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Original article

The pharmacological validation of medicinal plants used for digestive problems in Navarra, Spain

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Abstract

Introduction: To provide significant ethnopharmacological information on the plants used to treat digestive problems in the Navarra region of Spain.

Materials and methods: Information was collected using semi-structured, ethnobotanical interviews with 667 informants (mean age 72; 55.47% women, 44.53% men) in 265 locations. Monographs from the European Scientific Cooperative on Phytotherapy (ESCOP), the German Commission E, the World Health Organization (WHO), the European Medicines Agency (EMA), the European Pharmacopoeia (Ph. Eur.) and the Real Farmacopea Española (RFE) were used to confirm and validate the pharmacological actions for the reported uses of these plants. In cases when frequently reported plants were not covered by a monograph, a literature review was performed using a new tool from the University of Navarra: the UNIKA database.

Results: A total of 1214 pharmaceutical uses were reported by the informants of this study; these uses originated from 126 plants and 47 families and were mainly represented by *Asteraceae*, *Lamiaceae* and *Rosaceae*. The most frequently used parts of the plants were the inflorescences, followed by the flowered aerial parts and fruits. Thirty-three out of 126 plants (26%) and 322 of their identified 1214 popular uses (27%), have already been pharmacologically validated.

Conclusions: The authors propose that four species should be explored and validated (*Santolina chamaecyparissus* ssp. *squarrosa*, *Jasonia glutinosa*, *Jasonia tuberosa* and *Prunus spinosa*) because these species are frequently mentioned and show promise for therapeutic treatments.

Keywords: Digestive; Gastroenterological symptoms; Pharmacological validation; Traditional knowledge; Ethnopharmacology; Navarra

Introduction

The modern pharmaceutical industry is paying increased attention to medicinal plants as a resource for medicine development [1].

Additionally, in many developed countries, traditional medicine (TM) is becoming more and more prevalent. The percentage of the population that has used TM at least once in their lifetime is 48% in Australia, 70% in Canada, 42% in the USA, 38% in Belgium and 75% in France [2]. For this reason, the WHO has defined its role in TM by developing a strategy to address the issues of policy, safety, efficacy, quality, access and the rational use of TM [2].

Plants have been utilized as medicines throughout human history [3]. The use of herbs as medicines to treat ailments of the digestive tract is widespread. The human digestive system is a complex series of glands and hollow organs that process food. To use the food, the body must break it down into smaller molecules to build and nourish cells and to provide energy, and the body must also excrete the waste byproducts. The inner layer of these hollow organs is called the mucosa. In the mouth, stomach, and small intestine, the mucosa contains tiny glands that produce juices to help digest food. Two solid organs (the liver and pancreas) produce or store digestive chemical juices that reach the small intestine [4]. Taking into consideration that disorders of this system are usually closely interrelated, the medicinal plants

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used for treatment tend to be multipurpose and can be used for a variety of digestive symptoms and disorders [5].

Previous studies carried out by our research group in Navarra [6–9] have shown that the main ailments and/or purposes of treatment in traditional medicine are digestive problems, including carminative, tonic, aperitif, stomach ache, digestive, intestinal problems, evil tripe, diarrhea, liver problems, gallbladder problems, indigestion, toothache and a bad mood. The aim of the present paper is to identify the medicinal plants used for digestive problems in different regions of the Mediterranean basin that should be pharmacologically validated.

Methods

Study area

Navarra is a territory of 10,421 km^2 in the northern part of the Iberian Peninsula and can be differentiated into three zones: the mountains in the north, the riverside in the south, and a transitional zone, middle Navarra, that separates these two regions. In this region, there are two macro-bioclimates, the temperate and Mediterranean bioclimates. The oceanic temperate bioclimate appears in the northern part of the territory and is characterized by mild temperatures and high precipitation throughout the year. In the middle zone, the precipitation decreases, and the oceanic temperate climate with seasonal rainfall changes from the sub-Mediterranean variant with seasonal rainfall to the far south Mediterranean variant, which is characterized by a seasonal drought. These factors provide a great diversity of plant communities and a rich flora, with 2650 vascular plants [10].

