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SYSTEMATIC REVIEW ARTICLE

Efficacy of some Herbal Medicines in Osteoarthritis with a Focus on Topical Agents: A Systematic Review

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ARTICLE HISTORY

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Abstract: Osteoarthritis (OA) is a leading cause of musculoskeletal disorders that mainly affects the elderly population. Some herbal medicines have the potential to alleviate the pain associated with OA and improve physical activity mostly through anti-inflammatory and anti-oxidative properties. The aim of this study was to investigate the effects of herbal medicines, especially topical types, on osteoarthritis.

In this systematic review, the keywords "osteoarthritis", "herbal compounds", "herbal medicine", "topical drug", "hydrogels", "cream" and "treatment" were used to search publications published from 2010 to 2019 and indexed in databases including PubMed, SCOPUS, Web of Science and Google Scholar. After screening of titles and abstracts and detection of duplicate publications, 38 eligible articles were included in the main review. We also included herbal formulations *in vivo*.

Bioactive fractions of herbal medicines mostly worked on OA through suppression of interleukin-1β (IL-1β), inducing nuclear factor-κB (NF-κB) activation by inhibition of inhibitor of NF-κB (IκBα) phosphorylation, IκBα degradation, p65 phosphorylation, and p65 nuclear translocation, downregulation of NF-κB targets including COX-2 and MMPs, upregulation of collagen type II, cartilage-specific proteoglycans (CSPGs), β1-integrin, and expression of cartilage-specific transcription factor SOX-9 protein. Noticeably, herbal medicines do not produce desirable effects, thereby using their combinations with other therapeutic agents seem to exert substantial clinical outcomes.

Herbal gels have demonstrated robustly significant healing effects on knee pain, stiffness and mobility. It is worth considering that because OA is a chronic disease, longer duration of the studies/trials would even lead to obtaining more reliable judgments regarding topical treatment tolerability, safety and efficacy and clarify local or systemic adverse effects. Stability and standardization of a defined amount or concentrations of herbal gels would give promising effects on OA treatment and pain relief.

Keywords: Herbal medicine, topical drug, hydrogels, herbal cream, osteoarthritis, proteoglycans.

1. INTRODUCTION

Osteoarthritis (OA), as one of the main musculoskeletal disorders, is an inflammation associated with joint pain and loss of function mostly in the elderly population affecting 9.6% of men and 18% of women over 60 years and 25 million people in the United States [1, 2]. The rate of OA incidence is increasing due to enhancing the levels of risk factors such as sedentary lifestyle and obesity. Risk factors for developing OA mostly include obesity, previous knee injury, heberden's nodes, previous meniscectomy, advanced age, surgery and the elderly status of the 'baby boomer' generation [3]. Several therapeutic approaches have been applied for OA such as pharmacologic and physical treatments, lifestyle change and eventually surgical interventions. There is partial efficacy in controlling disease symptoms and side effects by using chemical therapies [4, 5]. Analgesics and corticosteroids have varying adverse effects from mild gastritis to gastric ulcers, bleeding and perforation, and several challenges in clinical practice. Hence, there is a large unmet need for desirable pharmacologic therapeutic interventions. These conclusions lead to applying other alternative compounds such as herbal medicine for more promising outcomes for chronic diseases [6-8].

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Herbal medicines, though not straightforward, act as appropriate medications exerting anti-oxidant, anti-nociceptive, anti-inflammatory and immunoregulatory effects [9-13]. Several active ingredients such as tannins, flavonoids, glycosides, steroids, cardiacglycosides, ebulitins, rosmarinic acid, caffeic acid derivatives, and volatile substances participate in herbal medicines curing properties. Several most common herbal medicines such as *Curcuma longa*, *Rosa canina*, *Salix alba*, *Perna canaliculus*, chicory root, avocado and soybean unsaponifiables, ginger, *Dracocephalum kotschyi* and *Harpagophytum procumbens* have been employed to ameliorate the effect of increasing OA prevalence and other diseases [14-19]. Topical medicinal plant products used for the treatment of OA act as skin irritants (for example Capsicum extract, stinging nettle leaf) and may also act similarly to some oral medicinal herbal products [20].

Biological effects of the herbal extracts on OA are mostly exerted through suppression of IL-1β induced NF-κB activation by inhibition of IκBα phosphorylation, IκBα degradation, p65 phosphorylation, and p65 nuclear translocation, downregulation of NF-κB targets including COX-2 and MMPs, upregulation of collagen type II, cartilage-specific proteoglycans (CSPGs), β1-integrin, and expression of cartilage-specific transcription factor SOX-9 protein. Noticeably, herbal medicines do not produce desirable effects, thereby using their combinations with other therapeutic agents seem to exert incredible clinical outcomes [21]. The aim of this study was to investigate the effects of herbal hydrogels on the treatment of osteoarthritis.

