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An ethnopharmacological and historical analysis of “Dictamnus”, a European traditional herbal medicine

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Abstract

Ethnopharmacological relevance and background: “Dictamnus” was a popular name for a group of medicinal herbaceous plant species of the Rutaceae and Lamiaceae, which since the 4th century have been used for gynaecological problems and other illnesses BCE and still appear in numerous ethnobotanical records.

Aims: This research has as four overarching aims:

Determining the historical evolution of medical preparations labelled “Dictamnus” and the different factors affecting this long-standing herbal tradition.

Deciphering and differentiating those medicinal uses of “Dictamnus” which strictly correspond to *Dictamnus* (*Rutaceae*), from those of *Origanum dictamnus* and other Lamiaceae species.

Quantitatively assessing the dependence from herbal books, and pharmaceutical tradition, of modern *Dictamnus* ethnobotanical records.

Determining whether differences between Western and Eastern Europe exist with regards to the *Dictamnus albus* uses in ethnopharmacology and ethnomedicine.

Methods: An exhaustive review of herbals, classical pharmacopoeias, ethnobotanical and ethnopharmacological literature was conducted. Systematic analysis of uses reported which were standardized according to International Classification of Diseases – 10 and multivariate analysis using factorial, hierarchical and neighbour joining methods was undertaken.

Results and discussion: The popular concept “Dictamnus” includes *Origanum dictamnus* L., *Ballota pseudodictamnus* (L.) Benth. and *B. acetabulosa* (L.) Benth. (Lamiaceae), as well as *Dictamnus albus* L. and *D. hispanicus* Webb ex Willk. (Rutaceae), with 86 different types of uses. Between 1000 and 1700 CE numerous complex preparations with “Dictamnus” were used in the treatment of 35 different pathologies. On biogeographical grounds the widespread *Dictamnus albus* is a far more likely prototypical “Dictamnus” than the Cretan endemic *Origanum dictamnus*. However both form integral parts of the “Dictamnus” complex.

Evidence exists for a sufficiently long and coherent tradition for *Dictamnus albus* and, *D. hispanicus*, use to treat 47 different categories of diseases.

Conclusions: This approach is a model for understanding the cultural history of plants and their role as resources for health care. “Dictamnus” shows how transmission of traditional knowledge about materia medica, over 26 centuries, represents remarkable levels of development and innovation. All this lead us to call attention to *Dictamnus albus* and *Dictamnus hispanicus* which are highly promising as potential herbal drug leads. The next steps of research should be to systematically analyse phytochemical, pharmacological and clinical evidence and to develop safety, pharmacology and toxicology profiles of the traditional preparations.

Keywords

Dictamnus, Western Mediterranean, Ethnobotany, Ethnomedicine, History of pharmacy, European herbal medicine

Abbreviations

CSS: Supreme Health Council of Poland (in the 19th century)

ICD-10: WHO International Statistical Classification of Diseases and Related Health Problems 10th Revision. Version for 2010

NHM: Natural History Museum of London

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1 Introduction

The plant complex “Dictamnus”¹ covers a set of different medicinal species with overlapping therapeutic uses (Brown, 1935). It offers a unique opportunity for analysing the concept of “traditional” in herbal medicines and to distinguish long term and short term traditions (Heinrich et al., 2006). This paper is a historical and botanical assessment and not one covering

¹ Throughout this article we will use “Dictamnus” as the generic term for this group of plants and *Dictamnus* for the genus of the *Rutaceae*.

the species' pharmacology and phytochemistry which was recently reviewed by Lv et al. (2015) for genus *Dictamnus* as a whole.

The existence of such complexes of medicinal plant species have been demonstrated for different cultural contexts, for example, by Linares and Bye (1987) in Mexico and the United States, and Obón et al. (2012) in the Iberian Peninsula.

The European Parliament (2004, 2008) adopted “traditional use” or alternatively “a sufficiently long and coherent tradition” for an herbal substance as a basis for using it as a safe product for treating a specified and generally self-limiting (minor) medical conditions. Specific preparation from certain taxa within the plant complex “*Dictamnus*” may well be developed into a Traditional Herbal Medical Product, provided that their tradition of use, and the quality as well as the safety of the specific commercial products can be demonstrated. However the identity of “*Dictamnus*” is unclear, despite its widespread use and references in classical literature (Brown, 1935).

Thus, we aim at:

Determining the historical evolution of medical preparations labelled “*Dictamnus*” and the different factors affecting this long-standing Cretan and European herbal tradition.

Deciphering and differentiating those medicinal uses of “*Dictamnus*” which strictly correspond to *Dictamnus* (*Rutaceae*), from those of *Origanum dictamnus* and other Lamiaceae species assessing which uses present a sufficiently long and coherent tradition.

Quantitatively assessing the degree of dependence of modern ethnobotanical records from herbal books and pharmaceutical tradition concerning *Dictamnus* medicinal uses and determine those for which evidence exists.

Determining whether differences between Western and Eastern Europe exist with regards to the *Dictamnus albus* uses in ethnopharmacology and ethnomedicine.

2 Methods

2.1 Sources of information

Classical texts of medicine, herbals and pharmacopoeias were retrieved and downloaded from the following main on-line repositories Archive (2015), Bayerische Staatsbibliothek (BSB, 2015), Biblioteca Digital Hispánica (BNE, 2015), Bibliothèque numérique Medica (Medica, 2015), Biodiversity Heritage Library (BHL, 2015), Corpus Medicorum Graecorum (CMG, 2015), Digitale Bibliothek (GNM, 2015), Gallica (2015), Google Books (Google, 2015).

Opsomer (1989) furnish an exhaustive index for “Dictamnus” citations in the herbals from 1st to 10th centuries. A total of 42 herbals were analyzed (1st-19th centuries). For recent medicinal uses of *Dictamnus* species (Rutaceae) in Eastern Europe and Turkey we found information in sources dated from 1989 to 2013. For Western Europe these were from 1915 to 2009. Recent medicinal uses of *Origanum dictamnus* were found in Chinou (2013), Liolios et al. (2010), Skoula and Kamenopoulos (1997).

