Review

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Revealing the magic of acupuncture based on biological mechanisms: A literature review

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SUMMARY Acupuncture has been used to treat various disease for more than 3,000 years in China and other Asian countries. As a complementary and alternative therapy, it has gained increasing popularity and acceptance among public and healthcare professionals in the West. Over the past few decades, basic and clinical research on acupuncture has made considerable progress. Internationally recognized evidence from clinical studies has been published, a preliminary system to clinically evaluate acupuncture has been created, and some clinical guidelines have been formulated. Moreover, scientists have strived to explore the physiological and biological mechanisms of acupuncture. Some basic studies have indicated that acupuncture has various actions, such as analgesic, muscle relaxing, anti-inflammatory, mild anxiolytic, and antidepressant actions, with possible biological mechanisms such as central sensitization, neurotransmitters, the intestinal flora, immune regulation, oxidative stress, and neuroinflammation. The current review describes the common indications for acupuncture recommended by the WHO and the use of acupuncture in China, the United States, Australia, and several other countries. This review then summarized the mechanisms by which acupuncture treats common conditions including lower back pain (LBP), ischemic stroke, depression, and irritable bowel syndrome (IBS) and it also cited specific acupuncture points for treating these conditions. The hope is that this review will provide useful information for both acupuncturists and researchers to better understand the mechanisms of acupuncture and reasons for its usage.

Keywords acupuncture, electroacupuncture, indications, biological mechanisms, common acupuncture points

1. Introduction

Acupuncture has been used to treat various disease for more than 3,000 years in China and other Asian countries, and it spread to Europe and America from the sixteenth to the nineteenth century. As one of the most popular complementary and alternative therapies, it has gained increasing popularity and acceptance among public and healthcare professionals in the West. The World Health Organization (WHO) listed 43 diseases and conditions that can be treated with acupuncture in 1979, and that number increased to 63 in 1996, as shown in Table 1 (*1*). Moreover, data from the WHO indicated that 103 of its 194 member countries use acupuncture as a treatment and that 29 had enacted laws to regulate traditional Chinese medicine (TCM), while 18 had included acupuncture in their medical insurance system (*2*). Thus, acupuncture plays an important role in the healthcare system worldwide.

In China, acupuncture is a longstanding legal medical practice widely used by doctors in Chinese medicine, with an estimated 18,404 doctors in acupuncture in Mainland China in 2018 (*3*). In Japan, acupuncture has been a part of Chinese medicine since 562 AD; it was introduced from China to Japan and is still used today (*4*). In South Korea, the government enacted the National Medicine Act in October 1951, which stipulates that Eastern and Western medicine have the same status (*4*). In United States, the National Institutes of Health (NIH) approved acupuncture as a treatment for patients in 1991, and the Food and Drug Administration (FDA) approved acupuncture needles as a medical device in 1996. Moreover, 47 states and Washington, D.C. in the United States have successively passed acupuncture laws, ensuring the legal use and development of acupuncture since 2014 (*4*). In Canada, acupuncture legislation

Table 1. Common indications for acupuncture recommended by WHO

Indications	Examples
Nervous system disease	Migraine, Tension headache, Trigeminal neuralgia, Facial nerve palsy, and Ischemic stroke.
Musculoskeletal diseases	Osteoarthritis (knee), Fibromyalgia, LBP, Neck pain, sciatica, and Postoperative pain.
Gastrointestinal diseases	Nausea and vomiting, Constipation, Postoperative ileus, and IBS.
Gynecological/reproductive diseases	Dysmenorrhea, Premenstrual Syndrome, Menopausal syndrome, and Infertility,
Respiratory diseases	Common cold, Acute bronchitis, Acute and chronic pharyngitis, Asthma, and Chronic obstructive pulmonary disease.
Oral disease	Toothache, Post tooth extraction pain, and Gingivitis.
Mental diseases	Anxiety, Depression, and Insomnia.
Addictions	Nicotine dependence and Alcohol dependence.
Endocrine diseases	Obesity.

Abbreviations: lower back pain (LBP), irritable bowel syndrome (IBS).

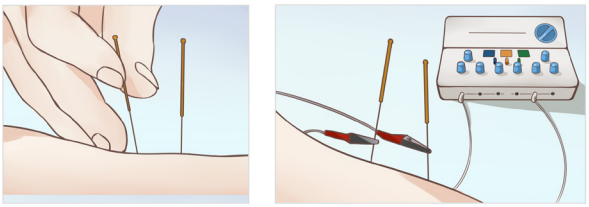

Figure 1. Different types of acupuncture.

has been approved by the governments of 5 provinces between 1988 and 2014 (*5*). In Australia, a national registration standard for TCM has been implemented since July 1, 2012, and Australia is the first Western country to legislate TCM. In addition to the countries discussed above, South Africa, Canada, France, Brazil, and Germany also have legislation on acupuncture (*4*). In all, the development of acupuncture has entered a new era worldwide.

Acupuncture is defined as the insertion of fine needles through the skin into specific body sites, known as acupuncture points, on meridians according to the ancient theory of TCM to improve the body's energy flow and maintain overall health and vitality (Figure 1A). Acupuncture points have been emphasized as key elements that account for the efficacy of acupuncture. TCM uses approximately 361 acupuncture points on 14 traditional channels and 34 extra points (*6*). The required efficacy is achieved only by the precise stimulation of specific acupuncture points. Electroacupuncture is a modification of acupuncture in which needles with attached electrodes are inserted to deliver a pulsed electrical current (Figure 1B). Although it is still controversial, electroacupuncture has been shown to achieve similar or even better effects compared to acupuncture (*7*).

Until now, numerous efforts have been made to determine the clinical efficacy and specificity of acupuncture. Internationally recognized evidence from clinical studies has been published. These clinical studies have indicated that acupuncture and electroacupuncture are effective for the management and treatment of various conditions including various types of pain, ischemic stroke, anxiety disorders, irritable bowel syndrome (IBS), and inflammatory bowel disease, which are common and tricky clinical conditions (*1,8,9,10*). Moreover, clinical practice guidelines on acupuncture have been formulated in countries such as China, Japan, South Korea, the United States, the United Kingdom, Australia, and Malaysia (as shown in Table 2) (*4,11*).

With the development of modern advanced science and technology, scientists have strived to explore the physiological and biological mechanisms of acupuncture. Some basic studies have indicated that acupuncture has various actions, such as analgesic, muscle relaxing, anti-inflammatory, mild anxiolytic, and antidepressant actions (*12*). Acupuncture might involve biological mechanisms such as central sensitization, neurotransmitters, the intestinal flora, immune regulation, oxidative stress, and neuroinflammation.

With increasing evidence of its efficacy, acupuncture is now a magic and widely practiced treatment modality in complementary and integrative medicine. The aim of the current review is to reveal the magic of acupuncture. The underlying mechanisms by which acupuncture treats common conditions including lower back pain (LBP), ischemic stroke, depression, and IBS will be discussed based on studies that have been published over the last two decades.

2. Acupuncture for LBP

LBP is defined as pain or discomfort localized between the costal margin and buttocks. It is one of the most common health problems in adults, with an average lifetime prevalence as high as 39% (*13*). Chronic LBP is a major cause of disability, absenteeism, and costly medical expenses, which place a great economic burden on society. Commonly, non-pharmacologic therapies are recommended as first-line treatment, which included acupuncture, massage, spinal manipulation, and yoga. Acupuncture, and pain relief in particular, is a characteristic non-pharmaceutical option to combat

Table 2. The clinical practice guidelines for acupuncture to treat common conditions in countries around the world

Countries/Numbers	Name /(Language)
China/20	1. Evidence-Based Clinical Practice Guidelines on Acupuncture for Adult Bronchial Asthma; /(in Chinese) 2. Evidence-Based Clinical Practice Guidelines on Acupuncture for Diabetic Peripheral Neuropathy; /(in Chinese) 3. Evidence-Based Clinical Practice Guidelines on Acupuncture Chronic Atrophic Gastritis; /(in Chinese) 4. Evidence-Based Clinical Practice Guidelines on Acupuncture for Knee Osteoarthritis; /(in Chinese) 5. Evidence-Based Clinical Practice Guidelines on Acupuncture for Depression; /(in Chinese) 6. Evidence-Based Clinical Practice Guidelines on Acupuncture for Primary Dysmenorrhea; /(in Chinese) 7. Evidence-based Clinical Practice Guidelines on Acupuncture for Insomnia; /(in Chinese) 8. Evidence-based Clinical Practice Guidelines on Acupuncture for Herpes Zoster; /(in Chinese) 9. Evidence-based Clinical Practice Guidelines on Acupuncture for Pseudobulbar Palsy after Stroke; /(in Chinese) 10. Evidence-based Clinical Practice Guidelines on Acupuncture for Lower Back Pain; /(in Chinese) 11. Evidence-Based Clinical Practice Guidelines on Acupuncture for Chronic Constipation; /(in Chinese) 12. Evidence-Based Clinical Practice Guidelines on Acupuncture for Migraine; /(in Chinese) 13. Evidence-based Clinical Practice Guidelines on Acupuncture for Cervical Spondylosis; /(in Chinese) 14. Evidence-based Clinical Practice Guidelines on Acupuncture for Frozen Shoulder; /(in Chinese) 15. Evidence-based Clinical Practice Guidelines on Acupuncture for Sudden Deafness; /(in Chinese) 16. Evidence-based Clinical Practice Guidelines on Acupuncture for Simple Obesity; /(in Chinese) 17. Evidence-Based Clinical Practice Guidelines on Acupuncture for Primary Trigeminal Neuralgia; /(in Chinese) 18. Evidence-based Clinical Practice Guidelines on Acupuncture for Allergies; /(in Chinese) 19. Evidence-based Clinical Practice Guidelines on Acupuncture for Bell's Facial Palsy; /(in Chinese) 20. Evidence-based Clinical Practice Guidelines on Acupuncture for Sciatica. /(in Chinese)
South Korea/4	1. Clinical Practice Guidelines on Acupuncture for Post-stroke Spasticity; /(in Korean) 2. Clinical Practice Guidelines on Acupuncture for Post-stroke Urinary Retention; /(in Korean) 3. Evidence-Based Clinical Practice Guidelines on Medical Manual Acupuncture for Shoulder Pain; /(in English) 4. Clinical Practice Guidelines for Acupuncture to Treat Adults with Acute Ankle Sprains. /(in English)
Japan/1	Clinical Practice Guidelines for the Management of Lower Back Pain. /(in Japanese)
United States/1	Diagnosis and Treatment of Low Back Pain: A Joint Clinical Practice Guideline from the American College of Physicians and the American Pain Society. /(in English)
United Kingdom/1	Guidelines for Providing Acupuncture Treatment for Cancer Patients. /(in English)
Australia/1	Practice Guidelines for Acupuncturists Using Acupuncture-assisted Treatment of Anorexia Nervosa. /(in English)
Malaysia/1	Practice Guidelines for Traditional Acupuncture and Complementary Medicine. /(in English)

the opioid crisis (*14*). LBP was the leading indication in American acupuncture clinics according to a cross-sectional study (*15*).

2.1. Acupuncture points frequently used for LBP

Appropriate selection of acupuncture points is fundamental to the efficacy of clinical acupuncture. Numerous studies have been conducted to investigate the acupuncture points most frequently used to treat LBP. According to a network analysis, acupuncture points BL 23, BL 25, BL 60, GB 30, and BL 26 appeared to be widely used to treat LBP (*16*). Lee *et al*. found that the bladder meridian (BL 23, BL 24, BL 25, BL 26, BL 32, BL 40, and BL 60) and the gall bladder meridian (GB 30, GB 40) were most frequently used to treat LBP based on 53 treatment regimens in clinical trials (*17*). These findings were highly consistent with the theories of traditional Chinese medicine, in which some acupuncture points, including BL 23, BL 25, GV 3, BL 40, GB 30, and KI 3, are commonly used to treat chronic LBP (*18*). Based on these studies and the current authors' own clinical experience, BL 23, BL 24, BL 25, BL 26, BL 32, BL 40, BL 60, GB 30, GB 40, KI 3, and GV 3 are the acupuncture points frequently used for LBP (Figure 2). These acupuncture points are stimulated to relax entrapped nerves and myofascia and to improve local blood circulation.

