



Medicinal plants used for ophthalmological problems in Navarra (Spain)



M. Isabel Calvo^a, Rita Yolanda Caveró^{b,*}

^a Department of Pharmacy and Pharmaceutical Technology, Faculty of Pharmacy, University of Navarra, Irunlarrea s/n, 31008 Pamplona, Spain

^b Department of Environmental Biology, Faculty of Sciences, University of Navarra, Irunlarrea s/n, 31008 Pamplona, Spain

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ABSTRACT

Ethnopharmacological relevance: Several plants have been found to have effective against number of ophthalmological problems in Navarra.

Material and methods: Information was collected using semi-structured ethnobotanical interviews with 686 informants in 267 locations. In order to confirm the pharmacological application of the uses more cited by the informants, a literature review was conducted.

Results: A total of 57 pharmaceutical uses were reported, for 19 plants and 13 families, mainly represented by *Asteraceae*. The most frequently used parts were inflorescences, flowers, aerial parts, leaves and flowered aerial parts. The related affections fell into eleven categories: bloodshot eyes, watery eyes and wounds, improve vision, irritated eyelids, rheums and styes, tired eyes, conjunctivitis, eyewash, ocular problems in general. The most cited plants were: *Chamaemelum nobile* (L.) All., *Santolina chamaecyparissus* L. ssp. *squarrosa* (DC.) Nyman, *Sambucus nigra* L. ssp. *nigra*, *Rosa agrestis* Savi and *Calendula officinalis* L. None of them have been pharmacologically validated by Official International Organisms. From the therapeutic point of view, *Allium sativum* L., *Foeniculum vulgare* Mill., *C. officinalis*, and *S. chamaecyparissus* ssp. *squarrosa* deserve special attention, because ethnobotanical and pharmacological studies suggest that these medicinal plants are effective for ophthalmological problems.

Conclusions: The present study constitutes a good basis for further phytochemical and pharmacological research of these four plants, which could be of interest in the design of new inexpensive, effective and safe drugs. The remaining plants are needed to be screened through standard pharmacological and clinical procedures for their activities.

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1. Introduction

According to estimations, more than 50,000 flowering plants are used for medicinal purposes throughout the world (Govaerts, 2001). Frequent ethnobotanical surveys made during past few years, indicate that useful information about medicinal uses of plants may be obtained by personal interviews and field visits with inhabitants of a particular locality (Ullah et al., 2016). There are valuable regional records of medicinal plants to treat different ailments, ophthalmologic problems, amongst them.

The eye is one of the most sensitive organs of human body and is permanently exposed to different environmental agents. The eye has several natural mechanisms to defend itself against infection or trauma. Such as, tears that keep the eye lubricated and physically clear away foreign particles, dust or microorganisms. In addition, the tears contain several substances that protect against

infection; the eyelids and eye lashes protect the ocular surface from the environment and help maintaining the surface of the eye moist. However, occasionally these defense mechanisms may be disrupted, resulting in ocular problems (Sandhu et al., 2011). From redness to loss of vision, the range of conditions and diseases that affect the eye are varied and wide. The most common ocular diseases are glaucoma, conjunctivitis, cataract, ocular allergies, ocular inflammation, retinal disorders, macular degeneration, diabetic eye problems, etc. (Rowe et al., 2004). The continuous use of screens and electronic devices can also contribute to increase the number of eye problems (Jameel and Verma, 2014). Due to side effects of drugs, now a days huge numbers of herbal drugs are used for treatment of ocular diseases; traditional uses of medicinal plants are providing clues to new areas of research; hence their importance is now well recognized (Sandhu et al., 2011).

The ethnopharmacological investigation carried out by our research group in Navarra began in 2003 and continues to the present. The high number of plants collected to date has allowed the publication of several manuscripts for various affections: digestive (Calvo et al., 2013), dermatological (Caveró et al., 2013),

* Corresponding author.

E-mail addresses: mcalvo@unav.es (M.I. Calvo), rcavero@unav.es (R.Y. Caveró).

cardiovascular (Calvo and Cavero, 2014), respiratory (Cavero and Calvo, 2014), musculoskeletal (Cavero and Calvo, 2015) and neurological and mental diseases (Calvo and Cavero, 2015). The aims of the present paper are: (i) to collect information about plant species used for ophthalmological problems in Navarra; ii) to compare this information with ethnopharmacological data from other Mediterranean areas; and iii) to look for coincidences of the reported uses in the scientific literature from a pharmacological point of view.

