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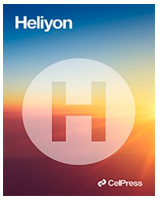

Review article

Comprehensive landscape-style investigation of the molecular mechanism of acupuncture at ST36 single acupoint on different systemic diseases

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ABSTRACT

The principle of acupoint stimulation efficacy is based on traditional meridian theory. However, the molecular mechanisms underlying the therapeutic effects of acupoints in treating diseases remain unclear in modern scientific understanding. In this study, we selected the ST36 acupoint for investigation and summarized all relevant literature from the PubMed database over the past 10 years. The results indicate that stimulation of ST36 single acupoints has therapeutic effects mainly in models of respiratory, neurological, digestive, endocrine and immune system diseases. And it can affect the inflammatory state, oxidative stress, respiratory mucus secretion, intestinal flora, immune cell function, neurotransmitter transmission, hormone secretion, the network of Interstitial Cells of Cajal (ICC) and glucose metabolism of the organism in these pathological states. Among them, acupuncture at the ST36 single point has the most prominent function in regulating the inflammatory state, which can mainly affect the activation of MAPK signaling pathway and drive the "molecular-cellular" mode involving macrophages, T-lymphocytes, mast cells (MCs) and neuroglial cells as the core to trigger the molecular level changes of the acupuncture point locally or in the target organ tissues, thereby establishing a multi-system, multi-target, multi-level molecular regulating mechanism. This article provides a comprehensive summary and discussion of the molecular mechanisms and effects of acupuncture at the ST36 acupoint, laying the groundwork for future in-depth research on acupuncture point theory.

1. Introduction

Acupoint needling is an important treatment tool in Chinese medicine, and acupoints are important concepts in traditional Chinese

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medicine theory. Acupoints mainly refer to special points or areas on the meridian lines of the human body and have different properties that make them good at treating different diseases. Acupoints require certain intervention means to truly play a therapeutic role. In the clinic, acupoints are usually stimulated by needling, electroacupuncture, moxibustion, etc. to treat relevant diseases, and the efficacy of acupoint stimulation has been confirmed in some existing clinical randomized controlled trials [1–5]. However, the underlying principle of how acupoint stimulation exerts a therapeutic role remains to be elucidated.

In recent years, research on the mechanism of acupuncture has emerged. The neuroanatomical mechanism behind the effect of electroacupuncture at ST36, as discovered by Professor Ma Qiufu's team, is associated with the presence of abundant PROKR2-Cre neuronal fibers at ST36. These fibers can activate the vagus-adrenal axis, leading to anti-inflammatory responses. This provides the scientific basis for using acupuncture at traditional acupoints in the treatment of diseases in modern medicine [6]. Thus acupoint needling can not only elicit changes in the local microenvironment of the acupoints, but also stimulate the functions of distal tissues or target organs innervated by the manipulated nerves, thereby regulating release of neurotransmitters, hormones and other signaling molecules [7].Taking ST36 as an example, metabolomics and proteomics analyses demonstrate that needling ST36 can affect proteins involved in transport, signaling pathways, and receptor interactions, and these proteins play key roles in regulating various metabolic pathways and may influence each other [8]. These include inflammatory response, immune response, oxidative stress, cell differentiation, hormone secretion, neural signaling, and intestinal flora. Therefore, the effects of acupoints result from the interaction of multiple factors. Such multi-linked, multi-factor, multi-systemic network regulation is considered the most fundamental model of acupoint stimulation effects and a current hot topic in acupoint research. Hence, the authors systematically reviewed the relevant literature, and took ST36 as an example to summarize the molecular effects of needling ST36 under pathological models. Approaching from a molecular biology perspective, they attempt to elucidate the mechanism underlying acupoint ST36 in treating diseases, comprehensively demonstrating the application scope of ST36. This lays the foundation for modern scientific interpretation of the action of ST36 and the possible mechanisms.

2. Literature retrieval methods

2.1. Retrieval strategy

We conducted a literature search on PubMed, focusing on articles published between January 2012 and October 2023. The search terms used in the title and abstract: ("Acupuncture" or "Stimulation" or "Electroacupuncture" or " Moxibustion") and ("ST36″ or "Zusanli"). No language restriction was applied and all literature was limited to animal studies. Applying the site's search engine for initial filtering, we identified 1778 relevant articles imported into Excel by removing 2878 duplicates from a total of 4816 documents.

2.2. Literature inclusion criteria

The literature included publications that were either published or had research results. It mainly consisted of basic research conducted on animal experiments. Intervention modalities were limited to manual acupuncture or electroacupuncture. Therapeutic point selection focused solely on studies involving a single ST36 point. The evaluation indexes of experimental results primarily involved biomolecular type, including genes, proteins, cytokines, hormones, etc.

2.3. Literature exclusion criteria

Literature was excluded with article type classified as review, data mining, systematic evaluation, meta-analysis. Additionally, Literature with article content related to case experience, clinical randomized controlled study was excluded. Articles were also excluded if they involved acupuncture used in combination with other therapies, such as acupuncture combined with drug injection to treat disease, acupuncture combined with moxibustion to treat disease, etc. Furthermore, literature in which the experimental point selection included ST36 but the number of points used was greater than or equal to two was excluded. Finally, we excluded non-molecular mechanism studies that evaluated experimental results based solely on physical indicators, such as blood pressure, gastrointestinal peristaltic rhythm, etc.

2.4. Literature analysis and results

Based on a number of published articles of the same type, we selected key data for extraction. A data source repository was created through Excel, and criteria for extracts were established, including authors, animal models, intervention methods, intervention parameters and measurements. Four authors extracted this data, and the remaining authors cross-checked it for final integration.

Before selecting the target literature, Excel was applied to import the relevant literature and manually screen the research literature that matched the topic. Among them, 63 articles of review and systematic evaluation, 131 articles of irrelevant literature (including data mining, meta-analysis and visualization analysis) and invalid literature (personal experience and articles without valid results) were excluded. Additionally, 190 articles of non-molecular mechanism studies, 142 articles of combination therapies (including combination of needles and drugs, combination of acupuncture and moxibustion, and etc.), 1026 articles of dual-acupuncture point or group-acupuncture point studies, and 36 articles of clinical studies were also excluded. Finally, 190 valid literatures were included in the study. This process involved data extraction by one author and proofreading by other researchers. The screening process is shown in Fig. 1.

3. Effect of acupuncture at ST36 on different systemic diseases

3.1. Respiratory system diseases

In respiratory diseases, acupuncture at ST36 may ameliorate respiratory symptoms by modulating the inflammatory state, oxidative stress and respiratory mucus hypersecretion mainly through the Janus kinase/Signal transducer and activator of transcription (JAK/STAT) signaling pathway, and acupuncture at ST36 may play a therapeutic role in models of acute lung injury (ALI), asthma, chronic obstructive pulmonary disease (COPD) and acute respiratory distress syndrome (ARDS). Details are shown in Table 1.

3.1.1. Regulation of inflammatory states

In respiratory diseases, including COPD, asthma, ALI, and ARDS, they all have varying degrees of inflammation in the lungs and respiratory tract, causing damage to pulmonary capillary endothelial cells and pulmonary epithelial cells, and can even induce bronchial smooth muscle spasms and dyspnea [18–20]. Research has found [9,10] that electroacupuncture at ST36 can alleviate inflammatory injury in lung tissues and periphery by reducing the release of inflammatory mediator interleukin-6 (IL-6) and inhibiting the activation of JAK1/STAT3 pathway in plasma and lung tissues of the ALI model, which in turn decreasing the expression of downstream signaling molecules, factors tumor necrosis factor α (TNF-α), Bcl-2-associated X (Bax) and Caspase-3. And downstream apoptotic factors such as B-cell lymphoma-2 (Bcl-2), Bax and Caspase-3 can also participate in eosinophil (EOS) -induced inflammatory changes in the airways [21]. Evidence suggests [11] that electroacupuncture stimulation at ST36 in asthmatic rats can regulate EOS cell function by up-regulating Fas mRNA and down-regulating Bcl-2 mRNA expression, attenuating the infiltration state of EOS locally in the airways and blocking their release of inflammatory mediators, relieving and reducing asthma attacks. Meanwhile, JAK1 can inversely regulate STAT3 activation by mediating the phosphorylation of silent mating type information regulation 2 homolog-1 (SIRT1) [22]. Moreover, in regulating inflammation, SIRT1 affects inflammation progression through the deacetylation of related proteins [23]. However, nuclear factor kappa-beta (NF-κB), as a downstream signaling pathway of JAK1, is widely involved in the inflammation process. SIRT1 can directly inhibit the NF-κB pathway by deacetylating the p65 subunit of the NF-κB complex, while IL-6-mediated cytokine storms may be mediated by phosphorylation of the NF-κB subunit p65 [24]. Evidence suggests [12] that electroacupuncture at ST36 promotes SIRT1 expression in lung tissues and inhibits the activation of the NF-κB signaling pathway, and reduces inflammatory factors TNF-α, interleukin-1β (IL-1β), and IL-6 production in lung tissues, bronchoalveolar lavage fluid (BALF), and plasma to reduce inflammatory infiltrative injury in the model of COPD. Electroacupuncture at ST36 may reduce inflammatory injury in lung tissues by regulating SIRT1 expression negatively feedback the activation of the JAK1/STAT3 pathway mediated by IL-6 and inhibiting NF-κB pro-inflammatory signaling cascade.

In other studies [13,14], electroacupuncture stimulation at ST36 in a COPD model can increase dopamine (DA) secretion by activating dopamine D2 receptors, which in turn reduces the levels of the inflammatory factors TNF-α, IL-1β, IL-6, and interleukin-8 (IL-8) in lung tissues and BALF. At the same time, lung function-related indices, including functional residual airflow, total airway resistance, and pulmonary dynamic compliance, etc. were improved. Furthermore, DA, as an important neurotransmitter, can negatively regulate NF-κB and JAK/STAT signaling pathways to participate in inflammatory changes [25]. Therefore, the process of electroacupuncture at ST36 single point to improve the inflammatory state through the dopamine pathway may be achieved through the JAK/STAT signaling pathway.

3.1.2. Modulation of oxidative stress

Oxidative stress is closely associated the severity of many chronic respiratory diseases such as asthma, COPD, pneumonia and lung cancer. Increased oxidative stress in the lungs can activate neutrophils and macrophages as well as lung epithelial cells causing large amounts of reactive oxygen species (ROS) production, which directly act on and destroy biochemical macromolecules such as proteins, lipids, and nucleic acids, leading to cellular dysfunction or death causing a protease-antiprotease imbalance and driving the release of inflammatory mediators [26,27]. Studies demonstrated [15,16] that electroacupuncture at ST36 can activate the antioxidant

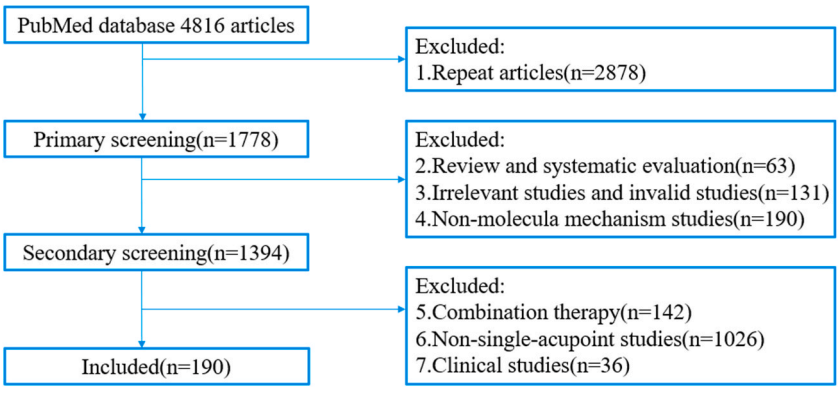

Fig. 1. Flow chart of the search strategy and process.

Table 1
Effect of intervention of ST36 on respiratory diseases.

Refs.	Model	Intervention Methods	Acupuncture Parameters	Biochemical Measurements
Xie (2020) [9]	ALI Rats	EA	Inserted depth: 5 mm; 1 mA, 2–14 Hz, 30 min	**Lung tissues**: TNF-α↓, IL-6↓, Bax↓, Caspase-3↓, *p*-JAK1↓, p-STAT3↓
Song (2015) [10]	ALI Rats	EA	3 Hz, 3 V, 2 ms, 12 min, 48 h, once every 8h	**Plasma**: IL-1β↓, IL-6↓, HMGB-1↓
Wu (2012) [11]	Asthma Rats	EA	Inserted depth: 4–5 mm; 1 mA, 30 Hz, 10 min, 12 d, QD	**Lung tissues**: Fas mRNA↑, Bcl-2 mRNA↓, EOS↓
Luo (2022) [12]	ALI Mice	EA	Inserted depth: 1.5 mm; 2 Hz, 1 mA, 10 min; 7 d	**Serum/BALF**: TNF-α↓, IL-1β↓, IL-4↑, IL-6↓, IL-10↑ **Lung tissues**: SIRT1↑, ACE2↑, NF-κB↓
Guan (2019) [13]	COPD Rats	EA	4–20 Hz, 0.5 ms, 5 mA, 30 min, 2 w, QD	**Plasma**: TNF-α↓, IL-1β↓, IL-6↓, IL-8↓, DA↑
Liu (2022) [14]	COPD Mice	EA	Inserted depth: 1 mm; 2/60 Hz, 30 min; 5 d	**BALF/Lung tissues**: TNF-α↓, IL-8↓, IL-1β↓ **Plasma**: TNF-α↓, IL-8↓, IL-1β↓, DA↑
Geng (2013) [15]	COPD Rats	EA	Inserted depth: 3 mm; 0.5 mA, 2/60 Hz, 30 min, 14 d	**BALF**: TNF-α↓, IL-1β↓, MDA↓
Zhang (2022) [16]	ARDS Mice	EA	Inserted depth: 3 mm; 0.5 mA, 4/20 Hz, 20 min, 3 d	**Lung tissues**: GPX4↑, SLC7A11↑, FTH1↑, GPX4 mRNA↑, SLC7A11 mRNA↑, FTH1 mRNA↑, Iron↓, MDA↓, GSH↑, ROS↓, IL-1β mRNA↓, TNF-α mRNA↓, α7nAchR↑
Lin (2021) [17]	COPD Rats	EA	4/20 Hz, 1–3 mA, 30 min, 2 w, QD	**Serum/BALF**: TNF-α↓, TGF-α↓, IL-8↓ **Lung tissues**: EGFR↓, p38MAPK↓, MUC5AC↓, EGFR mRNA↓, p38MAPK mRNA↓, MUC5AC mRNA↓, TNF-α↓, TGF-α↓, IL-8↓

↑, upregulated by acupuncture; ↓, downregulated by acupuncture.
ALI, Acute lung injury; COPD, Chronic obstructive pulmonary disease; ARDS, Acute respiratory distress syndrome; QD, once a day; EA, Electro-acupuncture; BALF, Bronchoalveolar lavage fluid; IL, Interleukin; TNF-α, Tumor necrosis factor-α; Bcl-2, B-cell lymphoma-2; Bax, BCL-2-associated X protein; JAK, Janus kinase; STAT3, signal transducer and activator of transcription 3; HMGB-1, High-mobility group box 1; SIRT1, Silent mating type information regulation 2 homolog-1; ACE2, angiotensin-converting enzyme 2; NF-κB, nuclear factor kappa-B; DA, dopamine; EOS, eosinophils; MDA, malondialdehyde; GPX4, glutathione peroxidase 4; SLC7A11, Solute Carrier Family 7, Member 11; FTH1, ferritin heavy chain 1; GSH, glutathione; ROS, reactive oxygen species; α7nAchR, α7 nicotinic acetylcholine receptor; TGF, transforming growth factor; EGFR, epidermal growth factor receptor; MUC5AC, mucin-5AC; MAPK, mitogen-activated protein kinases.

mechanisms. To be specific, this method can activate α7 nicotinic acetylcholine receptor (α7nAchR) through the sciatic and cervical vagal pathways to inhibit ferroptosis in alveolar epithelial cells, then reduce ROS and peroxide malondialdehyde (MDA) levels in lung tissue and BALF, and increase the levels of the antioxidant molecules glutathione peroxidase 4 (GPX4) and ferritin heavy chain 1 (FTH1). After that, the lipid peroxidation process triggered by ferroptosis enhanced, and the production of inflammatory factors in the COPD/ARDS model obstruct as well as to improve the mucus secretion of the airway and alleviate airway obstruction. Therefore, electroacupuncture at ST36 single point can induce the production of antioxidant factors through the cholinergic pathway, inhibit ferroptosis in respiratory pathology, and maintain the dynamic balance of the oxidative and antioxidative systems in the body. And there is a changing relationship between the cholinergic pathway and the JAK/STAT signaling pathway during oxidative stress [28]. Electroacupuncture at ST36 single point may reduce oxidative stress by activating the cholinergic pathway to release acetylcholine and inhibiting the activation of the JAK/STAT signaling pathway.

