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Review Article

Systematic Review of Hominis Placenta Pharmacopuncture in English and Korean Literature

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ABSTRACT

Background: Hominis placenta (HP) is used in Korean medicine to tonify qi and blood, and enrich yin and tonify yang. HP has been reported to have therapeutic effects.

Methods: A survey of international and Korean electronic databases was conducted using the search terms "hominis placenta pharmacopuncture" and "hominis placenta extract". The search was limited to material published up to May 31, 2017.

Results: A total of 83 studies were included in this systematic review: 50 were clinical studies, 25 were basic studies, and 8 were other types of study. Among clinical studies, the most frequently treated disease groups were musculoskeletal diseases and nervous system diseases. *In vitro* studies were conducted mainly on anti-inflammatory, analgesic, and anti-cell necrosis models. Most of the *in vivo* studies were performed in rheumatoid arthritis or diabetic complications models.

Conclusion: HP pharmacopuncture has effects in the treatment of various diseases. Further large-scale randomized controlled trials are needed to improve the level of evidence for HP pharmacopuncture. It would be helpful if future *in vitro* and *in vivo* studies could identify the mechanism of action of HP pharmacopuncture.

Introduction

Hominis placenta (HP) is prepared from the placenta of healthy pregnant females and is used in Korean medicine to tonify qi and blood (補氣養血), and enrich yin and tonify yang (滋陰補陽). HP is of interest in modern medicine because it is a rich source of bioactive substances such as polydeoxyribonucleotides, RNA, DNA, peptides, amino acids, enzymes, and trace elements [1,2]. HP has been reported to have therapeutic effects, including anti-inflammatory, anti-viral, anti-oxidative, anti-mutagenic and analgesic properties [3–5]. In hominis placenta pharmacopuncture (HPP), HP is diluted and filtered in normal saline. In clinical practice, HPP is used to treat various diseases such as gynecological conditions, skin issues, and pain.

There have been two systematic reviews on HPP: one in 2008 on the treatment of bronchial asthma with HPP [6], and one in 2012 on Korean clinical HPP studies [7]. As these two reviews were limited to clinical studies on asthma and Korean studies, there is currently an incomplete picture of HPP application. This systematic review of HPP that includes basic studies and those performed outside Korea is timely and can help to establish the clinical evidence for HPP and suggest future research direction.

Materials and Methods

The electronic databases that were surveyed for this review were:

International—PubMed, Cochrane Library, China National Knowledge Infrastructure;

Korean—Korean Traditional Knowledge Portal, Oriental Medicine Advanced Searching Integrated System, Research Information Services, National Assembly Library, Korean Medicine Database, National Discovery for Science Leader, Korea Citation Index.

The search terms "hominis placenta pharmacopuncture"

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and "hominis placenta extract" were used. "Jahageo (紫河車)" and "jahageo yagchim (紫河車 藥鍼)" were also used to search the Korean databases. For the China National Knowledge Infrastructure database, we used the cross-language search function.

The search was limited to material published up to May 31, 2017.

Results

A total of 308 studies were found (Table 1), which included *in vitro* studies, *in vivo* studies, and clinical studies. Almost three-quarters (225 papers) were excluded from the study because they were duplicates (194 papers), not related to HPP (29 papers), and because the full-text article could not be obtained (2 papers). Of the 83 papers that were included for review (Fig. 1), 50 were clinical studies, 25 were basic studies, and eight were studies on ingredients, manufacture and content of HPP (Table 2).

