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Melatonin as a treatment option for Bacterial Meningitis - A Comprehensive Review

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ABSTRACT

Bacterial meningitis (BM) is a global acute infectious central nervous system (CNS) illness that leaves 50% of survivors with long-term significant consequences. Acute bacterial meningitis is more common in low-resource areas than in high-resource areas. Bacterial survival and multiplication in the circulation, increased permeability of the blood brain barrier (BBB), oxidative stress, and an overactive inflammatory response in the CNS are all involved in the pathogenesis of BM. Because drug-resistant bacteria make treatment for meningitis more difficult, the vaccination has been confined to a few serotypes, and the BM morbidity rate remains high. With recent advances in neurology, there is hope for medication supplements that can successfully prevent and cure BM. Several in vivo and in vitro researches have been conducted to better understand how melatonin affects BM. Melatonin is primarily produced in the pineal gland and has the ability to cross the BBB. Melatonin and its metabolite have been found to be efficient antioxidants and anti-inflammatories, suggesting that they might be used to prevent and treat BM. Melatonin can protect the brain against bacterial meningitis through a variety of mechanisms, including immunological response, antibacterial capabilities, BBB integrity protection, free radical scavenging, anti-inflammation, signalling pathways, and gut microbiota. This paper highlights melatonin's primary neuroprotective processes and investigates prospective preventative and therapy strategies for BM nerve damage.

Keywords: Bacterial Meningitis, Neuron Injury, Melatonin, Neuroprotection

1. INTRODUCTION

Infants, adults, and elderly individuals are most commonly affected by bacterial meningitis (BM), which typically results in high mortality and leaves 50% of survivors with long-term neurological effects [1,2]. Neonate bacterial meningitis, adult bacterial meningitis, and senile bacterial meningitis are all examples of bacterial meningitis that can affect people of any age. Environmental factors and immunosuppressed individuals both increase a person's risk of contracting bacterial meningitis. The pathophysiology of bacterial meningitis is as follows: first, the bacteria colonise healthy people's skin or other mucosal surfaces; next, they spread via the blood and overcome the host's defences; and ultimately, they cause systemic infection and neuronal damage [3, 4]. The pathophysiology of BM is primarily characterised by high levels of bacteremia in the circulation, the breakdown of the BBB integrity, cerebrospinal fluid (CSF) pleocytosis, and a massive inflammatory response in the CNS, which causes significant nerve damage and even death [3,5,6]. Numerous studies have up to this point described the molecular processes of BM caused by bacterial ligand-receptor interactions, tight junction protein degradation, and increased production of matrix metalloproteinases (MMPs), oxidative stress, and related signalling cascades. Although antibiotics and vaccines have been able to significantly lower meningitis mortality for eradicating bacteria, BM still causes high morbidity and seriously detrimental neurological damage sequelae due to the emergence of drug-resistant bacteria and the limitations of vaccine serotype. Therefore, new preventative or therapeutic approaches must enhance BM. Melatonin plays role in several biological responses. Melatonin may be shown to be released by many different organs, including the skin, retina, kidneys, pancreas, ovaries, and gastrointestinal system [7,8,9]. It is originally discovered to be produced by the pineal gland. Amphiphilic melatonin readily crosses the blood brain barrier (BBB) to reach the CNS and cerebrospinal fluid (CSF) [7]. After the exogenous melatonin supplement, this is particularly crucial for the efficient prevention and treatment of CNS illnesses. First of all, circadian rhythms, sleep, and reproduction are all controlled by melatonin [10,11]. Further research has revealed that melatonin also regulates the immune system and the gut microbiota in addition to acting as an antibacterial, antioxidant, anti-inflammatory, and anti-apoptotic agent [12 - 15]. Currently, melatonin has been shown to have positive effects on BBB integrity protection, reducing neuronal and glial damage in a variety of CNS illness models [16 - 19]. Additionally, it was discovered that the elevated levels of melatonin metabolism in the CSF, N^1-acetyl-N^2-formyl-5-methoxykynuramine (AFMK), and N^1-acetyl-5-methoxykynuramine (AMK), which also play a crucial role in anti-inflammatory and neuroprotection in the CNS, exerted neurocyte-protective properties in the conditions of inflammation and oxidative stress [20].Therefore, the main focus of this review is on the neuroprotective properties of melatonin, which include antibacterial activity, blocking the interaction between bacteria and receptors, protection of BBB integrity, resistance to oxidative stress, anti-inflammatory activity, and major

signalling pathway in both in vivo and in vitro models.

2. Bacterial Meningitis

2.1. Epidemiological Characteristics

One of the top 10 infectious diseases that lead to mortality is bacterial meningitis, which affects nearly 1.2 million people annually worldwide and is expected to be deadly in 300,000 cases in 2023 [21,22]. In the meanwhile, 50% of survivors experience long-term neurological effects [1,23]. Numerous factors, including age, gender, socioeconomic status, seasonal fluctuations, immunisation history, and state of health, might influence the development of bacterial meningitis [24]. Meningitis morbidity is substantially greater in underdeveloped nations than it is in wealthy nations [2,25,26]. While the frequency of bacterial meningitis is 1-2 cases per 100,000 individuals in the UK, it can approach 1000 cases per 100,000 people per year in sub-Saharan Africa [27]. According to epidemiological studies released in 2018, the incidence of bacterial meningitis in Western nations (Finland, the Netherlands, the US, and Australia) gradually decreased to 0.7-11 per 100,000 people in the past 10–20 years, while it can still reach 10–40 per 100,000 people annually in African nations (Burkina Faso and Malawi) [22]. This discovery shows how strongly meningitis is connected with environmental and financial factors. Anyone can have bacterial meningitis; however various bacteria mostly infect hosts who are different ages. For instance, *Streptococcus pneumonia* and *Neisseria meningitides* primarily affect adults while Group B *Streptococcus* (GBS) and *Escherichia coli* K1 primarily cause meningitis in newborns and young children [3, 28 - 32].Bacterial meningitis can strike simultaneously an immunosuppressed newborn or child, an adult with digestive tract disorders, smoking, drinking, HIV, or cancer. The majority of cases of bacterial meningitis continue to be acute and serious illnesses with a significant risk of complications that can result in death or long-term effects. These side effects might include shock, organ failure, respiratory problems, cerebral problems including strokes, seizures etc [33 - 35]. Septicemia and respiratory failure were the leading causes of mortality in older patients with bacterial meningitis, while brain herniation was the most common consequence in younger patients [36]. If the host survives after infection, it may suffer from consequences particular to the disease, such as blindness, deafness, or various types of retardation.

