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Review

Efficacy and Applications of Pharmacopuncture for Pathologies of the Knee: A Narrative Review.

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Abstract

Background: The knee is a vital joint for lower limb function, responsible for supporting body weight, assisting movement, and absorbing shock. As the prevalence of knee impairments grows, negatively affecting patients' daily lives, research into therapeutic interventions is gaining attention. Pharmacopuncture, a modern therapy that combines acupuncture with medication, involves injecting pharmacological drugs or purified herbal medicines into acupuncture points.

Methods: This narrative review reports on the main findings and methodologies of recent studies that have used pharmacopuncture to treat various knee pathologies. The review includes a breakdown of the pharmacopuncture's composition and injection sites.

Results: The studies reviewed demonstrate that pharmacopuncture is an effective treatment for a range of knee conditions, including osteoarthritis, chronic pain, and meniscus tears. It consistently leads to significant reductions in pain and improvements in functional disability and quality of life. The therapeutic effect is believed to stem from the combined action of the injected substance and the stimulation of specific acupoints. However, not all findings were consistently positive; The reviewed studies utilised a wide variety of substances, from natural herbal extracts like *Ulmus davidiana* and bee venom to the neuropeptide mixture Cerebrolysin. Injection sites were also varied, ranging from specific knee acupoints and localised ashi points to a broader, systemic application.

Conclusions: Pharmacopuncture is a promising and viable treatment for several knee pathologies. However, the current body of literature has limitations that need to be addressed in future research. Many studies have limited numbers of participants, lack standardised protocols, and their findings are sometimes diluted by the use of multiple combined treatments. Furthermore, some conclusions are based on observational studies rather than robust randomised controlled trials. To fully establish the long-term effectiveness and solidify its role in integrative medicine, more rigorous and well-designed research is essential.

Keywords: Knee; Osteoarthritis; Pain; Meniscus Tear; Pharmacopuncture; Complementary Therapies; Traditional Chinese Medicine.

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1. Background

The knee is composed of two joints, the tibiofemoral and the patellofemoral, connecting three bones: the femur, the tibia, and the patella [1,2]. To ensure stability, the knee joint depends on its surrounding muscles and soft tissue structures, including cartilage, ligaments, and tendons [3].

The knee's functions include supporting body weight, assisting lower limb swing, and absorbing shock [4]. Therefore, knee impairments are common physical problems that negatively impact the daily lives and mental health of patients and the community and society as a whole [5-8].

However, some factors may increase the risk of developing knee problems. Some examples are excess weight, lack of physical activity that reduces muscle flexibility and strength, certain sport activities and occupations that add stress to the knee, and previous knee injuries [9].

Many conditions are associated with the knee, displaying particular symptoms.

Table 1 summarises the main conditions and symptoms according to the National Health Service (NHS) [10].

Table 1. Causes and symptoms of injury-related and non-injury-related knee pathologies.

Injury-related	
Possible cause	**Knee symptoms**
Sprain and strain.	Pain after overstretching, overusing or twisting, often during exercise.
Tendonitis.	Pain experienced in the area between the kneecap and shin, which is often a result of repetitive running or jumping.
Torn ligament, tendon or meniscus, cartilage damage.	Feeling of instability, the knee giving way when standing, an inability to straighten the leg, and a popping sound heard at the time of injury.
Patellar dislocation.	The patella changes shape after a collision or sudden change in direction.
Not injury-related	
Possible cause	**Knee symptoms**
Osteoarthritis.	Pain and stiffness in both knees, mild swelling, which is more common in older people.
Bursitis.	Warm and red, with pain and swelling that worsen with kneeling or bending.
Bleeding in the joint.	Swelling, warmth, and bruising, more common while taking anticoagulants.
Gout or septic arthritis.	Hot and red, sudden, striking pain.
Osgood-Schlatter's disease.	Teenagers and young adults with pain and swelling below the patella.

2. Pharmacopuncture

Pharmacopuncture, also known as acupoint (acupuncture point) injection, herbal acupuncture, aqua acupuncture, or aquapuncture, is a modern therapy that merges acupuncture with medication [11]. It involves injecting pharmacological drugs or purified herbal medicines into acupuncture points. This technique is now widely used in China and Korea for a variety of conditions [12].

