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Medicinal plants used for musculoskeletal disorders in Navarra and their pharmacological validation

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ABSTRACT

Ethnopharmacological relevance: This paper provides important ethnopharmacological information on plants used in musculoskeletal disorders in Navarra.
Material and methods: Information was collected using semi-structured ethnobotanical interviews. In order to confirm the pharmacological validation of the uses, monographs from Official International Agencies (ESCOP, Commission E, WHO and EMA) were reviewed. A literature review was conducted focusing on the plants that were widely used but had no published monograph.
Results: A total of 199 pharmaceutical uses were reported, for 38 plants and 24 families, mainly represented by *Asteraceae* and *Lamiaceae* (11%, each), *Rosaceae* (8%) *and Boraginaceae, Cucurbitaceae, Equisetaceae, Malvaceae, Oleaceae and Urticaceae* (5%, each). The most frequently used parts were the aerial parts, roots, followed by inflorescences and leaves. Nine out of 38 plants (24%) and 123 uses (62%), had already been pharmacologically validated.
Conclusions: The authors propose to validate four species for their use in musculoskeletal disorders: *Verbena officinalis*, *Symphytum tuberosum*, *Hypericum perforatum* and *Equisetum* ssp.

1. Introduction

Traditional medicine is used globally and has a rapidly growing economic importance. In developing countries, traditional medicine is often the only accessible and affordable treatment available. Moreover, this medicine is becoming more and more popular in many developed countries (Bussmann, 2013). Among the positive aspects of traditional medicine, researchers have pointed to its diversity, flexibility, ease of access, continued acceptance in developing countries and increasing popularity in developed countries, relative low cost, low levels of technological inputs, relatively low side effects and increasing economic importance (Payyappallimana, 2010).

The musculoskeletal system is an organ system that gives humans the ability to move using their muscular and skeletal systems. The term musculoskeletal disorder is used to describe a variety of conditions that affect the muscles, cartilage, tendons, ligaments, joints, and other connective tissue, which are usually progressive and associated with pain. Musculoskeletal conditions are the most common cause of severe long term pain and disability in the EU and lead to significant healthcare and social support costs (The European Musculoskeletal Conditions Surveillance and Information Network, 2012). As a major cause of work absence and incapacity they also have a significant economic cost through lost productivity. They can seriously affect the quality of life of those. Typically around 50% of the EU population report musculoskeletal pain at one or more sites for at least one week in the last month (www.ec.europa.eu). Different types of manual therapies and medications such as no steroidal anti-inflammatories or opioids may be used to treat inflammation or pain. The medicinal plants can also be considered for the treatment of these diseases (Cameron and Chrubasik, 2013).

Previous studies carried out by our research group in Navarra showed that the ailments commonly treated by traditional medicine are digestive (Calvo et al., 2013), dermatological (Cavero et al., 2013), cardiovascular (Calvo and Cavero, 2014) and respiratory (Cavero and Calvo, 2014) diseases. Following on from this, the aims of the present paper are: (i) to collect information using monographs from Official International Agencies to confirm the pharmacological validation of the uses and (ii) to propose highly plants reported for these diseases for pharmacological validation.

2. Methodology

Information has been collected for 12 years, since 2003 to the present, using semi-structured ethnobotanical interviews with 667 informants in 265 locations (Navarra, Spain) following the

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methodology described in previous papers (Calvo et al., 2011; Cavero et al., 2011a, 2011b).

In order to confirm the pharmacological validation of the uses claimed by the informants, monographs from Official International Agencies: ESCOP (2003–2009), Commission E (Blumenthal et al., 2000), WHO (1999–2009) and EMA (www.ema.europa.eu/ema/index) were reviewed. A literature review was carried out for the plants that were reported to be in widespread use, for which no monograph exists.

3. Results and discussion

A total of 199 pharmaceutical uses were reported, belonging to 38 plants (82% native and 18% introduced species from other continents, or other European regions). The complete catalog of the ethnoflora of the surveyed territory is given in Akerreta (2009).

