

History of Research on Pharmacopuncture in Korea

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Key Words

acupuncture, aquapuncture, herbal medicine, herbal acupuncture, review

Abstract

Objectives: This study introduces the history and types of Korean pharmacopuncture and reports trends of research on Korean pharmacopuncture.

Methods: Pharmacopuncture studies were searched from the first year of each search engine to 2014 by using seven domestic and foreign search databases. Selected studies were divided into the history of pharmacopuncture, kinds and features of pharmacopuncture, research types, and experimental and clinic studies and were then classified by year of publication, type of pharmacopuncture, disease, and topic.

Results: Pharmacopuncture can be classified into four large groups: meridian field pharmacopuncture (MFP), eight-principles pharmacopuncture (EPP), animal-based pharmacopuncture (ABP) and mountain-ginseng pharmacopuncture, which is a single-compound pharmacopuncture (SCP). The largest numbers of studies were reported from 1997 to 2006, after which the numbers decreased until 2014. Of experimental studies, 51.9%, 18.7%, 14.3%, 9% and 3.4% were on SCP, ABP, MFP, formula pharmacopuncture (FP), and EPP, respectively. Of clinical studies, 54.7%, 15.3%, 14.9%, 10.0% and 1.5% were on ABP, MFP, EPP, SCP, and FP (1.5%), respectively. Among clinical studies, case reports and case series accounted for 76.5%, followed by randomized controlled trials (RCTs, 16.4%) and non-

RCT (13.9%). Musculoskeletal diseases, toxicity and safety tests, anti-cancer effects, and nervous system diseases were mainly treated in experimental studies while musculoskeletal diseases, nervous system diseases, toxicity and safety tests, and autonomic nerve function tests were addressed in clinical studies. Bee venom (BV) was the most frequently-used pharmacopuncture in mechanism studies. Pharmacopuncture was mainly used to treat musculoskeletal diseases.

Conclusion: Pharmacopuncture and studies of it have made great progress in Korea. Studies on BV pharmacopuncture and musculoskeletal diseases accounted for most of the studies reported during the review period. Research on the types of pharmacopuncture and diseases has to be expanded. Especially, studies on the use of MFP and EPP for treating patients with various diseases are needed.

1. Introduction

Pharmacopuncture is a new acupuncture treatment in traditional Korean medicine (TKM) combining acupuncture based on the meridian theories and herbal medicine based on Qi and flavor theories [1]. Pharmacopuncture injects herbal medicine extract at acupuncture points related to diseases, tender points, or positive reaction points based on meridian theory. Pharmacopuncture treats diseases by regulating body function and improving the pathological condition of the body [2].

'Aqua-acupuncture' (AA) was developed in China and has been used since the 1950s. AA is regarded as an advanced dosage form because pill-type herbal medicine and all kinds of medicines that can be injected intramuscularly, from herbal medicines to Western

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medicines, have been used as materials in AA. Various experiments have studied AA as a union of Chinese and Western medicine; however, in studies involving AA the theory of traditional Chinese medicine (TCM) tends to be treated poorly [3]. In contrast, pharmacopuncture in Korea is exclusively associated with TKM, i.e., meridian theories, traditional herbal formulas, and Qi and flavor theories, because legal regulations keep TKM doctors from using Western medicines. The aim of this article is to introduce the history of Korean pharmacopuncture and the types of Korean pharmacopuncture and to report trends in research on Korean pharmacopuncture.

2. History of Pharmacopuncture in Korea

The definitive origin of pharmacopuncture in Korea is not known, but pharmacopuncture is presumed to have been used since the early 20th century based a report on pharmacopuncture in the Kwonup newspaper in 1914 [1]. In the book "God's Medicine (神藥)", Il-Hun Kim claimed that pharmacopuncture, such as the three treasure injection (三寶注射), the three treasure injection to tonify blood (三寶補血注射), and so on, had been manufactured and used before 1945. Not only the dosages and the indications of diseases, but also the manufacturing methods of three treasure injection, which adds Fel ursi, Bezoar, and Moschus to distilled water (three treasure water) extracted and distilled three times from the brain of a domestic duck, were recorded in detail in "God's Medicine (神藥)". Injections of bee venom (BV) and snake venom were also introduced. Kim's injection method proved to be the beginning of pharmacopuncture and provided a clue that the diverse treatment methods in Korean medicine should be tried as western medicine was being introduced [3].

