Review Article

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Multi-ingredient herbal topical preparations for the management of pain in osteoarthritis: A perspective from Persian Medicine

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Abstract

Osteoarthritis is one of the most common diseases worldwide today. Inflammation and pain caused by osteoarthritis greatly interfere with daily activities for those affected. Although many painkillers and medications are available in the pharmaceutical market for this condition, they often only offer temporary relief from joint pain and inflammation. They can also come with systemic side effects and pose challenges for long-term use in many patients. Accordingly, most patients prefer to use topical treatments that target specific areas of discomfort. In addition to pharmaceutical options, various topical herbal formulations for alleviating osteoarthritis symptoms can be found in traditional pharmacological literature. Persian Medicine, as a school with a thousand years of experience, is a significant source for drug discovery and the extraction of many medicinal formulations. In this regard, the current study aims to compile a collection of topical herbal formulations in the form of multi-ingredient herbal topical preparations from traditional pharmaceutical textbooks, such as Qarābādin Salehi, Azam, and Kabir. The selected preparations can be reformulated for evaluation in the management of osteoarthritis.

Keywords: Topical preparation, Osteoarthritis, Persian Medicine

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1. Introduction

1.1. Osteoarthritis

Osteoarthritis is defined by the American College of Rheumatology (ACR) as a group of conditions characterized by joint signs and symptoms associated with impaired integrity of articular cartilage and changes in the underlying bone at the joint margin (1). Pain is the most prominent symptom of osteoarthritis (2). Arthritis is a multifactorial disease with inflammatory, metabolic, and mechanical causes (1). The pathology of arthritis is characterized by progressive joint damage, including cartilage erosion, subchondral bone sclerosis, synovitis, bone remodeling with osteophyte formation, and meniscal damage, all of which may contribute to pain (3). There is a clear association between arthritis and increased mortality, often due to decreased mobility (3, 4).

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1.2. Pharmacological treatments for osteoarthritis

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Conventional pharmacological treatment to reduce pain, inflammation, and functional disability usually relies on the widespread use of non-steroidal anti-inflammatory drugs, corticosteroids, and various opioids (1, 5, 6). However, the main disadvantage of pharmacological treatment with anti-inflammatory medications is the frequent association with adverse effects; in particular, the toxicity associated with NSAIDs is related to the inhibition of prostaglandin synthesis (PGs), which disrupts gastric mucosa and renal homeostasis (7-9). On the other hand, the availability of selective (COX-2) inhibitors, despite the reduction of gastrointestinal toxicity, leads to a high risk of developing serious cardiovascular side effects (10). Chronic treatment with systemic corticosteroids may incur the cost of many severe and unwanted reactions, leading to hypertension, diabetes, glaucoma, gastric ulcers, osteoporosis, and psychiatric disorders (11). Finally, opioids, used alone or in combination with acetaminophen or nonsteroidal anti-inflammatory drugs, may cause a variety of side effects, with impact on quality of life and bowel dysfunction being among the most common problems. Therefore, new treatment options with comparable efficacy and better safety are warranted (11-13).

Intra-articular injections of long-acting glucocorticoids or hyaluronic acid are another treatment option for osteoarthritis. Intra-articular injections of corticosteroids generally result in short-term improvement lasting 4–8 weeks. Intra-articular injections of hyaluronic acid, a form of adjunctive therapy, have been widely used by orthopedic surgeons in the treatment of knee osteoarthritis (14).

Disease-modifying osteoarthritis drugs (DMOADs) are promising treatments for arthritis that target key factors in the pathologic process of the disease and aim to inhibit the deterioration of both biological and structural aspects of the joint, thereby improving physical function, not just pain. Currently, DMOADs delay cartilage degradation by targeting inflammatory factors, matrix-degrading proteases, the Wnt signaling pathway, or enhancing cartilage repair factors. However, regulatory agencies such as the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have not approved any drug as an effective DMOAD, as approval guidelines require that a potential DMOAD demonstrate a slowing of knee or hip joint space width (JSW) loss on X-ray imaging, along with improvement in associated symptoms (15-17). In addition, RNAi, CRISPR/Cas9, and PROTAC-based drugs are under development to stimulate cartilage regrowth (18).

1.3. Traditional medicine

The World Health Organization (WHO) defined traditional medicine in more detail in 2002 as follows: Traditional medicine is a general term that refers to both traditional medical systems, such as traditional Chinese medicine, Indian Ayurveda, and Greco-Arabic medicine, and various forms of indigenous medicine. Traditional medicine treatments include pharmacotherapy (the use of medicinal plants, animals, and mineral components) and non-pharmacological methods (such as acupuncture, massage, and psycho-psychological therapies) (19). Traditional medicine is a comprehensive set of knowledge, skills, and experience based on the beliefs, assumptions, and experiences indigenous to different cultures, which may or may not be explainable. This category is used to maintain health, including the prevention, diagnosis and improvement, and treatment of mental and physical illnesses (20).

