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REVIEW

Melatonin Exerts Positive Effects on Sepsis Through Various Beneficial Mechanisms

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Abstract: In recent years, our understanding of sepsis has greatly advanced. However, due to the complex pathological and physiological mechanisms of sepsis, the mechanisms of sepsis are currently not fully elucidated, and it is difficult to translate the research results into specific sepsis treatment methods. Melatonin possesses broad anti-inflammatory, antioxidant, and immune-regulatory properties, making it a promising therapeutic agent for sepsis. In recent years, further research has deepened our understanding of the potential mechanisms and application prospects of melatonin in sepsis. The mechanisms underlying the protective effects of melatonin in sepsis are multifaceted. In this review, based on a substantial body of clinical trials and animal research findings, we first highlighted the significance of melatonin as an important biomarker for disease progression and prognosis in sepsis. We also described the extensive regulatory mechanisms of melatonin in sepsis-induced organ damage. In addition to its broad anti-inflammatory, and anti-oxidant effects, melatonin exerts positive effects by regulating metabolic disorders, hemodynamics, cell autophagy, cellular ion channels, endothelial cell permeability, ferroptosis and other complex pathological mechanisms. Furthermore, as a safe exogenous supplement with low toxicity, melatonin demonstrates positive synergistic effects with other anti-sepsis agents. In the face of the urgent medical challenge of transforming the increasing knowledge of sepsis molecular mechanisms into therapeutic interventions to improve patient prognosis, melatonin seems to be a promising option.

Keywords: melatonin, sepsis, pathological mechanisms, biomarker

Introduction

Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection.[1] A recent global burden of disease report highlights that sepsis is highly prevalent, with nearly 50 million cases worldwide each year.[2] Despite over three decades of research, including more than 200 randomized controlled trials and numerous animal experiments, we do not have a treatment method that can consistently save the lives of sepsis patients.[3–5]

In recent years, the use of certain drugs has been shown to positively impact the prognosis of sepsis. Ulinastatin is a broad-spectrum protease inhibitor that modulates the inflammatory response by inhibiting NF-κB and NLRP3 inflammasome activation, thereby reducing cytokine levels such as TNF-α and IL-1β. It has been demonstrated to improve the APACHE II score and the short-term prognosis of the patients with severe sepsis.[6,7] However, its efficacy varies among patients, and it may not significantly reduce overall mortality. Xuebijing injection, a traditional Chinese medicine, possesses anti-inflammatory and immunomodulatory properties. It effectively reduces pro-inflammatory cytokines and enhances organ function in septic patients.[8,9] However, the optimal dosing and duration of treatment are still unclear. Continuing to explore effective pharmacological agents and their mechanisms of action for the treatment of sepsis is a crucial area of focus in sepsis research.

The development of sepsis is multifaceted, extending beyond the specific infection type and the initial response of the host. It encompasses diverse aspects, including inflammation, coagulation activation, vascular endothelial dysfunction,

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complement system activation, immune suppression, and changes in the microbiome.[10,11] Melatonin (N-acetyl-5-methoxytryptamine) is an endogenous indoleamine widely distributed in plants, unicellular organisms, algae, bacteria, invertebrates, and vertebrates.[12] Its widespread distribution forms an important basis for its protective effects against multiorgan damage.[13,14] Numerous studies have documented the wide-ranging properties of melatonin, including antioxidant, anti-inflammatory, anti-tumor, and anti-aging effects.[15]

This article provides an overview of the protective and therapeutic effects of melatonin in sepsis and emphasizes its potential clinical applications. Firstly, we reviewed the relevant studies on melatonin and the prognosis of sepsis patients in clinical research. Next, we discuss the mechanisms through which melatonin-mediated protection affects inflammatory responses, oxidative-reductive homeostasis (As shown in Figure 1), and the regulation of epithelial cell ion channels and endothelial cell permeability, etc. (As shown in Figure 2). Additionally, we explore the synergistic effects of combining melatonin with other biological agents in the treatment of sepsis in vivo. Overall, we offer insights into the anti-septic effects of melatonin and propose prospective strategies for guiding future melatonin-based sepsis treatments.

Melatonin Has a Protective Effect Against Sepsis Caused by Various Pathogens

Sepsis can be caused by various pathogens, with bacterial infections being the primary cause. However, up to 42% of sepsis patients have negative cultures, indicating that non-bacterial infections are also significant contributors to sepsis development.[16] Melatonin has shown positive therapeutic effects not only in bacterial sepsis but also holds promising potential in the management of viral sepsis. For example, in sepsis caused by the ongoing Covid-19 viral infection, significant differences in the development of sepsis have been observed between patients in the melatonin group and the control group. On the 17th day of symptom onset, 35.5% of patients in the control group (n=76 average age 55.7) developed sepsis, while only 8.5% of patients in the melatonin group (n=82 average age 56.8) did so (P<0.001).[17] In a recent clinical trial, it was found that daily intravenous administration of a 60 mg melatonin formulation improved sepsis patients, reducing their mortality rate to zero and decreasing their hospitalization time by 40%.[18]

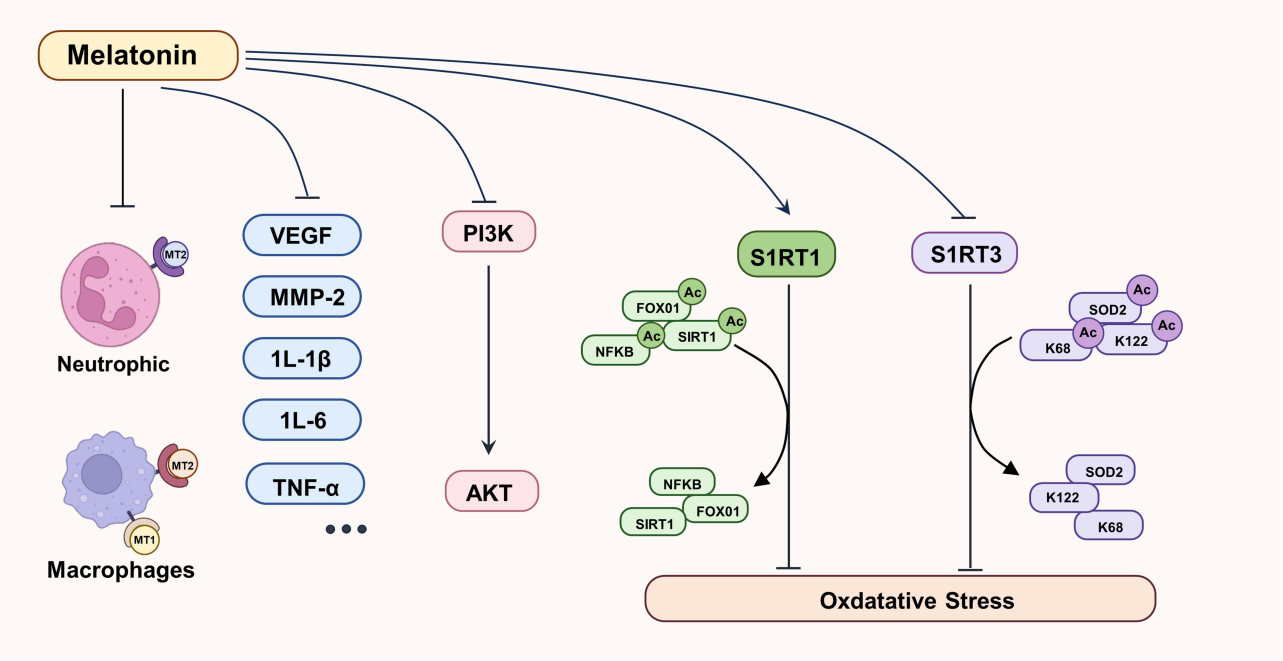

Figure 1 Melatonin can effectively inhibit inflammatory and oxidative stress responses in sepsis.
Abbreviations: MT, Melatonin; VEGF, Vascular Endothelial Growth Factor; MMP-2, Matrix Metallopeptidase-2; IL-1β, Interleukin-1 Beta; IL-6, Interleukin-6; TNF-α, Tumor Necrosis Factor Alpha; PI3K, Phosphoinositol-3 Kinase; AKT, Protein Kinase B; SIRT1, Sirtuin 1; SIRT3, Sirtuin 3; FOXO1, Forkhead Box O1; NFKB, Nuclear Factor Kappa B; SOD2, Superoxide Dismutase 2; Oxidative Stress; Ac, Acetylation; K68, Lysine 68; K122, Lysine 122.