The real research on pharmacopuncture in Korea began with Sang-Chun Nam in the early 1960's. After he had done research on the extraction of raw herbs and animal products, such as deer antler, astragalus, ginseng, *Ziziphi spinosae semen* (Chinese date seed), he published "Meridian Injection Treatment" in the Korean Pharmaceutical Industry News in 1965, after which he published "Meridian, Volume 1" in 1967. After that, he consistently published book and articles reporting on advances in his theory. He thought that subcutaneous fiber induration palpitation was the meridian reaction that resisted the six excesses of wind, cold, summer heat, dampness, dryness, and fire, so he asserted that he had found the true nature of the meridian. He classified the meridian field (MF) into six types, wind MF, fire MF, heat MF, dry MF, cold MF, and damp MF, according to the meridian reaction [1, 3, 4]. Han-Seong Kim reported "The practical research about the analgesic effect of *Ziziphi spinosae semen*" in 1978 and tried to popularize pharmacopuncture among Korean medicine doctors [5].

In his book "Miraculous Pharmacopuncture Treatment", Jung-Un Kim began in 1980 to use pharmacopuncture distilled and extracted from herbal formulas based on the eight principles and the theory of TKM. He diversified eight-principles pharmacopuncture (EPP)s according to conventional diagnosis methods such as eight prin-

ciples and visceral pattern identification and developed the pharmacopuncture treatment. As a result of his work, EPP can be applied to the treatment of patients with various diseases [6]. Since then, pharmacopuncture therapy has been practiced in Korean medicine clinics, and many research results have been reported. Therefore, one can conclude that pharmacopuncture therapy has developed rapidly in Korea.

Much scientific research on pharmacopuncture has been performed since the Korean Pharmacopuncture Institute (KPI) was established in 1990. Pharmacopuncture has used different terms, such as AA, acupuncture point injection therapy, and herbal acupuncture, but the KPI standardized the terminology as pharmacopuncture in 1990 [3, 7].

3. Type of Pharmacopuncture

Meridian field pharmacopuncture (MFP) is a unique theory and treatment developed by Sang-chun Nam based on clinical experience and research. MFP is a therapy that injects extracts from raw herbs and animal products, such as ginseng, deer antler, astragalus, and *Ziziphi spinosae semen*, into the induration area (meridian body) to prevent diseases and to treat patients with those diseases. When a disease occurs, the human body consumes much lubrication to produce Qi to resist the disease. In this process, fiber induration is formed, and this is called the meridian body (MB). The MB is easily palpated at acupuncture points, the upper part of the periosteum, ligaments, and tendons, and is formed in the muscles of the abdomen and the thigh. An imbalance in the body occurs during the process of vital activity and induces an imbalance in the six factors. The action to be triggered by the MB in order to treat the imbalance is called a meridian action. The MB supplies body lubrication (潤) to each organ and defends the external pathogens and six excesses: wind, cold, summer heat, dampness, dryness, and fire. The MB tries to prevent a sickly constitution and decrepitude, balances the six sources, and promotes pain and induces fever or perspiration, both of which help to expel foreign substances. The particular areas of the body, which express the identical properties of the acupuncture points and the MB in the part of body to diagnose and treat, are called the MF. The MF is divided into the heat MF and the cold MF. The heat MF includes the wind, heat, fire, and dry MFs and is formed in the area above diaphragm. The cold MF includes the cold and damp MFs [1, 4].

The MB generates Qi and consumes lubrication to overcome a disorder. Body lubrication is the nutrients, and Qi is an energy. Both are used in the prevention and the treatment of decrepitude and weak constitution. Diseases can be diagnosed and treated by using the principles of the MF and the MB. Aromatic and oil-based pharmacopuncture, two types of MFP, are applied to the MB or to responsive points related to the disease. Aromatic pharmacopuncture is used for acute pain disorders caused by Qi stagnation and Blood stasis and consists of Carthami-flos pharmacopuncture (CF), *Juglans sinensis* dode pharmacopuncture (JSD), *Cervi cornu parvum* pharmacopuncture (CC) and so on, whereas oil-based pharmacopuncture is ad-

ministrated for kinetic disorders caused by the deficiency of body lubrication and consists of BUM (Fel ursi + Bezoar + Moschus) and BU (Fel ursi + Bezoar bovis) [1, 8].

