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Biological effect of acupuncture on peripheral facial paralysis

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Peripheral facial paralysis is the dominant treatment disease of acupuncture. A large number of studies have proved the effectiveness of acupuncture in the treatment of peripheral facial paralysis. However, the underlying biological effect remains in an exploratory phase. This article will sort out and summarize the existing research mechanisms from the following aspects: inflammatory response, immune regulation, neurotransmitters, immune response, facial microcirculation, oxidative stress, changes in nerve structure and function, specificity of acupoints, acupuncture intervention time, and other potential mechanisms aiming to provide a scientific foundation for the role of acupuncture in the treatment of peripheral facial paralysis. Furthermore, the review discusses future directions for mechanistic research based on existing findings.

KEYWORDS

acupuncture, peripheral facial paralysis, neuroinflammation, molecular neurobiology, biological effect

1 Introduction

Peripheral facial paralysis is a prevalent clinical disorder characterized by inflammation and edema in the subnuclear motor neurons, resulting in facial nerve paralysis (1). In modern medicine, it is classified as a neurological disease (2). On average, 15–23 per 100,000 individuals are affected annually by peripheral facial paralysis, with a 12% likelihood of recurrence (3). Clinical symptoms of peripheral facial paralysis typically include loss of forehead wrinkles on the affected side, inability to raise the eyebrow, incomplete eyelid closure, the frequent tears on the eyelids, inability to puff the cheeks, and deviation of the mouth corner toward the healthy side (4). Patients with peripheral facial paralysis may also have difficulties in drinking water, eating, and other activities (5). Due to the paralysis of one side of the facial muscles, patients often have psychological problems such as anxiety and depression, resulting in social disorders and decreased quality of life (6).

According to the clinical practice guidelines of evidence-based acupuncture, peripheral facial paralysis is one of the dominant diseases of acupuncture (7). In 2023, the' Guidelines for the Treatment of Idiopathic Facial Paralysis' issued by the Japanese Facial Nerve Research Society recommended acupuncture as an effective intervention for the treatment of peripheral facial paralysis (8). This recommendation is based on the potential benefits of acupuncture in improving facial nerve function and promoting facial paralysis recovery. A bibliometric study (9) suggests that acupuncture can promote the functional recovery of facial nerves to varying degrees by improving some inflammatory factors. The early intervention of acupuncture does improve the prognosis of facial paralysis to a great extent (10). This is because acupuncture intervenes in the acute phase can accelerate the promotion of axon growth and improve neurotrophic nutrition (11, 12). Although

acupuncture has shown certain efficacy in the treatment of peripheral facial paralysis, the mechanism behind it is still not fully understood. In addition, there are relatively few review studies on the mechanisms of acupuncture for peripheral facial paralysis. Therefore, this paper aims to explore the mechanism of acupuncture in the treatment of peripheral facial paralysis by combing the existing relevant literature (Table 1).

1.1 Acupuncture improves facial inflammatory response

Inflammation is currently recognized as the pathogenesis of peripheral facial paralysis. After exiting the medulla oblongata from the cerebral bridge, the facial nerve traverses the narrow passage between the internal auditory canal and the mastoid foramen of the stem, where inflammatory pathogenic factors infiltrate the facial nerve, leading to demyelination of myelinated axons on the nerve fibers and the development of facial neuritis (13). Acupuncture can improve facial inflammation of peripheral facial paralysis by regulating inflammatory factors (Figure 1).

1.1.1 Acupuncture regulates the balance of anti-inflammatory and pro-inflammatory factors

Hs-CRP is a biomarker of inflammation, while mCRP is its subtype with pro-inflammatory properties. mCRP activates endothelial cells, releases pro-inflammatory cytokines such as MCP-1, IL-6, and IL-8, and promotes downstream inflammatory responses through the NF-κB pathway, thereby participating in the onset of inflammation (14, 15). The ratio of C-reactive protein to albumin in the serum of patients with facial neuritis is elevated, indicating the presence of an inflammatory response (16). Acupuncture can reduce the content of inflammatory factor hs-CRP in patients with peripheral facial paralysis and improve the inflammatory state (17). Acupuncture can also reduce the level of inflammation by regulating macrophages. Macrophages, a type of inflammatory cytokine, exist in two phenotypes: M1, which promotes the secretion of inflammatory cytokines, and M2, which inhibits the inflammatory response (18). Electroacupuncture modulates macrophage polarization by suppressing pro-inflammatory pathways (NLRP3/IL-1β) and activating anti-inflammatory mechanisms (Nrf2/HO-1/IL-10), effectively shifting macrophages from the M1 to M2 phenotype and improving inflammation (19). In addition, in a study of peripheral facial neuritis, it was found that the expression of Treg cells and Th17 cytokines in the peripheral serum of patients was unbalanced, the anti-inflammatory cytokine IL-10 released by Th17 cells was low, and the pro-inflammatory cytokines IL-6 and IL-17 released by Treg cells were highly expressed (20). However, acupuncture can down-regulate the expression of inflammatory cytokines IL-1β, TNF-α, and IL-6 in serum, inhibit the secretion of TNF-α, IL-17 protein, and mRNA, and promote the levels of serum anti-inflammatory cytokines IL-12 and IL-10 mRNA (21). This suggests that acupuncture exerts its therapeutic effect on peripheral facial paralysis by modulating the balance between pro-inflammatory and anti-inflammatory factors, thereby ameliorating the inflammatory response associated with peripheral facial paralysis.