The 38 medicinal plants belong to 24 families (Tables 1 and 2), mainly represented by *Asteraceae* and *Lamiaceae* (11%, each), *Rosaceae* (8%) and *Boraginaceae*, *Cucurbitaceae*, *Equisetaceae*, *Malvaceae*, *Oleaceae* and *Urticaceae* (5%, each).

The most frequently used parts of the plants were its aerial parts (58%), roots (9%), flowered aerial parts and leaves (8% each), bulbs (5%), fruits and inflorescences (3% each) and stem (2%)

Plants were used fresh (84%), dry (3%), or either (12%) and lost knowledge (1%) for administration in different forms. The percentage of external uses was three times higher than that for internal uses (72% and 27%, respectively, lost knowledge 1%), and the most important forms of preparation was direct application of the plant, or the macerated in oil, vinegar, or alcohol (47%), poultice (36%), to rub with wine or water decoction or infusion (10%) and ointment (6%). The most important excipients of poultices preparation was eggwhite, olive oil and infusion. For internal uses, infusion (47%), decoction (20%), food (18%), maceration in alcohol or in anisette (12%) and juice (2%) were used.

Nine out of 38 plants (24%) and 123 of 199 popular uses (62%) had already been pharmacologically validated for musculoskeletal diseases by ESCOP, Commission E, WHO and EMA Monographs (Table 1). It is important to highlight that two of nine plants already had monographs in the four agencies taken into consideration.

Two out of nine plants (22%) shown in Table 1 had no monograph in the European Pharmacopoeia and/or Real Farmacopea Española.

The remaining plants (76%, 76 uses, Table 2) were reported for musculoskeletal troubles and need to be screened through standard scientific procedures for their actions. We found that the most widely treated affections fell into seven pathological categories: back pains (3%), bruises (25%), muscular pains (17%), rheuma (26%), sprains and strains (16%), strengthen bones and bone fractures (11%), and tendinitis (3%).

The external administration of the macerated in oil and ointment with wax and olive oil of *Agrimonia eupatoria* was cited (2 uses of 76 total uses, 3%) for the back pains.

In this study, the results showed that *Verbena officinalis* was employed for bruises (16 uses of 76 total uses, 21%), muscular pains (4 uses, 5%) and rheuma (4 uses, 5%). A poultice of aerial parts using eggwhite as excipient is well known as the famous "verbena omelette" for these affections. In the same way, olive oil or alcohol maceration of flowered aerial parts from *Hypericum perforatum* was used for bruises (2 uses, 3%) and muscular pains (4 uses, 5%).

The two reported applications of roots from *Symphytum tuberosum* was for sprains and twists (9 uses, 12%) and for rheuma (1 use, 1%). It is important to highlight that in the first case, the external use was crushed and placed between cloths.

The sterile aerial part of two species of horsetail, *Equisetum arvense* and *Equisetum telmateia*, were cited to bone problems and to strengthen and for broken bones (5 uses, 7%). With the same therapeutic indication, *Portulaca oleracea* was also cited (2 uses, 3%); it is also remarkable that for tendinitis, this plant was the only cited (2 uses, 3%).

In summary, it is important to highlight that the most widely cited plant for musculoskeletal affections were *V. officinalis*, *H. perforatum*, *S. tuberosum* and *Equisetum* ssp.

V. officinalis, commonly known as vervain and verbena, has been used as folk medicine for thousands of years for the treatment of abdominal mass, amenorrhea, dysmenorrhea, malaria, pharyngitis, carbuncles, edema, etc. Previous studies carried out have shown the importance from the ethnopharmacological point of view for dermatological (Cavero et al., 2013), digestive (Calvo et al., 2013) and respiratory (Cavero and Calvo, 2014) problems.