1.4. Introduction to Traditional Persian Pharmacy

A major aspect of treatment in Traditional Persian Medicine (TPM) involves traditional pharmacy. TPM has a history spanning thousands of years with numerous medical and pharmaceutical manuscripts. The book

Firdaws al-Hikmah by Ibn Rabban al-Tabari is the first comprehensive medical book. Among other scholars in this field, Zakaria al-Razi is notable for his encyclopedia, the Liber Continens (*al-Ḥāwī fī al-ṭibb*). This book is a compendium of Greek, Syrian, and early Arabic medical knowledge, as well as some Indian medical practices. Another important book in the field of traditional pharmacy and traditional medicine is the Canon of Avicenna (1025 AD), written in five volumes; the second and fifth volumes have been dedicated to pharmacy. This book was the most important medical reference in Europe until the 17th century (21).

A comprehensive source in TPM is the Qarābādin textbooks. These encyclopedias describe methods for combining and formulating multi-component medicaments.

1.5. Qarābādin-e-Kabir

The book *Qarābādin-e-Kabir* is a significant work in traditional Persian pharmacy associated with Mohammad Hossein Aghili Alavi Khorasani Shirazi (1772 AD). The book includes an introduction and 28 sections, each containing several chapters, along with the number of Arabic letters. The introduction comprises twenty chapters covering topics such as the concepts of food and medicine, the characteristics and composition of the power, temperament, types of temperaments, recognizing temperament, drug combination qualities, identifying the temperament of compound drugs, and their dosages (22, 23).

1.6. Qarābādin-e-Azam

Qarābādin-e-Azam is written by the Persian physician *Hakim Muhammad Azam Khan* in Persian and focuses on compound products (1853 AD). The book consists of 26 chapters and a list that describes diseases of various organs of the human body, along with their corresponding medicines (24).

1.7. Qarābādin-e-Salehi

Qarābādin-e-Salehi (by Saleh bin Muhammad bin Muhammad Saleh Qaini Heravi in 1765 AD) has been compiled in the form of modern pharmacopoeias. The book includes an introduction and medicinal products listed alphabetically. In the section on medicinal products, the pronunciation of each item, the preparation methods, and related applications are explained (25).

1.8. Qarābādin-e-Qaderi

Qarābādin-e-Qaderi, written by Hakim Mir Mohammad Akbar Shah Arzani Shirazi, is one of the Persian works on traditional medicine. This work is gathered in twenty-three chapters and one conclusion. In each chapter, the author has mentioned the combined formulations for the treatment of a particular organ. The conclusion also states the generalities that are necessary to know in pharmacy (26).

2. Methods

In this study, four main Qarābādin textbooks (mentioned earlier) were examined to extract relevant topical multi-ingredient formulations effective for managing joint pain and inflammation related to osteoarthritis. Keywords used for data extraction included Zomād (topical semisolid or solid formulation), Talā (liquid topical dosage form), and Dohn (medicinal oil preparation). Mineral or animal ingredients were excluded. All herbal ingredients (in compound formulations) were subsequently identified by scientific names. Table 1 displays the compound formulations. Each row in the table lists the formulation components and their preparation methods separately. After data extraction, each medicinal plant was checked for the repeatability of the gathered formulations. Accordingly, the most common and abundant medicinal plants were investigated for related analgesic and anti-inflammatory activities, either through clinical trials or animal studies.

3. Discussion

Table 1. Topical herbal formulations related to osteoarthritis in the books of *Qarābādin-e-Salehi*, Qaderi, Kabir, and Azam (22-26).