2.2. Pathogenesis of Bacterial Meningitis

The majority of bacterial meningitis pathogens initially colonise the oropharynx, nasopharynx, or digestive mucosal surfaces and pass through the mucosal barrier. They then persist and spread throughout the circulation, attach to the BBB, and ultimately infiltrate the CNS [3]. Healthy people's mucosal surfaces can get colonised by meningitis bacteria such as *Streptococcus pneumonia*, *Neisseria meningitis*, Group B *Streptococcus*, *Streptococcus aureus*, or *Escherichia coli* K1. Bacterial survival and reproduction in the circulation are requirements for reaching the BBB, and pathogens can pass the mucosal barrier into the bloodstream [3]. The complement system and Toll-like receptors (TLR) are the crucial

factor in removing pathogens in bacterial meningitis. As an illustration, complement factors were made to accumulate on pathogens' surfaces to encourage the process of phagocytosis of phagocytes [37], while TLR activation inhibits bacterial growth by triggering inflammation [38 - 40].

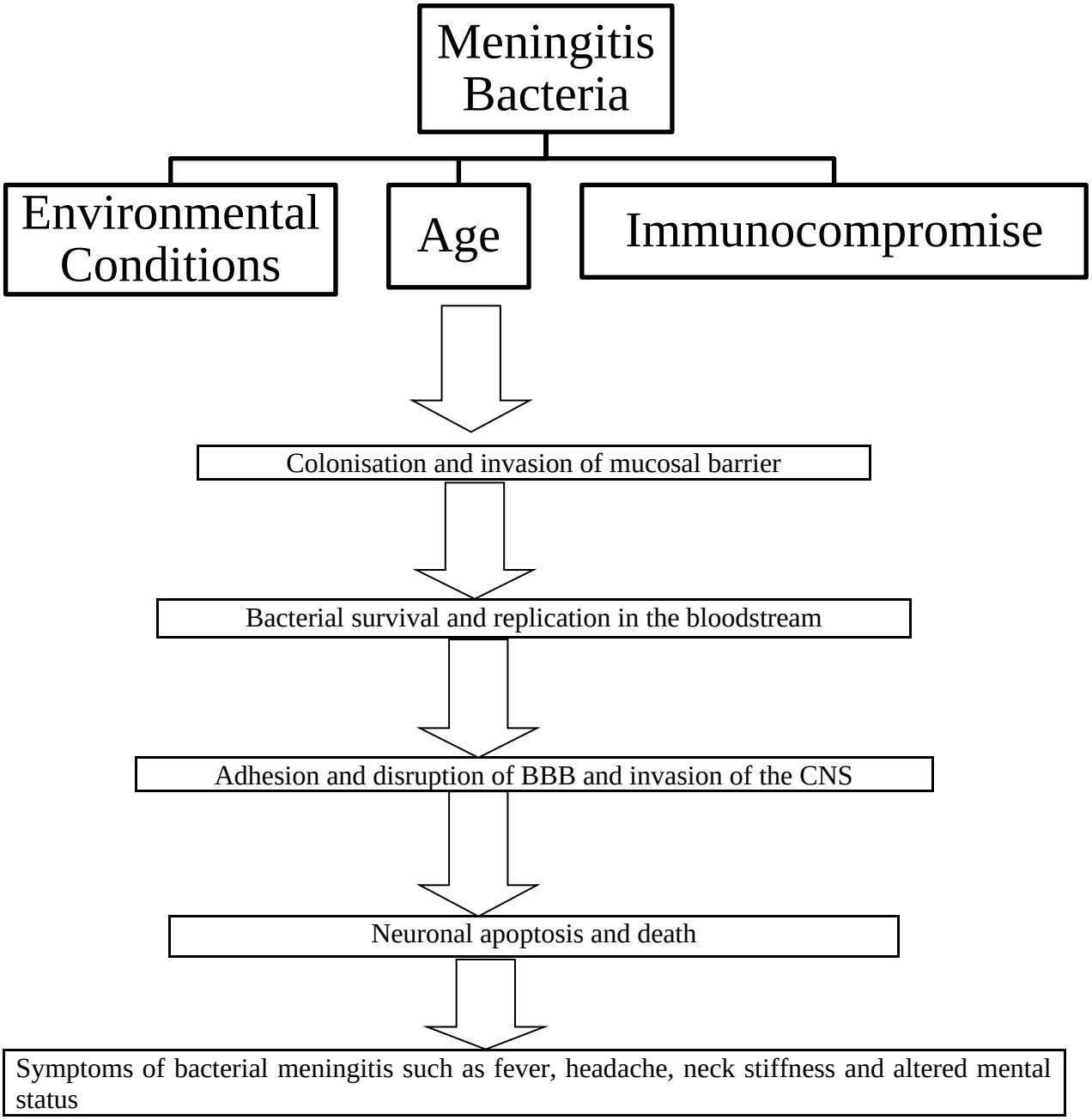

Figure - 1 : Overview of the pathogenic process in bacterial meningitis

By interacting with host receptors, bacteria first attach and penetrate the BBB. Afterward, they break down the BBB's tight junction proteins in order to enter the central nervous system (CNS) and may also use other components. In the meantime, the BBB is disrupted by a multitude of pro-inflammatory cytokines, Matrix metalloproteinases (MMPs) production, and free radicals. Bacteria have the ability to stimulate immune cells, including resident cells in the central nervous system and recruited neutrophils, increasing their production of pro-inflammatory cytokines, MMPs, and free radicals. Bacterial invasion of the central nervous system (CNS) results in neurocyte and neuronal damage. This is often brought on by bacterial products, an exaggerated inflammatory response, and important signalling pathways. Recent studies have revealed that gut abnormalities have a role in the development of meningitis and that the gut microbiota is one of the significant determinants in individuals with bacterial meningitis. Antibiotics are considered a crucial treatment in the early stages of bacterial meningitis in order to improve survival and lower morbidity. Reducing CNS damage and eliminating bacteria are the main therapy goals. In the central nervous system, the majority of antibiotics does not effectively penetrate the blood brain barrier and exert antimicrobial effects. Additionally, researchers investigate new treatment strategies to enhance the meningitis models used in experiments by adjusting reactive nitrogen species (RNS), blocking caspase or inflammatory factors, coagulant, or complement cascades [41 - 43]. For vaccines, researchers are interested in developing the efficacy of polysaccharide conjugates without serotype replacement or with broad and ideally universal coverage for different bacterial meningitis. Furthermore, the bacteria's released production can still trigger the immune system's reaction, encourage neutrophil invasion, and activate the CNS's resident immune cells, which can cause the death of nerve cells or serious nerve injury sequelae. Therefore, new treatments and more potent medications that can stop or cure bacterial meningitis and lessen nerve damage would be beneficial in lowering morbidity, mortality, and sequelae.