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2. MATERIALS AND METHODS

2.1. Search Strategy

In this systematic review, the terms "osteoarthritis", "herbal compounds", "herbal medicine", "topical drug", "hydrogels", "cream", and "treatment" were searched together in the search engines such as Google Scholar, PubMed, SCOPUS, and Web of Science. A total of 1950 articles were retrieved in the first step. After the screening of titles, abstracts and duplicate publications, 38 articles that met the criteria related to the topic and title of the study were screened and reviewed. We did not include meta-analyses due to the wide variety of samples and methods. The duplicate publications and those that were considered to be irrelevant after reading of title and abstract were removed. Eventually, full texts were screened and eligible publications were included and reviewed (Fig. **1**). The full texts included both herbal hydrogels and ointments or either of the two formulations that had been assessed for their healing effects on OA.

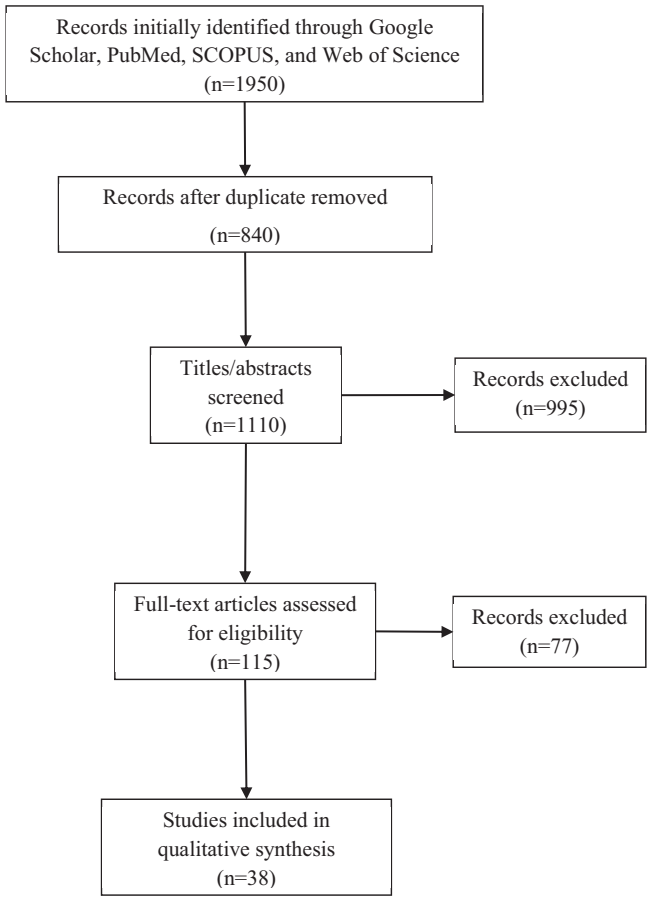

Fig. (1). The flowchart of the review study.

2.2. Inclusion Criteria

Primary source articles published in English in peer-reviewed journals were assessed. Among the retrieved publications, the articles regarding the effects of herbal medicines, especially topical types, on OA that met the inclusion criteria were included in the review.

2.3. Exclusion Criteria

The articles whose full texts were not accessible free of charge and *in vitro* studies (except for studies that evaluated the mechanism of action of the drug) were excluded. The articles regarding only chemotherapy and nutrigenomic effects on OA were also excluded.

3. RESULTS

A total of 1950 articles on the effects of herbal medicines on OA and arthritis were retrieved at the first step, of which 840 articles were excluded due to being duplicate and irrelevant. After the review of titles and abstracts and further screening, 995 ineligible articles were excluded. Therefore, after analysis of full texts, 77 articles were excluded and 38 papers were found to meet the inclusion criteria and were enrolled in the final review.