2.2 Botanical identification

The different plant species named “Dictamnus” in Greek, Roman and medieval medical writings offer a good example of how traditional materia medica passed through history to present days. Since 4th century BCE there exist written records, with descriptions of the plants, specific parts used and pathologies treated. Furthermore, some images (paintings in manuscripts or printed figures) help in the accurate identification of plant species. Without this continuous tradition it would be almost impossible to determine in scientific terms the meaning of “Dictamnus” and of the major part of the Classical Materia Medica. For pre-Linnaean works we almost exclusively rely on images in engravings (coloured or not) (Fig. 1) and detailed descriptions, where these were available in the different herbals analysed. Interpretation of these names by Tournefort (1700) and Linné (1753) were (Table 1) substantial to resolve the identity. For botanical texts contemporary or later to Linné (1753) we follow the principles of the International Code of Botanical Nomenclature (McNeil et al., 2011) and the accepted names at TPL (2014). This involves the study of herbarium specimens and in particular type specimens. In case of pharmacognosy monographs and standard pharmacopoeias we assumed botanical identity was correct.

2.3 Pathologies

Original Greek or Roman medical texts no longer exist; instead, their medieval manuscript versions were consulted. The European and Mediterranean medical tradition was continuously updating terminologies and adding new names, novel pathologies, and interpreting previous texts in contemporaneous terms (Appendix 2).

For understanding pathologies in medical texts dated from 1 to 1900 CE we needed specific studies of paleopathology and history of medicine. Neurological causes for morbidity/ illness were determined in classical and medieval texts according to Bouras (2014), Benbadis (2009), Guerrero et al. (2014), and Frutos and Guerrero (2010), mental disorders (Jackson, 1972; Kyziridis, 2005; Owen, 2014), eating disorders (Parry-Jones, 1991). The following sources were used for classifying specific groups of diseases - gynaecological uses are based on Riddle (1994), genitourinary disorders on Mezzogiorno et al. (2004), Oriel (1996), Touwaide, (2004, 2014), cerebrovascular on Karenberg and Hort (1998), malignant on Wells (1964),

musculoskeletal Jiménez et al. (2012), Rogers et al. (1981), infectious diseases on Cockburn (1971), Hudson (1972); Manchester (1986); Nutton (1983) and ear and adnexa on Maltby (2012).

Considering the continuity of medical traditions and the available evidence from paleopathological sources we used standardized names of diseases which are the nomenclature and classification for diseases and health-related problems adopted by the World Health Organisation with the purpose of a global statistics (ICD-10 or International Statistical Classification of Diseases and Related Health Problems 10th Revision) (WHO, 2014), the pathologies in Table 2 and Appendix 1 are thus named according ICD-10. Appendix 2 contains the original names of the diseases in the languages of the various works consulted with their equivalents in the ICD-10.

2.4 Data analysis

To compare in terms of medicinal uses, the evolution of the concept "Dictamnus" of and its relationships with *D. albus*, *D. hispanicus* and *O. dictamnus*, the information in Table 2 and Appendix 1 was, first, systematized in a crude matrix with seven units (Appendix 3): DICT_1-1200AD (records of "Dictamnus" uses in texts from 1 to 1200 CE), DICT_1200-1700AD ("Dictamnus" uses in texts from 1200 to 1700 CE), DICT_1700-1900AD (*Dictamnus albus* uses in texts from 1700 to 1900 CE), D.a._MODERN_WEST (*D. albus* uses in ethnobotanical records of Western Europe), D.h._MODERN_WEST (*D. hispanicus* uses in ethnobotanical records of Spain), D.a._MODERN_EAST (*D. albus* uses in ethnobotanical records of Eastern Europe), and *Origanum dictamnus* (*O. dictamnus* uses) and 86 variables which are the frequencies in percentage for each unit of the different categories of diseases and related health problems classified according to ICD-10 (WHO 2014). The number of uses in common allows us to know the degree of similarity between the different units in which we have grouped the data.

The crude matrix was used to compute a dissimilarity matrix using Darwin 5 V.5.0.158 (2009-07-06) (Perrier, Flori & Bonnot, 2003; Perrier & Jacquemoud-Collet, 2006). The chi square dissimilarity index was calculated. This measure expresses a value x_{ik} as its contribution to the sum x_i on all variables and is a comparison of unit profiles.

$$d_{ij} = \sqrt{\sum_{k=1}^K \frac{x_{..}}{x_{i.k}} \left(\frac{x_{jk}}{x_{i.}} - \frac{x_{jk}}{x_{j.}} \right)^2} ;$$

where d_{ij} - dissimilarity between units i and j ; x_{ik} , x_{jk} - values of variable k for units i and j ; $x_{i.}$, $x_{j.}$, $x_{k.}$: mean for units i and j or variable k ; $x_{..}$: overall mean. K : number of variables.

Principal coordinates analysis (PCoA), which works on dissimilarity matrices showing the distance between every possible pair of units (out of the seven described above), was used to give an overall representation of relationships within the complex, based on the comparison of “Dictamnus” medicinal uses in the different periods, and those of *D. albus*, *D. hispanicus* and *O. dictamnus*, with the lowest possible dimensional space.

A hierarchical tree was constructed to describe the relationships between the seven units based on the common agglomerative heuristic, which proceeds by successive ascending agglomerations. For updating dissimilarity during the tree construction the Ward criterion was adopted, which searches at each step for a local optimum to minimize the within-group or equivalently to maximize the between-group inertia.

A weighted Neighbor-Joining tree was used to verify close similarities between samples in terms of degree of coincidence in medicinal uses. The Neighbor-Joining method proposed by Saitou and Nei (1987) uses the criterion of relative neighbourhood, weighted average for dissimilarity updating, and adjustment to an additive tree distance. A bootstrap value is given to each edge that indicates the occurrence frequency of this edge in the bootstrapped trees. Bootstrap values range between 0 and 100.

In order to reduce the uncertainty level linked to likely misinterpretations of diseases names in terms of ICD-10 the information in Table 2 and Appendix 1 was secondly, systematized in a simplified crude matrix with the above seven units and 17 variables (Appendix 3, rows numbered with Roman numerals and with text in bold) which are the main categories of diseases and related health problems.

