

Ethnobotanical Investigation of Medicinal Plants to Manage Knee Pain Used in Ilam City in Southwest of Iran

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ABSTRACT

Ethnobotany knowledge is investigating how people of a particular tribe, culture, or region utilize native plants. In terms of plant biodiversity, Iran is one of the richest countries in southwest Asia. Ilam Province is located in the southwest part of Iran, which has a rich plant flora with over 400 plant species. The purpose of this study was to investigate the ethnobotanical properties of native medicinal plants that are used to treat knee pain. The data on consuming native medicinal plants was collected using a questionnaire. These data included the names of the plants used to treat knee pain, organs used, and methods of consumption. Then, the data was analyzed using ethnobotanical indices. The present study reports that local people consume Ziziphus rotundata, Elaeagnus angustifolia, Rosa canina L, Oliveria decumbens Vent, Punica granatum L, Pistacia atlantica, Curcuma longa, Salvia rosmarinus, Papaver macrostomum, Biebersteinia multifida, Syzygium aromaticum, Nigella sativa, Linum usitatissimum, Smyrnium cordifolium Boiss, Viola modesta Fenzl, Astragalus gossypinus Fischer, and Rhus coriaria L to reduce pain. There are a wide variety of medicinal plants in Ilam province consumed to treat knee pain. Between these plants, E. angustifolia, R. canina, P. granatum L, P. atlantica, N. sativa, and R. coriaria L are recommended for further clinical studies.

Keywords: Ethnobotanical, Medicinal Plants, Knee Pain

Mathematics Subject Classification Number: 62P20

1. INTRODUCTION

Knee pain, one of the significant causes of disability worldwide, has a great burden on the quality of life and overall health of all age groups. Prolonged knee pain reduces physical function and work productivity, and imposes financial costs that impact the economy (1). Knee pain may occur as a result of osteoarthritis (OA), patellofemoral pain, fractures, and meniscus tears. The goal of treatment

is managing chronic pain, which is the most persistent symptom. The first-line treatment is a rehabilitative approach that focuses on patient education, lifestyle improvements, and suitable exercises. Also, pain management to reduce pain is usually based on non-steroidal anti-inflammatory drugs (NSAIDs). NSAIDs are widely used for mild to moderate pain, but long-term use is not recommended. Besides, short-term use is associated with limitations in background diseases and the occurrence of severe side effects (2). These challenges prevent acceptable pain management and result in searching for other treatment options. Ethnobotany is the science of traditional usage of plants by a local culture, which investigates the therapeutic properties of plants, too. Considering the potential therapeutic effects of medicinal plants on pain management (3), we aimed to report plants used against knee pain, native to Ilam Province, Iran.

2. METHODS

Studied region

Ilam is a southwest province of Iran located between 31°58" and 34°15" North latitude, 45°24" and 48°10" East longitude, covering 20,133 square kilometers (Figure 1).



Fig 1. Geographic location of studied area

Climatic features of the studied area

Ilam province is land bordered by the country of Iraq to the west and adjoins Iranian cities from other geographical directions (Khuzestan province to the south, Lorestan province to the east and Kermanshah province to the north). Ilam city is the capital city of Ilam province. Its maximum altitude is 2,775 m and the minimum altitude is 36 m.

Study design

This cross-sectional study was conducted in Ilam city between August to November 2023. The inclusion criterion of the study was being a perfumer. A standard questionnaire was used to collect information, which included demographic information of the perfumers, plant names, used parts, and the methods of using them. Since every part of a plant contains various phytochemicals, knowing the used parts eases further studies on observed pharmacologic effects. The questionnaire was distributed to all perfumers in Ilam City (the list of perfumers in Ilam City was prepared by the Deputy Food and Drug Administration of Ilam province, which is under the supervision of the Ministry of Health and Medical Education).