2.2. Mechanisms by which acupuncture treats LBP

Despite its widespread use, the underlying mechanisms by which acupuncture induces analgesia are still not fully understood. In terms of current studies, acupuncture may have analgesic action by reducing inflammation, relieving central sensitization, and regulating adenosine triphosphate (ATP) metabolism. A brief description of the mechanisms by which acupuncture treats LBP is provided here (Table 3).

2.2.1. Anti-inflammatory action

Pro-inflammatory cytokines are known to be involved in the development of inflammatory pain. Endogenous cannabinoids and peripheral cannabinoid CB2 receptors (CB2Rs) are involved in the antinociceptive effect of

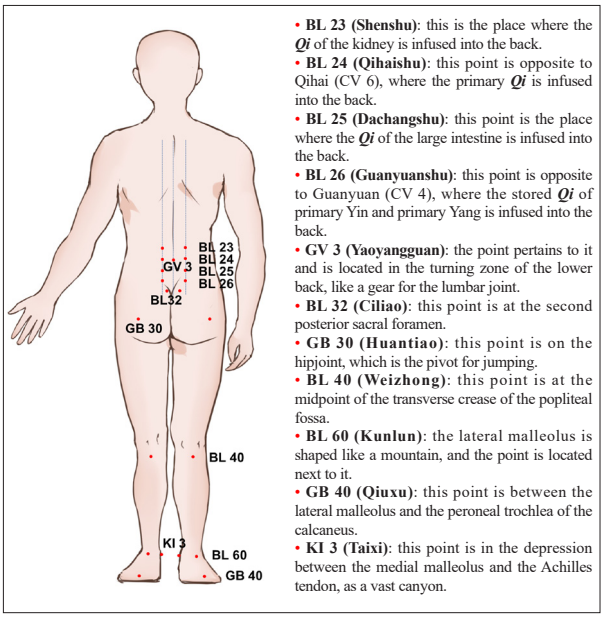

Figure 2. Acupuncture points frequently used for lower back pain (LBP) and their location on the human body according to the clinical trials reviewed.

electroacupuncture on inflammatory pain. Su *et al*. found that electroacupuncture applied to acupuncture points GB 30 and GB 34 significantly reduced thermal hyperalgesia and mechanical allodynia induced by tissue inflammation. Electroacupuncture reduced the levels of the pro-inflammatory cytokines IL-1β, IL-6, and TNF-α and it alleviated inflammatory pain in inflamed tissues *via* activation of CB2Rs (*19*).

Endogenous opioid peptides such as β-endorphin and met-enkephalin may also contribute to acupuncture-induced analgesia. They activate opioid receptors both at the level of the spinal cord as well as on peripheral sensory neurons at the site of inflammation. Wang *et al*. found that electroacupuncture applied to acupuncture point GB 30 stimulated opioid peptide release in inflamed tissue by regulating chemokine CXCL10 (IP-10, interferon gamma inducible protein 10) production. Electroacupuncture can induce an anti-inflammatory cytokine profile with increased expression of interferon-gamma (IFN-γ) and CXCL10 and increased numbers of opioid peptide-containing $CXCR3^{+}$ macrophages (*20*).

2.2.2. Relieving central sensitization

Central sensitization is defined as an amplification of neural signaling within the central nervous system (CNS) that elicits pain hypersensitivity. Hyperalgesia and allodynia are the two main characteristics of central sensitization (*21*). Many musculoskeletal disorders, including LBP, appear capable of triggering the phenomenon of central sensitization with an associated increase in sleep disturbance, fatigue, and widespread pain. Resting-state (RS) functional magnetic resonance imaging (fMRI) data have revealed deficient

Table 3. Proposed mechanisms and evidence for acupuncture to treat lower back pain (LBP)

Authors/*Ref.*	Species/model	Treatment	Acupuncture points	Manipulation	Course	Results of molecular expression	Mechanisms
Su *et al.* /(*19*), 2012	SD rats CFA injection	EA	GB 30 and GB 34	1 mA, 2 Hz, 30 min	Once every other day for 6 days	IL-1β, IL-6, and TNF-α ↓	Alleviating inflammatory pain in inflamed tissue through activation of CB2Rs.
Wang *et al.* /(*20*), 2014	Wistar rats CFA injection	EA	GB 30	2-2.5-3 mA, 100 Hz, 20 min	Every day for 2 days	IFN-γ and CXCL10 ↑	Stimulating opioid peptide release in inflamed tissue by regulating chemokine CXCL10 production.
Kim *et al.* /(*23*), 2020	Patients with LBP (n = 102)	MA	GV 3, BL 23, BL 40, and KI 3	0.20-0.25 mm diameter, 25-50 mm length, 20 min	4 weeks	S1-back gray matter volume and FA in the white matter adjacent to the S1-back subregion ↓	Improving tactile acuity over the back of patients with LBP by regulating somatotopically-specific structural S1 neuroplasticity.
Yu *et al.* /(*24*), 2020	Patients with LBP (n = 79)	MA	GV 3, BL 23, BL 40, KI 3, and 1-3 Ashi points bilaterally on the lower back and legs	25 min	6 times for 4 weeks	VTA/PAG rsFC ↑	The amygdala might be a key node linking the descending pain modulation and reward systems to produce an antinociceptive effect.
Ren *et al.* /(*27*), 2012	Rats with neuropathic pain	EA	—	—	—	A1 receptor ↑ P2X3 receptor ↓	Alleviating neuropathic pain *via* promoting the degradation of ATP to adenosine and regulating purinergic A1 and P2X3 receptors

Abbreviations: complete Freund's adjuvant (CFA), fractional anisotropy (FA), resting state functional connectivity (rsFC), periaqueductal gray (PAG), ventral tegmental area (VTA), P2X purinergic receptor 3 (P2X3), adenosine 5'-triphosphate disodium (ATP), Electroacupuncture (EA), Manual acupuncture (MA).

mesocorticolimbic connectivity in patients with LBP, with mesolimbic dysconnectivity potentially mediating the contribution of pain sensitization to chronic pain (*22*).

While multiple brain-based mechanisms of action for acupuncture have been proposed, a possible mechanism for LBP may involve neuroplasticity in somatosensory pathways and manifest in improvements in tactile acuity. According to a longitudinal neuroimaging study, Kim *et al*. found that after 4 weeks of acupuncture therapy, patients with LBP had improved tactile acuity over the back, and improvement was associated with a reduced S1 (primary somatosensory cortex)-back gray matter volume and increased fractional anisotropy (FA) in the white matter adjacent to the S1-back subregion (*23*). Yu *et al*. found that acupuncture may simultaneously modulate the resting state functional connectivity of key regions in the descending pain modulation and reward systems and that the amygdala may be a key node linking the two systems to produce an antinociceptive effect (*24*).

2.2.3. Regulating ATP metabolism

ATP is an important source of energy but it also plays an important role in regulating the biological activities of cells. Adenosine, the core molecule of ATP, is recognized by specific receptors that regulate neuronal and non-neuronal cellular functions. As a neurotransmitter, adenosine regulates pain transmission in both the spinal cord and in the periphery (*25*).

Numerous studies have indicated that acupuncture can trigger an increase in the extracellular concentration of ATP and its metabolite adenosine near acupuncture points. Acupuncture can induce the release of ATP from keratinocytes, the major type of cell in the skin, and from subcutaneous mast cells, and it can stimulate nociceptive terminals of sensory ganglia (*e.g*., dorsal root ganglion (DRG)) neurons. The signaling message is then relayed *via* the DRGs to the spinal cord and subsequently through ascending pathways to the brain stem, which contains motor neurons. Signals also travel to certain centers in the cortex that perceive pain and localize painful stimuli in the body. These centers can be modulated by locally released adenosine to deliver a message to inhibit pain (*26*).

According to a rat model, after acupuncture ATP in the extracellular space was broken down into adenosine, which in turn inhibited pain transmission by means of an adenosine A1 receptor-dependent process. Moreover, acupuncture might simultaneously act *via* adenosine A1 and P2X purinoceptor 3 (P2X3) receptors to have an analgesic effect on neuropathic pain (*27*). Yao *et al*. found that acupuncture can lead to an increase in intracellular Ca^{2+} in mast cells and release of ATP, which can activate nerve cells and modulate pain-processing pathways in response to acupuncture (*28*).

3. Acupuncture for ischemic stroke

Stroke is the second leading cause of death and the leading cause of disability worldwide. It affects 15 million people per year around the world, 5 million of whom die, and 5 million of whom are permanently physically disabled (*29*). In most cases, stroke is caused by an abrupt blockage of an artery (ischemic stroke), which accounts for 71% of all stroke cases, while in some instances stroke may be caused by bleeding into brain tissue when a blood vessel ruptures (hemorrhagic stroke) (*30*). Ischemic stroke is caused by cerebral vascular occlusion, and the decreased blood flow causes a shortage of oxygen and glucose in brain tissue, resulting in impairment of normal neurologic function. Numerous studies have revealed complex primary and secondary brain injuries after ischemic stroke, including blood-brain barrier (BBB) damage, brain edema, neuronal death, and neurological dysfunction (*31*).

Acupuncture, considered to be a promising strategy to prevent stroke, has been used to treat stroke for thousands of years in Asia. It is widely used to improve motor, sensory, speech, and other neurological functions in patients after a stroke. The WHO has recommended acupuncture as an alternative and complementary strategy for stroke and post-stroke rehabilitation. Numerous clinical trials and meta-analyses have indicated the efficacy of acupuncture in improving balance, reducing spasticity, and increasing muscle strength and general well-being post-stroke (*32*). Moreover, many basic studies have indicated that acupuncture is effective at facilitating ischemic stroke rehabilitation and reducing post-stroke infarct volume and neurological deficits (*9*).

3.1. Acupuncture points frequently used for ischemic stroke

Acupuncture points may be excitable muscle/skin-nerve complexes containing a high density of nerve endings. Acupuncture at particular points activates afferent fibers that send signals to the spinal cord (*33*). Numerous studies have been conducted to investigate the acupuncture points most frequently used to treat ischemic stroke. According to a review of 40 basic studies, Chavez *et al*. found that the acupuncture points most frequently used for ischemic stroke included GV 20, ST 36, LI 11, GV 26, GV 14, and LI 4 (*9*).

BBB disruption and tissue inflammation jointly provoke brain edema/swelling after cerebral ischemia/reperfusion injury (CIRI), while acupuncture and electroacupuncture can alleviate CIRI symptoms. Acupuncture/electroacupuncture at GV 20 and ST 36 similarly provided neuroprotection in a rat model of middle cerebral artery occlusion (MCAO) by modulating matrix metalloproteinase 2 (MMP2), aquaporin (AQP) 4, and AQP9 expression and inflammatory cell infiltration (*34*). Laser acupuncture at GV 20 significantly decreased the brain infarct volume and malondialdehyde level and increased catalase, glutathione peroxidase, and superoxide-

dismutase activity in rats with cerebral ischemia (*35*). Moreover, electroacupuncture at GV 20, GV 14, LI 11, and KI 1 dramatically ameliorated neurologic damage and alleviated degenerative changes to the ultrastructure of cortical neurons in rats with hypoxic-ischemic encephalopathy (*36*). Based on these studies and the current authors' own clinical experience, GV 20, GV 26, GV 14, ST 36, LI 11, and LI 4 are the acupuncture points frequently used for ischemic stroke (Figure 3).

