JAR Journal of Acupuncture Research

Review Article

pISSN 2586-288X • eISSN 2586-2898
J Acupunct Res 2023;40(4):329-343
https://doi.org/10.13045/jar.2023.00248

Research Trends on Immune Mechanisms of Acupuncture: A Literature Review

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Recently, acupuncture has demonstrated extraordinary clinical results in the treatment of several categories of health conditions worldwide. The mechanisms of action of acupuncture (including immune mechanisms) have been investigated by biomedical studies over the last few decades. The immune mechanisms of representative clinical conditions and their clinical effects were thoroughly assessed, with a comprehensive investigation into the mechanisms of action of acupuncture (including immune responses) in this study. Conditions such as stroke, migraine, depression, chronic fatigue syndrome, lower back pain, hypertension, irritable bowel syndrome, sepsis, and allergic diseases were meticulously examined. This in-depth analysis aims to ensure a foundational understanding of the immune mechanisms involved in acupuncture, thereby serving as an initial step toward integrating the impact of acupuncture on the immune system.

Keywords: Acupuncture; Immunity; Inflammation; Mechanism; Traditional medicine

Received: October 30, 2023; Revised: November 9, 2023; Accepted: November 14, 2023

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INTRODUCTION

Acupuncture, a treatment modality that has been practiced for over 3,000 years, modulates body physiology by stimulating specific body sites (acupoints) [1]. Acupuncture is derived from the Latin words "Acus," which means needle, and "puncture," which means insertion [2]. Acupuncture was performed using steel, silver, or gold needles inserted at specific points (acupoints), and it has been practiced in Korea, China, and Japan for several years. It has been gaining acceptance and is being increasingly used in the Western world [3]. Recently, widespread scientific studies have been reported on the effectiveness of acupuncture, with increasing evidence pointing to the role of acupuncture in the treatment of many diseases [4].

Accepting acupuncture from a medical perspective is challenging due to its obscure theory and the paucity of corroborating scientific evidence concerning its mechanisms of action. Nevertheless, recent advancements in research and large-scale clinical studies have shed light on the logical and systematic mechanisms of acupuncture, particularly in the context of medical and immunological modalities [5]. Unclear mechanisms of action have been unveiled thanks to the rapid advancement of biological techniques to explore the physiological and biological mechanisms of acupuncture [1].

Herein, we review current advances and trends in the well-proven immune mechanisms of acupuncture. In particular, the representative and well-studied mechanisms of action of acupuncture have been reviewed and described in a disease-specific manner.

MATERIALS AND METHODS

1. Search strategies

We searched the PubMed and Web of Science databases for relevant studies published between 2019 and August 2023, with the last search conducted in September 2023. The search terms used were "acupuncture" and "immune mechanism."

1) Inclusion criteria

Only review articles describing the immune mechanisms of acupuncture in these diseases were included. Articles that reviewed disease categories more widely were preferred over those that focused on specific diseases. Articles on specific diseases were also included subsequently at the completion of this review.

2) Exclusion criteria

To obtain the latest information, we selected and reviewed the most recent article. We excluded articles with overlapping subject matter and those published outside the study period. However, we included articles published before the period stipulated in the selection criteria if they were essential for the review, which exclusively focuses on acupuncture. Other traditional remedies (such as moxibustion and herbal remedies) were not within the scope of this review. Additionally, articles primarily centered on clinical trials, protocols, case reports, or meta-analyses, as well as those lacking full texts, were excluded.

RESULTS

Overall, 135 items were identified by the search performed using the keywords "acupuncture" and "immune mechanism." Five articles were chosen per the selection criteria (Fig. 1). The reasons for the nonselection of articles were as follows: nine papers had study periods that fell outside the reference period, 20 papers involved other interventions such as herbal medicine and moxibustion, 85 papers did not have content related to acupuncture or outside the concept of this review topic; 11 papers were randomized controlled trials, and five papers had original texts that could not be located.

DISCUSSION

The immune and nonimmune mechanisms of acupuncture are integrated in a disease-specific manner. They have been well investigated in patients with ischemic stroke, migraine, depression, chronic fatigue syndrome, lower back pain (LBP), hypertension, irritable bowel syndrome (IBS), sepsis, and allergies. The effects of acupuncture were explained as major actions, which are elaborated as mechanisms of action (Table 1).

1. Ischemic stroke

Acupuncture is known to be effective in facilitating the rehabilitation of ischemic stroke and reducing post-stroke infarct volumes and neurological deficits by inherent mechanisms related to neurogenesis, neuroinflammation, neuronal cell apoptosis, and oxidative stress [6].