Phytoacupuncture is, in part, a subtype of pharmacopuncture that refers exclusively to the injection of herbal or plant-based extracts (*phyto*- meaning plant) into acupuncture points. As a Traditional Chinese Medicine theory-based technique, the usage is based on the plants' properties, flavours and actions, as well as on the acupuncture points' functions [13,14].

Phytoacupuncture can be applied in two ways: either by dipping the tip of the acupuncture needle in a plant decoction before insertion or by injecting a specific volume of

the decoction [14]. The latter method is essentially the same as pharmacopuncture. Figure 1 depicts this relation.

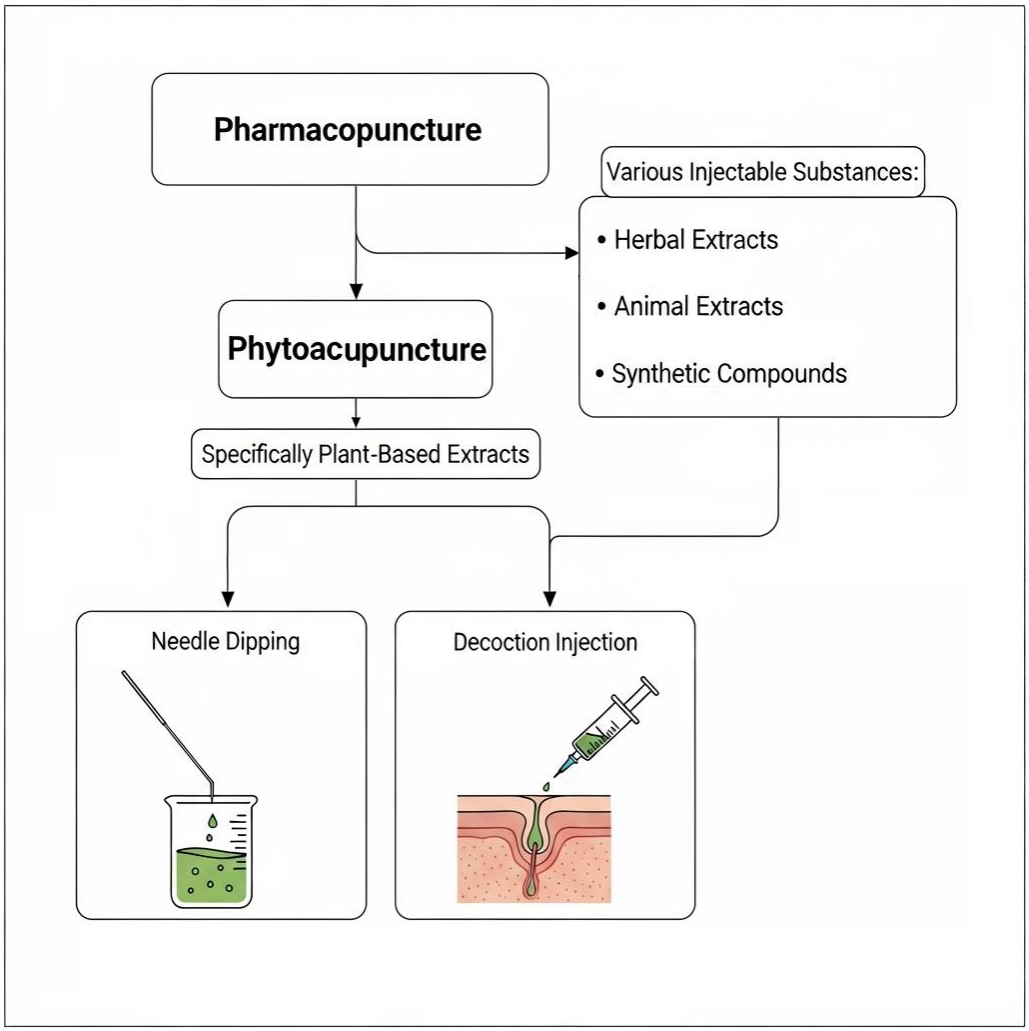


Figure 1. Phytoacupuncture as a part of pharmacopuncture, but not entirely.

3. Pharmacopuncture for knee pathologies

This section reports on the main findings and methodologies of studies that have used pharmacopuncture to treat knee pathologies.