After that, the data was analyzed to increase the probability of identifying promising pharmacologically effective plants. In the present study, ethnobotanical data was analyzed using ethnobotanical indices, including usage report index (UR) and relative frequency of citation (RFC). The UR index is the total number of usage reports for each plant. The RFC index is a qualitative index of the relative frequency of citations, which indicates the relative importance of each plant. The RFC index is obtained by the following formula:

$$RFC = FC / N.$$

In this formula, FC is the number of interviewees who reported a specific species and N is the total number of perfumers who were interviewed. This index ranges from zero (when no local knowledgeable person has stated the application for the plant in the interview) to one (when all local knowledgeable persons have stated the medicinal use for the plant in the interview).

Studied plants

Present study reports 17 medicinal plants, including *Ziziphus rotundata*, *Elaeagnus angustifolia* (Russian olive), *Rosa canina* L (Dog rose), *Oliveria decumbens* Vent (Moshkoorak), *Punica granatum* L (Pomegranate), *Pistacia atlantica* (Persian turpentine tree), *Curcuma longa* (Turmeric), *Salvia rosmarinus* (Rosemary), *Papaver macrostomum* (Poppy), *Biebersteinia multifida*, *Syzygium aromaticum* (Clove), *Nigella sativa* (Black cumin), *Linum usitatissimum* (Flaxseed), *Smyrniolum cordifolium* Boiss, *Viola modesta* Fenzl (Gilead), *Astragalus gossypinus* Fischer, and *Rhus coriaria* L (Sicilian sumac).

Ethical considerations

This study was approved by the ethics committee of the School of Medicine, Ilam University of Medical Sciences (Ilam, Iran; Ethical code: IR.MEDILAM.REC 1401.069). Written consent from all participating interviewees was obtained. The demographic information of perfumers is confidential.

3. RESULTS

Demographic information of local perfumers

A total of 25 perfumers in the 20-60 age range were interviewed. Most of them had a bachelor's degree (related or not related to ethnobotany) and speaking the Kurdish language. The demographic information of these perfumers is shown in Table 1.

Table 1. Demographical information of local perfumeries

Characteristics	Groups	Abundance	Relative abundance
Gender	Male	13	52%
	female	12	48%
Education	Diploma	5	20%
	Associate Degree	2	8%
	Bachelor's degree	15	60%
	Master's degree	3	12%
Age group	20-40	17	68%
	41-60	8	32%
Age	The least		26
	The most		55
Language	Kurdish	15	60%
	Lor	5	20%
	Persian	5	20%

Ethnobotanical information of the studied plants

Ethnobotanical information including scientific name, family, common name, local name, part used of plant, and using method are shown in Table 2. Among them, Apiaceae and Anacardiaceae families have been mentioned to relieve knee pain several times. In these plants, fruit was the most useful part used to manage knee pain. Also, "decoction" was the most widely used method in the local population.

Table 2. Ethnobotanical information of studied plants

Scientific name	Family	Common name	Local name	Part used of plant	Using method
<i>Ziziphus rotundata</i>	Rhamnaceae	-	Annab	Fruit	Fresh, decoction
<i>Elaeagnus angustifolia</i>	Elaeagnaceae	Russian olive	Senjed	Fruit	Fresh
<i>Rosa canina L.</i>	Rosaceae	Dog rose	Nastaran vahshi	Flowers	Brewed
<i>Oliveria decumbens Vent</i>	Apiaceae	Moshkoorak	Laal koohi	Flowers, flowering branch	Decoction
<i>Punica granatum L.</i>	Lythraceae	Pomegranate	Anar	Fruit	Fresh
<i>Pistacia atlantica</i>	Anacardiaceae	Persian turpentine tree	Peste koohi	Fruit	Oil, fresh
<i>Curcuma longa</i>	Zingiberaceae	Turmeric	Zard-Choobeh	Aerial parts	Decoction
<i>Salvia rosmarinus</i>	Lamiaceae	Rosemary	Rosemary	leaves	Decoction
<i>Papaver macrostomum</i>	Papaveraceae	Poppy	Persian poppy	Aerial parts	Plant poultice
<i>Biebersteinia multifida</i>	Geraniaceae	-	Adamak	Aerial parts	Decoction
<i>Syzygium aromaticum</i>	Myrtaceae	Clove	Cloves	Oil	Plant poultice
<i>Nigella sativa</i>	Ranunculaceae	Black cumin	Siah-dane	Seeds	Oil, decoction