2. Material and methods

2.1. Study area

Navarra is a territory of 10,421 km² placed to the North of the Iberian Peninsula, where three zones can be differed: the Mountain on the North, the Riverside on the South, and both separated by a zone of transition, the Middle Navarra. There are two climates, Temperate and Mediterranean. These factors provide a great biodiversity, 2650 vascular plants (Cavero et al., 2013).

2.2. Methodology

Information was collected using semi-structured ethnobotanical interviews as a technique for data collection from informants. Interviews were done since 2003–2015. Native people, 686 informants (mean age > 70 years) of 267 locations, were interviewed in Basque and Castilian, both official languages in Navarra. Interviews are generally carried out spontaneously with people who were born or have lived most of their lives in the region studied. The search for the informants in this study was performed by contacting participants through the following approaches: (a) town halls; (b) geriatrics and pensioners' clubs; (c) pharmacists in rural areas; (d) family, friends and contacts; and (e) spontaneous meetings.

In the field work we noted for each species the local name, place and collection method, drying and preservation system, parts or organs used and method of preparation, dosage and administration. The questionnaire was previously reported (Calvo et al., 2013). Voucher samples were kept in the PAMP Herbarium at the Faculty of Science (University of Navarra).

3. Results and discussion

All the information is compiled in Table 1, which includes, the plant nomenclature and voucher specimen, the main local name, part used, administration form, common popular use as claimed by the informants, preparation, total uses and ethnobotanical references in other Mediterranean areas.

A total of 57 pharmaceutical uses were reported, belonging to 19 plants (74% native and 26% introduced species from other continents, or other European regions).

The 19 medicinal plants belong to 13 families, mainly represented by *Asteraceae* (37%). The most frequently used parts were inflorescences (67%), flowers (8%), aerial parts (5%), and leaves and flowered aerial parts (3%, each one). Plants were used dry (61%), fresh (28%), or either (11%) and were administered in different forms, clean with infusion (62%), decoction (21%), direct application and maceration in olive oil (7%, each one), and ointment (3%). The percentage of external uses was 98%. The only cited plant for internal administration was *Allium sativum*.

The treated affections fell into eleven categories: bloodshot eyes, watery eyes and wounds (2%, each one), improve vision, irritated eyelids, rheums and styes (3.5%, each one), tired eyes (5%),

conjunctivitis (19%), eyewash (26%), ocular problems in general (30%).

The most widely cited plants for ophthalmological problems were: *Chamaemelum nobile* and *Santolina chamaecyparissus* L. ssp. *squarrosa* (14 uses, 23%, each one), *Sambucus nigra* ssp. *nigra* (6 uses, 10%), *Rosa agrestis* (5 uses, 8%) and *Calendula officinalis* (4 uses, 7%).

Two mixtures were cited for conjunctivitis, decoction of *Ch. nobile*, *R. agrestis* and *S. nigra* to clean eyes (mixture 1) and oil macerated of *H. perforatum*, *U. rupestris* and *V. sinuatum* as drops (mixture 2).

Five medicinal plants (26%) are cited for the first time for ophthalmological problems, *Cichorium intybus* and *Populus alba* for conjunctivitis, *Heliotropium europaeum* for eyewash, *Salvia officinalis* for irritated eyelids and *Veronica* ssp. for conjunctivitis and tired eyes. To the best of our knowledge, pharmacological references have not been found for these affections in the scientific literature.

Nine medicinal plants (47%) showed some ethnobotanical reference in another Mediterranean area: *Calendula officinalis*, *Hypericum perforatum*, *Olea europaea*, *Tanacetum parthenium* and *Umbilicus rupestris* in Catalonia, *Rosa agrestis* in Basque Country, *Helichrysum stoechas* in Catalonia and Valencian Community, *Verbascum sinuatum* in the Kingdom of Morocco, and *Allium sativum* in the Portuguese Republic and the Kingdom of Morocco.