EPP is the method of treating disease by using pharmacopuncture distilled and extracted from herbs based on the eight principles of Korean medicine, Yin/Yang, internal/external, cold/heat, and deficiency/excess, and on the syndrome differentiation of Korean medicine. In EPP, a distilled extract is injected into an alarm point, a transport point, other important acupuncture points related to the illness, and tender points to treat the diseases. The distilled herbal extract of EPP contains aromatic substances that are the energy of Qi. EPP is effective when symptoms are accurately diagnosed and treated by using the proper EPP based on the eight principles and can be applied to treat various diseases because EPP does not induce tolerance, toxicity, and addiction. EPP has various types, such as hwangyeonhaedoktang pharmacopuncture (HHP), anti-inflammatory pharmacopuncture (AIP), neutral-nature blood-stasis pharmacopuncture (NBSP), liver yang rising pharmacopuncture, and so on. For example, liver yang rising pharmacopuncture, among EPP, is applied to relieve the hypertension and palpitation caused by ascendant hyperactivity of liver yang [1, 6].

Animal-based pharmacopuncture (ABP) consists of BV, sweet bee venom (SBV) and Scolopendran (蜈蚣) pharmacopuncture (SP), all three of which contain toxic ingredients, Placenta (紫河車) pharmacopuncture (PP), and so on. In addition, much research has focused on ABP in attempts to develop anti-cancer medications or anesthetic agents by using the toad venom, as well as remedial agents to treat specific diseases by using viper venom, and so on. Such research will contribute to expanding the scope of TKM.

Bee venom pharmacopuncture (BVP) is a treatment combining acupuncture stimulation and the pharmacological action of BV extracted from the poison sac of a live honey bee (*Apis mellifera*) and refined, with the BVP being injected at acupuncture points. The BV therapy conducted in Western countries generally injects the BV subcutaneously into the region of pain or at trigger points while the BVP in Korea is applied to not only trigger points and regions of pain but also acupuncture points that are selected by using a diagnosis based on syndrome differentiation. Even a small quantity of BV can provide a large stimulus and induce anaphylactic shock or critical injury. Therefore, the proper protocols to use BVP and the skills to protect against possible side effects have to be acquired before clinical application [9, 10]. BVP has been reported to have anti-inflammation, analgesia, antipyretic action, activating blood (活血), anticonvulsant, and reinforcement of immunization effects, as well as others. Thus, BVP is applied to treat autoimmune diseases, cancer, painful diseases, and musculoskeletal diseases, such as lumbar spinal stenosis, herniation of an intervertebral disc, arthritis, neuralgia, myofascial pain syndrome, frozen shoulder, and so on [9, 10].

SBV is a pharmacopuncture that was developed to reduce the side effects, such as anaphylactic shock, of BVP and that contains refined melittin, molecular weight 2836, isolated from BV; 40% – 50% of BV is melittin. Based on

the principle that core allergens such as phospholipase A2 (PLA2) and other ingredients have molecular weights of more than 10,000, molecular peptides with molecular weights of more than 10,000 are removed from BV by using a protein separation technique, gel filtration. Not only does the use of SBV result in fewer local allergic and systemic immediate hypersensitive reactions than BVP does, the effect of SBV is as good as or even better than that of BVP. Furthermore, a high dosage of SBV can be applied to patients with severe symptoms at an early stage of treatment, and SBV can be injected at most acupuncture points [1, 11, 12].

PP is an ABP that is extracted and hydrolyzed from the villi tissue of the placenta. PP is generally injected into major acupuncture points of meridians, the alarm point, and the transport point to treat diseases. Placenta contains estradiol, progesterone, acetyl glucosamine, D-galactose, mannose, amino acids, cellular growth factors, interferons, interleukins, colony-stimulating factors, diverse hormones and precursors, and so on. PP is known to have the effects of promoting growth, preventing infections, increasing resistance, and improving liver function. PP is applied to treat patients with dysmenorrhea, sleep disorders, increased skin temperature, asthma, hwa-byung, and so on [13-16].