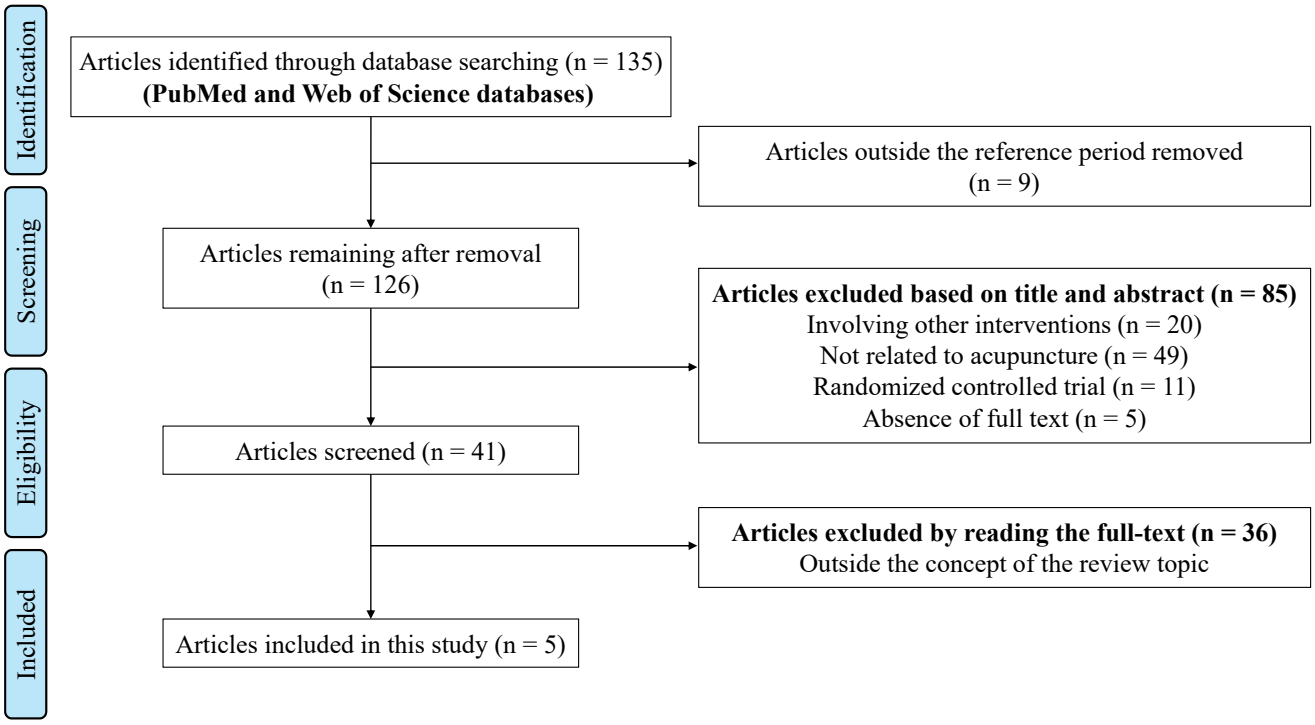

Fig. 1. Study selection flow chart for the review.

1) Alleviating neuroinflammation

Neuroinflammation plays a key role in the pathogenesis of ischemic stroke. Electroacupuncture (EA) has been reported to effectively attenuate inflammatory responses during the early stages of cerebral ischemia.

EA at LI11 and ST36 demonstrated the mitigation of motor impairment by inhibiting microglia-mediated neuroinflammation in the peri-infarct sensorimotor cortex [7]. EA appeared to attenuate the overactivation of microglia, suppressing the release of pro-inflammatory cytokines through the inhibition of NF-κB p65 nuclear translocation and the inactivation of p38 MAPK and MyD88 in the peri-infarct sensorimotor cortex following middle cerebral artery occlusion and reperfusion (MCAO/R) injury. The triggering receptor expressed on myeloid cells 2 (TREM2) is a microglia-specific receptor involved in the regulation of neuroinflammation in cerebral ischemia. EA at GV20, LI4, and LR3 has been reported to upregulate TREM2 expression by regulating the PI3K/Akt and NF-κB signaling pathways [8]. EA at TE5 and ST36 significantly increased the miR-223 levels, accompanied by a decrease in the NLRP3, caspase-1, and interleukin (IL)-1β, and IL-18 levels in the peri-infarct cortex. This resulted in the alleviation of inflammatory injury associated with brain ischemia/reperfusion [9].

2) Promoting neurogenesis

Acupuncture ameliorates neurological deficits and reduces brain edema in experimental stroke, which correlates with endogenous neurogenesis [10]. Acupuncture appears to promote the proliferation, migration, and differentiation of neural stem cells.

Acupuncture, specifically through EA at GV20 and ST36, reportedly decreased cerebral infarct sizes, enhanced neuronal function, and alleviated ultrastructural injuries to the hippocampus in a rat model of cerebral ischemia/reperfusion injury [11]. These effects appear to involve the down-regulation of the RhoA/ROCK signaling pathway, which regulates the myelin-associated inhibitors while promoting growth-associated protein 43 and brain-derived neurotrophic factor (BDNF) expression to ensure protection against cerebral ischemia/reperfusion injury.