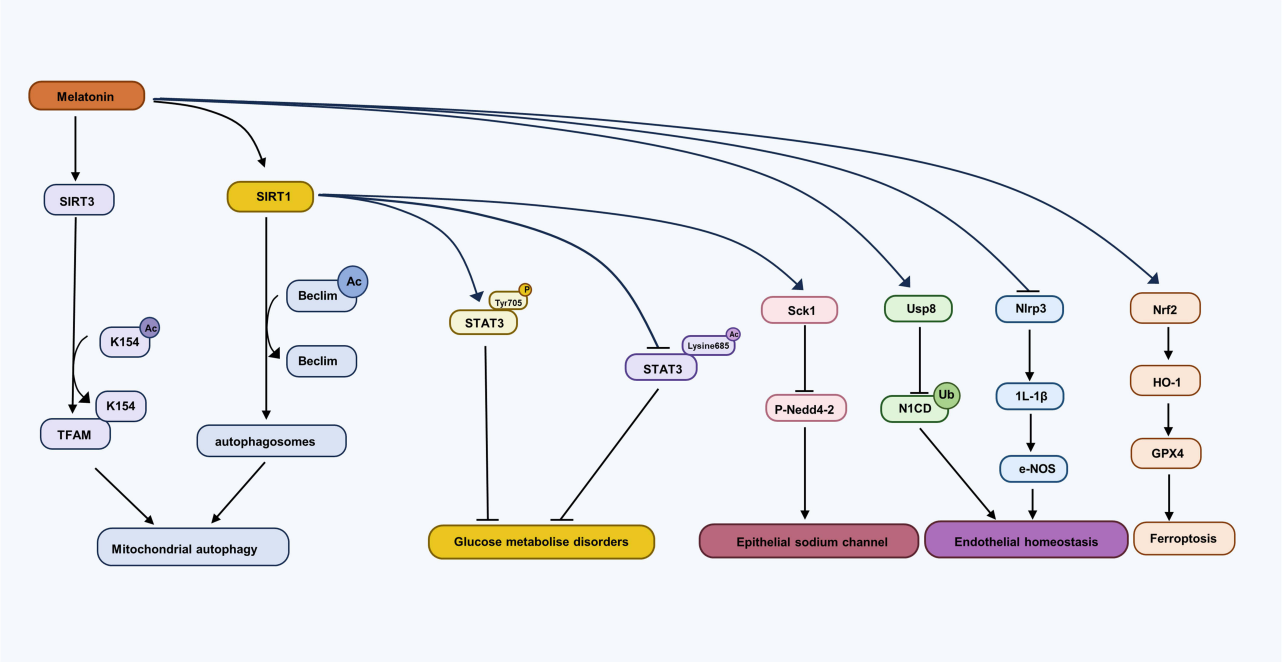

Figure 2 Melatonin can effectively restore damaged cellular homeostasis in sepsis, such as mitochondrial autophagy, impaired glucose metabolism, regulation of epithelial ion channels, and restoration of endothelial cell homeostasis.

Abbreviations: SIRT1, Silent Information Regulator 1; SIRT3, Silent Information Regulator 3; Ac, Acetylation; TFAM, Transcription Factor A, Mitochondrial; STAT3, Signal Transducer and Activator of Transcription 3; Tyr705, Tyrosine 705; P, Phosphorylation; Lysine685, Lysine 685; Sck1, Sterol-Cis-Delta-Isomerase 1; P-Nedd4-2, Pro-Neural Cell Adhesion Molecule 2; Usp8, Ubiquitin Specific Peptidase 8; NICD, Notch Intrinsically Disordered Region; Nlrp3, Nucleotide-Binding Domain, Leucine-Rich Repeat, Pyrin Domain Containing 3; Nrf2, Nuclear Factor Erythroid 2-Related Factor 2; HO-1, Heme Oxygenase-1; GPX4, Glutathione Peroxidase 4.

Another trial involving daily use of 9 mg melatonin in COVID-19 patients showed significant reductions in hospitalization time in the melatonin group (n=24 average age 50.75) ($P<0.05$) compared to the control group (n=20 average age 52.95). Clinical symptoms, CRP levels, and lung involvement were also improved in the melatonin group ($P<0.01$).[19] These studies indicate that melatonin has a broad regulatory effect on sepsis caused by different pathogens, demonstrating promising prospects for its application in the treatment of sepsis.

The Positive Role of Melatonin in Septic Patients in Clinical Practice

Early identification of sepsis is of great significance in providing appropriate and timely treatment to improve prognosis. Clinical studies on late-onset sepsis have shown that compared to the control group, the sepsis group has increased concentrations of melatonin (27.2±3.3 vs 11.4±3.2 pg/mL, p=0.001), which is positively correlated with HsCRP (r=0.952, p=0.001) and the Immature/Total Neutrophil ratio (I/T ratio) (r=0.326, p=0.015). When melatonin is combined with HsCRP in the detection of neonatal sepsis, the sensitivity and specificity are improved to 97.3% and 93.3%, respectively.[20] This indicates that endogenous melatonin levels are significantly increased in late-onset neonatal sepsis and can serve as a biomarker for sepsis, especially when used in conjunction with CRP. In a clinical study, it was found that septic AKI patients had higher levels of plasma melatonin. Additionally, plasma melatonin levels were higher in AKI recovery patients compared to AKI non-recovery patients, and patients with higher plasma melatonin levels recovered faster after AKI.[21] This suggests that melatonin can serve as a potential biomarker for the diagnosis of sepsis and is closely associated with the prognosis of septic patients.

In a controlled clinical trial, vitamin C (group 1: 1000 mg every 6 hours), vitamin E (group 2: 400 IU every 8 hours), and N-acetylcysteine (NAC) (group 3: 600 mg every 12 hours), along with melatonin (group 4: 50 mg once daily), were administered as adjuvant therapies to standard care in adult patients with septic shock and multiple organ dysfunction. This treatment was compared to standard care alone (group 5) over a period of 5 consecutive days. The results indicate that each of these antioxidants, particularly vitamin C and melatonin, significantly reduced the severity of organ

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dysfunction, as assessed by SOFA scores. Furthermore, notable reductions in plasma levels of oxidative stress and pro-inflammatory biomarkers, such as C-reactive protein (CRP), procalcitonin, and lipid peroxidation, were observed in patients receiving melatonin treatment.[22]

The Mechanisms Underlying the Beneficial Effects of Melatonin on Sepsis

Anti-Inflammatory Effects

The excessive expression of pro-inflammatory cytokines is necessary for the clearance of invading pathogens, but an excessive inflammatory response can also result in tissue inflammation and MODS.[23,24] Therefore, early suppression of the inflammatory response and maintaining a balance between pro-inflammatory and anti-inflammatory cytokines are considered key aspects of sepsis treatment.[25] Current research is focused on finding more effective treatment methods to simultaneously reduce inflammatory responses and enhance antimicrobial activity in order to achieve better treatment outcomes.

Many biomarkers used to monitor the clinical condition of patients. One of these biomarkers is vascular endothelial growth factor (VEGF). Elevated levels of VEGF are associated with the severity of sepsis and mortality, suggesting a poorer prognosis.[26] Matrix metalloproteinase-2 (MMP-2) can be considered as a poor prognostic factor because it causes extracellular matrix (ECM) damage during the process of sepsis.[27,28] TGF-β is another effective cytokine during the inflammatory process, influencing the differentiation and function of T cells. Research suggested that TGF-β has anti-inflammatory effects in inflammation and can inhibit MMP activation, thereby limiting ECM damage. In addition to its intervention on the aforementioned pro-inflammatory factors,[29] melatonin intervention can effectively reduce the levels of pro-inflammatory cytokines such as IL-1β, IL-6, TNF-α in sepsis.

