**Effect of Acupoints on Acupuncture-Moxibustion and its Therapeutic Mechanism**

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**Abstract**

The clinical efficacy of acupuncture-moxibustion (AM) mainly depends on acupoints, but the relationship between the acupoints and AM remains unclear. Improving clinical efficacy and clarifying the mechanisms of AM is critical. We found that the specificity and sensitivity of acupoints, the skill of operation, and reasonable amount of stimulation can significantly improve the efficacy of AM. In addition, some studies have shown that Neural-Endocrine-Immune network and metabolites are involved in this process, clarifying the therapeutic mechanism of acupoints. Therefore, how to effectively use acupoints to improve the clinical efficacy of AM is one of the key issues in need of an urgent solution. In summary, this article reviewed the Chinese and English databases on the clinical efficacy and underlying mechanisms of acupoints to clarify the relationship between acupoints and AM efficacy and ultimately improve clinical efficacy through effective and rational use of acupoints.

**Keywords:** Acupoints, clinical efficacy, acupuncture-moxibustion, specificities, neural-endocrine-immune network

**Introduction**

Acupoints are the basis of acupuncture-moxibustion (AM) efficacy. By receiving different stimuli, acupoints can stimulate and enhance the inherent regulatory functions of the human body to prevent or cure diseases. Acupoints may generate physical and chemical signals after stimulation. Then, the signals convert to biological signals, which manifest in reactions in the human body. This process helps to motivate the body’s regulatory functions and plays a positive role in regulating the target organs. Previous synchrotron radiation X-ray fluorescence analyses showed that the concentration of four chemical elements (Ca, Fe, Cu, and Zn) in the acupoints and surrounding areas was significantly higher compared to nonacupoints. These elements tend to be distributed in oval patterns with the long axis along meridians and centered at acupoints. Some researchers suggest that this phenomenon confirms the existence of acupoints.[1]

The tissue structure under acupoints mainly includes nerve, blood vessels, lymphoid, and receptors. The effect of acupoint tissue morphology on the effect of acupoints is related to the specificity of the tissue structure, and the quality and quantity of the tissue structure involved in different acupoints. The acupoints differ as a function of different distributions on the body surface. Acupuncture needles inserted at different depths will cause the stimulation of the different receptors in different tissues, whether in the same or different acupoints. This is followed by changing excitation of varying afferent nerve fibers, resulting in changes in the quality or degree of visceral function.[2]

Studies have shown that the infrared spectrum of Neiguan (PC6) in patients with coronary heart disease is different from...
that of healthy participants. Stimulation at Neiguan (PC6) by a CO$_2$ laser can also regulate heart rate and blood pressure in anesthetized rats, and improve cardiovascular function. Tissues in acupoint, nonacupoint, and different acupoint areas have different biological, physical, chemical properties, and also have different responses to sound, light, electricity, heat, ion concentration, and deep tissue oxygen partial pressure. In addition, the response of meridians and nonmeridians is different depending on whether the body is in a physiological state, pathological state, or acupuncture interventional state, such that acupoints have characteristics of high temperature and low resistance compared with nonacupoints. These factors may be the basis of acupoint specificity. To improve clinical efficacy by using acupoints appropriately has become a critical discussion worldwide. This article reviews the relationship between acupoints and AM efficacy.

**Effect of Acupoints on Acupuncture-Moxibustion**

*Deqi* is the basis of the acupuncture technique and the key to improving clinical efficacy

*Deqi*, usually called “Qi’s arrival” in ancient times, and is now often regarded to as “needling sensation.” It refers to feelings such as soreness, numbness, heaviness, and distension that patients feel through needle manipulation or long-time needle retention, and at the same time, the operator feels the needle sinking and wrapped in muscle fibers. *Deqi* is the basis of the acupuncture technique and the key to improving clinical efficacy. Compared with placebo acupuncture with no effective needle sensation, acupuncture with effective needle sensation can greatly improve symptoms of insomnia and anxiety. This curative effect also persists over time. There is also an effect of acupuncture on primary dysmenorrheal patients with the cold and damp syndrome, such that patients are arranged to have thicker needles, deeper insertion, and some manipulation for deqi or without deqi while needling at Sanyinjiao (SP6). Deqi also significantly reduces visual analog scale (VAS) scores, and the effect is greater than without deqi. Acupuncture with a needling sensation also has different effects on brain activity as compared to without a needling sensation. Functional magnetic resonance imaging (MRI) research has shown brain function differences as a function of deqi. Specifically, there was greater brain activation in several regions in the deqi condition, especially in the upper right marginal gyrus, the left value network, and the left central posterior gyrus. True acupuncture at the Waiguan (SJ5) acupoint with needling sensation activated Brodmann areas 3, 6, 8, 9, 10, 11, 13, 20, 21, 37, 39, 40, 43, and 47, the head of the caudate nucleus, the parahippocampal gyrus, the thalamus, and the red nucleus compared with sham needling, true needling also deactivated certain Brodmann areas. Acupuncture at Waiguan (SJ5) produces deqi feelings of soreness, numbness, distending, and heaviness and mainly activates the left temporal lobe and superior temporal gyrus, while acupuncture its neighboring nonacupoint chiefly induces a feeling of tingling which activated the left limbic cortex and hippocampal gyrus [Table 1].