Regarding musculoskeletal problems, a review of literature from etnopharmacological studies has showed that *V. officinalis* is used in different regions of Spain: Aragon, Basque Country, Catalonia, Navarra and Valencian Community; additionally, four ethnopharmacological references were found in other areas: Italian Republic, Portuguese Republic and Republic of Bulgaria (Akerreta, 2009, and references cited therein; Cavero et al., 2011a; Menendez-Baceta et al., 2014).

Pharmacological studies employing *in vitro* and animal models have found that verbena has anti-inflammatory (Speroni et al., 2007), topical analgesic (Sarris, 2007; Calvo, 2006) and antioxidant (Rehecho et al., 2011) activity. From the phytochemical point of view, the main constituents include iridoids, flavonoids and terpenoids (Rehecho et al., 2011; Zhang et al., 2011). These compounds, along with pharmacological spectrum mentioned above could support the use of verbena for the treatment of bruises, muscle pains and rheuma.

S. tuberosum is a perennial plant commonly known as comfrey. Two species of comfrey were used in Navarra without distinction for the symptomatic treatment of sprains and twists, *S. officinale* and *S. tuberosum*. The use of *S. officinale* for this therapeutic indication is scientifically supported by Official International Agencies (Table 2). *S. officinale* roots have been used in the traditional medicine externally (as ointment, compresses, or alcoholic maceration) for treatment of disorders of the locomotor system and inflammatory disorders of joints, bone fractures and distortions (Stickel and Seitz, 2000). In recent years, several references to support the use of this species have been published for the treatment of osteoarthritis of the knee (Chrubasik and Grunwald, 2007; Smith and Jacobson, 2011) and subacute low back pain (Jurcău and Jurcău, 2013). However, *S. tuberosum* is more used in Spain: Aragon, Catalonia and Navarra (Akerreta, 2009 and references cited therein; Cavero et al., 2011a). The botanical similarity of both species can justify the same therapeutic use (Tarle and Kosi-Culibrk, 1994).

St. John's wort (*H. perforatum*) has been intensively investigated for its antidepressant activity, but dermatological and muscle–skeletal applications also have a long tradition. Traditional use of these preparations was characterized by external applications, such as oils or tinctures are used for the treatment of minor wounds, sunburns, bruises, contusions, myalgia, sciatica, rheumatism, lumbago, cramps, muscular pains, and many others (Wölfle et al., 2014). Clinical research works in this field have been scarce compared to the numerous trials about depression and other psychiatric indications. Consequently, the European Medicines Agency regards none of these applications as scientifically well established but accepts the use of topical preparations for "symptomatic treatment of minor inflammations of the skin and as an aid in the healing of minor wounds " in the context of traditional

Table 1
Plants with validation from Official sources.

