Review Articles

Acupuncture and Herbal Medicine

Electroacupuncture targeting the immune system to alleviate sepsis

Mengyue Fang[1], Yuye Lan[2], Man Li[2], Chennan Li[2], Bin Xu[3], Yan Ma[4], Sulukkana Noiprasert[5], Xianghong Jing[6,*], Lingling Yu[7,*]

[1]Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; [2]School of Basic Medicine, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; [3]Key Laboratory of Integrated Acupuncture and Medicine Research of Ministry of Education, Nanjing University of Chinese Medicine, Nanjing, China; [4]Wuhan No. 1 Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; [5]School of Integrative Medicine, Mae Fah Luang University, Chiangrai, Thailand; [6]Institute of Acupuncture and Moxibustion, China Academy of Chinese Medical Sciences, Beijing, China; [7]Institute of Integrated Traditional Chinese and Western Medicine, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

Abstract

Sepsis is a life-threatening inflammatory syndrome with high morbidity and mortality rates. However, options for sepsis are still limited to general treatment in intensive care units (ICUs), and effective therapies that improve sepsis survival are required. Immune disturbances play a vital role in the pathology of sepsis and are associated with protracted inflammation, susceptibility to infections, and death. Therefore, many investigators have focused on the potential benefits of immunomodulation therapy for sepsis. Electroacupuncture (EA) has been practiced in clinics for many years and has shown advantages in treating infectious diseases. Over the last few decades, our understanding of the efficacy and mechanisms of EA in sepsis has undergone considerable developments. We searched the literature regarding "CNKI, Wan Fang Data, VIP Database, PubMed, and Ingenta Connect" from 2010 to 2023, using the keywords "sepsis" "septic" and "electroacupuncture" and 336 sources were searched. Finally, we included 82 studies that targeted the immune system to determine EA's anti-inflammatory and immunomodulatory effects on sepsis. In this review, we found that EA has clinical benefits in relieving septic inflammation, improving immune function, and attenuating related multi-organ injury through several mechanisms, such as activation of the cholinergic anti-inflammatory pathway (CAP), vagal-adrenal axis, inhibition of the nuclear factor Kappa-B (NF-κB) signaling pathway, signal transducers and activators of transcription (STAT) signaling pathway, and improvement of immune cell function. Therefore, EA may be a promising complementary therapy for sepsis treatment. We also expect these data will contribute to further studies on EA in sepsis.

Keywords: Cholinergic anti-inflammatory pathway, Electroacupuncture, Nuclear factor Kappa-B, Sepsis, Signal transducers and activators of transcription, Vagal-adrenal axis

Graphical abstract: http://links.lww.com/AHM/A87.

Introduction

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to an infection, as The Third International Consensus Definitions Task Force proposed in 2001[1]. It usually occurs in elderly individuals and affects patients with cancer or underlying immunosuppression[2]. If left untreated, sepsis can result in various complications, including encephalopathy, diffuse lung injury, subsequent infections, myocardial suppression, coagulation abnormalities, cholestasis, acute renal injury, intestinal barrier abnormalities, total blood cytopenia, and myopathy. Septic shock is a subset of sepsis in which the underlying circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than sepsis alone[3]. Although the definition, pathophysiology, and treatment of sepsis have progressed over the past half-century, it remains the leading cause of death in intensive care units (ICUs). According to a 2017 report, sepsis is thought to cause an estimated 48.9 million incident cases worldwide and 11.0 million fatalities, representing 19.70% of all deaths worldwide[4]. Sepsis remains a major global health issue and deserves greater public health attention[5].

Although much progress has been made in the management of sepsis, treatment options are still limited to the general treatment of ICUs, and no specific therapies exist[6–8]. Therefore, more effective therapies are required

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Mengyue Fang and Yuye Lan contributed equally to this work.

**Corresponding author. Lingling Yu, E-mail: 527679774@qq.com; Xianghong Jing, E-mail: jxhtjb@263.net.*

Received 4 May 2023 / Accepted 14 January 2024

***How to cite this article:** Fang MY, Lan YY, Li M, Li CN, Xu B, Ma Y, Noiprasert S, Jing XH, Yu LL. Electroacupuncture targeting the immune system to alleviate sepsis. Acupunct Herb Med 2024;4(1):56–67. doi: 10.1097/HM9.0000000000000092*

to improve survival in patients with sepsis. It is widely accepted that sepsis is primarily a pathology of cellular immune function triggered by infection, including hyper-inflammation, immune resolution, immune suppression, and molecular alterations that alter cellular phenotypes and functions. Sepsis-associated immune dysfunction is closely correlated with protracted inflammation, susceptibility to infections, and insurmountable death; therefore, more investigators have focused on the potential benefits of immune modulation therapy for sepsis.

A recent review showed that Traditional Chinese medicine (TCM) has clinical benefits for treating sepsis and related multi-organ injuries. This review summarizes several effective TCM methods for treating sepsis, including TCM compounds, herbal monomer extracts, and acupuncture. Among these, acupuncture is a promising non-pharmacological treatment that may be effective for sepsis[9]. It has been practiced in the clinic for over 2,000 years. Acupuncture is advantageous for treating infectious diseases such as inflammatory bowel disease (IBD)[10], sepsis[11], COVID-19[12], major Leishmania infection[13], acute pancreatitis[14], and inflammatory arthritis[15]. Electroacupuncture (EA) is a type of therapy that involves inserting acupuncture needles into acupoints and delivering a stimulating current to the acupoints. Substantial evidence confirmed that EA could induce endogenous anti-inflammatory effects and regulate immunity that acts through delivering electrical current to the specific acupoints, mostly known as “Zusanli (ST36)” and “Tianshu (ST25)”[11,16,17].