3.1. Evidence

The study by Kim *et al.* [15] aimed to determine the clinical effectiveness and safety of pharmacopuncture for knee osteoarthritis. The results showed that pharmacopuncture was more effective than normal saline injections in improving pain as measured by a Visual Analogue Scale (VAS) after the seventh treatment session. However, the study found no significant difference between the two groups when evaluating other metrics, including the Western Ontario and McMaster Universities pain score (WOMAC), total pain scores (total WOMAC), 36-Item Short Form Health Survey (SF-36), and Korean Health Assessment Questionnaire (KHAQ). No serious adverse effects were reported. The authors noted that the control group's normal saline injection may not have been an inert placebo, as it provided mechanical and needle-stimulation effects, which could have influenced the trial's statistically insignificant results in most measures. In fact, an Australian study [16] found that pharmacopuncture may produce a stronger clinical response than traditional acupuncture, as it was reported to induce a more intense *de-qi* sensation resulting from the puncture and liquid injection.

Lee *et al.* [17] compared the effectiveness of different pharmacopuncture injection methods for treating knee osteoarthritis: intra-acupoint and intra-articular combined, intra-acupoint only, and intra-articular only. All three groups showed significant improvement in pain and function, as measured by the VAS and the Korea Western Ontario and McMaster Universities Osteoarthritis Index (KWOMAC), with these effects lasting for at least four weeks after the final treatment. While there were no statistically significant differences in VAS and KWOMAC scores when comparing the three groups, the results indicated that intra-articular injection was more clinically effective than intra-acupoint injection. The combination of intra-acupoint and intra-articular injection was found to be the most effective among the three treatment methods.

Regarding the study of Ismailov *et al.* [18], the effectiveness of complex rehabilitation combined with pharmacopuncture for children with neuromotor system diseases was investigated. Results for knee issues showed that out of 28 patients with knee joint contracture before treatment, 16 were cured, 8 showed partial success, and 4 saw no change. Also relevant for this topic, out of 22 patients with steppage gait before treatment, 6 were cured, 11 had partial recovery, and the condition remained stable in 9. Gait disorders are often associated with knee pain syndromes [19-21].

Overall, the study concluded that the combination of pharmacopuncture and complex rehabilitation is effective for treating neuromotor system diseases in children.

Lee *et al.* [22] investigated the long-term effects of integrative Korean medicine treatment (IKMT) for primary knee osteoarthritis. The results showed significant improvements from admission to discharge and continuing through a long-term follow-up period. Specifically, the Numerical Rating Scale knee-pain score decreased at both discharge and follow-up, and the WOMAC score showed a substantial decrease, with continuous improvement in physical function. The EuroQol-5 dimension-5 level questionnaire (EQ-5D-5L) score also improved. Patients reported high satisfaction with pharmacopuncture, acupuncture, physical therapy, and herbal medicine, and 96.30% reported overall improvement according to the Patient Global Impression of Change (PGIC) scores.

The study concludes that IKMT is effective for improving pain, functional disability, and quality of life in patients with primary knee OA, with its effects being maintained over the long term.

As well, Lee *et al.* [23] evaluated the clinical effectiveness and long-term outcomes of IKMT for meniscus tears. The results demonstrated that IKMT treatment significantly reduced knee pain, improved knee joint function, and enhanced quality of life. Specifically, the numeric rating scale (NRS) for knee pain decreased at both discharge and during the long-term follow-up. WOMAC also showed a significant decrease during hospitalisation and continued to improve at follow-up. The EQ-5D-5L score also increased at both discharge and follow-up. The most common reason for being satisfied with treatment was pain relief (64%), and the most satisfactory treatment was acupuncture (54%), followed by herbal medicine (31%) and pharmacopuncture (31%) (above Korean physical therapy, Chuna manual therapy, cupping, and others).

The study concluded that IKMT treatment provides effective and long-lasting relief for patients with meniscus tears.

Jeong *et al.* [24] conducted a randomised controlled trial comparing the effectiveness of pharmacopuncture therapy and physical therapy for chronic knee pain. The results indicated that the pharmacopuncture therapy group showed significantly better improvement than the physical therapy group in several key areas. The pharmacopuncture therapy group had superior outcomes in reducing pain as measured by the NRS and VAS, also showing greater functional improvement based on the K-WOMAC scores. As well, the study found that the trial was feasible, with high adherence and low dropout rates, and no serious adverse events were reported. The study concluded that pharmacopuncture therapy is highly effective for pain relief and functional improvement in patients with chronic knee pain.