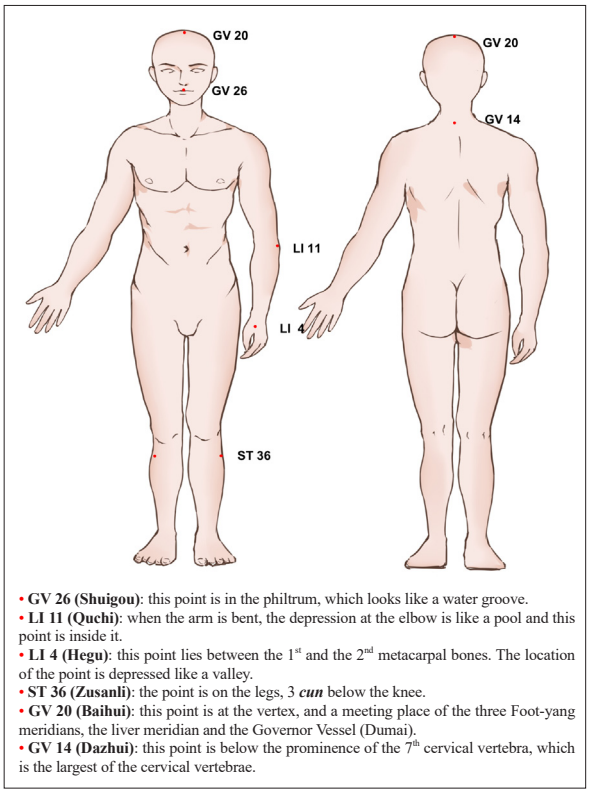

Figure 3. Acupuncture points frequently used for ischemic stroke and their location on the human body according to the clinical trials reviewed.

3.2. Mechanisms by which acupuncture treats ischemic stroke

Acupuncture is widely used for ischemic stroke, but the exact mechanisms underlying the beneficial effects of acupuncture in the treatment of stroke remain unclear. In terms of current studies, acupuncture is effective at facilitating ischemic stroke rehabilitation and reducing post-stroke infarct volume and neurological deficits; the mechanisms of those actions might involve neurogenesis, neuroinflammation, neuronal cells apoptosis, and oxidative stress (*9*). A brief description of the mechanisms by which acupuncture treats ischemic stroke is provided here (Table 4).

3.2.1. Promoting neurogenesis

Most stroke patients may have residual neurological deficits. The brain is reported to have the capability to generate new neurons, so neurogenesis has become a topic of interest. Promoting neurogenesis in a brain damaged by stroke will help stroke patients with chronic disabilities. Lu *et al*. conducted a systematic review and meta-analysis of preclinical studies to assess the current evidence for acupuncture's effect on neurogenesis in treating ischaemic stroke (*37*). Their findings indicated that acupuncture ameliorated neurological deficits and reduced brain edema in experimental ischemic stroke and that the mechanisms correlated with endogenous neurogenesis. Acupuncture may promote the proliferation, migration, and differentiation of neural stem cells (NSCs).

Electroacupuncture at GV 20 and ST 36 significantly reduced the cerebral infarct size, improved neuronal behavior, and alleviated ultrastructural injury to the hippocampus in a rat model of cerebral ischemia/reperfusion injury (*38*). The mechanism of that action might be by down-regulation of the RhoA/ROCK signaling pathway that regulates myelin-associated inhibitors (MAIs) and by promoting the expression of growth-associated protein 43 (GAP43) and brain-derived neurotrophic factor (BDNF) to protect against cerebral ischemia/reperfusion injury. In addition, electroacupuncture at GV 20 and GV 14 and mesenchymal stem cell (MSCs) transplantation reduced prominent atrophic changes in the striatum and induced proliferation of neural progenitor cells in the subventricular zone and the surrounding areas of the striatum in mice with middle cerebral artery occlusion (MCAO) (*39*). Electroacupuncture and MSC transplantation may activate the expression of neurotrophic factors such as BDNF and neurotrophin-4 (NT4), which are associated with neurogenesis in the ischemic brain.

In addition, exosomes released by the neural cells are reported to regulate the development and progression of nervous system diseases but to also play an important role in regeneration and remodeling of the nervous system after neural injury (*40*). Zhang *et al*. indicated that electroacupuncture enhanced the differentiation of endogenous neurogenesis and mitigated neurological deficits after ischemic stroke (*41*). Exosomal miR-146b is an important neuromodulator of neurogenesis that promotes endogenous neural stem cell differentiation into neurons in peri-ischemia after stroke. Electroacupuncture may promote endogenous neural stem cell differentiation into neurons in the peri-ischemic striatum and subventricular zone of the ischemic hemisphere *via* the up-regulation of miR-146b after ischemic stroke.

3.2.2. Alleviating neuroinflammation

Neuroinflammation plays a key role in the pathogenesis of ischemic stroke, and it has become a target for therapeutic intervention. Mounting evidence has indicated that electroacupuncture effectively attenuates inflammatory responses during the early stage of cerebral ischemia.

Table 4. Proposed mechanisms and evidence for acupuncture to treat ischemic stroke

Authors/*Ref.*	Species/model	Treatment	Acupuncture points	Manipulation	Course	Results of molecular expression	Mechanisms
Chen *et al.* /(*38*), 2020	SD rats MCAO/R model	EA	GV 20 and ST 36	1 mA, 2 Hz, 30 min	Once a day for 7 days	GAP43 and BDNF ↑	Promoting axonal regrowth by down-regulating the myelin-associated inhibitor-induced RhoA/ROCK pathway.
Kim *et al.* /(*39*), 2018	C57BL/6 mice MCAO model	EA + MSCs trs	GV 20 and GV 14	2 V, 2 Hz, 20 min	Once a day for 12 days	BDNF and NT4 ↑	Facilitating the amelioration of neurological impairment by enhanced neurogenesis.
Zhang *et al.* /(*41*), 2020	SD rats MCAO model	EA	LI 11 and ST 36	1 mA, 1/20 Hz, 30 min	Once a day for 21 days	Exosomal miR-146b ↑	Promoting the differentiation of endogenous neural stem cells *via* exosomal miR-146b.
Liu *et al.* /(*42*), 2016	SD rats MCAO/R model	EA	LI 11 and ST 36	0.2 mA, 1-20 Hz, 30 min	Once a day for 3 days	(*i*) TNF-α, IL1β, IL-6, NF-κB p65, p38 MAPK, and MyD88 ↓; (*ii*) IκB-α ↑	Mitigating motor impairment *via* inhibition of microglia-mediated neuroinflammation in the peri-infarct sensorimotor cortex.
Xu *et al.* /(*43*), 2018	SD rats MCAO model	EA	GV 20, LI 4, and LR 3	1 mA, 2/20 Hz, 30 min	Once a day for 3 days	(*i*) TNF-α, IL1β, and IL-6 ↓; (*ii*) IL-10 and Arg-1 ↑; (*iii*) TREM2 ↑	Attenuating neuroinflammation by promoting microglial TREM2 expression *via* the PI3K/Akt and NF-kB signaling pathways.
Sha *et al.* /(*44*), 2019	SD rats MCAO model	EA	TE 5 and ST 36	1 mA, 20 Hz, 30 min	Once a day for 7 days	(*i*) Neurological deficits and infarct volume ↓; (*ii*) miR-223 ↑; (*iii*) NLRP3, caspase-1, IL-1b, and IL-18 ↓	Alleviating neuroinflammation by inhibiting the miR-223/NLRP3 pathway.
Xing *et al* /(*45*), 2018	SD rats MCAO/R model	EA	LI 11 and ST 36	1 mA, 4/20 Hz, 30 min	Once a day for 3 days	(*i*) Neurological deficits and infarct volume ↓; (*ii*) caspase-3 ↓ and Bim and Bcl-2 ↑; (*iii*) p-ERK1/2, p-JNK, and p-p38 ↓; (*iv*) MK ↑	Alleviating neuronal apoptosis *via* the MK and ERK/JNK/p38 signaling pathways.
Xing *et al* /(*46*), 2018	SD rats MCAO/R model	EA	LI 11 and ST 36	4 V, 4 or 20 Hz, 30 min	Once a day for 2 days	(*i*) Neurological deficits, infarct volume, and the proportion of apoptotic cells ↓; (*ii*) PDK1, Akt, and GSK-3β ↑; (*iii*) p-PTEN and p-Akt ↓; (*iv*) Caspase-3 and cleaved-caspase-3 ↓ and Bim and Bcl-2 ↑	Providing neuro-protection by inhibiting apoptosis *via* the PTEN pathway.
Liu *et al.* /(*47*), 2018	SD rats MCAO/R model	EA	GV24 and GV20	1 or 20 HZ, 1 mA, 30 min	Once a day for 10 days	(*i*) Infarct volume ↓; (*ii*) JNK and p38 ↓; (*iii*) ERK1/2 ↑; (*iv*) Bcl-2/Bax ↑	Mediating neuronal cell apoptosis *via* multiple cellular pathways such as JNK, ERK, and P38.
Jittiwat /(*50*), 2017	Wistar rats MCAO model	LA	GV20	30 min	Once a day for 14 days	(*i*) Infarct volume and malondialdehyde level ↓; (*ii*) Catalase, glutathione peroxidase, and superoxide dismutase activity ↑	Mitigating brain damage and oxidative stress.
Liu *et al.* /(*51*), 2013	Wistar rats Cerebral multi-infarction model	MA	CV 17, CV 12, CV 6, ST 36, and SP 10	210 s	Once a day for 21 days (with a rest every 7 days)	Ref-1 ↑	Improving reference memory and displaying anti-oxidative action.
Jung *et al.* /(*52*), 2016	C57BL/6 mice MCAO model	EA	GV 20 and GV 14	20 min	Once a day for 3 days	(*i*) Infarct volume ↓; (*ii*) Neurological function ↑; (*iii*) ROS ↓; (*iv*) NOX4 ↓	Reducing ROS generation by down-regulating NOX4 and ameliorating blood-brain barrier disruption.
Sun *et al.* /(*53*), 2016	C57BL/6 mice MCAO model	EA	GV 20	1 mA, 2/15 Hz, 30 min	One time, 2 h before surgery	Mn-SOD ↑	Mitigating oxidative injury by activation of the Mn-SOD signaling pathway *via* CB1R-dependent STAT3 phosphorylation.

Note: abbreviations: ischemia/reperfusion (I/R) injury, middle cerebral artery occlusion (MCAO), middle cerebral artery occlusion and reperfusion (MCAO/R), growth-associated protein 43 (GAP43), mesenchymal stem cells (MSCs), brain-derived neurotrophic factor (BDNF), neurotrophin-4 (NT4), triggering receptor expressed on myeloid cells 2 (TREM2), midkine (MK), redox effector factor (Ref-1), reactive oxygen species (ROS), NADPH oxidase 4 (NOX4), manganese superoxide dismutase (Mn-SOD), cannabinoid receptor type 1 receptor (CB1R), Electroacupuncture (EA), MSCs transplantation (MSCs Trs), Laser acupuncture (LA), Manual acupuncture (MA).

Electroacupuncture at the acupuncture points LI 11 and ST 36 mitigated motor impairment by inhibiting microglia-mediated neuroinflammation in the peri-infarct sensorimotor cortex (*42*). The possible mechanism for this was because electroacupuncture attenuated the over-activation of microglia, which suppressed the release of pro-inflammatory cytokines by inhibiting NF-κB p65 nuclear translocation and by inactivation of p38 MAPK and MyD88 in the peri-infract sensorimotor cortex after middle cerebral artery occlusion and reperfusion (MCAO/R) injury. Triggering receptor expressed on myeloid cells 2 (TREM2) is a microglia-specific receptor in the CNS that is involved in regulating neuroinflammation in cerebral ischemia. Xu *et al*. found that electroacupuncture at the acupuncture points GV 20, LI 4, and LR 3 up-regulated TREM2 expression by regulating the PI3K/Akt and NF-kB signaling pathways (*43*). Moreover, electroacupuncture at the acupuncture points TE5 and ST36 markedly increased miR-223 levels, and this effect was accompanied by decreased NLRP3, caspase-1, IL-1β, and IL-18 levels in the peri-infarct cortex, which resulted in alleviated inflammatory injury associated with brain ischemia/reperfusion (*44*).