Main Meningitis Bacteria	**Mainly Infected Age Group**	**Vaccine**	**Antibiotic**	**Adjunctive Treatment**	**Reference**
Streptococcus pneumoniae	Children < 5 years; Adults > 50 years	Live attenuated vaccine (Whole-cell vaccine); Inactivated vaccine (Whole-cell vaccine); Subunit vaccine: Polysaccharide vaccine (PPV23), Conjugate vaccine (PCV7/10/13/15), Protein-based vaccine (PcsB,	Penicillin; Macrolides	Magnesium; Efflux pump inhibitors; C5 antibodies; Dexamethasone; Corticosteroids	[44 – 47]

		StkP, PsaA, PspA, PcpA, PhtD, PlyD1, Ply).			
Neisseria meningitis	Children < 5 years Adolescents	Conjugate vaccine (MenACWY, Hib_MenCY-TT, Men A conjugate vaccine, Men C conjugate vaccine); Polysaccharide vaccine (MPSV4); Protein-based vaccine (Multicomponent Men B vaccine, Men B bivalent vaccine)	Penicillin; Ceftriaxone; Ciprofloxacin; Rifampicin	BB-94 (MMP inhibitor); Doxycycline;	[48 - 50]
Group B *Streptococcus*	<3 months	CPS conjugate vaccines (CPS-CRM_{197} GBS conjugate vaccine); Protein-based GBS vaccines (Alpha-like protein, Rib, AlpC); Polysaccharide conjugates vaccine (serotypes Ⅰa, Ⅰb, and Ⅲ)	Penicillin G; Clindamycin; Erythromycin; Fluoroquinolones; Ampicillin; First-, second-, and third-generation cephalosporins; Carbapenems; Vancomycin	Gentamicin; Migration inhibitory factor inhibitor (ISO-1); Insulin; MAPK inhibitors; Brain-derived neurotrophic factors; Hypothermia	[51 - 58]
Streptococcus suis	Adults	Autogenous bacterins; Subunit vaccine (muraminidase-released protein, suilysin, extracellular factor); 6-phosphogluconate-dehydrogenase; SsnA (the cell wall-associated DNase); Subtilisins; Glycoconjugates; Capsular material coupled with botulinum toxin	Penicillin G; Ceftiofur; Amoxicillin; Gentamicin; Florfenicol; Fluoroquinolones	Aluminum hydroxide adjuvant; Imugen®; Rehydragel® and Emulsigen®	[59 - 61]

Escherichia coli K1	<3 months	Mutation of aro A gene; Recombinant ISS gene; Outer membrane protein A ($OmpA_{TM}$, transmembrane domain; $OmpA_{per}$, periplasmic domain; OmpAVac); Capsular polysaccharides	Gentamicin; Ceftriaxone; Penicillin G; Ampicillin; Amoxicillin; Meropenem	Pentoxifylline; Palmitoylethanolamide	[62 - 67]

Table – 1: Treatment options of bacterial meningitis

3. Melatonin

3.1. The Chemical and Physical Characteristics of Melatonin

A derivative of tryptophan, melatonin is a member of the indole heterocyclic molecule class. It is N-acetyl-5-methoxytryptamine, sometimeit is also called pineal hormone. Melatonin has a molecular weight of 232.28 and the chemical formula $C_{13}H_{16}N_2O_2$. Melatonin can effectively penetrate cells and traverse the blood brain barrier because of it is soluble in fat and water. Melatonin production in vertebrates follows a clear circadian cycle; it is active at night (60–200 pg/mL) and repressed during the day (0–20 pg/mL). In humans, melatonin is secreted at a rate of around 29 milligrammes per day.

3.2. The Synthesis and Metabolism of Melatonin

First, it was discovered that the pinealocytes in the pineal gland produce melatonin. Later several researches revealed that melatonin is also synthesised in other organs, with the gut secreting two orders of magnitude more melatonin than the pineal gland. The steps involved in the production of melatonin include methylation, acetylation, decarboxylation, and hydroxylation. Tryptophan hydroxylase converts tryptophan, the original precursor, into 5-hydrpxytryptophan. Next, 5-hydroxytryptophan decarboxylase converts 5-hydrotryptophan into 5-hydroxytryptamine, which is also referred to as serotonin. Next, serotonin N-acetyl transferase acetylates serotonin to produce N-acetylserotonin. N-acetyl-5-methoxytryptamine is the final product of the methylation of N-acetyserotonin [68]. Melatonin metabolism is more complicated than melatonin production, with several routes that involve diverse enzymatic, pseudoenzymatic, and free radical interaction activities [69]. Currently, the primary melatonin metabolism products are 6-hydroxymelatonin, 2-hydroxymelatonin, cyclic 3-hydroxymelatonin, N^1-acetyl-N^2-formyl-5 methoxykynuramine (AFMK), and N^1-acetyl-5-methoxykynuramine (AMK), all of which are crucial in oxidative stress conditions [20]. In the cerebral cortex, kidney, and heart of rats, cytochrome P450 may catabolise melatonin to 6-hydroxymelatonin, which is then conjugated to sulphate to

generate 6-hydroxymelatonin sulphate by enzymatic mechanisms. Melatonin can interact with ONOO−, ·OH, or under UV-B irradiation to generate 6-hydroxymelatonin in addition to enzymatic activities. 6-Hydroxymelatonin can reduce neurotoxicity by preventing lipoperoxidation and the generation of ROS. The formation of 2-hydroxymelatonin occurs when melatonin interacts with reactive oxygen species/ reactive oxygen species (ROS/RNS). It has also been shown that UV-B irradiation can cause melatonin to be converted into 2-hydroxymelatonin in cells. As an oxidative melatonin metabolite, cyclic 3-hydroxymelatonin is a popular biomarker of endogenous ·OH levels. Additionally, it was stated that melatonin's interaction with ONOO− encouraged the production of Cyclic 3-hydroxymelatonin. AFMK can be formed in the interim by cyclic 3-hydroxymelatonin scavenging radicals. Both in vitro and in vivo, the coexistence of AFMK and cyclic 3-hydroxymelatonin was often seen in the melatonin metabolic pathway [70]. AFMK was discovered to be an essential chemical and the source of original creation in the metabolism of melatonin. Initially, it was discovered that melatonin was catalysed by indoleamine 2,3-dioxygenase to make AFMK. Later, it was shown that melatonin interacts with H2O2 to produce AEMK. Later, it was shown that melatonin may be induced by UV irradiation to produce AFMK. Furthermore, arylamineformamidase, hemoperoxidases, or interactions with ROS/RNS may further deformylate AFMK into AMK. Numerous studies show that a variety of creatures, including humans, rodents, plants, unicellular algae, and metazoans, are capable of producing AFMK. In the meanwhile, tissues, particularly the central nervous system, may only metabolise melatonin through AFMK and AMK. For instance, the CSF of meningitis patients had a three-order-of-magnitude greater content of AFMK (13,200 pg/mL) than that of healthy individuals [71]. Another essential location for the production of AFMK is leukocytes. Activated leukocytes exhibited a considerable rise in AFMK levels. AFMK is mostly formed in the mitochondria of cellular organelles. Melatonin can be converted into AFMK by the mitochondrial cytochrome C.