**The sensibility and reactivity of acupoints are the basis of acupuncture-moxibustion efficacy**

The clinical experience of acupuncturists and a large number of modern studies have suggested that acupoints have specificity, such that some acupoints have specific effects on some diseases. For example, Daling (PC7), a specific acupoint, can significantly relieve heel pain caused by plantar fasciitis. Electroacupuncture (EA) at Baihui (DU20) and Qubin (GB7) stimulate motor areas of the brain associated with ischemic stroke, which helped to accelerate the functional recovery of these areas. Another study found that EA at Zusanli (ST36) increased the number of neurons in the colon muscular plexus of rats with constipation-predominant irritable bowel syndrome (IBS-C), increased the expression of protein produced at this site, and improve symptoms caused by visceral hypersensitivity. In addition, a study used Neiguan (PC6), Weizhong (BL40), Chize (LU5), Sanyinjiao (SP6), Renzhong (DU6), and nonacupoints to study the specificity of the acupuncture effect on a rat model with middle cerebral artery occlusion, and found that every acupoint had a different therapeutic effect due to different acupuncture parameter combinations, but PC6 had the best effect, while the nonacupoint group showed no effects. The therapeutic effect of the acupoint group was superior to that of the nonacupoint group, suggesting that acupoints have therapeutic specificity. In clinical practice, the specificity of each acupoint is often used to select appropriate acupoints to obtain the desired treatment. Therefore, the sensibility and reactivity of acupoints are the basis of AM.

Acupoint specificity is mainly reflected in different effects of acupoints and nonacupoints. For example, acupuncture at Neiguan (PC6) could reduce heart rate and increase heart rate variability index regulated by the vagus nerve. In contrast, acupuncture at a sham acupoint 1 cm to the ulnar side of PC6 can reduce heart rate, but does not change heart rate variability. Different acupoints on the same meridians or on different meridians also have specificity. EA at bilateral Neiguan (PC6) and Taichong (LR3) could increase heart rate and blood pressure, while EA at bilateral Zusanli (ST36) has the opposite result. Another study found that EA at the pericardium meridian, such as Daling (PC7), Ximen (PC4), and Quze (PC3), improve heart rate and cardiac function in bradycardia rats, and the effect on rat heart function increases from low to high for Daling (PC7), Ximen (PC4), and Quze (PC3), respectively, while EA at the stomach meridian points Jixi (ST41), Zusanti (ST36), and Dubi (ST35) have no significant effect on heart rate and cardiac function, except for Jixi (ST41).

In the treatment of migraines, Waiguan (SJ5), Yanglingquan (GB34), and Fengchi (GB20) showed more pronounced effects than nearby acupoints such as Pianli (LI6), Zusanti (ST36), and Touwei (ST8), which suggests that the function...
Table 1: Examples of needling response

<table>
<thead>
<tr>
<th>Study design</th>
<th>Subjects</th>
<th>Acupoints and intervention methods</th>
<th>Efficiency/result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized controlled trial</td>
<td>67 subjects with insomnia and anxiety experimental group (n=33), control group (n=34)</td>
<td>Acupuncture with needle sensation versus placebo-acupuncture with no effective needle sensation</td>
<td>Acupuncture with effective needle sensation can greatly improve the symptoms of insomnia and anxiety compared with the placebo-acupuncture</td>
</tr>
<tr>
<td>Randomized controlled trial</td>
<td>68 primary dysmenorrheal patients with cold and damp syndrome deqi-expectation group (n=15), No-deqi-expectation group (n=49)</td>
<td>Needling at SP6 with thicker needles, deeper insertion, and some manipulation for deqi versus thin filiform needle with shallow insertion for no-deqi</td>
<td>The VAS of patients with deqi was significantly lower than that of patients without deqi sensation</td>
</tr>
<tr>
<td>Systematic evaluation</td>
<td>10 medical literature databases and 5 clinical trial registration platforms</td>
<td>Compared the clinical trial literature on whether deqi after acupuncture was effective or not on the brain function</td>
<td>The activation of brain areas were more and the activation degree was stronger in the deqi condition compared to non-deqi condition, especially in the upper right margin, the left visual network and the left central posterior gyrus</td>
</tr>
<tr>
<td>Observational clinical study</td>
<td>12 healthy volunteers</td>
<td>Received sham and true needling at the SJ5 acupoint (nondeqi vs. deqi state)</td>
<td>True needling activated the functional regions of the brain, including some Brodmann areas, the head of the caudate nucleus, the parahippocampal gyrus, thalamus and red nucleus</td>
</tr>
<tr>
<td>Randomized controlled trial</td>
<td>18 normal volunteers control group (n=6), SJ5 group (n=6), non-acupoint group (n=6)</td>
<td>No acupuncture versus acupuncture at SJ5 versus acupuncture at nonacupoint</td>
<td>Acupuncture with obvious needling response substantially activated the temporal lobe and superior temporal gyrus of brain which was significantly different from those without needling response</td>
</tr>
</tbody>
</table>