One of the important pathways through which melatonin exerts its effects is by activating two types of membrane-specific receptors: MT1 and MT2. By binding to these receptors, melatonin regulates the expression of cytokines and the activation of signaling pathways.[30] Li et al found that in immature mice, macrophages express both MT1 and MT2 receptors, while neutrophils only express MT2 receptors. Other immune cells, including T cells, B cells, natural killer cells, and dendritic cells, do not express MT1 or MT2 receptors. In an in vitro experiment using a mixture of Escherichia coli and Staphylococcus aureus to infect isolated macrophages and neutrophils, the results showed an upregulation of MT2 mRNA levels in neutrophils, while the levels of MT1 and MT2 mRNA in macrophages remained unchanged. These data suggested that melatonin may act on neutrophils after bacterial infection.[31]

There were studies have shown that melatonin can effectively increase the levels of p-Akt in septic myocardial injury, indicating activation of the Akt pathway. Melatonin induced an increase in Bcl-2 expression and a decrease in Bax expression, suggesting it's inhibition of cell apoptosis. However, the PI3K inhibitor LY294002 can abolish all protective effects of melatonin.[32] The melatonin-mediated upregulation of SIRT1 is an important anti-inflammatory mechanism. The upregulation of SIRT1 can lead to the deacetylation of FoxO1 (Forkhead box O1), p53, and NF-κB, thereby inhibiting oxidative stress, cell apoptosis, and inflammatory responses, and reducing the expression levels of inflammatory factors.[33–36] Furthermore, melatonin can inhibit inflammatory responses in sepsis through various mechanisms, such as inhibiting the release of extracellular histones and directly blocking the NLRP3 inflammasome activation induced by histones.[37]

Antioxidant Effects

The enhanced generation of reactive oxygen species (ROS) is associated with the pathogenesis of MODS in sepsis.[38,39] Under normal physiological conditions, the production of ROS is balanced to maintain cellular activities.[40] However, excessive production of ROS can deplete many endogenous antioxidant systems, including superoxide dismutase (SOD) and catalase (CAT), and may lead to cell damage.[41] In sepsis-induced injury models, melatonin has been shown to effectively reduce the levels of malondialdehyde (MDA), myeloperoxidase (MPO), total oxidant status (TOS), and oxidative stress index (OSI). Additionally, melatonin increased the expression of SOD, glutathione (GSH), CAT, and glutathione peroxidase (GPx). These effects indicated that melatonin can attenuate oxidative stress and enhance antioxidant defense mechanisms in sepsis.[42]

Previously, it has been demonstrated that NO (nitric oxide) produced by iNOS is associated with the pathogenesis of organ dysfunction induced by endotoxins.[43–45] NO is primarily involved in maintaining physiological homeostasis. However, due to its free radical nature, NO can rapidly react with ROS, leading to the formation of high-energy oxidant peroxynitrite. This peroxynitrite is considered to be the cellular toxic potential of NO, causing oxidative stress and tissue damage.[46] Melatonin can reverse gastrointestinal dysfunction in septic mice. This beneficial effect of melatonin is associated with reduced lipid peroxidation, decreased transcription and expression of iNOS, and reduced production of nitrites in the intestinal tissue of septic mice. It also inhibits the activation of MAPK and NF-kappaB.[47]

Another potential mechanisms underlying the antioxidant action of melatonin is its upregulating effect on Sirtuins (SIRTs).[48] SIRTs regulate various physiological functions, from energy metabolism to stress responses, and they also exhibit significant antioxidant activity, primarily through their deacetylase and severe antioxidant enzyme activation. Melatonin can trigger the deacetylation of SOD2, increasing its activity and thereby reducing oxidative stress. However, this improvement can be blocked by the selective inhibitor of SIRT3, 3-TYP.[36]

As the powerhouse of the cell,[49] mitochondria play a crucial role in various aspects of cell signaling, intracellular calcium homeostasis, gene expression, as well as processes involving cell apoptosis, necrosis, ferroptosis, and autophagy.[50] Mitochondrial dynamics, mitophagy, and mitochondrial redox regulation are three key mechanisms that promote mitochondrial quality control by maintaining a balance between fission and fusion and by determining cellular fate and overall homeostasis to eliminate unhealthy mitochondria.[51] Excessive oxidative stress can lead to impaired mitochondrial quality control. The mitochondrial antioxidant enzyme SOD2 plays a crucial role in clearing free radicals by converting them into hydrogen peroxide and water.[52] Activation of SIRT3 can alleviate sepsis-induced acute lung injury (ALI) by improving mitochondrial bioenergetics and redox homeostasis.[53] However, reduced expression and activity of SIRT3 may lead to SOD2 inactivation through enhanced acetylation at K68 and K122 sites of SOD2.[54] In sepsis-induced lung injury, RNA sequencing was performed to analyze the differentially expressed genes (DEGs) in the lung tissues of septic mice and septic mice with melatonin intervention. The enrichment analysis of these DEGs indicated their association with mitochondrial fission, mitochondrial fusion, and oxidative stress. Melatonin can shift the dynamic processes of mitochondria from fission to fusion and inhibit mitochondrial autophagy and fatty acid oxidation in lung epithelial cells treated with LPS, both in vitro and in vivo. However, the protective effect of melatonin in acute lung injury was abolished by SIRT3 inhibition. Mechanistically, melatonin increased the activity and expression of SIRT3, further promoting the deacetylation of SOD2 at K122 and K68 sites.[55]

Regulating Metabolic Disorders

As a highly lethal disease, sepsis can induce numerous severe complications, including metabolic disturbances characterized by reduced food intake, increased energy expenditure, and impaired glucose homeostasis.[56] Sepsis commonly causes significant hyperglycemia and insulin resistance, primarily due to enhanced hepatic gluconeogenesis.[57]

In the liver of septic rats, the expression of glucose 6-phosphatase (G6Pase) and phosphoenolpyruvate carboxykinase (PEPCK), which are two crucial rate-limiting enzymes involved in gluconeogenesis, was significantly increased. Additional, the septic rats are characterized by significant increases in blood glucose and serum insulin levels, accompanied with enhanced gluconeogenesis and glucose intolerance, and the reduced insulin sensitivity.[35] Previous studies have confirmed the intricate and complex relationship between melatonin and glucose metabolism.[56,58] The signal transducer and activator of transcription 3 ((STAT3) are widely involved in various key cellular processes, especially in liver glycolipid metabolism.[59,60] The phosphorylation and deacetylation of STAT3 mediated by SIRT1 play a crucial metabolic regulatory role under septic conditions.[61–63] The upregulation of Sirt1 by melatonin has been widely confirmed.[64–66] Melatonin-induced SIRT1 expression partially restored phosphorylation of STAT3 at Tyr705, accompanied by the downregulation of lysine 685 acetylation. Furthermore, inhibition experiments using the specific inhibitor EX527 suggested that SIRT1 activity is necessary for the anti-inflammatory and anti-hyperglycemic effects of melatonin.[35]

Regulating Hemodynamics

Disseminated intravascular coagulation (DIC) is a common pathological phenomenon in the systemic inflammatory response of the body to infection, and it is a strong predictor of mortality in severe sepsis patients.[67,68] The characteristics of DIC include systemic coagulation activation, simultaneous loss of compensatory mechanisms such as fibrinolysis and anticoagulant proteins, leading to increased microvascular thrombosis formation and a tendency for bleeding. In septic patients and animal models of endotoxemia, fibrin deposition in the blood vessels caused by DIC may also result in red blood cell membrane damage, leading to the release of hemoglobin.[69]

A clinical trial targeting sepsis in newborns has provided initial evidence of the impact of melatonin on platelet count during sepsis. Compared to baseline values and untreated septic newborns, septic infants treated with melatonin showed a significant increase in platelet count at 24 and 48 hours after melatonin administration.[70]

The Regulation on Epithelial Sodium Channels

In most patients with ARDS, the ability to clear excessive alveolar fluid (AFC) is impaired, and the reduction in AFC is associated with higher mortality rates.[71] Epithelial sodium channels (ENaC) are heteromeric trimeric proteins that play a crucial role in reducing pulmonary edema and promoting AFC.[72]

The clearance rate of alveolar fluid is associated with active translocation of Na+ across the alveolar epithelium via apical epithelial sodium channels (ENaC) and basolateral Na+-K+-ATPase. ENaC is composed of three subunits and is located in the apical membrane of alveolar epithelial cells. The α subunit is the essential subunit for the formation of functional ENaC, while the β and γ subunits enhance the activity of the channel. The transport of Na+ creates an osmotic gradient that drives water reabsorption.[73] Therefore, ENaC is considered a rate-limiting factor for AFC in acute lung injury.