3 Results and Discussion

3.1 Early evidence for “Dictamnus” name and uses

“Dictamnus” can be found in Theophrastus in his ‘Enquiry Into Plants’ (4th century BCE) as the Cretan endemic *Origanum dictamnus* (Hort, 1916). The Committee on Herbal Medicinal Products of the European Medicines Agency (HMPC, 2014) included “*Origanum dictamnus herba*” in the priority list within a monograph for traditional use, on the base of the assessment report on *Origanum dictamnus herba* (Chinou, 2013) which in fact included several medicinal uses of “Dictamnus” without differentiating those of *Origanum* from those directly related with *Dictamnus* (Rutaceae). This in part is due to the attribution of all “Dictamnus” uses to *Origanum dictamnus* by Liolios et al. (2010) in their review on the botany and ethnopharmacology of the Dittany of Crete which was followed by the HMPC (2014) in the redaction of the *O. dictamnus* monograph.

The Greek Δίκτημος (*Diktamnus*) (“Dictamnus” in Latin) is linked to different place names of Crete (or Candia): Mount Dikte (Gledhill, 2008), *Dictaeus* or *Dictamnium*, a city of north Crete, (Smith, 1850), or even a goddess rescued from the sea with a fishing net (*Dikti*) (Smith, 1850; Liolios et al., 2010).

“Dictamnus” was used for healing wounds, in Greek and Roman Antiquity associated with religious cults (Folkard, 1884; Günther, 1905; Picton, 2000). “Dictamnus” grew in the holy mountain where Zeus was born (Folkard, 1884; Heilmeyer, 2007; Manniche, 2006; Snodgrass, 1994) and the gardens of Hecate (Graves, 1977; Roberts and Wink, 1998). “Dictamnus” appears in Greek mythology related to medicine: *Amaracus* (Picton, 2000; Chandler, 2004), *Chiron* (Delaveau, 1992) and was consumed in rituals of *Artemis* (Albert, 1978). Greco-Roman authors mention wild goats which eat “Dictamnus” after being wounded by the arrows of hunters, and interpreted this fact in the sense of the curative properties of this herb (the arrow would drop from their bodies and the wounds cured) (Hort, 1916; Mattioli, 1569). The Germanic and Slavic traditions mention animals with golden horns healing their wounds with "Triglav Rose" or “Dictamnus”, still called "Rozen" in the Balkans (Glonar, 1910; Kropelj, 2003). The use of “Dictamnus” in ancient Egypt (Manniche, 2006) and Persia is not sufficiently documented (Rivera et al., 2012).

Since Dioscorides, “Dictamnus” has been reported as an antidote for bites of poisonous organisms, notably snakes (Brown, 1935; López et al., 2006). It is cited in *De Villis Imperialibus* or *Capitulare* of Charlemagne and medieval *hortulus* (Barbaud, 1989; Botineau, 2003) and was later praised by the Salerno medical school (Garrido, 2005) although it is not included in the *Regimen Sanitatis* (Frutos, 2010). It also appears in medieval medical texts from the Iberian Peninsula both in Romanic languages (Vilanova, 1495) and in Arabic (Arvide, 1994; 1996). It appears in early pharmacopoeias as an ingredient (Sagaun and Aznarez, 1546; Valentian College of Pharmacists, 1601) of complex formulations in form of pills, powders, or teas, like the “*Pulveris Papae Benedicti XIII*” which was popular among Valencian Moriscos (Labarta 1981, Simó, 2010).

3.2 Genera and species within “Dictamnus”

Several genera and species of the Rutaceae and Lamiaceae fall within “Dictamnus” complex (Table 1). From the time of Aristotle and Theophrastus (4th century BCE) to Pliny the Elder (1st century CE) “Dictamnus” included at least two different Lamiaceae species (*Origanum dictamnus*, *Ballota pseudodictamnus* (L.) Benth.) (Bostock and Riley, 1856; Hort, 1916). Since the 1st century CE until the 10th century CE, “Dictamnus” appears in twenty different herbals, out of the over fifty revised by Opsomer (1989). Furthermore, "Dictamnus" juice is mentioned in three of these herbals, and leaves and root-bark each in one. Finally "Dictamnus Creticus" is

cited in four herbals. The analysis of the geographical information and uses strongly suggests that there were several species involved. According to Turner in 1548 in England “Dictamnus” was linked to *Lepidium sativum* L. (Britten, 1881). However it was not until the 16th century CE that Andrea Mattioli and Andrés Laguna deciphered the “Dictamnus” enigma recognising three groups: Diktamnon (*Origanum dictamnus*), Pseudodiktamnon (*Ballota pseudodictamnus*, *B. acetabulosa* (L.) Benth.), and, third Diktamnon (*Mentha* sp., *Salvia* sp. or *Horminium* sp.) (Valderas, 2000, 2003).

Fig. 1 approx. here.

Mattioli (1554, 1558, 1565, 1569) and Laguna (1555) in their editions of the *Materia Medica* of Dioscorides, clearly described four different Lamiaceae species associated with the Dittany of Crete (Table 1). Both Mattioli and Laguna, attach great importance to define the differences between a fifth species (*Dictamnus albus*) and Dittany of Crete (*Origanum dictamnus*) and associated Lamiaceae species, and highlight the popular uses of *D. albus* versus the officinal use of *O. dictamnus*. Andrea Mattioli (1565, 1569) also published three figures that identify accurately the main species of “Dictamnus” (*D. albus*, *O. dictamnus* and *Ballota pseudodictamnus*) (Fig. 1). Andrés Laguna (1555) in his Spanish edition published only two (*O. dictamnus* and *B. pseudodictamnus*) copying a previous edition of Mattioli (1554) which did not include *D. albus*. Bauhin (1623, 1658 and 1671) and subsequently Linné (1753) (Fig. 2), followed this distinction of several “Dictamnus” categories.

Table 1 approx. here.