1.1.2 Acupuncture activates the cholinergic anti-inflammatory pathway (CAP)

The cholinergic system involves neurotransmitters/molecules, acetylcholine (ACh), cholinergic receptors (AChRs), choline acetyltransferase (ChAT), and acetylcholinesterase (AChE) (22). These molecules participate in the body's immune response by binding to receptors on different immune cells, such as T cells, B cells, and lymphocytes, and in the complex cholinergic system, the activation of vagal efferents can mediate the release of acetylcholine from α7 nicotinic acetylcholine receptor (α7nAChR), which makes the expression of some pro-inflammatory cytokines decrease in the body, such as TNF-α, IL-6 and IL-18, forming cholinergic anti-inflammatory pathway (CAP) and alleviating inflammatory response (22, 23). Studies have found that electroacupuncture regulates inflammation by stimulating acetylcholine in the enteric nervous system, acting on α7nAChR expressed on inflammatory cells macrophages, and monocytes, which in turn inhibits the production of pro-inflammatory cytokines (24). Continuous acupuncture for 7 days increased the expression of α7nAChR in hippocampal neurons and decreased the expression of the downstream pro-inflammatory cytokines TNF-α and IL-1β (25). This suggests that acupuncture can regulate multiple downstream pro-inflammatory factors by activating the cholinergic anti-inflammatory pathway (CAP), thereby suppressing inflammation.

1.1.3 Acupuncture inhibits toll-like receptor 4 (TLR4)/NF-kB pathway transmission

A pathological manifestation of facial neuritis is the disappearance of axons on its nerve fibers, and the NF-kB pathway is involved in the initiation, growth, and branching of nerve fiber axons, and promotes myelin formation, and this process effectively aids in myelin sheath regeneration in peripheral facial paralysis, helping restore facial nerve function (26). However, NF-kB is regulated by TLR4, one of the players in inflammation, and TLR4 can activate tumor necrosis factor-receptor-associated factor 6 (TRAF6) via myeloid differentiation factor 88 (MyD88), which activates the downstream NF-κB pathway, followed by phosphorylation of residue S536 on the NF-κBp65 subunit, which allows NF-κB to bind to sites on promoters or enhancers of target genes, exerting inflammatory regulatory effects and leading to inflammation in the facial nerve (27–29). Additionally, patients with peripheral facial paralysis show significantly higher serum levels of tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) compared to healthy individuals, possibly due to the inflammatory cascade triggered by the activation of the TLR4/NF-κB pathway (30). A study has confirmed (31) that electroacupuncture can down-regulate the expression of TLR4 mRNA and protein as well as the level of NF-κBp65 phosphorylation, and effectively inhibit the TLR4/NF-kB pathway conduction in peripheral facial paralysis.

TABLE 1 Comprehensive overview of clinical and animal model studies for acupuncture's biological effects.

Author	Publication year	Research object	Intervention measures	Observation indicators	Reference
Chengcheng Han, et al.	2024	Patients with peripheral facial paralysis	Acupuncture	hs-CRP ↓ IL-6 ↓	(14)
Luyao Zhang, et al.	2021	Acute pancreatitis mice	Electroacupuncture	α7nAChR ↑ TNF-α IL-1β ↓ IL-6 ↓	(17)
Jiang Zhao, et al.	2020	Patients with peripheral facial neuritis	Electroacupuncture	TLR4 ↓ NF-κBp65 protein ↓	(20)
Xue Xiao, et al.	2023	Rats with primary dysmenorrhea	Electroacupuncture	PGE_2 ↑ $PGF_{2\alpha}$ ↓ TLR4 ↓ NF-κBp65 ↓ IL-1β ↓ IL-18 ↓	(21)
Shuangning Song, et al.	2018	Mice with acute colitis	Electroacupuncture	IL-1β ↓ TNFα ↓ IL-6 ↓ IL-12 ↓ IL17 ↓	(24)
Yanyu Xu, et al.	2017	Children with facial neuritis	Mouse nerve growth factor combined with acupuncture	IL-17 ↓ IL-6 ↓ TGF-β1 ↑ IL-10 ↑	(25)
Jun-peng Yao, et al.	2024	Facial nerve injury in rats	Electroacupuncture	GDNF ↑ PI3K ↑ mTOR ↑ Beclin-1 ↓ LC3 ↓	(36)
Jing Fei, et al.	2018	Facial nerve crush injury	Electroacupuncture	GDNF ↑ N-cadherin ↑	(37)
Na Zang, et al.	2023	Wind-cold type idiopathic facial nerve paralysis in acute stage patients	Electroacupuncture	GDNF ↑ NGF ↑	(38)
Cheng Tang, et al.	2024	Patients with acute-phase idiopathic facial nerve palsy	Alternating warm needle acupuncture combined with nerve growth factor from rats	GDNF ↑ NGF ↑ SOD ↑	(39)
Sun Yunhua, et al.	2011	Acute facial nerve injury rabbit model	Electroacupuncture	CNTFR ↑	(42)
Sun Zhongren, et al.	2006	Rabbits with peripheral facial nerve injury	Electroacupuncture	BNDF mRNA ↑	(44)
Zhou Shuxin, et al.	2018	Patients with facial paralysis	Acupuncture	Ig A ↓ Ig G ↓ Ig M ↓	(48)
Weiping Liang	2023	Patients with peripheral facial paralysis	Acupuncture	IgG ↓ IgM ↓	(49)
Sun Hui	2021	Patients after colorectal cancer radical operation	Warm-needle moxibustion	CD3+ ↑ CD4+ ↑ TNF-α ↓ IL-6 ↓ CRP ↓	(50)
Qianqian Cui, et al.	2024	Patients in the acute phase of peripheral facial paralysis	Acupuncture plus moxibustion	hs-CRP ↓ WBC ↓ NLR ↓ PLR ↓	(53)
Jia Shi, et al.	2024	Acute lung injury model in mice	Electroacupuncture	HO-1 ↓	(61)