3.1.3. Improved mucus hypersecretion

The inflammatory state of the lungs and respiratory tract can lead to a chronic mucus hypersecretion state, which can cause lung parenchymal damage. Meanwhile, a pathological increase in mucin-5AC (MUC5AC) in the airway mucus is the main component of airway mucoproteins. Usually, the pathological increase of MUC5AC is considered to be a feature of excessive airway and mucus secretion, which is mainly secreted by goblet cells [29–31]. Studies have demonstrated [17] that electroacupuncture at ST36 single point can improve lung ventilation by down-regulating the expression of MUC5AC mediated by the epidermal growth factor receptor/p38 mitogen-activated protein kinases (EGFR/p38MAPK) signaling pathway, thereby inhibiting the mucus hypersecretion state in COPD, which in turn reduces the levels of the cytokines transfer growth factor α (TGF-α), TNF-α and IL-8 in the lung tissue, BALF and serum. Additionally, p38 MAPK has the ability to interact with the JAK/STAT signaling pathway. In the regulation of respiratory mucus secretion, the specific molecular changes involve the phosphorylation of STAT transcription factors and increased levels of IL-5 [32]. It is worth noting that p38 MAPK can affect the activity of STAT3 by regulating its phosphorylation status [33]. Therefore, acupuncture at ST36 may inhibit MUC5AC protein expression by suppressing the activation of the MAPK signaling pathway, a process that may also be affected by the JAK/STAT signaling pathway, reducing inflammatory state-induced excessive respiratory mucus secretion, and improving pulmonary ventilation function.

3.2. Nervous system diseases

In neurological disorders, acupuncture at ST36 may regulate the inflammatory states, central neuron function and oxidative stress

through NOD-like receptor protein (NLRPs) signaling pathway and Toll like receptors 4 (TLR4)/MAPK signaling pathway. These pathways primarily involved a neuroglial cell-centered loop. By reducing neuronal damage and degeneration in the central brain, acupuncture at ST36 plays a therapeutic role in vascular dementia (VD), cerebral infarction, and Alzheimer's disease (AD) models. Details are shown in Table 2.

3.2.1. Regulation of inflammatory states

Neurological disorders such as AD, multiple sclerosis (MS), and others are often accompanied by an inflammatory state in the central nervous system (CNS) [42]. Among these, astrocytes and microglia are the most abundant neuroglial cell type in the CNS, are extensively involved in the inflammatory response of the CNS. During acupuncture treatment, needling peripheral acupoints was able to trigger calcium transients in astrocytes in the somatosensory cortex, suggesting that needling peripheral acupoints can cause changes in astrocyte activity in the CNS [43]. Evidence suggests [44,45] that electroacupuncture at ST36 inhibits the activation of spinal cord microglia (TMEM119) and astrocytes (GFAP) by recognizing TLR4 receptors on the surface of neuroglial cells, which in turn affects the downstream activation of the NF-κB signaling pathway and inhibits the release of pro-inflammatory factors IL-1α, TNF-α, and IL-1β in the spinal cord and serum. Meanwhile, TLR activation also induced downstream MAPK, Extracellular regulated protein kinases (ERK) and Jun N-terminal kinase (JNK) signaling phosphorylation. Acupuncture at ST36 reduced the release of inflammatory cytokines CX3C chemokine ligand 1 (CX3CL1), IL-1β, IL-6 and TNF-α in the spinal cord by decreasing the expression of p-p38, *p*-JNK, and *p*-ERK1/2, inhibiting the activation of the MAPK signaling pathway and astrocyte activation in the spinal cord [46–48]. Therefore, acupuncture at ST36 may ameliorate the inflammatory state of the CNS mainly through the glial cell-mediated TLR4/MAPK signaling pathway. It has also been shown [35] that acupuncture at ST36 single point in a VD model did not produce significant changes in astrocytes. This may be related to the heterogeneity of astrocytes themselves, and the regulation of astrocytes by acupuncture at ST36 may have different effects depending on different pathological states.

3.2.2. Regulation of central neuron function

The hippocampus is a key region of the brain for cognition, learning and memory, belonging to the temporal lobe structures of the limbic cortex, and is highly susceptible to functional abnormalities triggered by aging or ischemia [49]. Research has found [36] that electroacupuncture at ST36 single point prevented ethanol-induced spatial learning and memory deficits by increasing fos expression in the hippocampal CA1 region. Among other things, fos not only serves as a marker for active neurons but also has a guiding role in shaping hippocampal activity and function [50]. A study has found [37] that acupuncture at ST36 single point was shown to reverse cerebral infarction-induced hippocampal neuronal injury by activating the cyclic-adenosine monophosphate/protein kinase A/cAMP-response element binding protein (cAMP/PKA/CREB) signaling pathway and up-regulating the expression of cAMP, PKA, *p*-CREB and *p*-ERK in the hippocampus to improve cognitive and memory dysfunction in multiple cerebral infarction models. Meanwhile, the cAMP/PKA/CREB signaling pathway in the regulation of nerve injury may be associated to neuronal pyroptosis [51]. Evidence suggests [38] that electroacupuncture at ST36 single point can significantly downregulate the expression of NLRP1,

Table 2
Effect of intervention of ST36 on nervous diseases.

Refs.	Model	Intervention Methods	Acupuncture Parameters	Biochemical Measurements
Tida (2018) [34]	Hydrocephalic Rats	AP	Inserted depth: 2 mm; 21 d, 30 min, QD	**External capsule/CC**: Reactive astrocyte cell↓
Li (2015) [35]	VD Rats	AP	Inserted depth: 5 mm; 14 d, QD, with a rest day every 7 days, 120 rpm, 30 s	**Hippocampal CA1 Area**: Pyramidal neuron↑, Astrocytes↓
Lu (2014) [36]	Impairments of spatial learning and memory Rats	EA	Inserted depth: 3 mm; 2 Hz, 1.5–2 mA, 15 min	**Hippocampal CA1 Area**: Fos↑
Li (2015) [37]	Cerebral multi-infarction Rats	AP	Inserted depth: 3 mm; 14 d, QD, with a rest day every 7 days, 120 rpm, 30 s	**Hippocampus**: cAMP↑, PKA↑, *p*-CREB↑, *p*-ERK↑
Li (2023) [38]	Cognitive dysfunction Mice	EA	Inserted depth: 3 mm; 1 mA, 15 Hz, 15 min	**Hippocampal CA1 Area**: NLRP1↓, Caspase-1↓, GSDM D↓
Zhao (2022) [39]	ASD Rats	EA	Inserted depth: 7 mm; 1 mA, 2/15 Hz, 20 min	**PFC**: TXNIP↓, NLRP3↓, TXNIP mRNA↓, NLRP3 mRNA↓, IL-1β↓, Caspase 1↓
Ni (2023) [40]	AD Mice	EA	Inserted depth: 4 mm; 0.5 mA, 10 Hz, 15 min	**Hippocampus**: NLRP3↓, ASC↓, Caspase-1↓, IL-1β↓, IL-18↓
Zhao (2022) [41]	ASD Rats	EA	Inserted depth: 5 mm; 1 mA, 2/15 Hz, 20 min, 20 d, QD	**PFC**: NQO1↑, HO-1↑, Nrf2 cytosol protein↓, Nrf2 nuclear protein↑, Nrf2 mRNA↑, NQO1 mRNA↑, HO-1 mRNA↑ **Serum**: MDA↓, SOD↑, GSH↑, CAT↑, ROS↓

↑, upregulated by acupuncture; ↓, downregulated by acupuncture.
VD, Vascular dementia; ASD, Autism spectrum disorder; AP, Acupuncture; rpm, Revolutions Per Minute; PFC, Prefrontal cortex; CC, Corpus callosum; cAMP, cyclic-Adenosine monophosphate; PKA, Protein kinase A; CREB, cAMP-response element binding protein; Erk, Extracellular regulated protein kinases; BDNF, Brain-derived neurotrophic factor; TrkB, Tyrosine kinase receptor B; NTR, Neurotrophin receptor; Akt, Protein kinase B; TXNIP, Thioredoxin-interacting protein; NQO1, NADP(H) quinone oxidoreductase; NLRP3, NOD-like receptor protein 3; HO-1, Heme oxygenase-1; Nrf2, NFE-related factor 2; SOD, Superoxide dismutase; CAT, Catalase. TLR4, Toll like receptors 4.

Table 3
Effect of intervention of ST36 on digestive diseases.

Refs	Model	Intervention Methods	Acupuncture Parameters	Biochemical Measurements
Hu (2013) [57]	I/R Rats	EA	Inserted depth: 7 mm; 2–100 Hz, 2 mA, 30 min	**Lung/Liver/Plasma**: TNF-α↓, IL-8↓ **Intestinal**: TNF-α↓, IL-8↓, ZO-1↑
Geng (2017) [58]	I/R Rats	EA	2 mA, 2–100 Hz, 30min	**Intestine mucosal**: α7nAChR mRNA↑, NF-κB p65 mRNA↓ **Serum**: IL-6↓, TNF-α↓
Wang (2015) [59]	I/R Rats	EA	2 mA, 2–100 Hz, 1.5 h	**Plasma**: DAO↓
Lim (2020) [60]	Hepatitis Mice	EA	1.0 V, 1 Hz, 2 ms, 30 min	**Plasma**: TNF-α↓, TNF-α mRNA↓ **Liver tissues**: *p*-Erk1/2↓
Lei (2022) [61]	Liver injury Mice	EA	2 mA, 50 Hz, 45 min	**Plasma**: IL-10↑, IL-1β↓, IL-6↓, TNF-α↓, ALT↓, AST↓ **Intestinal tissues**: α7nAChR↑, HO-1↑, ZO-1↑, Occludin↑, Claudin-1↑, pNF-κBp65↓
Xue (2014) [62]	SAP Rats	EA	Inserted depth: 7 mm; 2–100 Hz, 2 mA, 30 min	**Serum**: ACh↑, TNF-α↓, IL-6↓
Xue (2014) [63]	SAP Rats	EA	Inserted depth: 5 mm; 2/100 Hz, 2 mA, 30 min	**Intestinal tissues**: NF-κB p65↓, Occludin↑
Zhang (2021) [64]	AP Mice	EA	Inserted depth: 3 mm; 2/15 Hz, 2 mA, 20 min	**Pancreas**: $CD11b^{+}Ly6G^{+}$↓, $CD11b^{+}F4/80^{+}$↓, $\alpha7nAChR^{+}$↑ **Plasma**: Amylase↓, TNF-α↓, IL-1β↓, IL-6↓ **Lung tissues**: MPO↓
Jin (2019) [65]	UC Rats	EA	**EA1**:25 Hz, 0.5 ms, 4.0 mA; **EA2**: 5 Hz, 0.5 ms, 4.0 mA	**Plasma**: TNF-α↓, IL-1β↓, IL-6↓ **Colonic tissues**: MPO↓
Yan (2013) [66]	Abnormal gastric motility	AP	Inserted depth: 7–9 mm; Twist angle 120°–180°, 120 rpm, 5 min	(Gastric hyperactivity) **Gastric antrum**: SP↓, MTL↓; **NRM:** SP↑, MTL↓ (Gastric hypoactivity) **Gastric antrum**: SP↑, MTL↑; **NRM:** SP↓, MTL↑
Zhang (2020) [67]	FD Rats	EA	25 Hz, 4 mA	**Plasma**: NE↓ **Stomach/Duodenum**: ACh↑ **NTS**: c-Fos↑
Guo (2016) [68]	NBD Rats	EA	Inserted depth: 5 mm; 2/15 Hz, 1–2 mA, 30 min, 14 d, QD	**Myenteric plexus**: nNOS-immunoreactive cells↓, nNOS mRNA↓, nNOS↓
Xu (2012) [69]	Stomach ache Rats	EA	4–16 Hz, 1–5 V, 50 min	**Pyloric sphincter**: NOS↑, AChE↑, VIP↑, CGRP↓
Wang (2021) [70]	FD Rats	EA	2 Hz, 0.5 mA, 30 min, 7 d, QD	**Gastric antrum/Colonic**: 5-HT7R↓, 5-HT7R mRNA↓
Chen (2021) [71]	Colitis Rats	EA	100 Hz, 0.5 ms, 0.5 mA	**Colonic tissues**: MC↓, NGF↓, TrkA↓ **S2–S4 DRGs**: TRPV1↓
Dong (2022) [72]	FD Rats	EA	Inserted depth: 5 mm; 2/50 Hz, 0.5 mA, 20 min, 14 d, QD	**Stomach**: PAR2↓, TRPV1↓, SP↓, CGRP↓
Dong (2022) [73]	FD Rats	EA	Inserted depth: 5 mm; 2/50Hz, 20 min, 14d, QD	**Colonic tissue**: NGF↓, NTRK1↓
Wang (2023) [74]	Colitis Rats	EA	Inserted depth: 7 mm; 1 mA, 2/100 Hz, 15 min, QD	**L6 DRG**: TRPV1↓, CGRP↓, MEK↓, *p*-MEK↓, CREB↓, *p*-CREB↓, TLR4↓, IRF3↓, *p*-IRF3↓, p-65↓, p-p-65↓ **Skin tissues**: SP↓, BK↓, PGI2↓, HA↓, 5-HT↓ **Serum**: TNF-α↓, IL-1β↓, PGE2↓, IL-6↓
Peng (2014) [75]	Partial bowel obstruction rats	EA	Inserted depth: 5 mm; 5/20 Hz, 28.5/15 ms, 2–4 mA, 30 min, 7 d	**Serum**: TNF-α↓, NO↓ **Intestinal tissues**: c-Kit↑
Yang (2020) [76]	NBD Rats	EA	Inserted depth: 5 mm; 3/15 Hz, 30 min, 14 d, QD	**Colonic tissues**: ICCs↑, c-Kit↑
Song (2021) [77]	POI Mice	EA	**HEA**: 100 Hz, 1 mA; **LEA**: 10 Hz, 1 mA	**Ileum**: MMφ↓, M1↓, IL-6↓, ICCs↑
Pan (2019) [78]	FD Rats	EA	Inserted depth: 7–10 mm; 4 Hz, 1 mA, 20 min, 7 d, QD	**Gastric antrum**: c-Kit↑, LC3-II/I↓, Beclin 1↓, *p*-AMPK↑, *p*-ULK1↑
Zhang (2016) [79]	FD Rats	EA	Inserted depth: 3–5 mm; 3–4 Hz, 1–2 V, 30 min, 10 d, QD	**Small intestine/Antrum**: Cx43↑
Huang (2022) [80]	CAG Rats	EA	Inserted depth: 3–5 mm; 4/50 Hz, 2–4 V, 30 min, 4 w	**Gastric mucosa**: p53↓, c-myc↓, Bcl-2↑