With the accumulation of clinical trials and animal experimental evidence, our understanding of the efficacy and mechanisms of EA in sepsis and related multi-organ injuries has undergone considerable development. More investigators have found that adding EA to the general treatment of sepsis could relieve multi-system symptoms in early stages, shorten hospital stays, and improve survival rates[11,18,19]. In addition, EA relieves sepsis by inhibiting inflammatory responses, activating the vagus nerve, boosting immunity, and improving immunological indicators and prognoses[17,19–23]. However, a comprehensive overview of the immunological evidence for the role of EA in sepsis is still lacking. In this review, we summarize the effects of EA on the changes in the immune system during sepsis and its complications reported over the past 10 years. A literature review was conducted using CNKI, Wan Fang Data, the VIP Database, PubMed, and Ingenta Connect. The terms “sepsis” “septic” and “electroacupuncture” were employed, with availability limited to 2010 and after. There are 82 studies targeting the immune system to determine the effects of EA on sepsis, and research on this topic has gradually increased (Figure 1).

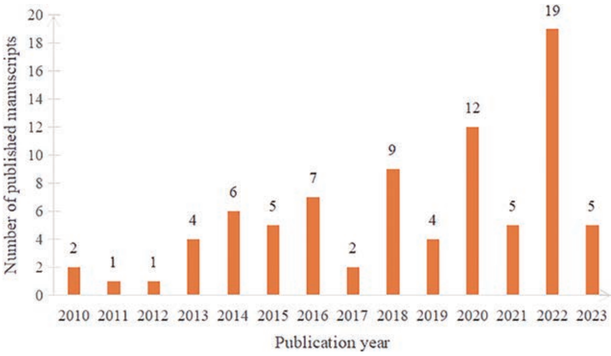

Figure 1. The number of publications from 2010 to 2023 on EA targeting the immune system for sepsis treatment. EA: Electroacupuncture.

Major immunological mechanisms of sepsis

Immune dysfunction

Sepsis is assumed to result from an unbalanced immune response in which an invading pathogen bypasses defenses and continues to spread, infecting more tissue than can be locally controlled. Consequently, the immune response fails to return to homeostasis, culminating in a pathological syndrome characterized by sustained excessive inflammation and immune suppression[24,25].

Sepsis has a detrimental effect on the immune system by directly affecting the lifespan, generation, and functionality of effector cells that maintain homeostasis[26,27]. The hematopoietic compartment replenishes terminally differentiated innate and adaptive effector cells essential for effective tissue regeneration, wound repair, and immune surveillance against aggravating pathogens[25]. Innate immunity comprises sensors or pattern-recognition receptors (PRRs), which are expressed on immune and non-immune cells and detect conserved compounds generated by pathogens or pathogen-associated molecular patterns (PAMPs) in diverse parts of the host cells[28]. Moreover, the adaptive immune system is activated by delivering antigen to B and T lymphocytes *via* dendritic cells (DC) and other cells. This causes the formation of pathogen-specific antibodies and creates a memory for future infections by the same pathogen[29]. In sepsis, endogenous chemicals known as damage-associated molecular patterns (DAMPs) are released by wounded cells and persistently stimulate the immune system. When DAMPs activate PRRs, which are also frequently detected, a vicious cycle of immunological activation and dysfunction is initiated[30]. Many immune mechanisms originally triggered to offer protection become harmful in an unbalanced response, in terms of both excessive inflammation and immune suppression[29]. Previously, it was believed that the inflammatory response caused early mortality within the first couple of days of sepsis and that the compensatory anti-inflammatory response induced organ failure, immunological suppression, and mortality several weeks later[31]. However, mounting data indicate that immunological suppression, which frequently results in subsequent bacterial, viral, or fungal infections and additional damage, is a crucial pathophysiological event in sepsis[32]. Additionally, new information revealed through the genomic analysis of tissue samples from critically damaged adult patients and septic patients who died has revealed an ongoing pro-inflammatory and anti-inflammatory state that is concurrently driven by dysregulated innate and suppressed adaptive immunity that together result in organ failure and patient death[33–36].

Both the innate and adaptive immune systems, as well as pro- and anti-inflammatory responses, are equally vital. These systems may act as targets for future immunotherapies to improve long-term sepsis outcomes[26,27,32,37].

Hyper-inflammation

It is accepted that exacerbation of the inflammatory response is a key factor in the etiology of sepsis[38]. During sepsis, the innate immune system is activated, releasing septic bacteria and inflammatory cytokines. The bacteria then released microbial motifs, such as peptidoglycan, lipopolysaccharide (LPS), and DNA. These events initiate inflammatory responses and cause multiple organ failure[39]. The term "cytokine storm" was first used in early preclinical research to describe the strong systemic release of pro-inflammatory cytokines in experimental animals exposed to intravenous challenges using viable bacteria or their products[40]. In sepsis, a cytokine storm initiates an inflammatory response and accelerates sepsis progression. Increased release of pro-inflammatory cytokines, such as tumor necrosis factor (TNF)-α, interleukin (IL)-1, IL-6, IL-8, monocyte chemotactic protein-1 (MCP-1), and high mobility protein B1 (HMGB1) are related to the development of sepsis[24,38]. So far, several inflammatory factor-related signaling pathways are involved in the onset of hyper-inflammation, including the nuclear factor Kappa-B (NF-κB) signaling pathway and signal transducers and activators of transcription (STAT) signaling pathway.

Sepsis endotoxins can cause an excessive amount of reactive oxygen species (ROS) in the body, resulting in an imbalance of oxidative/antioxidative activity, which in turn causes a significant increase in the production of the lipid peroxide malondialdehyde (MDA) and a decrease in enzymes such as superoxide dismutase (SOD). Neutrophils contribute to hyper-inflammation in sepsis[41]. During sepsis, neutrophil extracellular traps (NETs) are released into the vasculature, aiding host defense against infection; however, they also promote intravascular coagulation and multi-organ injury[42]. Oxygen radical damage, increased ROS generation, Ca^{2+} overload, nitric oxide (NO) damage, and decreased mitochondrial membrane potential are the major causes of mitochondrial damage during sepsis[38]. Insufficient energy production by cells due to mitochondrial malfunction causes gradual multi-organ failure[43].