Exosomes regulate the development and progression of nervous system diseases and play an important role in the regeneration and remodeling of the nervous system following neural injury [12]. EA enhances endogenous neurogenesis and mitigates neurological deficits following ischemic stroke [13]. Exosomal miR-146b has been identified as an important modulator of neurogenesis that promotes endogenous neural stem cell differentiation into neurons in the peri-ischemic striatum and sub-

Table 1. Main mechanisms of action of acupuncture for different diseases

Diseases or clinical conditions	Actions
Ischemic stroke	Alleviating neuroinflammation Promoting neurogenesis Inhibiting neuronal apoptosis Regulating oxidative stress
Migraine	Modulation of neuroinflammation Reduction of neuronal sensitization
Depression	Alleviating neuroinflammation Restoring hippocampal synaptic plasticity Regulating the HPA axis
Chronic fatigue syndrome	Regulation of the immune system Regulation of the neuroendocrine system Increase in antioxidative stress
Lower back pain	Anti-inflammatory action Regulating ATP metabolism Relieving central sensitization and neuroplasticity
Hypertension	Regulation of the neuroendocrine system Impact on the central nervous system Modulation of the renin-angiotensin-aldosterone system Rebalancing of the immune system Improvement of vascular structure Reduction of oxidative stress Reduced activation of the sympathetic nervous system
Irritable bowel syndrome	Alleviating visceral hypersensitivity Modulating the gut-brain axis and gut microbiota
Sepsis	Regulatory effects of acupuncture on immune function Enhancement effects of acupuncture on immunity under physiological conditions Bidirectional regulations of immune function by acupuncture under pathological conditions Anti-inflammatory effects of acupuncture
Allergy	Balancing the Th1/Th2 imbalance Reduction of the serum total IgE and specific IgE levels Reductions of total IgA and secretory IgA levels Increase in IL-10 levels Reduction of bronchiolar epithelium, smooth muscle thickness, and the number of goblet cells Downregulation of lung inflammation Reductions in the numbers of neutrophils and eosinophils

HPA, hypothalamic-pituitary-adrenal; ATP, adenosine triphosphate; Th1, T-cell subtype 1; IL, interleukin.

ventricular zone of the ischemic hemisphere by upregulating miR-146b following ischemic stroke.

3) Inhibiting neuronal cell apoptosis

Apoptosis is genetically programmed cell death. EA inhibits neuronal apoptosis, which leads to a reduction in neurological deficits and the restoration of injured cerebral cells following cerebral ischemic stroke. EA at LI11 and ST36 reportedly reduced the infarct volume, neurological deficits, and the number of apoptotic cells in the peri-infarct cortex in rats with cerebral ischemia [14]. The mechanism of the EA-induced reduction in apoptosis after ischemic stroke is presumably associated with the upregulation of the growth factor known as midkine and the mediation of the ERK/JNK/p38MAPK pathway. In another study, EA at LI11 and ST36 inhibited neuronal cell apoptosis, which was likely regulated by the PTEN pathway [15]. EA at GV20 and GV24 promotes functional recovery in poststroke rats by inhibiting neuronal cell apoptosis [16]. EA mediates neuronal apoptosis via multiple cellular pathways.

4) Regulating oxidative stress

Oxidative stress may cause neuronal apoptosis, inflammatory signaling pathway activation, and blood-brain-barrier impairment in ischemic stroke, thereby promoting

neurodegeneration and cell death [17]. Acupuncture exerts neuroprotective effects by alleviating cerebral ischemia-induced oxidative stress via the activation of the inherent antioxidant enzyme system and the inhibition of excessive reactive oxygen species (ROS) generation by regulating a battery of molecular signaling pathways involved in redox modulation. Laser acupuncture at GV20 significantly decreases the cerebral infarct volume alongside decreasing the malondialdehyde levels and increases in the catalase, glutathione peroxidase, and superoxide dismutase activity in rats with cerebral ischemia [18]. Based on this report, acupuncture was considered to have antioxidative effects in ischemic stroke. In addition, acupuncture reportedly increases the expression of redox effector factor 1, a sensitive marker of oxidative injury within the hippocampus, within the hippocampus, consequently producing antioxidative actions in rats with multiple cerebral infarcts [19]. EA at GV20 and GV14 delayed and reduced the development of ischemic brain edema by downregulating ROS generation and NAPDH oxidase 4 expression in mice with MCAO [20]. A key mechanism of neurodegenerative damage in ischemia/reperfusion injury is the overproduction of ROS. EA at GV20 induces manganese superoxide dismutase upregulation through cannabinoid receptor type 1 receptor-dependent signal transducer and activator of transcription 3 phosphorylation, which attenuates oxidative stress and results in neuroprotection [21].

2. Migraine

Migraine is an episodic, recurrent dysfunction of brain excitability characterized by moderate-to-severe unilateral throbbing and pulsating headaches [22]. Acupuncture is a widely used nonpharmacological therapeutic modality that provides favorable therapeutic effects with few adverse effects in the prevention and treatment of migraines [23].

The mechanisms of action of acupuncture are similar to those of other diseases. Based on basic experiments related to migraine, acupuncture appears to offer protective effects for neurons through various mechanisms [23]. Acupuncture may possess the ability to modulate neuroinflammation by reducing the release of trigeminal-activated neuropeptides (calcitonin gene-related peptide, substance P [SP], and pituitary adenylate cyclase-activating polypeptide), inhibiting dural immune cells (macrophages and mast cells), lowering the levels of inflammatory mediators (prostaglandin E2, IL-1β, cyclooxygenase-2, IL-6, tumor necrosis factor-alpha [TNF-α], vasoactive intestinal peptide, endothelin, and myosin light chain kinase). Additionally, acupuncture may reduce neuronal sensitization by decreasing the cytokine levels (BDNF, glutamate), relieving neuronal activation in the brain regions associated with migraines, and influencing the endocannabinoid and serotonin systems. This review explores the nonspecific modulatory effects of acupuncture on various brain regions involved in nociceptive perception and emotional disorders. Acupuncture may have a unique neural mechanism for alleviating pain and comorbidities associated with migraines. Studies have reported alterations in the brain following acupuncture in patients with migraine. These changes affect the regions associated with pain perception, emotional processing of nociception, and the occurrence of migraine auras.

