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## Research Paper

## Medicinal plants used for cardiovascular diseases in Navarra and their validation from Official sources

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## ABSTRACT

**Ethnopharmacological relevance:** This paper provides significant ethnopharmacological information on plants used to treat cardiovascular diseases in Navarra, Spain.

**Material 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. Official sources such as the European Scientific Cooperative on Phytotherapy (ESCOPE), German Commission E, World Health Organization (WHO), European Medicines Agency (EMA), European Pharmacopoeia (Ph. Eur.) and Real Farmacopea Española (RFE) monographs were consulted in order to establish the therapeutic efficacy of the reported uses and to obtain further details about quality and safety aspects. A literature review was carried out on the plants that were most frequently cited and were not the subject of a monograph, using a new tool developed by the University of Navarra, UNIKA.

**Results:** A total of 460 pharmaceutical uses were reported by the informants, belonging to 90 plant species and 39 families, mainly represented by *Urticaceae*, *Rosaceae*, *Asteraceae*, and *Equisetaceae*. The most frequently used parts of the plants were the aerial parts followed by leaves and flowers. Seventeen out of 90 plants (19%) and 208 out of 460 popular uses (45%) had already been pharmacologically validated in relation to their therapeutic efficacy and safety aspects.

**Conclusions:** The authors propose to validate five species for their use in cardiovascular diseases: *Rhamnus alaternus* L., *Potentilla reptans* L., *Equisetum telmateia* Ehrh., *Centaurium erythraea* Rafn and *Parietaria judaica* L.

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## 1. Introduction

Medicinal plants have been utilized as medicine throughout human history. It has been estimated that 80% of people living in developing countries are almost completely dependent on traditional medicine practices and utilize plants as drugs for their primary health care needs (Abdala et al., 2012). In this context, there is an increasing emphasis placed on proving product safety and efficacy scientifically when phytomedicines are to be used. Furthermore, the modern pharmaceutical industry is now paying more attention to medicinal plants, as scientists rediscover that they are an almost infinite source for the development of new drugs (Cavero et al., 2013).

The past two decades have seen a considerable global increase in cardiovascular diseases (Tibazarwa and Damasceno, 2014). Indeed, the European Union budget for cardiovascular disease is currently estimated at €196 billion a year, with about one half of this attributed to direct healthcare costs (Nichols et al., 2012). The number of people

who die from cardiovascular diseases, mainly from heart disease and stroke, will probably increase to 23.3 million by 2030 (Mathers and Loncar, 2006; WHO, 2011). Urgent investment in cardiovascular disease prevention is needed in order to improve health in European populations and to tackle the socioeconomic consequences of these diseases (Gylling et al., 2014).

Previous studies carried out by our research group in Navarra have already shown that the use of many traditional medicines targeting digestive and dermatological diseases can be scientifically supported (Calvo et al., 2013; Cavero et al., 2013). The aims of the present paper are: (i) to review the medicinal plants with clinical uses that have been scientifically validated by international organizations for cardiovascular affections, and (ii) to propose plants frequently reported as being used for these diseases in different regions of the Mediterranean basin for their scientific validation, with a view to promoting their safe and effective clinical use.

## 2. Methodology

Information was collected using semi-structured ethnobotanical interviews with 667 informants from 265 locations (Navarra,

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Spain) following the 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 (ESCAP, Commission E, WHO and EMA) were reviewed. A literature review was carried out including all the most frequently employed plants that had not been the subject of a monograph (Calvo et al., 2013; Cavero et al., 2013).

The data provided by informants were grouped into eight categories depending on the pathology in question (the exact translation of how categories were described by informants is indicated in parentheses): anemia ('to use when the body needs iron', 'iron deficiency'), antihypertensive ('to clean or purify the blood', 'to lower blood', 'to lower blood pressure'), blood circulation ('to improve blood circulation', 'to stimulate blood circulation'), depurative ('to purify or clean the body'), diuretic ('to urinate', 'to pee', 'if liquids are retained in the body'), heart problems ('heart'), hemorrhoids ('piles') and hypercholesterolemia ('for high cholesterol').

### 3. Results and discussion

A total of 460 pharmaceutical uses were reported by 667 informants, belonging to 90 plants (74% native species and 26% species introduced from other continents, or other European regions). The complete catalog of the ethnoflora of the territory surveyed is given in Akerreta (2009).

The 90 medicinal plants cited belonged to 39 families, mainly represented by *Urticaceae* (26%), *Rosaceae* (17%), *Asteraceae* (9%), *Equisetaceae* (8%), *Oleaceae* (7%), and *Rhamnaceae* (4%).

The most frequently used parts of the plants were the aerial parts (48%), leaves (18%), flowered aerial parts (11%), inflorescences (4%), and fruits and stems (3%).

Plants were used fresh (50%), dry (23%) or either (27%), and were administered in different forms. The percentage of internal uses was 91% and the most important methods of preparation were: infusion (57%), decoction (21%), food (11%), water, olive oil or alcohol maceration and direct application (2%, each).