Field studies

Information was collected using semi-structured ethnobotanical interviews with 667 informants (55.47% women and 44.53% men, mean age 72 years) in 265 locations. During the period of our study (2002–2012), we realized that elderly people possessed greater knowledge of the utilization of medicinal plants compared to the younger generation. In addition, the younger generations showed less interest in traditional practices, mostly due to a poor recognition of traditional medicine and the availability of modern health facilities. A similar scenario has been suggested by ethnobotanical studies in developed countries [3]. 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 [6–9].

During our field work, we noted, for each species, the local name, place and collection method, the drying and preservation system, the parts or organs used and the method of preparation, dosage and administration (Fig. 1). Plant vouchers were collected, mostly in collaboration with the informants, and authenticated according to Flora Iberica [11] and Flora of the Basque Country [12]. These specimens were authenticated by Dr. R.Y. Cavero (Department of Plant Biology–Botany). Voucher samples are kept in the PAMP Herbarium at the Faculty of Science (University of Navarra).

Plants with pharmacological validation

To confirm the pharmacological validation of the uses claimed by the informants, monographs from the European Scientific Cooperative on Phytotherapy (ESCOP), the German Commission E, the World Health Organization (WHO), the European Medicines Agency (EMA), the European Pharmacopoeia (Ph. Eur.) and the Real Farmacopea Española (RFE) were reviewed [13–18]. These monographs are responsible for evaluating the quality, security and efficacy of herbs.

The monographs, primarily published by the German European Commission, are an authoritative description of the uses and side-effects of over 300 herbs and herbal combinations (phytomedicines). The monographs are based on strict scientific investigation and are now recognized globally and used by herbalists, pharmacies, and medical doctors alike. The following three different types of monographs were published to determine how an herb would be regulated in Germany: Approved, Neutral and Unapproved. 'Approved' monographs allow for the use of the herb as a non-prescription drug; 'Neutral' monographs do not endorse a therapeutic benefit but still permit the sale of the herb without a safety concern; and 'Unapproved' monographs prohibit the normal sale of the herb because the risk of using the herb is deemed high [13].

New monographs are now produced by the European Scientific Cooperative on Phytotherapy (ESCOP) and are published under the name ESCOP Monographs. The ESCOP was founded as an umbrella organization of national associations for phytotherapy and consists of the majority of countries within the European Union as well as a number of non-EU countries. The ESCOP monographs constitute an up-to-date review of scientific information on the therapeutic uses of herbal medicines, including indications, dosage, contra-indications, interactions and undesirable effects, together with the summaries of pharmacological, clinical and toxicological data. These monographs provide the evidence base for the clinical use of herbal medicinal products [14].

The World Health Organization (WHO) published a series of 4 volumes referred to as the "*WHO monographs on selected medicinal plants*", which include data on the quality, safety and efficacy of herbs [15].

The European Medicines Agency (EMA) publishes a full scientific assessment report, called the *European public assessment report*, for every medicine granted a central marketing authorization by the European Commission. This search identifies *herbal substances* that are designated for assessment by the European Medicines Agency's Committee on Herbal Medicinal Products (HMPC). Each substance will be at a different stage of assessment, and various documents will be associated with the substance depending on where it is in the assessment process. The HMPC conclusions on the herbal substance at the end of the assessment process can be found in the final Community Herbal

Ethnobotany Interview

Date : Nº:

PERSONAL INFORMATION			
Name			
Date of birth		Sex	
Adress			
Locality		Zone	
Phone		e-mail	

GENERAL PLANT INFORMATION	
Local name	
Scientific name	
Habitat	

PLANT COLLECTION	
Place	
Harvest time	
Treatment or manipulation	

USED ORGAN									
Root		Rhizome		Bulb		Stem		Leaf	
Bark		Flower		Inflorescence		Fruit		Juice	

DRYING AND CONSERVATION			
Drying	No		
	Yes		
Method of drying			
Conservation			

METHOD OF PREPARATION									
Infusion		Decoction		Maceration		Tinture		Collyrium	
Syrup		Bath		Sitz bath		Footbath		Eyewash	
Hand bath		Poultice		Compress		Foment		Enema	
Lotion		Inhalation		Gargarism		Mouthwash		Irrigation	

ADMINISTRATION	
Dosage	
Method	
Pharmacological action	

OBSERVATION

Fig. 1. Example of the questionnaire.

Monograph and may also be found in the Community list entry [16].