SP is an ABP extracted from the giant scolopendrid centipede (*Scolopendra subspinipes mutilans*), whose head, legs, and tail have been removed. The treatment method combines the stimulation provided by acupuncture with the pharmacological action of the extract derived from the centipede. The centipede contains toxins, such as histamine and hemolytic proteins, the main ingredients of which are alanine, glycine, glutamic acid, and 16 types of amino acid, such as proline, arginine, asparagine, serine, and so on. It also contains tyrosin, leucine, formic acid, fatty oil, cholesterol, and so on. However, the head, legs, and tail, which contain the toxin, are removed before extraction, and the fatty oil is eliminated during extracting process [17, 18]. SP is used to treat entrapment neuropathy, inflammation diseases, herniation of a lumbar intervertebral disc, neuropathic pain, and so on because SP's pharmacological actions include central inhibition, anti-inflammation, analgesic, anti-spasm, and anti-bacterial effects, a lowering of the blood pressure, an improvement of blood circulation, and regulation of immunity. A skin test has to be performed before the SP procedure. SP is injected into the ashi points of the primary painful area, primary points pertaining to specific diseases, alarm and transport points, and five phase (transport) points [17, 18].

Mountain ginseng pharmacopuncture (MGP) is a typical single-compound pharmacopuncture (SCP) widely used in Korean medical clinics. MGP is a new type of pharmacopuncture distilled and extracted from either mountain-cultivated ginseng or mountain wild ginseng as identified by using a specific gene analysis technique. MGP was first injected into a vein in Korea. According to analyses using gas chromatography (GC) or GC-mass spectroscopy (MS), MGP contains diverse aromatic substances with low molecular weight between 86 – 213, which are presumed to be flavonoids, such as quercetin, hesperidin, and anthocyanidin, and sesquiterpene compounds, such as pan-

Table 1 Type of research done in clinical studies

Research type	n	%
Case report & series	276	67.5
Non-RCT	57	13.9
One group pre-post test	9	2.2
RCT	67	16.4
Total	409	100.0

RCT, randomized controlled trials.

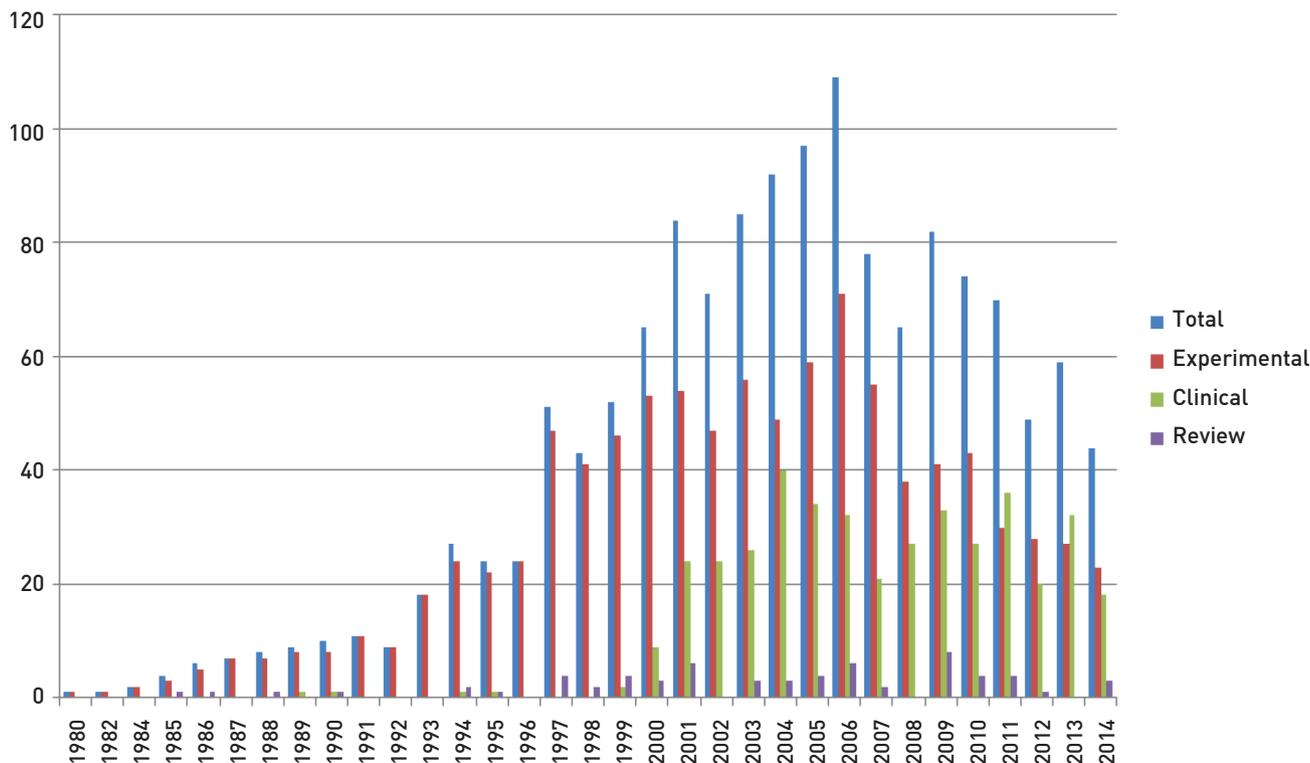
acene and β -elemene [19, 20]. The aromatic substances of MGP have been reported to have no toxicity, to have anti-oxidation and anti-cancer effects, to prevent normal cell from anti-tumor agents, and to inhibition cancer metastasis. MGP of high dosage ranging from 20 mL to 60 mL can be injected intravenously to treat most deficient conditions, especially Qi deficiency, terminal-stage cancer, immune diseases, and intractable diseases; it can also be used to help patients undergoing chemotherapy [19, 20].