Plant (Family, voucher specimen)	Part used	Ph	Preparation and administration	Popular use	FU	Monograph
Allium sativum L. (*Liliaceae*, 21718)	Bulb	A,B	Maceration in alcohol or anisette for 9 days, and the drops are taken in water (1st day: 1 drop; 2nd day: 2 drops; 3rd and 4th days: 3 drops; 5th day,2 drops; 6th, 7th, 8th, 9th days: 1 drop); food; decoction; poultice	Rheuma (7)	7	3
			Juice with honey and vinegar	Joint problems (1)	1	3
			Food: 3 or 4 cloves eaten fasting	Arthrosis (1)	1	3
Filipendula ulmaria (L.) Maxim (*Rosaceae*, 21939)	Flowed aerial part	A	Infusion	Arthritis (2)	2	4
Fraxinus angustifolia Vahl ssp. *angustifolia* (*Oleaceae*, 21844)	External bark Leaf	A,B	Decoction	Rheuma (1)	1	4[a]
			Decoction	Rheuma (1)	1	4
Fraxinus excelsior L. ssp. *excelsior* (*Oleaceae*, 21847)	Leaf	A	Infusion	Rheuma (1)	1	4
Rosmarinus officinalis L. (*Lamiaceae*, 21655)	Leaf		To rub with the macerated into alcohol	Rheuma (1); muscular pains (1); joint pains (1)	3	2,3,4
			Decoction	Pains (1); arthritis (1); rheuma (1)	3	2,3,4
	Aerial part		Infusion	Rheuma (1); strengthen bones (1)	2	2,3,4
			To rub with the macerated into alcohol, wine decoction or/and infusion; vapors with decoction	Muscular pains (18); bone pains (2); joint pains (18); rheuma (15)	53	2,3,4
			Poultice with boiled in wine	Sprains (1); strengthen broken wrists (1)	2	2,3,4
			To rub with the macerated into oil over 30–40 days	Strengthen bones (1)	1	2,3,4
	Flowed aerial part	A,B	To rub with the macerated into alcohol	Muscular pains (4); back pains (4)	8	2,3,4
			Compresses with the wine decoction	Sprains (1)	1	2,3,4
			Ointment with wax and olive oil	Bruises (1)	1	2,3,4
Sambucus nigra L. ssp. *nigra* (*Adoxaceae*, 18661)	Internal bark		Ointment with wax and olive oil	Arthritis (1)	1	3[a]
	Leaf, Branch		Poultice	Sore areas (2)	1	3[a]
	Inflorescence	A,B	Boiled in poultice	Joint pains especially knee (1)	1	3
	Fruit	A	Food	Rheuma (1)	1	3[a]
Symphytum officinale L. (*Boraginaceae*,18658)	Root		Ointment with wax and olive oil; poultice with clay	Bone fractures (1); sprains (2).	3	1,2,4
	Aerial part		Boiled in poultice	Wear of vertebrae (1); vertebrae break (1)	2	1,2,4
Urtica dioica L. (*Urticaceae*, 19661)	New shoot	A,B	Decoction; to rub	Rheuma (2)	2	1,2,3[a],4
	Aerial part	A,B	infusion	Knee pains (1); rheuma (1); arthrosis (1)	3	1,2,3[a],4
			To rub	Rheuma (17); arthrosis (1); lumbago (1)	19	1,2,3[a],4
Urtica urens L. (*Urticaceae*, 21760)	Aerial part	A,B	To rub	Rheuma (2)	2	1,2,3[a],4

Ph: Pharmacopeia; A: European Pharmacopoeia; B: Real Farmacopea Española; 1: ESCOP monograph; 2: German Commission E monograph; 3. WHO monograph; 4: EMA monograph.

[a] Different part used; FU: frequency of uses.

medicine. Increasing knowledge about pharmacological activities and its phytochemical compounds, such as phloroglucinols (hyperforin) and naphthodianthrones (hypericin), have given new impetus to investigate the potential of topical preparations in dermatological and muscle–skeletal problems (Vacek et al., 2007). Both types of compounds have potent antimicrobial, antioxidant and anti-inflammatory activity (Fathi and Ebrahimzadeh, 2013; Hammer and Birt, 2014; Orhan et al., 2013). There are some indications for synergistic activity of hyperforins and hypericins, as well as other constituents such as flavonoids, which may explain why traditional preparations seem to have robust effectivity in spite of their variable composition (Wölfle et al., 2014). Various ethnopharmacological studies carried out in different regions of Spain (Andalusia, Aragon, Cantabria, Catalonia, Galicia, Navarra and Region of Murcia) and in other Mediterranean countries (Italian Republic, Republic of Turkey and Republic of Serbia) have found the same use for the musculo-skeletal affections (Akerreta, 2009 and references cited therein).

Equisetaceae, also called the horsetail family, posses only one genus, *Equisetum*, which comprises more than twenty species, *E. arvense* and *E. telmateia* among them. Even though both species have similar chemical composition, mainly mineral salts of silicium, potassium, magnesium, aluminum and manganese, only the sterile aerial parts of *E. arvense* has monograph EMA as traditional herbal medicinal product to increase the amount of urine to achieve flushing of the urinary tract as an adjuvant in minor urinary complaints.