3.3. The Bioavailability of Melatonin

Melatonin is a commonly available health product in the market. It has been discovered in recent decades that humans have far lower melatonin bioavailability than rats. Human sexual differences, the heterogenic nature of cytochrome P450 subtype gene expression, and medication interactions are among the variables that influence melatonin bioavailability. Currently, melatonin is accessible as a 3 mg tablet in the commercial sector. While some people find this dosage helpful in promoting sleep, others may not find it efficient in relieving insomnia and other associated illnesses. For instance, after oral treatment, melatonin has a bioavailability of 16.8 ± 12.7% in females and 8.6 ± 3.9% in males [72]. Following intravenous injection, Fourtillan and colleagues' research revealed that the plasma level of melatonin in men was 165 pg/mL and in females, 200 pg/mL [72]. But after an hour, the melatonin levels in both males and females plummeted to 70 pg/mL, indicating that they were beyond the physiological threshold and were removed by

the liver. These findings revealed that the host's melatonin bioavailability was influenced by both the mode of administration and sexual orientation. However, due to severe irritation, intranasal delivery is not appropriate for clinical perpose. Melatonin starch microspheres were created by Mao et al. through enhanced intranasal delivery [73]. Melatonin's bioavailability and absorption are both significantly enhanced, although patients' circadian cycles are upset. Subsequently, to boost melatonin's absorption in humans, researchers have combined it with other medications. When melatonin and fluvoxamine, a cytochrome P450 inhibitor, are given together, the amounts of melatonin in the blood significantly rise in healthy individuals. Moreover, in human individuals, the combination of melatonin with coffee or vitamin E or vitamin C considerably increases its bioavailability. As a result, it is critical to comprehend the pharmacokinetics of melatonin in the serum, how it interacts with other drugs, and how to modify the dosage for differentpatients.

4. Neuroprotective Properties of Melatonin against Bacterial Meningitis

4.1. The Antibacterial Activity of Melatonin

Currently, early-stage bacterial meningitis mortality is associated with antibiotic therapy. However, antimicrobial resistance is a global issue. Treatment becomes more challenging, in particular, when dual antimicrobial resistance emerges. Furthermore, the BBB is poorly crossed by certain antibiotics, such as vancomycin, which significantly lowers the antibacterial efficacy. Human health is also at risk from antibiotic residue in animal products. The endogenous chemical melatonin has been extensively studied in cells and organisms, but the antibacterial properties of infectious disorders have received less attention. Melatonin has been proven by Tekbas et al. (2008) to suppress the growth of both gram-positive and gram-negative bacteria. The study found that methicillin-resistant *Staphylococcus aureus*, carbapenem-resistant *Acinetobacter baumannii*, carbapenem-resistant *Pseudomonas aeruginosa*, *Staphylococcus aureus* ATCC 29123, and *Pseudomonas aeruginosa* ATCC 27853 are all susceptible to melatonin's bacteriostasis effects. At 24 hours of incubation, the melatonin minimum inhibitory concentrations (MIC) were 250 μg/mL, 125 μg/mL, 125 μg/mL, 250 μg/mL, and 125 μg/mL, in that order. After 48 hours of incubation, the melatonin's MIC values were successively reduced to 250 μg/mL, 125 μg/mL, 125 μg/mL, 250 μg/mL, and 125 μg/mL. Furthermore, it has been discovered that melatonin, even at lower dosages, had a strong antibacterial effect. This effect may be attributed to the decrease in intracellular substrates, which causes bacteria to enter the death phase sooner [74]. For bacteria to proliferate, free iron must be bound. Because melatonin may bind free iron in the cytoplasm, it can inhibit the development of bacteria. Melatonin has a high affinity for metals like iron. Melatonin at 300 μg/mL has been shown by Konar et al. to efficiently inhibit *Candida albicans* via lowering lipid levels. Additionally, it has been reported that melatonin interacts with neutrophil receptors to enhance the formation of neutrophil extracellular traps (NETs), which in turn increases the neutrophils' antibacterial

capacity. This, in turn, helps to clear *S. aureus* and *E. coli* from mice, alleviating bacterial sepsis [75].

4.2. Melatonin and Immune Activation

Usually, the innate immune system is regarded as the first line of defense against invading pathogens. Through processes including complement-mediated phagocytosis and opsonisation of inflammation, the complement system is crucial in the removal of pathogens [37]. In a similar manner, *E. Coli*'s outer membrane protein A may attach to C4bp in order to withstand the bactericidal effect of serum [76]. Brain resident cells, with the exception of monocytes and macrophages, may create complement factors during bacterial infection and inflammation in the central nervous system. This leads to the recruitment of many leukocytes and the inflammatory storm. In certain instances, it was shown that the CSF of C1q and $CR3^{-/-}$ mice included less leukocytes, cytokines, and chemokines than those of WT mice [77]. Acute bacterial meningitis can be effectively treated with complement intervention, such as complement monoclonal antibody, according to a number of recent studies on the disease. Prior research has indicated a correlation between alterations in blood melatonin levels and the complement system. Alzheimer's disease (AD) Aβ deposits are linked to pro-inflammatory factors and complement proteins. Melatonin profoundly suppresses complement 1q and interleukin-1α (IL-1α) expression in the hippocampus of AD mice, which enhances learning and memory [78]. Serum melatonin levels in depression patients are highly correlated with complement 3 or complement 4 levels; nonetheless, a thorough investigation of the precise mechanism is needed. These findings support the theory that melatonin controls the production of complement proteins. But no related research has been done on how melatonin affects complement resistance to bacterial meningitis and other mechanisms. The immune cells' TLRs are able to identify various bacterial pathogen-associated molecular patterns (PAMPs). Activating TLRs is a crucial stage in the meningeal inflammatory response, as it stops the development of bacteria and contributes to tissue damage caused by meningitis [38 - 40]. TLR2, TLR4, and TLR9 are among the TLRs that have a role in the etiology of bacterial meningitis [79]. Lipoteichoic acid is the primary activator of TLR2, while pneumolysin or lipopolysaccharides (LPS) interact with TLR4. Bacterial DNA can interact with TLR9. TLR activation stimulates the MyD88 signalling molecule, which is required to trigger a successful immunological response. Zhang discovered that TLR2 and TLR9 with polymorphism gene were significantly higher in Chinese children with bacterial meningitis (seizures) in clinical tests of blood samples from child patients with meningitis and healthy adults. It is suggested that they may be related with severity and prognosis [80]. TLR2 and TLR4 are essential for controlling host inflammation and preventing pathogen invasion in pneumococcal meningitis. For instance, TLR2/4 double deletion mice had reduced production of antimicrobial peptides, an elevated *S. pneumoniae* burden, and a compromised immune response [81 - 83]. Many researchers now concentrate on finding efficient adjuvant treatments that block the TLR pathway; for example, activin A can

boost microglial cells stimulated by TLR2, TLR4, and TLR9 agonists' phagocytosis of *E. coli* k1 without exacerbating the inflammatory response [84]. Nevertheless, no research has been done on TLR innate signalling in order to investigate the protective mechanisms of melatonin in bacterial meningitis. However, mechanisms by which melatonin protects the liver effectively in hepatic ischemia or reperfusion studies by attenuating the increased level of TLR3, TLR4, and MyD88 protein expression have been thoroughly studied. It was also discovered that melatonin's inhibitory effects on the TLR system's MyD88 signalling pathway were related to the suppression of NF-κB and mitogen-activation protein kinases (MAPKs), which are processes that contribute to the pathogenesis of bacterial meningitis [85 - 87].