<i>Linum usitatissimum</i>	Linaceae	Flaxseed	Kataan	Seeds	Fresh
<i>Smyrniun cordifolium Boiss</i>	Apiaceae	-	Andol	Aerial parts	Decoction
<i>Viola modesta Fenzl</i>	Violaceae	Gilead	Banafshe	Flowers	Brewed
<i>Astragalus gossypinus Fischer</i>	Fabaceae	-	Gavan	Aerial parts	Decoction
<i>Rhus coriaria L.</i>	Anacardiaceae	Sicilian sumac	Somaq	Fruit	Fresh

Qualitative analyses of usage frequency

In this study, the most mentioned plants to manage knee pain were *Ziziphus rotundata*, *Elaeagnus angustifolia*, *Rosa canina*, *Oliveria decumbens Vent*, *Punica granatum L.*, and *Pistacia atlantica* (all of them reported for 57.6 % usage) (Table 3).

Table 3. Qualitative analyses of usage frequency

Scientific name of plants	Percentage of usage frequency	RCF	UR
<i>Ziziphus rotundata</i>	57.6 %	0.55	5
<i>Elaeagnus angustifolia</i>	57.6 %	0.55	5
<i>Rosa canina L.</i>	57.6 %	0.55	5
<i>Oliveria decumbens Vent</i>	57.6 %	0.55	5
<i>Punica granatum L.</i>	57.6 %	0.55	5
<i>Pistacia atlantica</i>	57.6 %	0.55	5
<i>Curcuma longa</i>	38.4 %	0.62	9
<i>Salvia rosmarinus</i>	38.4 %	0.62	9
<i>Papaver macrostomum</i>	38.4 %	0.62	9
<i>Biebersteinia multifida</i>	38.4 %	0.62	9
<i>Syzygium aromaticum</i>	34.6 %	0.58	6
<i>Nigella sativa</i>	34.6 %	0.58	6
<i>Linum usitatissimum</i>	19.2 %	0.54	4
<i>Smyrniun cordifolium Boiss.</i>	19.2 %	0.54	4
<i>Viola modesta Fenzl</i>	19.2 %	0.54	4
<i>Astragalus gossypinus Fischer</i>	15.3 %	0.59	7
<i>Rhus coriaria L.</i>	15.3 %	0.59	7

4. DISCUSION AND CONCLUSION

The aim of this study was to document the usage of medicinal plants by the local community in Ilam province, Iran, for the management of knee pain. As this knowledge has been transmitted orally across generations, it is crucial to record it in order to find and develop effective treatments. Knee pain is a common prolonged pain, experienced by almost everyone in lifetime. Treating this pain is limited to NSAID medications. Taking NSAIDs is limited to short-term periods. Also, adverse effects such as renal damage, gastrointestinal ulceration, and blood coagulation disorders may occur (2).

Exploring alternative approaches such as medicinal plants can be a potential solution, given the limited effective treatments. This study reports several native medicinal plants including *Ziziphus rotundata*, *Elaeagnus angustifolia* (Russian olive), *Rosa canina* L (Dog rose), *Oliveria decumbens* Vent (Moshkoorak), *Punica granatum* L (Pomegranate), *Pistacia atlantica* (Persian turpentine tree), *Curcuma longa* (Turmeric), *Salvia rosmarinus* (Rosemary), *Papaver macrostomum* (Poppy), *Biebersteinia multifidi*, *Syzygium aromaticum* (Clove), *Nigella sativa* (Black cumin), *Linum usitatissimum* (Flaxseed), *Smyrniun cordifolium* Boiss, *Viola modesta* Fenzl (Gilead), *Astragalus gossypinus* Fischer, and *Rhus coriaria* L (Sicilian sumac), which are discussed here in order of usage frequency. For each plant, attempts have been made to present ethnobotanical features of the same part that the local people use.