3. Depression

The action mechanisms of acupuncture in addressing depression are multifaceted, which include inhibiting the hypothalamic-pituitary-adrenal (HPA) axis hyperactivity, regulating neuropeptides and neurotransmitters, promoting signaling pathways, modulating the expression of particular genes, reducing proinflammatory cytokine levels, and restoring hippocampal synaptic plasticity [24].

1) Alleviating neuroinflammation

Neuroinflammation is the response of the brain to physical injury or infection. In recent years, increased inflammation in patients with major depressive disorder has been reported, which was marked by elevated activity of pro-inflammatory cytokines, including IL-6, IL-1β, and TNF-α. In particular, chronic low-grade inflammation seems to activate brain immune cells, such as microglia, astrocytes, and oligodendroglia, which alter the brain structure and synaptic plasticity and consequently result in neurodegeneration in patients with depression [25]. In a recent report, acupuncture was reported to inhibit neuroinflammation, improve hippocampal pathological changes, and alleviate depressive symptoms.

In depressed rats, EA at GV20 and GV29 mediated the onset of depressive symptoms and down-regulated the IL-6 and IL-1β levels in the hippocampus [26]. Thus, EA potentially alleviates depression through a mechanism involving neuroinflammation and immunological modulation.

EA at GV20 and GB34 in rats with chronic unpredictable stress exhibited antidepressant effects with significant attenuation of behavioral deficits [27]. The antidepressant action was accompanied by a marked decrease in IL-1β-related microglial activation induced by depression, potentially mediated by P2X7-NLRP3 inflammatory

signaling.

Indoleamine 2,3-dioxygenase (IDO) is a key enzyme involved in tryptophan degradation along the kynurenine pathway. Proinflammatory cytokines activate IDO, which is a critical event in the transition from sickness to depression [28]. EA treatment effectively attenuated depressive-like behavior induced by lipopolysaccharides (LPS) by reducing the levels of inflammatory cytokines such as IL-1β, IL-6, and TNF-α in the blood and hippocampus. Moreover, EA prevented the overactivation of IDO and restored NR2B expression after a challenge with LPS [29].

2) Restoring hippocampal synaptic plasticity

The hippocampus is a key anatomical region associated with depression. Changes in hippocampal plasticity have been observed in the hippocampal volume, number of synapses, synaptic plasticity, glutamate receptors, neurogenesis, and glial cell plasticity in both human and animal models of depression [30]. Acupuncture improves depressive symptoms by regulating synaptic plasticity in the hippocampus.

BDNF is a major protein known for promoting synaptic plasticity and neuronal growth, serving as a key biological marker of neuroplasticity in the brain. BDNF has been identified as a central player in antidepressant action in the previous decades. It acts as a transducer that bridges antidepressant and neuroplastic changes, resulting in the improvement of depressive symptoms [31].

EA at LI4 and LR3 demonstrated similar antidepressant effects to fluoxetine, with EA even outperforming fluoxetine in the alleviation of depression [32]. The mechanisms underlying these effects are described as involving the activation of BDNF expression and its receptor, TrkB.

3) Regulating the HPA axis

The HPA axis serves as the ultimate convergence point in the stress response and manifestation of depressive symptoms. The most prevalent neuroendocrine abnormalities observed in individuals with depressive disorders are alterations in the HPA axis activity, which lead to the release of multiple hormones, including cortisol and proinflammatory cytokines, corticotropin-releasing factor, adrenocorticotropin hormone (ACTH), and glucocorticoids, impacting the behavior and physical function through their release [33]. Acupuncture alleviates the excessive activation of the HPA axis induced by stress via the modulation of this axis within the context of stress response and depression.

Acupuncture at PC6 demonstrates efficacy in ameliorating chronic corticosterone-induced depressive disorders by modulating the HPA axis [34]. In a prior study, acupuncture was found to significantly reduce depression- and anxiety-like behaviors while influencing neuropeptide Y expression in the hypothalamus. In rats subjected to chronic unpredictable mild stress, EA modulated the HPA axis and enhanced hippocampal 5-HT/5-HT1AR expression, ultimately resulting in an improvement in depressive symptoms [35].

4. Chronic fatigue syndrome

Acupuncture is an effective treatment for chronic fatigue syndrome. Although the mechanisms of action of acupuncture in chronic fatigue syndrome are uniquely disease-specific, they are also common in other neurological disorders [36]. Acupuncture regulates the immune system (including the peripheral immune organs), immune cells and cytokines, and proinflammatory and anti-inflammatory cytokines. Acupuncture regulates the neuroendocrine system, including the hypothalamus-pituitary-adrenal axis, stress hormones, monoamine neurotransmitters, and opioid peptides. Acupuncture increases the antioxidative stress ability by reducing malondialdehyde and upregulating the activity of antioxidant enzymes such as superoxide dismutase and glutathione peroxidase.

