

# Traditional Medicine for Osteoarthritis

<sup>1</sup>Setareh Saei, <sup>2</sup>Fariba Shariffar

<sup>1</sup>Department of traditional pharmacy, faculty of Iranian medicine, kerman university of medical science, Kerman, Iran.

<sup>2</sup>Herbal and traditional medicine research center, department of pharmacognosy, faculty of pharmacy, kerman university of medical science, Kerman, Iran.

Received: 16 March 2020 Revised and Accepted: 16 June 2020

## Abstract

Osteoarthritis (OA) is a chronic disability which estimated to be the fourth leading cause of disability with the increasing number of aging. Many sufferers with OA are using traditional medicines such as herbal drug, acupuncture, Chinese medicine and Tuina etc. To alleviate their symptoms. In this article all relevant studies are reviewed. Four electronic databases (PubMed, Medline, Embase (OvidSP) and Cochrane Library) were searched and search language selected was English. The results suggest that various traditional medicines have significant effect on improvement of pain and stiffness for patients with osteoarthritis.

KEYWORDS: Osteoarthritis (OA), herbal drug, acupuncture, Chinese medicine

## 1. Introduction

Osteoarthritis (OA) is a chronic and degenerative disorder of synovial joints with multifactorial etiology which characterized by particular bone remodeling and degeneration of articular cartilage(1). It has been estimated that 33.6% of older people suffer from OA in the United States (2). This disease causes variable degrees of joint pain, limitation of activity, joint effusion and narrowing of the joint space, in severe cases which associated with limitation of activity and also stiffness after inactivity especially in elderly patients(3, 4). Goals of OA managing in Western medicine (WM) include pain control, improvement in the range of movement and health-related quality of life(5). In the Pharmacological medications, non-steroidal anti-inflammatory drugs (NSAIDs) have been the most prescribed pharmacological treatments for the past few years which usually associated with severe side-effects such as interference with hemostasis, Renal problems and gastrointestinal complications. Moreover, recent study showed that long-term application of NSAIDs has inhibitory effect on proteoglycan synthesis(6).

Considering different side effects of, so the use of alternative medicine for disease joints. The common alternative medicine which widely accepted by OA patients include Chinese herbal medicine, herbal patch, dry cupping, acupuncture or other alternative therapies(7, 8). Popularity of alternative medicine have been rapidly increasing among adults and previous studies showed that about 60% of adults used at least one form of alternative therapy in 2002. Another study has shown that 42% of patients referred to rheumatology clinic used complementary and alternative medicine(9). Due to the side effects and toxicity of current drugs, and also considering the prevalent use of alternative and complementary therapy among patients with OA, we explore the scientific evidence about these therapies used to treat OA and objective evidence of efficacy and safety.

## Aetiology

The etiology of OA is still not completely clear but the main risk factors related to this disease include age, genetic, inflammation and biomechanical and metabolic changes of the joints (7). Inheritance studies indicate that in 39–78% of OA cases, genetic factors underlie susceptibility of OA(10). This disease is a progressive disease characterized by depletion of the kidney and liver zang, which associated with release of proteolytic and hydrophilic enzymes. Some pathogenic factors also can obstruct blood circulation which consequently leads to pain. Functional impairment in body fluids transformation (due to spleen depletion) in over long periods, can lead to stagnation of

non-substantial phlegm (11). Stagnation of blood and phlegm leads to their accumulation in the joints which are considered as secondary pathogenic factors(12).

Moreover, several studies have revealed that anti-inflammatory and proinflammatory cytokines such as IL-1, IL-6, IL-7, IL-10, IFN- $\gamma$ , and TNF- $\alpha$  were raised in the OA joints(13, 14). Kidney and liver are the primary organ in the development of OA respectively because, the critical role of kidneys in bones formation declines with age increasing and can led to bone frail, tendons stiffening and movement impairment (15). Indeed, outgrowth of Osteophytes in bone is usually associated with OA. Beside this, the liver has nourishing and moistening functions because of his ability for store of blood and control of sinews like cartilages, ligaments and tendons(15, 16) General treatment principles for OA include diagnosis and understanding of disease pathogenesis which give consideration about root cause of a condition or branch. **The main root of OA is deficiency in kidney and liver blood which can result in invasion of pathogenic factors, phlegm stagnation and the pathogenic development of blood(17).**