The European Pharmacopoeia 7th ed. (2010) (*Ph. Eur.*) of the Council of Europe is a publication that lists a wide range of active substances and excipients used to prepare pharmaceutical products in Europe. It includes more than 2000 specific and general monographs and includes herbal drugs. The monographs give quality standards for all of the main medicines used in Europe. All of the medicines sold in the 36 Member States of the European Pharmacopoeia must comply with these quality standards so that consumers have a guarantee for the products obtained from pharmacies and other legal suppliers [17].

The Real Farmacopea Española 3rd ed. (2005) (*RFE*) is an authorized and revised translation of the European Pharmacopoeia and also includes monographs that are unique to Spain [18].

Plants without pharmacological validation

A literature review was carried out for the most frequently reported plants that do not have a monograph. The search was conducted using a new tool from the University of Navarra, UNIKA (www.unav.es/biblioteca/unika/informacion.html).

UNIKA presents the following advantages compared to a traditional search: (i) searches are carried out against an index of several hundred million records, (ii) the contents of this resource correspond exclusively to academic- and scientific-quality documents; (iii) the search process is simple and intuitive, and (iv) the system offers access to electronic or printed full-text.

References to published work were identified using the Latin name of the species as keywords for the search, for example, "*Jasonia glutinosa*".

Results and discussion

A total of 1214 pharmaceutical uses for digestive troubles were reported by the informants of this study, and these uses originated from 126 plants (79% native species and 21% species introduced from other continents or other European regions). The complete catalogue of the ethnoflora from the surveyed territory is given in [10].

The 126 medicinal plants belong to 47 families, mainly represented by *Asteraceae* (17%), *Lamiaceae* (15%), *Rosaceae* (12%), *Apiaceae* (3%), and *Clusiaceae*, *Liliaceae*, *Malvaceae*, *Oleaceae* and *Solanaceae* (2% each). According to the number of given uses, *Asteraceae* (57%), *Rosaceae* (14%), *Lamiaceae* (8%), and *Apiaceae* and *Urticaceae* (3% each) are the most represented families.

The most frequently used parts of the plants are the inflorescences (46%), followed by the flowered aerial parts and fruits (16% each), aerial parts (10%), leaves (4%), shoots and rhizomes (2% each), and the roots, flowers, bulbs, stem and bark (1% each).

Plants used in traditional remedies are prepared and administered in different forms. The percentage of internal uses is 97%, and the most important forms of preparation are tisanes (infusions 70%, decoctions 8%), followed by maceration (14%), particularly with anisette (87%), and direct administration or comestible and flavoring (2% each). The plants are consumed dry (60%), fresh (29%) or indistinctly (10%), and different forms of the uses of some plants are forgotten (0.22%).

Thirty-three out of the 126 plants (26%) and 322 of the 1,214 popular uses (27%) reported in the present survey have already been pharmacologically validated for digestive afflictions by the ESCOP, the Commission E, the WHO and the EMA Monographs (Table 1). Importantly, eight of the 33 plants (24%), *Achillea millefolium*, *Cinnamomum zeylanicum*, *Cynara scolymus*, *Glycyrrhiza glabra*, *Melissa officinalis*, *Mentha aquatica*, *Mentha spicata*, *Rosmarinus officinalis* and *Silybum marianum*, are present in monographs from the four agencies taken into consideration in this study. Nine of these plants (27%) have previously been reported in other studies but have not yet been pharmacologically validated (*Arctium minus*, *Centaurea cyanus*, *Ocimum basilicum*, *Olea europaea*, *Origanum vulgare* ssp. *virens*, *Origanum vulgare* ssp. *vulgare*, *Rubus idaeus*, *Tanacetum vulgare* and *Verbena officinalis*). The use of the plants for the purposes listed in their monographs has not been adequately demonstrated. Because the claimed efficacies have not been documented, a therapeutic application cannot be recommended.

The Commission E established a risk of consumption for *T. vulgare* and *O. basilicum*. The former plant contains an essential oil that usually includes thujone and possesses neurotoxic properties. For this reason, abusing large amounts of this herb or its essential oil could induce abortion and cause the following symptoms of intoxication: vomiting, abdominal pain, gastroenteritis, reddening of the face, severe spasm, mydriasis and papillary rigidity, kidney damage, and liver damage [13]. *O. basilicum* contains approximately 0.5% essential oil with up to 85% estragole. This compound, after metabolic activation, has a mutagenic effect. Because of the high content of this compound, *O. basilicum* should not be taken during pregnancy or nursing, by infants or toddlers, or over extended periods of time [13].