**VAS**: Visual analogue scale

of related acupoints have specificity to migraines.\(^{[20]}\) However, another perspective suggests that acupoint effectiveness is not about specificity, but differences in “quality” of the acupoints, such as the effect of with or without, increase or decrease, and promote or inhibit, rather than differences in “quantity.” That is, the comparison of acupoint and nonacupoints reflect a difference in strength and has no correlation with acupoint specificity but rather with the sparse density of nerve distribution in some regions, resulting in superior efficiency between acupoints.\(^{[21]}\) A study about basic and clinical characteristics of acupoints suggests that acupoint specificity does not exist when a VAS is adopted to assess pain, while hemodynamic and neuroimaging studies suggest the existence of acupoint specificity.\(^{[22]}\)

Therefore, there remains controversy about whether specificity exists. Some studies suggest that acupoint specificity does not exist and that acupuncture or sham acupuncture group can produce the same or similar clinical therapeutic effect.\(^{[23-25]}\) Although the study of acupoint specificity has shown that stimulating different acupoints can induce different hemodynamic and electrophysiological responses in the body as well as in different areas of the brain, there remains no conclusive evidence to support acupoint specificity in terms of its specific physiological foundation, underlying mechanisms, or laws.\(^{[26,27]}\) More high-quality clinical studies on acupoint specificity are required to provide comprehensive and objective evidence (Table 2).

Appropriate acupoint combinations can strengthen synergistic effects and reduce antagonistic effects

Based on syndrome differentiation of meridians in Traditional Chinese Medicine (TCM), acupoints are combined to maximize effects. Acupoint combinations include acupoints of upper and lower, front and back, left and right, and local acupoints, which are the basis of acupunctural treatment of disease. Appropriate acupoint combinations can strengthen synergistic effects and reduce antagonistic effects. For example, in acupoint combinations with Taichong (LR3), a study observed anti-hypertensive effects of different combinations of acupoints on 163 patients with essential hypertension randomly divided into a Taichong (LR3) group, Ligou (LR5) group, Neiguan (PC6) group, nonacupoint group, Taichong plus Ligou group (LR3 + LR5), Taichong plus Neiguan group (LR3 + PC6), and Taichong (LR3) plus nonacupoint group. The results showed that the effect of acupoint combinations was better than that of single and non-acupoints, and there was also a long-term effect on depressurization.\(^{[28]}\) Another study analyzed Taichong (LR3) with Sanyinjiao (SP6), Taichong (LR3) with Sanyinjiao (SP6) and Shangjuxu (ST37), Taichong (LR3) with San1yinjiao (SP6) and Tianshu (ST25), and Taichong (LR3) with Sanyinjiao (SP6) and Shangjuxu (ST37) and Tianshu (ST25) to observe the effect of different acupuncture point combinations on AQP4 related to liver depression and spleen deficiency rats. Although different acupoint combinations could regulate benign colon AQP4 content in rats, the Taichong (LR3) with Sanyinjiao (SP6), Shangjuxu (ST37), and Tianshu (ST25) combination had a stronger effect.\(^{[29]}\)

German researchers used AM to treat mild and moderate Crohn’s disease (CD). In the treatment group, Pishu (BL20), Zhongwan (BL21), Zusanli (ST36), Tianshu (ST25), and Daheng (SP15) were used as the main acupoints based on the deficiency of spleen qi. Moxibustion was added to Qihai (CV6), Weishu (RN12), and Sanyinjiao (SP6). For patients with kidney yang deficiency, moxibustion was added to Qihai (CV6), Shenshu (BL23), Baihui (GV20), and Mingmen (GV4). For patients with the stagnation of liver qi, Taichong (LR3),
Different acupuncture-moxibustion stimulation methods have different effects

Acupoint stimulation methods include conventional acupuncture, EA, acupoint injection, acupoint catgut embedding, moxibustion, bloodletting cupping, moving cupping, and so on. Different acupuncture methods have different effects on the body. In general, acupuncture at Tianshu (ST25) can promote blood circulation and remove blood stasis, which is effective for treating gastrointestinal blood stasis and dysmenorrhea, while moxibustion at Tianshu (ST25) can invigorate qi and hemostasis, which is effective for treating gastrointestinal bleeding and excessive menstruation. Acupuncture at Guanyuan (CV4), Shenshu (DL23), Daimai (GB26), and Sanyinjiao (SP6) can clear dampness and heat, and improve defecation and increase the heart rate.