(*continued on next page*)

Table 3 (*continued*)

Refs	Model	Intervention Methods	Acupuncture Parameters	Biochemical Measurements
Wang (2020) [81]	Chronic colitis Rats	EA	Inserted depth: 2–3 mm, 100 Hz, 1 mA, 30 min	**Colonic tissues**: TNF-α↓, IL-1β↓, iNOS↓, IL-10↑, TNF-α mRNA↓, IL-1β mRNA↓, IL-6 mRNA↓, iNOS mRNA↓, ZO-1↑, Occludin↑, E-Cadherin↑, MUC2↑, ZO-1 mRNA↑, Occludin mRNA↑, *p*-Erk1/2↑, *p*-JNK↑, p-p38↑ **Serum**: IL-6↓, IL-10↑
Liu (2020) [82]	UC Mice	EA	Inserted depth: 2–3 mm; 2 Hz, 1 mA, 15 min	**Colonic tissues**: CD11b↓, F4/80↓, TLR4↓, MyD88↓, Claudin-1↑, ZO-1↑ **Plasma**: CRP↓, IFN-γ↓, TNF-α↓, IL-6↓, Adiponectin↑
Zhan (2022) [83]	Sepsis Mice	EA	Inserted depth: 3 mm; 2.5 mA, 2–100 Hz, 30 min, 5 d, QD	**Serum**: IL- 1β↓, IL-6↓, TNF- α↓, IL-10↑ **Intestinal tissues**: Caspase 3↓, Cleaved Caspase 3↓, Bax/Bcl 2↓, TLR4↓, MyD88↓, p–NF–κB↓

↑, upregulated by acupuncture; ↓, downregulated by acupuncture.
I/R, Ischemia-reperfusion; SAP, Severe acute pancreatitis; UC, Ulcerative colitis; FD, Functional diarrhea; NBD, Neurogenic bowel dysfunction; POI, Postoperative ileus; CAG, Chronic atrophic gastritis; NRM, Nucleus Raphe Magnus; NTS, Nucleus tractus solitarius; DRG, Dorsal root ganglion; HEA, High-frequency EA; LEA, Low-frequency EA; ZO-1, Zonula occluden-1; DAO, Diamine oxidase; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; ACh, Acetylcholine; MPO, Myeloperoxidase; SP, Substance P; MTL, Motilin; NE, Noradrenaline; nNOS, neuronal nitric oxide synthase; AChE, Acetylcholinesterase; VIP, Vasoactive intestinal peptide; CGRP, Calcitonin gene-related peptide; 5-HT7R, 5-hydroxytryptamine type 7 receptor; MC, Mast cell; NGF, Nerve growth factor; TrkA, Tropomyosin receptor kinase A; TRPV, Transient receptor potential vanilloid; PAR2, proteinase activated receptor 2; NOx, nitrite/nitrate; ICC, interstitial cells of Cajal; MMφ, Muscularis macrophages; LC3-II/I, Light chain 3- II/I; AMPK, AMP-activated protein kinase; ULK1, Unc-51 like autophagy activating kinase 1; Cx43, Connexin 43; MUC2, Mucin 2; JNK, Jun N-terminal kinase; MyD88, Myeloid differentiation factor 88; CRP, C-reactive protein.

Caspase-1 and gasdermin-D (GSDM D) in hippocampal CA1 neurons and alleviate cognitive dysfunction and neuronal damage in septic mice. And NLRP1, as a downstream signaling factor of the cAMP/PKA/CREB signaling pathway, can mediate the regulation of neuronal pyroptosis [52]. Moreover, NLRP1, as an intracellular cytoplasmic receptor in the inflammatory vesicle signaling pathway, can also be in close contact with macrophages and affect the production of pro-inflammatory cytokines [53]. Therefore, electro-acupuncture at ST36 may regulate CNS neuronal injury and repair by activating the cAMP/PKA/CREB signaling pathway in the hippocampus to inhibit the NLRP1-mediated process of neuronal pyroptosis, leading to the growth of primitive synapses and the formation of new synapses.

3.2.3. Regulation of oxidative stress

Under physiological conditions, the brain has high oxygen demand and energy requirements, but weak antioxidant capacity, making it more susceptible to oxidative stress and neurological disorders [54]. As endogenous regulators of oxidative stress and inflammation in cells, thioredoxin-interacting protein (TXNIP) can be activated by binding to NLRP3 inflammatory vesicles, which recruits Caspase 1 to form an inflammatory complex, where caspase 1 is activated to induce the production of the pro-inflammatory cytokine precursor pro-IL-1β, leading to the release of IL-1β into the extracellular milieu to mediate oxidative stress and inflammatory responses [55]. Evidence suggests [39] that acupuncture at ST36 can reduce NLRP3 inflammatory vesicles by decreasing the expression of TXNIP in the prefrontal cortex and inhibiting NLRP3 inflammatory vesicle activation to attenuate oxidative stress and inflammatory responses in the prefrontal cortex of autism spectrum disorder (ASD) rats. Moreover, NLRP3 inflammatory vesicles are highly expressed mainly in microglia, and overactivated NLRP3 inflammatory vesicles stimulate microglia activation and contribute to their conversion to a proinflammatory phenotype (M1). Evidence suggests [40] that electroacupuncture at ST36 single point can reduce microglia activation by inhibiting the activation of NLRP3 inflammatory vesicles in the hippocampus, which in turn reduces the expression of NLRP3, ASC, and caspase-1 proteins in the hippocampus, modulates the inflammatory cytokines IL-1β and IL-18, and improves cognitive function in mice with AD models. In addition, the nuclear factor erythroid2-related factor 2 (Nrf2) signaling pathway is a key pathway in the antioxidant process, and electroacupuncture at ST36 also induced the activation of Nrf2 in the prefrontal cortex and promoted its translocation from the cytoplasm to the nucleus. This further induced up-regulation of the expression levels of NADP(H) quinone oxidoreductase (NQO1) and heme oxygenase (HO-1), reducing peroxide production [41]. Studies have shown [56] that the Nrf2 antioxidant pathway would be involved in the inhibition of the activation of NLRP3 inflammatory vesicles during oxidative stress. Electroacupuncture at ST36 may regulate oxidative stress by inhibiting TXNIP binding to NLRP3 inflammatory vesicles through activation of the Nrf2 signaling pathway, which in turn inhibits microglial cell activation.

3.3. Digestive system diseases

In digestive disorders, acupuncture at ST36 may regulate inflammatory states, the network of ICC and intestinal flora abnormalities mainly through MAPK signaling pathway and can affect neurotransmitter transmission through activation of central and peripheral nervous system and reduce functional abnormalities in pathological states of related organs of digestive system. It exerts therapeutic effects in models of intestinal ischemia-reperfusion (I/R), hepatitis, pancreatitis, ulcerative colitis (UC), functional diarrhea (FD), stomach ache, colitis and chronic atrophic gastritis (CAG). Details are shown in Table 3.

3.3.1. Regulation of inflammatory states

The cholinergic pathway is an important anti-inflammatory mechanism. The activation of cholinergic pathway mainly occurs through electrical or pharmacological activation of the vagus nerve, whereby the interaction of its main neurotransmitter, acetylcholine (ACh), and the α7nAChR, which is located on cytokine-expressing cells, inhibits the expression of pro-inflammatory cytokines [84]. Evidence suggests [57–59] that electroacupuncture at ST36 single point in an intestinal I/R model can significantly reduce intestinal mucosal injury and prevent intestinal barrier and remote organ dysfunction after intestinal ischemia by activating the cholinergic anti-inflammatory pathway, activating α7nAChR levels and NF-κB phosphorylation in gastrointestinal tissues, and decreasing cytokine IL-6, TNF-α, and IL-8 levels in the blood, and gastrointestinal tissues. The NF-κB signaling pathway serves as a key component in regulating various common pathways for the transcription of inflammatory factors, and its overactivation leads to a series of pathological responses, and IL-6, TNF-α, etc. often act as upstream signaling molecules of the NF-κB signaling pathway, which have a key role in the activation of the NF-κB pro-inflammatory signaling cascade response [85]. In models of hepatitis, colitis, and pancreatitis [60–65], acupuncture at ST36 single point similarly reduced the inflammation of the intestinal mucosa through the vaguely cholinergic anti-inflammatory pathway, reducing the levels of IL-1β, IL-6, and TNF-α in plasma and organ tissues, significantly up-regulating the expression of α7nAChR, decreasing the phosphorylation of ERK1/2 and NF-κB p65, and attenuating inflammatory injury. It can be seen that electroacupuncture at ST36 reduces the production of pro-inflammatory cytokines mainly through the MAPK/NF-κB signaling pathway by cholinergic pathway in gastrointestinal tissues and blood, and improves the inflammatory state of organs related to digestive system diseases.

3.3.2. Regulation of neural signal transduction

The central nervous system (CNS) provides the extrinsic neural input that regulates and controls gastrointestinal motility, but the digestive tract is mostly innervated by the peripheral autonomic nervous system control [86]. Research has found [66] that electroacupuncture at ST36 single point can induce the expression and release of cerebrospinal peptide substance P (SP) and motilin (MTL) in the nucleus raphe magnus (NRM) in a model of gastric motility hyperactivity and gastric motility inhibition, which in turn activated the peripheral nervous system regulates the levels of SP and MTL in the gastric sinus and is involved in inhibiting or promoting gastric motility. This may therefore be the basis for the bidirectional regulation of neural signal transduction by acupuncture at ST36 on the promotion or inhibition of gastric motility. It has also been shown [67] that electroacupuncture at ST36 may ameliorate gastric slow-wave rhythm disorders in FD models by decreasing plasma noradrenaline (NE) concentrations and increasing ACh concentrations in the stomach and duodenum, mediated through afferent central pathways involving the nucleus tractus solitaries (NTS) and vagal cholinergic efferent pathways. In addition, the enteric nervous system (ENS) is the largest component of the autonomic nervous system and has unique intrinsic circuits that allow it to coordinate gastrointestinal function independently of CNS input [87]. Evidence suggests [68,69] that electroacupuncture at ST36 single point can influence sphincter closure in models of stomachache and Neurogenic bowel dysfunction (NBD) by modulating the conduction of the neurotransmitters nitric oxide synthase (NOS), acetylcholinesterase (AChE), vasoactive intestinal peptide (VIP), and calcitonin gene-related peptide (CGRP) in the ENS and opening functions. Whereas this process of gut neurotransmitter regulation may originate from cholinergic neurons in the ENS [88].

However, the abnormal release of neurotransmitters may also lead to a state of visceral hypersensitivity, causing abnormal movements of the intestines, resulting in symptoms such as abdominal pain and diarrhea, which are commonly associated with various functional gastrointestinal disorders. Over-activated degranulation of MCs results in the release of 5-hydroxytryptamine (5-HT), an important neurotransmitter capable of high expression in a state of visceral hypersensitivity. Evidence suggests [70] that electroacupuncture at ST36 single point in a FD model reduces colonic tissue 5-HT7R protein expression and restores intestinal motility while ameliorating the hypersensitivity state. Moreover, protein expression of proteinase-activated receptor 2 (PAR2) and transient receptor potential vanilloid type 1 (TRPV1) proteins was activated in the visceral hypersensitivity state, promoting the release of neuropeptide SP, CGRP, which transmits injurious nociceptive information. Electroacupuncture at ST36 single point may inhibit the expression of nerve growth factor (NGF) and its receptor NTRK1 proteins through the mast cell-triggered NGF/TrkA/TRPV1 peripheral afferent pathway, and at the same time reduce the levels of PAR2, TRPV1 protein expression and the abnormal release of neurotransmitters in gastric tissues, and alleviate the visceral hypersensitivity state [71–73]. Furthermore, it has been shown [74] that electroacupuncture at ST36 modulates neurotransmitter changes in colonic inflammation and nociceptive hypersensitivity that may be related to L6 Dorsal root ganglion (DRGs), including SP, bradykinin (BK), and prostacyclin (PGI2), which are involved in inhibition of activation of the TRPV1/CGRP signaling pathway. Thus, electroacupuncture at ST36 may reduce the degree of MC degranulation and neurotransmitter release through inhibition of MC activation reducing injurious stress, and inhibiting TRPV1 protein expression levels, effectively improving the visceral hypersensitivity state to alleviate gastrointestinal dyskinesia.

3.3.3. Regulation of the network of ICC

ICCs regulate gastrointestinal dynamics by generating and propagating slow waves and transmitting signals between ENS and smooth muscle cells and are considered specialized intestinal pacemaker cells, thus ICCs are associated with a variety of gastrointestinal disorders [89,90]. c-Kit is a specific marker for ICC identification and has a role in promoting ICC development and phenotype maintenance, and ICC and smooth muscle cells co-originate from c-Kit^{+} primitive cells in the intestine [91]. Evidence suggests [75–77] that electroacupuncture at ST36 significantly increased c-Kit protein expression in a partial model of intestinal obstruction and neurogenic intestinal dysfunction, promoted differentiation of c-Kit positive precursor cells into ICC and facilitated the recovery of the ICC network. It also reduced the number of muscularis macrophages (MMφ) and inhibited their M1 polarization and IL-6 secretion to protect ICCs from accelerated intestinal function. In addition, electroacupuncture at ST36 could improve gastrointestinal motility disorders in rats with FD by modulating AMP-activated protein kinase/unc-51 like autophagy activating kinase 1 (AMPK/ULK1)

signaling pathway, promoting c-Kit expression, reducing the expression of autophagy-related proteins Beclin 1, light chain 3- II/I (LC3-II/I) and thus inhibiting the level of excessive autophagy in ICC, as well as affecting the level of connexin 43 (Cx43) [78,79]. Evidence suggests [92] that AMPK is an important regulator of autophagy, driving the cellular autophagy mechanism through the Liver Kinase B1 (LKB1)/AMPK/ULK1 axis, but LKB1 is affected by the MAPK signaling pathway, and thus AMPK can act as a downstream effector of MAPK signaling, and the two can interact with each other to regulate the autophagic process. It was shown that electroacupuncture at ST36 directly affected ICC morphology by regulating c-Kit expression through the AMPK signaling pathway, better binding to gap junction proteins, and increasing gap junction protein expression to shorten the signaling distance with smooth muscle cells, accelerating gastric slow wave transmission to provide power for smooth muscle contraction, which may also be affected by the MAPK signaling pathway.