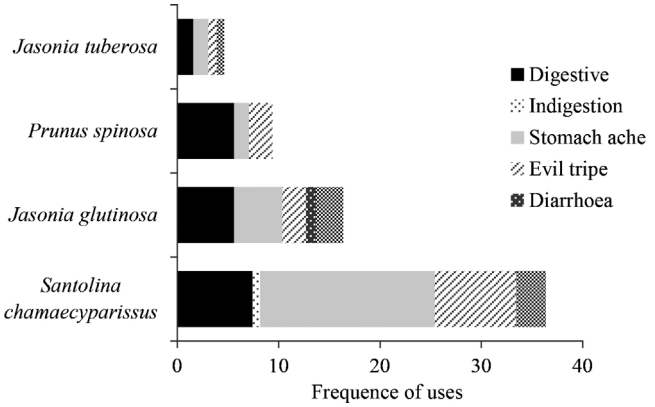

Fig. 2. The most used species and their frequency of use in the different digestive troubles.

In addition, most of the plants listed in Table 1 (79%) have monographs in the European Pharmacopoeia and/or Real Farmacopea Española.

The remaining 93 plants from the total 126 plants (74%) reportedly used for digestive troubles need to be screened through standard scientific procedures for their activities, if any. The most treated illnesses are grouped into six pathological afflictions: mouth (cleaning and disinfecting, phlegm and toothache), stomach (digestive) and intestine (anthelmintic, diarrhea, liver and gallbladder) (Table 2).

Fig. 2 shows the following most used species and the frequency of their use for various digestive troubles: *Santolina chamaecyparissus* (36%), *Jasonia glutinosa* (16%), *Prunus spinosa* (9%) and *Jasonia tuberosa* (5%).

S. chamaecyparissus ssp. *squarrosa* (Fig. 3) is an aromatic dwarf shrub commonly known as "Manzanilla de Mahón" or "Abrótano hembra." The flower of this plant is used in folk medicine due to its antispasmodic, digestive, anti-inflammatory, antiseptic and antimicrobial properties (Spain: *Andalusia* [19,20], *Aragon* [21,22], *Castile-La Mancha* [23], *Catalonia* [24–36], *Navarra* [7–9,37,38], *Region of Murcia* [39] and *Valencian Community* [40]). Many scientific articles have confirmed these pharmacological activities [41–51] and their correlation with the phytochemical composition: acetylenes [52,53], flavonoids [54], essential oils [55–57], monoterpenoids [58], sesquiterpenoids [59–61] and triterpenoids [62].

The antifungal activity of *S. chamaecyparissus* against the early blight fungus (*Alternaria solani*) has been investigated [48]. The inhibitory effect of this plant on radial mycelial growth as well as spore germination was measured *in vitro* at various concentrations. The apolar extract produced a relatively moderate antifungal activity that caused an inhibition of mycelial growth and spore germination at a concentration of 8–10%. Furthermore, *Santolina* oil was effective in controlling experimental candidiasis *in vitro* and *in vivo*. This oil had a synergistic effect on clotrimazole when controlling *Candida albicans in vitro* and significantly controlled experimental vaginal candidiasis and experimental systemic candidosis. *Santolina* oil was also able to control superficial cutaneous mycoses [51].

Table 1
Plants with pharmacological validation.