All subtypes of glucocorticoid regulated kinase (SGK) have been shown to promote ENaC activity, with SGK1 being the most potent stimulator of ENaC activity. Nedd4-2 is an E3 ubiquitin ligase that interacts with ENaC and promotes its ubiquitination, leading to the internalization and degradation of ENaC. However, SGK1 can phosphorylate neural precursor cell expressed developmentally downregulated 4-like (Nedd4-2) and inhibit its activity, thereby reducing the ubiquitination of ENaC. Wang et al found that melatonin increased the protein expression of α-ENaC and SIRT1 in lung tissue and in vitro. Additionally, melatonin improved the expression of SGK1 and inhibited the decreased expression of p-Nedd4-2 induced by sepsis.[74] The effect of melatonin was abolished by the SIRT1 inhibitor EX527. These results suggest that melatonin may upregulate ENaC expression and attenuate sepsis-induced reduction in alveolar fluid clearance (AFC) by activating the SIRT1/SGK1/Nedd4-2 signaling pathway.

Regulate Endothelial Cell Function

The abnormal expression and activity of endothelial nitric oxide synthase (eNOS) contribute to the pathogenesis of vascular dysfunction in sepsis.[75,76] The NLRP3 inflammasome is involved in vascular dilation and endothelial dysfunction during the early stages of sepsis by inhibiting the activity of eNOS.[76] In the mesenteric arteries of mice with sepsis induced by cecal ligation and puncture (CLP), the expression of eNOS was found to be downregulated. However, when NLRP3 was inhibited using a selective inhibitor called MCC950, the expression of eNOS was significantly upregulated. This suggests that NLRP3 may be responsible for the decreased expression of eNOS observed in late-stage sepsis. Furthermore, the NLRP3 inflammasome is involved in the maturation and release of proinflammatory cytokine IL-1β.[77] Interestingly, IL-1β was found to downregulate the expression of eNOS in human aortic endothelial cells (HAECs) in a time- and concentration-dependent manner. These findings indicate that the NLRP3/IL-1β axis may contribute to the downregulation of eNOS expression through proteasomal degradation pathways. Furthermore, melatonin was found to suppress the NLRP3/IL-1β axis and reduce eNOS proteolysis, resulting in improved endothelium-dependent vasorelaxation.[78]

The LPS can directly cause endothelial cells (ECs) injury, disrupting the cytoskeletal proteins, intercellular connections, and adhesion of ECs, which leads to the increased vascular permeability and fluid extravasation into the extravascular tissue, resulting in edema. Moreover, damaged ECs produce a significant amount of nitric oxide, and

sustained elevation of nitric oxide levels affects the function of vascular smooth muscle, further impairing vascular reactivity. This renders fluid resuscitation and vasopressor therapy ineffective.[79] The Notch1 signaling pathway is a conserved pathway that regulates vascular EC function.[80] When the Notch1 receptor is bound by its ligand, the Notch1 protein is cleaved by specific enzymes into extracellular and intracellular fragments. The intracellular segment region (Notch intracellular domain, NICD) is transported to the nucleus, where it forms a complex with DNA-binding proteins, thereby relieving the inhibition of target genes, particularly Hes1, and allowing them to be transcriptionally activated to fulfill their biological roles. There were studies have shown that LPS, IL-6, and sera from septic patients can inhibit the expression of NICD and its downstream regulator Hes1, thereby impairing endothelial barrier function and inducing endothelial cell (EC) apoptosis through the AKT pathway.[81] NICD is regulated by deubiquitinating enzymes (DUBs), and LPS increases the ubiquitination of NICD.[82,83] Melatonin can significantly increase the expression of ubiquitin-specific proteases 8 (USP8), thereby enhancing the continuous expression of NICD and its downstream signaling molecules by inhibiting NICD ubiquitination.

Regulation of Autophagy

Increasing evidence suggests that autophagy is associated with organ dysfunction induced by sepsis.[84] In sepsis, the activation of autophagy can significantly improve organ damage.[85–87] Recently, the antioxidant properties of melatonin have been acknowledged for their ability to safeguard mitochondria.[88] One potential mechanism underlying positive role of melatonin involves the upregulation of SIRTs.[48] SIRT1 is a conserved nicotinamide adenine dinucleotide (NAD+)-dependent protein deacetylase that is associated with various intracellular signals, such as aging, inflammation, cell apoptosis, and autophagy.[89,90] Melatonin is an effective modulator of SIRT1 in many diseases.[34] In sepsis-induced MODS, the beneficial effects of melatonin also demonstrate a close association with SIRT1.

Increased protein acetylation has been demonstrated to induce autophagy inhibition[91] and mitochondrial damage, while SIRT3, a major mitochondrial deacetylase, is involved in mitochondrial protein deacetylation.[92] Upon translocation into mitochondria, the full-length 44-kD SIRT3 undergoes activation through cleavage, resulting in the formation of a smaller 28-kD SIRT3.[93] In sepsis-induced kidney injury, Melatonin has been shown to significantly enhance the activation of SIRT3 and mitotic flux, thereby exerting a positive protective effect. Specifically, TFAM (Transcription Factor A, Mitochondrial) serves as the primary regulatory factor for mitochondrial function, with its expression being responsible for mtDNA transcription initiation.[94] In the case of impaired lysosomal function, defects in TFAM lead to compromised mitotic flux.[95] Acetylation at the K154 site of TFAM reduces its activity, while SIRT3-induced deacetylation at the K154 site promotes its activity.[96] Overall, Melatonin promotes mitochondrial autophagy by activating SIRT3 and enhancing the activity of TFAM.

Beclin-1 is an important autophagy effector that plays a central role in regulating the initiation and maturation of autophagosomes.[97] The genetic deficiency of Beclin-1 could lead to the inhibition of autophagy, thereby exacerbating the sepsis-induced organ damage.[85] The acetylation of Beclin-1 enhances its interaction with Rubicon (a negative regulator of autophagy), which is an important mechanism for autophagy inhibition.[98] The acetylation status of Beclin-1 is controlled by Sirt1.[99] In septic myocardial tissue, intervention with melatonin can increase the expression level of Sirt1 and inhibit the acetylation of Beclin-1. The inhibition of Sirt1 activity significantly attenuates the effect of melatonin on the deacetylation of Beclin-1. These results suggested that the deacetylation of Beclin-1 mediated by Sirt1 is also an important mechanism by which melatonin regulates autophagy.

Ferroptosis

Ferroptosis is a new form of cell death regulation caused by Fe2+-dependent lipid peroxidation, which was identified in 2012.[100] In recent years, ferroptosis has been extensively confirmed to be involved in the pathological processes of various diseases,[101] ferroptosis is also believed to exacerbate the development of sepsis.[102,103] The levels of the end products of lipid peroxidation, 4-hydroxynonenal (4-HNE) and malondialdehyde (MDA), are considered as biomarkers of ferroptosis. Among the key enzymes regulating the occurrence of ferroptosis, the most well-known is glutathione peroxidase 4 (GPX4). GPX4 expression is negatively correlated with iron-mediated cell death, as GPX4 functions by degrading lipid peroxides.[104] Melatonin can attenuate organ damage through the GPX4-related pathway.[105] Heme

oxygenase-1 (HO-1) is a cellular protective enzyme that plays a crucial role in maintaining redox balance and responds to cellular stress and iron levels.[106] As an upstream molecule of HO-1, nuclear factor erythroid 2-related factor 2 (Nrf2) is also a transcription factor that plays a key role in antioxidant defense.[107] In a sepsis-induced kidney injury model, intervention with melatonin significantly upregulates the expression of Nrf2/HO-1/GPX4, inhibits iron death, and thereby alleviates kidney damage. However, the HO-1 inhibitor Znpp and the Nrf2 inhibitor ML385 partially attenuate the upregulation of GPX4 by melatonin, reducing the inhibitory effect of melatonin on iron death. This suggests that the Nrf2/HO-1/GPX4 pathway may be an important mechanism through which melatonin inhibits iron death.

Synergistic Effects of Other Formulations

The synergistic effects of melatonin with other agents have been extensively studied. Melatonin can interact with various drugs or compounds such as antibiotics, antioxidants, anti-inflammatory drugs, enhancing their effects or producing synergistic effects.