Finally, ethnobotanical review showed five plants (26%) with numerous ethnobotanical studies in different Mediterranean areas: *Chamaemelum nobile*, *Chamomilla recutita*, *Foeniculum vulgare*, *Sambucus nigra* ssp. *nigra* and *Santolina chamaecyparissus* ssp. *squarrosa*.

From the therapeutic point of view, *A. sativum*, *C. officinalis*, *F. vulgare* and *S. chamaecyparissus* ssp. *squarrosa* deserve special attention, because published pharmacological studies could confirm some of these ophthalmological uses.

Allium sativum, commonly known as ajo or galic, is a species in the onion genus, *Allium*. It is native of central Asia and has long been a staple in the Mediterranean region, as well as a frequent seasoning in Asia, Africa and Europe. According to the results obtained in different clinical trials, garlic can be used as an adjunct in the prophylaxis of atherosclerosis and hyperlipidemia. It is also used to improve circulation in peripheral arterial vascular disorders: hypertension, arterial disease, intermittent claudication, prevention of thromboembolism (ESCOP, 2003–2009). For its antimicrobial action it is useful to combat colds and other respiratory tract infections (ESCOP, 2003–2009).

In the last few years, five pharmacological studies have been published in relation to the beneficial effect of garlic on certain ophthalmological affections, two of them for the treatment of keratoconjunctivitis (Polat et al., 2008; Bandyopadhyay et al., 2010), two anticataract (Javadzadeh et al., 2009; Raju et al., 2008), and the last one for the treatment of ocular infections against *Aspergillus flavus* (Ahmed et al., 2012). These studies confirm the ethnobotanical data for this species.

Calendula officinalis, commonly known as calendula, is widely distributed throughout the world as an ornamental plant. It has long history of usage by the folk systems because of its rich ethnomedicinal values. The European Medicines Agency (EMA-HMPC, 2008) has approved the traditional use of topical preparations for the symptomatic treatment of minor inflammations of the skin and as an aid in healing of minor wounds, and for the symptomatic treatment of minor inflammations in the mouth or the throat.

Although there are only two ethnobotanical references, in Navarra and Catalonia, two pharmacological studies have recently appeared related to ophthalmology. In the first one, Varzaru et al., (2015) determined by HPLC the content of several bioactive compounds (lutein and zeaxanthin, vitamin E and zinc) in *C. officinalis*,

Table 1. Ethnopharmacological characteristics of plants reported for ophthalmological problems in Navarra, including scientific name, common names, part used, popular uses and preparation, total uses and ethnobotanical references.