Traditionally its have been considered also hemostatic, healing and remineralizing. Some authors claim that the silicic compounds help to maintain the structure of the ground substance of connective tissue (collagen) and interact with the metabolism of calcium and phosphates; however these effects have not been demonstrated. Numerous ethnopharmacological studies carried out in different regions of Spain (Andalusia, Aragon, Balearic Islands, Basque Country, Canary Islands, Cantabria, Catalonia, Galicia, Navarra, Region of Murcia and Valencian Community) and in other Mediterranean countries (Italian Republic,

Table 2
Plant without pharmacological validation.

Affection	Plant (Family, voucher specimen)	Part used	A	Preparation (number of use reports)	FU	TFU
Back pains	*Agrimonia eupatoria* L. ssp. *eupatoria* (*Rosaceae*, 21932)	Aerial part	External (F)	Maceration in oil (1); ointment with wax and olive oil (1)	2	2
Bruises	*Hypericum perforatum* L. (*Clusiaceae*, 21555)	Flowered aerial part, inflorescence	External (F)	Macerated in olive oil (2)	2	
	Pallenis spinosa (L.) Cass. ssp. *spinosa* (*Asteraceae*, 18774)	Flowered aerial part	External (I)	To rub with the macerated into alcohol (1)	1	
	Verbena officinalis L. (*Verbenaceae*, 21770)	Aerial part	External (F)	Roasted with oil and egg whites in poultice and placed between cloths (16)	16	19
Muscular pains	*Artemisia herba-alba* Asso (*Asteraceae*, 21201)	Aerial part	External (F)	Poultice with boiled plant (1)	1	
	Artemisia verlotiorum Lamotte (*Asteraceae*, 21202)	Aerial part	External (D)	Baths with decoction (1)	1	
	Cucubalus baccifer L. (*Caryophyllaceae*, 21166)	Aerial part	External (F)	Crushed and placed between cloths (1)	1	
	Hypericum perforatum L. (*Clusiaceae*, 21555)	Flowered aerial part, inflorescence	External (F)	Maceration in alcohol for 42 days (2); maceration in olive oil for 40 days (2)	4	
	Malva sylvestris L. (*Malvaceae*, 21836)	Aerial part	External (F)	To clean with infusión (1)	1	
	Pseudotsuga menziezii (Mirb.) Franco (*Pinaceae*, 21884)	Bud	Internal (F)	Infusion (1)	1	
	Verbena officinalis L. (*Verbenaceae*, 21770)	Aerial part	External (F)	Roasted with oil and egg whites, in poultice (4)	4	13
Rheuma	*Achillea millefolium* L. ssp. *millefolium* (*Asteraceae*, 21185)	Inflorescence	Internal (D)	Infusion (1)	1	
	Althaea officinalis L. (*Malvaceae*, 18805)	Root	Internal (F)	Decoction 3 times/day for 15 or 30 days in autumn (1)	1	
	Brassica oleracea L. var. *oleracea* (*Brassicaceae*, 21159)	Leaf	External (F)	Poultice with infusion and clay; warmed and placed between cloths (1)	1	
	Bryonia dioica Jacq. (*Cucurbitaceae*, 21941)	Aerial part	External (F)	Poultice and put on the knee (1)	1	
	Ecballium elaterium (L.) A. Rich. ssp. *elaterium* (*Cucurbitaceae*, 21359)	Fruit	External (F)	Maceration in olive oil or alcohol (1)	1	
	Juglans regia L. (*Juglandaceae*, 22072)	External bark, leaf	External (F)	Maceration in vinegar over the night and direct application (1)	1	
	Marrubium vulgare L. (*Lamiaceae*, 21596)	Aerial part	Internal (F)	Infusion for 1–2 months (1)	1	
	Petroselinum crispum (Mill.) Fuss (*Apiaceae*, 22061)	Stem, leaf	Internal (F)	Food in salad (2)	2	
	Plantago media L. (*Plantaginaceae*, 21899)	Leaf	External (F)	Direct application (1)	1	