Ascorbic Acid

Ascorbic acid, also known as vitamin C, is an essential micronutrient with potent antioxidant properties.[108] Its administration has a positive effect on improving the prognosis of patients with sepsis.[109–113] The combined application of melatonin and ascorbic acid significantly alleviates sepsis-induced organ injury in male rats. The combination therapy significantly improves cardiac and renal function, as evidenced by decreased levels of CK-MB, cardiac troponin I, creatinine, and urea. Furthermore, this combination therapy effectively modulates key markers of inflammation, cellular injury, oxidative stress, and vascular function, including NO, VEGF, and SIRT1 expression. The combined application demonstrates a more effective protective effect than when these two agents are applied individually.[114] In a sepsis-induced lung injury model, the combined treatment of melatonin and ascorbic acid significantly reduced the levels of TNF-α and IL-1β, and improved the levels of peroxisome proliferator-activated receptor (PPAR), aromatic esterase (ARE), and paraoxonase (PON) in lung tissue. Histopathological examination showed reduced edema and lymphocyte infiltration. This suggests that melatonin and ascorbic acid have a beneficial synergistic effect in the treatment of sepsis.[42]

Traditional Antibiotics

Both azithromycin and vancomycin are traditional antibiotic used in the treatment of sepsis.[115,116] In experimental animal models of sepsis, both azithromycin and vancomycin were found to effectively reduce sepsis score, increase survival rates, and improve blood routine parameters, blood biochemical parameters, and cardiac function parameters. The combination of melatonin and azithromycin significantly reduces the sepsis score. However, compared to the use of azithromycin alone, it does not have a significant impact on blood biochemical parameters, blood routine parameters, and cardiac function parameters. Additionally, there is no significant difference in the effects of melatonin combined with vancomycin and the use of vancomycin alone on septic mice.[117]

Discussion

In recent years, melatonin has been the subject of extensive research due to its diverse positive regulatory effects and potential therapeutic applications. However, its effectiveness, safety, and potential adverse reactions are critical factors that must be considered in clinical practice, particularly for patients with sepsis. Clinical research on melatonin has made significant progress. Administered 20 mg of melatonin, which significantly improved the clinical prognosis of newborns with purulent infections.[69] Similarly, Abbas et al reported that in patients experiencing early adult purulent toxic shocks, a daily dose of 50 mg of melatonin for five consecutive nights significantly reduced SOFA scores and the need for vasopressor medications.[117] This treatment also decreased the duration of mechanical ventilation and the time on vasopressors, as well as reducing the lengths of ICU and hospital stays; however, no significant differences were observed in 28-day mortality rates. Furthermore, a single-center study suggested that the daily use of 10 mg of melatonin may help reduce the incidence of purulent infections and the mortality rate among patients with COVID-19.[17]

Melatonin is generally considered safe for short-term use in adults, presenting minimal risk of dependency or significant side effects. Long-term use has been investigated in certain populations, revealing no major adverse effects.

Nevertheless, its safety profile in specific groups, including pregnant women, breastfeeding mothers, and children, remains uncertain due to a lack of comprehensive research. Currently, there is no evidence of serious adverse reactions, such as hepatotoxicity and nephrotoxicity; however, potential risks including drowsiness, headache, and exacerbation of depression may arise in certain patients with specific conditions, such as mental and psychological disorders, or autoimmune diseases. Consequently, the use of melatonin in patients with sepsis must take into account the individual circumstances of each patient, carefully consider the timing and dosage of administration, and remain vigilant regarding potential interactions with other medications. Moreover, the research on the extensive regulatory mechanisms of melatonin in sepsis-induced organ damage primarily derives from animal studies, revealing a significant gap in investigations involving human subjects. Further clinical trials are necessary to elucidate the specific mechanisms through which melatonin exerts its beneficial effects in sepsis.

In summary, melatonin has shown promising clinical significance in sepsis. Recent clinical trials and basic research on the topic have demonstrated encouraging effects of melatonin in the treatment of sepsis. In our work, we have integrated and summarized the relevant studies on the application of melatonin in sepsis in recent years. Our findings are of great significance for advancing the understanding of melatonin's mechanisms of action in sepsis and promoting further clinical applications of melatonin. Melatonin is characterized by minimal side effects and a high safety profile, and it can exert protective effects through various molecular mechanisms. It may represent a promising therapeutic option for treating sepsis; however, its clinical application remains in the exploratory stage, necessitating a series of large-scale clinical studies to verify its effectiveness and safety.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare no competing interests in this work.

References

1. Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA*. 2016;315(8):801–810. doi:10.1001/jama.2016.0287
2. Rudd KE, Johnson SC, Agesa KM, et al. Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the global burden of disease study. *Lancet*. 2020;395(10219):200–211. doi:10.1016/S0140-6736(19)32989-7
3. Marshall JC. Why have clinical trials in sepsis failed? *Trends Mol Med*. 2014;20(4):195–203. doi:10.1016/j.molmed.2014.01.007
4. Evans L, Rhodes A, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. *Crit Care Med*. 2021;49(11):e1063–e143. doi:10.1097/CCM.0000000000005337
5. Vincent JL. Current sepsis therapeutics. *EBioMedicine*. 2022;86:104318. doi:10.1016/j.ebiom.2022.104318
6. Wang K, Zhu J, Gao W, Guo W, Guo Y. The effect of hybrid blood purification combined with ulinastatin for the treatment of severe sepsis on APACHE II score and levels of miR-146a and miR-155. *Int J Gen Med*. 2024;17:5897–5905. doi:10.2147/IJGM.S491193
7. Chen X, Wang Y, Luo H, et al. Ulinastatin reduces urinary sepsis-related inflammation by upregulating IL-10 and downregulating TNF-α levels. *Mol Med Rep*. 2013;8(1):29–34. doi:10.3892/mmr.2013.1480
8. Liu S, Yao C, Xie J, et al. Effect of an herbal-based injection on 28-day mortality in patients with sepsis: the EXIT-SEP randomized clinical trial. *JAMA Intern Med*. 2023;183(7):647–655. doi:10.1001/jamainternmed.2023.0780
9. Wang XT, Peng Z, An YY, et al. Paeoniflorin and hydroxysafflor yellow A in Xuebijing injection attenuate sepsis-induced cardiac dysfunction and inhibit proinflammatory cytokine production. *Front Pharmacol*. 2020;11:614024. doi:10.3389/fphar.2020.614024
10. van der Poll T, Shankar-Hari M, Wiersinga WJ. The immunology of sepsis. *Immunity*. 2021;54(11):2450–2464. doi:10.1016/j.immuni.2021.10.012
11. Wiersinga WJ, van der Poll T. Immunopathophysiology of human sepsis. *EBioMedicine*. 2022;86:104363. doi:10.1016/j.ebiom.2022.104363
12. Mundigler G, Delle-Karth G, Koreny M, et al. Impaired circadian rhythm of melatonin secretion in sedated critically ill patients with severe sepsis. *Crit Care Med*. 2002;30(3):536–540. doi:10.1097/00003246-200203000-00007
13. Stauch B, Johansson LC, McCorvy JD, et al. Structural basis of ligand recognition at the human MT(1) melatonin receptor. *Nature*. 2019;569(7755):2848. doi:10.1038/s41586-019-1141-3
14. Liu R, Luo X, Li J, et al. Melatonin: a window into the organ-protective effects of sepsis. *Biomed Pharmacother*. 2022;154:113556. doi:10.1016/j.biopha.2022.113556