4.3. Melatonin and Pro-inflammatory Cytokine

Cells in the central nervous system (CNS) and invasive immune cells from the bloodstream can release pro-inflammatory cytokines in response to bacterial components and replication after a bacterial infection. Pro-inflammatory cytokines were found in the CSF of patients in a research that involved bacterial meningitis. During the early phases of bacterial infection, brain microvascular endothelial cells (BMECs), astrocytes, and microglial cells generate IL-6, IL-1β, and tumour necrosis factor-α (TNF-α) [88]. Numerous adhesion factors on the BMECs might be expressed more often as a result of these early-produced cytokines, and this increases the recruitment of neutrophils into the CSF. Furthermore, severe inflammatory responses brought on by infections are a key component of bacterial meningitis and can lead to both structural and functional brain damage [89]. Numerous pathological investigations have demonstrated that pro-inflammatory cytokine production from activated microglial cells (e.g., IL-1β, IL-6, TNF-α) may facilitate neuronal death in the hippocampus areas [90,91]. Similarly, an overabundance of pro-inflammatory substances may compromise the integrity of the blood-brain barrier and disrupt the bioenergetic or metabolic function of damaged neurones [92]. Experts have recently provided compelling evidence of melatonin's anti-inflammatory qualities in reducing neuronal damage and enhancing the functional recovery of damaged neurones [93 - 95]. By reducing the expression of vascular endothelial growth factor and MMP-9, melatonin has been shown to inhibit the inflammatory response. This prevents the disruption of tight junction proteins, such as Zonula occluding-1 (ZO-1), occluding, and claudin-5, and lessens brain edema that results from BBB dysfunctions [96]. TNF-α, IL-1β, and IL-6 levels were shown to be considerably reduced in adult rats implanted with an acute *Klebsiella pneumonia* meningitis model after melatonin dosage delivery of 100 mg/kg [18]. Subsequently, the research has unequivocally shown that melatonin therapy may effectively prevent microglial activation, lessen inflammatory reactions in the hippocampus, and protect hippocampus neurones from apoptosis [18,95,97]. Nevertheless, melatonin had anti-inflammatory properties but did not lessen neuronal damage when administered after 12 hours in a rabbit model of *Streptococcus pneumonia* or *Escherichia coli* meningitis

[98]. The timing of the melatonin therapy may be the cause of this problem.

4.4. Melatonin and MMPs

Numerous findings using clinical and animal models over the past few years have shown that MMPs are crucial to the development of bacterial meningitis. In addition to cleaving extracellular matrix proteins, MMPs function as endopeptidases and regulate signalling molecules and receptors [99 - 101]. MMPs can be released during bacterial infection by blood-derived leukocytes such as neutrophils, macrophages, and lymphocytes, as well as resident activated cells such as microglia, astrocytes, and neurones [102 - 106]. MMPs break extracellular matrix and nonmatrix proteins under pathophysiological circumstances, and they are important mediators of BBB destruction and modulators of inflammation in the brain in bacterial meningitis [107 - 109]. Upregulation of MMP-9 in human BM has been found in 19 individuals throughout the course of previous years' clinical and experimental investigations [110]. Children with BM also have elevated MMP-8 levels in their CSF [110]. By breaking down collagen, proteoglycan, or basal laminin, MMP-9 can enhance the permeability of the blood-brain barrier, leading to leukocyte extravasation and pathogen invasion [111]. Moreover, MMPs have the ability to cleave and promote the synthesis of inflammatory cytokines and chemokines, which in turn cause hyperinflammatory responses that cause brain injury [112,113]. For instance, infected children with high levels of MMP-9 have been shown to have an increased risk of developing neurological damage, including secondary epilepsy and hearing impairment [114,115]. Numerous adjuvants that target MMPs are now used in clinical trials for meningitis caused by bacteria. Trocade, when used as an adjuvant, can reduce pro-inflammatory variables and mortality, suppress collagenases and gelatinase activity, and lessen CNS damage in baby rats with pneumococcal meningitis. Additionally, MMP-9 expression may be upregulated by antibiotic therapy, and in rats with *Streptococcus pneumonia*, MMP-9 expression may be downregulated by antibiotics including dexamethasone [116]. By controlling MMP gene expression and activity, melatonin treatment preserved the integrity of the blood-brain barrier and prevented neuroinflammation [117,118]. TIMP-1, or tissue inhibitors of metalloproteinase-1, binds to the catalytic domain of MMP in both normal and pathological settings to block MMP-9 activity [111]. Furthermore, exogenous melatonin treatment actually raises TIMP-1 expression through the induction of MAPK pathways, which in turn decreases MMP-9 activity and translation [111]. Increased BBB permeability can arise from disruptions to VE-cadherin, occluding, claudin-5, and ZO-1 caused by MMP-9 release mediated by IL-1β in pericytes [117]. In pericytes, melatonin can protect against IL-1β-induced breakdown of the BBB integrity by upregulating the expression of TIMP-1 gene and downregulating MMP-9 through regulation of the NOTCH3/NF-κB/p65 signalling system [117,119].Melatonin (5 mg/kg) was found to significantly attenuate cerebral MMP-9 activity following brain inflammation in a mouse model of LPS-induced meningitis.

Additionally, pretreatment or cotreatment with melatonin was found to effectively inhibit LPS-induced MMP-9 activation in RAW264.7 and BV2 cells [96]. Melatonin has been shown to cause MMP-9 downregulation by suppressing TNF-α and to modulate the redox-dependent negative regulation of the MMP-2 gene [108, 120]. In the meanwhile, MMPs have a role in neuronal apoptosis and death, and in MMP-9-deficient animals with global ischaemia, the damage to hippocampus neurones was lessened [121]. Several studies suggest that melatonin regulates MMP-9 activity, which in turn inhibits MMP-9 activation. Melatonin may have a strong binding action on the MMP-9 active site. Thus, melatonin may have a primary target in MMP-9 for neuroprotection against brain damage.