## 2. OA treatment

In general , OA treatment fall in to four categories include nonpharmacologic, pharmacologic, complementary ,alternative, and surgical *therapy* . The treatment process should being with least invasive therapies and at least some treatment from the first two categories should be used for all patients with OA. The first step in OA treatment is Nonpharmacologic therapy which often starts with exercise include muscle strengthening and range of motion exercises. In Pharmacological- based strategies acetaminophen usually offer for OA patient with mild to moderate joint pain. Although it may fails to adequately relieve pain in many patients but good efficacy, and low toxicity make it as initial therapy for OA patient.

Nonsteroidal anti-inflammatory drugs ( *NSAIDs*) *therapy* including the cyclooxygenase-2 (COX-2)–specific inhibitors is often used for patients who the acetaminophen fails to control symptoms or obtain adequate symptom relief. Use of NSAIDs can be associated with some adverse effects such as gastrointestinal bleeding, blood pressure elevation and renal dysfunction(18). Some COX-2–specific inhibitors such as celecoxib and rofecoxib have lower incidence of gastrointestinal side effects(19).

Opioids are used for patients who have severe pain. They often accompanied with some adverse effect such as respiratory depression and constipation(20).

Surgical management another option for osteoarthritis patients who do not improve with pharmacologic and behavioral therapy and who loss of function should receive(21).

### **Complementary medicine for OA**

Complementary medicine (CAM) is usually defined as form of health-related practice which is based on manipulative therapy. The most common of this therapy used to treat OA includes energy therapy, mind body therapy, yoga and tai chi(22).

The use of complementary therapy is prevalent among patients with OA and recent studied support the effectiveness of these approaches on symptom control and pain of OA. Moreover, studies have also reported that at least one-third who has chronic pain used some form of Complementary therapy in the past year. Although CAM users believe that these approaches is free from adverse effects but research in CAM shown that it's not free from adverse effects(23).

Yoga is an ancient physical practice originating in ancient India which used for managing persistent pain. Yoga postures consist of breathing exercises (pranayama), and meditative practices. Although the evidence to support the therapeutic use of yoga for OA is limited but its feasibility and safety have been conducted.(24) In addition, yoga exercise may improve physical fitness and decrease body fat which are known as preventive factors for OA(25).

Energy therapies such as therapeutic touch, reiki, and healing touch are perhaps the most mysterious approaches applied in complementary medicine (CAM) for healing and prevents illness. The aim of this therapy is to remove blockages that are cause disease and delay healing.

The evidence support the use of these therapies in OA has not been established (26).

Besides that, some natural products such as Glucosamine and Chondroitin have goodefficacy in alleviating pain and improved function. Glucosamine and Chondroitin are the most widely used supplements which provide the substrate for reparative processes in cartilage. These compounds have been used for many years for relief of arthritis symptoms. Recent laboratory studies show that these compounds have capable of increasing proteoglycan synthesis in articular cartilage(27, 28) Moreover, Capsaicin cream (derived from chili peppers ) and S-adenosylmethionine are another supplements applied to reduce functional limitation(29).

Comparative trials assessing have shown CAM therapies approaches has considerable roles in managing and reduce the pain of OA. Therefore more studies is necessary for these approaches to gain appropriate dosing for the various CAM therapies(30).

### **Traditional medicine for OA treatment**

The most proposed strategies for OA treatment are the use of traditional medicines on the basis of promoting blood circulation, tonifying the kidney and liver, resolving dampness and expelling wind(31) . Indeed, most of the traditional medicines have a particular strategy which often focus on specific stage of the disease process. For example, According to the Chinese medicine, invasion of wind, cold, and dampness are the most causes of OA. So the most common therapies used in Chinese medicine includes: pills, ointment and herbs with dispersing exogenous wind and dampness capacity (32).