15. Galano A, Reiter RJ. Melatonin and its metabolites vs oxidative stress: from individual actions to collective protection. *J Pineal Res*. 2018;65(1):e12514. doi:10.1111/jpi.12514
16. Phua J, Ngerng W, See K, et al. Characteristics and outcomes of culture-negative versus culture-positive severe sepsis. *Crit Care*. 2013;17(5):R202. doi:10.1186/cc12896
17. Hasan ZT, Atrakji D, Mehuaiden DAK. The effect of melatonin on thrombosis, sepsis and mortality rate in COVID-19 patients. *Int J Infect Dis*. 2022;114:79–84. doi:10.1016/j.ijid.2021.10.012
18. Acuña-Castroviejo D, Escames G, Figueira JC, de la Oliva P, Borobia AM, Acuña-Fernández C. Clinical trial to test the efficacy of melatonin in COVID-19. *J Pineal Res*. 2020;69(3):e12683. doi:10.1111/jpi.12683
19. Farnoosh G, Akbariqomi M, Badri T, et al. Efficacy of a low dose of melatonin as an adjunctive therapy in hospitalized patients with COVID-19: a randomized, double-blind clinical trial. *Arch Med Res*. 2022;53(1):79–85. doi:10.1016/j.arcmed.2021.06.006
20. El-Mashad AR, Elmahdy H, El-Dib M, Elbatch M, Aly H. Can melatonin be used as a marker for neonatal sepsis? *J Matern Fetal Neonatal Med*. 2016;29(17):2870–2873. doi:10.3109/14767058.2015.1107898
21. Deng Z, He M, Hu H, et al. Melatonin attenuates sepsis-induced acute kidney injury by promoting mitophagy through SIRT3-mediated TFAM deacetylation. *Autophagy*. 2023;1–15.
22. Taher A, Shokoohmand F, Abdoli E, Mohammadi Y, Mehrpooya M. A pilot study on the melatonin treatment in patients with early septic shock: results of a single-center randomized controlled trial. *Ir J Med Sci*. 2022;191(4):1913–1924. doi:10.1007/s11845-021-02758-1
23. Annane D, Bellissant E, Cavaillon JM. Septic shock. *Lancet*. 2005;365(9453):63–78. doi:10.1016/S0140-6736(04)17667-8
24. Aziz M, Jacob A, Yang WL, Matsuda A, Wang P. Current trends in inflammatory and immunomodulatory mediators in sepsis. *J Leukoc Biol*. 2013;93(3):329–342. doi:10.1189/jlb.0912437
25. Zhuo Y, Zhang S, Li C, Yang L, Gao H, Wang X. Resolvin D1 promotes SIRT1 expression to counteract the activation of STAT3 and NF-κB in mice with septic-associated lung injury. *Inflammation*. 2018;41(5):1762–1771. doi:10.1007/s10753-018-0819-2
26. Nieto JA, Bruscas MJ, Ruiz-Ribo D, et al. Acute venous thromboembolism in patients with recent major bleeding. The influence of the site of bleeding and the time elapsed on outcome. *J Thromb Haemost*. 2006;4(11):2367–2372. doi:10.1111/j.1538-7836.2006.02188.x
27. Kim ES, Kim MS, Moon A. TGF-beta-induced upregulation of MMP-2 and MMP-9 depends on p38 MAPK, but not ERK signaling in MCF10A human breast epithelial cells. *Int J Oncol*. 2004;25(5):1375–1382.
28. Vandenbroucke RE, Dejager L, Libert C. The first MMP in sepsis. *EMBO Mol Med*. 2011;3(7):367–369. doi:10.1002/emmm.201100146
29. Çokluk E, Doğanay S, Ramazan Şekeroğlu M, Betül Tuncer F, Çakıroğlu H, Boz M. Investigation of the effect of melatonin administration on inflammatory mediators; MMP-2, TGF-β and VEGF levels in rats with sepsis. *Int J Clin Pract*. 2021;75(11):e14832. doi:10.1111/ijcp.14832
30. Carrillo-Vico A, Lardone PJ, Alvarez-Sánchez N, Rodríguez-Rodríguez A, Guerrero JM. Melatonin: buffering the immune system. *Int J mol Sci*. 2013;14(4):8638–8683. doi:10.3390/ijms14048638
31. Xu L, Zhang W, Kwak M, Zhang L, Lee PCW, Jin JO. Protective effect of melatonin against polymicrobial sepsis is mediated by the anti-bacterial effect of neutrophils. *Front Immunol*. 2019;10:1371. doi:10.3389/fimmu.2019.01371
32. An R, Zhao L, Xi C, et al. Melatonin attenuates sepsis-induced cardiac dysfunction via a PI3K/Akt-dependent mechanism. *Basic Res Cardiol*. 2016;111(1):8. doi:10.1007/s00395-015-0526-1
33. Zhang WX, He BM, Wu Y, Qiao JF, Peng ZY. Melatonin protects against sepsis-induced cardiac dysfunction by regulating apoptosis and autophagy via activation of SIRT1 in mice. *Life Sci*. 2019;217:8–15. doi:10.1016/j.lfs.2018.11.055
34. Zhao L, An R, Yang Y, et al. Melatonin alleviates brain injury in mice subjected to cecal ligation and puncture via attenuating inflammation, apoptosis, and oxidative stress: the role of SIRT1 signaling. *J Pineal Res*. 2015;59(2):230–239. doi:10.1111/jpi.12254
35. Chen J, Xia H, Zhang L, Zhang H, Wang D, Tao X. Protective effects of melatonin on sepsis-induced liver injury and dysregulation of gluconeogenesis in rats through activating SIRT1/STAT3 pathway. *Biomed Pharmacother*. 2019;117:109150. doi:10.1016/j.biopha.2019.109150
36. Xu S, Li L, Wu J, et al. Melatonin attenuates sepsis-induced small-intestine injury by upregulating SIRT3-mediated oxidative-stress inhibition, mitochondrial protection, and autophagy induction. *Front Immunol*. 2021;12:625627. doi:10.3389/fimmu.2021.625627
37. Zhang Y, Li X, Grailer JJ, et al. Melatonin alleviates acute lung injury through inhibiting the NLRP3 inflammasome. *J Pineal Res*. 2016;60(4):405–414. doi:10.1111/jpi.12322
38. Jiang Z, Bo L, Meng Y, et al. Overexpression of homeodomain-interacting protein kinase 2 (HIPK2) attenuates sepsis-mediated liver injury by restoring autophagy. *Cell Death Dis*. 2018;9(9):847. doi:10.1038/s41419-018-0838-9
39. Singer M. The role of mitochondrial dysfunction in sepsis-induced multi-organ failure. *Virulence*. 2014;5(1):66–72. doi:10.4161/viru.26907
40. Adler S, Huang H. Oxidant stress in kidneys of spontaneously hypertensive rats involves both oxidase overexpression and loss of extracellular superoxide dismutase. *Am J Physiol Renal Physiol*. 2004;287(5):F907–13. doi:10.1152/ajprenal.00060.2004
41. Rhee C, Dantes R, Epstein L, et al. Incidence and trends of sepsis in US hospitals using clinical vs claims data, 2009-2014. *JAMA*. 2017;318(13):1241–1249. doi:10.1001/jama.2017.13836
42. Üstündağ H, Demir Ö, Çiçek B, Huyut MT, Yüce N, Tavacı T. Protective effect of melatonin and ascorbic acid combination on sepsis-induced lung injury: an Experimental study. *Clin Exp Pharmacol Physiol*. 2023;50(8):634–646. doi:10.1111/1440-1681.13780
43. Eskandari MK, Kalff JC, Billiar TR, Lee KK, Bauer AJ. LPS-induced muscularis macrophage nitric oxide suppresses rat jejunal circular muscle activity. *Am J Physiol*. 1999;277(2):G478–86. doi:10.1152/ajpgi.1999.277.2.G478
44. Calatayud S, García-Zaragozá E, Hernández C, et al. Downregulation of nNOS and synthesis of PGs associated with endotoxin-induced delay in gastric emptying. *Am J Physiol Gastrointest Liver Physiol*. 2002;283(6):G1360–7. doi:10.1152/ajpgi.00168.2002
45. de Winter BY, van Nassauw L, de Man JG, et al. Role of oxidative stress in the pathogenesis of septic ileus in mice. *Neurogastroenterol Motil*. 2005;17(2):251–261. doi:10.1111/j.1365-2982.2004.00618.x
46. Förstermann U. Janus-faced role of endothelial NO synthase in vascular disease: uncoupling of oxygen reduction from NO synthesis and its pharmacological reversal. *Biol Chem*. 2006;387(12):1521–1533. doi:10.1515/BC.2006.190
47. De Filippis D, Iuvone T, Esposito G, et al. Melatonin reverses lipopolysaccharide-induced gastro-intestinal motility disturbances through the inhibition of oxidative stress. *J Pineal Res*. 2008;44(1):45–51. doi:10.1111/j.1600-079X.2007.00526.x
48. Mayo JC, Sainz RM, González Menéndez P, Cepas V, Tan DX, Reiter RJ. Melatonin and sirtuins: a "not-so unexpected" relationship. *J Pineal Res*. 2017;62(2). doi:10.1111/jpi.12391