5. Lower back pain

The underlying mechanisms through which acupuncture induces analgesia are not completely understood, despite its widespread application in treatment [25]. Currently, the analgesic mechanism of acupuncture in LBP are explained by its anti-inflammatory actions, relief of central sensitization, and the regulation of adenosine triphosphate (ATP) metabolism.

1) Anti-inflammatory action

Pro-inflammatory cytokines play a major role in the development of inflammatory pain. The antinociceptive effects of EA are mediated by endogenous cannabinoids and peripheral cannabinoid CB2 receptors (CB2Rs) [25].

Acupuncture at acupoints GB30 and GB34 significantly reduced thermal hyperalgesia and mechanical allodynia attributed to tissue inflammation [37]. The levels of proinflammatory cytokines, such as IL-1β, IL-6, and TNF-α, were reduced by EA; inflammatory pain was alleviated in inflamed tissues via CB2R activation.

Endogenous opioid peptides, such as β-endorphin and met-enkephalin, play a role in inducing analgesic effects through acupuncture. These peptides activate opioid re-

ceptors at both the spinal cord level and in the peripheral sensory neurons at the site of inflammation [38]. The stimulation of opioid peptide release in the inflamed tissues is achieved via the application of EA on acupoint GB30, with the regulation of the chemokine CXCL10 (IP10, interferon [IFN]-γ-inducible protein 10). Consequently, EA may potentially prompt an anti-inflammatory cytokine profile characterized by increased expression of IFN-γ and CXCL10, along with an increased number of opioid peptide-containing CXCR3+ macrophages.

In this report, IFN-γ was discussed within the context of anti-inflammatory cytokines. Traditionally, IFN-γ has been classified as an inflammatory cytokine, which initially raised concerns because of its role in the stimulation of IP-10 (IFN-γ-inducing protein 10) and increased IFN-γ expression in the immunological mechanisms for analgesia during inflammation. In a previous study on regulatory B cells, IFN-γ was found to be capable of inducing the production of IL-10 by B cells [39]. This finding supports the role of IFN-γ in immune system regulation and balance, beyond its traditional classification as a simple inflammatory cytokine [40].

2) Regulating ATP metabolism

ATP plays an important role in the regulation of cellular biological activities and acts as an energy source. Adenosine, the core of the ATP molecule, regulates neuronal and non-neuronal cellular functions through recognition by specific receptors [41]. As a neurotransmitter, adenosine regulates pain transmission in the spinal cord and peripheral nerves.

Several studies have demonstrated that acupuncture may trigger an increase in the extracellular concentration of ATP and its metabolites near the acupoints [42]. Acupuncture-induced ATP is released from keratinocytes and subcutaneous mast cells. ATP stimulates the nociceptive terminals of sensory ganglia neurons, such as neurons of the dorsal root ganglion, and the signal is relayed via the dorsal root ganglia to the spinal cord and subsequently to the train stem through ascending pathways. Subsequently, the signals travel to certain centers in the cortex that receive pain and localize painful stimuli in the body. Locally released adenosine modulates these centers by delivering a signal that inhibits pain.

3) Relieving central sensitization and neuroplasticity

Central sensitization is defined as amplified neural signaling in the central nervous system (CNS) that elicits pain hypersensitivity as a memorized immune reaction. Two representative conditions for central sensitization are hyperalgesia and allodynia [43]. From the deficient mesocorticolimbic connectivity detected by resting-state functional magnetic resonance imaging (RS fMRI) in patients with LBP, mesolimbic dysconnectivity potentially mediates sensitization to chronic pain [44].

While several mechanisms of action for acupuncture have been proposed, many are brain-based. Neuroplasticity in somatosensory pathways emerges as a potential mechanism for addressing LBP and improving tactile acuity through this mechanism. A longitudinal neuroimaging study conducted in Korea reported reduced primary somatosensory cortex (S1)-back gray matter volume and increased fractional anisotropy in the white matter adjacent to the S1-back subregions, along with improved tactile acuity in patients with LBP [45]. Acupuncture simultaneously modulates reward systems; the amygdala have been suggested to be the key node that links two systems to produce antinociceptive effects [46].

6. Hypertension

Acupuncture is employed to regulate the neuroendocrine system, ultimately reducing blood pressure and providing protective metabolic effects [47]. Acupuncture regulates blood pressure through its impact on the CNS, the modulation of the renin-angiotensin-aldosterone system, the rebalancing of the immune system, the improvement of the vascular structure, and the reduction of oxidative stress. Acupuncture is considered a safer and more effective approach to the management of hypertension [48].

Acupuncture stimulation effectively reduces the activation of the sympathetic nervous system by activating the cholinergic system and opioid receptors in the rostral ventrolateral medulla [49,50]. This is in line with the previously reported naloxone-reversible cardiovascular depressant effect of acupuncture [51]. Notably, the heart rate responses, reflecting the autonomic nervous system's reaction to acupuncture, were found to vary according to the specific acupoints used [52].

7. Irritable bowel syndrome

Acupuncture is reportedly effective in attenuating IBS symptoms without any obvious adverse effects. Recent studies have demonstrated the mechanisms of action of acupuncture involving gastrointestinal (GI) motility, visceral hypersensitivity, and the brain-gut axis, neuroendocrine system, and immune system [25].