Table 1. Studies Found in the List of Databases Searched

Database	Studies found (*n*)
PubMed	7
Cochrane Library	5
CNKI	7
Korean Traditional Knowledge Portal	82
OASIS	36
RISS	52
National Assembly Library	46
Korean Medicine Database	19
NDSL	43
Korea Citation Index	11
Total	308

CNKI, China National Knowledge Infrastructure; OASIS, Oriental Medicine Advanced Searching Integrated System; RISS, Research Information Services; NDSL, National Discovery for Science Leader.
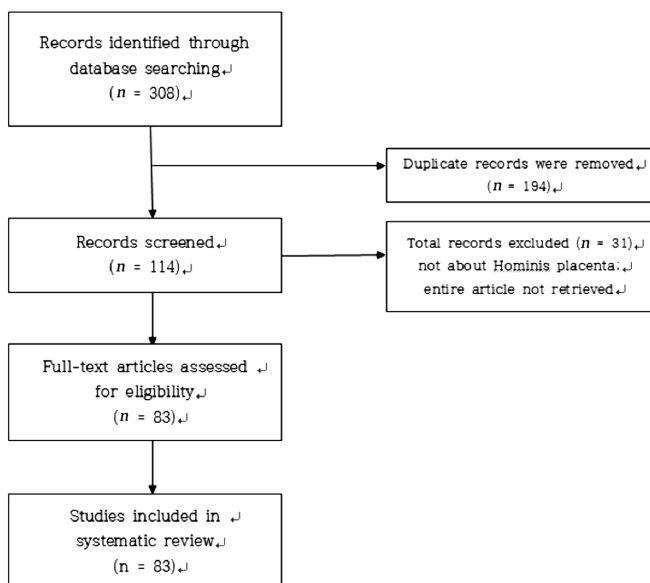

Fig. 1. Flowchart showing how studies were selected for inclusion.

Table 2. Classification of Studies

	No. of studies(*n*)
Clinical studies	50
Randomized controlled trials	4
Non-randomized controlled trials	12
Before and after studies	4
Case reports	30
Basic studies	25
In vitro studies	7
In vivo studies	15
In vitro & *in vivo* studies	3
Other types of studies	8
Total	83

Clinical studies

Disease

The most frequently addressed disease groups among the 50 clinical studies were musculoskeletal diseases (12/50, 24%) and nervous system diseases (12/50, 24%). The rest included gynecological, respiratory, psychiatric, and dermatological diseases, and stroke. There was one study each on anemia, andropathy, and chronic fatigue (Fig. 2).

With regard to specific diseases, Bell's palsy was the most common (8 studies), followed by insomnia (3 studies), and dysmenorrhea (2 studies).

There were three clinical trials of the effects of HPP in healthy people: the reaction of the body after HPP treatment [8], and change in body temperature after HPP treatment [9,10].

Number of patients

Of the 20 randomized controlled trials (RCTs), non-RCTs, and before-and-after studies, six studies involved fewer than 30 patients, seven studies involved 31–40 patients, five studies involved more than 40 to 60 patients, and two studies involved more than 60 patients (Fig. 3). The majority of case reports (20/30, 66.7%) were of only one patient. Five case reports were of two patients, four reports were of three patients, and only one report was of four patients.
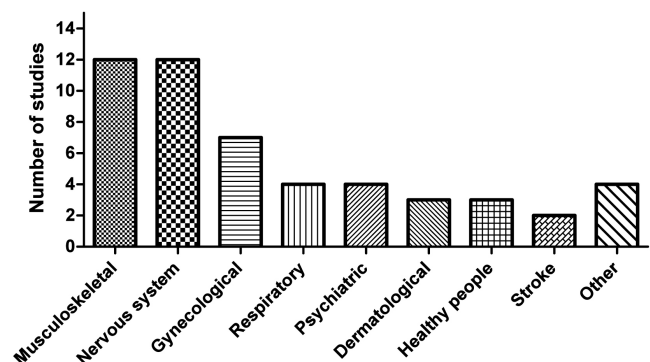

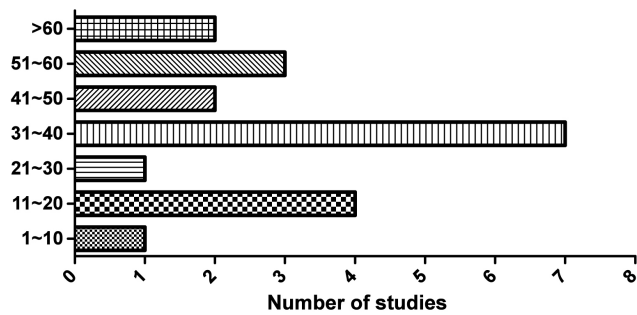Fig. 2. Number of studies by disease groups.