(Continued)

TABLE 1 (Continued)

Author	Publication year	Research object	Intervention measures	Observation indicators	Reference
Jianguo Li, et al.	2024	CUMS Rats	Acupuncture	CAT ↓ SOD ↓ GSH-Px ↓	(63)
Lv Shanguang, et al.	2016	Rat model of ischaemic facial paralysis	Acupuncture	NO ↑ ET ↓	(76)
Jin Liu	2016	Patients with acute idiopathic facial nerve palsy	"Qianzheng San" with warm acupuncture	EPCs ↑	(77)

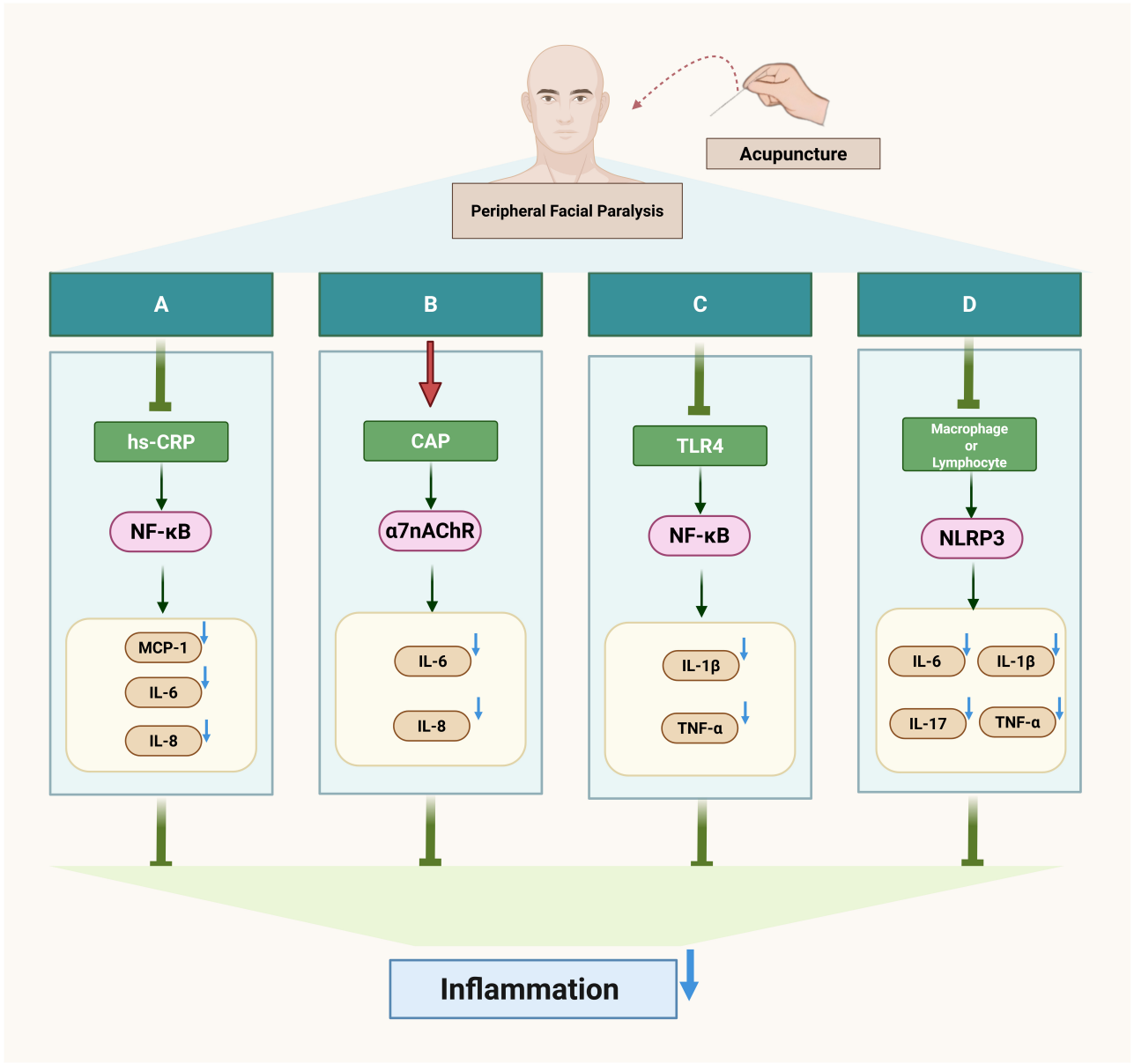

FIGURE 1
The anti-inflammatory process of acupuncture treatment of peripheral facial paralysis.