49. Bock FJ, Tait SWG. Mitochondria as multifaceted regulators of cell death. *Nat Rev mol Cell Biol*. 2020;21(2):85–100. doi:10.1038/s41580-019-0173-8
50. Banoth B, Cassel SL. Mitochondria in innate immune signaling. *Transl Res*. 2018;202:52–68. doi:10.1016/j.trsl.2018.07.014
51. Wu Y, Yao YM, Lu ZQ. Mitochondrial quality control mechanisms as potential therapeutic targets in sepsis-induced multiple organ failure. *J Mol Med*. 2019;97(4):451–462. doi:10.1007/s00109-019-01756-2
52. Sharma S, Bhattarai S, Ara H, et al. SOD2 deficiency in cardiomyocytes defines defective mitochondrial bioenergetics as a cause of lethal dilated cardiomyopathy. *Redox Biol*. 2020;37:101740. doi:10.1016/j.redox.2020.101740
53. Kurundkar D, Kurundkar AR, Bone NB, et al. SIRT3 diminishes inflammation and mitigates endotoxin-induced acute lung injury. *JCI Insight*. 2019;4(1). doi:10.1172/jci.insight.120722
54. Pi H, Xu S, Reiter RJ, et al. SIRT3-SOD2-mROS-dependent autophagy in cadmium-induced hepatotoxicity and salvage by melatonin. *Autophagy*. 2015;11(7):1037–1051. doi:10.1080/15548627.2015.1052208
55. Ning L, Rui X, Guorui L, et al. A novel mechanism for the protection against acute lung injury by melatonin: mitochondrial quality control of lung epithelial cells is preserved through SIRT3-dependent deacetylation of SOD2. *Cell mol Life Sci*. 2022;79(12):610. doi:10.1007/s00018-022-04628-0
56. Tordjman S, Chokron S, Delorme R, et al. Melatonin: pharmacology, functions and therapeutic benefits. *Curr Neuropharmacol*. 2017;15(3):434–443. doi:10.2174/1570159X14666161228122115
57. Marik PE, Raghavan M. Stress-hyperglycemia, insulin and immunomodulation in sepsis. *Intensive Care Med*. 2004;30(5):748–756. doi:10.1007/s00134-004-2167-y
58. Ríos-Lugo MJ, Cano P, Jiménez-Ortega V, et al. Melatonin effect on plasma adiponectin, leptin, insulin, glucose, triglycerides and cholesterol in normal and high fat-fed rats. *J Pineal Res*. 2010;49(4):342–348. doi:10.1111/j.1600-079X.2010.00798.x
59. Li L, Wei W, Zhang Y, et al. SirT1 and STAT3 protect retinal pigmented epithelium cells against oxidative stress. *Mol Med Rep*. 2015;12(2):2231–2238. doi:10.3892/mmr.2015.3570
60. Xu L, Li Y, Yin L, et al. miR-125a-5p ameliorates hepatic glycolipid metabolism disorder in type 2 diabetes mellitus through targeting of STAT3. *Theranostics*. 2018;8(20):5593–5609. doi:10.7150/thno.27425
61. Gao R, Ma Z, Hu Y, Chen J, Shetty S, Fu J. Sirt1 restrains lung inflammasome activation in a murine model of sepsis. *Am J Physiol Lung Cell mol Physiol*. 2015;308(8):L847–53. doi:10.1152/ajplung.00274.2014
62. Xu J, Li Y, Lou M, et al. Baicalin regulates SirT1/STAT3 pathway and restrains excessive hepatic glucose production. *Pharmacol Res*. 2018;136:62–73. doi:10.1016/j.phrs.2018.08.018
63. Williamson L, Ayalon I, Shen H, Kaplan J. Hepatic STAT3 inhibition amplifies the inflammatory response in obese mice during sepsis. *Am J Physiol Endocrinol Metab*. 2019;316(2):E286–e92. doi:10.1152/ajpendo.00341.2018
64. Xu D, Liu L, Zhao Y, et al. Melatonin protects mouse testes from palmitic acid-induced lipotoxicity by attenuating oxidative stress and DNA damage in a SIRT1-dependent manner. *J Pineal Res*. 2020;69(4):e12690. doi:10.1111/jpi.12690
65. Xia L, Sun C, Zhu H, et al. Melatonin protects against thoracic aortic aneurysm and dissection through SIRT1-dependent regulation of oxidative stress and vascular smooth muscle cell loss. *J Pineal Res*. 2020;69(1):e12661. doi:10.1111/jpi.12661
66. Ma F, Hao H, Gao X, et al. Melatonin ameliorates necrotizing enterocolitis by preventing Th17/Treg imbalance through activation of the AMPK/SIRT1 pathway. *Theranostics*. 2020;10(17):7730–7746. doi:10.7150/thno.45862
67. Levi M. The coagulant response in sepsis. *Clin Chest Med*. 2008;29(4):627–42,viii. doi:10.1016/j.ccm.2008.06.006
68. Dhainaut JF, Yan SB, Joyce DE, et al. Treatment effects of drotrecogin alfa (activated) in patients with severe sepsis with or without overt disseminated intravascular coagulation. *J Thromb Haemost*. 2004;2(11):1924–1933. doi:10.1111/j.1538-7836.2004.00955.x
69. Levi M. Disseminated intravascular coagulation. *Crit Care Med*. 2007;35(9):2191–2195. doi:10.1097/01.CCM.0000281468.94108.4B
70. Gitto E, Karbownik M, Reiter RJ, et al. Effects of melatonin treatment in septic newborns. *Pediatr Res*. 2001;50(6):756–760. doi:10.1203/00006450-200112000-00021
71. Zeyed YF, Bastarache JA, Matthay MA, Ware LB. The severity of shock is associated with impaired rates of net alveolar fluid clearance in clinical acute lung injury. *Am J Physiol Lung Cell mol Physiol*. 2012;303(6):L550–5. doi:10.1152/ajplung.00190.2012
72. Hummler E, Planès C. Importance of ENaC-mediated sodium transport in alveolar fluid clearance using genetically-engineered mice. *Cell Physiol Biochem*. 2010;25(1):63–70. doi:10.1159/000272051
73. Matalon S, Bartoszewski R, Collawn JF. Role of epithelial sodium channels in the regulation of lung fluid homeostasis. *Am J Physiol Lung Cell mol Physiol*. 2015;309(11):L1229–38. doi:10.1152/ajplung.00319.2015
74. Li J, Liu L, Zhou X, et al. Melatonin attenuates sepsis-induced acute lung injury through improvement of epithelial sodium channel-mediated alveolar fluid clearance via activation of SIRT1/SGK1/Nedd4-2 signaling pathway. *Front Pharmacol*. 2020;11:590652. doi:10.3389/fphar.2020.590652
75. Zhang ZS, Zhao HL, Yang GM, et al. Role of resveratrol in protecting vasodilatation function in septic shock rats and its mechanism. *J Trauma Acute Care Surg*. 2019;87(6):1336–1345. doi:10.1097/TA.0000000000002466
76. Luo M, Meng J, Yan J, et al. Role of the nucleotide-binding domain-like receptor protein 3 inflammasome in the endothelial dysfunction of early sepsis. *Inflammation*. 2020;43(4):1561–1571. doi:10.1007/s10753-020-01232-x
77. Rheinheimer J, de Souza BM, Cardoso NS, Bauer AC, Crispim D. Current role of the NLRP3 inflammasome on obesity and insulin resistance: a systematic review. *Metabolism*. 2017;74:1–9. doi:10.1016/j.metabol.2017.06.002
78. Hu S, Pi Q, Luo M, et al. Contribution of the NLRP3/IL-1β axis to impaired vasodilation in sepsis through facilitation of eNOS proteolysis and the protective role of melatonin. *Int Immunopharmacol*. 2021;93:107388. doi:10.1016/j.intimp.2021.107388
79. Shapiro NI, Aird WC. Sepsis and the broken endothelium. *Crit Care*. 2011;15(2):135. doi:10.1186/cc10044
80. Guruharsha KG, Kankel MW, Artavanis-Tsakonas S. The Notch signalling system: recent insights into the complexity of a conserved pathway. *Nat Rev Genet*. 2012;13(9):654–666. doi:10.1038/nrg3272
81. Liu T, Zhang C, Ying J, et al. Inhibition of the intracellular domain of Notch1 results in vascular endothelial cell dysfunction in sepsis. *Front Immunol*. 2023;14:1134556. doi:10.3389/fimmu.2023.1134556
82. Luo Z, Mu L, Zheng Y, et al. NUMB enhances Notch signaling by repressing ubiquitination of NOTCH1 intracellular domain. *J mol Cell Biol*. 2020;12(5):345–358. doi:10.1093/jmcb/mjz088