Plant (family, voucher specimen)	Part used	Ph	Popular use	Monograph
Achillea millefolium L. ssp. *millefolium* (*Asteraceae*, 21175)	Inflorescence	A	Digestive, stomach ache, evil tripe	1, 2, 3, 4
Agrimonia eupatoria L. ssp. *eupatoria* (*Rosaceae*, 21932)	Flowered aerial part	A and B	Weak gums; diarrhea	1, 2
Althaea officinalis L. (*Malvaceae*, 18805)	Root	A and B	Evil tripe	1, 2, 4
Arctium minus Bernh. (*Asteraceae*, 21193)	Root		Stomach ache, liver problems	2b
Centaurea cyanus L. (*Asteraceae*, 21220)	Inflorescence		Liver problems	2b
Centaurium erythraea Rafn (*Gentianaceae*, 21539)	Flowered aerial part	A and B	Lost of appetite	1,2,4
Chamaemelum nobile (L.) All. (*Asteraceae*, 21222)	Inflorescence	A and B	Digestive, evil tripe, stomach ache, carminative	2[b], 4
Chamomilla recutita (L.) Rauschert (*Asteraceae*, 21231)	Inflorescence	A and B	Evil ache, digestive, stomach ache	1, 2, 3
Chelidonium majus L. (*Papaveraceae*, 21859)	Leaf, aerial part	A and B	Laxant; liver problems	1, 2
Cichorium intybus L. (*Asteraceae*, 21237)	Root		Liver problems, dyspepsia	2
Cinnamomum zeylanicum Nees (*Lauraceae*, 21925)	Bark	A and B	Stomach ache	1, 2, 3, 4
Cynara scolymus L. (*Asteraceae*, 18563)	Leaf	A	Liver problems, dyspepsia	1, 2, 3, 4
Foeniculum vulgare Mill. (*Apiaceae*, 22039)	Shoot, leaf, Stem		Digestive, stomach acidity, stomach ache, tonic, antispasmodic, carminative, intestinal problems; mouth injuries	1[a], 2[a], 4[a]
	Fruit	A and B	Stomach ache, tonic, antispasmodic, carminative, intestinal problems; mouth injuries	1, 2, 4
Glycyrrhiza glabra L. (*Fabaceae*, 21523)	Rhizome	A and B	Stomach ache	1, 2, 3, 4
Juniperus communis L. ssp. *communis* (*Cupressaceae*, 21363)	Cone berry	A and B	Tonic	1, 2, 4
Lavandula angustifolia Mill. ssp. *angustifolia* (*Lamiaceae*, 21576)	Flowered aerial part	A and B	Tonic	1[a], 2
	Root		Stomach ache, ulcers	1[a], 2[a]
Linum usitatissimum L. (*Linaceae*, 21246)	Seed	A and B	Laxant	1, 2, 4
	Flower		Laxant	1[a], 2[a], 4[a]
Melissa officinalis L. (*Lamiaceae*, 21601)	Leaf	A and B	Stomach ache	1, 2, 3, 4
	Flower, aerial part		Stomach ache; digestive, carminative	1[a], 2[a], 3[a], 4[a]
Mentha aquatica × *Mentha spicata* (*Lamiaceae*, 21616)	Aerial part	A and B	Digestive, evil tripe, stomach ache	1, 2, 3, 4
Ocimum basilicum L. (*Lamiaceae*, 18695)	Leaf		Digestive	2[b]
Olea europaea L. var. *europaea* (*Oleaceae*, 21851)	Oil of fruit	B	Laxant	2[b]
Origanum vulgare L. ssp. *virens* (Hoffmanns and Link) Bonnier and Layens (*Lamiaceae*, 21627)	Inflorescence	A and B	Stomach ache	2[b]
Origanum vulgare L. ssp. *vulgare* (*Lamiaceae*, 21640)	Inflorescence	A and B	Digestive	2[b]
Plantago lanceolata L. (*Plantaginaceae*, 21887)	Leaf	A and B	Mouth injuries	1, 2, 4
Punica granatum L. (*Lythraceae*, 21783)	Fruit		Diarrhea	3
Quercus robur L. (*Fagaceae*, 21903)	External bark	A and B	Diarrhea	2, 4
Rosmarinus officinalis L. (*Lamiaceae*, 21658)	Aerial part, stem		Digestive; stomach ache	1[a], 2[a], 3[a], 4[a]
	Leaf	A and B	Stomach ache	1, 2, 3, 4
Rubus idaeus L. (*Rosaceae*, 21979)	Fruit		Evil tripe	2[a]/2[b], 4[a]
Salix alba L. (*Salicaceae*, 22000)	Leaf		Toothache	2[a], 3[a], 4[a]
Silybum marianum (L.) Gaertner (*Asteraceae*, 21304)	Fruit	A	Liver problems	1,2,3
	Leaf		To clean the liver	1[a], 2[a], 3[a], 4[a]
Tanacetum vulgare L. (*Asteraceae*, 21318)	Flowered aerial part		Antihelmintic	2[b]

Table 1 (*Continued*)

Plant (family, voucher specimen)	Part used	Ph	Popular use	Monograph
Taraxacum gr. *officinale* Weber (*Asteraceae*, 21321)	Leaf, aerial part	A	Liver problems	2, 4[a]
	Root	A	Liver problems	1, 2, 4
Verbena officinalis L. (*Verbenaceae*, 21770)	Aerial part	A	Toothache, intestinal problems	2[b]

Ph, pharmacopoeia; 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.