Dosage form	Num.	Formulation	Ref.
Zomād	1	Mix equal amounts of *Agrimonia eupatoria* (aerial parts), *Salvia macrosiphon* (seed), *Hordeum vulgare* (seed), and *Colchicum autumnale* (rhizome) with rose oil in egg yolk to prepare an ointment	(22, 25)
	2	*Capparis spinosa* (aerial parts), *Mentha pulegium* (leaf), *Anacyclus pyrethrum* (root), [2 parts of each]; *Saussurea costus* (root), *Eruca sativa* (aerial parts) (1 part of each) in olive oil (*Olea europaea*)	(25)
	3	*Urtica dioica* (root and leaf), *Withania somnifera* (root and leaf), *Citrullus colocynthis* (fruit), *Pistacia atlantica* (fruit), *Piper longum* (aerial parts), *Anacyclus pyrethrum* (root), *Dorema ammoniacum* (root and stem), *Commiphora wightii* (aerial parts), *Commiphora opobalsamum* (aerial parts), *Juniperus sabina* (aerial parts), *Aloe succotrina* (leaf), *Artemisia absinthium* (aerial parts), *Cyperus rotundus* (root), *Cymbopogon citratus* (leaf), and *Euphorbia Helioscopia* (aerial parts) in lily oil with honey and vinegar	(25)
	4	*Trigonella foenum-graecum* (seed) (boiled with equal parts water and vinegar, added with honey, application is for three days)	(24, 25)
	5	*Melilotus officinalis* (aerial parts), *Myrtus communis* (seeds), *Robinia Pseudoacacia* (aerial parts), *Crocus sativus* (Flower stigma), *Papaver somniferum* (aerial parts), *Mandragora officinarum* (root) (mixed with oil)	(25, 26)
	6	Five parts of rose oil, one part of *Euphorbia Helioscopia* (aerial parts), and three parts of *Crocus sativus* (Flower stigma) in a mixture	(25)
	7	*Papaver somniferum* (aerial parts) and *Crocus sativus* (Flower stigma) in equal amounts with milk or rose oil as a poultice	(25)
	8	*Ricinus communis* (seed) combined with honey and vinegar	(25)
	9	*Cyclamen persicum* (burned and mixed with equal amounts of honey and vinegar)	(25)
	10	*Aloe vera* (leaf), *Melissa officinalis* (leaf), *Crocus sativus* (Flower stigma), and *Brassica oleracea* juice in a vase of high fever with chicory juice.	(22, 24, 25)
	11	*Brassica oleracea* (leaves boiled in water with egg yolk)	(25)
	12	A mixture of *Colchicum autumnal* (rhizome), *Agrimonia eupatoria* (aerial parts), *Althaea officinalis* (aerial parts), *Lawsonia inermis* (leaf), *Myrtus communis* (seed), *Hordeum vulgare* (seed), *Commiphora myrrha* (gum), *Hyoscyamus niger* (leaf), *Vitis vinifera* (aerial parts), *Anacyclus pyrethrum* (root), *Saussurea costus* (root) (all in equal proportions with the wine)	(25)
	13	*Adenanthera pavonine* (leaf), *Punica granatum* (aerial parts), *Areca catechu* (seed), *Colchicum autumnale* (rhizome), and *Papaver somniferum* (aerial parts) (pounded, ground, and prepared as a poultice with *Solanum nigrum* juice	(25)
	14	A mixture of old olive oil (*Olea europaea*) and Trigonella foenum-graecum (seed) (15 parts of each), *Pistacia atlantica* (fruit) (10 parts of each), Euphorbia sp. (leaf) (2 parts), *Iris germanica* (rhizome) (4 parts)	(25)
	15	*Plantago ovata* (seed) (crushed and boiled in water) mixed with oil in an appropriate amount	(24)
	16	*Solanum nigrum*, *Cichorium intybus*, *Althaea officinalis* (aerial parts), *Coriandrum sativum*, *Lactuca sativa*, *Rosa damascena*, *Areca catechu*, *Colchicum autumnale* (rhizome), *Acroptilon repens*, *Robinia pseudoacacia* (aerial parts), *Curcuma longa*, *Pterocarpus santalinus* (mixed with *Papaver somniferum* (aerial parts) and water as a poultice)	(24)
	17	Equal amounts of *Crocus sativus* (Flower stigma) and milk with rose oil, or beeswax, or with boiled *Terminalia chebula* (equal quantities with water and vinegar)	(24)
	18	*Zingiber officinale* (rhizome) and *Colchicum autumnale* (rhizome) pounded with *Myristica fragrans* (seed) and *Papaver somniferum* (aerial parts) in chamomile [*Matricaria chamomilla* (flower)] or henna (*Lawsonia inermis* (leaf)), or sesame (*Sesamum indicum*) oil as a poultice	(24)
	19	Ground mixture of *Anacyclus pyrethrum* (root), *Zingiber officinale* (rhizome), and *Papaver somniferum* (aerial parts) with *Datura stramonium* (leaf juice) as a poultice	(24)
	20	A mixture of *Hordeum vulgare* (seed), *Viola odorata*, *Rosa damascena*, and *Lens culinaris* with milk and saffron [*Crocus sativus* (Flower stigma)] and rose oil as a poultice	(22, 24)

Continued Table 1.