1.2 Acupuncture promotes the secretion of neurotrophic factors to repair damaged nerves

The neurotrophic factor family includes nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), ciliary neurotrophic factor (CNTF), neurotrophic factor (NT-3) (32), and glial cell-derived neurotrophic factor (GDNF) (33). Neurotrophic factors have the effect of repairing peripheral nerve injury. The immediate manifestation of facial nerve injury is paralysis of the expression muscles controlled by it (34). Muscle atrophy occurs due to a decrease in total muscle protein metabolism and myoglycogen content, among other things, when skeletal muscle is removed from the innervation of the nerve (35, 36). The neurotrophic factors secreted by neurons can precisely be used as therapeutic targets for muscle atrophy (37).

1.2.1 Up-regulate nerve growth factor and glial cell line-derived neurotrophic factor (GDNF)

NGF can promote the development, differentiation, regeneration, and repair of central and peripheral neurons, and accelerate myelin repair as well as myelin production, and peripheral facial paralysis is a disease of demyelination of nerve fiber axons, so serum NGF may be a therapeutic target for facial neuritis (38, 39). Acupuncture can protect neurons by up-regulating nerve growth factors and promote axonal regeneration to improve facial paralysis symptoms (40). In addition, studies have found that activation of inositol phospholipid-3-kinase (PI3K) can phosphorylate protein kinase B (AKT), which can effectively protect nerve cells (41). By up-regulating the expression of cell-derived neurotrophic factors, electroacupuncture activates the PI3K-AKT-mTOR signaling pathway, down-regulates the levels of autophagy protein markers Beclin-1 and light chain 3 (LC3), inhibits the body's autophagy level, and promotes the repair of facial neurons (42). The study of Fei et al. confirmed that electroacupuncture can up-regulate the expression of GDNF, improve the degree of nerve injury, and promote neuronal regeneration (43). Similarly, Zang et al. (44) found that acupuncture combined with warm moxibustion in patients with facial nerve paralysis due to wind-cold syndrome increased the expression of GDNF and nerve growth factor (NGF) in serum. Tang et al.'s clinical study also confirmed that warm acupuncture combined with murine nerve growth factor significantly boosted GDNF and NGF levels, further supporting the therapeutic potential of acupuncture in nerve regeneration (45). These findings suggest that acupuncture may play a vital role in neural repair and regeneration through the regulation of neurotrophic factors.

1.2.2 Up-regulate ciliary neurotrophic factor (CNTF)

Ciliary neurotrophic factor (CNTF) is found in glial cells of the peripheral nervous system, where it binds to subunit α of the CNTFR complex, induces heterodimerization of the β-receptor subunit to undergo tyrosine phosphorylation, and activates STAT proteins to migrate to the nucleus and bind to specific DNA, acting as a neuroprotective agent (46). CNTF can also effectively improve facial nerve injury, promote facial nerve axon regeneration, and regulate synaptic plasticity (47). Studies have shown (48) that electroacupuncture can promote the expression of CNTF receptors in rats with acute-phase facial nerve injury, and the up-regulation of its receptor expression level implies an increase in the number of sites that bind to CNTF, which contributes to the protective and regenerative effects of CNTF on the facial nerve.

1.2.3 Up-regulate brain-derived neurotrophic factor (BDNF)

BDNF can protect neuronal survival and participate in the regulation of neuroinflammation. The combination of BDNF and tyrosine kinase (TrkB) receptors can increase the signal transduction of Ca_2^+neurons in the short term. It can also inhibit the inflammatory response by inhibiting glycogen synthase kinase-3β (GSK-3β). It can also induce Akt and ERK to activate NF-κB and CREB transcription factors to regulate genes, promote the regeneration of BDNF neurons, and prolong the survival cycle (49). BDNF can bind to receptors on the facial nerve and promote axonal regeneration, and after electroacupuncture stimulation of rabbits with facial nerve injury, the expression of BDNF as well as the corresponding receptors was significantly up-regulated, which effectively repaired the damage to the facial nerve (50).

1.3 Acupuncture improves the immune response

Imbalances in the regulation of immune function play an important role in the formation, development, and outcome of peripheral facial palsy and are mainly associated with abnormal expression of immunoglobulins, immune cells, and immune molecules (51, 52). Facial paralysis is prone to occur after immunocompromise, or after excessive fatigue (53). Acupuncture can improve the body's immune function by regulating a variety of cells in the endogenous immune system (54). Studies have shown (55, 56) that the concentration of immunoglobulins in patients with facial paralysis is too high, and acupuncture treatment of facial paralysis can significantly down-regulate the levels of immunoglobulins IgA, IgG, and IgM. A study has also confirmed that warm acupuncture can up-regulate the expression of T lymphocyte subsets CD3+ and CD4+ in immune cells, down-regulate the expression of CD8+, and improve the clinical manifestations of facial paralysis (57). This is because T lymphocytes are also involved in the immune response process in peripheral facial paralysis (13, 58). The study also found that neutrophil-lymphocyte ratio (NLR), a key biomarker for evaluating immune function, was highly expressed in the serum of patients with peripheral facial paralysis (59). Acupuncture can down-regulate the serum neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) in patients with acute-phase facial neuritis (60).