3.3.4. Regulation of intestinal microflora

The gut is the largest digestive organ in the human body, it is colonized by and continuously exposed to a myriad of microorganisms including *Bifidobacterium*, *Lacticacidbacteria*, and *Escherichiacoli*, and the gut microenvironment created by the intestinal flora and its products significantly influences immune function in this region [93]. Research has found [80] that electroacupuncture at ST36 was able to modulate the intestinal flora by decreasing the relative abundance of *Lactobacillus and Desulfobacterota* and increasing the relative abundance of probiotic bacteria such as *Oscillospirales, Romboutsia, and Christensenellaceae*, which attenuated the effect of Helicobacter on the p53, c-myc, and Bcl-2 genes in the gastric mucosa, and thus reduced gastrointestinal mucosal damage. Also, the modulation of gut flora is MAPK signaling pathway related [94]. Evidence suggests [81] that electroacupuncture at ST36 can activate the MAPK signaling pathway by modulating gut flora in a model of colitis, affecting ERK1/2 and JNK subfamily signaling molecules, upregulating the expression of intercellular junction complex proteins zona occludens 1 (ZO-1), Occludin, E-Cadherin, Mucin 2 (MUC2), and reduce apoptosis and oxidative stress in intestinal epithelial cells (IECs) to protect intestinal barrier integrity, and reduce

Table 4
Effect of intervention of ST36 on endocrine diseases.

Refs	Model	Intervention Methods	Acupuncture Parameters	Biochemical Measurements
Wen (2014) [95]	HFD Rats	EA	10 Hz, 20 min, 7 d, QD	**Plasma**: AST↓, ALT↓, TC↓, TG↓, FFA↓, TNF-α↓, IL-1↓, IL-6↓ **Adipose tissues**: SREBP-1c mRNA↓, FAS mRNA↓, ACC1 mRNA↓, SCD1 mRNA↓, TNF-α mRNA↓, IL-6 mRNA↓, Neutrophile↓, $CD11b^{+}$↓, $F4/80^{+}$↓, $F4/80^{+}$ mRNA↓, MCP-1 mRNA↓, CD68 mRNA↓
Wen (2015) [96]	Obesity Mice	EA	Inserted depth: 3 mm; 2 Hz, 0.5–1 mA, 10 min, three times a week	**Adipose tissues**: HIF-1α mRNA↓, VEGFA mRNA↓, Slc2a1 mRNA↓, GPX1 mRNA↓, F4/80 mRNA↓, TNF-α mRNA↓, MCP-1 mRNA↓, IL-6 mRNA↓, F4/80↓, NF-κB↓, IκBα↑
Chen (2013) [97]	Diabetic Rats	EA	**LEA**: 10 Hz, 1–3 mA, 30 min; **HEA**: 100 Hz, 1–3 mA, 30 min; 8 w, QD	**ICC-IM/ICC-MY/ICC-SM**: c-Kit↑, ICCs↑
Chen (2013) [98]	Diabetic Rats	EA	**LEA**:10 Hz, 1–3 mA; **HEA**: 100 Hz, 1–3 mA; 30 min, four or eight weeks, QD	**Serum**: S-SDF↑ **Gastric Antrum**: M-SDF↑, ICCs↑, c-Kit↑
Zhao (2018) [99]	Diabetic Mice	EA	Inserted depth: 2–3 mm; **LEA**: 10 Hz, 1 mA; **HEA**: 100 Hz, 1 mA; 30 min, QD, 8 w	**Stomach tissues**: GFP↑, SDF-1↑, CXCR4↑, mSDF↑, c-Kit↑, *p*-ERK↑, ETV1↑, GFP mRNA↑, SDF-1 mRNA↑, CXCR4 mRNA↑, mSDF mRNA↑, c-Kit mRNA↑, *p*-ERK mRNA↑, ETV1 mRNA↑
Tian (2017) [100]	Diabetic Mice	EA	**LEA**:10 Hz, 1–3 mA; **HEA**: 100 Hz, 1–3 mA	**Antrum/Corpus**: Ano1↑, c-Kit↑, c-Kit mRNA↑, mSDF↑, mSDF mRNA↑, ETV1↑, ETV1 mRNA↑
An (2019) [101]	Diabetic Mice	EA	**LEA**: 10 Hz, 1 mA; **HEA**: 100 Hz, 1 mA; 30 min, QD	**Colonic tissues**: CXCR4↑, SDF-1↑, TGF-β1↑, smad3↑, c-Kit↑, mSDF↑, *p*-ERK↑, pc-Jun↑, ETV1↑, CXCR4 mRNA↑, SDF-1 mRNA↑, TGF-β1 mRNA↑, smad3 mRNA↑, c-Kit mRNA↑, mSDF mRNA↑, *p*-ERK mRNA↑, pc-Jun mRNA↑, ETV1 mRNA↑
Man (2021) [102]	IDDM Rats	EA	Inserted depth: 5 mm; 15 Hz, 30 min	**Plasma**: Glucose↓, FFA↓ **Skeletal muscle**: GLUT4↑, IRS-1↑
Tzeng (2016) [103]	SIIR Rats	EA	15 Hz, 60 min	**Plasma**: FFA↓, IRS-1↑, GLUT4↑
Xu (2023) [104]	IR Mice	EA	Inserted depth: 4–5 mm; 2 Hz, 20 min	**Skeletal muscle**: Adipo↑, AdipoR1↑
Yuan (2021) [105]	T2DM Rats	EA	2 Hz, 0.1 mA, 20 min, QD, with a rest day every 6 days, 4 w	**Serum**: INS↓, FBG↓ **Pancreas/Hippocampus**: pS396↓, pT231↓, pGSK-3β↑

↑, upregulated by acupuncture; ↓, downregulated by acupuncture.
HFD, High-fat diet; IDDM, Insulin-dependent diabetes; SIIR, Steroid-induced insulin resistance; T2MD, Type 2 diabetes mellitus; TC, Total cholesterol; TG, Triglyceride; FFA, Free fatty acid; SREBP-1, Sterol regulatory element-binding protein-1; ACC, Acetyl-CoA carboxylase; SCD, Stearoyl-CoA desaturase; MCP-1, Monocyte chemoattractant protein-1; HIF-1α, Hypoxia-inducible factor-1α; VEGFA, Vascular endothelial growth factor A; Slc2a1, Glucose transporter type 1; GPX1, Glutathione peroxidase 1; IκBα, Inhibitory Subunit of NF Kappa Bα; SDF, Stromal Cell Derived Factor; GFP, Green fluorescent protein; CXCR4, CXC-chemokine receptor 4; ETV1, Ets variant 1; Ano1, Anoctamin 1; GLUT4, Glucose transporter type 4; IRS-1, Insulin receptor substrate type 1; INS, Insulin; FBG, Fasting blood glucose; pS396, phosphorylated tau at the sites of Ser 396; T231, Tau at the sites of Thr 231; GSK-3β, Glycogen synthase kinase-3β.

disease activity index (DAI) and histological scores in chronic colitis. Studies have found [82,83] that the overall structure of the intestinal flora was adjusted with the improvement of the degree of intestinal inflammation. Electroacupuncture at ST36 modulates and recognizes TLR on the IEC, which are channeled through the TLR4/myeloid differentiation factor 88 (MyD88) signaling pathway to induce activation of immune cell responses, while activation of the TLR4/MyD88 signaling pathway can affect the downstream NF-κB signaling pathway, modulating inflammatory signaling cascades and inhibition of the secretion of pro-inflammatory mediators C-reactive protein (CRP), interferon-γ (IFN-γ), TNF-α, IL-6, and Influence the overall structure of *Lactobacillus reuteri, Lactobacillus vaginalis, Bacteroidales, and Firmicutes*, and reduce colonic mucosal damage. It is evident that electroacupuncture at ST36 may affect the structure of intestinal microflora mainly through TLR4 and MAPK signaling pathways with IEC as the central link.

3.4. Endocrine system diseases

In endocrine system disorders, acupuncture at ST36 may ameliorate the chronic inflammatory state of obesity primarily by modulating macrophage function, regulating the network of ICC through the MAPK signaling pathway, and modulating glucose metabolism disorders mediated through the central nervous system. It plays a significant role in obesity, diabetic gastroparesis (DGP), type 2 diabetes mellitus (T2DM) and insulin resistance (IR) models. Details are shown in Table 4.

3.4.1. Regulation of inflammatory states

Obesity is a chronic metabolic disease characterized by excessive accumulation of body fat and excess body weight, and its pathogenesis is based on energy intake exceeding energy expenditure. Studies have shown [106,107] that obesity is often accompanied by a low-grade inflammatory response, with elevated inflammatory factors in serum and adipose tissue, which promotes the infiltration of inflammatory cells in adipose (e.g., macrophage and other immune cell infiltration), and may even cause insulin resistance. Research has found [95] that electroacupuncture at ST36 single point reduced the number of F4/80 and CD11b-positive macrophages in adipose tissue by ameliorating the obesity-associated factors sterol regulatory element-binding protein-1 (SREBP1), FAS, acetyl-CoA carboxylase 1 (ACC1), and stearoyl-CoA desaturase 1 (SCD1) in an obesity model, which, in turn, reduced macrophage recruitment and pro-inflammatory factor secretion, resulting in a significant reduction in body weight in an obesity model. At the same time, macrophage metabolism and activation are correlated with the expression of hypoxia-related signaling molecules [108]. Electroacupuncture at ST36 reduces the expression of hypoxia-related genes vascular endothelial growth factor A (VEGFA), glucose transporter type 1 (Slc2al) and GPX1 in adipose tissue through a hypoxia-inducible factor-1α (HIF-1α)-dependent pathway, affects F4/80-positive macrophage recruitment to adipose tissue, inhibits NF-κB signaling pathway activation and promote the expression of Inhibitory Subunit of NF Kappa Bα (IκBα), reduce the expression of pro-inflammatory-related factor genes, and prevent weight gain by reducing the inflammatory response in adipose tissue [96]. It can be seen that electroacupuncture at ST36 may improve the chronic inflammatory state of obesity by taking macrophages as the central link and affecting their recruitment to adipose tissue and secretion of pro-inflammatory factors.

3.4.2. Regulation of the network of ICC

DGP is part of diabetic autonomic neuropathy and is the most common gastrointestinal complication of diabetes, including intestinal symptoms such as diarrhea or constipation. ICC deficiency in diabetic gastroparesis models is thought to be a key component of this dysfunction [109]. Evidence suggests [97,98] that electroacupuncture at ST36 rescues the damaged ICC network by activating the stem cell factor (SCF)/c-Kit pathway, enhancing ICC proliferation in the stomach and inhibiting ICCs apoptosis, thereby improving diabetic gastroparesis symptoms. This may be due to the ability of electroacupuncture at ST36 to affect the differentiation of bone marrow-derived cells into ICCs and the migration of differentiated bone marrow-derived cells into the stomach via the Stromal cell-derived factor 1/C-X-C motif chemokine receptor 4 (SDF-1/CXCR4) signaling pathway [99]. There is an increase in c-Kit positive precursor cells in gastrointestinal tissues and their homeostasis is maintained by Ets variant 1 (ETV1), a downstream effector of the SCF/c-Kit signaling pathway [100]. Further activation of the MAPK signaling pathway phosphorylation by the mSCF/Kit--*p*-ERK/p-*c*-Jun-ETV1 signaling pathway predominantly regulates ICC cell proliferation and maintains the ICC activation state and network at near normal levels [101]. It is evident that electroacupuncture at ST36 may improve gastrointestinal symptoms in the DGP model by causing bone marrow-derived cells to migrate to the stomach and intestine primarily through the SDF-1/CXCR4 signaling pathway and differentiating them into ICC cells through the mSCF/Kit-*p*-ERK/p-*c*-Jun-ETV1 signaling pathway.

3.4.3. Improving disorders of glucose metabolism

Long-term disturbances in glucose metabolism in diabetes can cause serious complications, thereby severely affecting the quality of life of patients. Evidence suggests [102,103] that in insulin-dependent diabetes mellitus (IDDM) models and IR models, electroacupuncture at ST36 single point can affect insulin signaling and reduce free fatty acid (FFA) and blood glucose levels by modulating the plasma membrane translocation of insulin receptor substrate type 1 (IRS-1) and glucose transporter type 4 (GLUT4) proteins in plasma and skeletal muscle. It also improves insulin sensitivity. Moreover, the regulation of insulin resistance by electroacupuncture ST36 may be related to Pro-opiomelanocortin (POMC) neurons in the hypothalamus, which are able to activate the adiponectin (Adipo) response in skeletal muscle to regulate glucose metabolism [104]. This is important because the brain relies on glucose as its main source of energy. Therefore, the regulation of glucose metabolism is critical to brain physiology, and prolonged glucose metabolism disorders often lead to peripheral neuropathy with cognitive impairment, which can eventually progress to dementia [110]. One of the typical pathological changes in the brain of AD patients is the formation of neurofibrillary tangles from hyperphosphorylated tau protein aggregates [111]. Research has found [105] that there was a link between tau hyperphosphorylation in the

brain and reduced insulin sensitivity leading to insulin resistance. Glycogen synthase kinase 3β (GSK-3β) is a key kinase that causes hyperphosphorylation of tau protein, and electroacupuncture at ST36 single point could affect the expression level of phosphorylated tau protein in the hippocampus of rats by reducing the activity of GSK-3β signaling molecules in the islets, improving the morphology of diabetic damaged islets and reducing peripheral blood insulin levels. It can be seen that electroacupuncture at ST36 can improve glucose metabolism disorders and insulin resistance mainly by regulating the activity of insulinogenic substrates IRS-1 and GSK-3β signaling pathways, which are affected by the hypothalamus and hippocampus regions of the central nervous system.

3.5. Immune system diseases

In immune system diseases, acupuncture at ST36 may regulate immune homeostatic imbalances by affecting T-lymphocyte, macrophage and MC function primarily through the MAPK signaling pathway. It plays a role in models of sepsis, experimental autoimmune encephalomyelitis (EAE), allergic contact dermatitis (ACD) and rheumatoid arthritis (RA). Details are shown in Table 5.

3.5.1. Regulation of T-lymphocyte subsets

Lymphocytes are an important part of the immune system, in which the establishment and maintenance of the immune response, homeostasis, and memory depend on T lymphocytes [125]. T lymphocytes are divided into $CD4^+$ T cells ($CD3^+CD4^+$) and $CD8^+$ T cells ($CD3^+CD8^+$) [126]. $CD4^+$ T cells can be differentiated into helper T cells (Th) and Treg cells, the former of which include Th1, Th2, and Th17 cells [127]. $CD8^+$ T lymphocytes are cytotoxic T cells [128]. Electroacupuncture at ST36 single point increased the percentage of $CD3^+$, γ/δ, and $CD4^+$ T cells as well as the ratios of $CD3^+CD4^+/CD3^+CD8^+$ T cells and Treg/Th17 cells in the sepsis model [112,113]. It also promoted the secretion of the anti-inflammatory cytokine interleukin 4 (IL-4), which reduces the inflammatory state of sepsis and regulates the expression of the Bcl-2 family of proteins, increasing Bcl-2 protein expression and a decrease in Bax protein expression to inhibit lymphocyte apoptosis [114]. In addition, the spleen, as an important lymphoid organ, is able to store large numbers of T lymphocytes to participate in the peripheral immune response. Electroacupuncture at ST36 excites splanchnic sympathetic nerves, promotes differentiation of $CD4^+$ T cells in splanchnic tissues, decreases the number of Th1 (CD4+IFN-γ+) and Th17 (CD4+IL-17+) lymphocytes and increases the number of Th2 (CD4+IL-4+) lymphocytes to modulate the peripheral aberrant immune response in the

Table 5
Effect of intervention of ST36 on immune diseases.