The immune response to an infection involves complex interactions with other systems, particularly coagulation. In sepsis, the coagulation system is activated by a shift in the balance toward procoagulant factors and a decrease in natural anticoagulants. Cytokines promote the expression of tissue factors from various cells, including monocytes, stimulating the extrinsic coagulation system, factor FVII, and thrombin activation along with the intrinsic system, causing further amplification[44]. In contrast, stimulating the activation of the tissue and coagulation factors FVIIa, FXa, thrombin, and fibrin can further induce pro-inflammatory cell production[45]. Various NET components have been implicated in coagulation[42]. During coagulation, complement activation is an essential part of the body's defense mechanisms; however, unchecked activation can harm tissues and result in organ failure[46]. Furthermore, platelets improve neutrophil activation and leukocyte extravasation in inflammation. Endothelial cell adhesion also increases[47]. Moreover, Gasdermin D (GSDMD) cleavage and activation, which results in the release of F3, the primary initiator of blood coagulation, is triggered by a stimulator of interferon genes (STING)-dependent increase in cytosolic calcium[48]. Disseminated intravascular coagulation (DIC) can lead to wasting, multiple organ failure, and death.

Immune suppression

Immune suppression is a major contributor to the pathology of sepsis and is important for its clinical prognosis. Immune suppression usually occurs concomitantly with persistent inflammation and enables the development of persistent, recurrent, secondary, and nosocomial infections, leading to poor outcomes and increased long-term mortality[37].

The pathogenesis of sepsis starts with an inflammatory response. If this reaction is not regulated, inflammatory cytokines will continue to increase, and the anti-inflammatory response will increase. The body progressively enters an immunological paralysis or immunosuppressive state, and inflammation worsens[38]. Sepsis-induced immunosuppression results from disruption of immune homeostasis. It is characterized by 1) immune cell failure and apoptosis, specifically apoptosis and reduction of $CD4^+$ and $CD8^+$ T cells, B cells, natural killer (NK) cells, and DC, such as suppression of $CD4^+$ T helper (TH)1 cells, TH2 cells, and TH17 cells functions[24]. The immune cell failure and apoptosis permit the development of persistent, recurring, secondary, and nosocomial infections, which result in poorer results and higher long-term mortality[37,49]; 2) an increase in immunosuppressive cells, regulatory T cells (Treg cells) and myeloid-derived suppressor cells (MDSCs), which can inhibit the activity of effector T cells, NK cells, monocytes, and neutrophils[50,51]; 3) a reprogramming of monocytes and macrophages resulting in decreased surface expression of major histocompatibility complex (MHC) class II and diminished ability to produce pro-inflammatory cytokines in response to *ex vivo* stimulation with bacterial agonists (also known as "LPS tolerance")[29]; 4) decreased expression of activating cell surface molecules[29]; 5) The release of anti-inflammatory cytokines and the expression of immune checkpoints are also involved in immunosuppression[52]. Myeloid cell production and release of anti-inflammatory cytokines, for example, IL-10, transforming growth factor-β (TGF-β), and arginase (Arg), is elevated overall[53,54].

Sepsis suppresses the immune system by regulating signaling pathways. The first is the NF-κB signaling pathway. The NF-κB signaling pathway also regulates the expression of genes like B-cell lymphoma-2 (Bcl-2), a negative regulator of cell death. It upregulates Bcl-2-Associated X (Bax), which promotes apoptosis[55] in immune cells.

A class of membrane-bound receptors or ligands, known as checkpoint regulators, is expressed in immune cells to control how they react to the presentation of antigens and other immunological stimuli, including cytokines, chemokines, and complements[56]. The important immunosuppressive checkpoint regulator programmed death protein 1 (PD-1), which is largely produced by activated T cells, was first identified in T-cell lymphoma[57] and initiated the process of T-cell death. Increased PD-1 expression is linked to higher rates of secondary nosocomial infections and mortality during septic shock, as well as lower levels of mitogen-induced lymphocyte proliferation and higher levels of circulating IL-10[58].

EA utilized in sepsis and related multi-organ injury

Since the powerful anti-inflammatory effect of EA has been confirmed, much attention has been paid to the treatment of sepsis with EA. Usually, EA is used as a complementary treatment to general drug treatment and has been applied to simple sepsis and sepsis combined with gastrointestinal, lung, myocardial, and brain injuries[19,21,59–61].

EA can rapidly reduce fever in patients with simple sepsis[62], reduce their risks of multiple organ failure syndrome and sepsis-related death[20], manage extensive inflammation[20,62–64], enhance immunological function[11,18,62,65,66], and improve coagulation function[63]. In three early studies with medium sample sizes (50, 58, and 58 cases), EA treatment lasting 3 to 7 d significantly improved immune system function and decreased the inflammatory response in patients with sepsis, thereby achieving the goal of enhancing the efficacy of sepsis and its clinical prognosis[64–66]. Since then, three studies with relatively small sample sizes have revealed EA's efficacy in managing sepsis[11,20,67]. In a 112-patient sepsis randomized clinical trial, clinical symptoms, intestinal barrier function, and coagulation indicators improved, and inflammatory factor levels decreased after 7 days of EA treatment in 78.6% of patients[63]. Thirty minutes after EA treatment, patients in another controlled clinical trial of 120 sepsis patients demonstrated a lower reduction of fever, reduced inflammatory reaction, and improved immune function[62]. A recent randomized, double-blind, controlled trial involving 60 patients confirmed that immune function and clinical symptoms dramatically improved after 5 days of EA treatment[18]. Zusanli (ST36), Tianshu (ST25), and Shangjuxu (ST37) are the most frequently used acupoints for EA in the treatment of simple sepsis. The single point "Zusanli (ST36)" was the most often utilized prescription, followed by "Zusanli (ST36) + Tianshu (ST25) + Shangjuxu (ST37)." The EA frequency was typically adjusted to a continuous wave of 4 Hz for 30 min.