Ziziphus rotundata

Genus *Ziziphus* contains alkaloids, flavonoids, terpenoids, and saponin bioactive compounds, which have shown antimicrobial, anticancer, antidiabetic, antidiarrheal, anti-inflammatory, and anti-pyretic properties. Although the analgesic effects of this plant have not been studied yet, but its toxic effects have already been worked on mice and no toxicity has been seen. However, generalizing this result to humans requires further clinical trials (4).

Elaeagnus angustifolia

Elaeagnus angustifolia has been used for the relief of pain and inflammation in patients with rheumatoid arthritis in Iranian locals and also, as an antipyretic agent in Turkey (5). Fruit extract is rich in flavonoids, coumarone, saponins, carotenoids, and tannins (6). The same as NSAIDs, this fruit extract inhibits cyclooxygenase-2 enzyme (COX-2) that leads to MAPK pathway inhibition and relieves inflammatory pain subsequently (7). Besides that, antimicrobial and anti-tumor effects of ethanolic fruit extract on glioblastoma carcinogenesis were reported before (8,9). The mechanism of anti-tumor activity is based on modulating cell-cycle process, anti-proliferative properties, and cell invasion inhibition (10). Finally, further clinical studies are required to prove analgesic effects.

Rosa canina L

Roza canina L flowers have shown anti-tumor, immunomodulatory, antioxidant, analgesic, antidiabetic, and neuroprotective effects (11). The anti-inflammatory effect was explained by reducing C-reactive protein (CRP) (an acute inflammatory protein) levels (12,13), But a clinical study failed to prove it. This clinical study on 20 female patients with arthritis rheumatoid reported no improvement in symptoms (14). This result may be caused by the small sample size and unisex population since females intend to show greater immune responses (15). Performing more clinical studies clarifies this issue.

Oliveria decumbens Vent

A decoction of *O. decumbens*'s flowers has been used to treat pain in local people. Previous studies have shown analgesic, anti-inflammatory, and anti-tumor properties of *O. decumbens* (16,17). These properties can be caused by myristicin, thymol, and carvacrol compounds (18). To our findings, analgesic effects have not been experimented previously.

Punica granatum L.

The analgesic effects of *P. granatum* fruit have been previously stated through various mechanisms. Pomegranate fruit extract inhibits COX-2 enzyme. Inhibiting COX-2 leads to MAPK pathway inhibition,

which inhibits inflammation and pain (19,20). It also inhibits inflammation by inhibiting nitric oxide production (19). Pomegranate also inhibits peripheral pain. The peripheral analgesic effect is interpreted as inhibiting peripheral nociceptors and subsequently, inhibiting pain conduction. Nociceptive pain has two phases including the early phase and late phase. Previous studies on various experimental models showed that *P. granatum* fruit suppresses both phases, which result in suppressing inflammatory pain (21). Also, it contains ellagic acid, which acts as an agonist for gamma-aminobutyric acid (GABA) that inhibits neuropathic pain (22). Considering these results, *P. granatum* fruit is a good candidate as an analgesic agent. This plant also has other therapeutic actions, including anti-microbial properties (23).

Pistacia atlantica

Fruits of *P. atlantica* contain several compounds including sabinene, bornyl acetate, camphene, limonene, phenolic, and flavonoids. It seems that the antioxidant activity of *P. atlantica* fruits is a result of phenolic and flavonoid compounds (24–26). The anti-inflammatory and wound-healing potencies of fruit oil were observed in rats. Silver sulfadiazine (a medication for treating burn wound infections) was used as a positive control. In this study, fruit oil contracted the wounds and promoted epithelial layer formation (27). Besides that, the hydroalcoholic extract was examined for healing OA pain, in which OA was induced in 50 Wistar rats. After 12 weeks of treatment, the extract reduced pain significantly (28). Also, the analgesic potential of tree gum has been previously studied. This study included 84 Iranian patients for 12 weeks. In which the analgesic effect of tree gum was compared to diclofenac gel (an NSAID drug). Gum ointment improved pain more than diclofenac gel. This analgesic effect was related to oleoresin, a resin in the tree gum (29). A similar study on 60 Iranian patients compared *P. atlantica* gum against a placebo and revealed the same results (30).