Refs	Model	Intervention Methods	Acupuncture Parameters	Biochemical Measurements
Zhu (2015) [112]	Sepsis Rats	EA	Inserted depth: 6 mm; 2 mA, 2–100 Hz, 30 min	**Serum**: D-LA↓ **Intestinal mucosa**: sIgA↑, $CD3^+$↑, γ/δ↑, $CD4^+$↑, $CD4^+/CD8^+$↑
Xie (2020) [113]	Sepsis Rats	EA	3 Hz, 2 V, 15 min	**Serum**: TNF-α↓, IL-10↓, DAO↓, D-LA↓ **Intestinal tissues**: $CD3^+CD4^+/CD3^+CD8^+$↑, Treg/Th17↑
Lou (2022) [114]	Sepsis Rats	EA	Inserted depth: 7 mm; 2 mA, 2 Hz, 30 min, 3 d, QD	**Small intestinal tissues**: $CD4^+$↑, $CD8^+$↑, Bcl-2↑, Bax↓ **Intestinal mucosa**: IL-4↑, sIgA↑
Zhao (2021) [115]	EAE Mice	EA	Inserted depth: 2.5 mm; 2 Hz, 30 min, QD	**CNS**: T-bet↓, RORγt mRNA↓, POMC↑, miR-155↓ **Spleen tissues**: $CD4^+$IFN-γ^+↓, $CD4^+$IL-17^+↓, $CD4^+$IL-4^+↑
Wang (2023) [116]	EAE Mice	AP	Inserted depth: 3–4 mm; 30 min, QD	**Spleen tissues**:$CD4^+$IFN-γ^+↓, $CD4^+$IL-17^+↓, $CD4^+$IL-4^+↑
Lv (2022) [117]	Sepsis Mice	EA	10 Hz, 0.1 mA, 30 min, QD	**Serum**: IL-1β↓, IL-5↓, IL-6↓, IL-10↓, IL-17A↓, Eotaxin↓, IFN-γ↓, MIP-1β↓, KC↓, TNF-α↓, IL-4↓, IL-9↓ **Spleen**: T lymphocytes↓, Cleaved caspase-1↓
Wang (2017) [118]	DTH Mice	EA	2 Hz, 1–2 mA, 30 min	**Serum**: IgG↓, IgE↓ **Footpad tissues**: IFN-γ↓, TNF-α↓ **Spleen**: $CD4^+$IFN-γ^+↓, T-bet↓, T-bet mRNA↓
Wang (2017) [119]	ACD Rats	EA	2 Hz, 1–2 mA, 30 min	**Serum**: IgE↓ **Ears**: IFN-γ↓, TNF-α↓, IL-1β↓, IL-4↓, IL-5↓, IL-10↓ **Local point**: IFN-γ↓, IL-10↑, $CD4^+$IFN-γ^+↓, $CD4^+$IL-4^+↓, p-p38↓
Yang (2021) [120]	AIA Rats	AP	Inserted depth: 3 mm; Twist angle 180°, 28 min	**Ankle joints**: TNF-α↓, IL-1β↓, IL-18↓, IL-7↓, IL-4↓, M1↓, M2↑
Yu (2022) [121]	AIA Rats	AP	Inserted depth: 3 mm; Twist angle 180°, 28 min	**Ankle joints**: IL-1β↓, IL-6↓, TNF-α↓, IL-10↑, TGF-β1↑, M1↓
Wang (2019) [122]	ACD Rats	EA	2 Hz, 1–2 mA, 30 min	**Serum**: IgE↓ **Ear dermis**: MCs↓, p38 MAPK↓, CB2R↑
Wang (2018) [123]	ACD Rats	EA	2 Hz, 1–2 mA, 30 min	**Ear samples**: MC↓, IL-33↓ **RPMCs**: IL-6↓, TNF-α↓, IL-13↓, MCP-1↓, miR-155↓, IκBα↑, *p*-IKKα/β↓, NF-κB p65↓, p-P38↓, p-*c*-Jun↓
Chen (2019) [124]	Endotoxin Rats	EA	2 Hz, 1–2 mA, 30 min	**Serum**: TNF-α↓, IL-1β↓, IL-6↓ **Spleen**: TLR4↓, NF-κB p65↓, CB2R↑

↑, upregulated by acupuncture; ↓, downregulated by acupuncture.
DTH, Delayed-type hypersensitivity; ACD, Allergic contact dermatitis; EAE, Experimental autoimmune encephalomyelitis; AIA, Adjuvant-induced arthritics; D-LA, D-Lactose; sIgA, secretory immunoglobulin A; T-bet, Th1 cell transcription factor; RORγt, Retinoid-related orphan receptor-γt; POMC, Pro-opiomelanocortin; miR, microRNA; Ig, Immunoglobulin; MIP, Macrophage inflammatory protein; KC, Keratinocyte-derived chemokine; RPMCs, Rat peritoneal mast cells; CB2R, cannabinoid CB2 receptor.

EAE model [115,116]. Research has found [117] that electroacupuncture at ST36 also inhibited the cleavage activation of Caspase-1 by modulating the cysteoaspartic enzyme signaling pathway, and thus inhibited the apoptosis and apoptosis of T lymphocyte apoptosis and pyroptosis. It effectively blocked the increase of early pro-inflammatory cytokines TNF-α and IL-1β, which in turn reduced the levels of IL-6, eotaxin, macrophage inflammatory protein-1β (MIP-1β), and keratinocyte-derived chemokine (KC), and prevented the development of cytokine storm in septic mice. In an ACD model [118,119], electroacupuncture at ST36 attenuated the percentage of $CD4^{+}IFN\text{-}\gamma^{+}$ and $CD4^{+}IL\text{-}4^{+}$ T cells by inhibiting IFN-γ secretion and suppressing the expression of the IFN-γ initiating transcription factor, T-bet, and restored the Th1/Th2 balance by inhibiting the activation of the MAPK signaling pathway and preventing the differentiation of Th cells into Th1 cells. It can be seen that electroacupuncture at ST36 can affect the proliferation, apoptosis and differentiation of T lymphocyte subpopulations by regulating relevant cytokines through cysteine asparaginase and MAPK signaling pathways.

3.5.2. *Regulation of macrophage polarization*

Macrophages have different functional characteristics and show significant heterogeneity in the local microenvironment, which is important for maintaining the balance of the immune microenvironment in vivo, and T lymphocytes and cytokines (e.g. TNF-α, IL-10, etc.) can induce macrophage polarization via the MAPK signaling pathway. Among them, Th1, Th2, Th17 and Treg are subpopulations of naïve CD4 helper T cells with different functions. During inflammation, the production of cytokines such as IFN-γ and TNF-α by Th1 cells can mediate M1 macrophage polarization, whereas Th2 cytokines IL-4 and IL-13 and Treg cells can drive macrophage polarization towards the M2 phenotype [129]. In arthritis model [120,121], electroacupuncture at ST36 can induce macrophage polarization by modulating macrophage activation with upstream signaling factors including IL -4, IL-10, etc., affecting the number of Treg cell populations and the level of the macrophage signature expression factor TGF-β, driving macrophage polarization towards the M2 phenotype and inhibiting M1 macrophage activation. Therefore, acupuncture at ST36 may further regulate the macrophage polarization process by affecting cytokine secretion from T lymphocytes and activating the MAPK signaling pathway.

3.5.3. *Regulation of mast cell degranulation*

Mast cells are representative allergic effector cells containing cytoplasmic granules with many pre-stored mediators, including histamine and trypsin-like enzymes, which are released in large quantities in the blood stream after MC activation, triggering a

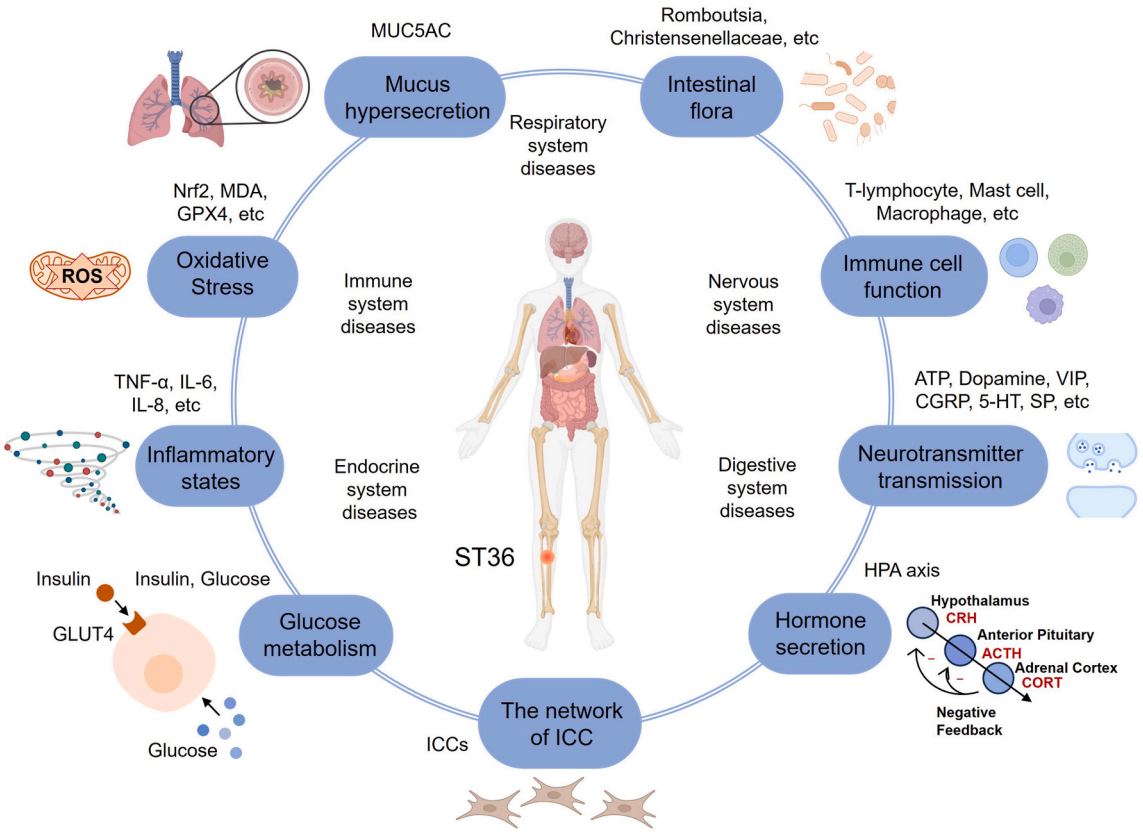

Fig. 2. Acupuncture at ST36 can affect abnormal states in pathological models of respiratory, neurological, digestive, endocrine, and immune system diseases. Meanwhile, acupuncture at ST36 modulates their inflammatory state, oxidative stress, respiratory mucus secretion, intestinal flora, immune cell function, neurotransmitter transmission, hormone secretion, the network of ICC, and glucose metabolism dysfunction.

hypersensitivity reaction [130]. Inhibition of MC degranulation is therefore an important mechanism in the treatment of allergic diseases. Evidence suggests [122–124] that electroacupuncture at ST36 single point inhibits NF-κB p65 activity by inhibiting p38MAPK phosphorylation, which in turn inhibits MCs activation and reduces mast cell infiltration and degranulation. Meanwhile, electroacupuncture at ST36 was able to increase the expression of cannabinoid CB2 receptor (CB2R) protein in the ear dermis of ACD model, which could participate in the activation of p38 MAPK signaling pathway, regulate the inactivation of TLR4/NF-κB signaling pathway, promote the apoptotic process of MCs and reduce the levels of inflammatory factors TNF-α, IL-1β and IL-6 in the peripheral blood. Thus, electroacupuncture at ST36 can mediate the MC degranulation process through a pathway dominated by the MAPK signaling pathway.

4. Conclusions

In clinical acupuncture treatments, there are usually two or more groups of acupoint prescriptions. In the majority of these clinical studies, one of the commonly selected acupoints is ST36, which is widely used [131–134]. However, if multiple acupoints are considered in basic research, it may be difficult to elucidate the mechanism of different acupoints. Through reviewing relevant literature on stimulating the single acupoints ST36, we have excluded research involving interventions such as bioactive substance injection, drug injection and etc. in the content we present. The reason is that these intervention methods have pharmacological effects in their own right and may affect the onset of ST36 through different pathways, which is not conducive to the exploration of the principles of action of stimulating the onset of action of the ST36 acupoints. Additionally, our study also excludes the content of moxibustion therapy. Moxibustion is made of moxa leaves made of moxa floss as combustion material, through the active ingredients in the moxa leaves and moxa smoke produced by the thermal effect to stimulate the specific acupoints on the surface of the body and produce therapeutic effects. The action of acupuncture and moxibustion have different characteristics, with acupuncture being effective in anti-inflammatory aspects and moxibustion being more skilled in regulating the immune microenvironment [135]. Therefore, we only collected studies that consisted of acupuncture or electroacupuncture as the only intervention modality acting locally on ST36, which is more conducive to revealing the molecular mechanism of action of acupuncture at ST36 single point in treating diseases.

Moreover, the molecular mechanism produced by acupuncture points is a network regulation involving multiple targets and systems. In summary of the above studies, it can be concluded that acupuncture at a single acupoint ST36 plays a therapeutic role in respiratory, nervous, digestive, endocrine, immune system disease models. It is mainly involved in the regulation of inflammatory state, oxidative stress homeostasis, immune cell function, hormone secretion, neurotransmitter transmission, respiratory mucus secretion, intestinal flora, ICC network and glucose metabolism (Fig. 2). It is mainly involved in regulating the activation of signaling pathways such as JAK, NLRPs, MAPK, TLR, AMPK and etc. Among them, the most prominent contribution to the regulation of the inflammatory state was made by acupuncture at a single point of ST36, which is in line with the findings in previous studies. The MAPK signaling pathway is the main pathway activated by acupuncture at ST36 to produce anti-inflammatory effects, and it is linked to the rest of the signaling pathways to varying degrees. Specifically, acupuncture at ST36 can regulate TLR4 receptor protein expression on the surface of immunocompetent cells (macrophages, MCs, T-lymphocytes, microglia) via the cholinergic pathway, and then regulate the activation of MAPK signaling to regulate cellular differentiation, degranulation, proliferation and apoptosis, inhibit the downstream NF-κB pro-inflammatory signaling cascade, and reduce the pro-inflammatory cytokine production, which is the main reason for the anti-inflammatory effect of acupuncture at ST36. A molecular mechanism of acupuncture at ST36 to regulate the inflammatory state of the organism with TLR4/MAPK/NF-κB signaling pathway as the core.

In addition to this, acupuncture at ST36 has therapeutic effects in other pathological models, including anxiety states and stress states. Corticotropin-releasing hormone (CRH) in the paraventricular nucleus (PVN) of the hypothalamus is important in controlling anxiety and stress-induced behavior. Electroacupuncture at ST36 single point reduces CRF receptor 2 (CRFr2) expression in the hypothalamus, which in turn inhibits CRH release to ameliorate anxiety-like behaviors caused by stress [136,137]. Meanwhile, CRF is considered to be a major regulator of the hypothalamic-pituitary-adrenal (HPA) axis. Evidence suggests [138,139] that electroacupuncture at ST36 single point can block post-traumatic stress disorder (PTSD) model-induced hyperactivation of the HPA axis by decreasing CRF protein expression in the PVN, mediating inhibition of plasma corticosterone (CORT) levels, and increasing c-Fos expression in the anterior cingulate cortex. It can be seen that electroacupuncture at ST36 may inhibit the activation of HPA axis induced by different emotions by inhibiting the release of CRH in the PVN, and improve the behavioral abnormalities under anxiety or stress.