3.2.3. Inhibiting neuronal cell apoptosis

Apoptosis, the genetically programmed process of cell death, is reported to play an important role in the progression of cerebral ischemia-reperfusion injury. Several studies have confirmed that inhibition of cell apoptosis can reduce ischemia-reperfusion injury. Electroacupuncture has a beneficial effect by reducing neurological deficits and by restoring injured cerebral cells after cerebral ischemic stroke by inhibiting neuronal apoptosis.

Xing *et al*. found that electroacupuncture at the acupuncture points LI 11 and ST 36 reduced the infarct volume and neurological deficits and it reduced apoptotic cells in the peri-infarct cortex in rats with cerebral ischemia (*45*). Electroacupuncture's mechanism of mitigating apoptosis after ischemic stroke might be associated with up-regulation of growth factor midkine (MK) and mediation of the ERK/JNK/p38MAPK pathway. In another study, Xing *et al*. also found that electroacupuncture at the acupuncture points LI 11 and ST 36 inhibited neuronal cell apoptosis, and they posited that these effects were probably regulated by the PTEN pathway (*46*). In addition, Liu *et al*. found that electroacupuncture at the acupuncture points GV 20 and GV 24 promoted functional recovery in post-stroke rats by inhibiting neuronal cell apoptosis (*47*). Electroacupuncture may mediate neuronal cell apoptosis *via* multiple cellular pathways such as JNK, ERK, and P38.

3.2.4. Regulating oxidative stress

Oxidative stress is defined as a pathologic state in which cells are subjected to excessive reactive oxygen or nitrogen species (ROS/RNS) and they cannot counterbalance the deleterious effects with the antioxidant defense system, commonly resulting in cellular damage and tissue destruction (*48*). In ischemic stroke, oxidative stress can cause neuronal apoptosis, activation of inflammatory signaling pathways, and impairment of the BBB, all of which promote neurodegeneration and cell death (*49*). Recently, several studies have indicated that acupuncture has the potential to alleviate oxidative stress caused by cerebral ischemia, which may be linked to the neuroprotective effect of acupuncture. By regulating a battery of molecular signaling pathways involved in redox modulation, acupuncture activates the inherent antioxidant enzyme system and it also inhibits the excessive generation of ROS.

Laser acupuncture at the acupuncture point GV 20 significantly decreased the brain infarct volume and malondialdehyde levels and it increased catalase, glutathione peroxidase, and superoxide-dismutase activity in rats with cerebral ischemia (*50*). These findings indicated that acupuncture displayed antioxidative action in ischemic stroke. Moreover, acupuncture increases the expression of redox effector factor (Ref-1), a sensitive marker of oxidative injury within the hippocampus, consequently producing antioxidative action in rats with multiple cerebral infarcts (*51*). In addition, Jung *et al*. found that electroacupuncture at the acupuncture points GV 20 and GV 14 delayed or mitigated the development of ischemic brain edema, which might be achieved *via* down-regulation of ROS generation and NADPH oxidase 4 (NOX4) expression in mice with MCAO (*52*). The overproduction of mitochondrial ROS is a key mechanism of injury during neurodegeneration damage, and especially in the context of ischemia/reperfusion injury. Sun *et al*. indicated that electroacupuncture at GV 20 induced up-regulation of manganese superoxide dismutase (Mn-SOD) *via* the cannabinoid receptor type 1 receptor (CB1R)-dependent signal transducer and activator of transcription 3 (STAT3) phosphorylation, thus attenuating oxidative stress and resulting in neuroprotection (*53*).

4. Acupuncture for depression

Depression is a serious neuropsychiatric disorder that involves symptoms such as a persistent feeling of sadness, loss of interest or pleasure in activities, changes in weight, difficulty sleeping or oversleeping, energy loss, feelings of worthlessness, psychomotor changes, and thoughts of death or suicide. There are several types of depression including major depressive disorder, adolescent depression, antenatal depression, postpartum depression, perimenopausal depression, drug-induced depression, and post-stroke depression. Depression is recognized as a major public health problem that has a serious impact on individuals and on society, affecting approximately 400 million people worldwide (*54*). In 2008, the WHO ranked

major depression as the third leading cause of the disease burden worldwide, and it projected that the disease would rank first by 2030. Antidepressants, psychotherapy, or both are all reasonable treatment options for depression (*55*). However, patients often report intolerable adverse reactions to antidepressants such as weight gain, sedation, dry mouth, nausea, blurred vision, constipation, and tachycardia. Psychotherapy appears to produce equivalent outcomes to those obtained with antidepressants, but it is not uniformly accepted thus far, and the rate of withdrawal from treatment is similar to that with antidepressants (*56*). In recent years, numerous randomized controlled trials (RCTs) and meta-analyses have indicated that acupuncture was effective at treating depression. Moreover, many basic studies have indicated that the mechanisms by which acupuncture treats depression may be through regulation of the hypothalamic-pituitary-adrenal (HPA) axis, neurotransmitters, anti-inflammatory, and signaling pathways.

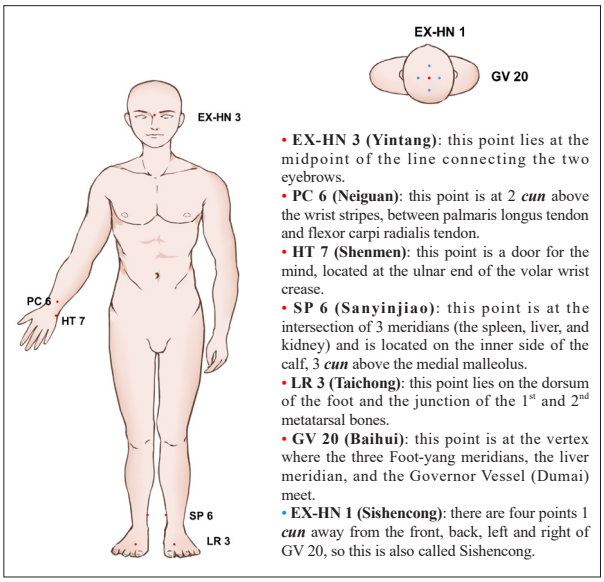

Figure 4. Acupuncture points frequently used for depression and their location on the human body according to the clinical trials reviewed.

4.1. Acupuncture points frequently used for depression

Available evidence regarding the ability of acupuncture to reduce the severity of depression is of low quality, but acupuncture is still widely used to treat depression as a complementary and alternative therapy around the world (*57*). Acupuncture appears to be more effective and safer than no treatment, control acupuncture, antidepressants, or psychotherapy. Numerous studies have been conducted to investigate the acupuncture points most frequently used to treat depression. Pilkington concluded that the four acupuncture points most frequently used for depression were GV 20, EX-HN 3, LR 3, and HT 7 (*58*). In addition, Smith *et al*. conducted a Cochrane review of 64 studies (7,104 participants) and they indicated that GV 20, EX-HN 3, PC 6, HT 7, EX-HN 1, LR 3, and SP 6 were the acupuncture points frequently used for depression (*57*). Based on these studies and the current authors' own clinical experience, GV 20, EX-HN 1, EX-HN 3, LR 3, PC 6, SP 6, and HT 7 are the acupuncture points frequently used for depression (Figure 4).

4.2. Mechanisms by which acupuncture treats depression

In recent years, research on the efficacy of acupuncture in treating depression has progressed considerably. Acupuncture involves multiple mechanisms, including inhibition of hypothalamo-pituitary-adrenal (HPA) axis hyperactivity, regulation of neuropeptides and neurotransmitters, promotion of signaling pathways, modulation of the expression of particular genes, a reduction in levels of proinflammatory cytokines, and restoration of hippocampal synaptic plasticity (*59*). A brief description of the mechanisms by which acupuncture treats depression is provided here (Table 5).

4.2.1. Regulating the HPA axis

The HPA axis is considered to be the final common pathway in the stress response and the symptoms of depression. Altered activity of the HPA axis is one of the most commonly observed neuroendocrine abnormalities in patients suffering from depressive disorder. Abnormal functioning of the HPA axis will affect behavior and physical function and induce the release of multiple hormones, including cortisol and pro-inflammatory cytokines, corticotropin-releasing factor (CRF), adrenocorticotropin hormone (ACTH), and glucocorticoids (GCs) (*60*). Several recent studies have suggested that acupuncture modulates the HPA axis, the stress response, and depression. Acupuncture may relieve the excessive excitation of the HPA axis induced by stress.

Lee *et al*. found that acupuncture at the acupuncture point PC 6 inhibited chronic corticosterone (CORT)-induced depression disorder, probably by modulating the HPA axis (*61*). Acupuncture significantly reduced depression- and anxiety-like behavior and increased NPY expression in the hypothalamus. Le *et al*. found that electroacupuncture acted on depression by modulating the HPA axis and enhancing hippocampal 5-HT/5-HT1AR in rats with chronic unpredictable mild stress (CUMS) (*62*). They indicated that electroacupuncture reversed the behavioral defects induced by CUMS in rats, it decreased expression of corticotropin-releasing hormone (CRH) mRNA in the hypothalamus, it decreased ACTH and CORT levels in plasma, and it markedly increased 5-HT levels and 5-HT1AR (mRNA and protein) expression in the hippocampus. In addition, Liu *et al*. found that electroacupuncture in the auricular concha region induced cardioinhibitory action similar to that of vagus nerve stimulation (VNS) and that electroacupuncture significantly mitigated depression induced by CUMS in rats (*63*). The antidepressant action of electroacupuncture