Table 2: Examples of acupoint specificity

<table>
<thead>
<tr>
<th>Study design</th>
<th>Subjects</th>
<th>Acupoints and intervention methods</th>
<th>Efficiency/result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized controlled trial[^1^]</td>
<td>53 patients with plantar fasciitis treatment (n=28) placebo (n=25)</td>
<td>Needling at PC7 point in treatment group versus L1 4 point in control group</td>
<td>Needling at the acupoint PC7 significantly reduce heel pain</td>
</tr>
<tr>
<td>A clinical observational study[^1^]</td>
<td>Six patients suffering from ischemic stroke</td>
<td>EA at DU20 and GB7</td>
<td>Accelerate the functional recovery of brain motor function parts</td>
</tr>
<tr>
<td>Animal experiment[^2^]</td>
<td>Rats with constipation-predominant (IBS-C)</td>
<td>Acupuncture at Neiguan (PC6), Weizhong (BL40), Chize (LU5), Sanyinjiao (SP6), Renzhong (DU6), and nonacupuncture respectively in each group</td>
<td>Improved defecation and increased the number of neurons in colon muscular plexus</td>
</tr>
<tr>
<td>Randomized and controlled animal experiment[^3^]</td>
<td>Rats with the middle cerebral artery occlusion</td>
<td>Acupuncture at Neiguan (PC6) point versus sham point (1 cm to the ulnar side of PC6) versus no acupuncture treatment</td>
<td>Every acupoint had different therapeutic effect, and PC6 had the best effect, but nonacupuncture group was of invalid result</td>
</tr>
<tr>
<td>Randomized controlled trial[^4^]</td>
<td>Healthy subject</td>
<td>Acupuncture at Neiguan (PC6) versus sham point (1 cm to the ulnar side of PC6) versus no acupuncture treatment</td>
<td>Acupuncture at P6 reduced the heart rate and increased the heart rate variability index while the sham point just reduced the heart rate</td>
</tr>
<tr>
<td>Randomized controlled trial[^5^]</td>
<td>Forty patients with stable angina</td>
<td>EA at Neiguan (PC6), Taichong (LR3) versus at Zusanli (ST36)</td>
<td>PC6 and LR3 acupuncture increase the heart rate and mean arterial pressure while Zusanli acupoint decrease the heart rate and mean arterial pressure</td>
</tr>
<tr>
<td>Animal experiment[^6^]</td>
<td>Rats with brachycardia</td>
<td>EA at pericardium meridian points PC7, Ximen (PC4) and Quze (PC3) versus EA at stomach meridian point Jiexi (ST41), Zusanli (ST36) and Dubi (ST35)</td>
<td>EA at pericardium meridian points improved the heart rate and cardiac function, while EA at stomach meridian point had no significant improving effect except the ST41 point</td>
</tr>
<tr>
<td>Randomized controlled trial[^7^]</td>
<td>Thirty patients with migraines (TAG, n=10), (CAG, n=10), (MG, n=10)</td>
<td>Acupuncture at typically used acupoints of Waiguan (SJ5), Yanglingquan (GB34), Fengchi (GB20) in the TAG versus nearby acupoints of Panlil (LI6), Zusanli (ST36), Touwei (ST8) in the CAG versus no treatment in the MG</td>
<td>Typically used acupoints showed more pronounced effects than nearby acupoints</td>
</tr>
</tbody>
</table>

IBS-C: Irritable bowel syndrome, EA: Electroacupuncture, TAG: Traditional acupuncture group, CAG: Control acupuncture group, MG: Migraine group

Table 3: Examples of optimal combination of acupoints

<table>
<thead>
<tr>
<th>Study design</th>
<th>Subjects</th>
<th>Acupoints and intervention methods</th>
<th>Efficiency/result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized controlled trial[^8^]</td>
<td>163 patients with essential hypertension single acupoint groups, acupoints combinations groups</td>
<td>Acupuncture respectively at Taichong (LR3), Ligou (LR5), Neiguan (PC6), non-acupoint in single acupoint groups versus acupuncture respectively at Taichong (LR3) with Neiguan (PC6), Taichong (LR3) with Ligou (LR5), and Taichong (LR3) with non-acupoint in combinations groups</td>
<td>The effect of acupoint combinations was better than that of single and nonacupuncture</td>
</tr>
<tr>
<td>Animal experiment[^9^]</td>
<td>Liver depression and spleen deficiency rats</td>
<td>EA at Taichong (LR3) with Sanyinjiao (SP6) versus LR3 with SP6 and Shangjuxu (ST37) versus LR3 with SP6 and Tianshu (ST25) versus LR3 with SP6, ST37 and Tianshu (ST25)</td>
<td>The LR3 with SP6, st37 and ST25 combination had the significant effect in regulating the colon benign AQP4 content in rats</td>
</tr>
<tr>
<td>Prospective, randomized, controlled, single-blind clinical trial[^10^]</td>
<td>51 patients with mild and moderate Crohn’s disease traditional acupuncture (TCM group, n=27) nonacupuncture points (control group, n=24)</td>
<td>Acupuncture and moxibustion at leading acupoints of Pishu (L20), Zhongwan (BL21), Zusanli (ST36), Tianshu (ST25), Daheng (SP15), and auxiliary acupoints of Qihai (CV6), Weishu (RN12), Sanyinjiao (SP6) and so on in the TCM group versus nonacupuncture points in the control group</td>
<td>Significant differences in lowering CDAI, improving clinical symptoms and quality of life, reducing serum α1 acid glycoprotein of TCM group compared with control group</td>
</tr>
</tbody>
</table>