Zomād	21	Mix *Matricaria chamomilla* (flower), *Althaea officinalis* (aerial parts), *Melilotus officinalis* (aerial parts), *Prangos ferulacea* (aerial parts), *Anethum graveolens* (aerial parts), and vinegar as a poultice	(26)
	22	A mixture of *Ricinus communis* (seed), clarified butter, honey, and vinegar	(26)
	23	A mixture of equal amounts of *Cordia myxa*, *Dorema ammoniacum* (root and stem), with vinegar and honey as a poultice	(26)
	24	Apply *Aloe vera* (leaf) and *Crocus sativus* (Flower stigma) with cabbage juice (*Brassica oleracea*), or chicory juice (*Cichorium intybus*)	(26)
	25	*Anacyclus pyrethrum* (root), *Lepidium sativum* (seed) in olive oil as a poultice	(22)
Oil	26	Boiled fat with olive oil	(25)
	27	A mixture of boiled *Matricaria chamomilla* (flower), *Melilotus officinalis* (aerial parts), *Origanum majorana* (aerial parts), *Aegypius monachus* (aerial parts), *Valeriana officinalis* (rhizome), *Lawsonia inermis* (leaf), *Gentiana Lutea* (root), *Myristica fragrans* (seed), *Withania somnifera* (root and leaf), *Colchicum autumnale* (rhizome), and *Anacyclus pyrethrum* (root) in water overnight, and boil in olive or sesame oil	(25)
	28	Sesame oil	(24, 25)
	29	Iris sp. or *Cheiranthus cheiri* oil	(25)
	30	A mixture of 4.6 g of basil syrup (*Ocimum basilicum*) with 3.5 g of *Cicer arietinum* and *Carum carvi* juice, mixed with sesame oil	(25)
	31	*Colchicum autumnale* (rhizome), fresh celery juice (*Apium graveolens*), and *Swertia chirayita* (rhizome) in sesame oil	(25)
	32	*Anethum graveolens* (aerial parts) extract is boiled with olive oil until the oil remains and the water evaporates	(25)
	33	Pieces of *Phragmites australis* (aerial parts) in olive or sesame oil for a few days	(25)
	34	Yielding the oil from freshly blossomed Pandanus sp. in olive or sesame oil	(25)
	35	Parsley leaf juice (*Petroselinum crispum*) boiled with sesame oil	(25)
	36	*Acorus calamus*, crushed and soaked in water for two days, and boiled in sesame oil subsequently	(25)
	37	Boiled henna leaves or flowers (*Lawsonia inermis*) in water (reduced to half), cooked with sesame oil until the water is gone	(24)
	38	Chopped *Nicotiana rustica* (leaf) should be boiled with *Matricaria chamomilla* (flower), *Zingiber officinale* (rhizome), and leek (*Allium iranicum*) juice, and then boiled with sesame oil until the water is removed	(24)
	39	*Lawsonia inermis* (leaf) and *Datura stramonium* (leaf) leaves should be mixed with equal amounts of water and sesame oil and boiled, then *Peganum harmala* (seed) and *Anethum graveolens* (seed) should be added. When the oil remains and the water evaporates, crushed *Colchicum autumnale* (rhizome) should be added	(24)
	40	Cuts of *Smilax china* (root) are boiled in water along with *Tradescantia pallida* leaves soaked in water as a mixture in sesame oil or rose oil, until the water evaporates, then strained, and *Colchicum autumnale* (rhizome) should be ground and added	(24)
	41	*Colchicum autumnale* (rhizome), *Cassia angustifolia* (aerial parts), *Terminalia chebula* (fruit), *Prunus dulcis* (fruit), and *Crocus sativus* (Flower stigma) mixed and soaked and prepared in an oil	(26)
	42	Nettle seed oil (*Urtica dioica*): distilled in water and subsequently boiled in sesame oil until	(26)
Tala	43	*Curcuma zedoaria* (root), *Laurus nobilis* (aerial parts), *Thymus vulgaris* (aerial parts), *Commiphora myrrha* (gum), *Boswellia thurifera* (gum), *Zingiber zerumbet* (rhizome), *Anacyclus pyrethrum* (root), ground and extracted in lily oil or bitter almond oil	(22)

In the above formulations, some herbs were repeated more frequently. These herbs are listed in the table below, arranged by number of citations in the manuscripts.

3.1. Colchicum autumnale L.

In the Unani System of Medicine (*Colchicum autumnale* L.), which belongs to the family of Liliaceae, it is primarily used to treat arthritis. A related investigation was conducted to evaluate the phytochemical constituents, antioxidant, and anti-inflammatory activities

of *C. autumnale*. Docking studies assessed the anti-inflammatory activity. Quantitative analysis indicated that the dichloromethane extract contains the highest amount of phenolic and flavonoid constituents. Docking analysis revealed that colchicoside inhibits IL-6, with a binding energy of -7.1 kcal/mol. The anti-inflammatory activity suggests that this plant can be used for relieving the symptoms of inflammation. Comparative docking studies revealed colchicoside to be the most potent anti-inflammatory compound compared to other medications and the standard drug diclofenac (27).