Finally, a case report by Hwang *et al.* [25] describes the treatment of a 47-year-old woman with a history of frequent sprains and acupuncture-associated vasovagal response. The patient had multiple knee sprains and also sprains in her thumbs, wrist, and ankle. The treatment involved using only pharmacopuncture for a total of 59 sessions over nine months.

The results showed that most of the patient's acute sprains were resolved within a few treatments, with pain improving to a VAS score of 1. For two specific injuries with moderate swelling and pain (VAS scores of 5-6), the symptoms significantly improved after a few sessions. The patient reported little pain during the procedure and was able to return to her activities immediately afterward, which was attributed to the quick procedure time and low level of discomfort. The case report concluded that pharmacopuncture could be an effective treatment for various acute sprains, especially for patients with a history of acupuncture-associated vasovagal response, due to its simple and fast administration.

3.2. Methodologies

This section outlines the composition and application sites (summarised in Table 2) for the pharmacopuncture treatments discussed in the preceding section.

Table 2. Injection sites and components of pharmacopuncture according to the included studies.

Study	Composition	Injection sites
Kim *et al.* [15]	Root bark of *Ulmus davidiana Planch, var. japonica Nakai*.	ST35 (*Dubi*), EX-LE5 (Xiyan), EX-LE2 (*Heding*), and *Ashi*.
Lee *et al.* [17]	Bee venom.	Intra-articular; ST35 (*Dubi*), GB34 (*Yanglingquan*), EX-LE5 (*Xiyan*), ST36 (*Zusanli*), and SP9 (*Yinlingquan*) on the affected side(s).
Ismailov *et al.* [18]	Cerebrolysin.	BL22 (*Sanjiaoshu*), BL23 (*Shenshu*), BL24 (*Qihaishu*), BL25 (*Dachangshu*), BL26 (*Guan Yuanshu*), BL36 (*Chengfu*), BL37 (*Yinmen*), BL39 (*Weiyang*), BL55 (*Heyang*), BL56 (*Chengjin*), BL57 (*Chengshan*), BL58 (*Feiyang*), SP10 (*Xuehai*), ST34 (*Liangqiu*), ST36 (*Zusanli*), ST41 (*Jiexi*), SP9 (*Yinlingquan*), BL60 (*Kunlun*), BL61 (*Pucan*), BL62 (*Shenmai*), KI3 (*Taixi*), KI4 (*Dazhong*), KI5 (*Shuiquan*), KI6 (*Zhaohai*), and GB40 (*Qiuxu*).
Lee *et al.* [22]	*Shinbaro* or *Jaseng* Bee Venom.	Acupoints around the knee joints (not specified).
Lee *et al.* [23]	Bee venom; Other (not specified).	Not specified.

Jeong *et al.* [24]	*Shinbaro*, or *Harpagoside*, or *Huang-Lian-Jie-Du-Tang*, or Joong*seongouhyul*, or *Placenta Hominis*.	Acupoints commonly indicated for knee pain (such as ST35, EX-LE4, and GB34). Not fully specified.
Hwang *et al.* [25]	7-herb extract: *Scutellaria baicalensis*, *Phellodendron amurense*, *Pulsatilla koreana*, *Sophora tonkinensis*, *Aucklandia lappa*, *Aquilaria agallocha*, and *Carthamus tinctorius L.*	4 to 6 *ashi* points.

3.2.1. *Pharmacopuncture compositions*

The reviewed studies utilised a wide range of substances. These included natural herbal extracts like the root bark of *Ulmus davidiana* and a complex 7-herb formula. Other studies used animal-derived substances, most notably bee venom. One study even used Cerebrolysin, a neuropeptide mixture, demonstrating that the term "pharmacopuncture" can apply to various types of injectable substances, not just those from traditional medicine.