Seventeen out of 90 plants (19%) and 208 of 460 popular uses (45%) reported in the present survey had already been pharmacologically validated in relation to their therapeutic efficacy and safety aspects for cardiovascular affections by ESCOP, Commission E, WHO and EMA Monographs (Table 1). It is important to highlight that only one of 17 plants, *Aesculus hippocastanum* L., had monographs in all four agencies. However, the side effects listed in the monograph of the Commission E for this plant should be taken into consideration: 'pruritus, nausea, and gastric complaints may occur in isolated cases after oral intake' (Blumenthal et al., 1998).

Four of them had previously been reported in other studies but not yet pharmacologically validated: *Calendula officinalis* L., *Calluna vulgaris* (L.) Hull, *Chamaemelum nobile* (L.) All. and *Prunus spinosa* L. (indicated as 2<sup>b</sup> in Table 1. Since the effects claimed have not been documented, a therapeutic application cannot be recommended.

Six out of 17 plants (35%) listed in Table 1 had no monograph in the European Pharmacopoeia and/or Real Farmacopea Española.

The remaining 73 plants (of total 90; 81%) have been reported for cardiovascular disorders and need to be screened through standard scientific procedures to determine their action. Taking into consideration only the uses mentioned by two or more independent informants (126 uses, Table 2), the most widely treated affections are grouped into eight pathological categories: anemia (1.6%), antihypertensive (24%), blood circulation (1.6%), depurative (23%), diuretic (27%), heart problems (1.6%), hemorrhoids (18%) and hypercholesterolemia (3%).

The leaves of *Rorippa nasturtium-aquaticum* (L.) Hayek are employed for treatment of anemia defined as low red blood cell counts with clinical symptoms such as shortness of breath, lethargy and heart palpitations (Blumenthal et al., 1998).

*Portulaca oleraceae* L. and *Malus sylvestris* (L.) Mill. were the only two plants cited for strengthen arteries and heart problems in general, respectively.

The most widely cited plants for lowering high blood pressure were *Centaureum erythraea* Rafn and *Rhamnus alaternus* L. (30%, 9 uses of 30 total uses for this affection each), *Equisetum telmateia* Ehrh. and *Thymus vulgaris* L. (13%, 4 uses each), and *Petrolesinum crispum* (Mill.) Fuss and *Silybum marianum* (L.) Gaertner (7%, 2 uses each).

It is important to highlight the importance of infusions for diuretic treatments (91%, 32 uses out of 34 total uses for this affection), *Equisetum telmateia* and *Zea mays* L. being the most cited plants (29% and 27%, respectively).

Fig. 1 shows that the most widely used species and their frequency of citation in the different cardiovascular problems were: *Rhamnus alaternus* (18 uses out of 126 total uses, 14%), *Potentilla reptans* L. (15 uses, 12%), *Equisetum telmateia* (14 uses, 11%), *Centaureum erythraea* and *Parietaria judaica* L. (11 uses, 9% each).

*Rhamnus alaternus* is an evergreen shrub of the Mediterranean climate regions known by the common name of Italian Buckthorn or Mediterranean Buckthorn. In this study, the results showed that the aerial parts are employed as antihypertensive (9 of 18 uses, 50%), depurative (7 uses, 39%), and against hypercholesterolemia (2 uses, 11%) (Fig. 1). This plant is traditionally used in different regions of Spain for cardiovascular problems: Aragon, Basque Country, Cantabria, Castile-La Mancha, Catalonia, Navarra, and Valencian Community (Akerreta, 2009, and references cited therein; Cavero et al., 2011b; Akerreta et al., 2013). We found no ethnopharmacological references in other Mediterranean areas for cardiovascular indications. Scientific studies have shown several pharmacological properties for extracts and metabolites isolated from *Rhamnus alaternus*. In fact, the more interesting pharmacological properties are due to the presence, amongst several different metabolites, of flavonoids (Cuoco et al., 2014), essential oils (Berka et al., 2008) and anthraquinones (Abou-Chaar et al., 1982). These compounds are secondary metabolites widely distributed in the higher plant kingdom and are known to show diverse biological and pharmacological actions. Compounds of *Rhamnus alaternus* have been evaluated for their in vitro antioxidant (Ammar et al., 2009), antiproliferative against human leukemia K562 cells, antimutagenic (Ammar et al., 2011), and antimicrobial (Kosalec et al., 2013) activities.

The only reported application for *Potentilla reptans* is the treatment of hemorrhoids (15 uses, 100%), 7 uses internally in tisane for 9 days, and 8 uses externally in different forms of administration: clean with infusion, direct application, sitz baths and boiled in poultice (Table 2). Numerous ethnopharmacological studies carried out in different regions of Spain (Andalusia, Aragon, Basque Country, Cantabria, Navarra and Valencian Community) and in other Mediterranean countries (Italian Republic and Republic of Turkey) have found the same uses for the cardiovascular system (Akerreta, 2009, and references cited therein; Cavero et al., 2011a, 2011b; Calvo et al., 2011; Akerreta et al., 2013).

Hemorrhoids, also called piles, are vascular structures in the anal canal which help with stool control (Schubert et al., 2009). They become pathological when swollen or inflamed (Lorenzo-Rivero, 2009). Therefore, the most appropriate pharmacological treatments for this type of affection are the use of cicatrizing and anti-inflammatory agents. The most important compounds of *Potentilla reptans* are A-type proanthocyanidins (Okuda et al., 1992), a class of secondary phenolic metabolites, belonging to the group of tannins,

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