4. Pharmacopuncture Research in Korea

According to reports found through the search engines (Pubmed, Scencedirect, EBSCOhost search databases, Korean Studies Information Service System (KISS), National Discovery for Science Leaders (NDSL), Science and

Technology Society Village, and Oriental Medicine Advanced Searching Integrated System (OASIS)), studies of pharmacopuncture have been reported since the 1980s. For the first ten years, few studies were published, but after the KPI was established in 1990, the number of studies started to increase. That number dramatically increased from 1997 to 2006, after which it decreased. Because comprehensive experimental studies are taken in large part from initial studies, the number of such studies has decreased from 2007 as the number of initial experimental studies has decreased. However, the number of clinical study has increased from 2000, and even more clinical studies than experimental studies were reported from 2011 to 2013 (Fig. 1). Among clinical studies, case reports and case series accounted for 67.5% of all such studies, followed by randomized controlled trials (RCTs) at 16.4%, non-RCTs at 13.9%, one-group pre-post tests at 2.2% (Table 1).

In 1990, the KPI was founded, and it systematically provided Korean medical doctors with pharmacopuncture so that they became more and more interested in pharmacopuncture, which seemed to lead to more and more research. Until 2006, various experiments seem to have been conducted to find diverse ingredients in the herbal and animal extracts used for pharmacopuncture. After pharmacopuncture had become established as a Korean medical treatment, various clinical case reports or case series were published from 2007; RCTs were reported as well. Among clinical studies, case reports or case series accounted for the highest number (67.5%), followed by RCTs at 16.4% and non-RCTs at 13.9%.

