



Persian Medicine Herbal Therapies for Osteoarthritis: a Review of Clinical Trials

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Abstract

Osteoarthritis (OA) of the knee is one of the important medical complications in elderly peoples. Various pharmacological and non-pharmacological therapies are described for treatment of knee OA, but considerable side effects especially in old populations are the limiting factors. Traditional, complementary and integrative medicines have a long history in treatment of chronic diseases such as OA. Many different oral and topical drugs have been introduced for curing of OA in Persian medicine (PM) as one of the most important and historical systems of medicine. The aim of this survey was to review the clinical trials related to pharmacological treatment of knee OA with medicinal methods of PM. The main databases including PubMed, Scopus and ISI Web of Knowledge were searched and consequently eight clinical trials were achieved. Some of common dosage forms such as gel and oil and some of traditional ones like “Marham” and “Dohn” were used for treatment of OA in these studies. The investigated plants were suppressors for different pathways of inflammatory responses. Antioxidant capacity and analgesic effects were other recognized effects for some of these herbs. In clinical aspect, seven of eight papers that were presented in this study, showed a significant effect in the treatment of OA; however, more researches are required to judge these traditional therapies.

Keywords: clinical trials; herbal therapy; osteoarthritis; Persian medicine

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Introduction

Osteoarthritis (OA) of the knee is one of the main complications with chronic pain and locomotor disability that most elderly populations all around the world suffer from [1]. Estimations have shown that 10%-15% of adults over 60 are affected by some degrees of osteoarthritis [2]. Medical strategies don't exactly cure OA and the aim of treatment is mostly the relief of symptoms, improvement of joint mobility and function and improving patient's quality of life [3]. Numerous non-pharmacological and pharmacological recommendations are provided for management

of knee OA. Acetaminophen, oral and topical NSAIDs, tramadol and intra-articular corticosteroid injections are recommended as pharmacologic treatments of knee OA [4]. Although pharmacotherapy is the best common and important medical intervention for OA, adverse effects are usually considered as a limiting factor. NSAIDs are of high risk for induction of gastrointestinal toxicity and renal insufficiency in elders [5]. Topical NSAIDs are safer than orals, but they show systemic adverse reactions in old people [6]. So, it is needed to

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find new therapies for OA with minimizing adverse pharmacological reactions and improving treatment responses.

Traditional, complementary and integrative systems of medicines are usually considered as one of the natural sources to find new remedies and have been used in both prevention and treatment, in particular for chronic ailments [7]. Popularity of traditional and complementary medicine is increasing in both developed and developing countries [8]. It is believed that they are accessible and affordable with low cost and lower side effects. They are also having a deep relation with culture and folklore of nations [9]. In this regard, Persian medicine (PM) is one of the prominent, popular and ancient medical systems among various traditional systems of medicine [10].

Arthritis of the knee and hand is named “Vaja-al-mafasel” in PM manuscripts. Dystemperament in the whole body or in ordering organs and bad humors are two main reasons of osteoarthritis that are mentioned in the Canon of medicine [11]. The main approach of PM in treatment of various disorders like arthritis is to eliminate the underlying cause of the disease in order to obtain better responses for relieving pain. There are three steps; correction of life style, especially dietary regimen, is the first step; pharmacotherapy and using medicinal plants are the second step and using manipulation is the third one [12,13]. Many different oral or topical remedies have been introduced in PM literatures to cure osteoarthritis that are consisting of some medicinal plants [14,15].

Because PM methods and remedies to manage and treat OA are going to be common and popular among researchers the intention of this study was reviewing the clinical trials related to pharmacological treatments of OA with medicinal methods of PM in the literature.

Methods

The strategy of finding related papers was searching in the indexing databases including PubMed, Scopus and ISI Web of Knowledge, from 2000 to 2017. The search was limited by English language and the key words used in the study were Iranian traditional medicine, Persian traditional medicine, Iranian Medicine, Persian medicine; accompanied with osteoarthritis. The studies were also limited to randomized clinical trials (RCTs), evaluating the effects of Persian medicine interventions for treatment of OA, as

the inclusion criteria. We have considered herbal therapies which were applied orally or topically.

Results and Discussion

There were 44 articles (18 in PubMed, 19 in Scopus and 7 in ISI Web of Knowledge) by searching the databases with the help of the mentioned keywords. Then, duplicated articles were removed and after filtering using the inclusion criteria, 8 articles (RCT works) were selected (figure 1).

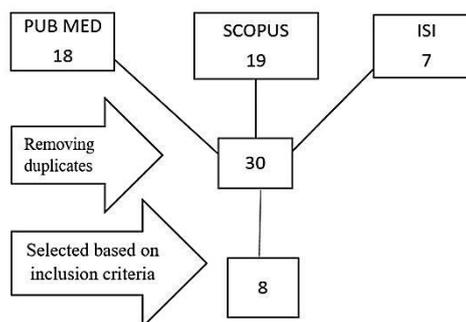


Figure 1. Flowchart of searching strategy

All eight selected articles were investigated and their documents were summarized (table 1); these articles are from 2010 to 2017. Increased number of these evidence-based studies in recent years (2016-2017) is an important point for development of complementary and traditional medicine in medical interventions.