Scientific name (Family, voucher specimen)	Common names	Part used	A	Common popular uses (number of use reports) and preparation	TU	Ethnobotanical references
<i>Allium sativum</i> L. (<i>Liliaceae</i> , 21,718)	ajo, garlic	Bulb	Internal (F)	Improve vision (1): maceration in alcohol for 40 days, and the drops are taken consecutively (1st day: 1 drop; 2nd day: 2 drops; until 40th day: 40 drops; then gradually decreases the number of drops, from 40 to 1; it can be dissolved in water.	1	SPAIN: Navarra (Akerreta, 2009). PORTUGUESE REPUBLIC (Camejo-Rodríguez, 2001). KINGDOM OF MOROCCO (Hseini and Kahouadj, 2007).
<i>Calendula officinalis</i> L. (<i>Asteraceae</i> , 18,788)	caléndula, calendula	Inflorescence	External (F)	Conjunctivitis (2): infusion (1), ointment with wax and olive oil (1). Irritated eyelids (2): infusion (1), ointment with wax and olive oil (1).	4	SPAIN: Catalonia (Bonet and Vallès, 2006), Navarra (Akerreta, 2009).
<i>Chamaemelum nobile</i> (L.) All. (<i>Asteraceae</i> , 21,222)	manzanilla, kamamila, roman chamomille	Inflorescence	External (D)	Conjunctivitis (3): infusion (2), mixture 1: decoction of <i>Ch. nobile</i> , <i>R. agrestis</i> and <i>S. nigra</i> (1). Eyewash (5): decoction (4), infusion (1). Ocular problems (2): infusion. Rheum (1): infusion. Styte (1): infusion. Watery eyes (1): infusion. Wounds (1): infusion.	14	SPAIN: Basque Country (Peillen, 1994), Cantabria (Pardo de Santayana, 2004), Castile-La Mancha (Verde, 2002), Navarra (Akerreta, 2009; Cervero et al., 2011; Fernández, 1981, 1990;), Principality of Asturias (San Miguel, 2004). PORTUGUESE REPUBLIC (Pinto, 2005; Rivera and Obón, 1995).
<i>Chamomilla recutita</i> (L.) Rauschert (<i>Asteraceae</i> , 21,230)	manzanilla, chamomille	Inflorescence	External (D)	Ocular problems (1): infusión.	1	SPAIN: Andalusia (Casado, 2003; Espinosa et al., 2001; Fernández-Ocaña, 2000; González-Tejero, 1989; Martínez-Lirola et al., 1997; Ortuño, 2003), Aragon (Ferrández and Sanz, 1993; Villar et al., 1987), Castile-La Mancha (Verde, 2002), Catalonia (Agelet, 1999; Agelet et al., 2002; Bonet and Vallès, 2006; Muntané, 2002, 2005; Parada et al., 2002; Raja, 1995; Raja et al., 1997; Vallès et al., 1996), Galicia (Blanco et al., 1999), Navarra (Akerreta 2009; Fernández, 1981; Lakar and Telletxea, 2006; Nieto, 1992), Region of Murcia (Obón and Rivera, 1991). ITALIAN REPUBLIC (Ballero et al., 2001; Guarrera et al., 2005a, 2005b; Pieroni et al., 2004). HELLENIC REPUBLIC (Hanlidou et al., 2004).
<i>Cichorium intybus</i> L. (<i>Asteraceae</i> , 21,237)	achicoria, chicory	Root	External (F)	Conjunctivitis (1): infusión.	1	SPAIN: Navarra (Akerreta, 2009).
<i>Foeniculum vulgare</i> Mill. (<i>Apiaceae</i> , 22,039)	hinojo, fennel	Shoot, fruit	External (F,I)	Improve vision (1): direct application. Tired eyes (1): maceration in olive oil.	2	SPAIN: Andalusia (Casana, 1993; Galán, 1993; González-Tejero, 1989; Ortuño, 2003), Canary Islands (Pérez and Hernández, 1999), Castile-La Mancha (Verde, 2002), Catalonia (Bonet and Vallès, 2006; Muntané, 2005), Navarra (Akerreta 2009; Fernández, 1990), Region of Murcia (Obón and Rivera, 1991), Valencian Community (Mulet, 1991). PORTUGUESE REPUBLIC (Neves et al., 2009). REPUBLIC OF TURKEY (Polat and Satil, 2012). ISLAMIC REPUBLIC OF PAKISTAN (Mahmood et al., 2013).
<i>Helichrysum stoechas</i> (L.) Moench ssp. <i>stoechas</i> (<i>Asteraceae</i> , 21,247)	manzanilla, manzanilla fina, everlasting flower	Inflorescence	External (D)	Ocular problems (2): infusión.	2	SPAIN: Catalonia (Agelet, 1999; Bonet and Vallès, 2006), Navarra (Akerreta 2009), Valencian Community (Mulet, 1991).
<i>Heliotropium europaeum</i> L. (<i>Boraginaceae</i> , 21,122)	heliotropo silvestre, european heliotrope	Flowered aerial part	External (F)	Eyewash (1): infusión.	1	SPAIN: Navarra (Akerreta, 2009).
<i>Hypericum perforatum</i> L. (<i>Clusiaceae</i> , 21,555)	hipérico, St. John's Wort	Flowered aerial part	External (F)	Conjunctivitis (1): mixture 2. maceration in oil of <i>H. perforatum</i> , <i>U. rupestris</i> and <i>V. sinuatum</i> for 40 days; it applies as drops.	1	SPAIN: Catalonia (Agelet, 1999), Navarra (Akerreta 2009).
<i>Olea europaea</i> L. var <i>europaea</i> (<i>Oleaceae</i> , 21,855)	olivo, european olive	External bark	External (F)	Bloodshot eyes (1): egg white boiled and apply between cloths	1	SPAIN: Catalonia (Bonet and Vallès, 2006), Navarra (Akerreta 2009).
<i>Populus alba</i> L. (<i>Salicaceae</i> , 21,930)	álamo blanco, white poplar	Leaf	External (I)	Conjunctivitis (1): decoction.	1	SPAIN: Navarra (Akerreta, 2009).
<i>Rosa agrestis</i> Savi (<i>Rosaceae</i> , 21,970)	rosa, tapaculos, rose	Flower	External (I)	Conjunctivitis (1): see mixture 1. Eyewash (1): infusion. Ocular problems (3): infusion (2), decoction (1).	5	SPAIN: Basque Country (Menéndez-Baceta et al., 2014), Navarra (Akerreta, 2009).
<i>Salvia officinalis</i> L.	gallocresta, sage	Seed	External	Irritated eyelids (1): direct application within the eyelid.	1	SPAIN: Navarra (Akerreta, 2009).