**Figure 1** Papers published on pharmacopuncture by year.

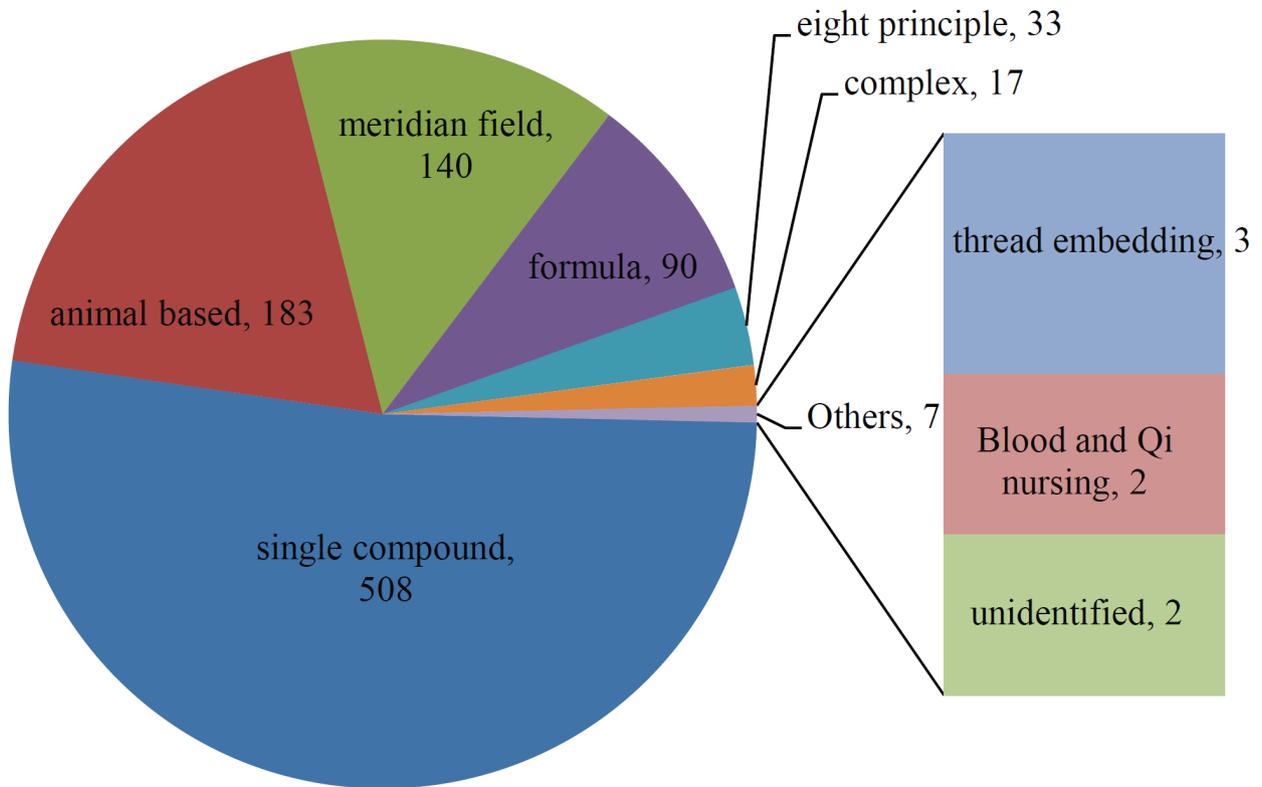


Figure 2 Types of pharmacopuncture and numbers of experimental studies including *in-vitro* and *in-vivo* studies.