1) Alleviating visceral hypersensitivity

Visceral hypersensitivity is the main mechanism under-

lying abdominal pain in patients with IBS. Several mechanisms for visceral hypersensitivity have been reported, including inflammation, psychosocial factors, and altered sensorimotor function of the gut, as major components in the peripheral and central sensitization of the visceral afferent neuronal pathways [53].

Immune cells within the mucosal wall, including mast cells and enterochromaffin cells, play an important role in the sensitization of afferent nerves by releasing their mediators. Recent reports have highlighted the effective reduction of visceral hypersensitivity in IBS through acupuncture [25].

Mental stress is an important factor contributing to the onset and aggravation of IBS symptoms. CRH plays an important role in the stress response, leading to elevated levels of ACTH. This, in turn, significantly increases GI motility and visceral hypersensitivity in people with IBS [54]. SP, a GI peptide found in the CNS and GI tract, is a signaling molecule that connects the nervous system to the immune system [55]. Acupuncture regulates visceral hypersensitivity by alleviating mental stress in patients with IBS.

Chronic visceral hypersensitivity is closely related to central sensitization at the spinal level. The central sensitization of the spinal cord plays a crucial role in the activation of the NMDAR (N-methyl-D-aspartate receptor) [56], as the NMDAR is an ionotropic glutamate receptor expressed in the nervous system, which is expressed in the nervous system, which is involved in excitatory synaptic transmission. EA at ST36 and ST37 significantly inhibited the hyperphosphorylation of spinal cord NMDAR in a rat model of chronic visceral hypersensitivity [25]. EA appears to offer a promising therapeutic approach for alleviating chronic visceral hypersensitivity in IBS by modulating the activity of spinal cord NMDAR, thus regulating central sensitization.

2) Modulating the gut-brain axis and gut microbiota

The gut-brain axis is a bidirectional communication system that integrates brain and GI functions, such as gut motility, appetite, and weight. Microbiota play a critical role in the gut [57].

The gut-brain axis consists of the enteric nervous system, CNS, peripheral gut wall, and HPA axis. The pathogenesis of IBS is suspected to be associated with abnormalities in the gut-brain axis and gut microbiota. Changes in gut microbiota alter the immunity and integrity of the gut, modulating the gut-brain axis and gut neuromuscular junction [58]. Acupuncture specifically attenuates IBS symptoms by restoring the balance of the gut-brain axis and gut microbiota [59].

In a randomized controlled clinical trial, EA and mild-warm moxibustion at ST25 and ST37 significantly improved symptoms in patients with IBS and constipation; EA was more effective than mild-warm moxibustion [60]. These effects seem to be mediated through the modulation of the gut-brain axis.

Alterations in gut microbiota composition are important in IBS because they play an important role in the pathophysiology of IBS by increasing the permeability of the intestinal mucosal barrier and modulating cytokine secretion. IL-18, a pro-inflammatory factor in the GI tract, excites macrophages, differentiates T-cell subtype 1 (Th1) cells, induces the production of IL-1β and TNF-α by Th1 and natural killer (NK) cells, and promotes the synthesis of TNF and other chemokines [61]. Postinflammatory IBS is associated with a significant increase in IL-18 levels and changes in the microbiota diversity. EA appeared to improve IBS symptoms by decreasing the IL-18 levels and altering the composition of the microbiota, especially fusobacteria.

8. Sepsis

Although sepsis is initiated by infection, it is associated with immunoregulation. Therefore, the pathophysiology of immunological control should be understood for effectively controlling sepsis. To understand the mechanism of action of acupuncture in sepsis, it is necessary to understand the pathophysiology of sepsis.

1) Pathophysiology of sepsis

The clinical manifestations and pathological complications of sepsis are caused by the dysregulation of host immune responses rather than by the direct actions of the invading pathogens [62].

When pathogens stimulate the immune and infected tissue cells, they release a host of cytokines and pro-inflammatory substances, including ILs (IL-1, IL-8, IL-18), TNF-α, IL-6, IL-33, as well as type I and type III IFN. This is known as a primary cytokine storm [63]. These cytokines have a positive feedback effect that can activate the immune system to release more cytokines, leading to a secondary cytokine storm that further strengthens the inflammatory response to effectively kill pathogens [64].

In this situation, progression to a worsening course of the disease is observed in several patients, leading to the development of sepsis, along with conditions such as acute respiratory distress syndrome, septic shock, and multiple organ dysfunction syndrome. The central issue

in sepsis lies in the dysregulation of the immune system. The pathophysiological mechanism of sepsis involves a cytokine storm, characterized by excessive inflammatory reactions in the early stages of infection, clinically referred to as cytokine release syndrome. In a normal inflammatory response, the release of pro-inflammatory factors is balanced by the release of anti-inflammatory factors such as IL-4, IL-10, IL-11, IL-13, and IL-1Ra. This self-regulation of the immune system is known as the "compensatory anti-inflammatory response" (CARS) [63]. Essentially, sepsis arises from the dynamic equilibrium between the pro-inflammatory and anti-inflammatory factors being disrupted, with an initial hyperactive immune response followed by the activation of CARS to limit tissue damage. While CARS can be beneficial in restoring immune balance, it can also result in the shutdown of the immune response when it overreacts and fails to regulate the immune response in a timely manner. This ultimately results in a state of immune paralysis, in which both the innate and adaptive immune functions are severely compromised. These conditions make clearing the damaged tissues challenging in later stages; moreover, latent pathogens may become reactivated, causing secondary infections. In this state, the immune response becomes exhausted. Thus, careful regulation of the immune system according to the immunopathogenesis of sepsis and septic shock is imperative.