1.4 Acupuncture inhibits oxidative stress

Oxidative stress is a state of imbalance between the oxidation system and the antioxidant defense system in the body, which is caused by excessive production of reactive oxygen species in the body, inducing apoptosis and damaging nerves (61). Overexpression of oxidative stress can damage nerves, so it may be a mechanism of facial nerve injury. The classical Mitogen-activated protein kinase/extracellular regulated protein kinase (MAPK/ERK) pathway is involved in the process of oxidative stress. In this pathway, extracellular stimuli activate and phosphorylate MEK, which in turn activates extracellular regulated protein kinases 1/2(ERK1/2), which is also phosphorylated to continue to activate downstream substrates and regulate cellular responses (62). It has been found that under hypoxia-induced oxidative stress environment, reactive oxygen species are increased in astrocytes, and activated transcription factor 1 (ATF-1) in the MAPK/ERK pathway may mediate ROS to inhibit thrombospondin-1(TSP-1) protein expression (63). ROS can bind to cell macromolecules and cause oxidative damage to the body through oxidation (64). Acupuncture can inhibit oxidative stress response (65). By stimulating specific acupoints, acupuncture can reduce the level of lipid peroxidation and activate the antioxidant enzyme system, to balance the oxidative stress state of the body (66). This process involves multiple pathways, including acupuncture regulating ROS production, affecting antioxidant enzyme pathways, repairing damaged biomolecules, and inhibiting apoptosis or autophagy (67). The rat model of acute lung injury confirmed that acupuncture inhibited the production of ROS by inhibiting the content of HO-1 and enhancing mitochondrial function, thereby protecting the damaged lung tissue (68). Acupuncture can also regulate gene expression, especially activate the antioxidant main regulatory factor Nrf2 (69), enhance SOD activity, inhibit oxidative stress, reduce oxygen free radical production, and reduce oxidative stress levels in inflammatory diseases (25). Acupuncture reduces the level of oxidative stress by increasing the expression of antioxidant enzymes. Acupuncture treatment significantly up-regulated the expression levels of antioxidant enzymes catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GSH-Px) in the depressive symptom model constructed by chronic unpredictable stress (CUMS) in rats (70). Acupuncture can also regulate the signal transmission process *in vivo* by blocking the MAPK/ERK signaling pathway, thereby effectively inhibiting oxidative stress (71). In addition, Acupuncture can modulate the expression of nitric oxide (NO), Malondialdehyde (MDA), and SOD in the body, which reflect the level of oxidative stress in patients with facial paralysis (72).

1.5 Acupuncture improves facial microcirculation

Facial microcirculation is also one of the current pathogenesiss of facial paralysis, and facial neuritis occurs when the facial nerve becomes ischaemic and oedematous (73, 74). Inflammatory tissues are generally hypoxic, and under hypoxic conditions, the regulation of NO on the stability of the hypoxia-inducible factor HIF-1α subtype is weakened, resulting in excessive activation and accumulation of HIF-1α, while continuous hypoxia will reduce the biological activity of NO (75, 76). NO belongs to vasodilator, and endothelin belongs to vasoconstrictor. Both of them regulate vasoconstriction and relaxation. Under pathological conditions, the ability of NO to inhibit the production and release of endothelin (ET) is weakened, and ET is released in large quantities, resulting in increased vascular resistance, slowed blood flow, and vascular microcirculation disorder (77). Acupuncture may significantly improve microcirculation by activating acupoints, regulating hemodynamics, affecting vasoactive substances, and adjusting hormone levels (78–80). According to relevant research, the key mechanism of acupuncture activating meridian-acupoints is to increase blood perfusion, thereby achieving the effect of improving microcirculation (81). In patients with peripheral facial paralysis in the acute stage, acupuncture at Hegu acupoints was examined by laser speckle technique, and the results showed that patients' facial perfusion was significantly elevated, confirming the effectiveness and importance of acupuncture at Hegu acupoints to improve facial microcirculation (82). A study has confirmed that acupuncture intervention in rats with ischemic facial paralysis can improve facial microcirculation by increasing the level of NO and reducing the level of ET in the body (83). It has also been shown (84) that the combination of acupuncture and medicine in the treatment of peripheral facial paralysis can promote the content of peripheral blood vascular endothelial progenitor cells (EPCs), which in turn promotes the regeneration and repair of facial blood vessels and improves facial microcirculation. In addition, it was found (85) that in patients with peripheral facial paralysis in the acute phase, the facial artery showed a significant decrease in blood flow velocity and elevated resistance compared to the healthy side, whereas a significant increase in blood flow velocity and a decrease in resistance of the facial artery appeared after needling the facial acupoints. So the blood flow velocity and flow resistance indices of the facial arteries can be used as potential biomarkers of peripheral facial palsy.

1.6 Acupuncture improves brain functional connectivity and structure

In the early stage of peripheral facial paralysis, brain function has abnormal connectivity (86). Acupuncture can activate the related brain regions that regulate peripheral facial never (87). Electroacupuncture activates functional areas such as the cerebellum, superior frontal gyrus, superior temporal gyrus, and precentral gyrus, resulting in enhanced signaling connectivity in these areas (88, 89). Not only that, early and precise acupuncture treatment for facial paralysis also promotes cortical reorganization in patients with facial paralysis (90). Currently, there is a relative lack of research utilizing computed tomography (CT) and functional magnetic resonance imaging (fMRI) to investigate changes in brain tissue and network connectivity in patients with peripheral facial paralysis treated with acupuncture and moxibustion. However, neuroimaging-based approaches hold significant potential for evaluating the effects of acupuncture on brain structure and functional connectivity in these patients.

Further advancements in this field are expected to provide deeper scientific insights and identify novel biological markers for the acupuncture-based treatment of facial paralysis.