### **Classification of OA in traditional medicines:**

OA has been classified as a painful obstruction disease of bone known as bi syndrome. However, some recent emergent theories have argued that OA should be categorized as a disease of the sinews rather than ‘bi syndrome of bone. The main reason for this theory is that pathogenic changes of OA often occur in the articular cartilage and the tissue around joints which are classified as ‘sinews’ in some traditional medicines and considered to be an extension of the Liver(33, 34).

Moreover, the knees are considered as a Palace of tendons so any disorder in bending or straightening a joint properly can be a sign of tendon degeneration. Furthermore, blood deficiency in liver can led to lack of moistening and nourishment in sinews which may cause spasm, contraction, impaired flexion, muscle cramps and tingling(35). In addition, stasis of Liver blood led to lack of suppleness in sinews which can result in disability in functional activities, stiffness, rigidity and pain of the joints(36).Based on new hypothesis in Chinese medicine, OA is the result of combination of bi and wei syndrome. Wei syndrome is a progressive weakening of the limbs caused by a deficiency of blood, essential life energy (qi) and body fluids which considered the fundamental disorder(35).

### **Scientific evidence- base herbal therapies in OA**

Although conventional treatment of OA has an outstanding success in relief of the pain but can also accompanied with some adverse effects such as gastrointestinal and cardiovascular complications especially in long-term use(37).Numerous trials have investigated the effect of medicinal plants in treatment of OA. In a study, the effectiveness of a topical cream from *Zingiber officinalis*.on osteoarthritis has been studies and results indicated that the hebal ointment could induce significant changes in pain and stiffness of OA(32). Furthermore, some interventions can alleviate the pain and stiffness and reduce the side effects and contraindications of concomitant use of synthetic drugs (38).The effectiveness of *Harpagophytum procumbens* has been studied for pain killing in OA. The authors reported evidence for effectiveness of 60 mg harpagoside in the treatment of OA(39).

Recent study has shown that dry powder, Hyben Vital made from subtype of *Rosa canina*, has anti-inflammatory properties through reducing the generation of oxygen radicals and chemotaxis in polymorphonuclear cells (40). Moreover,the efficacy of *Populus tremula*, *Solidago virgaurea*, *Fraxinus excelsior*, *Zingiber officinalis*, *Trichosanthes kirilowii*, *Clematis mandshurica*, and *Prunella vulgaris* have been assessed in a number of studies (41, 42). The results have confirmed positive effect of these plants in reducing the pain, improving mobility and also a reduction in the dose of non-steroidal anti-inflammatory drugs. Although herbal therapy approach has shown

promising evidence in symptomatic treatment of OA, but the side effects and /or contraindications of the plants should not be ignored and not be unaware of the herb–drug interactions or risk of overdose. In general, the current evidence provide a reliable assessment of the herbal efficacy in OA which sufficiently encouraging to warrant large-scale in medicines(40).

### **Acupuncture**

Acupuncture is another form of alternative therapy for OA which widely has been used over the past two decades. Acupuncture is based on improving the flow of essential life energy (qi) and removing energy blockages related to disease processes such as elimination of inflammatory edema, and relieve pain that for sustain normal vital activities. It enhances muscle relaxation and relieves muscle spasm (43). Warm acupuncture has a significant effect on improving the symptoms in patients in a long term consumption, although it cannot eliminate the osteophytes(44). Electroacupuncture is another type of this method which can effectively alleviate the clinical symptoms in OA patients and suppresses the secretion of various inflammatory factors such as interleukin-1, interleukin-6, tumor necrosis factor  $\alpha$ , matrix metalloproteinases-3 and prostaglandin E $2\alpha$  in the knee fluid(45).

### **Traditional Chinese medicine (TCM)**

In Traditional Chinese medicine (TCM), the causes of OA are attributed mostly to various factors, such as deficiency of **blood in** Gan (Liver) and Shen (Kidney), deficiency of qi and blood, obstruction of channels, qi and blood stagnation ,attack of wind-cold, dampness evils, and long standing pathological risk factors(32). Chinese patent medicine internal use is nourishing the Gan and Shen via strengthen the muscles and bones, which can improve the body resistance to diseases. Therapeutic effect of external Chinese medicine is through unblocking the blood circulation, meridians and collaterals, fumigation, hot compressed iontophoresis and relieve local symptoms(46, 47).