[b] Neutral German Commission E monograph.

On the other hand, the essential oil from *S. chamaecyparissus* has been evaluated for its potential antimicrobial activity using the agar diffusion disc method against gram-negative bacteria (*Pseudomonas aeruginosa*, *Escherichia coli*, and *Klebsiella pneumoniae*), gram-positive bacteria (*Staphylococcus aureus* and *Staphylococcus epidermis*) and the fungus *C. albicans* [43].

S. chamaecyparissus hexanic extracts have a spasmolytic effect on a variety of smooth muscle preparations (rat duodenum,

Table 2
Plant without scientific validation (mentioned by three or more independent informants).

Affection	Plant (Family, voucher specimen)	Part used	Preparation	FC
Mouth				
To clean, disinfect	*Rubus ulmifolius* Schott (*Rosaceae*, 21985)	New bud	Gargarism with infusion	3
Phlegmon, toothache	*Sambucus nigra* L. ssp. *nigra* (*Adoxaceae*, 21165)	Inflorescence	Poultice, smoke inhalation	25
Stomach				
Digestive	*Anthemis arvensis* L. ssp. *arvensis* (*Asteraceae*, 21187)	Inflorescence	Infusion	10
	Bidens aurea (Aiton) Sherff (*Asteraceae*, 19669)	Flowered aerial part	Infusion	5
	Cucumis sativus L. (*Cucurbitaceae*, 18532)	Fruit	Maceration in anisette	12
	Helichrysum stoechas (L.) Moench ssp. *stoechas* (*Asteraceae*, 21250)	Inflorescence	Infusion	31
	Jasonia glutinosa (L.) DC. (*Asteraceae*, 21252)	Flowered aerial part	Infusion	126
	Jasonia tuberosa (L.) DC. (*Asteraceae*, 21272)	Flowered aerial part	Infusion	38
	Juglans regia L. (*Juglandaceae*, 18683)	Fruit, leaf	Maceration in anisette or wine	12
	Laurus nobilis L. (*Lauraceae*, 21715)	Leaf	Condiment, infusion	4
	Malus sylvestris (L.) Mill. (*Rosaceae*, 21940)	Leaf, fruit	Maceration in anisette	13
	Malva sylvestris L. (*Malvaceae*, 18748)	Flower, aerial part	Infusion, decoction, enema	4
	Mentha spicata L. (*Lamiaceae*, 18694)	Aerial part, leaf	Infusion	14
	Prunus cerasus L. (*Rosaceae*, 21873)	Fruit	Maceration in anisette	18
	Prunus spinosa L. (*Rosaceae*, 21969)	Fruit	Maceration in anisette	77
	Rosa agrestis Savi (*Rosaceae*, 21973)	Fruit	Maceration in anisette	3
	Santolina chamaecyparissus L. ssp. *squarrosa* (DC.) Nyman (Asteraceae, 18775)	Inflorescence	Infusion	298
	Sideritis hyssopifolia L. (*Lamiaceae*, 18750)	Flowered aerial part	Infusion	3
	Tanacetum parthenium (L.) Schultz Bip. (*Asteraceae*, 21309)	Inflorescence	Infusion	6
	Thymus vulgaris L. (*Lamiaceae*, 21713)	Flowered aerial part	Decoction, infusion, condiment	22
Intestine				
Antihelmintic	*Allium sativum* L. (*Liliaceae*, 21718)	Bulb	Infusion, comestible, decoction with milk	4
	Cydonia oblonga Mill. (*Rosaceae*, 21921)	Fruit	Comestible, decoction with water and sugar	7
Diarrhoea	*Hypericum perforatum* L. (*Clusiaceae*, 21555)	Flower, flowered aerial part	Infusion	6
	Jasonia glutinosa (L.) DC. (*Asteraceae*, 21252)	Flowered aerial part	Infusion	8
	Lythrum salicaria L. (*Lythraceae*, 18706)	Flowered aerial part, aerial part	Decoction, infusion, condiment	5
	Rosa canina L. (*Rosaceae*, 21974)	Fruit	Maceration in anisette, infusion, decoction	11
	Rubus ulmifolius Schott (*Rosaceae*, 21985)	New bud	Infusion, decoction with sugar and water, decoction	21
Liver, gallbladder	*Parietaria judaica* L. (*Urticaceae*, 21746)	Aerial part	Infusion, decoction, comestible	21

FC, frequency of citations.