3.2. Crocus sativus L.

Investigations on the antinociceptive and anti-inflammatory effects of saffron (*Crocus sativus*) extracts and/or active constituents in different experimental models are summarized in Table 3. Inflammatory processes, elevated levels of reactive oxygen species (ROS), and subsequently oxidative stress have been known as critical factors in the development of neuropathic pain via involvement in the central sensitization of the spinal cord (28, 29). Applications of antioxidants that suppress cytokines have been considered to be useful in the treatment of neuropathic pain (30, 31). The beneficial effects of saffron, including anti-allodynia and anti-hyperalgesia, have been primarily attributed to the antioxidant and anti-inflammatory properties of its active ingredients. From different *in vitro* and *in vivo* studies of saffron extracts, crocetin, crocin, and safranal have been repeatedly shown to have radical scavenging activities. Meanwhile, the highest antioxidant capacity was shown by crocin (32, 33). In a hemorrhagic shock model, crocetin reduced mRNA expressions of TNF-α, interleukin 1β (IL-1β), and iNOS in rat liver. Crocin was also reported to have an anti-inflammatory effect in some inflammation models. Additionally, the benefits of saffron extracts and safranal in inflammatory conditions were demonstrated in formalin-induced inflammation in the rat model. Studies indicated that aqueous saffron extract inhibited formalin-induced paw edema in the chronic phase. Meanwhile, L-NAME, a nonselective inhibitor of nitric oxide synthase (NOS), enhanced the extract's effects. In one study, intravenous injection of crocetin blocked LPS-induced aqueous flare elevation and partially prevented prostaglandin E2 (PGE2)-induced aqueous flare in rabbits (34).

3.3. Anacyclus pyrethrum (L.) Link

A. pyrethrum is a plant commonly used in Moroccan traditional medicine to treat inflammatory and painful conditions. A related study has evaluated the antinociceptive, anti-inflammatory, and antioxidant activities of aqueous and methanol extracts of the plant's root. The antinociceptive activity was assessed in mice using the acetic acid-induced writhing test, the hot plate test, and the formalin test. Both extracts significantly decreased edema. Chronic treatment with both extracts also significantly alleviated persistent pain hypersensitivity. *A. pyrethrum* could be potentially useful for treating pain and inflammatory disorders in humans (35).

3.4. Papaver somniferum L.

P. somniferum is a member of the Papaveraceae family. The most important alkaloids of *P. somniferum* are morphine, codeine, thebaine, and noscapine. The most important application of Papaver alkaloids is due to their analgesic properties. Use of opium poppy as a medicinal plant has been described in the ancient literature of the Indian system of medicine (Ayurveda) (36). In 1905, German scientist Sertüner first isolated the main pain-relieving component of this plant, the alkaloid morphine. However, the mechanism behind the analgesic action of morphine was largely unknown until the last century, when the existence of endogenous peptide opioids such as ß-endorphin, met-enkephalin, and dynorphin was first reported. Later, several research

groups significantly expanded our understanding of how opioid drugs produce pain relief by identifying three classical Mammalian opioid receptors are named mu (μ), delta (δ), and kappa (κ). Recently, the genes encoding these receptors were cloned and found to be members of the seven-transmembrane G-protein-coupled receptor family (37, 38).

3.5. Lawsonia inermis L.

Studies have shown that *L. inermis* leaves can also lower normal body temperature, whereas paracetamol and nonsteroidal anti-inflammatory drugs only reduce temperature during a fever. The ability of *L. inermis* leaves to decrease normal body temperature suggests a central mechanism that may not involve the cyclooxygenase pathway, which is targeted by nonsteroidal anti-inflammatory drugs. Additionally, the results indicate that the plant's leaves contain anti-inflammatory compounds. Notably, the anti-inflammatory activity of *L. inermis* leaf extract decreased at 3 hours and then increased again later (after 4 hours) (39).

3.6. Hordeum vulgare L.

Barley (*H. vulgare*) has a long history of use as food and medicine. In Unani medicine, barley is a key remedy commonly used to treat many disorders of the respiratory, gastrointestinal, musculoskeletal systems, skin, and more. It is used for obesity, diabetes, headache, pain, throat inflammation, acute joint swelling, gout, chronic swellings, diarrhea, fever, skin eruptions, hyperpigmentation, and other conditions. Recent studies show that barley contains beta-glucan and various bioactive compounds with many biological activities, such as lowering blood sugar, reducing cholesterol, anti-inflammatory, antioxidant, anti-obesity, anticancer, and wound healing properties. Barley is a powerful remedy offering numerous health benefits, most of which have been confirmed through preclinical and clinical research. (40).