A systematic review indicated that as many as 40% of OA patients have been used complementary therapies especially herbal medicines. Low adverse effects of herbal medicine in treatment of OA make it as a good alternative for individuals with long-term chronic OA. The result from 35 clinical trials demonstrated the efficacy of chine herbal medicine in treatment of OA (48-54).

However, there are still some problems during the treatment of OA with Chinese such as lack of standards for diagnosis and evaluation of efficacy and also lack of efficacy in advanced stage.

### **Search methods**

In this overview, Four electronic databases (PubMed, Medline, Embase (OvidSP) and Cochrane Library) have been used .The literature search was composed of MeSH terms for traditional medicine and osteoarthritis which were adopted for different databases. For example, the search strategy on the PubMed database was documented as follows: (Osteoarthritis [Mesh Terms] OR osteoarthritis [Title/Abstract] OR traditional medicine and osteoarthritis [Title/Abstract] OR osteoarthritis and, traditional medicine [Title/Abstract] OR, traditional medicine for osteoarthritis of [Title/Abstract] AND (Review [Publication Type] OR meta-analysis [Title/Abstract], OR systematic review [Title/Abstract] OR Meta-Analysis [Publication Type]).

## **3. Discussion**

Traditional medicine has a long history of effectiveness in the East. Several studies support the useOf traditional therapies for OA. The use of symptom multimodal management has an essential role in this approach in order to improving function and overall quality of life (55, 56). Traditional therapies approaches play roles in the pain managing, depression and anxiety. However, further study is needed to provide clear answers on whether a therapy's use is supported(23). This review investigated the evidence for traditional therapies in the treatment of osteoarthritis.

Since herbal medicines consist of numerous components instead of a single component, their mechanisms are still unknown. Moreover, because of some synergistic effects within these systems, use of whole systems research which focused on qualitative as well as quantitative analyses is also critical to capture the effects of traditional therapies and also data are needed on appropriate dosing for the various traditional therapies approach. It's also essential to consider using other new methodologies for traditional medicine which addresses the complexities of

traditional medicine interventions(21). Additionally, the quality of clinical trials of traditional medicine should also be mentioned because differences in product formulation and provider services may affect study results. So data increase, is necessary to include proven traditional medicine therapies in the multimodal management of OA. In conclusion this study indicated that traditional medicine is a popular option for patients suffering from OA with low incidence of adverse effects that may offer a much-needed alternative for individuals with long-term chronic OA. This review might provide the most promising targets for large-scale, definitive studies.