CDAI: Crohn’s disease activity indexes, TCM: Traditional Chinese Medicine
while moxibustion at these points has the effect of dissipating cold and dispelling dampness. Cupping and moving cupping can stimulate the acupoint area, so that they induce the expande or rupture of small blood vessels at the stimulation site, resulting in congestion or blood stasis, thereby improving blood circulation, promoting cell metabolism, relieving pain, and enhancing immunity. Acupoint injection combines acupuncture with medicine. Acupuncture catgut embedding has continuous stimulation on the acupoint and then stimulates meridians, regulates qi and the blood, and has a lasting effect. All kinds of acupuncture and moxibustion methods can have an effect by inducing local histological changes in the acupoint area.

In clinical treatment, the proper method or combination of methods must be chosen based on patient condition. For example, acupuncture combined with ginger moxibustion at the affected Heding (EX-LE2) point is more effective than simply using either of them in knee osteoarthritis patients with yang deficiency and cold-stagnation syndrome.\textsuperscript{[23]} One study also showed that Zusanli (ST36) and Neiguan (PC6) acupoints were selected to treat nausea and vomiting caused by chemotherapy by using EA, or warm acupuncture combining with EA and ginger moxibustion, and found that the complete control rate and effective control rate of EA and warm acupuncture combined with EA for acute vomiting were greater than the effects of ginger moxibustion; while the complete control rate of the combined treatment for delayed vomiting was significantly higher than that of EA, ginger moxibustion, and the effective control rate was higher than that of ginger moxibustion. Further, serum 5-hydroxytryptamine (5-HT) content in patients with combined treatment was lowest after chemotherapy, indicating that different acupuncture and moxibustion methods have different effects on acute and delayed vomiting after chemotherapy.\textsuperscript{[32]} In a previous study, we used different types of moxibustion, including herb-partitioned, ginger-partitioned, garlic-partitioned, and mild moxibustion to stimulate Tianshu (ST25) in rats with ulcerative colitis. General differences in the infrared intensities were found in ST25 at various wavelengths in rats from different groups.\textsuperscript{[33]} Thus, appropriate treatment should be selected according to the clinical circumstances [Table 4].

### Clinical efficacy requires a certain amount of stimulation on acupoints

In order to have an effect, AM must achieve a certain quantity, and different amounts of stimulation may produce different clinical effects. The stimulation quantity of acupuncture mainly includes stimulus intensity and stimulus time. Transcutaneous electrical stimulation at 2/100 Hz at acupuncture could alleviate protracted withdrawal symptoms and opioid craving, thus reducing the positive rate on urine tests in patients with opiate addiction during rehabilitation.\textsuperscript{[34,35]} It can also improve sleep conditions in morphine withdrawal rats,\textsuperscript{[36]} and compensate for the immunocompromised state caused by morphine exposure.\textsuperscript{[37]} Compared with high-frequency EA, the gene expression levels in the the nuclear region can be more effectively regulated than low-frequency EA, which may be the underlying mechanism of low-frequency EA.\textsuperscript{[38]} However, a study on single nucleotide polymorphisms showed that the effects of EA at 2 Hz and 100 Hz on pain tolerance were the same.\textsuperscript{[39]} EA could increase cerebral blood flow and decrease ischemic brain damage in a rat model of middle cerebral artery occlusion, and, using an EA device with a current of 1.0–1.2 mA and 5–20 Hz frequency significantly reduced ischemic infarction, nerve damage, and mortality. However, when the current was lower than 0.6 mA or the frequency was higher than 40 Hz, no similar effects were observed.\textsuperscript{[40]} Studies on the appropriate amount of moxibustion have also attracted the attention of physicians. For example, high doses of moxibustion have better effects than regular doses in the treatment of lumbar disc herniation.\textsuperscript{[41]} Rats with transient middle cerebral artery occlusion received 40 min of suspended moxibustion with tail temperature increasing, and showed significantly smaller infarct volume and lower neurological deficit scores than did those without decreasing levels of cyclooxygenase-2 as well as cortical expression of caspase-3. While the production of inducible nitric oxide synthase was increased,\textsuperscript{[42]} these effects were significantly superior to moxibustion that lasted for 15 min.\textsuperscript{[43]} Another study assessed the effect of needle retaining time in electro-acupuncture on the repair of acute gastric mucosal injury and found that both short- and long-time acupuncture at Zusanli