Secondly, acupuncture at ST36 single point can also play a role in improving pain perception and increasing pain threshold of the organism in some pain models. These include complete Freund's adjuvant (CFA)/Carrageenan-induced inflammatory pain, Oxaliplatin/paclitaxel (PTX)-induced neuropathic pain and fibromyalgia (FM) pain models. Specifically, acupuncture at ST36 can cause a short-term increase in local eATP at the acupoint, and subsequently accelerate ATP hydrolysis by regulating the levels of the Nucleoside triphosphate diphosphohydrolases (NTPDase)-2/3 in the DRG and ecto-5′NT in the spinal cord, and the sequence of hydrolysis is in the following order: "ATP→ADP→AMP→ADO" [140,141]. Eventually, ADO can bind to A1 receptors to affect purinergic signaling, inhibit ATP binding to purinergic P2 receptors, reduce neurotransmission between neurons, and exert analgesic effects [142–144]. Evidence suggests [145] that acupuncture at ST36 single point also induces a localized increase in acupoint macrophage elevation, and the acupuncture signal promotes macrophage differentiation to M2 type and reduces the production of M1 type macrophages. Whereas M1-type macrophages may cause rapid accumulation of ATP, M2-type macrophages can promote the conversion of ATP to ADO [146]. This suggests that acupuncture ST36 regulates purinergic signaling cascades involved in the peripheral mechanism of analgesia may be related to the local macrophage recruitment and polarization at acupoints triggered by acupuncture at

ST36. In addition, the transmission of acupuncture signals and pain signals from the periphery to the centre was able to inhibit TRPV1 protein expression-dominated pathways in parts of the prefrontal cortex, somatosensory cortex (SSC), hippocampus, spinal cord, hypothalamus, and cerebellum, inducing $Calcium^{2+}$/calpain-mediated ablation of axon terminals, and decreasing central synaptic transmission of pain signals and central sensitization [147–150].

Studies have shown [151] that acupuncture at ST36 in a physiological state also triggers a series of molecular changes in the organism. Needling across the local skin of ST36 acupoints causes deformation of the local connective tissue at the acupoints, and promotes MC recruitment in the subcutaneous tissue region of the acupoints by upregulating local intercellular adhesion molecule-1 (ICAM-1) mRNA expression [152]. It also causes α6 and β1 integrin activation in the acupoint region to mediate phosphorylation of ERK1/2 signaling, which transmits mechanosensory signals from the acupoints locally to the afferent nerve fibers, and increases in the DRG by P2X3 purinergic receptor and growth-associated protein 43 (GAP-43) protein expression was elevated, while c-Fos expression in the dorsal vagal nucleus (DMV) was elevated, and the regulation of visceral organs by vagal excitability [153,154]. Thus, the acupuncture signals are transmitted locally from the acupoints to central DMV integration via DRG, which may be one of the molecular biological bases for the organism to perceive acupuncture signals and regulate visceral functions.

With the in-depth development of the acupuncture discipline, clinical translation of basic research is the primary theme of acupuncture research today. Accurate and scientific selection of acupoints is the main purpose of exploring the molecular mechanism of acupuncture at acupoints, and it may also be one of the breakthroughs in the clinical translation of acupuncture research. Therefore, in the future, how acupuncture at acupoints treat diseases can be systematically meditated from the perspective of molecular mechanisms to enrich the connotation of acupuncture theory for treating diseases.

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Data availability statement

No data was used for the research described in the article.

CRediT authorship contribution statement

Xiaojing Fan: Writing – original draft. **Yunlong Liu:** Writing – review & editing, Writing – original draft. **Shanshan Li:** Writing – original draft. **Yongrui Yang:** Data curation. **Yinghui Zhao:** Data curation. **Wenxi Li:** Data curation. **Jiaxin Hao:** Data curation. **Zhifang Xu:** Data curation. **Bo Zhang:** Data curation. **Wei Liu:** Writing – review & editing. **Suzhao Zhang:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] H.Y. Lee, O.J. Kwon, J.E. Kim, M. Kim, A.R. Kim, H.J. Park, et al., Efficacy and safety of acupuncture for functional constipation: a randomised, sham-controlled pilot trial, BMC Complement Altern Med 18 (2018) 186.
[2] T. Bao, A.D. Seidman, L. Piulson, E. Vertosick, X. Chen, A.J. Vickers, et al., A phase IIA trial of acupuncture to reduce chemotherapy-induced peripheral neuropathy severity during neoadjuvant or adjuvant weekly paclitaxel chemotherapy in breast cancer patients, Eur. J. Cancer 101 (2018) 12–19.
[3] T. Friedemann, E. Kark, N. Cao, M. Klaßen, G. Meyer-Hamme, J.H. Greten, et al., Acupuncture improves chemotherapy-induced neuropathy explored by neurophysiological and clinical outcomes - the randomized, controlled, cross-over ACUCIN trial, Phytomedicine 104 (2022) 154294.
[4] Y. Du, L. Zhang, W. Liu, C. Rao, B. Li, X. Nan, et al., Effect of acupuncture treatment on post-stroke cognitive impairment: a randomized controlled trial, Medicine (Baltim.) 99 (2020) e23803.
[5] Z. Wang, M. Xu, Z. Shi, C. Bao, H. Liu, C. Zhou, et al., Mild moxibustion for Irritable bowel syndrome with diarrhea (IBS-D): a randomized controlled trial, J. Ethnopharmacol. 289 (2022) 115064.
[6] S. Liu, Z. Wang, Y. Su, L. Qi, W. Yang, M. Fu, et al., A neuroanatomical basis for electroacupuncture to drive the vagal-adrenal axis, Nature 598 (2021) 641–645.
[7] Z.J. Zhang, X.M. Wang, G.M. McAlonan, Neural acupuncture unit: a new concept for interpreting effects and mechanisms of acupuncture, Evid Based Complement Alternat Med (2012) 429412, 2012.
[8] A. Zhang, G. Yan, H. Sun, W. Cheng, X. Meng, L. Liu, et al., Deciphering the biological effects of acupuncture treatment modulating multiple metabolism pathways, Sci. Rep. 6 (2016) 19942.
[9] C. Xie, S. Wu, Z. Li, B. Huang, W. Zeng, Electroacupuncture protects septic rats from acute lung injury through the JAK1/STAT3 pathway, J. South. Med. Univ. 40 (2020) 1662–1667.
[10] X.M. Song, X.J. Wu, J.G. Li, L.L. Le, H. Liang, Y. Xu, et al., The effect of electroacupuncture at ST36 on severe thermal injury-induced remote acute lung injury in rats, Burns 41 (2015) 1449–1458.
[11] Z.L. Wu, C.R. Li, Z.L. Liu, Q.R. Zhang, Effects of acupuncture at "Zusanli" (ST 36) on eosinophil apoptosis and related gene expression in rats with asthma, Chin. Acupunct. Moxibustion 32 (2012) 721–725.
[12] D. Luo, L. Liu, H.M. Zhang, Y.D. Zhou, M.F. Zhou, J.X. Li, et al., Electroacupuncture pretreatment exhibits lung protective and anti-inflammation effects in lipopolysaccharide-induced acute lung injury via SIRT1-dependent pathways, Evid Based Complement Alternat Med 2022 (2022) 2252218.
[13] J.S. Guan, X.M. Liu, T. Fan, B. Mao, Effects of acupuncture at zusanli on plasma dopamine and lung function of rats with COPD, J. Sichuan Univ. 50 (2019) 203–209.

[14] X. Liu, T. Fan, J. Guan, A. Luo, Y. Yu, D. Chen, et al., Dopamine relieves inflammatory responses through the D2 receptor after electroacupuncture at ST36 in a mouse model of chronic obstructive pulmonary disease, Acupunct. Med. (2022) 9645284221107684.
[15] W. Geng, Z. Liu, N. Song, W. Geng, G. Zhang, W. Jin, et al., Effects of electroacupuncture at Zusanli (ST36) on inflammatory cytokines in a rat model of smoke-induced chronic obstructive pulmonary disease, J Integr Med 11 (2013) 213–219.
[16] Y. Zhang, L. Zheng, H. Deng, D. Feng, S. Hu, L. Zhu, et al., Electroacupuncture alleviates LPS-induced ARDS through α7 nicotinic acetylcholine receptor-mediated inhibition of ferroptosis, Front. Immunol. 13 (2022) 832432.
[17] X.G. Lin, W. Li, S.Y. Xiang, S.B. Wu, X.F. Zhang, C.W. Jiang, et al., Electroacupuncture improves lung function by suppressing mucin-5AC mediated EGFR-p38MAPK signaling and inflammation reaction in chronic obstructive pulmonary disease rats, Acupunt Res 46 (2021) 180–186.
[18] L.A. Huppert, M.A. Matthay, L.B. Ware, Pathogenesis of acute respiratory distress syndrome, Semin. Respir. Crit. Care Med. 40 (2019) 31–39.
[19] L.D.J. Bos, L.B. Ware, Acute respiratory distress syndrome: causes, pathophysiology, and phenotypes, Lancet 400 (2022) 1145–1156.
[20] A. Banno, A.T. Reddy, S.P. Lakshmi, R.C. Reddy, Bidirectional interaction of airway epithelial remodeling and inflammation in asthma, Clin Sci (Lond). 134 (2020) 1063–1079.
[21] R.F. Li, G.F. Wang, JAK/STAT5 signaling pathway inhibitor ruxolitinib reduces airway inflammation of neutrophilic asthma in mice model, Eur. Rev. Med. Pharmacol. Sci. 22 (2018) 835–843.
[22] W. Wang, F. Li, Y. Xu, J. Wei, Y. Zhang, H. Yang, et al., JAK1-mediated Sirt1 phosphorylation functions as a negative feedback of the JAK1-STAT3 pathway, J. Biol. Chem. 293 (2018) 11067–11075.
[23] Y. Yang, Y. Liu, Y. Wang, Y. Chao, J. Zhang, Y. Jia, et al., Regulation of SIRT1 and its roles in inflammation, Front. Immunol. 13 (2022) 831168.
[24] J.P. Hussman, Cellular and molecular pathways of COVID-19 and potential points of therapeutic intervention, Front. Pharmacol. 11 (2020) 1169.
[25] P. Xin, X. Xu, C. Deng, S. Liu, Y. Wang, X. Zhou, et al., The role of JAK/STAT signaling pathway and its inhibitors in diseases, Int Immunopharmacol 80 (2020) 106210.
[26] P.J. Barnes, Oxidative stress-based therapeutics in COPD, Redox Biol. 33 (2020) 101544.
[27] K. Dua, V. Malyla, G. Singhvi, R. Wadhwa, R.V. Krishna, S.D. Shukla, et al., Increasing complexity and interactions of oxidative stress in chronic respiratory diseases: an emerging need for novel drug delivery systems, Chem. Biol. Interact. 299 (2019) 168–178.
[28] T. Li, S. Wu, S. Li, X. Bai, H. Luo, X. Zuo, SOCS3 participates in cholinergic pathway regulation of synovitis in rheumatoid arthritis, Connect. Tissue Res. 59 (2018) 287–294.
[29] L.R. Bonser, D.J. Erle, Airway mucus and asthma: the role of MUC5AC and MUC5B, J. Clin. Med. 6 (2017) 112.
[30] K. Okuda, G. Chen, D.B. Subramani, M. Wolf, R.C. Gilmore, T. Kato, et al., Localization of secretory mucins MUC5AC and MUC5B in normal/healthy human airways, Am. J. Respir. Crit. Care Med. 199 (2019) 715–727.
[31] J. Ma, B.K. Rubin, J.A. Voynow, Mucins, mucus, and goblet cells, Chest 154 (2018) 169–176.
[32] T. Southworth, S. Mason, A. Bell, I. Ramis, M. Calbet, A. Domenech, et al., PI3K, p38 and JAK/STAT signalling in bronchial tissue from patients with asthma following allergen challenge, Biomark. Res. 6 (2018) 14.
[33] Y.T. Yeung, F. Aziz, A. Guerrero-Castilla, S. Arguelles, Signaling pathways in inflammation and anti-inflammatory therapies, Curr. Pharmaceut. Des. 24 (2018) 1449–1484.
[34] J.A. Tida, C.H.R. Catalão, C.A.B. Garcia, A.C. Dos Santos, C.E.G. Salmon, L. da S. Lopes, Acupuncture at ST36 exerts neuroprotective effects via inhibition of reactive astrogliosis in infantile rats with hydrocephalus, Acupunct. Med. 36 (2018) 386–393.
[35] F. Li, C.Q. Yan, L.T. Lin, H. Li, X.H. Zeng, Y. Liu, et al., Acupuncture attenuates cognitive deficits and increases pyramidal neuron number in hippocampal CA1 area of vascular dementia rats, BMC Complement Altern Med 15 (2015) 133.
[36] B. Lu, Z. Ma, F. Cheng, Y. Zhao, X. Zhang, H. Mao, et al., Effects of electroacupuncture on ethanol-induced impairments of spatial learning and memory and Fos expression in the hippocampus in rats, Neurosci. Lett. 576 (2014) 62–67.
[37] Q.Q. Li, G.X. Shi, J.W. Yang, Z.X. Li, Z.H. Zhang, T. He, et al., Hippocampal cAMP/PKA/CREB is required for neuroprotective effect of acupuncture, Physiol. Behav. 139 (2015) 482–490.
[38] Y. Li, Z. Li, F. He, C. Qin, R. Fan, F. Zhang, et al., Electroacupuncture alleviates cognitive dysfunction and neuronal pyroptosis in septic mice, Acupunct. Med. 41 (2023) 246–256.
[39] P. Zhao, H. Fu, H. Cheng, R. Zheng, D. Yuan, J. Yang, et al., Acupuncture at ST36 alleviates the behavioral disorder of autistic rats by inhibiting TXNIP-mediated activation of NLRP3, J. Neuropathol. Exp. Neurol. 81 (2022) 127–134.
[40] H. Ni, J. Ren, Q. Wang, X. Li, Y. Wu, D. Liu, et al., Electroacupuncture at ST 36 ameliorates cognitive impairment and beta-amyloid pathology by inhibiting NLRP3 inflammasome activation in an Alzheimer's disease animal model, Heliyon 9 (2023) e16755.
[41] Y.H. Zhao, H.G. Fu, H. Cheng, R.J. Zheng, G. Wang, S. Li, et al., Electroacupuncture at Zusanli ameliorates the autistic-like behaviors of rats through activating the Nrf2-mediated antioxidant responses, Gene 828 (2022) 146440.
[42] L. Liberale, L. Badimon, F. Montecucco, T.F. Lüscher, P. Libby, G.G. Camici, Inflammation, aging, and cardiovascular disease: JACC review topic of the week, J. Am. Coll. Cardiol. 79 (2022) 837–847.
[43] X.Y. Chang, K. Chen, T. Cheng, P.T. Lai, L. Zhang, K.F. So, et al., In vivo neuronal and astrocytic activation in somatosensory cortex by acupuncture stimuli, Neural Regen Res 17 (2022) 2526–2529.
[44] Y.X. Zhao, M.J. Yao, Q. Liu, J.J. Xin, J.H. Gao, X.C. Yu, Electroacupuncture treatment attenuates paclitaxel-induced neuropathic pain in rats via inhibiting spinal glia and the TLR4/NF-κB pathway, J. Pain Res. 13 (2020) 239–250.
[45] M. Sui, S. Lessans, T. Yan, D. Cao, L. Lao, S.G. Dorsey, Mechanism of electroacupuncture on "Zusanli (ST 36)" for chemotherapy-induced peripheral neuropathy, Chin. Acupunct. Moxibustion 36 (2016) 512–516.
[46] Y. Li, Z. Fang, N. Gu, F. Bai, Y. Ma, H. Dong, et al., Inhibition of chemokine CX3CL1 in spinal cord mediates the electroacupuncture-induced suppression of inflammatory pain, J. Pain Res. 12 (2019) 2663–2672.
[47] C. Shi, Y. Liu, W. Zhang, Y. Lei, C. Lu, R. Sun, et al., Intraoperative electroacupuncture relieves remifentanil-induced postoperative hyperalgesia via inhibiting spinal glial activation in rats, Mol. Pain 13 (2017) 1744806917725636.
[48] S. Kim, X. Zhang, S.C. O'Buckley, M. Cooter, J.J. Park, A.G. Nackley, Acupuncture resolves persistent pain and neuroinflammation in a mouse model of chronic overlapping pain conditions, J. Pain 19 (2018), 1384.e1-1384.e14.
[49] A. Plachti, S. Kharabian, S.B. Eickhoff, S. Maleki Balajoo, F. Hoffstaedter, D.P. Varikuti, et al., Hippocampus co-atrophy pattern in dementia deviates from covariance patterns across the lifespan, Brain 143 (2020) 2788–2802.
[50] N.L. Pettit, E.L. Yap, M.E. Greenberg, C.D. Harvey, Fos ensembles encode and shape stable spatial maps in the hippocampus, Nature 609 (2022) 327–334.
[51] J. Yan, W. Xu, C. Lenahan, L. Huang, J. Wen, G. Li, et al., CCR5 activation promotes NLRP1-dependent neuronal pyroptosis via CCR5/PKA/CREB pathway after intracerebral hemorrhage, Stroke 52 (2021) 4021–4032.
[52] Z. Zhai, P.K. Vaddi, J.M. Samson, T. Takegami, M. Fujita, NLRP1 functions downstream of the MAPK/ERK signaling via ATF4 and contributes to acquired targeted therapy resistance in human metastatic melanoma, Pharmaceuticals 14 (2020) 23.
[53] F. Sposito, S. Northey, A. Charras, P.S. McNamara, C.M. Hedrich, Hypertonic saline induces inflammation in human macrophages through the NLRP1 inflammasome, Gene Immun. 24 (2023) 263–269.
[54] J. Li, B. Jia, Y. Cheng, Y. Song, Q. Li, C. Luo, Targeting molecular mediators of ferroptosis and oxidative stress for neurological disorders, Oxid. Med. Cell. Longev. 2022 (2022) 3999083.
[55] S. Du, X. Wang, W. Zhu, Y. Ye, J. Yang, S. Ma, et al., Acupuncture inhibits TXNIP-associated oxidative stress and inflammation to attenuate cognitive impairment in vascular dementia rats, CNS Neurosci. Ther. 24 (2017) 39–46.
[56] J. Zeng, Y. Chen, R. Ding, L. Feng, Z. Fu, S. Yang, et al., Isoliquiritigenin alleviates early brain injury after experimental intracerebral hemorrhage via suppressing ROS- and/or NF-κB-mediated NLRP3 inflammasome activation by promoting Nrf2 antioxidant pathway, J. Neuroinflammation 14 (2017) 119.