1.7 The biological specificity mechanism of acupuncture stimulating acupoints

1.7.1 Specificity of acupoints

Acupoints are a combination of visceral and somatic afferents that activate sensory afferents over a small diameter area of the skin surface, releasing neuropeptides, which are thought to be the response points of neurogenic inflammation in the skin (91), Acupoints have close connection with the nervous system, muscles, and blood vessels, and when they receive different external stimulation such as acupuncture, electroacupuncture, and moxibustion, they produce the biomolecule adenosine (92), After adenosine binds to its receptor, it can effectively inhibit downstream pro-inflammatory cytokine secretion and exert anti-inflammatory effects by modulating the NF-kB signaling pathway (93). Not only that, external stimulation of acupoints actives somatic afferent nerve endings and regulates nerve conduction, but it also promotes the release of neuropeptides such as interleukin-1β (IL-1β), interleukin-6(IL-6), or immune cytokines from immune cells, which regulates immune function (94) and adjusts substances such as substance P (SP), and calcitonin gene-related proteins (CGRP) (95, 96). Therefore, the biospecific effects of acupoints and the optimization of acupuncture point combinations play a crucial role in the effectiveness of acupuncture in treating diseases like peripheral facial paralysis (97). Acupuncture treatment of peripheral facial paralysis often uses Dicang, Jiache, Yangbai, Xiaguan, Taiyang, Sibai, Chengjiang, Quanliao, Yingxiang, and Yifeng, these acupoints are commonly used in clinical consensus acupoints (98) (Table 2). These acupoints belong to different meridians and are primarily distributed on the face, with their main therapeutic effect being the regulation and unblocking of the meridians. The biological specificity of these points has been confirmed through various studies. For example, after electroacupuncture at Dicang in patients with facial paralysis, the signal connection of the brain region of the patient changed (99). Moreover, the corresponding anatomical position of Dicang is the orbicularis oris muscle, which can improve the symptoms of drooping mouth angle in patients with facial paralysis. The location of the Yifeng point is just at the outlet of the main trunk of the facial nerve, which directly stimulates the facial nerve (99, 100). Another study (101) confirmed that Taiyang point through Dicang, and Jiache point could play a role in improving facial paralysis by down-regulating by substance P (SP), vasoactive intestinal peptide (VIP), calcitonin gene-related peptide (CGRP). A study found that Yangbai (GB14), Sibai (ST2) and Jiache (ST6) have nerve fiber tissue in their local area, forming a regional nerve tissue network, and acupuncture and moxibustion as an external signal can stimulate these nerves, and then dominate the muscles and blood vessels around the acupoints (102). Further research showed that electroacupuncture at different facial acupoints induces varying levels of neural excitability, suggesting that the specificity of each acupoint may underlie its therapeutic mechanism (103). Therefore, this points to the importance of acupoint specificity and combination formulas in maximizing the therapeutic effects of acupuncture for conditions like peripheral facial paralysis.

1.7.2 Selectivity of acupoints

The selectivity of acupoints for appropriate diseases also plays a very important role in the treatment of diseases. The acupoints used clinically to treat peripheral facial paralysis mostly belong to the stomach meridian of foot yangming and the large intestine meridian of hand yangming in the 12 meridians. This is because the stomach and large intestine meridians run through the face of the human body, and the acupoints have the effect of treating local diseases. From a traditional Chinese medicine (TCM) perspective, the Yangming meridian is abundant in qi and blood, which promotes the circulation and recovery of facial qi and blood. The qi here refers to an intangible, functional energy that flows through the meridians and can enter and exit the acupoints (104). The blood is tangible, traveling through the meridians and resuscitating the five organs, and the qi generates and pushes the blood flow (105). Additionally, some acupuncturists will cooperate with Hegu to treat peripheral facial paralysis. This is based on the traditional experience of traditional Chinese medicine. The Hegu acupoint is located on the hand Yangming large intestine meridian, at the midpoint on the radial side of the second metacarpal bone, between the first and second metacarpal bones on the dorsum of the hand (106). Hegu has a special therapeutic effect on facial and oral diseases. Modern research supports this practice, for the reason that needling bilateral Hegu acupoints improves facial blood perfusion and enhances facial microcirculation (107).

1.8 The biological effects of different acupuncture intervention times on the body

As an effective traditional Chinese medicine therapy, the timing of acupuncture intervention is very important in the treatment of peripheral facial paralysis. Acupuncture can be intervened within 24 h after the onset of peripheral facial paralysis, and this conclusion is supported by the clinical research results of Song and Mou (108). Because the onset time of peripheral facial paralysis and the starting time of remission directly affect its prognosis, the earlier the intervention, the better the speed and effect of recovery (109). That will reduce the possibility of recurrence of facial paralysis (110). However, there is some controversy about whether acupuncture intervention will aggravate facial nerve inflammation and edema in the early stage of the disease (1). In fact, acupuncture can relieve acute facial inflammation and edema by stimulating facial nerves and acupoints (111), promote facial blood circulation, improve neurotrophy, reduce nerve compression, and accelerate facial muscle function recovery (110). In addition, a systematic evaluation showed that the timing of acupuncture intervention for peripheral facial paralysis had a significant effect on recovery and that early acupuncture treatment was able to speed up recovery, improve prognosis, and reduce the occurrence of sequelae (112). A large randomized controlled

TABLE 2 Common acupoints for peripheral facial paralysis.