In a double-blind clinical study, the healing effect of ginger on knee OA was evaluated. Ginger exhibited a strong analgesic effect in subjects and no significant difference was observed between piroxicam and ginger gels [14]. The herbal agent SKI 306X, in comparison with dexamethasone and two NSAIDs, diclofenac and rofecoxib, was reported to suppress proteoglycan (PG) degradation and chondroprotective effects at 200 mg/kg dose *in vivo*, which were not observed for other drugs [22]. *Caesalpinia sappan* extracts could inhibit the NF-κB (p65/p50) signaling and reduce cartilage breakdown, leading to pain relief in OA [22]. PG201 (600 mg) and celecoxib (200 mg) were both well tolerated and no statistically significant differences were observed in the tolerability profile between the groups. PG201 was as effective and safe as celecoxib for the treatment of symptomatic knee OA and might be a new useful medication for the treatment of symptomatic knee OA [23]. Boiogito, a Japanese traditional medicine, exhibited a significantly better healing effect on knee OA compared to loxoprofen group after 12 weeks of treatment [24]. Also some traditional chinese herbal patches such as Fufang Nanxing Zhitong Gao (FNZG) and Shangshi Jietong Gao (SJG) were evaluated which had limited effect to improve knee pain, stiffness and physical function in a 7 days treatment [25]. In the study of Dehghan (2016), the effect of topical application of *Eugenia caryophylata* on OA was compared to topical diclofenac and placebo for four weeks. The results revealed a significant alleviation of overall pain ($p = 0.005$) and daytime stiffness ($p = 0.001$) [8]. In another study by Dehghan *et al*. (2019), *Thymus daenensis* gel improved the symptoms in patients as Diclofenac did [4].

In a study by Jabbari *et al*., the efficacy and short-term safety of topical *Sambucus ebulus* were evaluated and compared with 1% Diclofenac gel in patients with knee OA [26]. It was revealed that after 1-2 weeks (3 times a day), the pain and stiffness scores in *S. ebulus* group were significantly lower than those in Diclofenac group without any adverse effects. The potential mechanisms of *S. ebulus* have been attributed to ingredients such as ebulitin, quercetin3-O-glucoside, ebulin1, flavonoid and anthocyanin. In the study of Madhu, 120 patients (37 males and 83 females) with primary knee OA were treated with *Curcuma lunga* compared to placebo. It was shown that the severity of pain ($p < 0.05$) and function of the affected knee ($p < 0.01$) were significantly different compared to *C. lunga* group and tolerability and acceptability profile was better [16]. Similarly, the pain-relieving effect of NR-INF-02, a derivative of *C. lunga*, has been demonstrated along with reducing acetaminophen. Application of 3,000 mg/day (a high dose) of New Zealand green-lipped mussel (GLM) extract over 8 weeks to 21 subjects with OA by Coulson demonstrated promising effects in terms of WOMAC ($p < 0.001$) and GSRS ($p = 0.005$) scores [27]. The application of *Symphytum officinale L* in female patients with OA also yielded desirable effects [28]. In addition, significant improvements in the pain and physical function scores ($p < 0.001$), rather than stiffness score ($p > 0.05$), were observed using curcuminoid therapy of OA (1500 mg/day in 3 divided doses; n = 19) [29]. Another study demonstrated that bioactive extract of chicory root in phase 1, placebo-controlled, double-blind, dose-escalating trial for the treatment of OA was well-tolerated except for one patient. In a study by Campus, *Cichorium intybus* root extract exhibited protec-

Table1. The action mechanisms of some herbs effective on the symptoms of osteoarthritis.

Herb Name	Duration	Effect	References
Zingiber officinale	12 weeks	No significant difference between control and treated group with ginger extract gel in terms of pain relief, stiffness and function	[35]
Ganghwaljetongyeum (ChondroT)	5 days	Notably improved articular cartilage damage and plantar withdrawal response, decreased TNF-α, IL-1β, IL-6 and PGE_2, but increased serum ALT and AST levels	[36]
Artemisia annua	2 weeks	Increased IGF-1 level; decreased OPN, CTX-II levels in the serum and SF; and inconsistent results were observed in the cartilage tissues	[37]
Green tea	3 month	Changes in the synovial fluid properties with respect to the protein concentration, molecular size of hyaluronic acid, and chondroitin 6-sulphate concentration were also observed	[34]
Rosa agrestis	-	Inhibition of IL-1β-induced NO and PGE2 production, as well as iNOS and COX-2 expression. Inhibition of IL-1β-induced NF-κB and MAPK activation in human OA chondrocyte	[38]
Bletilla striata	-	BSP hydrogel exerted anti-oxidant activity in chondrocytes, no toxicity against normal cells, cell proliferation induction at 5 μg/ml to 1000 μg/ml and significant downregulation of inflammatory markers	[39]
Boswellia Carterii (Oliban oil)	6 weeks	Mitigation of pain, stiffness, and discomfort indices of the Osteoarthritis Outcome Score questionnaire	[40]
Salvia miltiorrhiza	5 weeks	Pain relief, inhibition of NF-κB signaling pathway	[41]
Matricaria chamomilla L. (Chamomile oil)	3 weeks	Pain relief, no significant differences in WOMAC questionnaire domains compared to Diclofenac and placebo were observed	[42]
Tribulus terrestris	24 hours	Osteoarthritis treatment through downregulation of nitric oxide (NO) synthase 2, COX-2, TNF-α and IL-6	[43]
Anthriscus sylvestris	8 weeks	Chondroprotective through MAPKs and NF-κB signaling regulation	[44]