Fig. 3. Number of patients in the studies.

HPP treatment

Various doses of HPP were injected at a single acupoint: 0.1 ml (10/50 studies, 20%), 0.2 ml (10/50, 20%), 0.3 ml (4/50, 8%), 0.4 ml (3/50, 6%), 0.5 ml (3/50, 6%), and 1.0 ml (3/50, 6%). However, 17 studies (34%) did not mention injected dose at single acupoints.

The total dose of HPP that was administered during treatment also varied: 2.0 ml (3/50 studies, 6%), 1.0 ml (10/50, 20%), 0.5 ml or more to less than 1.0 ml (7/50, 14%), and less than 0.5 ml (4/50, 8%). There were 26 studies that did not mention total dose.

The number of times that patients were treated per week varied: once a week (1/50 study, 2%), twice a week (8/50, 16%), three times a week (17/50, 34%), five to six times a week (6/50, 12%), and even daily (8 studies) and twice daily (1 study) treatments. In three studies, only one treatment was performed before the study ended. In two studies, treatment frequency gradually changed from high frequency to low frequency. In four studies, no mention was made of how often patients were treated.

Duration of the study period also varied, with treatments completed within: 1 week (2/50 studies, 4%), 2 weeks (6/50, 12%), 4 weeks (14/50, 28%), 8 weeks (14/50, 28%), and more than 8 weeks (8/50, 16%). Three studies (6%) ended with only one treatment performed, and three studies (6%) did not mention treatment duration.

Concurrent treatment

Of the RCTs, non-RCTs, and before-and-after studies, almost half (9/20, 45%) were on HPP with no concurrent treatment. The remaining studies (11/20, 55%) included concurrent treatment in both control and experimental groups. Concurrent treatments comprised acupuncture (12 studies; 2 on electroacupuncture), herbal medicine (6 studies), moxibustion (1 study), and physical therapy (4 studies). Seven studies had combined concurrent treatment of two or more Korean medicine therapies.

Of the case reports, only 1 study (3.3%) did not have concurrent treatment. Twenty-five studies (83.3%) had combined concurrent treatment of two or more Korean medicine therapies such as catgut embedding, external therapy, other pharmacopuncture, bee venom and chuna.

Side effects

Only one study [11] reported on side effects. Patients (5/34, 14.7%) had fever and itching that subsided after 30 minutes.

RCTs

The subjects of the four RCTs were: postpartum symptoms, dysmenorrhea, leg spasticity of stroke patients and Bell's palsy.

Kim et al's study [12] was on the effects of HPP on postpartum women's feeling of heat, sweat and thirst. Women in the control and HPP treatment groups were injected with normal saline or HPP, respectively, at CV4 and BL23. Thirst, as assessed by visual analog scale, was significantly decreased in the HPP group compared to the control group, which suggests that HPP treatment is useful for postpartum women.

Kim et al [13] evaluated the effects of HPP on dysmenorrhea. Women in the control and HPP treatment groups were injected with normal saline or HPP, respectively, at CV4 and ST36, SP9 and SP6. All of the women answered the Measure of Menstrual Pain and Menstrual Symptom Severity List questionnaires. Although women in the HPP group had decreased scores compared to the control group, the difference was not significant.

Rho [14] investigated the effects of HPP on leg spasticity in stroke patients. Patients in the control and HPP treatment groups were injected with distilled water pharmacopuncture or HPP, respectively, at ST36, GB34, BL55, BL56, and BL57. Modified Ashworth Scale, H-reflex/M-response ratio, Berg Balance Scale and Timed Up and Go (TUG) test were used for evaluation. The HPP group showed significant improvements in Modified Ashworth Scale, Berg Balance Scale and TUG while the control group did not. These results indicate that HPP may decrease lower limb spasticity and increase leg motor function in stroke patients.