### Table 4: Examples of different acupuncture-moxibustion stimulation methods

<table>
<thead>
<tr>
<th>Study design</th>
<th>Subjects</th>
<th>Acupoints and intervention methods</th>
<th>Efficiency/result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized controlled trial\textsuperscript{[31]}</td>
<td>90 patients of KOA with yang-deficiency and cold-stagnation syndrome acupuncture group (n=30), ginger moxibustion group (n=30), and a combination group (n=30)</td>
<td>Acupuncture versus ginger moxibustion versus acupuncture combine with ginger moxibustion at Heding (EX-LE2) point</td>
<td>Acupuncture combine with ginger moxibustion are more effective than simple acupuncture or simple ginger moxibustion</td>
</tr>
<tr>
<td>Randomized controlled trial\textsuperscript{[32]}</td>
<td>163 patients with nausea and vomiting caused by chemotherapy EA group (n=42), warm acupuncture combined with EA group (n=37), ginger moxibustion group (n=44), control group (n=40)</td>
<td>EA versus warm acupuncture combined with EA versus ginger moxibustion at Zusanli (ST36) and Neiguan (PC6) versus tropisetron hydrochloride</td>
<td>Different acupuncture methods had different clinical effects on acute vomiting and delayed vomiting</td>
</tr>
<tr>
<td>Animal experiment\textsuperscript{[33]}</td>
<td>Rats with ulcerative colitis</td>
<td>Herb-partitioned moxibustion versus garlic-partitioned moxibustion versus mild moxibustion at Tianshu (ST25)</td>
<td>General differences of the infrared intensities were found at various wavelengths in different moxibustion groups</td>
</tr>
</tbody>
</table>

KOA: Knee osteoarthritis
Acupoints and effect of acupuncture-moxibustion

Acupuncture-Moxibustion has a Positive Role in the Regulation of Neural, Endocrine, and Immune Systems and Can Regulate Metabolism

The integrative regulatory effect of AM is closely related to the neural-endocrine-immune network and body metabolism. AM mainly takes effect through regulating the Neural-Endocrine-Immune system and body metabolism. A clinical study showed that palpable positive reaction points in the shape of knots or streaks can be felt subcutaneously in corresponding parts of the body. Meridians are the connection between the reaction points and the internal organs. When acupuncture is administered at the acupoint, the calcium ion concentration in the acupoint significantly increases, and the calcium ion concentration in other acupoints of the same meridian also increases. Modern studies suggest that this is closely related to the role of the nerve segments. Meridians, acupoints, and organs form a functional set dominated by nerves in which antagonist effects may occur through the vagus nerve pathway. Guowei Li found two spinal sensory neuron/tracts with unidirectional projections, which were spino-solitary tracts (SST) and dorsal column postsynaptic (DCPS) spino-medullary neurons, as well as three spinal sensory neuron/tracts with bidirectional projections, along the spino-cervical tract (SCT)-DCPS, SST-DCPS, and SST-SCT in animals.

The excitability was found to be regulated by the NMDAR-PKC-NO membrane signal transduction system. A study found that EA at different segments of the rabbit heart meridian could generate discharge activity of the heart sympathetic plexus and enhance left ventricular function, which is closely related to the trunk of the heart meridian at the wrist and left ventricular function. Stimulation of this area produced better results than stimulation of the elbow or axilla. Acupuncture also improved the cognitive deficits of middle-aged SAMP8 mice through increasing neuron density of the hippocampus. Laser acupuncture at Shenmen (HT7) could improve neuron degeneration and memory impairment in a rat model of Parkinson’s disease via reducing oxidative stress and improving cholinergic and dopaminergic function. EA at the stomach meridian of foot yangming (ST meridian) increases the response of c-Fos immunoreactive neurons, and the neuron response rates of acupoints on the ST meridian were significantly higher than were those for nonacupoints. MRI research has shown fluid channels in real-time in the connective tissues of living animals and humans, which is consistent with the meridian trend recorded in classical literature. However, no fluid channels were observed when injected in non-acupoint areas. Acupoints play a positive role in promoting central and peripheral nerve regeneration probably through the following mechanisms: (1) Improving the local microenvironment of nerve growth, and promoting the expression of neurotrophic factors to play a continuous role in nerve regeneration; (2) Repairing the microcirculation of injured nerve tissue; and (3) Inhibiting apoptosis of damaged neurons and inducing neural stem cell proliferation.