2) Regulatory effects of acupuncture on the immune function

According to ancient and contemporary literature, acupuncture works rapidly, often quickly reversing critical conditions [63]. However, the combination of acupuncture and medical treatment is considered appropriate for the control of sepsis and septic shock currently. Acupuncture has been suggested as a promising clinical anti-inflammatory therapeutic option.

EA applied at ST36 acupoints has demonstrated the ability to suppress zymosan- or carrageenan-induced paw inflammation [65]. Intriguingly, low-frequency (1 Hz) EA produces a localized suppressive effect through the activation of postganglionic neurons, essentially creating a somatic-sympathetic reflex. In contrast, high-frequency (120 Hz) EA suppression operates via the sympathoadrenal medullary axis, leading to the production of systemic catecholamines, resulting in effects throughout the entire body. Furthermore, selective stimulation of acupoint ST25, which connects to the same spinal cord segment responsible for sympathetic innervation to the spleen, triggers the somatic-sympathetic-splenic reflex, culminating in a systemic effect of immune modulation [66]. These recent findings concerning distinct immune reflex pathways suggest the possibility of selectively treating specific organs and local tissues affected by inflammation and dysfunction.

Acupuncture modulates multiple physiological systems, including the immune system, to maintain homeostasis by activating the peripheral nerves to evoke physiological reflexes (spinal and supraspinal reflex) and central integration [63]. Research on the impact of acupuncture on immune function has been attempted since the middle of the last century and has produced tremendous pieces of evidence revealing the various regulatory effects of acupuncture on the immune system over the last decades.

3) Enhancement effects of acupuncture on immunity under physiological conditions

Acupuncture enhances immunity in normal humans and physiological animal models and can enhance innate immune functions [63]. EA at ST36 upregulated the function of NK cells and macrophages, which play a central role in the innate immune response, especially in killing virus-infected cells in rat models [67]. Acupuncture also increased the weight of the mouse thymus. Acupuncture can increase the number of lymphocytes in peripheral blood and the lymphocyte transformation rate in animals and humans. Acupuncture increased T lymphocyte function in an aging animal model [68]. In the elderly, immunoglobulin (Ig)G and IgM levels increased after acupuncture for 20 days [69].

Splenic NK cell activity increased by EA, which correlated with the activation of the hypothalamus [63]. Acupuncture-induced immune enhancements do not present with selective destruction of the lateral hypothalamic area [70]. However, the effects of acupuncture on immunity are state-dependent. For instance, under diseased conditions, the effects of acupuncture may differ from those under normal conditions.

4) Bidirectional regulations of immune function by acupuncture under pathological conditions

Acupuncture has bidirectional regulatory effects on the body's homeostasis, depending on the individual's condition (whether they are in a hyper- or hypo-functional state according to patients or pathological animal models) [63]. For example, EA at ST36 both stimulates stress-induced delayed gastric emptying and inhibits stress-induced colonic transit acceleration [71].

Acupuncture enhanced the suppressed innate immune

functions by upregulating the decreased function of NK cells and macrophages [63]; conversely, acupuncture downregulated the activity of these immune cells and related cytokines when they were in a hyperactive state such as inflammation.

Acupuncture has bidirectional regulatory effects on T-lymphocyte function [72]. The balance between Th1/Th2 in different diseases is modulated by acupuncture [73]. Acupuncture downregulates Th2-specific cytokines [74,75] to improve Th2-dominant disorders such as allergic rhinitis [76] and chronic fatigue syndrome [77]. Acupuncture also modulates Th1/Th2 balance by inhibiting Th1 responses in Th1 dominant disorders such as rheumatoid arthritis [78], ulcerative colitis [79], and depression. These bidirectional regulatory effects of acupuncture are a unique characteristic. A patient-tailored approach by acupuncture is possible due to its bidirectional regulatory effects.

5) Anti-inflammatory effects of acupuncture

Acupuncture and EA are effective in modulating immunity in animals and humans [63]. In animal models, acupuncture at ST36 has demonstrated considerable benefits in protecting multiple organs from sepsis-induced injuries and maintaining immune balance to attenuate inflammation [80]. Acupuncture was confirmed to possess a reliable anti-inflammatory effect, uncovering new features and mechanisms through the utilization of a specific strategy [66].

EA inhibited the release of key pro-inflammatory factors. Notably, the levels of pro-inflammatory factors such as TNF, IL-6, monocyte chemoattractant protein-1, and INF-γ in the acupuncture group were significantly reduced. Conversely, the anti-inflammatory factor IL-10 was either increased [81,82] or did not change significantly [83]. These findings indicate that acupuncture does not merely suppress the immune response but rather modulates its balance. Nevertheless, the anti-inflammatory effect of acupuncture is evident with acupuncture demonstrating similar efficacy as indomethacin (a classic nonsteroidal anti-inflammatory drug) in suppressing cytokines in both peripheral and brain stem tissues [82].