3.7. Matricaria chamomilla L.

In a study involving 130 patients, 99 of whom were ultimately eligible, patients were randomly assigned to one of three experimental drug groups containing chamomile, diclofenac, or a placebo. The results showed a significant beneficial effect of a traditional topical formulation of chamomile flower oil on patients with OA, particularly in reducing the use of analgesics. Additionally, chamomile oil demonstrated some beneficial effects on pain, stiffness, and physical activity. Chamomile is rich in flavonoids; for example, apigenin 7-O-glucoside can strongly inhibit prostaglandin E2 levels. It interferes with the COX-2 pathway and has anti-inflammatory effects similar to NSAIDs. The chamomile's polyphenolic compounds can also exhibit anti-inflammatory effects comparable to corticosteroids by inhibiting pro-inflammatory biomarkers. Chamomile consumption significantly reduced the need for acetaminophen to relieve OA pain. For these patients, chamomile was as effective as diclofenac but at a much lower cost (41).

4. Conclusion

All mentioned medicinal plants, Colchicum autumnale, Crocus sativus, Anacyclus pyrethrum, Papaver somniferum, Lawsonia inermis, Hordeum vulgare, and Matricaria chamomilla have demonstrated demonstrated their anti-inflammatory and analgesic effects in clinical trials, in vivo, and in vitro. Formulations that include these compounds, as documented in studied textbooks, are likely to be effective in reducing pain and inflammation in patients. Formulations such as No. 1, 5, 7, 12, 13, 18, 27, 39, and 41, which combine two or more of these plants, have an even greater likelihood of being effective and ultimately being produced on a mass scale.

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Conflict of Interest

The authors declare that they have no conflict of interest.