Needling depth is closely related to the anatomical structure where the acupoint is located. Different needling depths can also produce different effects with varying amounts of stimulation from each level of tissue structure of acupoints. For example, 22 healthy volunteers who performed repeated eccentric contractions to induce muscle soreness in their extensor digital muscle were assigned randomly to a control group, skin group (depth of 3 mm: The extensor digital muscle), muscle group (depth of 10 mm: The extensor digital muscle), and nonsegmental group (depth of 10 mm: The anterior tibial muscle). The pressure pain thresholds of the skin group and muscle group were significantly higher than they were in the control group, whereas the electrical pain threshold at the fascia of the muscle group was significantly higher than it was in the control group. Thus, the needle penetration depth is important for relieving muscle pain. However, one study compared the difference between superficial and deep needling on the right hand at the Hegu (LI4) acupoint of healthy volunteer participants. The functional MRI data showed that acupuncture stimulation at the superficial and deep depths of needling cannot induce different hemodynamic responses. Possible reasons for the different results may be that in clinical practice, an increase of needle insertion depth may not induce an equal increase of efficacy. Meanwhile, the depth of needle insertion is relevant as it pertains to stimulation at the effective acupoint in the effective layer.

Acupuncture treatment assigns considerable importance to the use of acupuncture manipulations. Lifting, thrusting, and twirling can improve the efficacy of acupoints. One study compared the effects of different needling methods at the Neiguan point on hand spasms in stroke patients. The lifting-thrusting-twirling needling manipulation and the rapidly twirling needling manipulation had the best therapeutic effect. Another study showed that the effect of acupuncture on the affected side of the Weizhong point with the lifting-thrusting reducing method was better than that with a simple acupuncture method. TCM believes that the essence of acupuncture and moxibustion for reinforcing and reducing is to regulate the body’s functional state, on the basis of deqi, using certain manipulations to return the body to a stable state of yin and yang balance. Reasonable application of the reinforcing and reducing method is beneficial to improve clinical efficacy. At the same acupoint, different reinforcing and reducing methods will lead to different effects, such as reinforcing the Hugu point and reducing the Fuliu point can cause sweating, while reducing the Hugu point and reinforcing the Fuliu point can stop sweating [Table 5].

(ST36), Neiguan (PC6), and Zhongwan (CV12) on rats with acute gastric mucosa injury could up-regulate the expression of HSP60 and TNF-α. The effect of 15-min and 30-min groups was significantly greater than the 30-s, 3-min, 5-min, and 10-min groups.

Acupuncture-eralu has a positive role in the regulation of neural, endocrine, and immune systems and can regulate metabolism.
At the same time, acupuncture points affect neurotransmitter transmission. The analgesic effects of acupuncture reduced when collagens in the acupoint area were damaged, suggesting that collagen fibers play a role in the conversion and transmission of acupuncture signals.\(^{[38]}\) Our group established an IBS rat model with chronic visceral pain in previous research to study the central and peripheral mechanisms of the analgesic effect of moxibustion. We found that after moxibustion intervention, the concentrations of endogenous endorphin opioid peptides, dynorphin, and enkephalin in corresponding spinal cord segments were increased\(^{[59,60]}\) in addition to decreases in the expression of corticotrophin-releasing hormone mRNA in the hypothalamus, as well as 5-HT, prokineticin 1 (PK1), and its receptor in the colon of IBS rats.\(^{[61,63]}\)

Research on the proteomic response in the nervous system after acupuncturing Taichong (LR3) in spontaneously hypertensive rats (SHRs) found that compared with a nonacupoint group, seven proteins were down-regulated and six proteins were up-regulated in the medulla of the Taichong (LR3) group. Further, the antioxidant enzymes in the medulla of the SHRs were also increased by acupuncture, which may provide a partial explanation for the antihypertensive effect of acupuncture.\(^{[64]}\)

Acupuncture can also cause changes in many endogenous metabolites. AM at certain acupoints can cause changes in many endogenous metabolites. A study found that acupuncture at Zusanli (ST-36) could perturb canonical metabolic pathways, including alpha-linolenic acid metabolism, d-glutamine, d-glutamate metabolism, citrate cycle, alanine, aspartate, glutamate metabolism, vitamin B6 metabolism, and 53 differential metabolites were also identified as potentially associated with the physiological basis and mechanism of ST-36 and its therapeutic effect.\(^{[65]}\) Another study compared changes and differences of metabolites in the cortex of rats with ulcerative colitis after acupuncture at an acupoint on the meridian of foot yang ming and nonmeridian non-acupoints, results showed that the difference of water-soluble extract in the cerebral cortex was differed more, while the difference of lipid-soluble metabolite was not significantly different between the meridian acupoints and non-meridian non-acupoints.\(^{[66]}\) Therefore, changes in