Park et al's study [15] was on the effects of HPP and bee venom on Bell's palsy. Patients in the HPP and bee venom treatment groups were injected with HPP or bee venom pharmacopuncture, respectively, at BL2, ST02, ST04, and ST06. The Yanagihara scores of the bee venom group were higher than those of the HPP group, but the difference was not statistically significant. It would appear that both HPP and bee venom are equally effective in Bell's palsy.

Basic studies

There were seven *in vitro* studies, 15 *in vivo* studies, and three that were both *in vitro* and *in vivo* studies.

In vitro studies

Cells used in studies: RAW 264.7 cells were used in four studies, PCG-β cells in two studies, and one study each used BV2 microglial cells, PC12 cells, HT22 cells, B16 melanoma cells, and melanocytes.

Disease model and cell status: The inflammatory state model was used in four studies. Among the inflammatory conditions, there were two of rheumatoid arthritis and one of arthritis. Also, there were two necrosis models, one Parkinson's disease model and one vitiligo model. Two were models for studying gene expression in normal cells.

Mechanism: *In vitro* studies have been conducted mainly on anti-inflammatory, analgesic, and anti-cell necrosis models. A study of the effects of HPP in a Parkinson's disease model found that HPP protected neurons from 1-methyl-4-phenylpyridinium and toxicity, and has an anti-inflammatory effect [16]. Another study reported that HPP induces the production of reactive oxygen species and inhibits NF-kB activity in RAW 264.7 cells [17]. It has also been reported that HPP inhibits prostaglandin E2 and nitric oxide (NO) synthesis by inhibiting cyclooxygenase-2 and inducible nitric oxide synthase [18].

In particular, anti-inflammatory and analgesic effects on arthritis have been actively studied. It has been reported that by inhibiting macrophage migration inhibitory factor activity, HPP blocks the initial progression of rheumatoid arthritis [19]. HPP was also reported to inhibit tissue necrosis factor (TNF)-α activity, thereby alleviating tissue damage in a rheumatoid arthritis cell model [20]. In research on genes associated with HPP and arthritis treatment,

HPP was found to induce expression of the gene for acrosin and inhibit the expression of genes for phospholipase A2, group IB and neurofilament in RAW 264.7 cells, but there were no significant changes in the levels of gene expression [21].

In the two cell necrosis models, HPP was found to inhibit iNOS and caspase-3 and H_2O_2-induced apoptosis in PGT-b cells [22], and decrease the occurrence of H_2O_2-induced apoptotic features (nuclear fragmentation and sub-G1 phage fraction) on morphological study and biochemical analysis [23]. It has also been reported that HPP activates tyrosine and increases melanin synthesis in melanoma cells [24,25].

In vivo studies

Animals used in studies: Sprague-Dawley rats were used in nine studies, C57BL/6 mice in five studies, and BALB/c mice in three. In one study, DBA/1J mice were used in the HPP group and ICR mice were used in the control group.

Disease model and animal status: There were five studies using rheumatoid arthritis models—the most on a single disease. Three studies were on diabetic complications: two on wound healing in diabetes; one on renal dysfunction in diabetes. Two studies were on nerve injury: one on spinal cord injury and the other on sciatic nerve injury. There was one study each on Alzheimer's disease, Parkinson's disease, endometriosis, cancer, asthma and mercurialism. In addition, two studies were conducted on healthy animals to determine the characteristics of HPP itself. One study examined the toxicity and lethal dose of HPP and the other looked at the effects of HPP on blood characteristics and antioxidant enzyme activation [26,27].