In short, for many centuries two different groups of plants were classified and used under the common denominator “Dictamnus”, and, therefore, these species form the plant complex (Linares and Bye, 1987) discussed here:

Since 8th century CE common or white Dittany (*Dictamnus albus*, *D. hispanicus*) (Fig. 3) are part of European traditions (Arvide, 1994 and 1996; Barbaud, 1989; Biewer, 1992; Bingen, 2008; Madaus, 1979). Dittany of Crete (*Origanum dictamnus* and other Lamiaceae (*Ballota* and *Mentha*) is part of the classical Greek tradition (Fig. 1).

Later, names and traditional uses of “Dictamnus” were exported to America. The term was applied to local species which showed similar medicinal properties, the American Dittany: *Drosera cendeensis* Tamayo & Croizat (Morton, 1975; Alvarado, 2007 Pers. Com.) (Droseraceae), *Maranta arundinacea* L. (Marantaceae) (Plantamed, 2014) (“*Ditame*” in Brazil), *Passiflora mexicana* Juss. (Passifloraceae) (Gaspar, 2009), *Cunila origanoides* (L.) Britton (Lamiaceae) (Rafinesque, 1828-1830), and *Euphorbia tithymaloides* L. (syn.: *Pedilanthus*

tithymaloides (L.) Poit.) (Euphorbiaceae), grown in gardens of La Havanna under the name of “*Dictamno real*” (Colmeiro, 1871; Humboldt, 1826; Ortiz et al., 2009).

3.2.1 *Origanum dictamnus*

Origanum dictamnus (Fig. 1) is endemic to Crete where it has a restricted distribution with an area of occupancy of 250 km². It grows on calcareous cliffs but also on stony and rubbly ground such as gorge beds. Found from sea level to 1,900 m asl. The main threat for *Origanum dictamnus* is overexploitation of the natural populations mainly for the trade of the dried plant for its medicinal properties. *Origanum dictamnus* is listed on Annex II of the Habitats Directive and under Appendix I of the Convention on the Conservation of European Wildlife and Natural Habitats (Bern Convention). It is protected in Greece by the Presidential Decree 67/81 (IUCN, 2015).

Since Dioscorides *O. dictamnus* was an object of trade throughout the Mediterranean (López et al., 2006), often adulterated or replaced with different plants with similar medicinal properties (Delaveau, 1992; Mattioli, 1569; Laguna, 1555). Linocier (1584) mentions that *O. dictamnus* was largely adulterated with “bastard Dictamnus” (*Ballota pseudodictamnus*). While in Crete and the continental Greece, this species was an important ethnobotanical resource (Hanlidou et al., 2004; Liolios et al., 2010), for the rest of Europe it was not. There, on the contrary, different local species of *Dictamnus* were given the names and uses of “Dictamnus”. Laguna (1555) in two passages mentions that the “Dictamnus” commonly used in the pharmacies of Spain (16th century CE) was *D. albus* instead of *O. dictamnus*.

3.2.2 *Dictamnus* species

Since the 8th Century CE *Dictamnus albus* became the most commonly used species of the “Dictamnus” complex because it extends in Europe from the Iberian Peninsula to the Caucasus, entering Anatolia, and thus, for the apothecaries of the time, it was easier to obtain. Mattioli (1569) and Laguna (1566) attributed to *D. albus* the same or greater qualities as those of the Dittany of Crete (Delaveau, 1992). All references consulted from Eastern and Western Europe cited *Dictamnus albus* (Table 2). Ray (1738) offer unambiguous details e.g. “*Siliquae et contactu prurimum facium flowers*”, which refer to the contact phototoxicity produced by *D. albus* (Phillips, 1792). Actually, *D. albus* is also called “burning bush”, referring to the high flammability presenting their essential oils, allowing it to set fire around rapidly (Bruneton, 2001; Font-Quer, 1985; Gómez, 1784; Kubeczka et al., 1990; Madaus, 1979; Portolés, 1952).

In Bulgaria *D. albus* is called *росен* (Rossen) and *самодиви* (samodivi flower) (Petkov, 1982). It is very popular and is collected on the eve of Ascension Day, with the belief in that it has a greater healing power (Marinov, 1994).

Elio Antonio de Nebrija (1492) (Carrera and Codoñer, 2001; Nebrija, 1545) in his Latin-Spanish dictionary named “Dictamnus” as “diptamo real” (royal or true) associated with the Arabic name *Mescatramesir* (*Dictamnus albus* and likely *D. hispanicus*) while defining the Dittany of Crete (*O. dictamnus*) as “Puleio indicum”. In Spain *Dictamnus hispanicus* is used in southern Catalonia and Aragon, Valencia, Murcia, Castile-La Mancha, and eastern Andalusia while *D. albus* is used in Castile-Leon, Castile-La Mancha Western, Central Andalusia, Navarre, northern Aragon and Catalonia (Table 2). *D. hispanicus* is placed by The Plant List (TPL, 2014) as a synonym of *D. albus*. However, it is clearly distinguished from this species (Fig. 3) for its almost glabrous leaves with numerous segments (13-17 instead of 7-9) thinner and shorter (3.5-12 mm wide x 10-24 mm long instead of 11-40 x 25-75 mm), and the surface of stems, leaves and flowers densely covered of glands containing essential oils (Portolés, 1952; Portolés and Cabo, 1953; San Miguel, 2011).

Fig. 2 approx. here.

During the 15th to 16th century the influence of Germanic Materia Medica was decisive in Europe in the process of cultural transfer of “Dictamnus” from *Origanum* sp. to *Dictamnus* sp. (Fournier, 1947; Madaus, 1979). Subsequently Linné adopted *Dictamnus* for the genus in the Rutaceae and not the Lamiaceae (Madaus, 1979). Linnaeus (1753) published the genus *Dictamnus* and the type species for this genus (*D. albus*) in *Species Plantarum* 1: 383 with provenance: “Habitat in Germania, Gallia, Italia.” Type specimen: Lectotype: Herb. Clifford: 161, *Dictamnus* 1, sheet A (BM-000558738) (Fig. 2) (designated by: Nair in Jarvis & al. (ed.), *Regnum Veg.* 127: 42 (1993) although Townsend in Rechinger, *Fl. Iranica* 36: 1. (1966) indicated 536.1 (LINN) as type, but this sheet is unannotated by Linnaeus and cannot be original material for the name) (NHM, 2015).