#### 4. References

1. Glyn-Jones S, Palmer A, Agricola R, Price A, Vincent T, Weinans H, et al. Osteoarthritis. *The Lancet*. 2015;386(9991):376-87.
2. Helmick CG, Felson DT, Lawrence RC, Gabriel S, Hirsch R, Kwoh CK, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States: Part I. *Arthritis & Rheumatism*. 2008;58(1):15-25.
3. Qin J, Barbour KE, Murphy LB, Nelson AE, Schwartz TA, Helmick CG, et al. Lifetime risk of symptomatic hand osteoarthritis: the Johnston County Osteoarthritis Project. *Arthritis & Rheumatology*. 2017;69(6):1204-12.
4. Robinson WH, Lepus CM, Wang Q, Raghu H, Mao R, Lindstrom TM, et al. Low-grade inflammation as a key mediator of the pathogenesis of osteoarthritis. *Nature Reviews Rheumatology*. 2016;12(10):580.
5. Felson DT, Lawrence RC, Dieppe PA, Hirsch R, Helmick CG, Jordan JM, et al. Osteoarthritis: new insights. Part 1: the disease and its risk factors. *Annals of internal medicine*. 2000;133(8):635-46.
6. Hua B, O'Brien K. Osteoarthritis and Chinese medicine: an overview of theories and evidence. *Journal of Chinese Medicine*. 2010;94:44-9.
7. Chen F-P, Chang C-M, Hwang S-J, Chen Y-C, Chen F-J. Chinese herbal prescriptions for osteoarthritis in Taiwan: analysis of national health insurance dataset. *BMC complementary and alternative medicine*. 2014;14(1):91.
8. Shen X-H, Cui Y. Progress in traditional Chinese and Western medicine treatments and nursing care of knee osteoarthritis. *Chinese Nursing Research*. 2015;2(2-3):71-4.
9. Breuer G, Orbach H, Elkayam O, Berkun Y, Paran D, Mates M, et al. Perceived efficacy among patients of various methods of complementary alternative medicine for rheumatologic diseases. *Clinical and experimental rheumatology*. 2005;23(5):693.
10. Jordan JM, Kraus VB, Hochberg MC. Genetics of osteoarthritis. *Current rheumatology reports*. 2004;6(1):7-13.
11. Wang H-m, Liu J-n, Zhao Y. Progress on integrated Chinese and Western medicine in the treatment of osteoarthritis. *Chinese journal of integrative medicine*. 2010;16(4):378-84.
12. Xiao L. Formation of the Differentiation Theory and Treatment Principle of the Bi Syndrome of Bone (Osteoarthritis) During Qin, Han and Sui Dynasties. *Journal of Fujian College of TCM*. 2004;14(2):43-5.
13. MacFarlane RJ, Graham SM, Davies PS, Korres N, Tsouchnica H, Heliotis M, et al. Anti-inflammatory role and immunomodulation of mesenchymal stem cells in systemic joint diseases: potential for treatment. *Expert opinion on therapeutic targets*. 2013;17(3):243-54.
14. Li F, Yao J, Tian H, Duan Z, Yan Y, Cao J. Correlations between Traditional Chinese Medicine syndromes and IL-1, MMP and TIMP-1 in knee osteoarthritis. *Int J Clin Exp Med*. 2017;10(10):14660-6.
15. Eckman P. Traditional Chinese Medicine-Science or Pseudoscience? A Response to Paul Unschuld. *Journal of Chinese Medicine*. 2014(104).
16. Ni M. *The Yellow Emperor's Classic of Medicine: A new translation of the Neijing Suwen with commentary*: Shambhala Publications; 1995.

