arabidopsis* (209). Furthermore, it has been discovered that melatonin can active MPK3 and MPK6 signaling (members of MAPKs), which are independent of G-protein and Ca^{2+} signaling, and the inhibition of MPK3 and/or MPK6 induces reduced expression of defense and pathogen resistance-related genes (e.g. *PR1*, *PR2*, and *PR5*) (55). Indeed, melatonin activates MPK3 and MPK6 *via* four MKKs (i.e., MKK4/5/7/9) (210), and MAPKKK 3 and OXI 1 (oxidative signal-inducible 1) kinases are responsible for triggering
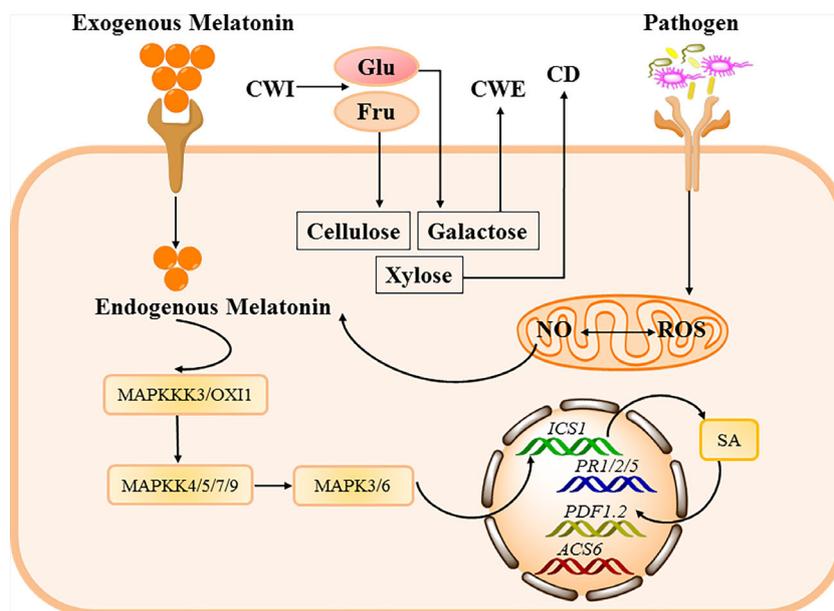
FIGURE 3 | The bacteriostatic mechanisms of melatonin in plants. Antibacterial mechanisms against plant pathogenic bacteria are characterized by up-regulation of defense genes such as *plant defensin1.2* (*PDF1.2*), *plant resistance 1/2/5* (*PR1/2/5*), and *1-aminocyclopropane-1-carboxylate synthase 6* (*ACS6*) through several signal transduction pathways, including augmentation of NO levels in plants, which collaborates with melatonin in up-regulating SA. Moreover, melatonin can stimulate mitogen-activated protein kinases (MAPKs) cascades, which in turn up-regulate SA biosynthesis gene *isochorismate synthase 1* (*ICS1*). Additionally, high cell wall invertase (CWI) activity within melatonin-treated *Arabidopsis* leads to improved cell wall strengthening and callose-depositing factors (cellulose, xylose, and galactose).

melatonin-induced defense signaling pathways (211). Therefore, melatonin could mediate pathogen resistance in *Arabidopsis* and tobacco by activating MAPKs signaling *via* MKK4/5/7/9-MPK3/6 cascades through the activation of MAPKKK 3 and OXI 1 (**Figure 3**). In conclusion, melatonin plays a critical bacteriostatic role in *Pst* DC3000-infected *Arabidopsis* by MAPKs pathway. Moreover, melatonin could improve cell wall strengthening and callose-depositing factors (cellulose, xylose, and galactose) by increasing cell wall invertase (CWI) activity in *Arabidopsis* infected with *Pst. DC3000* (**Figure 3**) (207). However, whether melatonin could function as a signaling molecule in modulating defense responses of other plants infected by various pathogenic bacteria are still poorly defined.

CONCLUDING REMARKS

Melatonin has multifarious functions, like circadian rhythm regulation (212, 213); anti-inflammatory/anti-tumor effects (214, 215); and, with particular relevance to this article, anti-bacterial function. Here, we summarize melatonin can directly influence bacteria *in vitro* (e.g., inhibition of growth) by reducing intracellular substrates. Considering that intestinal bacteria, *Enterobacter aerogenes*, responds to the melatonin by an increase in swarming activity, which is expressed rhythmically (216); thus, it is meaningful to further investigate the potential effects of melatonin in synchronizing bacterial rhythms *in vitro*. Notably, melatonin resists pathogenic bacterial infections *in vivo* by various pathways, such as NF-κB, TLR2/4, and ROS. Other pathways seem to get involved as well, but further experimental validation is needed. Furthermore, intestinal microbiota play a crucial role in the progress of different diseases, including bacterial infections *in vivo* (183, 217); therefore, it is necessary to further investigate the intestinal microbiota-mediated defensive roles of melatonin in attenuating bacterial infections *in vivo*. Melatonin serves as a signaling molecule to resist bacterial infections in *Arabidopsis* mainly through MAPK pathway, whether other specific pathways connecting to the bacteriostatic actions of melatonin in other plants or even other specific bacteria also remain an open question.

In addition to its significant antibacterial effect, it is thought that melatonin plays crucial roles in the fighting viral infections (61). Melatonin was found to effective against Ebola hemorrhagic shock syndrome by inhibiting Rho/ROCK signaling (218). Melatonin was also shown to protect mice infected with the Venezuelan equine encephalitis virus (VEEV) by reducing viral loads, brain apoptosis and oxidative stress (219, 220). Additionally, melatonin also was reported to exert protective and therapeutic effects against hemorrhagic disease virus (221), respiratory syncytial virus (RSV) (222), aleutian disease virus (223) and influenza virus (224). Recently, melatonin was proposed to be a potential candidate drug as an adjuvant treatment for patients with COVID-19 based on its antioxidant, anti-inflammatory and immunomodulatory properties (81, 225–227).

Overall, this review highlights melatonin as a novel and feasible preventive and therapy to tackle the increasing threat by bacterial infections. Based on the various physiological/pharmacological functions of melatonin and its significant anti-pathogenic effects, melatonin can be possibly used as clinical agent against pathogens and even viruses in the future.

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