3.3 Medicinal uses of “*Dictamnus*”

3.3.1 Evolution of Medicinal uses for “*Dictamnus*” in the Classical Materia Medica

3.3.1.1 Complex mixtures

The use of complex herbal formulas with dozens of ingredients became an element of western medicine between 1000 and 1700 CE (Delaveau, 1992; Obón et al., 2014) but has rarely survived in the Mediterranean Area and Portugal (Rivera and Obón, 1995a,1995b). Antidotes or universal remedies are frequent with such complex preparations, as Mithridato or Theriaca formulas with over 100 ingredients (plants, animals, minerals and rocks), including *Dictamnus*.

In the Spanish kingdoms the Valencian physician Arnau de Villanova (1495) promoted these formulae which persisted in the *Concordia dels Apotecaris de Barcelona* of 1511 (Duch 2000) and the *Concordia Aromatariorum Civitatis Caesar Augustae* (Sagaun and Aznarez, 1546) which is the fourth oldest pharmacopoeia of Europe, where *Dictamnus* occurs in 4 % of their master formulas. There is a tradition of *Dictamnus* medicinal uses in the eastern half of the Iberian Peninsula which could eventually be linked to pharmaceutical formulas, as the “Diasenet”, in use among the Moriscos during the 16th century CE (Labarta, 1981).

Mixtures with “*Dictamnus*” were used between 1000 and 1700 CE in treatments of 35 different categories of diseases. The most frequently cited ones concern nervous system and behavioural diseases (affective disorders, acute and transient psychotic disorders, cerebral palsy and other paralytic syndromes, epilepsy, generalized idiopathic epilepsy and epileptic syndromes (juvenile), and migraine) uro-genitary and gynaecological (calculus of kidney and ureter, absent scanty and irregular or delayed menstruation, pain and other conditions associated with female genital organs and menstrual cycle), infectious and parasitic diseases (helminthiasis, intestinal infectious diseases, protozoal intestinal disease unspecified, plague, smallpox), respiratory (asthma), digestive (flatulence and related conditions). These mixtures reached their peak of diversity between 1200 and 1700 CE, and, although simplified, persisted in use until the 19th century (Jourdan, 1829; Palacios, 1725; Villalón, 1731).

3.3.1.2 “*Dictamnus*” as a sole ingredient of medicines

Between 1 to 1900 CE unspecific products labelled “*Dictamnus*” as a sole ingredient were mainly used to treat 43 different pathologies, according to 161 records (Appendix 1, 2 and 3): being the core features its value as an antidote (contact with venomous animals and especially venomous snakes and lizards), and genito-urinary and gynaecological uses (spontaneous abortion, retained placenta and membranes without haemorrhage, absent, scanty and rare menstruation, long labour, pain and other conditions associated with female genital organs and menstrual cycle, calculus of kidney and ureter). Other important uses include as anti-infective and anti-parasitic (helminthiasis, plague, multiple open unspecified wounds) agents, for respiratory (acute bronchitis, asthma), digestive (gastritis and duodenitis, dyspepsia), nervous system diseases (epilepsy, dissociative [conversion] disorders, migraine, cerebral palsy and other paralytic syndromes, unspecified fever).

3.3.1.3 Uses abandoned prior to 1700 CE

The lack of recorded modern use does not imply that it is not used at all but simply that the use is no longer recorded in the literature or that unclear medical descriptions prevent us from correlating it with biomedical concepts (ICD-10). Notably ancient uses for which no record is available after 1700 CE include (Appendix 1 and 3) include intestinal protozoal diseases,

urogenital trichomoniasis, smallpox, diseases of spleen, juvenile epilepsy and epileptic syndromes, migraine, stroke not specified as haemorrhage or infarction, haemorrhoids, asthma, other respiratory diseases principally affecting the interstitium, dermatitis and eczema, androgenic alopecia, non-scarring unspecified hair loss, eccrine sweat disorders, retained placenta and membranes without haemorrhage, dysuria, dizziness and giddiness, headache, venom of scorpion, venom of other arthropods (centipedes), and contact with venomous snakes and lizards. Certainly the reasons for this lack of records about these diseases are multifold, and linked to cultural and epidemiological factors.

Protozoal intestinal diseases are no longer a relevant cause of mortality, notably in children, as it formerly was in Europe (WHO, 2015c) and, also, the control of urogenital trichomoniasis seems to have been a success in Europe because of the regular access to health care (Bowden and Garnett, 2000). Therefore, modern records of *Dictamnus* against these pathologies are lacking.

Since smallpox was declared eradicated in 1980, following a global immunization campaign led by the World Health Organization (WHO, 2015a), it clearly would no longer be treated with any medication. Similarly this could be expected for uses against the plague. Since at least 1954 there are no reports of plague for European countries (WHO, 2015b). The only exception is the recorded use of *Dictamnus* in Zagori (Greece) in the treatment of the plague (Vokou et al., 1993) which we interpret as an influence of ancient texts on modern records (Leonti 2011). The lack of modern records, except in Romania (Tita et al. 2009) for its use as antidote against venom of scorpion, venom of other arthropods (centipedes), and contact with venomous snakes and lizards can be due to the lower frequency of such cases of poisoning and the use of more active antidotes.

The lack of modern records for the treatment of ill-defined sites within the digestive system, and diseases of spleen, is likely related to unclear medical descriptions in ethnobotanical records. In developed countries the treatment of generalized idiopathic epilepsy and epileptic syndromes (juvenile), is based in the use of: anti-epileptic drugs that can successfully control seizures for most people with epilepsy, surgery and dietary therapy (Goldenberg, 2010) whereas “many herbs” are blamed for increasing the risk for seizures (Samuels et al., 2008). However Redzic (2010), Ivanova et al. (2004), Tița et al. (2009), Popović et al. (2012) still record the use of *Dictamnus albus* decoction in the Balkans for the treatment of epilepsy in general (Table 2).