Commonly used acupoint for peripheral facial paralysis	Affiliated meridian	The function of acupuncture points	Reference
Dicang (ST4)	Stomach meridian	Dredging meridians, dispelling wind and relieving pain	(124)
Jiache (ST6)	Stomach meridian	Dispersed wind heat, switch winding	(124)
Yangbai (GB 14)	Gallbladder meridian	Promote the operation of qi and blood	(125)
Xiaguan (ST 7)	Stomach meridian	Activating blood, detumescence and relieving pain	(126)
Taiyang	Extraordinary points	Clearing heat and detumescence, relieving pain and soothing collaterals	(124)
Sibai (ST2)	Stomach meridian	Loosen tendons ligament	(127)
Chengjiang (CV24)	Stomach meridian	Loosen tendons ligament	(128)
Quanliao (SI18)	Small intestine meridian	Detumescence Qufeng	(129)
Yingxiang (LI20)	Large intestine meridian	Wind clearing heat	(130)
Yifeng (TE17)	Sanjiao meridian	Wind dredging collaterals	(131)

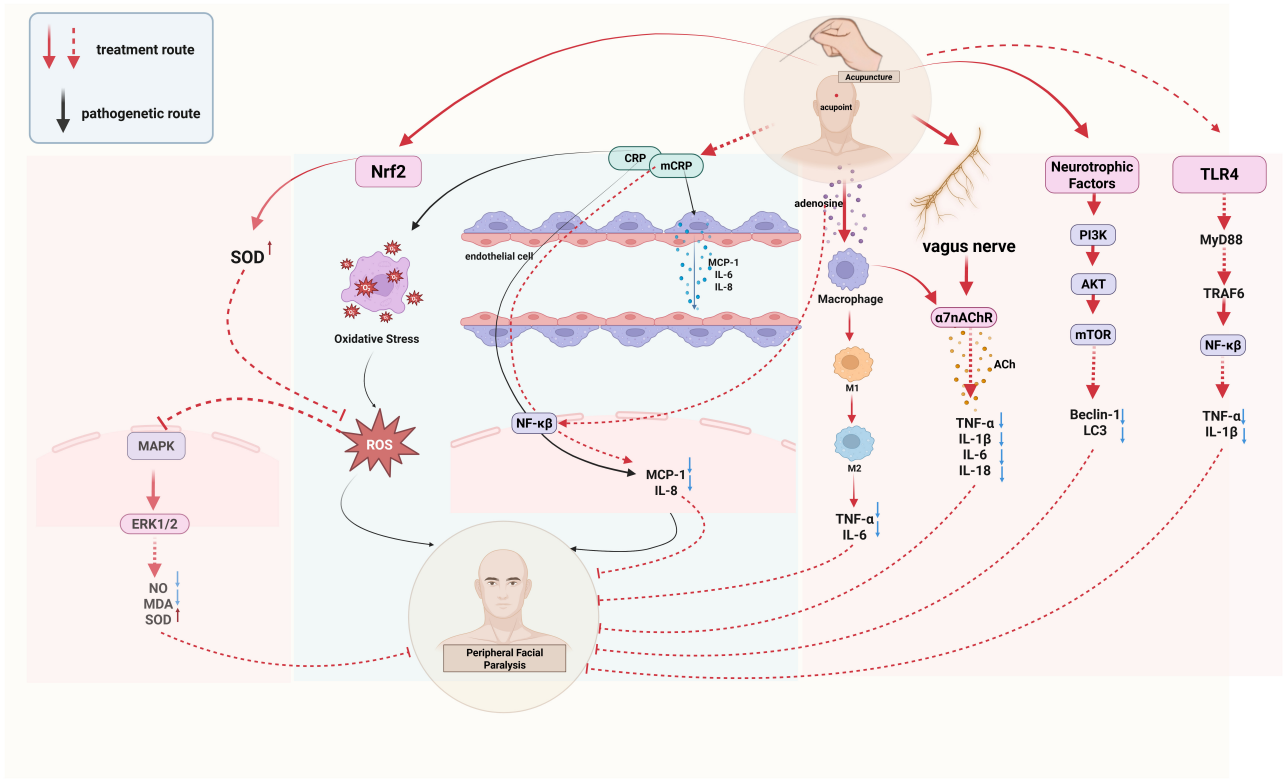

FIGURE 2
The biological process of acupuncture treatment of peripheral facial paralysis.

clinical study showed that starting treatment within 3 days after the onset of facial paralysis can effectively promote nerve recovery and shorten the healing time, and waiting until the condition enters the recovery period has a more limited effect (113). In addition, several studies (114, 115) have recommended the use of acupuncture from the early stage of the disease to clarify the safety and efficacy of acupuncture in the acute phase of peripheral facial paralysis from the perspective of evidence-based medicine.

1.9 Other potential mechanisms

Studies have found that electroacupuncture can reduce the expression of cytokine signal transduction inhibitory protein-3(SOCS-3), thereby inhibiting the JAK-STAT pathway, which may also be an important mechanism of acupuncture intervention in peripheral facial paralysis (116, 117). In addition, the mechanical stimulation of acupuncture can also be considered as a mechanism for acupuncture treatment of peripheral facial paralysis. This is