[57] S. Hu, M.H. Du, H.M. Luo, H. Wang, Y. Lv, L. Ma, et al., Electroacupuncture at zusanli (ST36) prevents intestinal barrier and remote organ dysfunction following gut ischemia through activating the cholinergic anti-inflammatory-dependent mechanism, Evid Based Complement Alternat Med (2013) 592127, 2013.
[58] Y. Geng, D. Chen, J. Zhou, H. Jiang, H. Zhang, Role of cholinergic anti-inflammatory pathway in treatment of intestinal ischemia-reperfusion injury by electroacupuncture at zusanli, Evid Based Complement Alternat Med (2017) 6471984, 2017.
[59] H. Wang, L. Wang, X. Shi, S. Qi, S. Hu, Z. Tong, et al., Electroacupuncture at zusanli prevents severe scalds-induced gut ischemia and paralysis by activating the cholinergic pathway, Evid Based Complement Alternat Med (2015) 787393, 2015.
[60] H.D. Lim, K.J. Kim, B.G. Jo, J.Y. Park, U. Namgung, Acupuncture stimulation attenuates TNF-α production via vagal modulation in the concanavalin A model of hepatitis, Acupunct. Med. 38 (2020) 417–425.
[61] W. Lei, C. Zhao, J. Sun, Y. Jin, Z. Duan, Electroacupuncture ameliorates intestinal barrier destruction in mice with bile duct ligation-induced liver injury by activating the cholinergic anti-inflammatory pathway, Neuromodulation 25 (2022) 1122–1133.
[62] Q. Xue, N. Li, P. Xue, C. Wang, Q. Wen, Therapeutic effects of electroacupuncture at ST36 acupoint on sodium-taurocholate-induced severe acute pancreatitis, Chin. J. Integr. Med. 20 (2014) 695–700.
[63] Q.M. Xue, L. Huang, H. Pan, N. Li, Effects of electroacupuncture at Zusanli (ST 36) on the expressions of small intestinal occludin protein and nuclear factor kappa-B in rats with severe acute pancreatitis, Chin. Acupunct. Moxibustion 34 (2014) 267–271.
[64] L. Zhang, Z. Wu, J. Zhou, S. Lu, C. Wang, Y. Xia, et al., Electroacupuncture ameliorates acute pancreatitis: a role for the vagus nerve-mediated cholinergic anti-inflammatory pathway, Front. Mol. Biosci. 8 (2021) 647647.
[65] H. Jin, J. Guo, J. Liu, B. Lyu, R.D. Foreman, Z. Shi, et al., Autonomically mediated anti-inflammatory effects of electrical stimulation at acupoints in a rodent model of colonic inflammation, Neuro Gastroenterol. Motil. 31 (2019) e13615.
[66] C.C. Yan, Y. Peng, Y.P. Lin, S.X. Yi, P. Chen, Y.L. Hou, et al., Effect of manual acupuncture stimulation of "Zusanli" (ST 36) on gastric motility, and SP and motilin activities in gastric antrum and nucleus raphe magnus in gastric hyperactivity and hypoactivity rats, Acupunct. Res. 38 (2013) 345–351.
[67] S. Zhang, Y. Liu, S. Li, F. Ye, R.D. Foreman, J.D.Z. Chen, Effects of electroacupuncture on stress-induced gastric dysrhythmia and mechanisms involving autonomic and central nervous systems in functional dyspepsia, Am. J. Physiol. Regul. Integr. Comp. Physiol. 319 (2020) R106–R113.
[68] J. Guo, Y. Zhu, Y. Yang, X. Wang, B. Chen, W. Zhang, et al., Electroacupuncture at Zusanli (ST36) ameliorates colonic neuronal nitric oxide synthase upregulation in rats with neurogenic bowel dysfunction following spinal cord injury, Spinal Cord 54 (2016) 1139–1144.
[69] X. Xu, Q. Li, L. Zhou, L. Ru, Neurochemical mechanism of the gastrointestinal interdigestive migrating motor complex in rats with acute inflammatory stomach ache, Neural Regen Res 7 (2012) 2136–2143.
[70] X.Y. Wang, C.Y. Li, Y.N. Zhang, C.Y. Fu, S.S. Gao, S.J. Wang, Effect of electroacupuncture on 5-HT7R in gastric antrum and colon tissues of functional diarrhea rats, Acupunct. Res. 46 (2021) 549–554.
[71] Y. Chen, J. Cheng, Y. Zhang, J.D.Z. Chen, F.M. Seralu, Electroacupuncture at ST36 relieves visceral hypersensitivity via the NGF/TrkA/TRPV1 peripheral afferent pathway in a rodent model of post-inflammation rectal hypersensitivity, J. Inflamm. Res. 14 (2021) 325–339.
[72] J.Z. Dong, P.J. Rong, T.M. Ma, D. Wang, X.T. Wang, Y. Qiao, Influence of electroacupuncture of"Zusanli"(ST36) on mast cells/TRPV1 signaling pathway in visceral hypersensitivity rats with functional dyspepsia, Acupunct. Res. 47 (2022) 592–597.
[73] J.Z. Dong, P.J. Rong, X.T. Wang, D. Wang, M.H. Leng, L.J. Xiao, Effect of electroacupuncture at "Zusanli" (ST 36) on duodenal mast cells, NGF and NTRK1 in rats with functional dyspepsia, Chin. Acupunct. Moxibustion 42 (2022) 767–772.
[74] Y.L. Wang, H.Y. Zhu, X.Q. Lv, X.Y. Ren, Y.C. Peng, J.Y. Qu, et al., Electroacupuncture zusanli (ST36) relieves somatic pain in colitis rats by inhibiting dorsal root ganglion sympathetic-sensory coupling and neurogenic inflammation, Neural Plast. 2023 (2023) 9303419.
[75] M. Peng, K. Li, C. Wang, X. Zhu, Z. Yang, G. Zhang, et al., Therapeutic effect and mechanism of electroacupuncture at Zusanli on plasticity of interstitial cells of Cajal: a study of rat ileum, BMC Complement Altern Med 14 (2014) 186.
[76] Y. Yang, J. Cheng, Y. Zhang, J. Guo, B. Xie, W. Zhang, et al., Electroacupuncture at zusanli (ST36) repairs interstitial cells of cajal and upregulates c-kit expression in rats with SCI-induced neurogenic bowel dysfunction, Evid Based Complement Alternat Med 2020 (2020) 8896123.
[77] S. Song, J. An, S. Liu, Electroacupuncture accelerates the delayed intestinal transit in POI by suppressing M1 like muscularis macrophages and IL-6 secretion, Neuro Gastroenterol. Motil. 33 (2021) e14066.
[78] X.L. Pan, L. Zhou, D. Wang, Y.L. Han, J.Y. Wang, P. Xu, et al., Electroacupuncture at "Zusanli"(ST36) promotes gastrointestinal motility possibly by suppressing excessive autophagy via AMPK/ULK1 signaling in rats with functional dyspepsia, Acupunct. Res. 44 (2019) 486–491.
[79] G. Zhang, S. Xie, W. Hu, Y. Liu, M. Liu, M. Liu, et al., Effects of electroacupuncture on interstitial cells of cajal (ICC) ultrastructure and connexin 43 protein expression in the gastrointestinal tract of functional dyspepsia (FD) rats, Med Sci Monit 22 (2016) 2021–2027.
[80] W. Huang, Y. Yau, J. Zhu, Y. Wang, Z. Dai, H. Gan, et al., Effect of electroacupuncture at zusanli (ST36) on intestinal microbiota in rats with chronic atrophic gastritis, Front. Genet. 13 (2022) 824739.
[81] L. Wang, J. An, S. Song, M. Mei, W. Li, F. Ding, et al., Electroacupuncture preserves intestinal barrier integrity through modulating the gut microbiota in DSS-induced chronic colitis, Life Sci. 261 (2020) 118473.
[82] G.H. Liu, H.M. Liu, Y.S. Chen, T.Y. Lee, Effect of electroacupuncture in mice with dextran sulfate sodium-induced colitis and the influence of gut microbiota, Evid Based Complement Alternat Med 2020 (2020) 2087903.
[83] L. Zhan, H. Liu, J. Zheng, J. Meng, D. Fu, L. Pang, et al., Electroacupuncture at zusanli alleviates sepsis by regulating the TLR4-MyD88-NF-kappa B pathway and diversity of intestinal flora, Evid Based Complement Alternat Med 2022 (2022) 6706622.
[84] R. Piovesana, M.S. Salazar Intriago, L. Dini, A.M. Tata, Cholinergic modulation of neuroinflammation: focus on α7 nicotinic receptor, Int. J. Mol. Sci. 22 (2021) 4912.
[85] J.E. Oh, S.N. Kim, Anti-inflammatory effects of acupuncture at ST36 point: a literature review in animal studies, Front. Immunol. 12 (2021) 813748.
[86] M. Camilleri, Gastrointestinal motility disorders in neurologic disease, J. Clin. Invest. 131 (2021).
[87] A.M. Holland, A.C. Bon-Frauches, D. Keszthelyi, V. Melotte, W. Boesmans, The enteric nervous system in gastrointestinal disease etiology, Cell. Mol. Life Sci. 78 (2021) 4713–4733.
[88] X. Wang, L. Lu, L. Zi, H. Hu, H. Li, Y. He, et al., Electroacupuncture at acupoint ST36 (zusanli) improves intestinal motility dysfunction via increasing the proportion of cholinergic neurons in rat ileal myenteric ganglia after severe acute pancreatitis, Evid Based Complement Alternat Med 2022 (2022) 7837711.
[89] D. Foong, J. Zhou, A. Zarrouk, V. Ho, M.D. O'Connor, Understanding the biology of human interstitial cells of cajal in gastrointestinal motility, Int. J. Mol. Sci. 21 (2020) 4540.
[90] R. Yadak, M. Breur, M. Bugiani, Gastrointestinal Dysmotility in MNGIE: from thymidine phosphorylase enzyme deficiency to altered interstitial cells of Cajal, Orphanet J. Rare Dis. 14 (2019) 33.
[91] P. Radu, M. Zurzu, V. Paic, M. Bratucu, D. Garofil, A. Tigora, et al., Interstitial cells of cajal—origin, distribution and relationship with gastrointestinal tumors, Medicina (Kaunas) 59 (2022) 63.
[92] J.M. Yuan, X.D. Dong, J.J. Yap, J.C. Hu, The MAPK and AMPK signalings: interplay and implication in targeted cancer therapy, J. Hematol. Oncol. 13 (2020) 113.
[93] B. Zhou, Y. Yuan, S. Zhang, C. Guo, X. Li, G. Li, et al., Intestinal flora and disease mutually shape the regional immune system in the intestinal tract, Front. Immunol. 11 (2020) 575.
[94] H. Zhao, L. Kong, M. Shao, J. Liu, C. Sun, C. Li, et al., Protective effect of flavonoids extract of Hippophae rhamnoides L. on alcoholic fatty liver disease through regulating intestinal flora and inhibiting TAK1/p38MAPK/p65NF-κB pathway, J. Ethnopharmacol. 292 (2022) 115225.
[95] C.K. Wen, T.Y. Lee, Electroacupuncture decreases the leukocyte infiltration to white adipose tissue and attenuates inflammatory response in high fat diet-induced obesity rats, Evid Based Complement Alternat Med (2014) 473978, 2014.
[96] C.K. Wen, T.Y. Lee, Electroacupuncture prevents white adipose tissue inflammation through modulation of hypoxia-inducible factors-1α-dependent pathway in obese mice, BMC Complement Altern Med 15 (2015) 452.