Ulmus davidiana, also known as the David elm, is a small, deciduous tree. It can be found in a wide variety of locations, including China, Mongolia, Korea, Siberia, and Japan, typically growing in streamside wetlands at elevations of 2000–2300 m [26]. The therapeutic effects of *Ulmus davidiana* are generally attributed to its antioxidant, anti-inflammatory, and anticancer properties, as supported by references [27-31].

On the other hand, bee venom pharmacopuncture is derived from the venom of live honeybees, which is then extracted and refined [32]. This substance possesses various therapeutic properties, including anti-inflammatory, analgesic, neurotoxic, antibacterial, and antipyretic effects, as well as the ability to promote blood circulation [17]. These properties make it useful for treating a range of conditions such as acute and chronic arthritis, muscle pain, and neuralgia [33,34]. Due to the presence of antigens from heterologous proteins [35], bee venom pharmacopuncture can cause stronger allergic reactions compared to other pharmacopunctures. For this reason, treatments often start with a small dose and are gradually increased to allow the body's immune system to stabilise [17,36].

While the scope of this review does not allow for a deep exploration of the formula, the therapeutic effects of the 7-herb extract used in the Hwang *et al.* [25] study may be a result of the specific properties of its individual components (such as their anti-inflammatory [37-39] and anticancer [39,40] actions) and the synergy they create when combined. In vitro studies have shown that the extract inhibits the production of nitric oxide and inflammatory cytokines, such as IL-6 and TNF-α [41]. The extract was developed in 2015 to treat musculoskeletal diseases and injuries from traffic accidents [42]. As a result, it has not been widely used, and only a few clinical studies have investigated its therapeutic effects on conditions like thoracic pain caused by seat belts [43].

Finally, Cerebrolysin is a neurotrophic drug composed of low-molecular-weight peptides purified from pig brain. It has been studied for its potential to promote neural growth and repair. Cerebrolysin is used to treat a variety of neurological disorders, including stroke, traumatic brain injury, and dementia [44-46], although some applications are yet to be fully supported [45,46].

3.2.2. *Pharmacopuncture injection sites*

The application sites for the treatments were just as varied as the compositions. Some studies focused on points directly related to the knee joint, such as ST35 (*Dubi*), EX-LE5 (*Xiyan*), and GB34 (*Yanglingquan*), which are common acupoints for knee pain. Others, such as the case study of Hwang *et al.* [25], used *ashi* points, which are determined by the patient's localised tenderness. One study even combined traditional acupoint injections with a direct intra-articular injection into the joint space Lee *et al.* [17]. Furthermore, a study using Cerebrolysin employed a much broader range of points across the body (e.g., BL22, BL23, BL24), indicating a systemic approach rather than one focused solely on the knee [18].

4. Final remarks and limitations

Recent studies show that pharmacopuncture is an effective treatment for various knee conditions. It significantly reduces pain and improves function and quality of life for knee osteoarthritis, chronic knee pain, and meniscus tears. The therapeutic effects seem to come from the combined action of the injected substance and the stimulation of specific points.

However, the findings are not consistently positive across all measures. For instance, one study found that while pharmacopuncture was effective for pain relief on one scale, it showed no significant difference on others. The non-inert placebo was noted as a methodological failure that may have undermined the study's results.

Despite the promising findings, the current body of literature has several other limitations that need to be addressed in future research. Many studies on pharmacopuncture for knee conditions have a limited number of participants and lack standardised protocols, which can make it difficult to compare results across trials. Some of the reviewed studies also did not specify the exact composition of every pharmacopuncture used, and some had no specified injection sites, highlighting a need for more detailed reporting.

Moreover, a significant limitation in some of the studies is that their findings are diluted because they report on the combined effects of multiple treatments rather than isolating the results of a single intervention. This makes it difficult to determine the specific contribution of each therapy to the overall outcome.

In addition, a limitation is the lack of a robust study design in many of the included reports. Since some studies are not proper randomised controlled trials, some of our conclusions are based on observational studies.

To fully confirm its long-term effectiveness and secure its role in integrative medicine, more rigorous and well-designed research is needed on this topic.

5. Conclusions

Based on the reviewed studies, pharmacopuncture is an effective treatment for various knee conditions, demonstrating significant improvements in pain, function, and quality of life. However, the evidence is limited by a lack of robust randomised controlled trials on the topic. Therefore, more rigorous research is essential to fully confirm its efficacy.

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