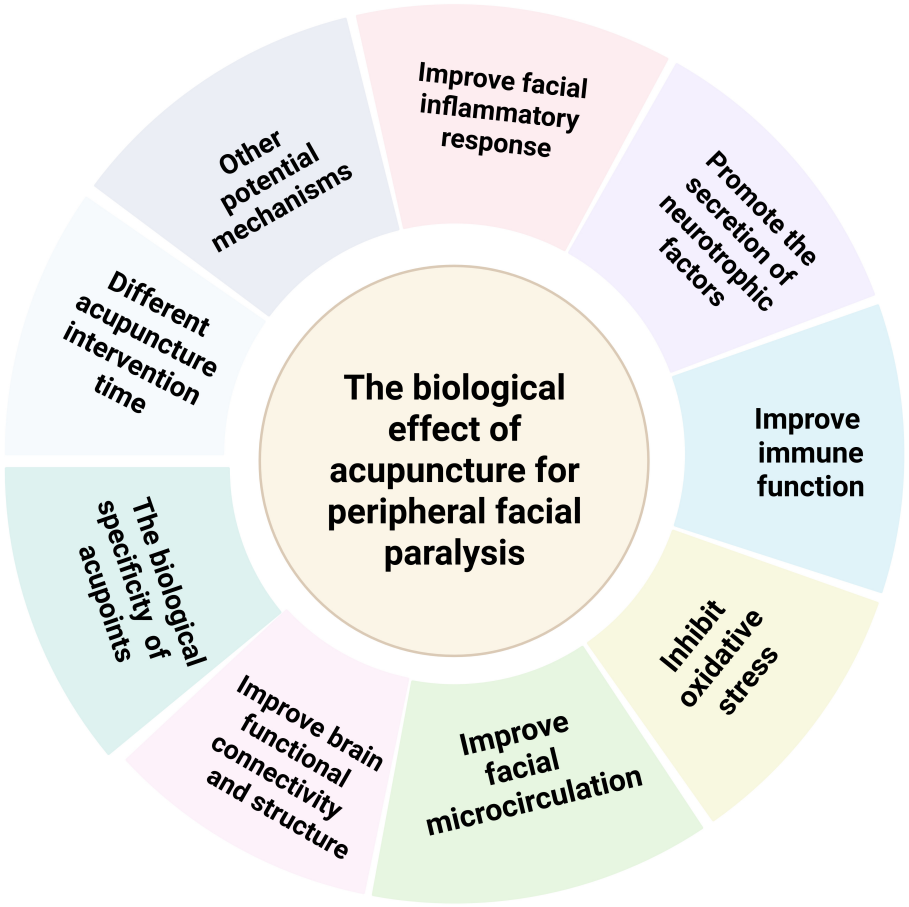

FIGURE 3
Biological effect of acupuncture intervention in peripheral facial paralysis.

because the mechanical stimulation of acupuncture activates the mechanically sensitive neurons on the body surface, transduces the signal afferent nerve fibers to the central neurons, and then passes from the efferent nerve to the related pathways, and then regulates the body movement and sensation (118).

2 Conclusion and outlook

This paper provides an overall overview of the changes in biological effects that occur in the body when acupuncture treats peripheral facial paralysis (Figure 2). The biological effects (Figure 3) of acupuncture intervention in peripheral facial paralysis are reflected in inflammatory mediators, immune system, nervous system, facial microcirculation, oxidative stress levels, abnormalities in structural and functional brain connectivity, and biological properties of acupoints. Current research primarily investigates acupuncture as an external stimulus that triggers one or more pathways, subsequently regulating downstream biological signaling to treat diseases. However, there is no clear answer to the current clinical research and experimental research on which pathway acupuncture has the most obvious regulatory effect. There are still some pathways such as JAK-STAT, Wnt/β-catenin signaling pathway (119), and PI3K/Akt signaling pathway (120), that have not been studied in depth, and repetitive studies are needed to get a clearer answer. In addition to the commonly discussed pathways associated with peripheral facial paralysis, a review (121) also highlights that the TGF-β/Smad signaling pathway can alleviate neuroinflammation by regulating cytokines. This suggests a potential direction for future research, where scholars may explore the use of acupuncture as a therapeutic approach to modulate peripheral facial paralysis. Furthermore, the Hippo signaling pathway has been found to interact with the production of reactive oxygen species and oxidative stress, thereby regulating cell differentiation, proliferation, survival and tissue regeneration (122). This finding provides a more comprehensive physiological and pathological mechanism direction for future research on acupuncture treatment of neuroinflammation, such as peripheral facial paralysis. In addition, recent studies have found that magnesium deficiency also seems to be a cause of peripheral facial paralysis (123), which may be a future research direction.

3 Discussion

At present, the research on the biological effect mechanism of acupuncture in the treatment of peripheral facial paralysis

remains to be further studied. Future research should focus on revealing the biological basis of acupoint stimulation, exploring the biological changes brought about by different acupoint combinations, and examining the effect of treatment timing on biological effects. With the rise of individualized medical treatment, the personalization and precision of acupuncture treatment have become a new trend. In addition, interdisciplinary cooperation and technological innovation are crucial for the development of this field. It is necessary to strengthen cooperation with molecular biology, immunology, and other disciplines, and use advanced technologies such as metabolomics, proteomics, and magnetic resonance imaging to further explain the biological mechanism of acupuncture in the treatment of peripheral facial paralysis, and provide a scientific basis for acupuncture treatment of peripheral facial paralysis.

Author contributions

WD: Writing – original draft, Writing – review & editing. DC: Writing – review & editing. ZH: Conceptualization, Formal analysis, Writing – review & editing. YZ: Conceptualization, Formal analysis, Writing – review & editing. SL: Conceptualization, Formal analysis, Writing – review & editing. CW: Funding acquisition, Resources, Writing – review & editing. HZ: Resources, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The author(s) declare that no Gen AI was used in the creation of this manuscript.

Publisher's note

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