Table 5: Examples of certain stimulation amount

<table>
<thead>
<tr>
<th>Study design</th>
<th>Subjects</th>
<th>Acupoints and intervention methods</th>
<th>Efficiency/result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Animal experiment(^{[44]})</td>
<td>Rats pretreatment with opioid receptor antagonist, CBI1 cannabinoid antagonist or D1 dopamine receptor antagonist</td>
<td>EA stimulation at Zusanli (ST36) and Sanyinjiao (SP6) acupoints with 2Hz</td>
<td>2 Hz EA is capable of inducing CPP in rat via the activation of the endogenous opioid-, cannabinoid- and dopamine-systems</td>
</tr>
<tr>
<td>Randomized controlled trial(^{[45]})</td>
<td>154 patients with opiate addiction HANS group (treatment (n=78)), Mock-HANS group (control (n=76))</td>
<td>Transcutaneous electrical acupoint stimulation at Hegu, Laogong, Neiguan, Waiguan with 2/100 Hz in the treatment group versus mock stimulation at same acupoints in the control group</td>
<td>2 Hz EA exert a reward effect in the brain’s reward circuitry</td>
</tr>
<tr>
<td>Animal experiment(^{[46]})</td>
<td>Rats with morphine withdrawal</td>
<td>EA stimulation at Zusanli (ST36) and Sanyinjiao (SP6) with the frequency of 2Hz or 100Hz</td>
<td>2/100 Hz transcutaneous electrical acupoint stimulation could alleviate protracted withdrawal symptoms, opioid craving and reduce positive rate of urine test</td>
</tr>
<tr>
<td>Animal experiment(^{[46]})</td>
<td>Rats with middle cerebral artery occlusion</td>
<td>EA at Shuigou (Du 26), Baihui (Du 20) with the parameters of 1.0-1.2 mA and 5-20 Hz versus that lower than 0.6 mA or the frequency was higher than 40 Hz</td>
<td>Improving sleep conditions, compensating for the immunocompromised state</td>
</tr>
<tr>
<td>A meta-analysis of randomized controlled trials(^{[47]})</td>
<td>Patients with lumbar discerhination</td>
<td>Heat-sensitive moxibustion at heat sensitive acupoint versus traditional moxibustion at conventional acupoint</td>
<td>Appropriate EA treatment could reduce ischemic infarction, nerve damage and mortality</td>
</tr>
<tr>
<td>Animal experiment(^{[48,49]})</td>
<td>Rats with transient middle cerebral artery occlusion</td>
<td>Suspend moxibustion at Dazhui (DU 14) for 40 min with tail temperature increase versus suspended moxibustion for 15 min</td>
<td>High doses of moxibustion had better effects than regular doses, and 40 min of moxibustion showed smaller infant volume and lower neurological deficit scores than the 15 min</td>
</tr>
<tr>
<td>Animal experiment(^{[44]})</td>
<td>Rats with acute gastric mucosa injury blank group, model group, six EA treatment groups with different needle retaining times</td>
<td>Acupuncture at Zusanli (ST36), Neiguan (PC6) and Zhongwan (CV12) acupoints for 30-s, 3-min, 5-min 10-min, 15-min, 30-min respectively in the EA treatment groups</td>
<td>The effect of 15-min and 30-min groups were more significantly compare with the 30-s, 3-min, 5-min ,10-min groups</td>
</tr>
<tr>
<td>Randomized controlled trial(^{[50]})</td>
<td>22 healthy volunteers that were induced muscle soreness control group, skin group, muscle group, nonsegmental group</td>
<td>Needle insertion with a de3 ph of 3 mm in skin group, depth of 10 mm in muscle group, depth of 10 mm that located the anterior tibial muscle in non-segmental group</td>
<td>Both the pressure pain thresholds and electrical pain threshold at fascia in muscle group were significantly higher than control group</td>
</tr>
<tr>
<td>Observational clinical study(^{[51]})</td>
<td>17 healthy volunteer participants</td>
<td>Superficial versus deep needling at Hegu (LI-4) acupoint</td>
<td>The blood oxygen level dependent responses in the two depths of needling had no significant different</td>
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</tbody>
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CPP: Conditioned place preference

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metabolites may play a key role in the effect of acupuncture at specific acupoints.

**Conclusion**

Currently, in-depth investigations of the mechanisms of acupoint effect have partly elucidated the basic principles of AM, but there are still some limitations. Specific acupoints are the basis for improving the efficacy of acupuncture. We need to further understand the material basis of meridians and acupoints, the characteristics of the tissue structure, the relationship between acupoints and nerves, blood vessels, lymph, fascia, and body fluids, and even cellular and gene-level effects. In this way, it is of considerable importance that studies of acupoints focus on detailing the specific correlations between the structure and function of acupoints, identifying the chemical substances present in acupoint areas, and explaining the relationships between receptive acupoints and the effects of AM [Figure 1].

Further investigations should be carried out. Large sample, multi-center randomized controlled clinical trials will be needed. The multidisciplinary, integrated, and systematic use of modern scientific methods should be applied to design rigorous experiments about diseases that can be treated by AM effectively. In the future, we will optimize acupoint combinations, conduct studies characterizing the amount–effect relationship, determine optimal stimulation amounts, identify ideal AM methods for diseases, and finally improve clinical efficacy.

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**Conflicts of interest**

There are no conflicts of interest.

**References**

Acupoints and effect of acupuncture-moxibustion

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