83. Moretti J, Chastagner P, Gastaldello S, et al. The translation initiation factor 3f (eIF3f) exhibits a deubiquitinase activity regulating Notch activation. *PLoS Biol*. 2010;8(11):e1000545. doi:10.1371/journal.pbio.1000545
84. Hsieh CH, Pai PY, Hsueh HW, Yuan SS, Hsieh YC. Complete induction of autophagy is essential for cardioprotection in sepsis. *Ann Surg*. 2011;253(6):1190–1200. doi:10.1097/SLA.0b013e318214b67e
85. Sun Y, Yao X, Zhang QJ, et al. Beclin-1-dependent autophagy protects the heart during sepsis. *Circulation*. 2018;138(20):2247–2262. doi:10.1161/CIRCULATIONAHA.117.032821
86. Liu Q, Wu J, Zhang X, et al. Circulating mitochondrial DNA-triggered autophagy dysfunction via STING underlies sepsis-related acute lung injury. *Cell Death Dis*. 2021;12(7):673. doi:10.1038/s41419-021-03961-9
87. Deng Z, Sun M, Wu J, et al. SIRT1 attenuates sepsis-induced acute kidney injury via Beclin1 deacetylation-mediated autophagy activation. *Cell Death Dis*. 2021;12(2):217. doi:10.1038/s41419-021-03508-y
88. Shen M, Cao Y, Jiang Y, Wei Y, Liu H. Melatonin protects mouse granulosa cells against oxidative damage by inhibiting FOXO1-mediated autophagy: implication of an antioxidation-independent mechanism. *Redox Biol*. 2018;18:138–157. doi:10.1016/j.redox.2018.07.004
89. Qiu R, Li W, Liu Y. MicroRNA-204 protects H9C2 cells against hypoxia/reoxygenation-induced injury through regulating SIRT1-mediated autophagy. *Biomed Pharmacother*. 2018;100:15–19. doi:10.1016/j.biopha.2018.01.165
90. Arunachalam G, Samuel SM, Marei I, Ding H, Triggle CR. Metformin modulates hyperglycaemia-induced endothelial senescence and apoptosis through SIRT1. *Br J Pharmacol*. 2014;171(2):523–535. doi:10.1111/bph.12496
91. Sun M, Li J, Mao L, et al. p53 deacetylation alleviates sepsis-induced acute kidney injury by promoting autophagy. *Front Immunol*. 2021;12:685523. doi:10.3389/fimmu.2021.685523
92. Kim SC, Sprung R, Chen Y, et al. Substrate and functional diversity of lysine acetylation revealed by a proteomics survey. *Mol Cell*. 2006;23(4):607–618. doi:10.1016/j.molcel.2006.06.026
93. Jin L, Galonek H, Israelian K, et al. Biochemical characterization, localization, and tissue distribution of the longer form of mouse SIRT3. *Protein Sci*. 2009;18(3):514–525. doi:10.1002/pro.50
94. Bonekamp NA, Jiang M, Motori E, et al. High levels of TFAM repress mammalian mitochondrial DNA transcription in vivo. *Life Sci Alliance*. 2021;4(11):e202101034. doi:10.26508/lsa.202101034
95. Baixauli F, Acín-Pérez R, Villarroya-Beltrí C, et al. Mitochondrial respiration controls lysosomal function during inflammatory T cell responses. *Cell Metab*. 2015;22(3):485–498. doi:10.1016/j.cmet.2015.07.020
96. Liu H, Li S, Liu X, Chen Y, Deng H. SIRT3 overexpression inhibits growth of kidney tumor cells and enhances mitochondrial biogenesis. *J Proteome Res*. 2018;17(9):3143–3152. doi:10.1021/acs.jproteome.8b00260
97. Maejima Y, Isobe M, Sadoshima J. Regulation of autophagy by Beclin 1 in the heart. *J mol Cell Cardiol*. 2016;95:19–25. doi:10.1016/j.yjmcc.2015.10.032
98. Sun T, Li X, Zhang P, et al. Acetylation of Beclin 1 inhibits autophagosome maturation and promotes tumour growth. *Nat Commun*. 2015;6(1):7215. doi:10.1038/ncomms8215
99. Ren J, Yang L, Zhu L, et al. Akt2 ablation prolongs life span and improves myocardial contractile function with adaptive cardiac remodeling: role of Sirt1-mediated autophagy regulation. *Aging Cell*. 2017;16(5):976–987. doi:10.1111/acel.12616
100. Dixon SJ, Lemberg KM, Lamprecht MR, et al. Ferroptosis: an iron-dependent form of nonapoptotic cell death. *Cell*. 2012;149(5):1060–1072. doi:10.1016/j.cell.2012.03.042
101. Jiang X, Stockwell BR, Conrad M. Ferroptosis: mechanisms, biology and role in disease. *Nat Rev mol Cell Biol*. 2021;22(4):266–282. doi:10.1038/s41580-020-00324-8
102. Zhang H, Liu J, Zhou Y, et al. Neutrophil extracellular traps mediate m(6)A modification and regulates sepsis-associated acute lung injury by activating ferroptosis in alveolar epithelial cells. *Int J Biol Sci*. 2022;18(8):3337–3357. doi:10.7150/ijbs.69141
103. Xl L, Gy Z, G R, C N. Ferroptosis in sepsis: the mechanism, the role and the therapeutic potential. *Front Immunol*. 2022;13:956361. doi:10.3389/fimmu.2022.956361
104. Yang WS, SriRamaratnam R, Welsch ME, et al. Regulation of ferroptotic cancer cell death by GPX4. *Cell*. 2014;156(1–2):317–331. doi:10.1016/j.cell.2013.12.010
105. Ma H, Wang X, Zhang W, et al. Melatonin suppresses ferroptosis induced by high glucose via activation of the Nrf2/HO-1 signaling pathway in type 2 diabetic osteoporosis. *Oxid Med Cell Longev*. 2020;2020:9067610. doi:10.1155/2020/9067610
106. Lever JM, Boddu R, George JF, Agarwal A. Heme oxygenase-1 in kidney health and disease. *Antioxid Redox Signal*. 2016;25(3):165–183. doi:10.1089/ars.2016.6659
107. Loboda A, Damulewicz M, Pyza E, Jozkowicz A, Dulak J. Role of Nrf2/HO-1 system in development, oxidative stress response and diseases: an evolutionarily conserved mechanism. *Cell mol Life Sci*. 2016;73(17):3221–3247. doi:10.1007/s00018-016-2223-0
108. Chambial S, Dwivedi S, Shukla KK, John PJ, Sharma P. Vitamin C in disease prevention and cure: an overview. *Indian J Clin Biochem*. 2013;28(4):314–328. doi:10.1007/s12291-013-0375-3
109. Lamontagne F, Masse MH, Menard J, et al. Intravenous vitamin C in adults with sepsis in the intensive care unit. *N Engl J Med*. 2022;386(25):2387–2398. doi:10.1056/NEJMoa2200644
110. Kuhn SO, Meissner K, Mayes LM, Bartels K. Vitamin C in sepsis. *Curr Opin Anaesthesiol*. 2018;31(1):55–60. doi:10.1097/ACO.0000000000000549
111. Shi M, Zheng D, Sun L, et al. XB130 promotes proliferation and invasion of gastric cancer cells. *J Transl Med*. 2014;12(1):1. doi:10.1186/1479-5876-12-1
112. Armour J, Tyml K, Lidington D, Wilson JX. Ascorbate prevents microvascular dysfunction in the skeletal muscle of the septic rat. *J Appl Physiol (1985)*. 2001;90(3):795–803. doi:10.1152/jappl.2001.90.3.795
113. Wu F, Wilson JX, Tyml K. Ascorbate protects against impaired arteriolar constriction in sepsis by inhibiting inducible nitric oxide synthase expression. *Free Radic Biol Med*. 2004;37(8):1282–1289. doi:10.1016/j.freeradbiomed.2004.06.025
114. Üstündağ H, Doğanay S, Kalındemirtaş FD, et al. A new treatment approach: melatonin and ascorbic acid synergy shields against sepsis-induced heart and kidney damage in male rats. *Life Sci*. 2023;329:121875. doi:10.1016/j.lfs.2023.121875
115. Parnham MJ, Erakovic Haber V, Giamarellos-Bourboulis EJ, Perletti G, Verleden GM, Vos R. Azithromycin: mechanisms of action and their relevance for clinical applications. *Pharmacol Ther*. 2014;143(2):225–245. doi:10.1016/j.pharmthera.2014.03.003

116. McConeghy KW, Bleasdale SC, Rodvold KA. The empirical combination of vancomycin and a β-lactam for Staphylococcal bacteremia. *Clin Infect Dis*. 2013;57(12):1760–1765. doi:10.1093/cid/cit560
117. Di W, Jin Z, Lei W, et al. Protection of melatonin treatment and combination with traditional antibiotics against septic myocardial injury. *Cell Mol Biol Lett*. 2023;28(1):35. doi:10.1186/s11658-022-00415-8