Although the use in the treatment of asthma, and other respiratory diseases principally affecting the interstitium, is no longer recorded, the use of *Dictamnus hispanicus* against acute bronchitis was recorded in ethnobotanical interviews in Albacete (Rivera et al., 2008; Verde et al., 2008) and Valencia (Pellicer, 2001).

The uses of *Dictamnus* species in the treatment of diseases of the skin and subcutaneous tissue such as dermatitis and eczema, androgenic alopecia, nonscarring hair loss unspecified, and eccrine sweat disorders are no longer recorded since the 18th century (Appendix 1), instead were recorded in ethnobotanical studies the use of *Dictamnus albus* in the treatment of psoriasis in Turkey and xerosis cutis in Romania and Spain (Table 2).

3.3.2 'Traditional medicinal uses of *Dictamnus albus* and *D. hispanicus*

Here we focus on uses unambiguously attributed to *Dictamnus* (Rutaceae) which account to 143 records. *Dictamnus albus* (Fig. 3), and, to a lesser extent, *D. hispanicus* (Fig. 3), are used to treat 47 different categories of diseases (Table 2 and Appendix 3). The most salient ones in order of decreasing frequencies are: helminthiases, dyspepsia, flatulence, fever, amenorrhoea, hypertensive diseases, disorders of urinary system and epilepsy.

Fig. 3 approx. here.

Among Spanish physicians and apothecaries of the 16th century CE (Laguna, 1555), white Dittany (*D. albus*) enjoyed considerable fame. This could reach lay people through a process of vernacularization or popularization (García Ballester, 1984; Herrera, 1992; Labarta, 1981) often linked to written records (Leonti 2011). In the 18th century Gómez (1784) recommended the root of *D. albus* as "invigorating, antidote, and for plague,... against the bite of poisonous animals, worms, cold diseases of the matrix, and to excite urine and menstruation, to induce childbirth, calm bowels cramps, dissolve the sands of the kidneys and enters into the drinks that are ordered for internal injuries". Part of this report was clearly copied from Mattioli (1554, 1558) and Laguna (1555).

Table 2 approx. here.

Generally, all parts of the *Dictamnus albus*, and *D. hispanicus*, are used for medicinal purposes. However there are specific indications which relate exclusively to the use of a specific part of the plant. Approximately 60% of the different uses recorded are interchangeably treated with more than one of the parts of the plant. Roots and root bark are the plant part more frequently used. Diseases of blood and blood-forming organs, reaction to severe stress, eating disorders, chronic rhinitis, nasopharyngitis and pharyngitis, cough, jaundice, anorexia, and toxic effect of contact with venomous animals are exclusively treated with roots and root bark.

Dried leaves were used as a substitute for tea (Gmelin, 1768) and notably to treat helminthiases, and dyspepsia. Aerial parts are often used to treat hypertensive diseases, flatulence, demoralization and apathy, amenorrhoea, and dysmenorrhoea. Intestinal infectious diseases, colitis, gastroenteritis, cerebral palsy and other paralytic syndromes, pain and open wounds are exclusively treated with aerial parts.

Flowers and flowering branches are used to treat dyspepsia. Flowering tops are the most frequently collected plant part for medicinal purposes in the Spanish tradition. Balsam of Fioravanti was made with the essential oil and used to induce profuse sweating (Portolés, 1952). Fruits and seeds are used to treat notably calculus of kidney and ureter, and calculus in bladder.

The whole plant is used to treat helminthiases, flatulence and in prophylactic immunotherapy.

Fig. 4 approx. here.

Dictamnus hispanicus (Fig. 3) presents a pattern of uses similar to those recorded in Western Europe for *D. albus* (Appendix 3, Fig. 4-6). However recent ethnobotanical records refer exclusively to the use of aerial parts (Table 2). *D. hispanicus* is an endemic species of the Iberian Peninsula, which is collected as a medicinal tea plant. It is a medicinal resource for rural isolated populations in the mountains of Castellón, Valencia and Alicante (Martínez-Francés and Ríos, 2005, 2007), where the Spanish Moors left their cultural imprints (García Ballester 1984, 2001).

Fig. 5 approx. here.

Fig. 6 approx. here.

The use of *D. hispanicus* for dyspepsia and other diseases of the digestive system involves the maceration in alcoholic beverages, steeping fresh leaves or flowering tops into spirits of 25 to 40 % of ethanol, in simple formulas ("gitam") but often more complex, then called ("beatamaria", "herberet", "herbero"), some of them with up to 30 medicinal species which in recent decades have gained popularity as digestive tonics and are used within a broad social context (Ríos and Martínez-Francés, 2003, 2008a, 2008b; Martínez-Francés and Ríos, 2005, 2007). Ray (1738) and Weinmann (1739) recommended wine as vehicle for *Dictamnus* medicinal uses. The decoction or infusion is still prepared in mountains of the Valencia community, although it is less common.

3.3.3 Analysis of *Origanum dictamnus* (Lamiaceae) traditional uses compared with those of *Dictamnus* (Rutaceae)

Origanum dictamnus (Fig. 1) is used to treat 32 different categories of diseases (Appendix 3), classified in 11 main groups of the 22 recognised by the ICD-10 (WHO, 2014). Within this analysis 46.7% of uses are linked exclusive to *O. dictamnus*, 21.3% are shared both with the "Dictamnus" complex as a whole (i.e. are unresolved) and *Dictamnus* (Rutaceae), 21.3% shared

only with "Dictamnus" complex (again are unresolved) and 10.7% are modern, shared only with *Dictamnus* (Rutaceae).

The following diseases are treated with *Origanum* but not with *Dictamnus*: diabetes mellitus, obesity and disorders of lipoprotein metabolism and other lipidaemias, sexual dysfunction, acute nasopharyngitis [common cold], acute pharyngitis, acute tonsillitis, gingivitis and periodontal diseases, other disorders of teeth and supporting structures (toothache), diseases of liver, and gastric ulcer. These seem to be relatively novel developments related to the wide modern use of the *Origanum* herbal tea in the Balkans.