OPN: Osteopontin, IGF-1: Insulin-like growth factor-1, CTX-II: C-telopeptides of type II collagen, TNF: Tumor necrosis factor, IL: Interleukin, MAPK: Mitogen-activated protein kinases, BSP: *Bletilla striata* polysaccharide, NF-κB: Nuclear factor κB, COX-2: Cyclooxygenase-2.

tive, relieving and restructuring activities on the skin [30]. Additionally, curcumin microemulsion (10 mg) could improve the bioavailability of curcumin, giving insight into the formulation of an approach to healing OA [31]. A randomized controlled trial by Razavi exhibited no significant difference between topical galbanum oil and topical Diclofenac for knee pain and stiffness [32]. Furthermore, icariin conjugated hyaluronic acid/collagen (Ica-HA/Col) hydrogel facilitated chondrogenesis and osteogenesis. More cells aggregation encapsulated in the gel was observed and chondrogenic genes' expression levels were significantly increased. Moreover, osteogenic genes, including RUNX2, ALP, and OCN, were also up-regulated [33]. It was revealed that green tea reduced pain and had antioxidant properties for healing OA [34]. The action mechanism of some herbs effective on the symptoms of osteoarthritis has been represented in Table **1**.

The overall healing effects of herbal medicines are illustrated in Fig. **2**. Additionally, the concentrations of herbal medical gels for the improvement of OA *in vivo* have been demonstrated to be higher than synthetic drugs and their durations have been varying. It is notable that achieving a stable and standard amount of herbal gels (considering their pharmacokinetics and bioavailability) for OA treatments would be essential for future studies. Furthermore, a combination of herbal gels with drugs would mitigate the side effects and exert better clinical outcomes. A recent systematic review has reported that NSAIDs are appropriate drugs for knee pain alleviation, but the efficiency of herbal topical formulations needs further research [45]. However, the underlying mechanisms remain poorly understood.

4. DISCUSSION

As a chronic and one of the most common types of arthritis, OA needs prompt and accurate attention due to its significant impact on the population. It has been reported that both pharmacologic and nonpharmacologic therapies are needed to resolve OA-related complications [46-48]. Because of expensiveness and side effects of chemotherapies (palliative therapies) and consistent adverse clinical outcomes, the application of alternative treatments could help to achieve better outcomes [5, 49]. In this regard, some studies have demonstrated the healing properties of herbal medicines as natural and cost-effective resources. It is worth considering that most herbal medicines have negligible cytotoxicity. Consequently, patients tend to seek out alternative treatments. Although Diclofenac gel has been reported to be a satisfactory healing approach for knee OA than oral NSAIDs, it is essential to apply some herbal gels to achieve better results [45]. Topical treatment has been recommended for knee OA by England National Institute for Health. A reduction of 46-54.7% in OA knee pain was observed following a regimen of comfrey cream, with a significant difference to placebo [28].

Curcumin exerts anti-inflammatory effects and protects chondrocytes against the catabolic effects of IL-1β, including upregulation of MMP-3, type II collagen and β1-integrin synthesis, and repression of matrix synthesis. Curcumin can also antagonize IL-