(<i>Lamiaceae</i> , 1676)			(F)	
<i>Sambucus nigra</i> L. ssp. <i>nigra</i> (<i>Adoxaceae</i> , 18,661)	Saúco, elder	Leaf, inflorescence	External (F,D,I)	Conjunctivitis (2): infusion (1), see mixture 1 (1). Eyewash (1): infusión. Ocular problems (2): decoction (1), inhaled into eyes (1). Rheum (1): decoction.
<i>Santolina chamaecyparissus</i> L. ssp. <i>squarrosa</i> (DC.). Nyman (<i>Asteraceae</i> , 18,775)	manzanilla, manzanilla del monte, garden cypress	Inflorescence	External (D)	Conjunctivitis (1): infusion. Eyewash (5): infusion. Ocular problems (6): infusion. Styes (1): infusion. Tired eyes (1): infusion.
<i>Tanacetum parthenium</i> (L.) Schultz Bip. (<i>Asteraceae</i> , 21,309)	San Juan Lorek, manzanilla, feverfew	Inflorescence	External (D)	Eyewash (2): infusión.
<i>Umbilicus rupestris</i> (Salisb.) Dandy (<i>Crassulaceae</i> , 21,347)	ombligo de venus, navelwort	Aerial part	External (F)	Conjunctivitis (1): see mixture 2.
<i>Verbascum sinuatum</i> L. (<i>Scrophulariaceae</i> , 22,013)	Gordolobo, mullein	Flower	External (F)	Conjunctivitis (1): see mixture 2.
<i>Veronica</i> sp. (<i>Plantaginaceae</i> , 22,021)	Verónica, common speedwell	Aerial part	External (I)	Conjunctivitis (1): decoction. Tired eyes (1): decoction.
				6 <u>SPAIN</u> : <i>Andalusia</i> (Alcántara 1990; Fernández-Ocaña, 2000), <i>Aragon</i> (Ferrández and Sanz, 1993; Villar et al., 1987), <i>Balearic Islands</i> (Carrió and Vallès, 2012), <i>Basque Country</i> (Menéndez-Baceta et al., 2014; Peillen, 1994), <i>Canary Islands</i> (Perera López, 2006), <i>Cantabria</i> (Pardo de Santayana, 2004), Castile and León (Gallego, 2009; García Jiménez, 2007; González, 2009; González et al., 2010; Velasco et al., 2010), <i>Catalonia</i> (Agelet, 1999; Agelet, 2008; Agelet et al., 2002; Bonet 2001; Bonet and Vallès, 2006; Bonet et al., 1999; Llongarriu and Sala, 2005; Mulet, 1990; Muntané, 2002, 2005; Parada, 2007, 2008; Parada et al., 2002, 2009; Raja, 1995; Rigat, 2005; Rigat et al., 2007; Royo et al., 2008; Selga, 1998; Vallès et al., 2004), <i>Galicia</i> (Anllo Naveiras, 2011; Blanco, 1996; Blanco et al., 1999), <i>Navarra</i> (Akerreta, 2009; Fernández, 1981, 1990), <i>Principality of Asturias</i> (San Miguel, 2004), <i>Region of Murcia</i> (Obón and Rivera, 1991; Rivera et al., 1994, 2008), <i>Valencian Community</i> (Conca and Oltra, 2005; Fresquet et al., 2001; Mulet, 1991). <u>ITALIAN REPUBLIC</u> (Ballero et al., 2001; Guarrera, 2005; Guarrera et al., 2005a). <u>HELLENIC REPUBLIC</u> (Malamas and Marselos, 1992). <u>PORTUGUESE REPUBLIC</u> (Camejo-Rodrigues, 2001).
				14 <u>SPAIN</u> : <i>Catalonia</i> (Bonet et al., 1999; Carrió et al., 2012; Parada et al., 2002, 2007; Vallès et al., 1996), <i>Navarra</i> (Akerreta, 2009; Akerreta et al., 2007; Calvo et al., 2011; Caveró et al., 2011), <i>Valencian Community</i> (Mulet, 1991).
				2 <u>SPAIN</u> : <i>Catalonia</i> (Agelet, 1999; Agelet and Vallès, 2003; Parada, 2007; Vallès et al., 1996), <i>Navarra</i> (Akerreta, 2009).
				1 <u>SPAIN</u> : <i>Catalonia</i> (Bonet et al., 1999; Parada, 2007; Parada et al., 2002) <i>Navarra</i> (Akerreta, 2009).
				1 <u>SPAIN</u> : <i>Navarra</i> (Akerreta, 2009). KINGDOM OF MOROCCO (Bellakhdar et al., 1991; Merzouki et al., 2000).
				2 <u>SPAIN</u> : <i>Navarra</i> (Akerreta, 2009).