Records of *Origanum dictamnus* indicate similar uses as in case of the "Dictamnus" complex and *Dictamnus* (Rutaceae) for the treatment of epilepsy. However this use is against convulsive seizures which, in addition to epilepsy, can be associated to parasitic diseases. The use for gastritis, duodenitis and dyspepsia shows a coincidence in the appreciation of this "Dictamnus" complex as a digestive. Renal tubulo-interstitial diseases, calculus of kidney and ureter, absent scanty and rare menstruation, open wounds, inflammatory polyarthropathies and pain in joint, and cough are also recorded for the all three groups.

Treatment of headache, acute nephritic syndrome, spontaneous abortion and long labour, and pain and other conditions associated with female genital organs and menstrual cycle with *O. dictamnus* are shared only with the medieval "Dictamnus" complex.

Treatment of xerosis cutis, dysmenorrhoea and disorder of urinary system with *Origanum dictamnus* are modern uses shared with *Dictamnus* (Rutaceae) but not recorded for the complex "Dictamnus". This suggests a parallel evolution of medicinal uses within an adaptive context of modern ethnomedicine.

3.4 Geographical patterns for uses of *Dictamnus* (Rutaceae) in the ethnopharmacology and ethnomedicine of Europe.

3.4.1 Similarities

A total of 47 different medicinal uses for the genus *Dictamnus* in Europe have been recorded. Most (42) are linked to *D. albus*. In eastern Spain *D. hispanicus* (a local endemic species) is used for 19 different applications. We must emphasize that there is considerable overlap of recorded uses for the two species, with fourteen identical uses (Fig. 7).

The use of *D. albus* presents notable differences between Western Europe and Eastern Europe with only thirteen common uses of the 42 analysed.

The core of identical medicinal uses of the two species within the two regions of Europe considered in the analysis is limited to eight of the forty-two recorded uses: xerosis cutis,

flatulence, dyspepsia, fever, amenorrhoea and dysmenorrhoea, disorders of urinary system, and helminthiases.

Fig. 7 approx. here.

3.4.2 Western Europe

The most frequent uses in modern records of Western Europe (Appendix 3) concern the digestive system, genito-urinary, circulatory, infectious and parasitic, respiratory and nervous diseases (Fig. 8).

Fig. 8 approx. here.

The Batavian Pharmacopoeia (Niemann, 1823) recorded the use of *D. albus* for persistent leucorrhoea, fever and epilepsy. The Polish Pharmacopoeia (CSS, 1825) described the roots of *Dictamnus albus* as materia medica but without specifying uses. The Russian and Finish Pharmacopoeia (Anonymous, 1825) recognised the root's gynaecological properties and for treating helminthiasis, epilepsy and respiratory complaints.

The Spanish Pharmacopoeia (Anonymous, 1826) accepted the bark of *Dictamnus* roots. Formulations with *D. albus* were still in use in 2002 in the Phytotherapy of Spain with two simple preparations and a compound preparation with eight other species used as a digestive, carminative, for intestinal pain, kidney and liver disease, and kidney stones (Vanaclocha and Cañigüeral, 2003). However, considering the acute toxicity (liver injury after oral ingestion) (Jang, 2008) and induced phytophotodermatitis (Beis et al., 2005, Henderson and DesGroseilliers, 1984) (Fig. 8) reported for different *Dictamnus* species it is important to evaluate the potential risks of its continued use.

Fig. 9 approx. here.

3.4.3 Eastern Europe and Turkey

Modern records of *Dictamnus* include thirty different medicinal uses in Eastern Europe classified into eleven different groups of ICD-10 (Appendix 3). Notably, certain infectious and parasitic diseases (12%), which presents a high relevance, in the Balkans, where helminthiases continue to be a serious public health problem. For instance, food-borne helminthiasis, including hydatidosis/echinococcosis (Dakkak, 2010; Sotiraki et al., 2003), trichinellosis, opistorchiasis, and taeniasis-cysticercosis (Hotez & Gurwith, 2011; Neghina et al., 2011), and soil-transmitted helminth infections (ascariasis, trichuriasis and toxocariasis) (Hotez and Gurwith, 2011) are relatively frequent causes of morbidity. On the other hand, the treatment of

plague (Vokou et al., 1993) is likely a misunderstanding or directly a copy from old herbals considering the epidemiological evidence for Greece during the last 100 years (WHO, 2015b).

Epilepsy and sleep disorders [insomnias] are also remarkable. However, in the case of epilepsy cysticercosis (see helminthiasis above) is one of the most common causes of seizures which can be seen as epileptic episodes. Diseases of the genitourinary system (18% in terms of frequency) is the more relevant group of diseases treated with *Dictamnus* in Eastern Europe.

3.4.4 Differences

Remarkable differences are found in medicinal uses of *Dictamnus albus* between Western and Eastern Europe. Amongst the 15 exclusive uses found for Eastern Europe, the Balkans and Turkey the following are particularly frequent: Mood [affective] disorders, renal tubulo-interstitial diseases and symptoms and signs involving emotional state. In parallel amongst those exclusive of *D. albus* in Western Europe, up to a total of 11, are remarkable, most notably anorexia, unspecified malaria and calculus in bladder. Finally, *D. hispanicus* presents four exclusive uses: gastroenteritis and colitis of infectious origin, cerebral palsy and other paralytic syndromes, pain not elsewhere classified and multiple open wounds unspecified.

4 Conclusions

“Dictamnus” is not a compound medicine, although it was used in numerous compound medicines in Roman and Mediaeval pharmacies, instead it is a complex of different species. Therefore, “during centuries Dictamnus” has been a phytopharmaceutical name given to a set of medicinal plants belonging to different plant genera and, even, families. These plants are not similar in shape, geographical provenance or habitat. Their main common features are thus pharmaceutical name and medicinal uses.

“Dictamnus” shows how transmission of traditional knowledge about medicinal uses and vernacular plant names, and identification of crude material of the materia medica along 25 centuries present remarkable levels of development and innovation. “Dictamnus” experienced successive innovations which led to the replacement of ancient uses. There are 23 different types of uses for which no record is available after 1700 CE. In parallel, novel uses were recorded for *D. albus*, *D. hispanicus* and for *Origanum dictamnus* in W and E Europe.