	Potentilla reptans L. (*Rosaceae*, 21958)	Aerial part	External (F)	Poultice (1)	1	
	Pseudotsuga menziezii (Mirb.) Franco (*Pinaceae*, 21884)	Bud	Internal (F)	Infusion (1)	1	
	Quercus ilex L. ssp. *ballota* (Desf.) Samp. (*Fagaceae*, 21536)	Branch	External (F)	To clean with decoction, twice a day for 10–12 days (1)	1	
	Rhamnus alaternus L. (*Rhamnaceae*, 19666)	Branch	Internal (F)	Decoction on an empty stomach (1)	1	
	Symphytum tuberosum L. ssp. *tuberosum* (*Boraginaceae*, 18659)	Root	Internal (F)	Maceration in alcohol, 10 drops in water; infusion (1)	1	
	Thymus vulgaris L. (*Lamiaceae*, 21713)	Aerial part	Internal (D)	Infusion (1)	1	
	Verbena officinalis L. (*Verbenaceae*, 21770)	Aerial part	External (F)	Roasted with oil and egg whites, in poultice (4)	4	20
Sprains and twists	*Symphytum tuberosum* L. ssp. *tuberosum* (*Boraginaceae*, 18659)	Root	External (F)	Crushed and placed between cloths (9)	9	
	Brassica oleracea L. var. *oleracea* (*Brassicaceae*, 21159)	Leaf	External (F)	Poultice with infusion and clay; warmed and placed between cloths (1)	1	
	Prunella vulgaris L. (*Lamiaceae*, 21648)	Whole plant	External (I)	Crushed and placed between cloths (1)	1	
	Triticum aestivum L. (*Poaceae*, 21905)	Fruit (seed)	External (D)	Decoction in wine and placed between cloths (1)	1	12
Strengthen bones and bone fractures	*Citrus limon* (L.) Burm. (*Rutaceae*, 21189)	Fruit	Internal (F)	Maceration a raw egg with lemon juice overnight, and drink the juice on an empty stomach (1)	1	
	Equisetum arvense L. (*Equisetaceae*, 18670)	Sterile aerial part	Internal (I)	Infusion (3)	3	
	Equisetum telmateia Ehrh. (*Equisetaceae*, 21394)	Sterile aerial part	Internal (I)	Infusion (2)	2	
	Portulaca oleracea L. ssp. *oleracea* (*Portulacaceae*, 21911)	Aerial part	External (F), internal (F)	Poultice (1); infusion or food (1)	2	8
Tendinitis	*Portulaca oleracea* L. ssp. oleracea (Portulacaceae, 21911)	Aerial part	External (F), internal (F)	Poultice (1); infusion or food (1)	2	2

A: Administration; F: fresh; D: dry; I: without distinction; FU: frequency of uses; TFU: total frequency of uses.

Republic of Turkey and Republic of Bulgaria) have found the same use for the musculo-skeletal affections, such as strengthen bones and fractures (Akerreta, 2009 and references cited therein; Blanco, 1996; Carriò, 2013; Cavero et al., 2011a; Menedez-Baceta et al., 2014; Parada et al., 2009; Pardo de Santayana, 2008; Pérez de Paz and Medina, 1988; Rivera et al., 2008).

Ethnobotanical, pharmacological and phytochemical studies described above could provide the basis for preparing monographs

to validate the safety and efficacy of these herbs and for approval by Official International Agencies.

4. Concluding remarks

Twenty-four percent of the medicinal plants used in Navarra for musculoskeletal disorders have been pharmacologically validated by Official International Organisms. Of the remaining 76%, the authors highlight *V. officinalis*, *H. perforatum*, *S. tuberosum* and *Equisetum* ssp. for its validation.

Numerous ethnobotanical, phytochemical and pharmacological studies suggest that these medicinal plants have proved to be effective for musculoskeletal problems and could be used after its validation, which might lead to relatively inexpensive, effective and safe therapies.

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