Mechanism: Studies on rheumatoid arthritis have shown that HPP can inhibit early progression and relieve symptoms. HPP inhibited macrophage migration inhibitory factor activation, interleukin (IL)-6Rα and MMP-9 in a mouse model of rheumatoid arthritis [19]. By inhibition of prostaglandin E2 and cyclooxygenase-2, HPP reduced the degree of increase in capillary permeability in the early stage of rheumatoid arthritis [28]. HPP also appears to inhibit the activity of inflammatory substances and enzymes that produce inflammatory substances. A study showed that HPP significantly inhibited TNF-α and NF-kB p65 activation, synovial hyperplasia, angiogenesis and fibrosis in the synovial membrane of the knee joint of mice [20]. HPP was also observed to alleviate arthritic symptoms (heat and swelling) in adjuvant-induced arthritic rats with regard to joint appearance and the expression profiles of inflammatory cytokines (TNF-α, IL-β, IL-6) [29,30].

With regard to wound healing in diabetes, significantly faster wound closure rates were observed in the HPP-treated group than in the control group [31]. Compared to the control group, the HPP group also showed reduced localization of inflammatory cells in wounded skin, significantly increased expression of fibroblast growth factors, and thicker collagen layer. Another study reported that HPP promoted angiogenesis and affected the formation of extracellular matrix [32]. These findings indicate that HPP has beneficial anti-inflammatory and skin regeneration effects in diabetes. With regard to renal dysfunction in diabetes, a study found that HPP appears to have a renoprotective effect, possibly through suppression of transforming growth factor-β1 and fibronectin in the kidney [33].

In a mice model of Alzheimer's disease, HPP showed significant inhibitory effect on memory deficit as measured by stop-through latency and distance movement-through latency. HPP also suppressed the over-expression of IL-1β protein, TNF-α protein, malondialdehyde and CD68/CD11b [34]. HPP may be effective for the prevention and treatment of Alzheimer's disease. In Parkinson's disease, HPP treatment showed a tendency to improve movement ability and protected dopaminergic cells and fibers in the substantia nigra and striatum [16]. HPP could be a potential treatment strategy in neurodegenerative diseases.

Motor behavior tests (Basso, Beattie, Bresnahan Locomotor Rating Scale, grid walk test) and western blot in contused spinal cord rats showed that HPP treatment and electroacupuncture therapy can play a role in facilitating recovery of locomotion following spinal cord injury; in western blot, the treatments led to a significant increase in brain-derived neurotrophic factor and neurotrophin-3 synthesis [35]. Another study analyzed protein levels at the site of sciatic nerve injury after HPP was injected: western blot and immunofluorescence staining showed increased growth associated protein-43 and cell division cycle-2 protein levels. HPP treatment of cultured dorsal root ganglion sensory neurons significantly increased neurite arborization and elongation [36]. These two studies showed that HPP promotes the regeneration of injured nerves by upregulating the synthesis of regeneration-related protein factors.

In a mouse model of experimentally-induced endometriosis, HPP inhibited endometrial tissue development by decreasing expression of monocyte chemoattractant protein-1, TNF-α and cyclooxygenase-2, and inhibited endometrial neovascularization by decreasing vascular endothelial growth factor expression [37].

In an experimental tumor mouse model where colon 26-L5 cancer cells were inoculated into the mice's backs, enzyme-linked immunosorbent assay showed that HPP increased interferon-γ and decreased IL-4 production [38]. These results indicate that HPP can suppress tumor growth via a mechanism that leads to a T-helper-1 dominant immune state.

The effects of HPP on immune cells and cytokines in a murine asthma mouse model was studied; eosinophils, IL-4, IL-5, IL-13 and immunoglobulin E in the bronchoalveolar lavage fluid of the HPP group decreased significantly compared to that of the control group. The number of CD3e-/CCR3+, CD3e+/CD69+ and CD11b+/Gr-1+ cells in the HPP group was also significantly decreased compared to that of the control group [39]. HPP has beneficial effects on asthma by inhibiting the activation of immune cells and their infiltration into tissues.