References

1. Sarzi-Puttini P, Cimmino MA, Scarpa R, Caporali R, Parazzini F, Zaninelli A, Atzeni F, Canesi B. Osteoarthritis: an overview of the disease and its treatment strategies. S*emin Arthritis Rheum*. 2005 Aug;35(1 Suppl 1):1-10. doi: 10.1016/j.semarthrit.2005.01.013. PMID: 16084227.
2. Miller RE, Miller RJ, Malfait AM. Osteoarthritis joint pain: the cytokine connection. *Cytokine*. 2014 Dec;70(2):185-93. doi: 10.1016/j.cyto.2014.06.019. Epub 2014 Jul 24. PMID: 25066335; PMCID: PMC4254338.
3. Wood MJ, Miller RE, Malfait AM. The Genesis of Pain in Osteoarthritis: Inflammation as a Mediator of Osteoarthritis Pain. *Clin Geriatr Med.* 2022 May;38(2):221-238. doi: 10.1016/j.cger.2021.11.013. PMID: 35410677; PMCID: PMC9053380.
4. Hawker GA. Osteoarthritis is a serious disease. *Clin Exp Rheumatol.* 2019 Sep-Oct;37 Suppl 120(5):3-6. Epub 2019 Oct 14. PMID: 31621562.
5. Tang S, Zhang C, Oo WM, Fu K, Risberg MA, Bierma-Zeinstra SM, et al. Osteoarthritis. *Nat Rev Dis Primers.* 2025 Feb 13;11(1):10. doi: 10.1038/s41572-025-00594-6. PMID: 39948092.
6. Lohmander LS, Roos EM. Clinical update: treating osteoarthritis. *Lancet*. 2007 Dec 22;370(9605):2082-4. doi: 10.1016/S0140-6736(07)61879-0. PMID: 18156017.
7. Sohail R, Mathew M, Patel KK, Reddy SA, Haider Z, Naria M, et al. Effects of Non-steroidal Anti-inflammatory Drugs (NSAIDs) and Gastroprotective NSAIDs on the Gastrointestinal Tract: A Narrative Review. *Cureus*. 2023 Apr 3;15(4):e37080. doi: 10.7759/cureus.37080. PMID: 37153279; PMCID: PMC10156439.
8. Simon LS, Hatoum HT, Bittman RM, Archambault WT, Polisson RP. Risk factors for serious nonsteroidal-induced gastrointestinal complications: regression analysis of the MUCOSA trial. *Fam Med.* 1996 Mar;28(3):204-10. PMID: 8900554.
9. Hawkey CJ. COX-2 inhibitors. *Lancet*. 1999 Jan 23;353(9149):307-14. doi: 10.1016/s0140-6736(98)12154-2. PMID: 9929039.
10. FitzGerald GA, Patrono C. The coxibs, selective inhibitors of cyclooxygenase-2. *N Engl J Med.* 2001 Aug 9;345(6):433-42. doi: 10.1056/NEJM200108093450607. PMID: 11496855.
11. Richard MJ, Driban JB, McAlindon TE. Pharmaceutical treatment of osteoarthritis. *Osteoarthritis Cartilage.* 2023 Apr;31(4):458-466. doi: 10.1016/j.joca.2022.11.005. Epub 2022 Nov 19. PMID: 36414224.
12. Fuggle N, Curtis E, Shaw S, Spooner L, Bruyère O, Ntani G, et al. Safety of Opioids in Osteoarthritis: Outcomes of a Systematic Review and Meta-Analysis. *Drugs Aging.* 2019 Apr;36(Suppl 1):129-143. doi: 10.1007/s40266-019-00666-9. PMID: 31073926; PMCID: PMC6509215.
13. Yip K, Oettinger J. Why are we still using opioids for osteoarthritis? *Int J Clin Pract.* 2020 Jan;74(1):e13416. doi: 10.1111/ijcp.13416. Epub 2019 Oct 23. PMID: 31508873.
14. Sinusas K. Osteoarthritis: diagnosis and treatment. *Am Fam Physician*. 2012 Jan 1;85(1):49-56. Erratum in: Am Fam Physician. 2012 Nov 15;86(10):893. PMID: 22230308.
15. Shavlovskaya O. DMOADs and DMARDs in the treatment of patients with joint and spine diseases. Farmakoekonomika Modern Pharmacoeconomics and Pharmacoepidemiology. 2023;16(4):700-7. doi: 10.17749/2070-4909/farmakoekonomika.2023.226.
16. Oo WM, Little C, Duong V, Hunter DJ. The Development of Disease-Modifying Therapies for Osteoarthritis (DMOADs): The Evidence to Date. *Drug Des Devel Ther.* 2021 Jul 6;15:2921-2945. doi: 10.2147/DDDT.S295224. PMID: 34262259; PMCID: PMC8273751.
17. Jiang P, Hu K, Jin L, Luo Z. A brief review of current treatment options for osteoarthritis including disease-modifying osteoarthritis drugs (DMOADs) and novel therapeutics. *Ann Med Surg (Lond)*. 2024 Jun 4;86(7):4042-4048. doi: 10.1097/MS9.0000000000002214. PMID: 38989236; PMCID: PMC11230824.
18. Mancarella C, Morrione A, Scotlandi K. PROTAC-Based Protein Degradation as a Promising Strategy for Targeted Therapy in Sarcomas. *Int J Mol Sci.* 2023 Nov 15;24(22):16346. doi: 10.3390/ijms242216346. PMID: 38003535; PM-