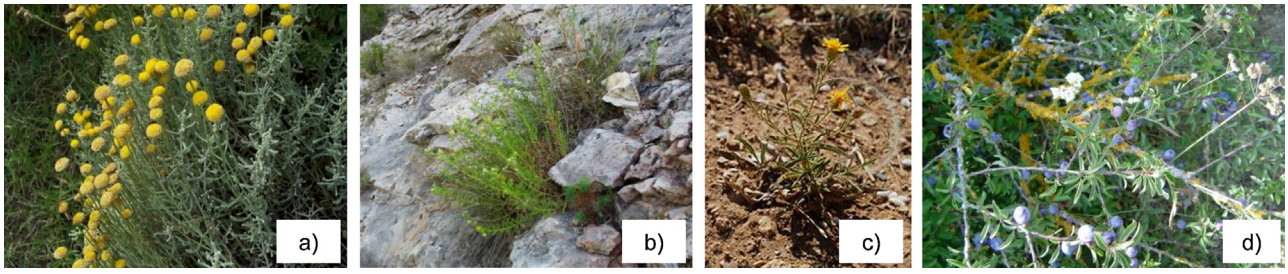

Fig. 3. (a) *Santolina chamaecyparissus*; (b) *Jasonia glutinosa*; (c) *Jasonia tuberosa*; (d) *Prunus spinosa*.

guinea pig ileum, rat uterus and rat vas deferens) [46]. The antagonism from chloroformic and polar extracts to histamine and to serotonin could explain, in part, the anti-inflammatory effects of this plant on carrageenan-induced rat paw edema [44], as both agonists are known mediators of the inflammatory process. The hexanic and chloroformic extracts of *S. chamaecyparissus* were potent antagonists of the thermic analgesia test, with the former extract also being active in the mechanical analgesia test. The chloroformic extract and, to a lesser extent, the ethyl acetate extract and lyophilized infusion demonstrated noteworthy activity as anti-inflammatory agents [45].

J. glutinosa and *J. tuberosa* (Fig. 3) are two species widely consumed in Navarra as "té" (tea). The former plant (known as "rock tea") is mostly used by inhabitants close to the calcareous mountain ranges. This usage pattern occurs because this plant has an exclusive habitat in cracks, rock ledges and fissures that receive abundant sunlight; therefore, its area of use is primarily influenced by the substrate. *J. tuberosa* only grows in flat locations with a marl substrate and in the Mediterranean environment, and it is used in places where *J. glutinosa* disappears, indicating that the use of one plant thereby replaces the other.

J. glutinosa is very popular as a stomachic as well as a component in preparations that present beneficial effects, including antispasmodic and anti-inflammatory drugs (Iberian Peninsula [63,64], Spain: *Andalusia* [20,65–67], *Aragon* [21,22], *Cantabria* [68,69], *Catalonia* [24,26–28,31,36,70], *Navarra* [7–9,37,38,71,72] and *Valencian Community* [40]).

Various phytochemical studies performed on *J. glutinosa* demonstrated that this plant contains essential oils [73,74], flavonoids [75] and sesquiterpenoids [76–79]. Sesquiterpenes and flavonoids are secondary metabolites that are widely distributed in the higher plant kingdom and are known to possess diverse biological and pharmacological actions. For this reason, these compounds have been evaluated for their *in vitro* anti-inflammatory activity in cellular systems generating cyclooxygenase (COX) and 5-lipoxygenase (5-LOX) metabolites. Both types of compounds showed a significant effect on thromboxane B2 (TXB2)-release induced by calcium ionophores in human platelets, although with less potency than the reference drug ibuprofen [80].