When the effects of HPP in rats intoxicated with mercuric chloride were studied, the HPP group showed reduced serum creatinine, and decreased expressions of the 70-kDa heat shock protein and the 78-kDa glucose regulated protein compared to control group [40]. HPP may protect against kidney damage from mercurialism.

Other types of studies

There were eight studies that were not clinical or *in vitro* or *in vivo* studies. Among them, two studies were on the antioxidant effects of HPP and two were systematic reviews [6,7]. There was one study each on HPP ingredients, physical sensation at the site of HPP injection, manufacturing method of HPP, and quality and management of HPP.

Studies on antioxidant effects of HPP

In a study that assessed NO concentrations in a vitamin C group and a HPP group by the administration of S-nitroso-N-acetylpenicillamine (which secretes NO), it was found that while HPP is not superior to vitamin C (a potent antioxidant), HPP also significantly eradicates NO [41]. The physiological activity of HPP was assessed by measuring 2,2-diphenyl-1-picrylhydrazyl radical scavenging ability and superoxide dismutase-like activity; the results showed that HPP has excellent antioxidant effects [42].

Systematic reviews

In a systematic review of the efficacy of HPP in bronchial asthma, the authors concluded that while HPP appears to have various effects on asthma in in vivo studies and case reports, further experiments and well-designed RCTs are needed to elucidate the mechanism of HPP on asthma [6]. A systematic review of clinical studies of HPP performed in Korea was published in 2012 [7]. The studies involved in these two systematic reviews [6,7] are all included in this study.

Other studies

Alanine and leucine were determined to be the index components of HPP (the levels found were 211.02 ± 7.28 μg/ml and 372.03 ± 7.58 μg/ml, respectively) [43]. In a questionnaire survey, patients who were injected with HPP reported feeling "dull" and "cool" sensations, which were the less strong sensations felt by patients who were injected with normal saline [44]. Dried HP can be taken 1.0–4.5 g per session and HPP can be injected 2 mL per session subcutaneously or intramuscularly [45]. With regard to the quality and management of HPP, it was suggested that a method for homogenizing the components of HPP be established [46].

Discussion

Although studies of HPP have been actively conducted, there is a lack of a systematic review of these studies. This systematic review is intended to include all national (Korean) and international journals, and it has significance as a comprehensive review that covers both clinical research as well as basic research and other research.

More than half of the clinical studies were case reports. There were only five studies (controlled and before-and-after studies) that involved more than 50 people. Clearly, the level of clinical research on HPP is still insufficient. To elucidate the efficacy of HPP, a large-scale RCT is necessary.

Among the 50 clinical studies, the most frequently treated types of disease were musculoskeletal diseases and nervous system diseases (facial palsy and spasm in particular). Patients with these conditions frequently visit Korean medicine hospitals and clinics [47]. With regard to these diseases, there are studies of bee venom and other pharmacopuncture that are similar to those of HPP [48–50]. Hence, to prove the specific efficacy of HPP as distinct from bee venom or other herbal medicine, the effects of HPP in diseases other than musculoskeletal or facial diseases should be actively conducted, for example gynecological diseases.

This systematic study also revealed that many clinical studies of HPP were performed with concurrent treatments. To determine what are the treatment effects due solely to HPP, it is advisable to eliminate the concurrent treatments. Also, side effects of HPP were reported in only one study, and most studies made no mention of safety. Future studies should aim to accurately evaluate the effects of HPP by eliminating concurrent treatments, and seek to assess the clinical safety of HPP by recording side effects.

There were many *in vitro* studies performed on inflammatory state models and *in vivo* studies on arthritis. They showed that HPP has anti-inflammatory effects via various mechanisms. These results have important implications for the treatment of arthritis with HPP in clinical practice.

The results of *in vitro* and *in vivo* studies conducted on other models suggest that HPP can be applied to various other diseases such as neurological diseases, endocrine diseases, gynecological diseases and cancer. However, these have not been as extensively studied as the arthritis and anti-inflammatory models have been. Further research should be actively conducted in these various other fields to build up the evidence base for HPP.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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