OPEN ACCESS Freely available online

Internal Medicine: Open Access

Review Article

The Therapeutic Potential and Predictive Significance of 5-Methoxytryptophan in Mitigating Sepsis-Induced Organ Dysfunction

Yang Liu[1], Xue Sun[2], Zhongcheng Li[1], Pengli Luo[2*]

[1]Department of Thoracic Surgery, Affiliated Hospital of Qinghai University, Xining, China; [2]Department of Nephrology, Affiliated Hospital of Qinghai University, Xining, China

ABSTRACT

5-Methoxytryptophan (5-MTP) is a recently identified metabolite of tryptophan that exerts a range of therapeutic effects, including anti-inflammatory, antioxidant, anti-tumor, and anti-fibrotic actions. It modulates a variety of signal transduction pathways, exhibiting the characteristic of acting on multiple targets and pathways, which is highly relevant to the management of organ damage induced by sepsis. As an endogenous compound, 5-MTP possesses the potential for predictable safety profiles, suggesting that it and its synthetic analogues could be viable candidates for human disease prevention and treatment. Future research should focus on uncovering additional signaling pathways through which 5-MTP interacts with diseases and potentially slows disease progression through targeted interventions. This overview of 5-MTP's biological functions and mechanisms serves as a reference for its ongoing development, research, and clinical application.

Keywords: Sepsis; 5-methoxytryptophan; Inflammation; Biomarker

INTRODUCTION

Sepsis is a critical clinical condition characterized by life-threatening organ dysfunction due to a dysregulated host response to infection. Epidemiological studies reveal a persistent rise in sepsis incidence, with an annual growth rate of 8.7%. Timely diagnosis of sepsis is imperative; for every hour that treatment is delayed, the average survival rate plummets by 7.6%. Research indicates that prompt initiation of assessment and monitoring within the first hour of clinical management of sepsis, along with early antibiotic administration, can significantly reduce mortality. However, due to the heterogeneity inherent in sepsis, many biomarkers fall short in diagnosing sepsis and its associated organ damage in a timely and effective manner. In the realm of sepsis treatment, there is an acknowledged absence of specific pharmacological interventions. Consequently, the quest for potent drugs capable of preventing and treating sepsis has emerged as a focal point in medical research [1].

5-Methoxytryptophan (5-MTP) is a recently identified metabolite of tryptophan, synthesized by various cells within the body through the tryptophan metabolic pathway. Over the past few years, 5-MTP has been implicated in a spectrum of diseases, demonstrating its role in stabilizing endothelial function, inhibiting tumor growth and metastasis, reducing inflammation, combating oxidation, and preventing fibrosis, among other physiological effects. 5-MTP is biosynthesized from intracellular tryptophan through a two-step enzymatic process: Initially, Tryptophan Hydroxylase (TPH) catalyzes the conversion of L-tryptophan to 5-hydroxytryptophan (5-HTP), which is subsequently transformed into 5-MTP by the action of Hydroxyindole O-methyltransferase (HIOMT). Extensive research has confirmed the potent anti-inflammatory capabilities of 5-MTP. Experimental evidence from both *in vivo* and *in vitro* studies has consistently shown that the therapeutic administration of 5-MTP can ameliorate organ dysfunction caused by sepsis, highlighting its potential as a therapeutic intervention. This review delves into the mechanisms by which 5-MTP mitigates sepsis-induced organ dysfunction and explores its potential as a biomarker for sepsis, reflecting the latest research advancements in this field [2].

Correspondence to: Pengli Luo, Department of Thoracic Surgery, Affiliated Hospital of Qinghai University, Xining, China; E-mail: qhlpl2108@163.com

Received: 21-Dec-2024, Manuscript No. IME-24-36036; **Editor assigned:** 25-Dec-2024, PreQC No. IME-24-36036 (PQ); **Reviewed:** 08-Jan-2025, QC No. IME-24-36036; **Revised:** 05-May-2026, Manuscript No. IME-24-36036 (R); **Published:** 12-May-2026, DOI: 10.35248/ 2165-8048.26.16.547

Citation: Liu Y, Sun X, Li Z, Luo P (2026) The Therapeutic Potential and Predictive Significance of 5-Methoxytryptophan in Mitigating Sepsis-Induced Organ Dysfunction. Intern Med. 16:547.