4.5. Melatonin and Oxidative Stress

Brain damage is mostly caused by oxidative stress, which includes excessive lipid content, ROS, and RNS [41, 42, 122, 123]. The production of free radicals (ROS, RNS) and the antioxidant response are often balanced in physiological settings. On the other hand, excessive ROS or RNS production or low antioxidant levels under pathological settings might result in oxidative stress [124, 125]. Research on bacterial meningitis in people and experimental animals has demonstrated that ROS, RNS, nitric oxide, and per-oxynitrite govern BBB disintegration and neuronal damage [126, 127]. For instance, by downregulating the expression of tight junction proteins (claudin-5, occludin, ZO-1, and junction adherensive molecular-1), oxidative stress promotes the breakdown of the blood-brain barrier. During pneumococcal meningitis, oxidative stress can also significantly activate MMPs and compromise the integrity of the blood-brain barrier. In group B streptococci meningitis, Leib and colleagues have discovered that ROS is mostly generated by polymorphonuclear leukocytes in the subarachnoid and ventricular regions, cortical arteries, and endothelial cells [128,129]. Additionally, *E. coli* lipopolysaccharides, cytokines (TNF-α and interleukin-1β), and microglia, neurones, and astrocytes all produce a significant amount of reactive oxygen species (ROS) [130–133]. Free radicals or oxidative stress have grown in importance in the development of neuronal damage during bacterial meningitis. Peroxynitrite, for instance, can cause neuronal cell death by inhibiting mitochondrial activity, which depletes NAD^+ and ATP and causes cytotoxicity [134,135]. Phenyl N-t-butylnitrone (PBN), a radical scavenger, stopped group B streptococcal meningitis from injuring the central nervous system in vivo, while NAC, an antioxidant, can lessen neuronal death brought on by pneumococcal meningitis [136]. Furthermore, NAC has been used for a number of years in clinical therapy with just mild side effects. Melatonin has both direct and indirect benefits and is a potent antioxidant and free radical scavenger. Considerable nerve damage is brought on by the excessive generation of ROS and RNS. Melatonin removes ROS such as hydroxyl radicals, peroxyl radicals, hydrogen peroxide, and hypochlorous acid. It also possesses directly nonreceptor-mediated free radical scavenging action [137,138]. Lipid peroxidation is typically thought to be an indicator of oxidative stress [139 - 141]. Pneumococcal meningitis patients'

cerebrospinal fluid (CSF) has higher levels of the lipid peroxidation markers 4-hydroxynonenal and malondialdehyde, both of which lead to the formation of superoxide anion (O_2^-) [142,143]. According to a research [144], melatonin may considerably lower the concentrations of malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE), which can suppress oxidative stress and lipid peroxidation against acute tissue damage. Furthermore, melatonin also inhibits lipoxygenase and nitric oxide synthase [144 - 147]. Inducible Nitric Oxide Synthase (iNOS) is stimulated by bacterial meningitis, which raises NO levels in the brain and causes neurotoxicity [3,148]. Fat By triggering NF-κB signalling cascades in the choroid plexus epithelium, which is a component of the blood–CSF barrier against microbial pathogens and is essential for the brain inflammatory processes involved in bacterial meningitis, a therapy increases the expression of iNOS [149]. In the meanwhile, brain damage brought on by *E. coli* K1 was totally avoided by inhibiting iNOS expression. The accelerated invasion of *E. coli* K1 into human brain microvascular endothelial cells (HBMECs), an in vitro model of the blood-brain barrier, is likewise caused by NO, a significant inflammatory mediator [150]. Melatonin immediately lowers the quantity of nitrite, which are a measure of iNOS expression in microglial cells and the CSF of *Streptococcus pneumonia*-infected rabbits. This minimises neuronal damage [151, 152]. Melatonin can also indirectly contribute to antioxidants via promoting the production of antioxidant-producing enzymes [153,154]. Superoxide dismutase (SOD), MnSOD, CuZnSOD, glutathione peroxidase, glutathione reductase, and catalase are just a few of the antioxidative enzymes that melatonin has been proven to boost in recent years, according to a number of animal studies on the hormone [145,155]. For instance, CAT may detoxify H_2O_2, while SOD can catalyse the breakdown of superoxide in H_2O_2 and oxygen molecules [145]. In order to neutralise the free radical, lipid peroxidation produces reactive oxygen species (ROS), which is linked to the activity of SOD in meningitis patients [41]. In a rat model of bacterial meningitis, pre-treatment with SOD mimetics might reduce cerebral oedema, intracranial pressure, and the number of leukocytes in the CSF [156]. In a research involving rabbits infected with *Streptococcus pneumonia*, melatonin was found to greatly boost SOD activity and lower nitrite concentrations in order to help the animals survive oxidative stress [98]. Meningitis patients had much lower amounts of glutathione in their CSF, which increases the likelihood of oxidative stress and severe neurological dysfunction [98,157,158]. By inducing γ-glutamylcysteine synthase, melatonin can elevate intracellular GSH levels and shield the neurological system from oxidative injury [159].

4.6. Melatonin and Mitochondrial Dysfunction

Numerous investigations have shown that mitochondrial dysfunction has a similar role in the bacterial meningitis pathogenesis [127, 160, 161]. In order to produce energy and preserve cellular homeostasis, the mitochondrion typically plays a significant role in aerobic metabolism [162,163]. It is commonly recognised that brain neurones are

more vulnerable to a decrease in energy metabolism due to their high metabolic rate and abundance of mitochondria [126]. The creation of ATP, oxidative stress, calcium homeostasis, and apoptosis are only a few of the numerous biochemical processes in the brain that are controlled by mitochondria [161]. In the epidemiological study, around half of the patients who had bacterial meningitis showed signs of brain oxidative metabolism impairment, which suggests mitochondrial malfunction [127]. For instance, by measuring the cerebral interstitial lactate/pyruvate (LP) ratio in patients with severe streptococcus meningitis, the study was able to record data that can reflect the cerebral cytoplasmic redox state; an increase in the LP ratio denotes impaired cerebral oxidative metabolism, which is attributed to mitochondrial dysfunction [126]. Then, oxidative phosphorylation—which is dependent on a number of respiratory enzyme complexes found in the inner mitochondrial membrane—is used to produce cell energy [126]. Experimental research has shown that pneumococcal meningitis can disrupt the brain's mitochondrial chain complex I, impairing energy metabolism and promoting the pathogenesis [164]. Actually, abnormalities in the mitochondrial chain brought on by excessive ROS production in bacterial meningitis might hinder oxidative phosphorylation, which encourages the creation of ATP and more ROS [165]. Apoptosis-inducing components that carry out the caspase-independent route have been shown to be released into the cytoplasm when ROS levels rise to a point where mitochondrial malfunction is reached [166]. Moreover, in animal models of pneumococcal meningitis, a higher concentration of polymorphonuclear leukocytes might enhance the release of pro-apoptotic substances into the cytosol, such as cytochrome c from mitochondria, which triggers caspase-3 cleavage and neuronal apoptosis [167,168]. Therefore, substances or medications those are able to preserve mitochondrial function while blocking related apoptotic signalling pathways will be useful in the fight against bacterial meningitis. Because of the deposition of melatonin at large quantities on mitochondria in pathological circumstances, mitochondria are considered a major target of melatonin [169]. By scavenging free radicals, controlling the electron transport chain, and boosting antioxidase activities, melatonin can alleviate mitochondrial dysfunction. Melatonin has been shown in both in vivo and in vitro trials to mitigate mitochondrial dysfunction in sepsis and shield mitochondria from oxidative damage by scavenging free radicals [170]. By enhancing the electron transport chain's activity, enhancing the synthesis of ATP, reducing calcium excess, minimising ER stress, controlling the expression of mitochondrial genes, and averting mitochondrial apoptosis, melatonin also plays a vital role in safeguarding mitochondria [171]. Research has demonstrated that, under normal physiological settings, melatonin may interact with complexes I and IV of the mitochondrial electron transport chain to boost electron flow, which in turn increases ATP synthesis and preserves mitochondrial homeostasis [172 - 174]. Furthermore, melatonin boosts the production of GSH to strengthen the mitochondrial defence system [175]. Melatonin can also boost brain mitochondria's