Table 5. Proposed mechanisms and evidence for acupuncture to treat depression

Authors/*Ref.*	Species/model	Treatment	Acupuncture points	Manipulation	Course	Results of molecular expression	Mechanisms
Lee *et al.* /(*61*), 2009	SD rats CORT injection	MA	PC 6 or TE 5	5 min	Once a day for 19 days	(*i*) Depression- and anxiety-like behavior ↓; (*ii*) NPY ↑	Stimulation of PC 6 suppressing the symptopathology of the hypoactivated HPA axis
Le *et al.* /(*62*), 2016	SD rats CUMS model	EA	ST 36 and CV 4	2/100HZ, 1 mA, 20 min	Once a day for 14 days	(*i*) CRH mRNA in the hypothalamus ↓; (*ii*) ACTH and CORT levels in plasma ↓; (*iii*) 5-HT and 5-HT1AR in the hippocampus ↑	Stabilizing the HPA axis and increasing hippocampal 5-HT/5-HT1AR
Liu *et al* /(*63*), 2013	Wistar rats CUMS model	EA	Auricular concha region	2 HZ, 1 mA, 20 min	Once a day for 14 days	Plasma cortisol ↑ and ACTH levels ↓	*Via* normalization of HPA axis hyperactivity
Guo *et al.* /(*65*), 2014	SD rats Chronic restraint stress model	EA	GV 20 and GV 29	2 HZ, 1 mA, 20 min	Once a day for 21 days	IL-1β and IL-6 in the hippocampal CA3 region ↓	Alleviating depression *via* a potential mechanism of immunological modulation
Yue *et al.* /(*66*), 2018	SD rats CUS model	EA	GV 20 and GB 34	2/100 Hz, 0.3 mA, 30 min	Every other day for 4 weeks	(*i*) NLRP3 and IL-1β ↓; (*ii*) P2X7 receptor, Iba-1, IL-18, TNF-α, and IL-6 ↓	Reversing depression-induced IL-1β-related microglial activation *via* P2X7-NLRP3 inflammatory signaling.
Zhang *et al.* /(*68*), 2020	Wistar rats LPS injection	EA	GV 20 and GV 29	2 HZ, 20 min	Once a day for 7 days	(*i*) IL-1β, IL-6, and TNF-α ↓; (*ii*) IDO ↓; (*iii*) 5-HT ↑; (*iv*) NR2B ↓	Inhibiting the inflammatory response, regulating the tryptophan degradation pathway mediated by IDO, and inhibiting NR2B activation
Han *et al.* /(*70*), 2018	Wistar-Kyoto rats depression model	EA	GV20 and EX-HN3	2 HZ, 4 mA, 15 min	Once a day for 3 weeks	5-HTT and 5-HT1A in the hippocampus CA1 region ↓	Restoring hippocampal synaptic plasticity *via* modulation of 5-HT receptors
Chen *et al.* /(*71*), 2020	Wistar rats CUMS model	EA	GV 20 and GV 29	2 HZ, 0.6 mA, 30 min	Once a day for 14 days	5-HT1A ↑	Promoting the expression of 5-HT1A receptor mRNA and protein, thereby improving synaptic plasticity in the hippocampus
She *et al.* /(*73*), 2015	Wistar-Kyoto rats depression model	EA	GV20 and EX-HN3	2 HZ, 3 mA, 15 min	Once a day for 21 days	(*i*) LTP ↑; (*ii*) GluN2B ↑	Alleviating depression-like behavior and reversing the impairment of LTP by regulating GluN2B
Zhang *et al.* /(*74*), 2021	Wistar rats CUMS model	EA	GV 20 and GV 29	2 HZ, 20 min	Once a day for 21 days	(*i*) MAP-2, PSD-95, and SYN ↑; (*ii*) GluN2B and CaMKII ↓; (*iii*) p-CREB ↑	Alleviating depression-like behavior and hippocampal plasticity *via* the GluN2B/CaMKII/CREB pathway
Kang *et al.* /(*76*), 2021	Rats Model of post-stroke depression	EA	LI 4 and LR 3	2-20 HZ, 30 min	Once a day for 21 days	BDNF and TrkB ↑	Relieving depression by regulating BDNF and its receptor TrkB

Abbreviations: corticosterone (CORT), hypothalamic-pituitary-adrenal (HPA) axis, neuropeptide Y (NPY), chronic unpredictable mild stress (CUMS), corticotropin-releasing hormone (CRH), chronic unpredictable stress (CUS), lipopolysaccharide (LPS), indoleamine-2,3-dioxygenase (IDO), long-term potentiation (LTP), microtubule-associated protein 2 (MAP-2), postsynaptic density 95 (PSD-95), synaptophysin (SYN), N-methyl-D-aspartic acid receptor (NMDAR), brain-derived neurotrophic factor (BDNF), tyrosine receptor kinase B (TrkB), Manual acupuncture, Electroacupuncture (EA).

in the auricular concha region was possibly mediated by the normalized activity of the HPA axis.

4.2.2. Alleviating neuroinflammation

Neuroinflammation is defined as the brain's response to physical injury or infection. Over the last few years, a number of studies have suggested that patients who had major depressive disorder had changes in immunologic markers including increased activity of pro-inflammatory cytokines such as IL-6, IL-1β, and TNF-α and increased inflammation. Moreover, chronic low-grade inflammation may result in activation of brain immune cells such as microglia, astrocytes, and oligodendroglia and changes in brain structure and synaptic plasticity, leading to neurodegeneration in patients with depression (*64*). Several recent studies have suggested that acupuncture might inhibit neuroinflammation and hence have a beneficial effect on pathological changes in the hippocampus and depressive symptoms.

Guo *et al*. reported that electroacupuncture at acupuncture points GV 20 and GV 29 mediated the onset of depressive symptoms and down-regulated the levels of IL-6 and IL-1β in the hippocampus of depressed rats, suggesting that electroacupuncture may potentially alleviate depression through a mechanism involving neuroinflammation and immunological modulation (*65*). Yue *et al*. conducted a study to assess the effectiveness of electroacupuncture at acupuncture points GV 20 and GB 34 on depressive-like behavior in rats with chronic unpredictable stress (CUS) (*66*). They found that electroacupuncture significantly attenuated behavioral deficits caused by CUS. Moreover, the antidepressant action of electroacupuncture was accompanied by a markedly decrease in IL-1β-related microglial activation induced by depression, which might be mediated by P2X7-NLRP3 inflammatory signaling.

Proinflammatory cytokines have been reported to activate indoleamine 2,3-dioxygenase (IDO) as a critical event in the switch from sickness to depression. IDO is a key enzyme responsible for tryptophan degradation along the kynurenine pathway (*67*). Zhang *et al*. found that electroacupuncture successfully corrected depressive-like behaviour induced with lipopolysaccharides (LPS) and that it reduced levels of inflammatory factors such as IL-1β, IL-6, and TNF-α in the blood and hippocampus, prevented over-activation of IDO and restoring NR2B expression after a challenge with LPS (*68*). The antidepressant action of electroacupuncture might be related to inhibition of the inflammatory response, regulation of the tryptophan degradation pathway mediated by IDO, and inhibition of NR2B activation.

4.2.3. Restoring hippocampal synaptic plasticity

The hippocampus is a key anatomical brain region associated with depression. Numerous studies have confirmed that changes in hippocampal plasticity including hippocampal volume, the number of synapses, synaptic plasticity, changes in glutamate receptors, neurogenesis, and glial cell plasticity are evident in both human patients with depression and rodent models of depression (*69*). Several recent studies have indicated that acupuncture is involved in the regulation of synaptic plasticity in the hippocampal region and that it alleviates the symptoms of depression.

According to various studies, the 5-HT system plays an important role in the treatment of depression. Han *et al*. found that electroacupuncture at acupuncture points GV 20 and EX-HN 3 in a model of depression involving Wistar-Kyoto (WKY) rats ameliorated depressive-like behavior by restoring hippocampus CA1 synaptic plasticity, which might be mainly mediated by regulating 5-HT receptor levels (*70*). Moreover, Chen *et al*. found that electroacupuncture at acupuncture points GV 20 and GV 29 alleviated depression-like symptoms in rats with CUMS (*71*). The underlying mechanism might include promotion of the expression of 5-HT1A receptor mRNA and protein, thereby improving synaptic plasticity in the hippocampus.

N-methyl-D-aspartic acid receptor (NMDAR) is an ionic glutamate receptor, and acute or chronic stress increases the levels of glutamate around synapses in the hippocampus and thereby leads to NMDAR over-activation. The interaction of death-associated protein kinase 1 (DAPK1) with the 2B subunit (GluN2B) C-terminus of NMDAR plays a critical role in the pathophysiology of depression and is considered to be a potential target for the structure-based discovery of new antidepressants (*72*). She *et al*. found that electroacupuncture at acupuncture points GV 20 and EX-HN 3 significantly alleviated depression-like behavior in the WKY rat model of depression (*73*). This effect might be related to the increased NMDAR subunit expression of GluN2B and enhanced long-term potentiation (LTP) in the hippocampus. Moreover, Zhang *et al*. indicated that electroacupuncture at acupuncture points GV 20 and GV 29 mitigated depression-like behaviour and improved synaptic plasticity in the hippocampal neurons of rats with CUMS and that these effects were potentially related to the GluN2B/CaMKII/CREB signalling pathway (*74*).

Brain-derived neurotrophic factor (BDNF), a neurotrophic factor, plays a key role in promoting synaptic plasticity and neuronal growth and it has been put forward as a biological marker of brain neuroplasticity. Over the last decade, mounting evidence has highlighted BDNF as a key player in antidepressant action. BDNF serves as a transducer, acting as the link between an antidepressant and the neuroplastic changes that result in the alleviation of depressive symptoms (*75*). Kang *et al*. indicated that electroacupuncture at Siguan acupoints (LI 4 and LR 3) had the same antidepressant action as fluoxetine and that electroacupuncture was more effective than fluoxetine in

relieving depression in rats with post-stroke depression (PSD) (*76*). The mechanism for this might be related to activation of the expression of BDNF and its receptor TrkB.

5. Acupuncture for IBS

IBS is a chronic, relapsing, remitting functional disorder of the gastrointestinal tract, and it is the most prevalent of those disorders. It is a symptom-based condition defined by the presence of abdominal pain or discomfort, with altered bowel habits that lack a known structural or anatomic explanation (*77*). According to the WHO DMS-IV code classification for IBS and its subcategories, IBS can be classified as either diarrhea-predominant (IBS-D), constipation-predominant (IBS-C), or with an alternating stool pattern (IBS-A) or pain-predominant. A debilitating gastrointestinal disorder, IBS affects 9-23% of the population worldwide, and women are two to four times more likely to develop IBS than men (*78*). IBS can impact the quality of an individual's daily life, cause socioeconomic problems, and potentially damage the patient-physician relationship.

The exact pathophysiology of IBS is still not completely understood, but low-grade inflammation, alterations in the gut-brain axis, visceral hypersensitivity, altered gastrointestinal motility, altered serotonin levels, microbial changes, and genetics may all contribute to symptom development (*79*). Traditionally, first-line therapies for IBS have focused on alleviating diarrhea (*e.g.*, loperamide and probiotics) or constipation (*e.g.*, fiber supplements and laxatives). Moreover, dietary and lifestyle changes are also considered as first-line treatment for all IBS subtypes (*77*). However, in the United States, only one-third of IBS patients are satisfied with their current therapy (*80*). Lack of effectiveness and associated adverse effects are common reasons for dissatisfaction. Given these gaps in treatment, some patients turn to traditional, complementary, and integrative medicine. Evidence of the efficacy of complementary and integrative treatment approaches, including behavioral therapy, herbal medicines, moxibustion, and acupuncture, is emerging. According to a Delphi expert consensus study conducted by Su *et al*., most experts (> 90%) agreed that acupuncture might be used to relieve clinical symptoms and improve quality of daily life in mild and moderate IBS (*81*). In addition, several recent studies have indicated that acupuncture alleviated the clinical symptoms of IBS and reduced recurrence *via* mechanisms such as gastrointestinal (GI) motility, visceral hypersensitivity, the immune system, neurotransmitters, and the brain-gut axis (*82*).

5.1. Acupuncture points frequently used for IBS

Selection of specific acupuncture points is critical to treatment of a given condition and can result in greater efficacy. A Delphi expert consensus study conducted by Su *et al*. recommended the acupuncture points ST 25, ST 36, and CV 12 for IBS (*81*). A systematic review and meta-analysis of 21 relevant RCTs indicated that the top six most commonly used acupuncture points for IBS-D were ST 36, ST 25, LR 3, SP 6, ST 37, and CV 12; these points were considered to have played an important role in invigorating the spleen, mitigating diarrhea, relieving the liver, and alleviating pain (*83*). Moreover, Zhu *et al*. conducted a network meta-analysis which found that acupuncture at acupuncture points such as ST 25, ST 36, ST 37, SP 6, GV 20, and EX-HN 3 might alleviate IBS-D more than drugs and with fewer adverse reactions (*84*). According to a pragmatic trial by Stuardi *et al*., the acupuncture points most frequently used for IBS included CV 12, LR 3, LI 4, ST 36, and SP 6 (*85*). Based on these studies and the current authors' own clinical experience, ST 25, ST 36, ST 37, SP 6, CV 12, LI 4, LR 3, GV 20, and EX-HN 3 are the acupuncture points frequently used for IBS (Figure 5).

5.2. Mechanisms by which acupuncture treats IBS

Numerous studies have noted the efficacy of acupuncture in attenuating the symptoms of IBS without causing obvious adverse effects. Moreover, several recent studies indicated that the mechanisms by which acupuncture treats IBS involved GI motility, visceral hypersensitivity, the brain-gut axis, the neuroendocrine system, and the immune system (*82*). A brief description of the mechanisms by which acupuncture treats IBS is provided here (Table 6).

