**A review on the effect of tanshinone on sepsis**

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**Abstract：**

Sepsis, defined as a systemic inflammatory response to infection, has been a prominent area of medical research due to the complexity and variability of its pathological mechanisms. In recent years, tanshinone has demonstrated considerable promise as a treatment for sepsis due to its distinctive pharmacological properties. This paper aims to examine the chemical structure of tanshinone, define sepsis and its intricate pathophysiological processes, and review the potential role of tanshinone in sepsis treatment and the latest research findings. This analysis will inform future research directions.

**I. Introduction**

Sepsis, defined as a systemic inflammatory response to infection, has been a prominent area of medical research due to the complexity and variability of its pathological mechanisms[1]. In recent years, tanshinone has demonstrated considerable promise as a treatment for sepsis due to its distinctive pharmacological properties. This paper aims to examine the chemical structure of tanshinone, define sepsis and its intricate pathophysiological processes, and review the potential role of tanshinone in sepsis treatment and the latest research findings. This analysis will inform future research directions.

**II. Chemical Properties of Tanshinone**

Tanshinone, a principal active component of Danshen, possesses a distinctive phenanthrenequinone structure[2]. Among these, tanshinone IIA has become the focus of research due to its notable biological activity and favorable water solubility. Tanshinone IIA is an orange-red needle-like crystal with a high melting point and is readily soluble in organic solvents, such as ethanol and acetone. Its distinctive chemical structure endows tanshinone with a range of pharmacological effects, including anti-inflammatory, antioxidant, anticoagulant, and others[3].

**III. Definition of sepsis and its pathological mechanism**

Sepsis is defined as a dysregulation of the host response to infection, resulting in life-threatening organ dysfunction. Its pathological mechanism is intricate and encompasses multiple facets of the immune system, coagulation system, endocrine system, and others. The systemic inflammatory response initiated by infection represents the crux of sepsis, with the release of copious amounts of inflammatory cytokines and mediators leading to tissue damage and organ dysfunction. Additionally, sepsis frequently presents with pathological alterations, including aberrant coagulation function and microcirculation disorders.

**IV. A potential role for tanshinone in the treatment of sepsis and an analysis of existing studies**

**1. Anti-inflammatory and immunomodulatory effects**

The distinctive pharmacological effects of tanshinone IIA, a natural active ingredient, are of particular importance when investigating anti-inflammatory and immunomodulatory strategies in the context of modern medicine. Studies have demonstrated that tanshinone IIA can inhibit the aberrant activation of core inflammatory signaling pathways, such as NF-κB, thereby effectively reducing the excessive release of inflammatory cytokines. This mechanism can mitigate the exacerbation of systemic inflammation and reduce the risk of concomitant tissue damage at the source.

Specifically, inappropriate activation of NF-κB, a key intracellular transcription factor, often triggers a cascade of inflammatory mediators, including TNF-α and IL-1β. The overproduction of these mediators acts as a catalyst for the inflammatory response, exacerbating tissue damage. The intervention of tanshinone IIA, however, acts as a precisely regulated inhibitor, effectively curbing the uncontrolled development of this process and protecting the healthy state of tissues.

Moreover, tanshinone IIA has demonstrated considerable efficacy in immunomodulation. It is capable of regulating the activity of immune cells, promoting equilibrium and stability within the immune system, and averting the "immune storm" that can result from the exaggerated response of immune cells during an infection. This contributes to more effective infection control and reduced tissue damage[4].

**2. Antioxidant and cell protection**

In severe pathological conditions such as sepsis, the body produces a substantial quantity of oxygen radicals and other reactive oxygen species, which exert a considerable destructive effect on cells. However, tanshinone IIA, due to its robust antioxidant capacity, is capable of effectively scavenging these deleterious free radicals and safeguarding cells from oxidative stress. Its antioxidant effect can be conceptualized as the establishment of a robust defensive barrier for cells, ensuring the integrity of their structural and functional integrity.

Moreover, tanshinone IIA facilitates the repair and regeneration of damaged cells. It can be considered a meticulous restorer, providing essential support and nourishment for damaged cells, accelerating their recovery and reconstruction, and thus promoting the overall recovery and regeneration of tissues[5].

**3. Enhancement of microcirculation and organ function**

Microcirculation represents a pivotal conduit for the exchange of substances between the blood and tissues. Its optimal functioning is indispensable for the maintenance of the organism's physiological stability. In pathological conditions such as sepsis, microcirculation is frequently impaired, resulting in inadequate blood perfusion and diminished oxygen supply to tissues. Tanshinone IIA has been demonstrated to effectively enhance microcirculation by dilating blood vessels and reducing blood viscosity, increasing blood perfusion and oxygen supply to tissues. This effect can be likened to the beneficial effects of precipitation on arid tissues, effectively alleviating hypoxia and dysfunction of the tissues, and improving the survival rate and quality of life of patients.

**4. Anticoagulation and Antithrombosis**

Sepsis is a systemic inflammatory response to infection, and its pathophysiologic process is complex and variable. During the development of sepsis, there is a close interaction between the inflammatory response and the coagulation response, whereby the former can activate the latter and vice versa. On the one hand, the inflammatory response can activate the coagulation system, leading to increased release of plasminogen activator, platelet activation, and subsequent thrombus formation. On the other hand, the coagulation response can also exacerbate the inflammatory response, forming a vicious circle. This coagulation abnormality not only increases the risk of thrombosis but also further impairs organ function, leading to multi-organ failure. Given the elevated risk of coagulation abnormalities and thrombosis in sepsis, anticoagulation and antithrombotic therapy are of particular importance. By inhibiting platelet aggregation and thrombus formation, the incidence of cardiovascular complications can be significantly reduced, and the prognosis of patients can be improved. Concurrently, anticoagulant therapy can also reduce the activation of the coagulation system by the inflammatory response, thus breaking the vicious circle between inflammation and coagulation.