17. Gong C, Liu W. Acupuncture for Knee Osteoarthritis. *International Journal of Clinical Acupuncture*. 2017;26(1).
18. Towheed T, Maxwell L, Judd M, Catton M, Hochberg MC, Wells GA. Acetaminophen for osteoarthritis. *Cochrane Database of Systematic Reviews*. 2006(1).
19. Da Costa BR, Reichenbach S, Keller N, Nartey L, Wandel S, Juni P, et al. Effectiveness of non-steroidal anti-inflammatory drugs for the treatment of pain in knee and hip osteoarthritis: a network meta-analysis. *The Lancet*. 2017;390(10090):e21-e33.
20. Shirley PY, Hunter DJ. Managing osteoarthritis. *Australian prescriber*. 2015;38(4):115.
21. Verhoef MJ, Lewith G, Ritenbaugh C, Boon H, Fleishman S, Leis A. Complementary and alternative medicine whole systems research: beyond identification of inadequacies of the RCT. *Complementary therapies in medicine*. 2005;13(3):206-12.
22. Quandt SA, Chen H, Grzywacz JG, Bell RA, Lang W, Arcury TA. Use of complementary and alternative medicine by persons with arthritis: results of the National Health Interview Survey. *Arthritis Care & Research*. 2005;53(5):748-55.
23. Nik Shafii NAH, Yaacob LH, Ishak A, Kadir AA. Traditional and complementary medicine use in knee osteoarthritis and its associated factors among patients innortheast peninsular Malaysia. *Oman Medical Journal*. 2018;33(2):148.
24. Tran MD, Holly RG, Lashbrook J, Amsterdam EA. Effects of Hatha yoga practice on the health-related aspects of physical fitness. *Preventive cardiology*. 2001;4(4):165-70.
25. Cheung C, Wyman JF, Savik K. Adherence to a yoga program in older women with knee osteoarthritis. *Journal of aging and physical activity*. 2016;24(2):181-8.
26. Bauer BA, Tilburt JC, Sood A, Li G-x, Wang S-h. Complementary and alternative medicine therapies for chronic pain. *Chinese journal of integrative medicine*. 2016;22(6):403-11.
27. Uebelhart D, Thonar EJA, Zhang J, Williams JM. Protective effect of exogenous chondroitin 4, 6-sulfate in the acute degradation of articular cartilage in the rabbit. *Osteoarthritis and cartilage*. 1998;6:6-13.
28. Fransen M, Agaliotis M, Nairn L, Votrubec M, Bridgett L, Su S, et al. Glucosamine and chondroitin for knee osteoarthritis: a double-blind randomised placebo-controlled clinical trial evaluating single and combination regimens. *Annals of the rheumatic diseases*. 2015;74(5):851-8.
29. Valdes A, Ravipati S, Poussinis P, Menni C, Mangino M, Chapman V, et al. Lipidomic profiling of human synovial fluid: metabolites generated by the soluble epoxide hydrolase are associated with increased risk of knee osteoarthritis and radiographic progression. *Osteoarthritis and Cartilage*. 2018;26:S40.
30. Ernst E. Complementary or alternative therapies for osteoarthritis. *Nature Reviews Rheumatology*. 2006;2(2):74.
31. Zhou Q, Liu J, Xin L, Song Q, Guo J, Huang D. Analysis on Traditional Chinese Medicine Prescription Patterns in 3609 Patients with Osteoarthritis Based on The Real World. *World Science and Technology-Modernization of Traditional Chinese Medicine*. 2017;19(12):1942-8.
32. Chen W-h, Liu X-x, Tong P-j, Zhan H-s, Committee OP, Committee JP. Diagnosis and management of knee osteoarthritis: Chinese medicine expert consensus (2015). *Chinese journal of integrative medicine*. 2016;22(2):150-3.
33. Yuelong C, Hongsheng Z, Jian P, Feiyue L, Shaojian X, Jinghua G, et al. Individually integrated traditional Chinese medicine approach in the management of knee osteoarthritis: study protocol for a randomized controlled trial. *Trials*. 2011;12(1):160.
34. Yang J-m, Zhang K-y, Zhang B-m. Therapeutic efficacy of tuina in treating 48 cases with knee osteoarthritis. *Journal of Acupuncture and Tuina Science*. 2014;12(3):190-3.
35. Hou P-W, Fu P-K, Hsu H-C, Hsieh C-L. Traditional Chinese medicine in patients with osteoarthritis of the knee. *Journal of traditional and complementary medicine*. 2015;5(4):182-96.