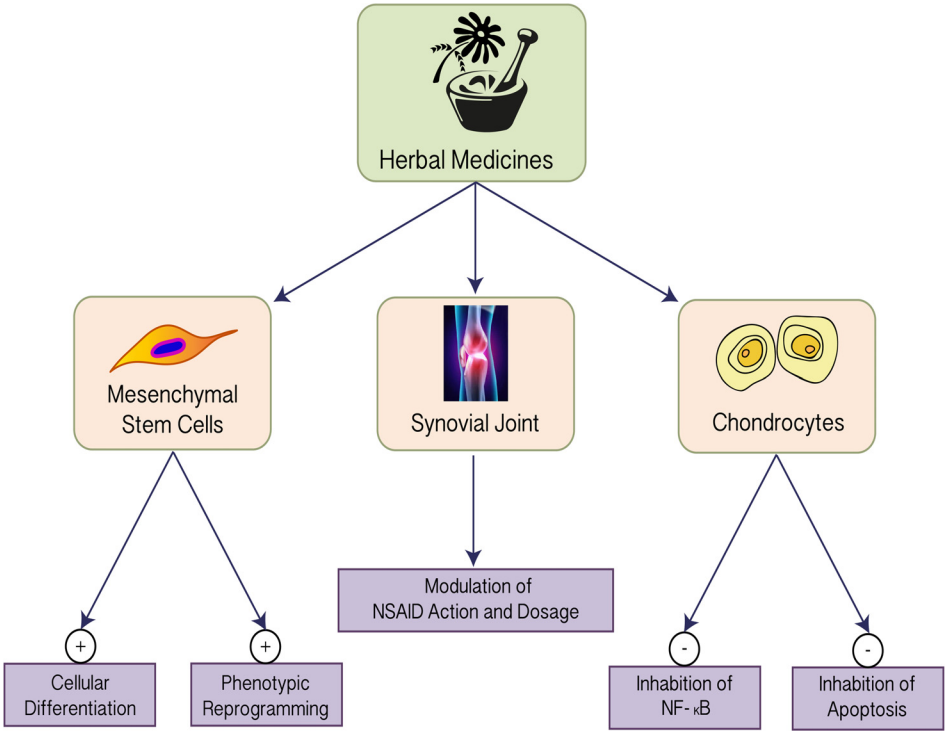

Fig. (2). The beneficial effects of herbal medicines on osteoarthritis (**Figure** from Dr. Mobasheri) [22].

1β-induced caspase-3 activation in chondrocytes and suppress the IL-1β-induced NF-κB activation [29]. Several active ingredients such as tannins, flavonoids, glycosides, steroids, cardiacglycosides, ebulitins, rosmarinic acid, caffeic acid derivatives, and volatile substances participate in herbal medicines curing effects. Several common herbal medicines employed to ameliorate the effect of increasing OA prevalence such as *Curcuma longa*, *Rosa canina*, *Salix alba*, green-lipped mussel (*Perna canaliculus*), chicory root, avocado and soybean unsaponifiables, Flavocoxid, Ginger, *Harpagophytum procumbens*, for symptoms relief have been largely contentious. Biological effects of the herbal extracts on OA have been mostly through suppression of IL-1β-induced NF-κB activation by inhibition of IκBα phosphorylation, IκBα degradation, p65 phosphorylation, and p65 nuclear translocation, downregulation of NF-κB targets including COX-2 and MMPs, upregulation of collagen type II, cartilage-specific proteoglycans (CSPGs), β1-integrin, and expression of cartilage-specific transcription factor SOX-9 protein. Noticeably, herbal medicines do not produce desirable effects, thereby using their combinations together with other therapeutic agents can lead to substantial clinical outcomes [50]. It has been demonstrated that the effects of herbal active fractions need 2-3 weeks to be exerted [29], but oral consumption of *Boswellia serrata* was found to relieve OA pain in short term [51].

Other antinociceptive activities of herbal gels are exerted *via* significantly hindering the concentrations of IL-1alpha, IL-1beta, and TNF alpha chemokines, interfering with COX-2 pathway and inhibiting carrageenan-and serotonin-induced hind paw edema and immune cells [52]. It is notable that achieving a stable and standard amount of herbal gels (considering their pharmacokinetics and bioavailability) for OA treatment would be essential for future studies. Furthermore, a combination of herbal gels and drugs would mitigate the side effects and result in better clinical outcomes [53]. In addition, this review can help to outline an idea to direct the research toward the various formulations which will enhance the technologies. Furthermore, formulating the herbal actives into novel technologies such as liposomes, phytosomes, and transdermal drug delivery would be a potential area [47]. Therefore, rapid diagnostic methods of OA are required and due to inadequate data regarding the efficacy of herbal gels in clinical trials, treatment of complications and application of these compounds, as alternative drugs, will open new avenues toward effective treatment for OA [54-56].

CONCLUSION

Relief of pain and stiffness in knee OA in older individuals often entails a combination of nonpharmacologic and pharmacologic therapies to achieve the best possible outcomes. The evidence regarding herbal gels reveals that these compounds can be recommended for alleviating symptoms of patients with knee OA, though higher concentrations are occasionally more necessary (low quality of evidence). Additionally, to obtain more promising achievements, the combination of herbal gels together with analgesics might lead to more healing effects and is essential for achieving a comprehensive understanding of their pharmacokinetics, efficacy and safety. It is worth considering that because OA is a chronic disease, studies/trials of longer duration would lead to obtain even more definitive arguments on topical therapies tolerability, safety and efficacy and clarify local or systemic adverse effects. Stability and standardization of a defined amount or concentrations of herbal gels would yield promising effects on OA therapy and pain relief. Topical NSAIDs, capsaicin, and salicylates, and physical treatments have been shown to be most beneficial.

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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