Copyright: © 2026 Liu Y, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

LITERATURE REVIEW

Anti-inflammatory effect of 5-MTP in sepsis-mediated lung injury

Lipopolysaccharide (LPS), originating from the cell wall of gram-negative bacteria, is a powerful trigger of acute sepsis. It binds to the pattern recognition receptor Toll-Like Receptor 4 (TLR4), initiating a cascade of signal transduction that activates key signaling pathways such as Nuclear Factor kappa-B (NF-κB) and Mitogen-Activated Protein Kinase (MAPK). The initiation triggers the secretion of pro-inflammatory cytokines, including Tumor Necrosis Factor-alpha (TNF-α), Interleukin-1 beta (IL-1β), and Interleukin-6 (IL-6). Concurrently, the expression of High Mobility Group Box 1 (HMGB1) is elevated, further intensifying the inflammatory response. The MAPK pathway is a crucial transducer of extracellular signals, bridging the cell surface to the nucleus. Stimulated by oxidative stress and an array of pro-inflammatory stimuli, it exerts a substantial influence on a wide range of intracellular signaling processes. Research has confirmed that 5-MTP mitigates the LPS-induced activation of the IL-6 promoter and subsequent IL-6 production in macrophages, and additionally downregulates the expression of TNF-α protein. 5-MTP is known to block the NF-κB pathway by inhibiting the p38 MAPK signaling, and it suppresses NF-κB transcription in a concentration-dependent manner. In animal models of LPS-induced sepsis, the intraperitoneal administration of 5-MTP has been shown to ameliorate LPS-induced lung injury and reduce sepsis-related mortality, the fundamental mechanism by which 5-MTP exerts its effects involves in reduction in the expression of Cyclooxygenase-2 (COX-2) and inducible Nitric Oxide Synthase (iNOS) within lung tissue, as well as the suppression of chemokine production in macrophages [3].

The NLRP3 inflammasome is a central player in inflammation, and Nuclear factor erythroid 2-related factor 2 (Nrf2) is a critical regulator in the activation of Antioxidant Response Element (ARE)-dependent cytoprotective protein expression. Nrf2 is vital for orchestrating cellular antioxidant defenses and preserving redox equilibrium. Nrf2, a transcription factor central to antioxidant responses and cellular homeostasis, triggers the expression of HO-1, which is instrumental in curbing NLRP3 inflammasome activation a key mechanism in defending against sepsis-induced organ damage, notably in LPS-induced acute lung injury models. The intervention with 5-MTP has been demonstrated to inhibit NLRP3-mediated pyroptosis through the Nrf2/HO-1 signaling axis, effectively mitigating Acute Lung Injury (ALI) [4].

DISCUSSION

Anti-inflammatory effects of 5-MTP in sepsis-induced kidney injury

Nrf2 facilitates anti-inflammatory responses by orchestrating the recruitment of inflammatory cells and modulating gene expression *via* AREs. The Keap1/Nrf2/ARE signaling axis primarily governs the expression of anti-inflammatory genes and curbs the escalation of inflammation. In Human Mesangial Cells (HMC) treated with LPS, LPS notably increased the expression of pro-inflammatory markers, including phospho-IκBα (p-IκBα), NF-κB p65, and COX-2, while concurrently suppressing the expression of Nrf2 and HO-1. Intervention with 5-MTP can attenuate the LPS-induced upregulation of p-IκBα and NF-κB p65 and enhance the expression of Nrf2 and HO-1, thereby rectifying the dysregulated expression profiles triggered by LPS. By suppressing the IκB/NF-κB pathway and activating the Nrf2 pathway, 5-MTP exerts anti-inflammatory effects and provides renal protection. Oxidative stress is intricately linked to renal injury. Our study demonstrates that 5-MTP robustly neutralizes LPS-induced renal tubular inflammation and oxidative stress, while also promoting mitophagy. This protective effect is attributed to the upregulation of Nrf2, the activation of the Nrf2 signaling pathway, and the triggering of antioxidant and anti-inflammatory responses [5].

Anti-inflammatory effects of 5-MTP on sepsis-induced cardiomyopathy

In a Sepsis-Induced Cardiomyopathy (SIC) model, preconditioning with 5-MTP significantly mitigated cardiac dysfunction and morphological alterations induced by LPS. Post-LPS stimulation, there was a notable increase in the levels of pro-inflammatory cytokines (IL-6, TNF-α, and NLRP3) and a corresponding decrease in anti-inflammatory cytokine levels. 5-MTP preconditioning ameliorated the inflammatory response by inhibiting the activation of the NF-κB signaling pathway in SIC, thereby downregulating inflammatory mediators and NLRP3 expression. Administration of 5-MTP prior to exposure significantly attenuated LPS-triggered apoptosis in cardiac cells, as evidenced by alterations in the expression of critical apoptotic factors. Notably, 5-MTP increased the expression of the anti-apoptotic protein Bcl-2 and decreased the levels of the pro-apoptotic proteins caspase-1, caspase-3, and Bax, thereby reversing the cell death induced by LPS in the heart. *In vitro*, 5-MTP preconditioning also exerted similar cardioprotective effects on LPS-stimulated cultured cardiac fibroblasts. In conclusion, Preliminary administration of 5-MTP has been observed to reduce LPS-induced cardiac inflammation and apoptosis, positioning it as a potential therapeutic agent for SIC. This insight opens new therapeutic horizons for SIC [6].