A: Administration; F: fresh; D: dry; I: without distinction; TU: total uses.

which could be benefic in treating inflammatory eye disorders. However these authors considered that future research is needed regarding the pharmacokinetics, safety and efficacy in patients (clinical trials). In the second study, solid lipid nanoparticles were loaded. The results suggested that this formulation could provide a controlled therapeutic alternative for reducing disease-related symptoms and improving epithelium repair in ocular surface (Arana et al., 2015).

Foeniculum vulgare, commonly known as hinojo or fennel, is a hardy, perennial herb with yellow flowers and feathery leaves. It is indigenous to the shores of the Mediterranean but has become widely naturalized in many parts of the world, especially on dry soils near the sea-side and on riverbanks. It is a highly aromatic and flavored herb with culinary and medicinal uses. The European Medicines Agency (EMA-HMPC, 2007) has approved the traditional use for symptomatic treatment of mild, spasmodic gastrointestinal complaints including bloating, and flatulence, symptomatic treatment of minor spasm associated with menstrual periods, and as expectorant in cough associated with cold.

Recently, trans-anethole, one of the main compounds from *F. vulgare* fruits, has shown activity on the inhibition of aldose reductase and anti-cataract action (Dongare et al., 2012). The aqueous seed extract also showed significant oculohypotensive activity (Agarwal et al., 2008).

Santolina chamaecyparissus, commonly known as manzanilla del monte or garden cypress, is a hardy aromatic, dwarf evergreen shrub native to the West and Central Mediterranean area (growing wild, e.g., in Spain, Italy, Tunisia and Morocco, and being naturalized in parts of Britain). The infusion of this specie is employed for the treatment of conjunctivitis, eyewash, styes, tired eyes and ocular problems in general (Table 1). In relation with ophthalmological problems, it has shown inhibitory activity of free radicals in the cornea (Serra et al., 1991).

These data constitute a good basis for further phytochemical and pharmacological research of these four plants, which could be of interesting in order to design new inexpensive, effective and safe drugs. It is also important to highlight that the remaining plants needed to screen through standard pharmacological and clinical procedures for their activities.

4. Concluding remarks

This investigation is the first one in Navarra to focus on plants for ophthalmological problems. This is the first step in pharmaceutical bioprospection, and these data may be the starting point for further research aimed at obtaining products for therapeutical uses. Nineteen were the cited for ophthalmological problems. However, the safety and efficacy of their uses has not been pharmacologically validated by Official International Organizations.

From the therapeutic point of view, *A. sativum*, *C. officinalis*, *F. vulgare* and *S. chamaecyparissus* ssp. *squarrosa* deserve special attention, because ethnobotanical, phytochemical and pharmacological studies suggest that these medicinal plants are effective for ophthalmological problems. The evidence of these folk uses could be the key information in simplified procedures established by the European Union for the registration of herbal medicinal products based on traditionally used plants, reinforcing the already recognized role of ethnopharmacology in the mentioned applied research and development field.

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