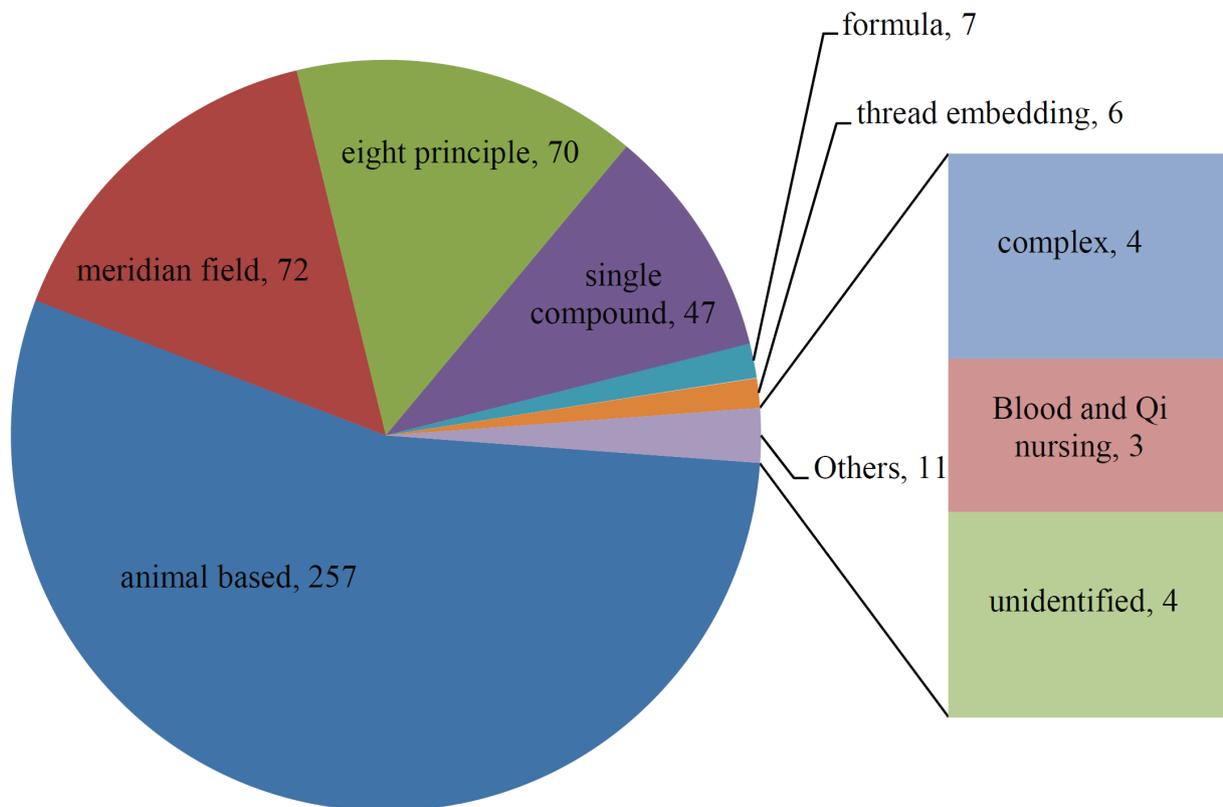


Figure 3 Types of pharmacopuncture and numbers of clinical studies.

Table 2 Diseases and topics on pharmacopuncture in experimental and clinical studies

Diseases and topics	Experimental study (n) (%)	Clinical study(n) (%)
Musculoskeletal diseases	142 (14.9)	181 (44.3)
Toxicity & safety tests	105 (11.0)	17 (4.2)
Anti-cancer effects	89 (9.3)	17 (4.2)
Nervous system diseases	82 (8.6)	93 (22.7)
Circulatory diseases	75 (7.9)	7 (1.7)
Anti-inflammatory effects	63 (6.6)	1 (0.2)
Antioxidant effects	54 (5.7)	0 (0.0)
Endocrine diseases	51 (5.3)	1 (0.2)
Urogenital diseases	45 (4.7)	10 (2.4)
Autonomic nerve functions	0 (0.0)	17 (4.2)
Liver injuries	38 (4.0)	0 (0.0)
Digestive diseases	32 (3.4)	3 (0.7)
Immune disorders	27 (2.8)	0 (0.0)
Autoimmune diseases	0 (0.0)	2 (0.5)
Respiratory diseases	27 (2.8)	8 (2.0)
Obesity	23 (2.4)	3 (0.7)
Anti-allergic effects	13 (1.4)	3 (0.7)
Ingredient analyses	18 (1.9)	2 (0.5)
Body reactions	0 (0.0)	9 (2.2)
Kidney injuries	12 (1.3)	0 (0.0)
Gynecological diseases	11 (1.2)	5 (1.2)
Skin diseases	10 (1.0)	17 (4.2)
Pediatric diseases	5 (0.5)	0 (0.0)
Acupuncture sensations	0 (0.0)	2 (0.5)
Antibacterial treatments	5 (0.5)	0 (0.0)
Syndrome differentiation	3 (0.3)	0 (0.0)
Mental disorders	3 (0.3)	6 (1.5)
Antibiotic effects	3 (0.3)	0 (0.0)
Physiology	2 (0.2)	0 (0.0)
Ophthalmic diseases	2 (0.2)	1 (0.2)
Pharmacopuncture needles	2 (0.2)	0 (0.0)
Biliary tract diseases	0 (0.0)	1 (0.2)
Otolaryngologic diseases	0 (0.0)	1 (0.2)
Placebos	0 (0.0)	1 (0.2)
Fatigue	0 (0.0)	1 (0.2)
Others	1 (0.1)	0 (0.0)
Metabolic diseases	1 (0.1)	0 (0.0)
Sasang constitution	1 (0.1)	0 (0.0)
Total	955 (100.0)	409 (100.0)

The most common experimental studies were of SCP, followed by studies of ABP (18.7%), MFP (14.3%), formula pharmacopuncture (FP) (9%) and EPP (3.4%) (Fig. 2). The

reason for this seemed to be the large number of investigations of various herbs for use in pharmacopuncture. Herbs used in SCP studies were *Panax ginseng* (2.6%),

Table 3 Diseases and topics on pharmacopuncture in experimental and clinical studies in animals

Diseases and topics	Experimental study (n) (%)	Clinical study (n) (%)
Musculoskeletal diseases	0 (0.0)	1 (33.3)
Respiratory diseases	0 (0.0)	1 (33.3)
Skin diseases	0 (0.0)	1 (33.3)
Total	0 (0.0)	3 (100.0)