These findings suggest that, despite the varied mechanisms through which 5-MTP acts in sepsis-induced organ damage, the exogenous administration of 5-MTP can markedly alter the functional impairments associated with sepsis. Further investigation into the crosstalk of signaling pathways is essential to enhance our understanding of how 5-MTP can mitigate organ damage in sepsis [7].

5-Methoxytryptophan serves as a biomarker for monitoring disease progression

Biomarkers are pivotal in the diagnostic process, facilitating the early detection of organ dysfunction, risk assessment, prognosis determination, and overall patient management, including the strategic use of antibiotics. There is a pressing demand for biomarkers that are highly sensitive, distinctive, and simple

operation to monitor disease dynamics in patients. 5-MTP, an endogenous metabolite of tryptophan, has emerged as a promising candidate. Current research indicates that the serological and histological expression levels of 5-MTP not only offer protective effects but also serve as valuable indicators for gauging disease progression and prognosis across a spectrum of illnesses [8].

5-MTP as a predictive biomarker for sepsis and sepsis-induced kidney injury

Emerging evidence indicates that 5-MTP, an endogenous tryptophan metabolite, exhibits reduced serological levels in both sepsis patients and corresponding animal models. When compared with traditional inflammatory markers of sepsis, such as serum hypersensitive C-reactive protein and IL-1β, 5-MTP demonstrates a sensitivity of 83% and a specificity of 94% in clinical samples. These findings suggest that 5-MTP could serve as a prognostic biomarker for sepsis and other systemic inflammatory conditions, with animal model results corroborating clinical observations. Our research team has discovered that the plasma levels of 5-MTP in patients with Sepsis-Associated Acute Kidney Injury (S-AKI) are markedly elevated compared to those with sepsis alone. Moreover, the concentration of 5-MTP correlates closely with renal function, suggesting its potential as a predictive biomarker for the development of S-AKI. The new research findings suggest that 5-MTP may be closely associated with the prognosis of certain diseases. However, the correlation between 5-MTP levels and sepsis prognosis remains unexplored, with no existing studies addressing this relationship. Our team plans to conduct additional research in this area to elucidate these connections in the future [9].

CONCLUSION

The quest for therapeutic drugs in sepsis has remained a focal point in medical research. 5-MTP, an endogenous metabolite derived from tryptophan, exhibits potential as a predictable toxicity compound, suggesting that 5-MTP and its synthetic analogs could be viable for human disease prevention and treatment. This substance activates various signaling pathways to protect against organ damage triggered by sepsis. Notably, serological expression levels of 5-MTP vary across different diseases and stages, which could elucidate its interaction with disease pathology and potential involvement in other signaling pathways. Unraveling the specific molecular mechanisms of 5-MTP in sepsis and assessing its adverse reactions are crucial for understanding its role in mitigating sepsis-induced organ damage. The determination of serum 5-MTP in clinical practice may provide valuable insights for early disease outcome assessment and prognosis in sepsis cases.

FINANCIAL SUPPORT

This manuscript was funded by the provincial Clinical Core Specialty Construction of Qinghai Province.

REFERENCES

1. Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, et al. Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock 2021. Crit Care Med. 2021;49:e1063–e1143.
2. Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. N Engl J Med. 2003;348:1546–1554.
3. Kumar A, Roberts D, Wood KE, Light B, Parrillo JE, Sharma S, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med. 2006;34:1589–1596.
4. Teggert A, Datta H, Ali Z. Biomarkers for point-of-care diagnosis of sepsis. Micromachines (Basel). 2020;11:286.
5. Wang YF, Hsu YJ, Wu HF, Lee GL, Yang YS, Wu JY, et al. Endothelium-derived 5-methoxytryptophan is a circulating anti-inflammatory molecule that blocks systemic inflammation. Circ Res. 2016;119:222–236.
6. Chang TC, Hsu MF, Shih CY, Wu KK. 5-methoxytryptophan protects MSCs from stress-induced premature senescence by upregulating FoxO3a and mTOR. Sci Rep. 2017;7:11133.
7. Chu LY, Wang YF, Cheng HH, Kuo CC, Wu KK. Endothelium-derived 5-methoxytryptophan protects endothelial barrier function by blocking p38 MAPK activation. PLoS One. 2016;11:e0152166.
8. Wu KK. Control of tissue fibrosis by 5-methoxytryptophan, an innate anti-inflammatory metabolite. Front Pharmacol. 2021;12:759199.
9. Wu KK, Cheng HH, Chang TC. 5-methoxyindole metabolites of L-tryptophan: control of COX-2 expression, inflammation and tumorigenesis. J Biomed Sci. 2014;21:17.