Among the numerous pharmaceutical agents with anticoagulant properties, tanshinone IIA has garnered considerable attention due to its distinctive pharmacological actions and favorable clinical outcomes. Tanshinone IIA is a principal active component of Danshen, a herbal remedy with a multitude of pharmacological effects, including anti-inflammatory, antioxidant, and anticoagulant properties. In the context of anticoagulation, tanshinone IIA has been demonstrated to inhibit platelet aggregation and thrombus formation, primarily through the following mechanisms:

1) Inhibition of platelet activation: Tanshinone IIA can inhibit the glycoprotein receptors on the surface of platelets, such as GP IIb/IIIa, thereby blocking the binding of platelets to fibrinogen and inhibiting platelet activation and aggregation.

2) Inhibition of thrombin generation: Thrombin is a key enzyme in the coagulation process and its generation is regulated by a variety of factors. Tanshinone IIA can inhibit the release and activity of plasminogen activator, thereby reducing thrombin generation and the risk of thrombosis.

3) Modulation of the inflammatory response: As mentioned above, there is a close relationship between the inflammatory response and the coagulation response. Tanshinone IIA is able to reduce the activation of the coagulation system by the inflammatory response by inhibiting the release and activity of inflammatory factors, thus further reducing the risk of thrombosis.

**V. Conclusion and outlook**

In summary, tanshinone exhibits a variety of potential pharmacological effects in the treatment of sepsis. However, the specific mechanisms regarding tanshinone in sepsis treatment are not yet fully clarified and the clinical studies are insufficient. Therefore, the pharmacological mechanism of tanshinone and clinical trial studies need to be further strengthened in the future in order to clarify its exact efficacy and safety in sepsis treatment, and to provide a new and effective means for the treatment of sepsis.

**VI. Future research directions and challenges**

1. In-depth mechanism study: Although it has been shown that tanshinone has significant effects in anti-inflammatory, antioxidant and microcirculation improvement, its specific molecular mechanism has not been fully elucidated. Future research should focus on the interaction between tanshinone and cell signaling pathway, gene expression regulation and other levels, in order to reveal the exact mechanism of its treatment of sepsis.

2. Optimization of drug formulation: At present, the extraction and purification process of tanshinone is relatively mature, but the stability and bioavailability of its drug formulation still need to be improved. Through nanotechnology, liposome technology and other modern drug formulation technologies, tanshinone preparations with higher bioavailability and targeting can be prepared, thus improving its therapeutic effect.

3. Multi-center clinical trials: In order to verify the effectiveness and safety of tanshinone in sepsis treatment, multi-center, large sample, randomized controlled clinical trials are needed. This will help to determine the optimal therapeutic dose, mode of administration and timing of tanshinone treatment, and provide a reliable basis for clinical application.

4. Combination drug study: The treatment of sepsis often requires the combined use of multiple drugs. Future research can explore the effect of tanshinone in combination with other antibiotics and anti-inflammatory drugs, in order to play a synergistic effect, improve the therapeutic effect and reduce the side effects of drugs.

5. Individualized treatment strategy: The pathogenesis and clinical manifestations of sepsis have individual differences, so it is particularly important to develop individualized treatment strategies. Future research can combine the genotype, immune status and other individual differences of patients to develop a targeted tanshinone treatment plan, in order to achieve precision medicine.

**VII. Conclusion**

Tanshinone, as a traditional Chinese medicine ingredient, shows a broad application prospect in the treatment of sepsis. With the in-depth study of its pharmacological mechanism and the continuous promotion of its clinical application, tanshinone is expected to become one of the important drugs in the treatment of sepsis. However, there are still many challenges to overcome in order to achieve this goal, including in-depth mechanism study, optimization of drug formulation, and conducting multi-center clinical trials. It is believed that in the near future, with the continuous progress of science and technology and in-depth clinical research, tanshinone will play a more important role in the treatment of sepsis.

**Reference：**

[1] Faix J D. Biomarkers of sepsis[J]. Crit Rev Clin Lab Sci, 2013, 50(1): 23-36.

[2] Jiang Q, Chen X, Tian X, et al. Tanshinone I inhibits doxorubicin-induced cardiotoxicity by regulating Nrf2 signaling pathway[J]. Phytomedicine, 2022, 106: 154439.

[3] Zhang X, Wang Q, Wang X, et al. Tanshinone IIA protects against heart failure post-myocardial infarction via AMPKs/mTOR-dependent autophagy pathway[J]. Biomed Pharmacother, 2019, 112: 108599.

[4] He X, Yang F, Wu Y, et al. Identification of tanshinone I as cap-dependent endonuclease inhibitor with broad-spectrum antiviral effect[J]. J Virol, 2023, 97(10): e0079623.

[5] Huang X, Jin L, Deng H, et al. Research and Development of Natural Product Tanshinone I: Pharmacology, Total Synthesis, and Structure Modifications[J]. Front Pharmacol, 2022, 13: 920411.