Curcuma longa

Curcuma longa has been a common spice in Asian countries for centuries. It is rich in antioxidant compounds, containing large quantities of flavonoids, phenols, tannins, and vitamin C. These compounds have various effects, including antioxidant, anticancer, and anti-inflammatory activities (31,32). The most explained mechanisms of anti-inflammatory effects are the removal of reactive agents, the chelation of metals, and elevated serum levels of inflammatory mediators (33,34). Increasing total antioxidant capacity was observed by taking daily supplementations of curcumin, the main constituent of *C. longa* (33). Pain healing effect of curcumin in OA patients was confirmed in a previous systematic review study (35). Also, a clinical study investigated the analgesic effect of *C. longa* in knee's OA patients. Daily doses of curcumin tablets (1000 mg) and ibuprofen (1200 mg) (a NSAID drug) were taken for 30 days. Curcumin showed the same potency as ibuprofen (36). The advantages of curcumin over ibuprofen are less serious gastrointestinal adverse effects and less limitation of its use in background diseases. Curcumin tablets are widely used to control pain. The toxicity profile of the plant was evaluated; no toxicity in rats (37) and no liver toxicity in healthy human subjects have been observed (38).

Salvia rosmarinus

Salvia rosmarinus, referred to as rosemary, has shown various pharmacologic activities including antimicrobial, anti-aging, anti-inflammatory, anti-tumor, and anti-nociceptive activities (39–41). The major phytochemicals of the aqueous extract of wild rosemary leaves that cause these effects are alkaloids, flavonoids, tannins, and saponins (42). Topical ointment of rosemary has been used to reduce inflammatory pain for sports injuries (43). Besides, a clinical study was performed on 111

geriatric patients with OA. In this study, rosemary was compared to ibuprofen (an NSAID drug) and both had the same efficacy in reducing pain (44). For several years, the use of rosemary ointments to reduce joint pain has been part of the treatment regimen for OA patients (45).

Papaver macrostomum

Papaver macrostomum has been used as a significant pain killer since ancient times (46). Opioids, synthetic derivatives of *P. macrostomum*, are potent analgesics and cornerstone of severe pain management in a clinical setting (46–49). Opioid alkaloids are found mostly in the aerial parts of the genus *Papaver* (50). Despite the therapeutic effects, pain management with opioids has been encountered with limitations, including drug dependency, addiction, and tolerance to analgesic effects (46,51,52). In order to investigate the toxicokinetics of poppy seeds, a recent study reported three patients. They showed adverse effects such as metabolic acidosis, convulsions, myalgia, etc. Poppy seeds contain thebaine, an alkaloid compound. Authors have claimed that observed clinical symptoms are related to thebaine blood concentration, considering previous neurotoxic effects of thebaine in animals (53). The toxicological profile of this plant should be considered in further clinical studies to determine an appropriate therapeutic window.

Biebersteinia multifida

Anti-inflammatory, analgesic, antioxidant, and anti-tumor effects of *Biebersteinia* species are supposed to be caused by flavonoids, alkaloids, phenylpropanoids, terpenoids, essential oils, and fatty acids content (54). *B. multifida* extracts have shown cytotoxic activity on breast cancer, ovarian cancer, and human cervix cancer cell lines (55). To our knowledge, there is no previous study on the analgesic effect of *B. multifida*.

Syzygium aromaticum

S. aromaticum essential oil is reported to heal pain as a plant poultice. The main constituent of this plant is eugenol, which has shown several therapeutic properties including analgesic, antioxidant, anti-inflammatory, and anti-tumor activity (56–58). *S. aromaticum* has been shown to strengthen the cells' apoptotic process that clarifies indications in cancer treatment (59). Analgesic effects of *S. aromaticum* are yet to be investigated.

Nigella sativa

Nigella sativa has been referred to as a miracle herb, because of its significant pain healing power. Anticancer, antiulcer, analgesic, immunomodulatory, and anti-inflammatory properties have been reported previously (60,61). Having anti-inflammatory activity, the seeds are effective in treating disrupted inflammatory diseases such as arthritis rheumatoid, which is a result of thymoquinone, the main active phytochemical of seed oil (62). Further clinical studies are required to prove analgesic effects.