NADH dehydrogenase activity to protect against neurotoxicants [176,177]. Numerous investigations on neurological damage have shown that melatonin has a protective effect against apoptosis [166]. Melatonin has been shown to reduce apoptosis by either upregulating pro-apoptotic proteins like Bax or downregulating anti-apoptotic proteins like B-cell lymphoma-2 (Bcl-2) [178]. For example, pre-treatment with melatonin can cause overexpression of Bcl-2 and prevent the release of Cyt C or caspase 3 in the presence of oxidative stress [178]. Additionally, melatonin promotes Bax's translocation into the mitochondria, which lowers the propensity to undergo apoptosis [178]. Studies on melatonin's ability to reduce mitochondrial damage in bacterial meningitis are scarce, nevertheless. Therefore, it is worthwhile to investigate melatonin's many methods or roles in order to safeguard mitochondria from malfunction brought on by oxidative stress or other diseases.

4.7. Melatonin and Signaling Pathways

Numerous investigations have demonstrated the involvement of many key intracellular signalling pathways, including the mitogen-activation protein kinase (MAPK) route, phosphoinositide 3-kinase (PI3K)/Akt system, and nuclear factor kappa B (NF-κB) pathway, in the pathogenesis of bacterial meningitis. The development of the bacterial meningitis process is aided by these signalling pathways. For example, most bacteria can trigger the NF-κB pathway by phosphorylating serine residues on the IκB proteins once the pathogens have invaded the BBB. This causes a rise in inflammatory factors, chemokines, bacterial invasion of BMECs, and polymorphonuclear (PMN) migration across the BBB. To promote bacterial invasion and PMN transmigration across the BBB, for instance, the IbeA protein of E. coli K1 interacted with vimentin of BMEC and stimulated NF-κB and extracellular signal-related kinases 1/2 (ERK1/2) activation [179,180]. Concurrently, it has been revealed that the NF-κB pathway and the PI3K/Akt/mammalian target of rapamycin (mTOR) signalling pathway are engaged in suppressing autophagy to raise the intracellular survival rate of bacteria in *E. coli* K1 meningitis [181]. By interacting with the epidermal growth factor receptor, Streptococcus Suis serotype 2 (SS2) may trigger the NF-κB and MAPK-ERK1/2 pathways in hBMEC, which in turn promotes the release of proinflammatory cytokines and chemokines [182]. We now have more options for treating or preventing bacterial meningitis thanks to this data. It has been shown in previous years that brain-derived neurotrophic factor (BDNF) is critical for both anti-inflammatory and anti-apoptotic effects in CNS illnesses. By controlling the NF-κB pathway and the PI3K/Akt/mTOR signalling pathway, BDNF supplementation can substantially decrease inflammation and hippocampus apoptosis in the rat model of pneumococcal meningitis [181]. In vitro neuroinflammation has been efficiently inhibited by signalling pathway inhibitors, such as BAY-11072 (NF-κB inhibitor), CAY10657 (MAPK inhibitor), and U0126 (MAPK inhibitor), which have been utilised in cases of bacterial meningitis. MyD88/NF-κ B signalling has been linked to neurological damage in bacterial meningitis [96], and melatonin suppresses NF-κ B-driven

signalling in LPS-stimulated RAW 264.7 and BV2 cells to provide protective and anti-inflammatory effects. Furthermore, melatonin effectively inhibits proMMP9 activation and post-inflammatory NF-κ B translocation after LPS-induced meningitis [183]. Likewise, certain research has indicated the significance of the PI3K/Akt signalling system in mitigating neuronal death and enhancing neuronal survival [184]. Melatonin can also promote cellular survival and prevent neuronal death. In rodent studies, melatonin administration decreased p53 phosphorylation through the PI3K/Akt pathway, hence reducing brain apoptosis [85]. In the meanwhile, melatonin boosts cellular survival via survival kinases both in vivo and in vitro and controls the expression of brain and muscle Arnt-like protein 1 (Bmal 1) via the PI3K/Akt pathway [185]. Therefore, melatonin may be considered a unique approach for the treatment and prevention of bacterial meningitis that targets the main signalling route.

4.8. Other Functions of Melatonin in Bacterial Meningitis

In order for an infection to progress, bacterial adhesion must first connect with surface adhesion receptors particular to the host in order to take up nutrients, which in turn promotes bacterial invasion and immune evasion. The mucosal barrier and the blood-brain barrier (BBB) are the two natural defences against meningitis bacteria before they enter the central nervous system. Meningitis bacteria can attach to surface receptors of barriers to invade the central nervous system (CNS) by using adhesion or other bacterial virulence factors. For instance, by focussing on CD147 receptors on BMEC, type IV pili can help N. meningitides adhere to the BBB [186]. We discovered that OmpA and IbeA in APEC TW-XM (isolated from duck) could, respectively, increase the expression of gp96 and caspr1 receptors. They could also promote bacterial adherence and compromise the integrity of the blood-brain barrier by triggering the focal adhesion kinase (FAK) pathway. Next, we discovered that melatonin can lower OmpA and IbeA expression, which lowers APEC TW-XM adhesion and invasion. Many researchers concentrate on investigating how bacteria attach to host receptors during bacterial infection. Few research, nonetheless, have looked at the methods melatonin uses to influence the way meningitis bacteria and host receptors interact. Therefore, it might be a novel and practical target with a wide range for the treatment or prevention of meningitis bacteria. After that, the gut microbiota offers defence against external infections. In order to fight off infections, commensal microorganisms in the gut can secrete bacteriocins, control metabolism and immunity, and make use of nutrition depletion processes. Numerous researches on infectious disorders have demonstrated that pathogens and cytokine-induced dysbiosis in the stomach led to gut dysbiosis and subsequent pathogen colonisation. Furthermore, it has been shown that antibiotic therapy mediates microbiota degradation and increases vulnerability to bacterial meningitis in immunocompromised hosts. It has been documented that commensal bacteria in Listeria monocytogenes meningitis can reduce bacterial adherence. In particular, commensal bacteria's clostridiales showed