Some clinical studies have found that EA has numerous beneficial therapeutic effects in sepsis, as well as inducing complications. In cases of sepsis combined with gastrointestinal injury, EA may assist patients by fostering the rehabilitation of the intestinal barrier and coagulation function[63], regulating their inflammatory response[68], and improving gastrointestinal permeability and function[68–71]. EA treatment lasting 3 to 7 days effectively decreased the inflammatory indices of sepsis combined with gastrointestinal injury, accelerated the recovery of bowel sounds and intra-abdominal pressure, enhanced intestinal permeability, and restored intestinal function as quickly as possible in two early studies with medium sample sizes (50 and 68 cases)[70,71]. Since then, two studies with large sample sizes have proven EA's efficacy in managing sepsis combined with gastrointestinal injury[68,69]. The three acupoints Zusanli (ST36), Guanyuan (RN4), and Tianshu (ST25) are the most commonly used for EA in the management of sepsis combined with gastrointestinal injury. The most often used prescription was "Zusanli (ST36) + Guanyuan (RN4)," which was followed by "Zusanli (ST36) + Tianshu (ST25) + Shangjuxu (ST37) + Xiajuxu (ST39)." The EA frequency was adjusted to a continuous wave at 4 Hz for 60 min. After 5 d of treatment, EA at "Zusanli (ST36) + Chize (LU5)" at a longitudinal wave frequency and 2/50 Hz for 30 min can help patients recover from their injuries and decrease their inflammation, according to a randomized clinical trial on 60 patients with sepsis combined with lung injury[59]. After 7 d of treatment, another controlled clinical trial involving 60 patients with sepsis and myocardial injury revealed that EA at "Neiguan (PC6) + Zusanli (ST36) + Shenmen (HT7) + Taichong (LR3) + Xuehai (SP10) + Geshu (BL17) + Sanyinjiao (SP6) + Hegu (LI4)" can aid in the recovery from myocardial injury[60]. EA at "Baihui (GV20) + Shuigou (DU26)" at the frequency of a longitudinal wave and 2/15 Hz for 30 min can aid in the recovery from brain injury in sepsis combined with brain injury, according to a recent randomized, double-blind controlled trial in 70 patients[61].

Immunological basis of EA to alleviate sepsis

Regulation of body fluids

Accumulating evidence has indicated that EA regulates systemic sepsis inflammation by inhibiting inflammatory cytokine concentrations in body fluids[72–76]. Zusanli (ST36) is an acupoint frequently used for treating sepsis and other inflammatory diseases[16,77]. A study by Zhang et al.[78] showed that EA at Zusanli (ST36) significantly attenuated the release of TNF-α and MCP-1 in peripheral blood of cecum ligation and puncture (CLP) rats and accordingly increased the survival rate of rats. Similarly, another two studies published in 2018 found that EA could alleviate inflammatory response and organ damage in septic rats, as well as inhibit the release of TNF-α, NO, myeloperoxidase (MPO), IL-1, IL-6, and HMGB1[79,80]. Interestingly, pre-treatment with EA also had a protective effect against sepsis-induced multi-organ injury. In rats with acute lung injury (ALI), EA pretreatment at "Chize (LU5)" and "Zusanli (ST36)" improved lung function and pathology by inhibiting the levels of TNF-α, IL-1β, and IL-8[81]. In addition, EA can improve cerebral, renal, and intestinal functions by decreasing cytokines levels[72,73,76]. In general, the anti-inflammatory effect of EA may be related to the activation of autoimmune reflexes, such as the somatic sympathetic-splenic, somatic sympathetic-adrenal, somatic vagal-splenic, and somatic vagal-adrenal reflexes, as well as the stimulation of peripheral nerves to induce localized reflexes, such as the somatic sympathetic-pulmonary reflex[82]. EA also works primarily by modulating several inflammatory factor-related signaling pathways to lower inflammatory factors in sepsis and its associated complications[83,84].

Several inflammatory cytokines involved in sepsis have been employed in EA research to increase its therapeutic effect on sepsis.

Effects on autonomic pathway

Activation of cholinergic anti-inflammatory pathway

The cholinergic anti-inflammatory pathway, which involves the cholinergic vagus nerve and its transmitters, controls systemic inflammation[85]. The CAP, a neurological mechanism that suppresses inflammation, was first discovered by Borovikova et al[86]. They revealed that parasympathetic nervous system activity, initially called the "cholinergic anti-inflammatory pathway," influences circulating TNF levels and the shock response to endotoxemia. CAP has received considerable attention over the past 20 years and is now widely recognized. Huston et al. discovered that the vagal nerve-mediated CAP was abolished after splenectomy[87,88], demonstrating the significance of the spleen in CAP. In the case of acupuncture induced by CAP, somatic sensory fibers convey a signal to the brain's central nervous system (CNS) *via* the spinal cord, where it is received. The CNS stimulates the efferent vagal neurons in the dorsal motor nucleus of the vagus (DMV), causing them to produce acetylcholine (Ach). Ach affects splenic sympathetic nerves directly or indirectly through the celiac ganglion[89]. Norepinephrine and other neurotransmitters are released into the spleen when the efferent vagus nerve stimulates the splenic nerve[89]. Norepinephrine then activates choline acetyltransferase-expressing T-cells, possibly *via* adrenergic receptors (AR), and promotes the production and release of ACh from T-cells. The ACh then interacts with the α7 nicotinic acetylcholine receptor (α7nAChR) on macrophages and other immune cells to stop the release of pro-inflammatory cytokines, protecting the body from harm[90,91]. The CAP pathway is also known as the cholinergic vagosplenic anti-inflammatory pathway[92]. CAP also refers to the release of ACh from efferent vagal nerve endings, which activates cholinergic receptors on inflammatory cells, effectively inhibiting the release of various inflammatory factors (TNF, IL-1, IL-6, and IL-18) and significantly reducing local and systemic inflammatory response[85]. Finally, the anti-inflammatory effects of cholinergic anti-inflammatory signals are exerted intracellularly through the pathways of NF-κB, mitogen-activated protein kinase (MAPK), and STAT3[93].