There are 8 different medicaments used in these studies. In one of them, a combination of two herbs was used and in the others, only one medicinal herb as a single drug was applied. Dosage forms are topical (in five studies) and oral (in three studies). Topical ones consisted of gel, oil and some of traditional dosage forms such as “Marham” (combination of fine herb powder with beeswax, oils and animal fats) and “Dohn” (traditional oil) [24].

Traditional formulations were compared with placebo (in five studies), positive control (in two studies) and placebo beside positive control (in one study). The duration of treatment was 3 to 6 weeks in topical and 2 to 14 month for oral formulations. Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and Visual analogue scale (VAS) were applied in 5 and 4 studies, respectively. Knee injury and osteoarthritis outcome score (KOOS), Serum concentration of nitric oxide and CRP were other methods that were used as evaluation criteria in these studies too.

Table 1. Randomized Clinical Trials of Persian medicine herbal therapies in the treatment of osteoarthritis

Author/(year)	Intervention	Type of trial	Comparison group	Dosage	Period of treatment	Sample size	Evaluation criteria	Outcome
Soltanian et al. (2010) [16]	Marhame Mafasel (mixture of <i>Arnebia euchroma</i> (Royle) Jonst. and <i>Matricaria chamomilla</i> L.)	Double-blind crossover	Placebo	1.5 g (topical)	Every 8 h over six weeks	42 patients	WOMAC ^a	“Marhame-Mafasel” has significant effects for disease severity, physical function, stiffness and pain in comparison to placebo (p<0.05).
Bohlooli et al. (2012) [17]	Virgin olive oil (<i>Olea europaea</i> L.)	Pilot prospective, comparative, randomized, double blinded	Piroxicam gel	1 g (topical)	3 times/day for 4 weeks	71 patients	WOMAC	The decrease in WOMAC physical function and pain subscales in olive oil group was more than in piroxicam gel group significantly (p<0.001).
Abolhassanzadeh et al. (2014) [18]	Traditional harmel oil (<i>Peganum harmala</i> L.)	Double blind controlled randomized	Placebo	4 drops (topical)	3 times/day for 4 weeks	54 patients	WOMAC and VAS ^b	WOMAC (pain and difficulty in function except for stiffness) and VAS variables were significantly (p<0.001 and p<0.05) decreased in harmel oil group.
Shoara et al. (2015) [19]	Traditional chamomile oil (<i>Matricaria chamomilla</i> L.)	Three-arm, blinded, randomized, placebo-controlled	Diclofenac and placebo	1.5 mL of oils, a pea size diclofenac (topical)	3 times/day for 3 weeks	99 patients	WOMAC	There were no significant changes in WOMAC between groups but, it was significant in compared with their baseline values (P<0.001) and Chamomile oil decreased the need for acetaminophen significantly (p<0.001) compared to other groups.
Jabbari et al. (2016) [20]	Topical dwarf elder gel (<i>Sambucus ebulus</i> L.)	Pilot randomized, double-blind, active-controlled	Diclofenac gel 1%	Fingertip unit (topical)	3 times/day for 4 weeks	79 patients	WOMAC and VAS	The total WOMAC and VAS scores for pain was lower in <i>S. ebulus</i> group compared with the diclofenac gel group significantly (p=0.04 and p<0.001, respectively).
Rafraf et al. (2016) [21]	Pomegranate peels extract (<i>Punica granatum</i> L.)	Randomized Double-blind Placebo controlled	Placebo	500 mg (oral)	Twice daily for 8 weeks	66 patients	VAS and KOOS ^c	In treatment group the VAS score decreased and the mean scores of KOOS increased significantly greater than those in the control group (p<0.05).

Table 1. Continued

Author/(year)	Intervention	Type of trial	Comparison group	Dosage	Period of treatment	Sample size	Evaluation criteria	Outcome
Naderi et al. (2016) [22]	Ginger powder (<i>Zingiber officinale</i> Rosc.)	Double-blind randomized placebo-controlled	Placebo	500 mg (oral)	Two capsules daily for 3 months	120 patients	Serum concentration of NO ^d and CRP ^e	Inflammatory markers (CRP and NO) serum concentration decreased in the ginger group greater than the placebo group (p<0.001).
Salimzade et al. (2017) [23]	Black cumin seed powder (<i>Nigella sativa</i> L.)	Prospective, randomized, double-blind, placebo-controlled	Placebo	500 mg (oral)	2 g/day in divided doses for 12-week	110 patients	KOOS and VAS	The mean result of KOOS and number of acetaminophen tablets taken did not indicate significant differences between two groups.