Angelica Gigantis (2.1%), *Scutellaria baicalensis* (1.8%), *Astragali Radix* (1.6%), *Mountain-ginseng* (1.3%), *Salvia miltiorrhiza* (1.0%), *Ephedrae Herba* (1.0%), *Artemisia asiatica* Nak (1.0%), BVP (13.6%), PP (1.8%), and SP (1.2%) were mainly investigated in ABP studies. For MFP, *Cornu Cervi Parvum* (5.1%), *Juglandis Semen* (3.3%), *Carthami Semen* (3.3%), BUM (1.7%) and BU (1.4%) were studied, and for EPP, AIP (1.0%), HHP (1.0%) and NBSP (0.9%) were studied.

For clinical reports, studies of ABP (54.7%) were most common, leading those of MFP (15.3%), EPP (14.9%), SCP (10.0%) and FP (1.5%) (Fig. 3). Studies of BV (34.4%) led those of ABP in clinical reports due to their having the highest usage in clinics, followed by Placenta (9.4%), SBV (4.8%), and Scolopendra (4.8%). In research on MFP, *Carthami Semen* (6.4%), BUM (3.0%), *Cornu Cervi Parvum* (2.6%), BU (2.0%) and *Juglandis Semen* (1.4%) were studied, and in research on EPP, HHP (6.2%), AIP (3.6%), NBSP (3.2%) and kidney yin-deficiency pharmacopuncture (腎陰虛) (0.6%) were studied. For SCP, MGP was studied the most, followed by *Astragali Radix* (0.6%), *Zizyphi Spinosi Semen* (0.4%), *Zingiber officinale* (0.4%), *Rehmanniae Radix Crudus* (0.4%), *Harpagophytum Procumbens* (0.4%) and so. The types of pharmacopuncture used in actual Korean medical clinics were similar to the types of pharmacopuncture researched in clinical studies, and the results of clinical studies about ABP, especially BV and SBV, have been applied in clinics more frequently than the results of studies on MFP and EPP have.

Diseases studied in experimental studies, in decreasing order of frequency, were musculoskeletal diseases, nervous system diseases, circulatory diseases, endocrine diseases, urogenital diseases, digestive diseases and so on. In addition, toxicity and safety; anti-cancer, anti-inflammatory, and anti-oxidant effects; and liver injuries were studied, again in order of decreasing frequency. Diseases studied in clinical studies, in decreasing order of frequency, were musculoskeletal diseases, nervous system diseases, skin diseases, urogenital diseases, respiratory diseases, circulatory diseases, mental disorders and so on; also studied were toxicity and safety, autonomic nerve functions, anti-cancer effects, and body reactions, again in decreasing order of frequency. Musculoskeletal diseases were the most studied diseases; nervous system diseases, toxicity & safety tests, and anti-cancer effects were also investigated in many studies (Table 2).

Studies on animal diseases are rarely reported in Korea, and when they are, they are usually case reports. Among animal diseases, dog diseases such as canine demodicosis,

canine tracheal collapse, and canine intervertebral disc disease were studied (Table 3).

5. Discussion & Conclusion

After the invention of and the dissemination of information on pharmacopuncture, studies on pharmacopuncture have been actively pursued since the late 1990s. Though the history is short, progress has been great. Domestically, studies searching for the various ingredients in the animal and herbal extracts used for pharmacopuncture have been numerous. Because pharmacopuncture is injected, many toxicity and safety tests have been conducted. In clinical reports, studies on ABP outnumber those on MFP and EPP. BVP as a SCP was most frequently investigated in experimental/clinical studies and mechanism studies. The conditions most frequently addressed in experimental/clinical studies were musculoskeletal diseases because most patients who had visited TKM clinics suffered from musculoskeletal diseases.

Pharmacopuncture is one of the unique treatments of TKM and is considered to have strong potential for further development. According to the trend in current research, it can be applied to treat various diseases. Furthermore, the clinical use of MFP and EPP should be studied. Applying traditional Korean medicine to experimental studies of MFP and EEP is difficult, so clinical studies should be the focus. As experimental research, not only constant studies of toxicity and safety but also pharmacodynamic studies on such topics as the mechanism through which pharmacopuncture exerts its effect, as well as absorption and metabolism, seem to be needed.

Conflict of interest

The authors declare that there are no conflict of interest.

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