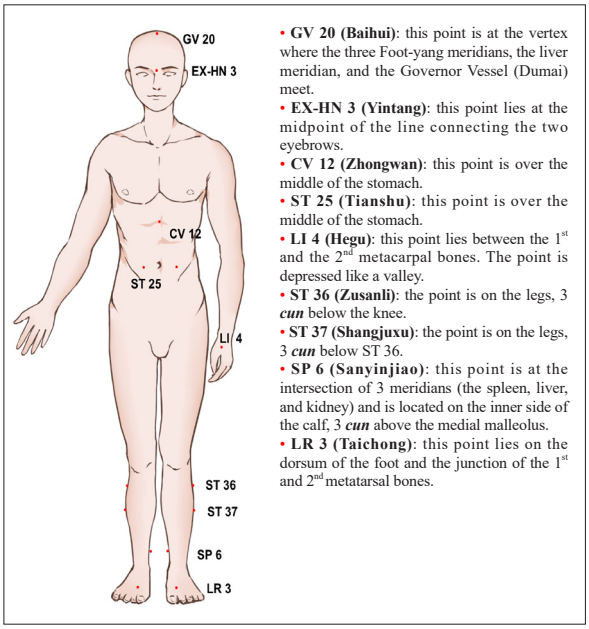

Figure 5. Acupuncture points frequently used for irritable bowel syndrome (IBS) and their location on the human body according to the clinical trials reviewed.

Table 6. Proposed mechanisms and evidence for acupuncture to treat irritable bowel syndrome (IBS)

Authors/*Ref.*	Species/model	Treatment	Acupuncture points	Manipulation	Course	Results of molecular expression	Mechanisms
Yang *et al.* /(*88*), 2019	Visceral hypersensitivity rat model	EA	ST 36	5/100 HZ, 1 mA, 30 min	Once a day for 5 days	TLR4, MCT, IL-1β, and IL-8 ↓	Ameliorating visceral hypersensitivity by decreasing the levels of pro-inflammatory cytokines and regulating TLR4 expression
Ma *et al.* /(*91*), 2009	IBS rat model	EA	ST 25 and ST 37	2/50 Hz, 15 min	Once a day for 7 days	(*i*) The number of mucosal MC ↓; (*ii*) SP and SPR ↓; (*iii*) CRH ↓	Decreasing the number of MC, the expression of SP and SPR in colon, and the CRH level in the hypothalamus
Tian *et al.* /(*93*), 2008	IBS rat model	EA	ST 36 and ST 37	4/100 Hz, 1 mA, 30 min	Once a day for 3 days	pNR1 ↓	Attenuating chronic visceral hypersensitivity by regulating spinal cord NMDA receptor phosphorylation
Sun *et al.* /(*96*), 2015	D-IBS rat model	EA	ST 25, ST 36, and LR 3	2/15 Hz, 0.8-1.3 mA, 15 min	Once a day for 14 days	(*i*) 5-HT and CGRP ↓; (*ii*) NPY ↑	Restoring the balance of the brain-gut axis
Song *et al*, /(*99*), 2020	TNBS-induced IBS rat model	EA	ST 25 and ST 36	2/15 Hz, 0.5-1.0 mA, 30 min	Once a day for 10 days	IL-18 ↓	Regulating IL-18 and gut microbial dysbiosis

Abbreviations: toll-like receptor 4 (TLR4), mast cell tryptase (MCT), mast cells (MC), substance P (SP), substance P receptor (SPR), corticotropin-releasing hormone (CRH), N-methyl-D-aspartic acid (NMDA), phosphorylated NMDA receptor subunit 1 (pNR1), diarrhea-predominant irritable bowel syndrome (D-IBS), calcitonin gene-related peptide (CGRP), neuro-peptide Y (NPY), trinitrobenzene sulfonic acid (TNBS), Electroacupuncture(EA).

5.2.1. Alleviating visceral hypersensitivity

Visceral hypersensitivity is an important hallmark feature of IBS and is the main mechanism underlying abdominal pain in patients with IBS. The pathogenesis of visceral hypersensitivity has yet to be fully elucidated, but several mechanisms have been proposed, such as inflammation, psychosocial factors, and altered sensorimotor function of the gut, a major component of which is believed to be peripheral and central sensitization of visceral afferent neuronal pathways (*86*). Especially importantly is that immune cells in the mucosal wall, such as mast cells, and enterochromaffin cells may sensitize afferent nerves *via* the release of their mediators. Several recent studies have indicated that acupuncture effectively reduced visceral hypersensitivity in IBS.

The expression of TLR4 is up-regulated in the colonic mucosa of patients with IBS and rat models of visceral hypersensitivity (*87*). Yang *et al*. indicated that electroacupuncture at acupuncture point ST36 ameliorated visceral hypersensitivity in a model of colon sensitization (*88*). The potential mechanism for this involved inhibition of the expression of TLR4 in the mast cells of colonic tissues and reduction of the levels of inflammatory factors IL-1β and IL-8 in serum. These results suggest that acupuncture can regulate visceral hypersensitivity by alleviating inflammation in patients with IBS.

Mental stress is considered as one of the factors for the induction or aggravation of the symptoms of IBS. CRH, which plays an important role in the stress response, can induce a higher level of ACTH, profound enhancement of GI motility, and visceral hypersensitivity in patients with IBS (*89*). Substance P (SP) is a gastrointestinal peptide hormone found in the CNS and gastrointestinal tract and a signaling molecule connecting the nervous system to the immune system (*90*). Ma *et al*. indicated that electroacupuncture at ST 25 and ST 37 decreased the number of mucosal mast cells, it down-regulated the expression of CRH in the hypothalamus, and it decreased the expression of SP and substance P receptor (SPR) in the colon of rats with IBS (*91*). These findings suggest that acupuncture might regulate visceral hypersensitivity by alleviating mental stress in patients with IBS.

The occurrence of chronic visceral hypersensitivity is closely related to the phenomenon of central sensitization at the spinal level. Pivotal in the development of spinal cord central sensitization is the activation of the N-methyl-d-aspartate receptor (NMDAR) (*92*). NMDAR is an ionotropic glutamate receptor widely expressed in the nervous system that plays key roles in excitatory synaptic transmission. Tian *et al*. indicated that electroacupuncture at ST 36 and ST 37 significantly inhibited hyperphosphorylation of spinal cord NMDAR in a rat model of chronic visceral hypersensitivity (*93*). This finding suggests that the activity of spinal cord

NMDAR can be affected by electroacupuncture and that acupuncture can be a promising physical therapy to alleviate chronic visceral hypersensitivity in patients with IBS by regulating central sensitization.

5.2.2. Modulating the gut-brain axis and gut microbiota

The gut-brain axis is a bidirectional communication system that integrates brain and GI functions, such as gut motility, appetite, and weight, and the microbiota plays a critical role in the gut (*94*). The gut-brain axis includes the enteric nervous system (ENS), the CNS, the gut wall in the periphery, and the HPA axis. Mounting evidence has suggested that the pathogenesis of IBS is associated with an abnormality of the gut-brain axis as well as gut microbiota. Changes in the gut microbiota alter the immunity and integrity of the gut and further modulate the gut-brain axis and the gut neuromuscular junction (*95*). Several recent studies have indicated that acupuncture seems to be a specific therapy that alleviates IBS symptoms and that also restores the balance of the gut-brain axis and gut microbiota (*82*).

5-HT is a major neurotransmitter in the gut-brain axis. Calcitonin gene-related peptide (CGRP) and its receptors are enriched in DRG and correlate with visceral hypersensitivity. Neuro-peptide Y (NPY) is a major neurotransmitter in the enteric plexus, and an increase in NPY may affect cholinergic transmission in the inferior mesenteric ganglion and regulate stress and mood by affecting the hippocampus and hypothalamus. Sun *et al*. found that electroacupuncture at ST 25, ST 36 and LR 3 alleviated IBS-D symptoms, and they encouraged its clinical use in patients with IBS (*96*). Moreover, electroacupuncture decreased the levels of 5-HT, CGRP, and NPY in the gut-brain axis, which indicated that electroacupuncture can restore the balance of the brain-gut axis in IBS-D. In addition, a randomized controlled clinical trial indicated that both electroacupuncture and mild-warm moxibustion treatment at ST 25 and ST 37 significantly alleviated some of the most intrusive symptoms in patients with IBS-C and that electroacupuncture was more effective than mild-warm moxibustion (*97*). The efficacy of these two therapies might be through modulation of the gut-brain axis (Registration No. ChiCTRTRC-11001349).

IBS is closely linked to alterations in gut microbiota composition, which can lead to increased permeability of the intestinal mucosal barrier and modulation of cytokine secretion, thus playing an important role in the pathophysiology of IBS. IL-18 is an important pro-inflammatory factor in the GI tract. It can excite macrophages, differentiate Th1 cells, induce the production of IL-1β and TNF-α by T-cell subtype 1 (Th1) and NK cells, and promote the synthesis of TNF and other chemokines (*98*). Song *et al*. indicated that post inflammatory-IBS was associated with a significant increase in IL-18 levels as well as changes in microbiota diversity and that electroacupuncture at ST 25 and ST 37 in a rat model reversed those changes (*99*). Electroacupuncture appeared to alleviate IBS symptoms by decreasing IL-18 levels and altering the composition of microbiota, and especially Fusobacteria.

6. Conclusion

With the increasing availability of acupuncture around the world, patients are increasingly seeking and using acupuncture to treat a multitude of symptoms and conditions to maintain health and prevent illness. Over the past few decades, basic and clinical research on acupuncture has made considerable progress. Internationally recognized evidence from clinical studies has been published and a preliminary system to clinically evaluate acupuncture has been created. Moreover, scientists have strived to explore the physiological and biological mechanisms of acupuncture. Some basic studies have indicated that acupuncture has various actions, such as analgesic, muscle relaxing, anti-inflammatory, mild anxiolytic, and antidepressant actions, with possible biological mechanisms such as central sensitization, neurotransmitters, the intestinal flora, immune regulation, oxidative stress, and neuroinflammation. The current review described the common indications for acupuncture recommended by the WHO and the use of acupuncture in China, the United States, Australia, and several other countries. This review then summarized the mechanisms by which acupuncture treats common diseases including LBP, ischemic stroke, depression, and IBS and it also cited specific acupuncture points for treating these conditions.

The hope is that this review will provide useful information for both acupuncturists and researchers to better understand the mechanisms of acupuncture and reasons for its usage. However, most current research on acupuncture is still in its infancy, and much of the scientific evidence surrounding it is fragmentary. There are still great challenges on how to fully integrate acupuncture into the Western medical paradigm. Therefore, both acupuncturists and researchers must continue to conduct studies to further investigate and provide more evidence of the merits of acupuncture.