Linum usitatissimum

Nutrient seeds of *L. usitatissimum* (also known as flax) contain fatty acids, fibers, phytoestrogen lignans, cyanogenic glycosides, flavonoids, and antioxidant compounds (63,64). These seeds have been used to treat anti-inflammatory diseases worldwide (65), which can be indicated as an analgesic outcome. On the other hand, seeds contain cyanogenic glycosides, producing hydrogen cyanide that leads to acute cyanide poisoning. This toxic potential limits the seed's daily intake. Besides that, young men and pregnant women should take precautions taking seeds, since it has phytoestrogenic

lignans. These lignans can cause hormonal disorders in the mentioned people (66). Although Ilamian local people use this plant to control pain, considering these challenges, *L. usitatissimum* does not seem to be a suitable option for pain relief.

Smyrniolum cordifolium Boiss

This medicinal plant has been used to treat gastrointestinal pain, anxiety, and insomnia previously (67). Essential oils of this plant prolong the onset time of seizure and decrease the duration of seizure through GABAergic activity (68), which can treat anxiety, insomnia, and pain. Also, the aqueous extract has high antioxidant activity which may be caused by phenolic and flavonoid contents (69). These findings promote *S. cordifolium* as an analgesic agent.

Viola modesta Fenzl

The present study reports that locals brew *V. modesta* flowers to reduce pain. This plant is a native plant that grows in the western parts of Iran. As it has been detected most recently, there are limited studies that have investigated it (70). According to Bahramnejad and colleagues, this plant contains cyclotides (71). Cyclotides are disulfide-rich peptides which are coming to attention as a molecular scaffold for peptide-based therapeutics (72). These peptides are expressed in all parts of *V. modesta*. The highest level is in capsules of flowers (71). Considering the lack of data, the analgesic effect of *V. modesta* is yet to be discovered.

Astragalus gossypinus Fischer

Tragacanth gum of *A. gossypinus*, commonly known as "*Katira*", has been applied topically as an analgesic by local Iranians (73). Major phytochemicals of *A. gossypinus* are cycloartane triterpene glycosides, labdane diterpenoids, flavonoids, and polysaccharides, which are responsible for the antioxidant activity of *A. gossypinus* (74). Further experimental studies are required to prove the analgesic effects of *A. gossypinus*.

Rhus coriaria L

Rhus coriaria's fruit, sumac, has been a common spice in Iran since old times. Sumac has been related to antioxidant, antidiabetic, and anti-nociceptive properties (75). Several studies have focused on its anti-nociception effects. The pain healing effect of sumac was compared to triamcinolone (a medium-high potency steroid). This study investigated patients with recurrent aphthous stomatitis, which is characterized by painful aphthous ulcers in the oral space. Sumac was used for six days and reduced lesion size and pain subsequently (76) but it seems that the observed analgesic effect may be due to reducing the lesion size. Another study compared hydroalcoholic leaf extract with two positive controls including morphine (an opioid drug) and aspirin (an NSAID). Anti-nociception was examined by writhing, tail flick, and formalin tests. The extract showed significant analgesic effects compared to both positive controls. Therefore, it can inhibit pain via both the central and peripheral routes and may inhibit prostaglandin synthesis (77). Prostaglandins are inflammatory mediators that contribute to pain exacerbation (78). In the mentioned *in vivo* study, the anti-nociceptive effect was related to its flavonoid content (77). These studies prove sumac's potential for analgesic effect.

This study reports on 17 medicinal plants. Some of these are currently used for treating patients. For others, there are insufficient previous studies. Some of these plants are not recommended for pain relief owing to the presence of toxic substances. Some of them are novel and have the potential to be used in future studies. These results encountered some limitations including a small sample population and limited previous pharmacologic data on phytochemicals.

. Among the medicinal plants that llamain people use to treat knee pain, *C. longa* and *S. rosmarinus* pharmaceutical products are currently on the market. The present study recommends performing further clinical studies on *E. angustifolia*, *R. canina*, *P. granatum* L, *P. atlantica*, *N. sativa*, and *R. coriaria* L.

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