^a Western Ontario and McMaster Universities; ^b Visual analogue scale; ^c Knee injury and osteoarthritis outcome score; ^d Nitric oxide; ^e C-reactive protein.

Placebo control studies showed that applied Persian medicine remedies including “Marham-e mafasel”, pomegranate peels extract, traditional harmel oil and ginger powder had significantly more positive effects in comparison with placebo on decreasing WOMAC and VAS scores and increasing KOOS score; but black cumin had not shown any significant effect. On the other hand, in the positive control included studies, chamomile oil had a similar effect with diclofenac gel as the standard treatment. But, other studies showed that the Persian herbal medicines including topical dwarf elder gel and virgin olive oil had significantly better effects in comparison with diclofenac and piroxicam gel as the standard treatments, respectively.

Among considered trials, two of them had used traditional oils in the treatment progress. Traditional oils are common dosage forms in PM [25]. More than thirty species of medicinal plants are used in preparing traditional oils that are applied in various diseases such as arthritis, sciatica and muscle aches. These oils mostly show analgesic and anti-inflammatory effects [26]. Oils in PM are divided into two categories; those that are taken directly from the oily parts of plants (fixed oils) such as virgin olive oil and those that are taken from extraction of non-oily parts of a plant to an oily vehicle such as harmel and chamomile oil [27].

Results of these investigated trials demonstrated that PM related therapies showed positive changes in some evaluated parameters significantly. But the number of RCTs was low and each of them studied different plants. So it is necessary to design more complete and various

trials about these herbal remedies and also other therapeutic methods of PM in treatment of OA.

In PM, it was believed that "Vaja-al-mafasel" was often caused by imbalance in body humor toward cold and moist temperament [28]; therefore, most of the medicinal plants studied in the investigated clinical trials, were “warm” and “dry” in temperament based on PM humoral theory. So it is expected that these plants help treating OA by adjusting the temperament. On the other hand, the efficacy of these PM remedies can be interpreted based on current findings. Oxidative stress has a key role in the pathophysiology of OA [29] through destruction of the joint's organic molecules and extra production of pain mediators by reactive oxygen species and nitric oxide [30-33]. Also, Pro inflammatory cytokines such as IL-1, IL-6 and tumor necrosis factor-alpha (TNF-a), are increased in OA patients caused by degradation of cartilage [34].

PM herbal remedies that were reviewed in this study, have several mechanisms against pathophysiologic pathways of OA; polyphenolic compounds available in chamomile, pomegranate, olive oil, ginger and dwarf elder can decrease or inhibit pro inflammatory factors (TNF-a, IL-1, matrix metalloproteinase 1(MMP-1), prostaglandins (PG) and leukotrienes) productions/(synthesis) by suppressing the COX-2 and lipoxygenase pathways [25,35-37].

High contents of terpenoids and flavonoids in chamomile [38] and oleocanthal in fresh extra virgin olive oil have an effect similar to NSAIDs [39-42]. Flavones and flavonols in pomegranate

peels decrease the NO and PGE2 production that cause hardness of joint damage [43].

Sambucus ebulus has shown to have highest total antioxidant capacity (TAC), among anthocyanin containing plants [44]. Its analgesic mechanisms may be related to exogenous effect of steroids or endogenous release of glucocorticoids, interfering with serotonergic system, alpha-2adrenoceptor or tachykinin pathway [45]. Also, *S. ebulus* is an anti-inflammatory agent [46] because of significant decreasing in TNF alpha and IL-1 (alpha and beta) concentrations and its ursolic acid contents [47].

Even though anti-inflammatory and antioxidant effects of these medicinal herbs are confirmed in various studies, communalizing the results of the mentioned trials have multiple limitations such as lack of comparison of the study intervention with an OA standard medication, using subjective variables for outcome measurements or small sample sizes in some of them. There is only one study for each PM treatments in this review and it is not sufficient to ensure the efficacy and safety of these medicaments for OA patients.

Conclusion

Osteoarthritis is one of the main complications in conventional medicine. Many oral and topical formulations have been described for treatment of OA in PM. Clinical trials are being planned for introducing evidence-based information from traditional medicine to the world medical society. Despite the fact that PM has many methods for treating OA, the number of studies and clinical trials in this field are limited. There were only eight clinical trials about different PM remedies; therefore, each trialed remedy had only one document to be evaluated. Although, seven of eight these papers showed positive effects for the treatment or management of OA, it seems that judging about the effectiveness of Persian medicine therapies about all remedies of OA requires more researches and clinical studies.

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Author contributions

Sahar Bagheri, Zahra Taghipour and Nastaran Ebadi contributed to data gathering and drafting the manuscript; Tayebeh Toliyat, Mehran

Mirabzadeh Ardakani and Arman Zargaran contributed to the study design and analysis of the data. All authors approved the final draft of the manuscript.

Declaration of interest

The authors declare that there is no conflict of interest. The authors alone are responsible for the content of the paper.

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Abbreviations

PM: Persian Medicine; OA: Osteoarthritis