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References

1. Zheng Y. TCM, acupuncture enhance world's medical field. https://global.chinadaily.com.cn/a/201908/12/WS5d50c142a310cf3e35565241.html (accessed December 16, 2021).
2. Zhuang Y, Xing JJ, Li J, Zeng BY, Liang FR. History of acupuncture research. Int Rev Neurobiol. 2013; 111:1-23.
3. Fan AY, He D, Gu S, Tian H, Ouyang H, Wei H, Gong C, Alemi SF, Zhao X. Estimated number of acupuncture practitioners in Mainland China in 2018: Multiperspectives. Med Acupunct. 2020; 32:310-319.
4. Yang F, Yang Y, Daisuke W, Kim K, Guo Y, Zhao X, Guo Y, Chen Z, Lin H, Gao Y. A summary of acupuncture standardization in Australia, Korea, Japan and the USA. World Journal of Acupuncture-Moxibustion. 2017; 27:20-26.
5. Cao BB. Current status and future prospects of acupuncture and traditional Chinese medicine in Canada. Chin J Integr Med. 2015; 21:166-172.
6. Chapple W. Proposed catalog of the neuroanatomy and the stratified anatomy for the 361 acupuncture points of 14 channels. J Acupunct Meridian Stud. 2013; 6:270-274.
7. Han QQ, Fu Y, Le JM, Ma YJ, Wei XD, Ji HL, Jiang H, Gao Y, Wu H. The Therapeutic effects of acupuncture and electroacupuncture on cancer-related symptoms and side-effects. J Cancer. 2021; 12:7003-7009.
8. Chon TY, Lee MC. Acupuncture. Mayo Clin Proc. 2013; 88:1141-1146.
9. Chavez LM, Huang SS, MacDonald I, Lin JG, Lee YC, Chen YH. Mechanisms of acupuncture therapy in ischemic stroke rehabilitation: A literature review of basic studies. Int J Mol Sci. 2017; 18:2270.
10. Zhang XY, Qiu H, Li CS, Cai PP, Qi FH. The positive role of traditional Chinese medicine as an adjunctive therapy for cancer. BioSci Trends. 2021; 15:283-298.
11. Wu XD, Yuan JY, Zhao NQ, Liu QG, Dong GF, Wang X. Investigation and analysis on the current situation of clinical practice guidelines for acupuncture and moxibustion at home and abroad. Zhongguo Zhen Jiu. 2021; 41:923-927. (in Chinese w/ English abstract)
12. Cheng KJ. Neurobiological mechanisms of acupuncture for some common illnesses: A clinician's perspective. J Acupunct Meridian Stud. 2014; 7:105-114.
13. Comachio J, Oliveira CC, Silva IFR, Magalhães MO, Marques AP. Effectiveness of manual and electrical acupuncture for chronic non-specific low back pain: A randomized controlled trial. J Acupunct Meridian Stud. 2020; 13:87-93.
14. Zhang B, Xu H, Wang J, Liu B, Sun G. A narrative review of non-operative treatment, especially traditional Chinese medicine therapy, for lumbar intervertebral disc herniation. BioSci Trends. 2017; 11:406-417.
15. Wang H, Yang G, Wang S, Zheng X, Zhang W, Li Y. The most commonly treated acupuncture indications in the United States: A cross-sectional study. Am J Chin Med. 2018; 46:1387-1419.
16. Lee SH, Kim CE, Lee IS, Jung WM, Kim HG, Jang H, Kim SJ, Lee H, Park HJ, Chae Y. Network analysis of acupuncture points used in the treatment of low back pain. Evid Based Complement Alternat Med. 2013; 2013:402180.
17. Lee IS, Lee SH, Kim SY, Lee H, Park HJ, Chae Y. Visualization of the meridian system based on biomedical information about acupuncture treatment. Evid Based Complement Alternat Med. 2013; 2013:872142.
18. Berman BM, Langevin HM, Witt CM, Dubner R. Acupuncture for chronic low back pain. N Engl J Med. 2010; 363:454-461.
19. Su TF, Zhao YQ, Zhang LH, Peng M, Wu CH, Pei L, Tian B, Zhang J, Shi J, Pan HL, Li M. Electroacupuncture reduces the expression of proinflammatory cytokines in inflamed skin tissues through activation of cannabinoid CB2 receptors. Eur J Pain. 2012; 16:624-635.
20. Wang Y, Gehringer R, Mousa SA, Hackel D, Brack A, Rittner HL. CXCL10 controls inflammatory pain *via* opioid peptide-containing macrophages in electroacupuncture. PLoS One. 2014; 9:e94696.
21. Sanzarello I, Merlini L, Rosa MA, Perrone M, Frugiuele J, Borghi R, Faldini C. Central sensitization in chronic low back pain: A narrative review. J Back Musculoskelet Rehabil. 2016; 29:625-633.
22. Yu S, Li W, Shen W, Edwards RR, Gollub RL, Wilson G, Park J, Ortiz A, Cao J, Gerber J, Mawla I, Chan ST, Lee J, Wasan AD, Napadow V, Kaptchuk TJ, Rosen B, Kong J. Impaired mesocorticolimbic connectivity underlies increased pain sensitivity in chronic low back pain. Neuroimage. 2020; 218:116969.
23. Kim H, Mawla I, Lee J, *et al*. Reduced tactile acuity in chronic low back pain is linked with structural neuroplasticity in primary somatosensory cortex and is modulated by acupuncture therapy. Neuroimage. 2020; 217:116899.
24. Yu S, Ortiz A, Gollub RL, Wilson G, Gerber J, Park J, Huang Y, Shen W, Chan ST, Wasan AD, Edwards RR, Napadow V, Kaptchuk TJ, Rosen B, Kong J. Acupuncture treatment modulates the connectivity of key regions of the descending pain modulation and reward systems in patients with chronic low back pain. J Clin Med. 2020; 9:1719.
25. Hayashida M, Fukuda K, Fukunaga A. Clinical application of adenosine and ATP for pain control. J Anesth. 2005; 19:225-235.
26. Tang Y, Yin HY, Rubini P, Illes P. Acupuncture-induced analgesia: A neurobiological basis in purinergic signaling. Neuroscientist. 2016; 22:563-578.
27. Ren W, Tu W, Jiang S, Cheng R, Du Y. Electroacupuncture improves neuropathic pain: Adenosine, adenosine 5'-triphosphate disodium and their receptors perhaps change simultaneously. Neural Regen Res. 2012; 7:2618-2623.
28. Yao W, Yang H, Yin N, Ding G. Mast cell-nerve cell interaction at acupoint: Modeling mechanotransduction pathway induced by acupuncture. Int J Biol Sci. 2014; 10:511-519.
29. Maida CD, Norrito RL, Daidone M, Tuttolomondo A, Pinto A. Neuroinflammatory mechanisms in ischemic stroke: Focus on cardioembolic stroke, background, and therapeutic approaches. Int J Mol Sci. 2020; 21:6454.
30. GBD 2016 Lifetime Risk of Stroke Collaborators, Feigin VL, Nguyen G, *et al*. Global, regional, and country-specific lifetime risks of stroke, 1990 and 2016. N Engl J Med. 2018; 379:2429-2437.
31. Ye A, Li W, Zhou L, Ao L, Fang W, Li Y. Targeting pyroptosis to regulate ischemic stroke injury: Molecular mechanisms and preclinical evidences. Brain Res Bull.

2020; 165:146-160.
32. Wu HM, Tang JL, Lin XP, Lau J, Leung PC, Woo J, Li YP. Acupuncture for stroke rehabilitation. Cochrane Database Syst Rev. 2006; (3):CD004131.
33. Manni L, Albanesi M, Guaragna M, Barbaro Paparo S, Aloe L. Neurotrophins and acupuncture. Auton Neurosci. 2010; 157:9-17.
34. Xu H, Zhang Y, Sun H, Chen S, Wang F. Effects of acupuncture at GV20 and ST36 on the expression of matrix metalloproteinase 2, aquaporin 4, and aquaporin 9 in rats subjected to cerebral ischemia/reperfusion injury. PLoS One. 2014; 9:e97488.
35. Jittiwat J. Laser Acupuncture at GV20 improves brain damage and oxidative stress in animal model of focal ischemic stroke. J Acupunct Meridian Stud. 2017; 10:324-330.
36. Xu T, Li W, Liang Y, Yang Z, Liu J, Wang Y, Su N. Neuroprotective effects of electro acupuncture on hypoxic-ischemic encephalopathy in newborn rats Ass. Pak J Pharm Sci. 2014; 27:1991-2000.
37. Lu L, Zhang XG, Zhong LL, Chen ZX, Li Y, Zheng GQ, Bian ZX. Acupuncture for neurogenesis in experimental ischemic stroke: A systematic review and meta-analysis. Sci Rep. 2016; 6:19521.
38. Chen S, Wang H, Xu H, Zhang Y, Sun H. Electroacupuncture promotes axonal regrowth by attenuating the myelin-associated inhibitors-induced RhoA/ROCK pathway in cerebral ischemia/reperfusion rats. Brain Res. 2020; 1748:147075.
39. Kim YR, Ahn SM, Pak ME, Lee HJ, Jung DH, Shin YI, Shin HK, Choi BT. Potential benefits of mesenchymal stem cells and electroacupuncture on the trophic factors associated with neurogenesis in mice with ischemic stroke. Sci Rep. 2018; 8:2044.
40. Zheng Y, He R, Wang P, Shi Y, Zhao L, Liang J. Exosomes from LPS-stimulated macrophages induce neuroprotection and functional improvement after ischemic stroke by modulating microglial polarization. Biomater Sci. 2019; 7:2037-2049.
41. Zhang S, Jin T, Wang L, Liu W, Zhang Y, Zheng Y, Lin Y, Yang M, He X, Lin H, Chen L, Tao J. Electro-acupuncture promotes the differentiation of endogenous neural stem cells *via* exosomal microRNA 146b after ischemic stroke. Front Cell Neurosci. 2020; 14:223.
42. Liu W, Wang X, Yang S, Huang J, Xue X, Zheng Y, Shang G, Tao J, Chen L. Electroacupuncture improves motor impairment *via* inhibition of microglia-mediated neuroinflammation in the sensorimotor cortex after ischemic stroke. Life Sci. 2016; 151:313-322.
43. Xu H, Mu S, Qin W. Microglia TREM2 is required for electroacupuncture to attenuate neuroinflammation in focal cerebral ischemia/reperfusion rats. Biochem Biophys Res Commun. 2018; 503:3225-3234.
44. Sha R, Zhang B, Han X, Peng J, Zheng C, Zhang F, Huang X. Electroacupuncture alleviates ischemic brain injury by inhibiting the miR-223/NLRP3 pathway. Med Sci Monit. 2019; 25:4723-4733.
45. Xing Y, Yang SD, Wang MM, Dong F, Feng YS, Zhang F. Electroacupuncture alleviated neuronal apoptosis following ischemic stroke in rats *via* midkine and ERK/JNK/p38 signaling pathway. J Mol Neurosci. 2018; 66:26-36.
46. Xing Y, Wang MM, Feng YS, Dong F, Zhang F. Possible involvement of PTEN signaling pathway in the anti-apoptotic effect of electroacupuncture following ischemic stroke in rats. Cell Mol Neurobiol. 2018; 38:1453-1463.
47. Liu J, Wang Q, Yang S, Huang J, Feng X, Peng J, Lin Z, Liu W, Tao J, Chen L. Electroacupuncture inhibits apoptosis of peri-ischemic regions *via* modulating p38, extracellular signal-regulated kinase (ERK1/2), and c-Jun N terminal kinases (JNK) in cerebral ischemia-reperfusion-injured rats. Med Sci Monit. 2018; 24:4395-4404.
48. Chen H, Yoshioka H, Kim GS, Jung JE, Okami N, Sakata H, Maier CM, Narasimhan P, Goeders CE, Chan PH. Oxidative stress in ischemic brain damage: Mechanisms of cell death and potential molecular targets for neuroprotection. Antioxid Redox Signal. 2011; 14:1505-517.
49. Su XT, Wang L, Ma SM, Cao Y, Yang NN, Lin LL, Fisher M, Yang JW, Liu CZ. Mechanisms of acupuncture in the regulation of oxidative stress in treating ischemic stroke. Oxid Med Cell Longev. 2020; 2020:7875396.
50. Jittiwat J. Laser acupuncture at GV20 improves brain damage and oxidative stress in animal model of focal ischemic stroke. J Acupunct Meridian Stud. 2017; 10:324-330.
51. Liu CZ, Li ZG, Wang DJ, Shi GX, Liu LY, Li QQ, Li C. Effect of acupuncture on hippocampal Ref-1 expression in cerebral multi-infarction rats. Neurol Sci. 2013; 34:305-312.
52. Jung YS, Lee SW, Park JH, Seo HB, Choi BT, Shin HK. Electroacupuncture preconditioning reduces ROS generation with NOX4 down-regulation and ameliorates blood-brain barrier disruption after ischemic stroke. J Biomed Sci. 2016; 23:32.
53. Sun S, Chen X, Gao Y, Liu Z, Zhai Q, Xiong L, Cai M, Wang Q. Mn-SOD upregulation by electroacupuncture attenuates ischemic oxidative damage *via* CB1R-mediated STAT3 phosphorylation. Mol Neurobiol. 2016; 53:331-343.
54. Rahman S, Alzarea S. Glial mechanisms underlying major depressive disorder: Potential therapeutic opportunities. Prog Mol Biol Transl Sci. 2019; 167:159-178.
55. Malhi GS, Mann JJ. Depression. Lancet. 2018; 392:2299-2312.
56. Li M, Niu J, Yan P, Yao L, He W, Wang M, Li H, Cao L, Li X, Shi X, Liu X, Yang K. The effectiveness and safety of acupuncture for depression: An overview of meta-analyses. Complement Ther Med. 2020; 50:102202.
57. Smith CA, Armour M, Lee MS, Wang LQ, Hay PJ. Acupuncture for depression. Cochrane Database Syst Rev. 2018; 3:CD004046.
58. Pilkington K. Anxiety, depression and acupuncture: A review of the clinical research. Auton Neurosci. 2010; 157:91-95.
59. Han X, Gao Y, Yin X, Zhang Z, Lao L, Chen Q, Xu S. The mechanism of electroacupuncture for depression on basic research: A systematic review. Chin Med. 2021; 16:10.
60. Thomson F, Craighead M. Innovative approaches for the treatment of depression: Targeting the HPA axis. Neurochem Res. 2008; 33:691-707.
61. Lee B, Shim I, Lee HJ, Yang Y, Hahm DH. Effects of acupuncture on chronic corticosterone-induced depression-like behavior and expression of neuropeptide Y in the rats. Neurosci Lett. 2009; 453:151-156.
62. Le JJ, Yi T, Qi L, Li J, Shao L, Dong JC. Electroacupuncture regulate hypothalamic-pituitary-adrenal axis and enhance hippocampal serotonin system in a rat model of depression. Neurosci Lett. 2016; 615:66-71.
63. Liu RP, Fang JL, Rong PJ, Zhao Y, Meng H, Ben H, Li L, Huang ZX, Li X, Ma YG, Zhu B. Effects of