Several earlier studies have demonstrated that stimulation of the vagus nerve plays a major role in the effects of EA on sepsis[62,94–97], including lowering inflammatory factors, inhibiting oxidative stress, and preventing multiple organ damage. The benefits of EA are considerably diminished or eliminated when the vagus nerve is severed, which also causes tissue TNF-α levels to increase and worsen organ damage. The next research focused on the cholinergic receptor α7nAChR of CAP, according to Yue et al.[98–100], EA can reduce the inflammatory response in infected mice by triggering CAP. TNF-α and HMGB1 levels were significantly decreased in the EA group, whereas the levels of inflammatory factors in the cholinergic receptor α7nAchR inhibitor group were significantly higher. MiRNA146 is involved in the expression of numerous inflammatory genes and transcription factors at the post-transcriptional level in the inflammatory response in a negative feedback form, in contrast to the effect of α7nAchR agonists in reducing macrophage inflammatory factor release, which occurs at the post-transcriptional level. Therefore, post-transcriptional levels were studied. Furthermore, Wang[101] found that EA activation of the vagus nerve increased the expression of miRNA146 in macrophages, which inhibited the expression of inflammatory factors and significantly increased the survival rate of septic mice while minimizing organ damage and systemic inflammatory response. In the cholinergic receptor activator group, inflammatory factors were dramatically reduced and miRNA146 levels were significantly elevated; in the EA group, miRNA146 levels were significantly higher than those in the cholinergic receptor inhibitor group, and *vice versa*; in the anti-miRNA146 group, inflammatory factors were significantly higher, survival rate was significantly lower, and organ damage and systemic inflammatory response were significantly increased; in the high expression miRNA146 group, inflammatory factors significantly decreased, survival rate significantly increased, and organ damage and systemic inflammatory response were significantly reduced (all $P < 0.05$).

Activation of the vagal-adrenal axis

The significant role of the vagal-adrenal axis in the anti-inflammatory effects of EA was inspired[23]. They found that systemic inflammation in sepsis could be inhibited by EA at the sciatic nerve by inducing vagal activation of aromatic l-amino acid decarboxylase, leading to the production of dopamine in the adrenal medulla. In turn, the anti-inflammatory effects of EA were prevented in adrenalectomized mice[23].

Subsequently, Villegas-Bastida et al.[102] showed EA at ST36 could mitigate the inflammatory response and acute organ injury induced by CLP through vagal activation and a catecholamine-dependent mechanism. They found that the inhibition of serum TNF, IL-6, nitrite, and HMGB1 in CLP rats induced by EA at ST36 was prevented by subdiaphragmatic vagotomy or pharmacological blockade of catecholamines. Sepsis is associated with the overactivation of the sympathetic nervous system and elevated levels of endogenous catecholamines.

A recent study published in the journal *Neuron* demonstrated that low-intensity EA at ST36 drives the vagus-adrenal anti-inflammatory axis and produces anti-inflammatory effects dependent on neuropeptide Y (NPY) + adrenal chromophores by activating NPY + noradrenergic neurons through the spinal-sympathetic axis[17]. More evidence points to the fact that EA's anti-inflammatory benefits are preferable to those of low-intensity sluggish waves, which are safer and easier to manage, and that the vagal-adrenal anti-inflammatory axis predominantly drives these effects. In general, this research demonstrates that EA can activate different sympathetic nerve pathways, and somatization and stimulation intensity regulate the state of systemic inflammatory disease in a dependent manner. These findings have implications for improving the effectiveness and safety of EA practices.

Effects on other somatosensory autonomic pathways

EA at "Tianshu (ST25)" produces high-intensity electrical stimulation of the abdomen, which can have pro- or anti-inflammatory effects[17]. Additionally, body acupuncture therapy for immunological diseases can activate the cholinergic vagal-myenteric plexus system[16,103]. The cholinergic vagal immunomodulation pathway can function directly through post-parasympathetic neurons (the myenteric plexus) found in visceral organs independent of the spleen[92]. Through this cholinergic vagal-myenteric plexus route, it has been demonstrated that EA activation of ST36 can reduce pancreatitis, intestinal ischemia-reperfusion injury, and postoperative ileus-induced inflammatory responses[104–106]. However, the effect of the cholinergic vagal-myenteric plexus pathway in EA on sepsis is still unclear, so further research is required to determine how the cholinergic vagal-myenteric plexus route affects EA on sepsis.

Effects on signaling pathway

Inhibition of NF-κB signaling pathway

The association between EA and the NF-κB signaling pathway for sepsis and the associated complications of lowering inflammatory factors has received the most attention. After IκB kinase (IKK) catalyzes the phosphorylation of the IκB subunit, the IκB subunit is degraded and derepressed from NF-κB, which mediates the production of TNF-α, IL-6, IL-1, and other genes by binding to the promoters of numerous inflammatory factors[55]. Therefore, inhibiting the NF-κB signaling pathway could lower the inflammatory factors and suppress the sepsis inflammation.

First, Geng et al.[83] stated the effect of EA on the NF-κB signaling pathway. According to their research, EA at "Zusanli (ST36)" could lower the levels of NF-κB signaling pathway-related proteins (p65 and IκBα), preventing the release of inflammatory factors like TNF-α, IL-6, and IL-1β. This lowered the inflammatory response and reduced myocardial injury in septic rats. Other studies have also demonstrated that EA can reduce septic inflammation and improve multi-organ injury[107,108]. Next, the upstream molecules of the NF-κB signaling pathway are the research hotspot. Zhan et al. first focused on Toll-like receptors (TLRs). It is generally accepted that TLR4 functions as a transmembrane signaling molecular for LPS. Then, LPS activates IKK *via* myeloid differentiation factor 88 (MyD88), which phosphorylates IKKβ. Activated IKK, in turn, phosphorylates IκB and degrades it. Degradation of IκB allows the NF-κB complex to reach the nucleus and initiate transcription of genes encoding inflammatory factors[109]. By downregulating the TLR4/MyD88/NF-κB signaling axis, Zhan et al.[110] further demonstrated that EA at "Zusanli (ST36)" could reduce the production of inflammatory factors such as IL-1β, IL-6, and TNF-α, consequently inhibiting the inflammatory response and stopping the progression of sepsis. Huang et al.[111] identified another upstream molecule STING. It is primarily found in the endoplasmic reticulum, is activated by exogenous DNA, and is a crucial signaling molecule in the intrinsic immune response *in vivo*. STING activation starts the target-activated natural killer (TANK) binding kinase 1 (TBK1), the downstream signaling cascade interferon regulatory factor 3 (IRF-3), as well as the NF-κB signaling pathway, leading to the production of type I interferon and inflammatory factors[112]. Huang et al.[111] discovered that EA at "Zusanli (ST36)" and "Feishuxue (BL13)" reduced the activity of the proteins STING and its downstream related proteins (phosphorylated TBK1 (P-TBK1)/TBK1, phosphorylated NF-κB (P-NF-κB)/NF-κB), which suppressed the inflammatory response and lessened ALI in sepsis-infected mice by preventing the release of the inflammatory factors TNF-α and IL-6.