The anti-inflammatory effects of EA are primarily achieved by activating the vagal-splenic [66,83-85], vagal-adrenal medulla-dopamine [63], and sympathetic-splenic pathways [66] rather than activating the HPA cortical axis. This was proven by the finding that EA pretreatment did not increase the serum corticosteroid levels in an animal model of sepsis [83].

Acupuncture is applicable as an adjuvant therapy owing to its advantages of easy use, low cost, lack of chemical side effects, and the ability to modulate both immune and multiple organ functions. Acupuncture should be included in the comprehensive treatment plan for sepsis. The protocols were designed to induce the somatic-autonomic reflex by stimulating the peripheral nerves that produce sympathetic or vagal effects on the functional regulation of organs or physiological systems, including the immune system.

The spinal somatic-sympathetic reflex follows the anatomical neurachy by the segmental control of the spinal cord. The effect of a somatic-sympathetic reflex on a specific organ is obtained in a limited manner by stimulating the somatic nerve connected to the spinal cord segments (usually 1–5 segments), similar to that of other organs. The spleen is innervated by the sympathetic nerve from the T5–T8 spinal cord segment and only stimulation from the somatic nerve zone belonging to the T5–T8 segments produces a reflex effect on the spleen. Similarly, T8–L1 for the adrenal medulla and T1–T5 for the lung were stimulated according to the relevant anatomy.

The somatic-vagal reflex is unique. The vagal reflex, which controls the GI tract, is induced by the stimulation of the peripheral nerves or the acupoints at the limbs (not the trunk) with high-intensity (activating Aδ and C fibers) stimulation [67,86]. For the activation of the vagal-adrenal reflex, the stimulation of 0.5 mA (lower than the threshold of Aδ) is sufficient [66].

EA at ST36 and CV4 decreased thymocyte apoptosis in a rat model of sepsis, and acupuncture prevented immune paralysis in animals with sepsis. Acupuncture reduces plasma IL-10 levels in patients with chronic allergic rhinitis [63]. The release of pro-inflammatory factors was suppressed and the release of anti-inflammatory factors decreased simultaneously, with the latter being triggered by the former. Reducing pro-inflammatory factors by acupuncture at an early stage also reduces anti-inflammatory factors thereafter, which may help avoid the CARS to prevent immune paralysis and consequently increase the survival rate of animals with sepsis.

9. Allergy

Acupuncture involves the stimulation of acupoints located at the meridian lines that correspond to the flow of energy through the body [87]. Acupuncture stimulation elicits anti-inflammatory effects via reflexive central inhibition of the innate immune system. Acupuncture has been proven to balance the Th1/Th2 imbalance in al-

lergic diseases; however, further studies are warranted.

1) Allergic rhinitis

Acupuncture using the SF-35 form was potent in reducing symptoms and medication scores, with a significant reduction in the serum IgE levels, in a meta-analysis of over 2,000 patients with allergic rhinitis in 13 trials [88].

In another review article that summarized six randomized controlled trials on acupuncture for allergic rhinitis, the total and specific IgE levels remained unchanged, accompanied by an increase in the IL-10 level and negligible alterations in the IL-4 and IFN-γ levels [89].

2) Bronchial asthma

The bronchiolar epithelium, smooth muscle thickness, and the number of goblet cells were reduced by acupuncture performed at BL13 and BL13 + ST36 [90]. Acupuncture at BL13 undermines acetylcholine synthesis and release, with the downregulation of inflammatory infiltration of the lung tissue [91].

Acupuncture at GV14, BL12, and BL13 on alternate days for five days in allergic asthma dramatically reduced the concentrations of secretory IgA and total IgA in the saliva and nasal secretions, with a significant decrease in the total IgE levels and IL-2R+ T cell and eosinophil counts in the serum [92].

The mechanisms of action of acupuncture in asthma were reviewed in an article that included eight studies involving 1,083 patients. In this study, pulmonary function improved with a decrease in the total IgE and IL levels; however, no significant change in the eosinophil cation protein level was observed [93]. Acupuncture significantly undermined IL-6 levels in another review [94].

3) Atopic eczema

Reduced basophil counts have been detected in patients with atopic eczema [95]. Acupuncture at BL13 + ST36 significantly reduced the neutrophil count, while acupuncture at both BL13 and BL13 + ST36 reduced the eosinophil counts.

CONCLUSION

The mechanisms of action of acupuncture are reportedly diverse, involving different pathways, axes, reflexes, and systemic immunologic responses according to the relevant diseases from several review articles and original articles.

To fully comprehend the mechanisms of action of acupuncture, studying the traditional medicine of East Asia (which is rooted in experimental theories) through the lens of modern research supported by empirical evidence is essential. In conclusion, numerous immunological mechanisms of acupuncture are shared among various diseases, despite some mechanisms of action being uniquely disease-specific. To advance and further develop acupuncture, these well-established immune mechanisms should be systematically integrated with novel perspectives in future studies.

AUTHOR CONTRIBUTIONS

Conceptualization: JN, JHK. Data curation: JN, JSY, YGS, SS. Funding acquisition: JHK. Investigation: JN, GN, SPB, JHK. Methodology: JN, GN, JHK. Supervision: JN, JL, JCS. Writing – original draft: JN, JHK. Writing – review & editing: All authors.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

FUNDING

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korean government (MSIT) (No. NRF-2021R1A2C2007041).

ETHICAL STATEMENT

This research did not involve any human or animal experiment.

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