electroacupuncture at auricular concha region on the depressive status of unpredictable chronic mild stress rat models. Evid Based Complement Alternat Med. 2013; 2013:789674.
64. Nettis MA, Pariante CM. Is there neuroinflammation in depression? Understanding the link between the brain and the peripheral immune system in depression. Int Rev Neurobiol. 2020; 152:23-40.
65. Guo T, Guo Z, Yang X, Sun L, Wang S, Yingge A, He X, Ya T. The alterations of IL-1Beta, IL-6, and TGF-beta levels in hippocampal CA3 region of chronic restraint stress rats after electroacupuncture (EA) pretreatment. Evid Based Complement Alternat Med. 2014; 2014:369158.
66. Yue N, Li B, Yang L, Han QQ, Huang HJ, Wang YL, Wang J, Yu R, Wu GC, Liu Q, Yu J. Electro-acupuncture alleviates chronic unpredictable stress-induced depressive- and anxiety-like behavior and hippocampal neuroinflammation in rat model of depression. Front Mol Neurosci. 2018; 11:149.
67. Christmas DM, Potokar J, Davies SJ. A biological pathway linking inflammation and depression: Activation of indoleamine 2,3-dioxygenase. Neuropsychiatr Dis Treat. 2011; 7:431-439.
68. Zhang K, Liu R, Gao Y, Ma W, Shen W. Electroacupuncture relieves LPS-induced depression-like behaviour in rats through IDO-mediated tryptophan-degrading pathway. Neuropsychiatr Dis Treat. 2020; 16:2257-2266.
69. Xu W, Yao X, Zhao F, Zhao H, Cheng Z, Yang W, Cui R, Xu S, Li B. Changes in hippocampal plasticity in depression and therapeutic approaches influencing these changes. Neural Plast. 2020; 2020:8861903.
70. Han X, Wu H, Yin P, Chen Z, Cao X, Duan Y, Xu J, Lao L, Xu S. Electroacupuncture restores hippocampal synaptic plasticity *via* modulation of 5-HT receptors in a rat model of depression. Brain Res Bull. 2018; 139:256-262.
71. Chen L, Yao Z, Qu S, Zhang J, Zhang J, Zhang Z, Huang Y, Zhong Z. Electroacupuncture improves synaptic plasticity by regulating the 5-HT1A receptor in hippocampus of rats with chronic unpredictable mild stress. J Int Med Res. 2020; 48:300060520918419.
72. Tu G, Fu T, Yang F, Yao L, Xue W, Zhu F. Prediction of GluN2B-CT1290-1310/DAPK1 interaction by protein-peptide docking and molecular dynamics simulation. Molecules. 2018; 23:3018.
73. She Y, Xu J, Duan Y, Su N, Sun Y, Cao X, Lao L, Zhang R, Xu S. Possible antidepressant effects and mechanism of electroacupuncture in behaviors and hippocampal synaptic plasticity in a depression rat model. Brain Res. 2015; 1629:291-297.
74. Zhang K, Liu R, Zhang J, Wei X, Gao Y, Ma W, Li Y, Cai W, Shen W. Electroacupuncture ameliorates depression-like behaviour in rats by enhancing synaptic plasticity *via* the GluN2B/CaMKII/CREB signalling pathway. Evid Based Complement Alternat Med. 2021; 2021:2146001.
75. Björkholm C, Monteggia LM. BDNF - A key transducer of antidepressant effects. Neuropharmacology. 2016; 102:72-79.
76. Kang Z, Ye H, Chen T, Zhang P. Effect of Electroacupuncture at Siguan acupoints on expression of BDNF and TrkB proteins in the hippocampus of post-stroke depression rats. J Mol Neurosci. 2021; 71:2165-2171.
77. Okawa Y. Can irritable bowel syndrome be detected by ultrasound? Drug Discov Ther. 2020; 14:213-217.
78. Radovanovic-Dinic B, Tesic-Rajkovic S, Grgov S, Petrovic G, Zivkovic V. Irritable bowel syndrome - From etiopathogenesis to therapy. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2018; 162:1-9.
79. Masuy I, Pannemans J, Tack J. Irritable bowel syndrome: Diagnosis and management. Minerva Gastroenterol Dietol. 2020; 66:136-150.
80. Hulisz D. The burden of illness of irritable bowel syndrome: Current challenges and hope for the future. J Manag Care Pharm. 2004; 10:299-309.
81. Su XT, Wang LQ, Zhang N, Li JL, Qi LY, Wang Y, Yang JW, Shi GX, Liu CZ. Standardizing and optimizing acupuncture treatment for irritable bowel syndrome: A Delphi expert consensus study. Integr Med Res. 2021; 10:100728.
82. Yaklai K, Pattanakuhar S, Chattipakorn N, Chattipakorn SC. The role of acupuncture on the gut-brain-microbiota axis in irritable bowel syndrome. Am J Chin Med. 2021; 49:285-314.
83. Yan J, Miao ZW, Lu J, Ge F, Yu LH, Shang WB, Liu LN, Sun ZG. Acupuncture plus Chinese herbal medicine for irritable bowel syndrome with diarrhea: A systematic review and meta-analysis. Evid Based Complement Alternat Med. 2019; 2019:7680963.
84. Zhu L, Ma Y, Ye S, Shu Z. Acupuncture for diarrhoea-predominant irritable bowel syndrome: A network meta-analysis. Evid Based Complement Alternat Med. 2018; 2018:2890465.
85. Stuardi T, MacPherson H. Acupuncture for irritable bowel syndrome: Diagnosis and treatment of patients in a pragmatic trial. J Altern Complement Med. 2012; 18:1021-1027.
86. Akbar A, Walters JR, Ghosh S. Review article: Visceral hypersensitivity in irritable bowel syndrome: molecular mechanisms and therapeutic agents. Aliment Pharmacol Ther. 2009; 30:423-435.
87. Belmonte L, Beutheu Youmba S, Bertiaux-Vandaële N, Antonietti M, Lecleire S, Zalar A, Gourcerol G, Leroi AM, Déchelotte P, Coëffier M, Ducrotté P. Role of toll like receptors in irritable bowel syndrome: differential mucosal immune activation according to the disease subtype. PLoS One. 2012; 7:e42777.
88. Yang J, Shang B, Shi H, Zhu S, Lu G, Dai F. The role of toll-like receptor 4 and mast cell in the ameliorating effect of electroacupuncture on visceral hypersensitivity in rats. Neurogastroenterol Motil. 2019; 31:e13583.
89. Fukudo S. Role of corticotropin-releasing hormone in irritable bowel syndrome and intestinal inflammation. J Gastroenterol. 2007; 42 Suppl 17:48-51.
90. Sohn W, Lee OY, Lee SP, Lee KN, Jun DW, Lee HL, Yoon BC, Choi HS, Sim J, Jang KS. Mast cell number, substance P and vasoactive intestinal peptide in irritable bowel syndrome with diarrhea. Scand J Gastroenterol. 2014; 49:43-51.
91. Ma XP, Tan LY, Yang Y, Wu HG, Jiang B, Liu HR, Yang L. Effect of electro-acupuncture on substance P, its receptor and corticotropin-releasing hormone in rats with irritable bowel syndrome. World J Gastroenterol. 2009; 15:5211-5217.
92. Qi Q, Chen F, Zhang W, Wang P, Li Y, Zuo X. Colonic N-methyl-d-aspartate receptor contributes to visceral hypersensitivity in irritable bowel syndrome. J Gastroenterol Hepatol. 2017; 32:828-836.
93. Tian SL, Wang XY, Ding GH. Repeated electro-acupuncture attenuates chronic visceral hypersensitivity

and spinal cord NMDA receptor phosphorylation in a rat irritable bowel syndrome model. Life Sci. 2008; 83:356-363.
94. Raskov H, Burcharth J, Pommergaard HC, Rosenberg J. Irritable bowel syndrome, the microbiota and the gut-brain axis. Gut Microbes. 2016; 7:365-383.
95. Tang HY, Jiang AJ, Wang XY, Wang H, Guan YY, Li F, Shen GM. Uncovering the pathophysiology of irritable bowel syndrome by exploring the gut-brain axis: A narrative review. Ann Transl Med. 2021; 9:1187.
96. Sun J, Wu X, Meng Y, Cheng J, Ning H, Peng Y, Pei L, Zhang W. Electro-acupuncture decreases 5-HT, CGRP and increases NPY in the brain-gut axis in two rat models of diarrhea-predominant irritable bowel syndrome (D-IBS). BMC Complement Altern Med. 2015; 15:340.
97. Zhao JM, Lu JH, Yin XJ, Wu LY, Bao CH, Chen XK, Chen YH, Tang WJ, Jin XM, Wu HG, Shi Y. Comparison of electroacupuncture and mild-warm moxibustion on brain-gut function in patients with constipation-predominant irritable bowel syndrome: A randomized controlled trial. Chin J Integr Med. 2018; 24:328-335.
98. Pages F, Berger A, Lebel-Binay S, Zinzindohoue F, Danel C, Piqueras B, Carriere O, Thiounn N, Cugnenc PH, Fridman WH. Proinflammatory and antitumor properties of interleukin-18 in the gastrointestinal tract. Immunol Lett. 2000; 75:9-14.
99. Song YF, Pei LX, Chen L, Geng H, Yuan MQ, Xu WL, Wu J, Zhou JY, Sun JH. Electroacupuncture relieves irritable bowel syndrome by regulating IL-18 and gut microbial dysbiosis in a trinitrobenzene sulfonic acid-induced post-inflammatory animal model. Am J Chin Med. 2020; 48:77-90.

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