antibacterial activity in vitro and increased resistance against L. monocytogenes in germ free mice. These investigations suggested a tight relationship between the illness process and the gut flora [187]. Melatonin may be able to balance the gut flora and treat a number of illnesses, according to many studies. Ren and associates discovered that by altering the intestinal microbiota in weanling mice, melatonin administration might reduce intestinal ETEC infection and relieve weanling stress. In the meanwhile, this study also showed that melatonin was ineffective in reducing weanling stress and preventing ETEC infection in both germ free and antibiotic treated weanling mice [14]. It has been proposed that melatonin may modulate the gut microbiota to mitigate illness. Dysfunction of the gastrointestinal system is a common symptom in the spinal cord injury (SCI) mice model, and changes to the gut microbiota may have an impact on the course of the disease. It has been shown that melatonin therapy can control the makeup of the intestinal microbiota (including an increase in Lactobacillus and Lactobacillales and a decrease in Clostiddiales) in addition to improving some of the primary pathologies of SCI. In a model of intestinal dysbiosis in mice brought on by antibiotic therapy, the neuroprotective effect of melatonin on SCI was markedly attenuated [188]. Few researches have been conducted to far on how melatonin affects gut microorganisms and how it might prevent or cure bacterial meningitis. Our investigation revealed that melatonin might shield Institute of Cancer Research (ICR) mice against APEC TW-XM-induced bacterial meningitis by preserving their gut microbiota. Additionally, APEC TW-XM can cause gut dysbiosis. After injecting melatonin intraperitoneally, we observed that while it could keep the gut microbiome in a balanced state by promoting the growth of Lactobacillus, Parabacteroides, and Alistipes and reducing the number of Strenotrophomonas, it was no longer able to prevent antibiotic-treated ICR mice (unpublished data). Thus, one may consider intestinal microbes to be melatonin's target. By promoting gut dysbiosis, melatonin may improve host metabolism and increase resistance to infections, as well as lessen nerve damage in cases of bacterial meningitis.

5. DISCUSSION AND CONCLUSION

The breakdown of the blood-brain barrier, exaggerated inflammatory reactions, and death of nerve cells are associated with the consequences of bacterial meningitis. Bacterial meningitis remains surprisingly causes substantial morbidity and death among children, elderly patients, and immuno-compromised individuals, despite advancements in antibiotic treatment and vaccine research. The variety of infections and significant nerve damage make bacterial meningitis the hardest to avoid and cure. However, vaccine and antibiotic resistance limitations make it more difficult to prevent and cure bacterial meningitis and make it impossible to promptly and effectively shield brain tissue from harm. Treatment for bacterial meningitis is further complicated by the BBB's ineffectiveness in allowing certain antibiotics or macromolecular medications to enter the brain. The therapeutic effects of melatonin on neurological disorders have been well shown. Melatonin's chemical and biological properties mostly determine these

actions. The majority of research conducted in the past several years have shown that high solubility melatonin, which mostly exits the pineal gland and crosses the blood-brain barrier, is a functionally varied molecule that affects immunological response, physiological control, and neuroprotective activity [189,190]. We have demonstrated in this review the significant roles that melatonin plays in scavenging free radicals, regulating the immune system, and acting as an antioxidant. Moreover, melatonin has been the subject of several clinical investigations on neuroprotection in a variety of neurological conditions. For instance, it has been shown that a 20 mg melatonin supplement might lower blood inflammation and improve the prognosis of sepsis-affected neonates [191]. Furthermore, melatonin applied five times a day at a dose of 10 mg/kg may lessen the incidence of new epilepsy in babies as well as brain abnormalities. By lowering MDA, melatonin supplements at a dose of 5 mg per day have the potential to improve the quality of life for 102 people with multiple sclerosis. Thus, these findings have a favourable impact on melatonin's widespread usage [192]. Melatonin has not yet been the subject of any clinical trials for the prevention or treatment of meningitis in humans. According to research on the CSF of meningitis patients, N^1-acetyl-N^2-formyl-5-methoxykynuramine (AFMK) levels were impressively high in the presence of the melatonin metabolite, which was intended to reduce the severity of the inflammatory process by scavenging reactive oxygen species [71]. Therefore, it is widely accepted that the rise in AFMK concentration observed in meningitis due to melatonin metabolite may be a natural reaction intended to prevent brain tissue damage [71]. Melatonin and its metabolites have been shown in vivo or in vitro investigations to have the capacity to pass the blood-brain barrier into the central nervous system (CNS), which protects nerve cells from damage and stimulates neuritogenesis [98]. The effective dose of melatonin for neuroprotection may vary owing to bacterial meningitis produced by different infections, even if there are currently no negative effects of melatonin at different doses on the mouse meningitis model. Melatonin was administered as an adjuvant therapy at a dosage of 1.67 mg/kg 12 hours after infection in a rabbit Streptococcus pneumoniae meningitis model. This treatment exhibited anti-inflammatory effects, but it did not reduce neuronal damage. Furthermore, at a dosage of 100 mg/kg, melatonin successfully attenuated the inflammatory response, microglial activation, and the number of apoptotic neurones in the rat *Klebsiella pneumonia* meningitis model [18]. We must take into account the patient's age, autoimmunity, and kind of bacteria when determining the appropriate dosage, stage at which to supplement, method, and duration of melatonin supplementation. Additionally, we must think about the safety of melatonin in the event that future bacterial meningitis clinical studies use it. The goal is to increase the function of melatonin in meningitis caused by bacteria. Therefore, more clinical research is required to determine the safety and efficacious therapeutic approaches of melatonin for patients with bacterial meningitis. In summary, it has been discovered that melatonin protects against bacterial meningitis through a number of

ways. Numerous investigations have indicated that melatonin appears to have great promise. However, further research is needed to debate and create recommendations for the therapeutic application of melatonin for people suffering from bacterial meningitis, whether it is to prevent or treat the condition.

Abbreviations

BM	Bacterial meningitis
CNS	Central nervous system
BBB	Blood Brain Barrier
GBS	Group B Streptococcus
HIV	Human immunodeficiency virus
CM	Cryptococcal meningitis
HiB	Haemophilus influenzae
MIC	Minimum inhibitory concentration
TNF-α	Tumor necrosis factor-α
TLR	Toll-like receptors
IL-1α	Interleukin-1α
NLRs	Nod-like receptors
LPS	Lipopolysaccharides
PAMPs	Pathogen-associated molecular patterns
NF-κB	Nuclear factor kappa B
MAPK	Mitogen-activation protein kinase
PBN	Phenyl N-t-butylnitrone
4-HNE	4-Hydroxynonenal
MDA	Malondialdehyde
iNOS	inducible Nitric Oxide Synthase
HBMEC	Human Brain Microvascular Endothelial Cell
IL-6	Interleukin-6
ROS	Reactive oxygen species
RNS	Reactive nitrogen species
MMPs	Matrix metalloproteinases
CSF	Cerebrospinal fluid
BMECs	Brain microvascular endothelial cells
AJs	Adherens junctions
TJs	Tight junctions
ZO-1	Zonula occluding-1
CSF	Cerebrospinal fluid
SOD	Superoxide dismutase
PMN	Polymorphonuclear
mTOR	Mammalian target of rapamycin
Bmal 1	Brain and muscle Arnt-like protein 1
FAK	Focal Adhesion Kinase
LP	Lactate/pyruvate
MyD88	Myeloid differentiation factor 88
ERK1/2	Extracellular signal-related kinases 1/2
EGFR	Epidermal growth factor receptor
AFMK	N^1-acetyl-N^2-formyl-5-methoxykynuramine
PCV	Pneumococcal conjugate vaccines
PPV	Pneumococcal polysaccharide vaccine
PspA	Pneumococcal surface protein
Ply	Pneumolysin

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