The *in vitro* antimicrobial and antifungal activity of either ethyl acetate or dichloromethane extracts from *J. glutinosa* were studied using the agar dilution method against the following different microorganisms: *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *C. albicans*, *Mycobacterium phlei* and *Rhizopus stolonifer*. Bioautography demonstrated that the antimicrobial activity is likely due to flavonoids, terpenoids and essential oils [49].

Several protozoa are human parasites, causing diseases that include malaria, amoebiasis, giardiasis, toxoplasmosis, cryptosporidiosis, trichomoniasis, Chagas disease, leishmaniasis, sleeping sickness and dysentery, among others. The antiprotozoal activity of acetonic extracts and sesquiterpenoids from *J. glutinosa* against *Entamoeba histolytica*, *Leishmania donovani* (promastigote forms), *Trichomonas vaginalis* and *Plasmodium falciparum* has been studied [80].

Apart from a few reports detailing the isolation and characterization of various volatile components of this plant [73,74], to the best of our knowledge, no reports have been published that describe the activity of these compounds from *J. glutinosa.*

J. tuberosa, although less used in traditional medicine (Iberian Peninsula: [63,64], Spain: *Aragon* [22] and *Navarra* [6–9,37]), replaces *J. glutinosa* in some places. For this reason, there have been no published references detailing the chemical composition and/or pharmacological activity of this species.

The maceration in anisette of *P. spinosa* (Fig. 3) is often used in folk medicine for digestive problems (Spain: *Andalusia* [81,82], *Aragon* [22], *Basque Country* [83–85], *Cantabria* [68], *Catalonia* [24,28,33,34], *Castile* and *Leon* [86,87], *Navarra* [7–9,38,71,72,88,89], *Valencian Community* [40]. Greece [90], Italian Republic [91–96], Italian Republic/Republic of Bulgaria [97], Montenegro [98], Portuguese Republic [99,100] and Romania [101]).

The phytochemical composition of this species has already been studied. The most important compounds are A-type proanthocyanidins [102–104], a class of secondary phenolic metabolites that belong to the group of tannins and consist of units of flavan-3-ol bound by one or two interflavan bonds. The A-type varieties with twice-bonded structures are not often found in nature, and their distribution is limited to the species *Ericaceae*, *Sapindaceae*, *Lauraceae*, and *Rosaceae*. Flavonols of *P. spinosa* [105–112], all of which have been shown to possess vitamin P as well as hypocholesterolemic, spasmolytic, antitoxic, anti-inflammatory, positive inotropic, diuretic, and natriuretic properties [113]. The amino acid and fatty acid compositions of the fruits from these species also have a great importance from health and nutritional perspective [114]. Other minor compounds include aldehydes/alcohols [115], coumarins [116], cyanoglycosides [113], isoprenoids [117] and phenylpropanoids [118].

Numerous ethnopharmacological studies on *S. chamaecyparissus* ssp. *squarrosa*, *J. glutinosa*, *J. tuberosa* and *P. spinosa* suggest that these medicinal plants have been proven to be effective for the prevention and cure of various digestive disorders and can be used after their validation to improve the outcome of these disorders, thereby leading to relatively inexpensive, effective, and safe therapies. Further research on each of the four plants is still needed to provide evidence of their potential effectiveness in the treatment of digestive afflictions and their associated symptoms.

Concluding remarks

A large proportion of the populations of developing countries use traditional medicine alone, or in combination with Western drugs, to treat a wide variety of ailments. The use of many medicinal plants for the treatment of digestive system disorders has been previously described. Many of these plants have been used since ancient times, and the knowledge of their use has been passed down from generation to generation, thereby supporting the potential therapeutic efficacy and safety of these medicinal plants.

Twenty-six percent of the medicinal plants used in Navarra for digestive problems have been scientifically validated by official international organizations. Among the remaining 74%, we have highlighted four species that are ideal for validation (*S. chamaecyparissus* ssp. *squarrosa*, *J. glutinosa*, *J. tuberosa* and *P. spinosa*). These species are commonly used in traditional medicine in Navarra and in other regions of the Mediterranean basin. Currently, *in vitro* and *in vivo* pharmacological studies and phytochemical analyses on some of the reported plants from the survey area are under way to achieve pharmacological validation. In light of these results, we conclude that these plants merit further investigation to assess their effectiveness.

Conflict of interest

The authors declare that they have no conflict of interest with regards to this article.

Competing interest

The authors declare that they have no competing interests with regards to this article.

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