36. Zhang GG, Lee W, Bausell B, Lao L, Handwerger B, Berman B. Variability in the traditional Chinese medicine (TCM) diagnoses and herbal prescriptions provided by three TCM practitioners for 40 patients with rheumatoid arthritis. *Journal of Alternative & Complementary Medicine*. 2005;11(3):415-21.
37. Shah SMA, Akram M, Rashid A, Daniyal M, Ali B, Anjum A, et al. EPIDEMIOLOGY AND HERBAL TREATMENT OF OSTEOARTHRITIS. *Pak J Med Biol Sci*. 2017;1(2).
38. Gemmell HA, Jacobson BH, Hayes BM. Effect of a topical herbal cream on osteoarthritis of the hand and knee: a pilot study. *Journal of manipulative and physiological therapeutics*. 2003;26(5):322.
39. Gagnier JJ, Chrubasik S, Manheimer E. Harpgophytum procumbens for osteoarthritis and low back pain: a systematic review. *BMC complementary and alternative medicine*. 2004;4(1):13.
40. Rein E, Kharazmi A, Winther K. A herbal remedy, Hyben Vital (stand. powder of a subspecies of *Rosa canina* fruits), reduces pain and improves general wellbeing in patients with osteoarthritis—a double-blind, placebo-controlled, randomised trial. *Phytomedicine*. 2004;11(5):383-91.
41. Klein-Galczinsky C. Pharmacological and clinical effectiveness of a fixed phytogetic combination trembling poplar (*Populus tremula*), true goldenrod (*Solidago virgaurea*) and ash (*Fraxinus excelsior*) in mild to moderate rheumatic complaints. *Wiener medizinische Wochenschrift (1946)*. 1999;149(8-10):248-53.
42. Walker-Bone K. 'Natural remedies' in the treatment of osteoarthritis. *Drugs & aging*. 2003;20(7):517-26.
43. Teixeira J, Santos M, Matos L, Machado J. Evaluation of the effectiveness of acupuncture in the treatment of knee osteoarthritis: A case study. *Medicines*. 2018;5(1):18.
44. Li C, Huang X, Yang X, Wang Q, Huang S. Observation on therapeutic effect of warming needle moxibustion on knee osteoarthritis of deficiency-cold type. *Zhongguo zhen jiu= Chinese acupuncture & moxibustion*. 2006;26(3):189-91.
45. Wu M-x, Li X-h, Lin M-n, Jia X-r, Mu R, Wan W-r, et al. Clinical study on the treatment of knee osteoarthritis of Shen (肾)-Sui (髓) insufficiency syndrome type by electroacupuncture. *Chinese journal of integrative medicine*. 2010;16(4):291-7.
46. Ferreira AS, Lopes AJ. Chinese medicine pattern differentiation and its implications for clinical practice. *Chinese journal of integrative medicine*. 2011;17(11):818-23.
47. Berle CA, Cobbin D, Smith N, Zaslowski C. A novel approach to evaluate traditional Chinese medicine treatment outcomes using pattern identification. *The Journal of Alternative and Complementary Medicine*. 2010;16(4):357-67.
48. Bian H, Zhou C. Clinical observation of Bu Shen Zhuang Jin decoction for treatment of osteoarthritis accompanying with osteoporosis (article in Chinese). *Journal of Traditional Chinese Orthopedics and Traumatology*. 2005;17(10):37-8.
49. Cao Y, Shi W, Xu N, Shen P, Shi Y. Experimental Study on Yangxue Ruanjian Capsule in Anti-inflammation and Analgesia (article in Chinese). *Acta Universitatis Traditionis Medicalis Sinensis Pharmacologiaeque Shanghai*. 2004;18(1):49-51.
50. Chen Y, Qiu R, Shen R, Lin C, Wen W, Yang X. A clinical observation of knee osteoarthritis with treatment principle of Tonifying Kidney and Ivigorating Blood: a 49 cases report (article in Chinese). *International Medicine & Health Guidance News (China)*. 2005;11(14):114-5.
51. Dang J, Liu M, Zhang J. cases clinical trial of osteoarthritis with Qiangjinjiangu pill (article in Chinese). *Shaanxi Journal of Traditional Chinese Medicine*. 24(9):801-2.
52. Fan K. A clinical report of knee osteoarthritis with treatment of Bu Shen Zhuang Gu decoction for 35 cases (article in Chinese). *Hunan Journal of Traditional Chinese Medicine*. 2006;22(1):28-9.
53. He X, Gao L, Wei C, Chen X, Wang D. Outcome of Arthroscopic Operation Plus Administration of Qi-invigoring, Kidney-supplementing, Blood-activating Decoction on Treatment of Knee Osteoarthritis (article in Chinese). *China Journal of Orthopaedics and Traumatology*. 2005;18(8):449-51.

54. Zhen H, Wang Y, Liu X. Observation on therapeutic effect of warming needle moxibustion on chronic pelvic inflammation of cold-damp stagnation type. *Zhongguo zhen jiu= Chinese acupuncture & moxibustion.* 2008;28(10):736-8.
55. Losina E, Paltiel AD, Weinstein AM, Yelin E, Hunter DJ, Chen SP, et al. Lifetime medical costs of knee osteoarthritis management in the United States: impact of extending indications for total knee arthroplasty. *Arthritis care & research.* 2015;67(2):203-15.
56. Miller LE, Sloniewsky MJ, Gibbons TE, Johnston JG, Vosler KD, Nasir S. Long-term clinical benefit and cost-effectiveness of an 8-week multimodal knee osteoarthritis management program incorporating intra-articular sodium hyaluronate (Hyalgan®) injections. *Journal of pain research.* 2017;10:1045.