CID: PMC10671294.
19. Gaffari F, Naseri M, Khodadoost M. Traditional Iranian medicine and the need for its revival and development. Journal: Medicine and Spiritual Cultivation. 2010;19: 63-71
20. Aghebati A, Safdari R, Dargahi H, Gushehgir S, Saharkhiz P. Evaluation of information Traditional medicine. *JIITM* 2014; 5 (3) :263-269.
21. Khosravi A, Changizi-Ashtiyani S, Amini S. The Interaction between Hellenic and Persian Pharmacology: What's the output? *Open Public Health J*. 2022, e187494452208190.
22. Aghili SM. Qarabadeen-e-Kabir: Vol. I (Urdu Translation by Hadi Husain Khan). Matba munshi nawal kishore, Lucknow, India. 1897;561.
23. Zarshenas MM, Zargaran A, Müller J, Mohagheghzadeh A. Nasal drug delivery in traditional persian medicine. *Jundishapur J Nat Pharm Prod*. 2013 Aug;8(3):144-8. doi: 10.17795/jjnpp-9990. Epub 2013 Jul 16. PMID: 24624204; PMCID: PMC3941896.
24. Khan M. Qarabadeen azam. Central Council for Research in Unani Medicine, Department of AYUSH, Government of India, New Delhi. 2009.
25. Ghaeni Heravi M. Qarabadin Salehi. Tehran, Iran: Chogan. 2013:252.
26. Baranifard M, Khazaei MM, Jamshidi S, Zarshenas MM, Zargaran A. A critical comparison between dosage forms in traditional Persian pharmacy and those reported in current pharmaceutical sciences. *Res j pharmacogn.* 2017;4(3):67-74..
27. Hailu T, Sharma R, Mann S, Gupta P, Gupta RK, Rani A. Determination of bioactive phytochemicals, antioxidant and anti-inflammatory activity of Colchicum autumnale L.(Suranjanshireen). *Indian J Nat Prod Resour.* 2021; 12(1):52-60.
28. Chung JM. The role of reactive oxygen species (ROS) in persistent pain. *Mol Interv.* 2004 Oct;4(5):248-50. doi: 10.1124/mi.4.5.3. PMID: 15471906.
29. Vallejo R, Tilley DM, Vogel L, Benyamin R. The role of glia and the immune system in the development and maintenance of neuropathic pain. *Pain Pract*. 2010 May-Jun;10(3):167-84. doi: 10.1111/j.1533-2500.2010.00367.x. Epub 2010 Apr 5. PMID: 20384965.
30. Comelli F, Giagnoni G, Bettoni I, Colleoni M, Costa B. Antihyperalgesic effect of a Cannabis sativa extract in a rat model of neuropathic pain: mechanisms involved. *Phytother Res.* 2008 Aug;22(8):1017-24. doi: 10.1002/ptr.2401. PMID: 18618522.
31. Kandhare AD, Raygude KS, Ghosh P, Ghule AE, Bodhankar SL. Neuroprotective effect of naringin by modulation of endogenous biomarkers in streptozotocin induced painful diabetic neuropathy. *Fitoterapia*. 2012 Jun;83(4):650-9. doi: 10.1016/j.fitote.2012.01.010. Epub 2012 Feb 9. PMID: 22343014.
32. Assimopoulou AN, Sinakos Z, Papageorgiou VP. Radical scavenging activity of Crocus sativus L. extract and its bioactive constituents. *Phytother Res.* 2005 Nov;19(11):997-1000. doi: 10.1002/ptr.1749. PMID: 16317646.
33. Rezaee R, Hosseinzadeh H. Safranal: from an aromatic natural product to a rewarding pharmacological agent. *Iran J Basic Med Sci.* 2013 Jan;16(1):12-26. PMID: 23638289; PMCID: PMC3637901.
34. Zeinali M, Zirak MR, Rezaee SA, Karimi G, Hosseinzadeh H. Immunoregulatory and anti-inflammatory properties of Crocus sativus (Saffron) and its main active constituents: A review. *Iran J Basic Med Sci.* 2019;22(4):334–344.
35. Manouze H, Bouchatta O, Gadhi AC, Bennis M, Sokar Z, Ba-M'hamed S. Anti-inflammatory, Antinociceptive, and Antioxidant Activities of Methanol and Aqueous Extracts of Anacyclus pyrethrum Roots. *Front Pharmacol.* 2017 Sep 5;8:598. doi: 10.3389/fphar.2017.00598. PMID: 28928658; PMCID: PMC5591861.
36. Bharti P, Singh M, Singh AK. Role of Ahiphena (Papaver sominiferum) in modern and ancient treatment. *J Ayurveda Integr Med Sci* 2023;8(10):164-6.
37. Calixto JB, Scheidt C, Otuki M, Santos AR. Biological activity of plant extracts: novel analgesic drugs. *Expert Opin Emerg Drugs.* 2001 Oct;6(2):261-79. doi: 10.1517/14728214.6.2.261. PMID: 15989526.
38. Butnariu M, Quispe C, Herrera-Bravo J, Pentea M, Sarac I, Küşümler AS, et al. Papaver Plants: Current Insights on Phytochemical and Nutritional Composition Along with Biotechnological Applications. *Oxid Med Cell Longev.* 2022 Feb 3;2022:2041769. doi: 10.1155/2022/2041769. PMID: 36824615; PMCID: PMC9943628.
39. Ali BH, Bashir AK, Tanira MO. Anti-inflammatory, antipyretic, and analgesic effects of

Lawsonia inermis L. (henna) in rats. *Pharmacology.* 1995 Dec;51(6):356-63. doi: 10.1159/000139347. PMID: 8966192.

40. Alvi M, Saleem MN. A Systematic Review of Barley (Hordeum vulgare Linn.) in Unani Medicine with Recent Advances. *J Drug Deliv Ther.* 2024;14(9):201-14. https://doi.org/10.22270/jddt.v14i9.6793.

41. Shoara R, Hashempur MH, Ashraf A, Salehi A, Dehshahri S, Habibagahi Z. Efficacy and safety of topical Matricaria chamomilla L. (chamomile) oil for knee osteoarthritis: A randomized controlled clinical trial. *Complement Ther Clin Pract*. 2015 Aug;21(3):181-7. doi: 10.1016/j.ctcp.2015.06.003. Epub 2015 Jun 9. PMID: 26256137.