Inhibition of STAT signaling pathway

The STAT signaling pathway is another important signaling pathway. The release of additional inflammatory factors is mediated by Janus kinase (JAK) phosphorylation, which attracts and phosphorylates STAT. It allows STAT to enter the nucleus as a dimer, bind to target genes, control the transcription of downstream genes, and mediate the release of additional inflammatory factors, leading to a cascade of amplified inflammatory responses. Therefore, inhibiting the STAT signaling pathway can reduce inflammatory factors and decrease sepsis-induced inflammation.

According to Xie et al.[84], EA at "Neiguan (PC6)" and "Zusanli (ST36)" could downregulate the JAK1/STAT3 pathway, thereby blocking the release of the inflammatory factors TNF-α and IL-6, decreasing the inflammatory response and lung damage in septic rats. In addition, transfection with calpain-1 siRNA or other pharmacological calpain inhibitors reduced the elevation of TNF-α expression caused by LPS[113]. Moreover, LPS increases calpain activity in myocardial tissue, and STAT3, a protein that stimulates cardiac inflammation, has a biological role similar to calpain in cardiac myocytes. Therefore, according to research by Li et al.[114], in septic mice, the release of the inflammatory factors TNF-α, IL-1β, and IL-6 was inhibited by EA at "Neiguan (PC6)" and "Zusanli (ST36)" pre-treatment to downregulate the cardiac calpain-2/STAT3 pathway. This reduced cardiac inflammation. In cardiac myocytes treated with LPS, STAT3 phosphorylation, and inflammatory factors, it has decreased, along with the inhibition of calpain-2 by applying the appropriate siRNA.

Inhibition of oxidative stress

Evidence has shown that inhibiting oxidative stress can decrease sepsis inflammation and improve multi-organ injury. According to Hu et al., the exogenous antioxidant emodin reduced inflammation and decreased heart, liver, and lung damage in animal models of sepsis[115].

With higher levels of SOD and catalase (CAT) in hippocampal tissue and lower levels of MDA, TNF-α, IL-6, and neuron specific enolase (NSE) in hippocampal tissue (all $P < 0.05$), EA at "Zusanli (ST36)" has been shown by Li et al.[116] to effectively reduce brain damage, decrease inflammatory factors, and enhance cognitive function in septic mice after surgery. An important antioxidant enzyme is heme oxygenase 1 (HO-1), which primarily catalyzes the breakdown of heme into ferrous iron, carbon monoxide, and biliverdin. On the one hand, the degradation of the heme moiety makes it easier to block its pro-oxidant effects; on the other hand, the byproduct biliverdin and its reduced bilirubin have effective ROS scavenging activity against peroxides, peroxynitrite, hydroxyl, and superoxide radicals. Nuclear factor erythroid-2-related factor-2 (Nrf2) can directly control the activity of the HO-1 promoter and trigger the expression of HO-1 mRNA and protein[117]. Li et al.[118] further demonstrated that by triggering the Nrf2/HO-1 signaling pathway, EA at "Baihui (GV20)" "Quchi (LI11)" and "Zusanli (ST36)" might reduce oxidative stress in the hippocampi of rats suffering from sepsis-related encephalopathy.

In addition, Mu et al.[119] first demonstrated that EA at "Zusanli (ST36)" and "Baihui (GV20)" improved LPS-induced hippocampal injury by improving mitochondrial function and that EA treatment reduced neuronal damage in LPS-exposed mice while improving mitochondrial respiratory function, energy metabolism, and mitochondrial morphology. It was also discovered that HO-1 knockdown exacerbated LPS-induced hippocampal injury, decreased mitochondrial respiratory function, increased mitochondrial swelling, cristae relaxation, and vacuolar degeneration and that EA did not reverse the hippocampal injury and mitochondrial dysfunction caused by LPS after HO-1 knockdown. Mu et al.[120] also suggested that HO-1 is involved in ameliorating mitochondrial damage. HO-1 was involved in the process of reducing cognitive dysfunction in mice with sepsis-associated encephalopathy by EA at "Zusanli (ST36)" and "Baihui (GV20)" and the mechanism could be related to the dynamic balance of mitochondrial fusion-division. In the EA group, the expression of mitochondrial fusion protein 2 (Mfn2) and optic nerve atrophy-associated protein 1 (OPA1) were upregulated in the hippocampus. In contrast, the expression of mitochondrial dynamics-related protein 1 (Drp1) was downregulated, resulting in shorter escape latency and longer target quadrant exploration time ($P < 0.05$). The time spent exploring the target quadrant was also reduced ($P < 0.05$). Hippocampal Mfn2 and OPA1 expression was downregulated in the HO-1 knockout group, whereas Drp1 expression was upregulated, evasion latency was increased, and the target quadrant exploration duration was shortened ($P < 0.05$).

Regulation of the coagulation system

As described in the preceding section, cytokines promote coagulation system activation[44], which can further induce pro-inflammatory cell production[45]. Therefore, regulation of the coagulation system may help control sepsis-related inflammation. In experimental and preliminary clinical trials, the restoration of anticoagulant and physiological anticoagulation processes has been demonstrated as beneficial to treating sepsis[45]. Genetic or pharmacological inhibition of the STING-GSDMD-F3 pathway blocked systemic coagulation and improved animal survival in three models of sepsis (cecal ligation, puncture, and bacteremia with *Escherichia coli* or *Streptococcus pneumoniae* infection)[48].

A study by Niu et al.[121] first demonstrated that sepsis activates the coagulation system, inhibits anticoagulation mechanisms, and induces inflammation. Increased levels of tissue-type fibrinogen activator (t-PA), D-dimer, plasma fibrinogen activator inhibitor-1 (PAI-1) and TNF-α, decreased anticoagulation III (AT-III) activity were seen in the LPS group (all $P < 0.05$). It was then found that EA at "Zusanli (ST36)" had a significant impact on coagulation and fibrinolytic dysfunction and inflammation, with decreased t-PA, D-dimer, PAI-1, and TNF-α levels, increased AT-III activity in the EA group (all $P < 0.05$). They further demonstrated that CAP was associated with EA's improvement in coagulation and fibrinolytic activity. Further evidence showed higher t-PA, D-dimer, PAI-1, and TNF-α levels and lower AT-III activity in the vagotomy and silver cyclops groups (all $P < 0.05$).