[97] Y. Chen, J.J. Xu, S. Liu, X.H. Hou, Electroacupuncture at ST36 ameliorates gastric emptying and rescues networks of interstitial cells of Cajal in the stomach of diabetic rats, PLoS One 8 (2013) e83904.
[98] Y. Chen, J. Xu, S. Liu, X. Hou, Electroacupuncture at ST36 increases contraction of the gastric antrum and improves the SCF/c-kit pathway in diabetic rats, Am. J. Chin. Med. 41 (2013) 1233–1249.
[99] J. Zhao, J. An, S. Liu, Electroacupuncture at ST36 increases bone marrow-derived interstitial cells of cajal via the SDF-1/CXCR4 and mSCF/kit-ETV1 pathways in the stomach of diabetic mice, Evid Based Complement Alternat Med (2018) 7878053, 2018.
[100] L. Tian, B. Zhu, S. Liu, Electroacupuncture at ST36 protects ICC networks via mSCF/kit-ETV1 signaling in the stomach of diabetic mice, Evid Based Complement Alternat Med (2017) 3980870, 2017.
[101] J. An, J. Zhao, S. Liu, Bone marrow-derived interstitial cells of cajal are increased by electroacupuncture in the colon of diabetic mice, J. Gastroenterol. Hepatol. 34 (2019) 1357–1367.
[102] K.M. Man, Y.C. Lee, Y.I. Chen, Y.H. Chen, S.L. Chang, C.C. Huang, Electroacupuncture at bilateral ST36 acupoints: inducing the hypoglycemic effect through enhancing insulin signal proteins in a streptozotocin-induced rat model during isoflurane anesthesia, Evid Based Complement Alternat Med 2021 (2021) 5852599.
[103] C.Y. Tzeng, Y.C. Lee, J.J. Chung, J.C. Tsai, Y.I. Chen, T.H. Hsu, et al., 15 Hz electroacupuncture at ST36 improves insulin sensitivity and reduces free fatty acid levels in rats with chronic dexamethasone-induced insulin resistance, Acupunct. Med. 34 (2016) 296–301.
[104] W. Xu, J. Li, C. Ji, D. Fang, L. Yao, N. Xu, et al., Activation of POMC neurons to adiponectin participating in EA-mediated improvement of high-fat diet IR mice, Front. Neurosci. 17 (2023) 1145079.
[105] F. Yuan, X.P. Hong, Y.J. Duan, J.R. Chen, Y.M. Han, Electroacupuncture at "Zusanli"(ST36) ameliorates tau hyperphosphorylation in pancreas and hippocampus of diabetic rats, Acupunct. Res. 46 (2021) 901–906.
[106] M.N. Amin, M.S. Hussain, M.S. Sarwar, M.M. Rahman Moghal, A. Das, M.Z. Hossain, et al., How the association between obesity and inflammation may lead to insulin resistance and cancer, Diabetes Metab Syndr 13 (2019) 1213–1224.
[107] R. Liu, B.S. Nikolajczyk, Tissue immune cells fuel obesity-associated inflammation in adipose tissue and beyond, Front. Immunol. 10 (2019) 1587.
[108] P. Díaz-Bulnes, M.L. Saiz, C. López-Larrea, R.M. Rodríguez, Crosstalk between hypoxia and er stress response: a key regulator of macrophage polarization, Front. Immunol. 10 (2019) 2951.
[109] A.E. Bharucha, Y.C. Kudva, D.O. Prichard, Diabetic gastroparesis, Endocr. Rev. 40 (2019) 1318–1352.
[110] J. Palomo-Osuna, H. De Sola, M. Dueñas, J.A. Moral-Munoz, I. Failde, Cognitive function in diabetic persons with peripheral neuropathy: a systematic review and meta-analysis, Expert Rev. Neurother. 22 (2022) 269–281.
[111] G. Plascencia-Villa, G. Perry, Preventive and therapeutic strategies in alzheimer's disease: focus on oxidative stress, redox metals, and ferroptosis, Antioxid Redox Signal 34 (2021) 591–610.
[112] M.F. Zhu, X. Xing, S. Lei, J.N. Wu, L.C. Wang, L.Q. Huang, et al., Electroacupuncture at bilateral zusanli points (ST36) protects intestinal mucosal immune barrier in sepsis, Evid Based Complement Alternat Med (2015) 639412, 2015.
[113] D.P. Xie, G.B. Zhou, R.L. Chen, X.L. Qin, J.D. Du, Y. Zhang, et al., Effect of electroacupuncture at zusanli (ST36) on sepsis induced by cecal ligation puncture and its relevance to spleen, Evid Based Complement Alternat Med 2020 (2020) 1914031.
[114] Y. Lou, Z.Q. Zhu, L.L. Xie, Y.R. Feng, Electroacupuncture at "Zusanli"(ST36) protects intestinal mucosal immune barrier by suppre-ssing apoptosis of intestinal lymphocytes and regulating expression of Bcl-2 and Bax in sepsis rats, Acupunct. Res. 47 (2022) 386–392.
[115] P. Zhao, X. Chen, X. Han, Y. Wang, Y. Shi, J. Ji, et al., Involvement of microRNA-155 in the mechanism of electroacupuncture treatment effects on experimental autoimmune encephalomyelitis, Int Immunopharmacol 97 (2021) 107811.
[116] J. Wang, F. Zhu, W. Huang, C. Yang, Z. Chen, Y. Lei, et al., Acupuncture at ST36 ameliorates experimental autoimmune encephalomyelitis via affecting the function of B cells, Int Immunopharmacol 123 (2023) 110748.
[117] Z.Y. Lv, Y.L. Shi, G.S. Bassi, Y.J. Chen, L.M. Yin, Y. Wang, et al., Electroacupuncture at ST36 (zusanli) prevents T-cell lymphopenia and improves survival in septic mice, J. Inflamm. Res. 15 (2022) 2819–2833.
[118] Z. Wang, T. Chen, M. Long, L. Chen, L. Wang, N. Yin, et al., Electro-acupuncture at acupoint ST36 ameliorates inflammation and regulates Th1/Th2 balance in delayed-type hypersensitivity, Inflammation 40 (2017) 422–434.
[119] Z. Wang, T. Yi, M. Long, Y. Gao, C. Cao, C. Huang, et al., Electro-acupuncture at zusanli acupoint (ST36) suppresses inflammation in allergic contact dermatitis via triggering local IL-10 production and inhibiting p38 MAPK activation, Inflammation 40 (2017) 1351–1364.
[120] F. Yang, Y. Gong, N. Yu, L. Yao, X. Zhao, S. Hong, et al., ST36 acupuncture alleviates the inflammation of adjuvant-induced arthritic rats by targeting monocyte/macrophage modulation, Evid Based Complement Alternat Med 2021 (2021) 9430501.
[121] N. Yu, F. Yang, X. Zhao, Y. Guo, Y. Xu, G. Pang, et al., Manual acupuncture at ST36 attenuates rheumatoid arthritis by inhibiting M1 macrophage polarization and enhancing Treg cell populations in adjuvant-induced arthritic rats, Acupunct. Med. (2022) 9645284221085278.
[122] Z. Wang, M. Lu, J. Ren, X. Wu, M. Long, L. Chen, et al., Electroacupuncture inhibits mast cell degranulation via cannabinoid CB2 receptors in a rat model of allergic contact dermatitis, Acupunct. Med. 37 (2019) 348–355.
[123] Z. Wang, T. Yi, M. Long, F. Ding, L. Ouyang, Z. Chen, Involvement of the negative feedback of IL-33 signaling in the anti-inflammatory effect of electro-acupuncture on allergic contact dermatitis via targeting MicroRNA-155 in mast cells, Inflammation 41 (2018) 859–869.
[124] T. Chen, Y. Xiong, M. Long, D. Zheng, H. Ke, J. Xie, et al., Electro-acupuncture pretreatment at zusanli (ST36) acupoint attenuates lipopolysaccharide-induced inflammation in rats by inhibiting Ca2+ influx associated with cannabinoid CB2 receptors, Inflammation 42 (2019) 211–220.
[125] B.V. Kumar, T. Connors, D.L. Farber, Human T cell development, localization, and function throughout life, Immunity 48 (2018) 202–213.
[126] C.M. Mousset, W. Hobo, R. Woestenenk, F. Preijers, H. Dolstra, A.B. van der Waart, Comprehensive phenotyping of T cells using flow cytometry, Cytometry 95 (2019) 647–654.
[127] M. Ruterbusch, K.B. Pruner, L. Shehata, M. Pepper, In vivo CD4+ T cell differentiation and function: revisiting the Th1/Th2 paradigm, Annu. Rev. Immunol. 38 (2020) 705–725.
[128] Q. Wang, S. Li, S. Qiao, Z. Zheng, X. Duan, X. Zhu, Changes in T Lymphocyte subsets in different tumors before and after radiotherapy: a meta-analysis, Front. Immunol. 12 (2021) 648652.
[129] J. Wang, S. Lu, F. Yang, Y. Guo, Z. Chen, N. Yu, et al., The role of macrophage polarization and associated mechanisms in regulating the anti-inflammatory action of acupuncture: a literature review and perspectives, Chin. Med. 16 (2021) 56.
[130] A. Giannetti, E. Filice, C. Caffarelli, G. Ricci, A. Pession, Mast cell activation disorders, Medicina (Kaunas). 57 (2021) 124.
[131] E. Cho, W. Kim, Effect of acupuncture on diabetic neuropathy: a narrative review, Int. J. Mol. Sci. 22 (2021) 8575.
[132] Y. Zhong, J. Cao, H. Lu, Z. Huang, L. Liu, C. Wen, et al., Publication trends in rehabilitative effects of acupuncture: a visual analysis of the literature, Evid Based Complement Alternat Med 2022 (2022) 7705256.
[133] Y. Tian, L. Wang, T. Xu, R. Li, R. Zhu, B. Chen, et al., Acupuncture for osteoporosis: a review of its clinical and preclinical studies, J Acupunct Meridian Stud 15 (2022) 281–299.
[134] C. Chen, J. Zhan, H. Wen, X. Wei, L. Ding, C. Tao, et al., Current state of research about acupuncture for the treatment of COVID-19: a scoping review, Integr Med Res 10 (2021) 100801.
[135] J. Jiang, X. Wang, X. Wu, Z. Yu, Analysis of factors influencing moxibustion efficacy by affecting heat-activated transient receptor potential vanilloid channels, J. Tradit. Chin. Med. 36 (2016) 255–260.
[136] Y. Zhao, C. Cui, X. Yu, J. Xin, F. Lu, J. Gao, et al., Electroacupuncture ameliorates abnormal defaecation and regulates corticotrophin-releasing factor in a rat model of stress, Acupunct. Med. 35 (2017) 114–121.
[137] Y.X. Zhao, C.X. Cui, J.H. Gao, J. Liu, Q. Liu, F.Y. Lu, et al., Electroacupuncture ameliorates corticotrophin-releasing factor-induced jejunal dysmotility in a rat model of stress, Acupunct. Med. 39 (2021) 135–145.

[138] Z. Zhao, B.H. Lee, F. Lin, Y. Guo, S. Y. Wu, et al., Effects of acupuncture at Zu-San-Li (ST36) on the activity of the hypothalamic–pituitary–adrenal axis during ethanol withdrawal in rats, J Acupunct Meridian Stud 7 (2014) 225–230.
[139] L. Liu, H. Liu, Y. Hou, J. Shen, X. Qu, S. Liu, Temporal effect of electroacupuncture on anxiety-like behaviors and c-Fos expression in the anterior cingulate cortex in a rat model of post-traumatic stress disorder, Neurosci. Lett. 711 (2019) 134432.
[140] D. Shen, Y.W. Zheng, D. Zhang, X.Y. Shen, L.N. Wang, Acupuncture modulates extracellular ATP levels in peripheral sensory nervous system during analgesia of ankle arthritis in rats, Purinergic Signal. 17 (2021) 411–424.
[141] W.M. Zuo, Y.J. Li, K.Y. Cui, D. Shen, D. Zhang, Y.W. Zheng, et al., The real-time detection of acupuncture-induced extracellular ATP mobilization in acupoints and exploration of its role in acupuncture analgesia, Purinergic Signal. 19 (2023) 69–85.
[142] Q.X. Dai, L.P. Huang, Y.C. Mo, L.N. Yu, W.W. Du, A.Q. Zhang, et al., Role of spinal adenosine A1 receptors in the analgesic effect of electroacupuncture in a rat model of neuropathic pain, J. Int. Med. Res. 48 (2020) 300060519883748.
[143] Q.X. Dai, S. Li, M. Ren, X. Wu, X.Y. Yao, F.H. Lin, et al., Analgesia with 5' extracellular nucleotidase-mediated electroacupuncture for neuropathic pain, Arq Neuropsiquiatr 80 (2022) 289–295.
[144] W. Li, D. Dai, A. Chen, X.F. Gao, L. Xiong, Characteristics of zusanli dorsal root ganglion neurons in rats and their receptor mechanisms in response to adenosine, J. Pain 23 (2022) 1564–1580.
[145] M. Yan, R. Wang, S. Liu, Y. Chen, P. Lin, T. Li, et al., The mechanism of electroacupuncture at zusanli promotes macrophage polarization during the fibrotic process in contused skeletal muscle, Eur. Surg. Res. 60 (2019) 196–207.
[146] R.F. Zanin, E. Braganhol, L.S. Bergamin, L.F.I. Campesato, A.Z. Filho, J.C.F. Moreira, et al., Differential macrophage activation alters the expression profile of NTPDase and ecto-5'-nucleotidase, PLoS One 7 (2012) e31205.
[147] J.G. Lin, C.L. Hsieh, Y.W. Lin, Analgesic effect of electroacupuncture in a mouse fibromyalgia model: roles of TRPV1, TRPV4, and pERK, PLoS One 10 (2015) e0128037.
[148] V. Arora, J.N. Campbell, M.K. Chung, Fight fire with fire: neurobiology of capsaicin-induced analgesia for chronic pain, Pharmacol. Ther. 220 (2021) 107743.
[149] C. Inprasit, Y.W. Lin, TRPV1 responses in the cerebellum lobules V, VIa and VII using electroacupuncture treatment for inflammatory hyperalgesia in murine model, Int. J. Mol. Sci. 21 (2020) 3312.
[150] B. Lottering, Y.W. Lin, Functional characterization of nociceptive mechanisms involved in fibromyalgia and electroacupuncture, Brain Res. 1755 (2021) 147260.
[151] N. Li, Y. Guo, Y. Gong, Y. Zhang, W. Fan, K. Yao, et al., The anti-inflammatory actions and mechanisms of acupuncture from acupoint to target organs via neuro-immune regulation, J. Inflamm. Res. 14 (2021) 7191–7224.
[152] X. Song, M. Luo, J. Jiang, J. Zhang, Effects of electroacupuncture stimulation of "Zusanli" (ST 36) on the regional vascular intercellular Adhesion Molecule-1 mRNA expression and mast cell activity in normal rats, Acupunct. Res. 39 (2014) 461–465.
[153] M.H. Kim, Y.C. Park, U. Namgung, Acupuncture-stimulated activation of sensory neurons, J Acupunct Meridian Stud 5 (2012) 148–155.
[154] H.C. Shin, J.Y. Park, H.D. Lim, U. Namgung, Induction of α6 and β1 integrins by acupuncture stimulation in rats, Biochem. Biophys. Res. Commun. 491 (2017) 629–635.