The regulatory function of immune cells

As described above, sepsis involves prolonged immune suppression after inflammation. At this stage, some immune cells, such as $CD4^+$ and $CD8^+$ T cells, B cells, NK cells, and DC, will go through failure and apoptosis[122]. Additionally, an increase in immunosuppressive cells, Tregs, and MDSCs leads to the inhibition of effector T cells, NK cells, monocytes, and neutrophils[50,51]. Immune suppression usually occurs concomitantly with persistent inflammation, which increases long-term mortality[37]. Sepsis prognosis can be enhanced by inhibiting lymphocyte apoptosis[37]. For example, blocking Treg activity enhances microbial killing and immune function[24]. Therefore, regulating immune cells may control the immune suppression in sepsis and decrease mortality.

A study by Sun et al.[123] found that EA at "Zusanli (ST36)" and "Guanyuan (CV4)" could increase the number of immune cells like $CD3^+$ cells, $CD4^+$ cells, and the $CD4^+/CD8^+$ cell ratio in septic rats. Their study further found that EA at "Zusanli (ST36)" and "Guanyuan (CV4)" reduced the rate of apoptosis in thymus and spleen cells, respectively[124]. Furthermore, Xie et al.[125] found that EA at "Zusanli (ST36)" and "Tianshu (ST25)" increased the ratio of $CD3^+CD4^+/CD3^+CD8^+$ cells to Treg/Th17 cells. These results suggest that the reduction in apoptosis, an increase in immune cells, and the reversal of the immune cell/immunosuppressive cell imbalance are the primary manifestations of EA's effects on immune cells in sepsis and its complications.

EA boosts immune cells in sepsis by regulating several signaling pathways associated with apoptosis. The NF-κB signaling pathway regulates the expression of Bcl-2[55], a major negative regulator of cell death. Therefore, research focused on the relationship between Bcl-2 and EA during sepsis-induced immune cell apoptosis. Lei et al.[126] demonstrated that sepsis caused by abdominal infection resulting from CLP can increase the apoptosis of splenic lymphocytes and reduce Bcl-2 protein content in splenic lymphocytes. Next, they found that EA at "Zusanli (ST36)" reduced apoptosis of splenic lymphocytes in rats with abdominal infection caused by CLP. This process may be associated with stimulating Bcl-2 gene expression and increasing Bcl-2 protein levels in splenic lymphocytes. Then, a study by Sun et al.[123] investigated the relationship of NF-κB signaling pathway and EA on sepsis immune cells apoptosis. They demonstrated that stimulation of the "Zusanli (ST36)" and "Guanyuan

(CV4)" with EA may lessen immune cell apoptosis in septic rats by downregulating the TLR4/NF-κB signaling pathway, lessen immunosuppression, and increase CD3+, CD4+, and other immune cells as well as CD4+/CD8+ cell ratios, promoting disease recovery.

The important immunosuppressive checkpoint regulator PD-1[57] starts the process of T cell death independently. Anti-PD-1 antibody-mediated blockade of the PD-1:programmed cell death-ligand 1 (PD-L1) pathway reduces apoptosis and enhances immune cell activity in patients[127]. Studies have focused on the relationship between PD-1 and EA during septic immune cell apoptosis. Yang et al.[18] demonstrated that EA at "Zusanli (ST36) + Guanyuan (CV4) + Qihai (CV6)" might control immunological function and reduce inflammatory reactions in patients with sepsis by inhibiting the PD-1 pathway. The level of soluble PD-1 (sPD-1) in the EA group was lower than that in the conventional Western medicine group, and the percentages of CD4+ T lymphocytes, NK cells, and lymphocytes in the EA group were significantly higher than those in the conventional Western medicine group 5 d after treatment. Additionally, the levels of neutrophils, neutrophil-to-lymphocyte ratio, C-reactive protein (CRP), and TNF-α were significantly lower in the EA group, and the acute physiology and chronic health evaluation (APACHE)-II score was significantly lower than that of the conventional Western medicine group.

Some major immune cells in sepsis contribute to immunity by regulating the expression of multiple receptors or cytokine secretion, which play important roles in regulating immune reactivity in sepsis[122]. Immune cell abnormalities significantly increase sepsis mortality[37]. Therefore, regulating immune cells could control immune suppression in sepsis and decrease mortality. EA can inhibit sepsis immune suppression by inhibiting the NF-κB signaling pathway and PD-1 pathway, thereby decreasing sepsis mortality.

Conclusions

This literature review focused on how EA relieves sepsis and regulates the immune system in sepsis models. We found that the anti-inflammatory and immunomodulatory effects of EA depend on several mechanisms, including activation of CAP, activation of vagal-adrenal anti-inflammatory axis, activation of HO-1 signaling pathway, inhibition of NF-κB signaling pathway, inhibition of STAT signaling pathway, and inhibition of PD-1 signaling pathway (Figure 2).

However, there are limitations in the field of acupuncture research on sepsis. For example, it remains unclear which somatosensory fiber subtype mediates the immunomodulatory effects of EA. According to Xin et al.[128], systemic analgesia induced by EA with higher intensity

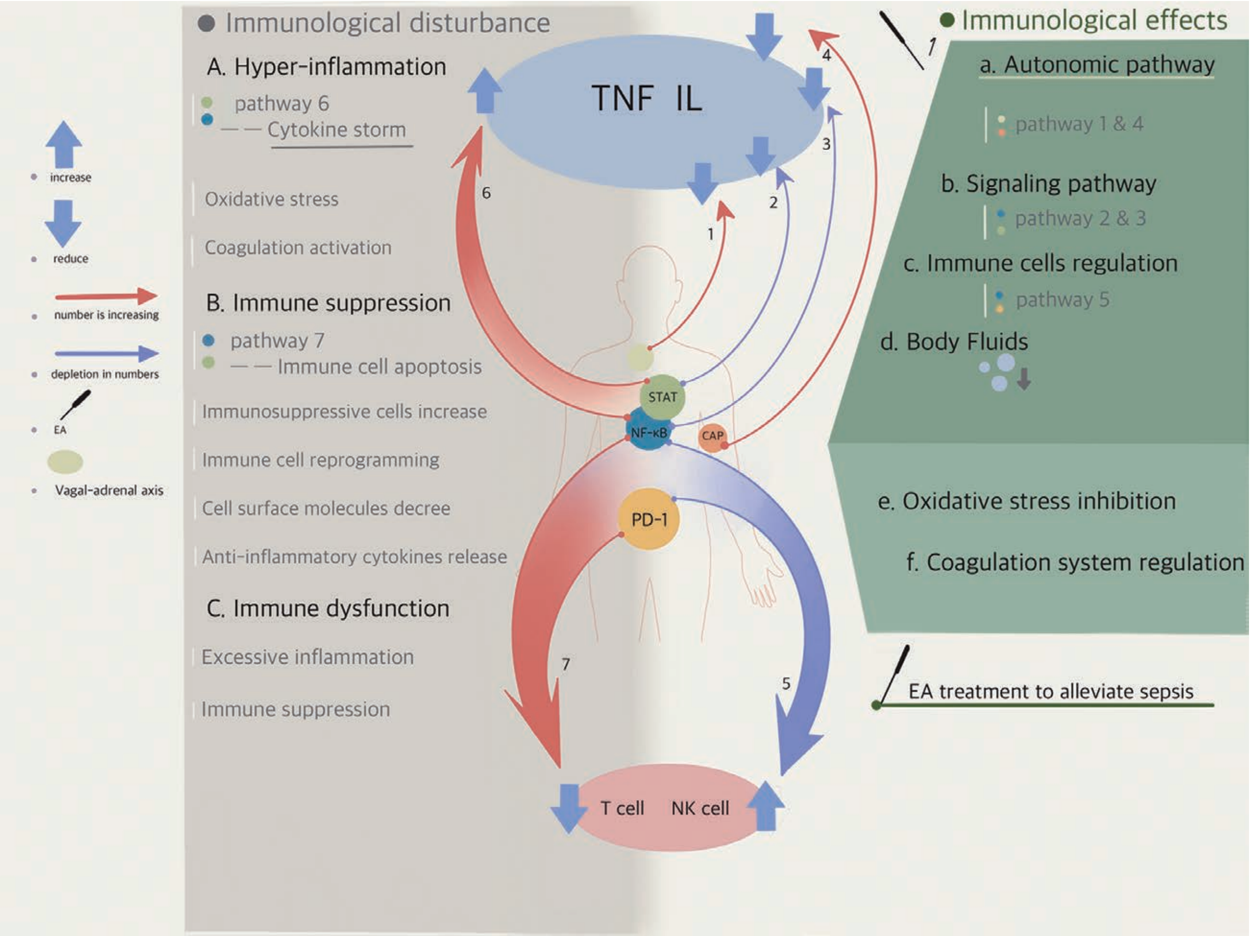

Figure 2. Immunological mechanisms of EA for alleviating sepsis and its complications. CAP: Cholinergic anti-inflammatory pathway; EA: Electroacupuncture; IL: Interleukin; NF-κB: Nuclear factor Kappa-B; NK: Natural killer; PD-1: Programmed death protein 1; STAT: Signal transducers and activators of transcription; TNF: Tumor necrosis factor.

is most probably caused by the transient receptor potential vanilloid subfamily member 1 (TRPV1) receptor on Aδ- and C-fibers, whereas segmental analgesia caused by EA at ST36 with lower intensity is partially mediated by the acid-sensing ion channel subunit 3 (ASIC3) receptor on Aβ-fiber. Liu et al.[129] showed that low-intensity EA stimulation (0.5 mA) with PROKR2Cre-marked Aδ-fiber reliant can trigger this vagal-adrenal axis from the hindlimb ST36 acupoint but not from the abdominal ST25 acupoint. However, few studies have discussed the subtypes of somatosensory fibers in the EA in sepsis. Based on the aforementioned papers, we hypothesize that the PROKR2Cre-marked Aδ-fiber, which can elicit the vagal-adrenal axis from the hindlimb ST36 acupoint to exert an anti-inflammatory impact, may be predominantly responsible for the immunomodulatory effects of EA on sepsis. Further research is required to determine the somatosensory fiber subtype that mediates the therapeutic benefits of EA in sepsis.

The following areas should be the focus of future studies: first, to carry out inhibitory studies to show which signaling pathways are crucial for EA to function and play a significant role in the treatment of sepsis; second, to determine whether there are synergistic, facilitative, inhibitory, and linking effects between various signaling pathways; third, to carry out direct mechanism tests to examine the direct interaction of EA with significant molecules in signaling pathways; fourth, to explore the bidirectional regulatory effect of EA on sepsis; and fifth, to explore which subtype of somatosensory fibers mediates the therapeutic effects of EA on sepsis.

In conclusion, EA offers great potential for use and development in treating sepsis and its complications, and its precise mechanism merits further research. With these results, our study will help reveal the potential mechanisms of EA and inform future research related to the role of EA as an anti-inflammatory and immunomodulatory medication. This study is also expected to contribute to further EA experimental and clinical trials. We believe this study is worthy of fundamental research on the inflammatory inhibition and immune adjustment effects of EA.

Conflict of interest statement

The authors declare no conflict of interest.

Funding

This research was funded by the National Key Research and Development Program (2022YFC3500704) and the National Natural Science Foundation of China (82174500, 82004491).

Author contributions

Mengyue Fang, Yuye Lan, Man Li, Bin Xu, Xianghong Jing, and Lingling Yu contributed to the idea of this article. Mengyue Fang, Yuye Lan, Xianghong Jing, and Lingling Yu contributed to performing the literature search and data analysis. Mengyue Fang, Yuye Lan, Xianghong Jing, and Lingling Yu drafted the manuscript. All authors contributed to the revision of the manuscript. Bin Xu obtained the funding.

Ethical approval of studies and informed consent

Not applicable.

Acknowledgments

None.

Data availability

All data generated or analyzed during this study are included in this published article.

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