Dictamnus albus (Rutaceae) is the prototypical representative of the classical and medieval “Dictamnus” complex although *Origanum dictamnus*, a Cretan endemic, is also relevant within this complex. Evidence exists for a sufficiently long and coherent tradition for *D. albus* and, to a lesser extent, *D. hispanicus*, used to treat 47 different categories of diseases. Western and

Eastern Europe present differences in the repertory of medicinal uses of *D. albus*. Generally, the roots and root bark are preferred for medicinal purposes, although aerial parts are also used.

The paper highlights the challenges of working with historical texts and our analysis has disentangled the different species associated with the plant complex “Dictamus”. However, not all uses of the plant complex can be linked to a specific plant genus and species

The next steps of research should be to systematically analyze phytochemical, pharmacological and clinical evidence and to develop safety pharmacology and toxicology studies in relation with the indications, plant parts and traditional procedures of preparation and administration here recorded, notably concerning the treatment of helminthiases, dyspepsia and flatulence, acute bronchitis, absent or delayed menstruation and epilepsy. It is urgent to determine whether the actual uses of *Dictamnus* including the maceration of the aerial parts in spirits as they are practiced in Europe are safe enough or not. In the context of the toxicity concerns of *Dictamnus* spp., this needs to be addressed with priority. Also, clearly, many of the uses are not likely to be acceptable as OTC uses, therefore, one key focus will have to be on (minor) conditions, which can be controlled with self-treatment.

All this lead us to call attention to two highly promising European species of the Rutaceae: *Dictamnus albus* and *Dictamnus hispanicus* which have been of common medicinal use over centuries.

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Table 1 List of “Dictamnium”– common names and their botanical equivalent based on Linné (1753)

Linné Scientific	Mattioli (1554)	Laguna (1555)	Mattioli (1563)	Bauhin (1623)
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names	(Latin)	(Spanish)	(Italian)	(Latin)
1. <i>Origanum dictamnus</i> L.	“Dictamnnum”	“Dictamno verdadero”, “Dictamno”, “Poleo salvage”	“Dittamo”, “Pulegio salvatico”	“Dictamnus creticus”
2. <i>Ballota pseudodictamnus</i> (L.) Benth.	“Pseudodictamnnum”	“Dictamno falso”, “PseudoDictamno”	“Dittamo falso”	“Pseudodictamnus verticillatus inodorus”
3. <i>Ballota acetabulosa</i> (L.) Benth.	“Dictamnnum alterum”	“Otro Dictamno Candioto”	“Un’altro Dittamo di Candia”	“Pseudodictamnus acetabulis Moluccae”
4. <i>Mentha</i> sp.?	“Dictamnnum alterum”	“Otro Dictamno Candioto”	“Un’altro Dittamo di Candia”	“Pseudodictamnus alter odoratus?”
5. <i>Dictamnus albus</i> L.	“Dictamnnum album”	“Dictamno blanco”, “Fresnillo”	“Dittamo bianco”, “Frassinello”	“Dictamnus albus vulgo sive Fraxinella”

Table 2. Ethnopharmacological evidence for medicinal uses of *Dictamnus*. **Note:** Pathologies were standardized following the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) Version for 2010 (WHO 2014), for original names of pathologies see Appendix 2. **Abbreviations: Species:** Da: *D. albus*, Dh: *D. hispanicus*. **Parts used:** AP: aerial parts, F: flowers and flowering branches, FR: fruits and seeds, L: leaves, R: roots, RB: root bark, WP: whole plant, YL: young leaves; **Preparation:** CWW: boiled with water and wine, DEC: decoction, DR: dried more or less grinded, TEA: tea, LIQ: liquor; **Administration:** IVAP: Inhalation of vapours, OR: oral, VAP: the injured body part is exposed to the vapours; **n.d.:** no data. **Type of source:** ETHNPH modern ethnobotany and ethnopharmacology, OTH: other.

<i>Diseases and Related Health Problems</i>	Type of source	Geographic zone, country	Parts used	Preparation	Administration	References
I Certain infectious and parasitic diseases						
Intestinal infectious diseases (A00-A09)	OTH	Valencian region, Spain	AP	TEA	OR	Pellicer (2001)

<i>Diseases and Related Health Problems</i>	Type of source	Geographic zone, country	Parts used	Preparation	Administration	References
A09.0 Other and unspecified gastroenteritis and colitis of infectious origin	OTH	Valencian region, Spain	AP	TEA	OR	Pellicer (2001)
A20 Plague	OTH	Zagori (Greece)	AP / R / WP	DEC	OR	Vokou et al. (1993)
B54 Unspecified malaria	OTH	Germany	R	DEC	OR	Kölbl (1990)
B54 Unspecified malaria	OTH	France	R / FR	TEA / DEC	OR	Fournier (1947)
Helminthiasis (B65-B83)	OTH	France	L	TEA / DEC	OR	Fournier (1947)
Helminthiasis (B65-B83)	OTH	Germany	R	DEC	OR	Kölbl (1990)
Helminthiasis (B65-B83)	OTH	Zagori (Greece)	AP / R / WP	DEC	OR	Vokou et al. (1993)
Helminthiasis (B65-B83)	OTH	Greece, Croatia	L	TEA	OR	Gelenčir (1989), Souleles (1989)
Helminthiasis (B65-B83)	OTH	Spain	R / RB	DEC	OR	Reyes-Prosper (1915)
Helminthiasis (B65-B83)	ETHNPH	Romania	R / RB	DEC	OR	Tița et al. (2009)
Helminthiasis (B65-B83)	ETHNPH	Serbia	R	TEA	OR	Popović et al. (2014)
Helminthiasis (B65-B83)	ETHNPH	Serbia, Bulgaria	WP	n.d.	n.d.	Ivanova et al. (2004), Popović et al. (2012)
Helminthiasis (B65-B83)	ETHNPH	Albacete, Castilla-La Mancha, Spain	RB	TEA	OR	Verde et al. (2008)
III Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism						
D50.8 Other iron deficiency anaemias	OTH	France	R / FR	TEA / DEC	OR	Fournier (1947)

<i>Diseases and Related Health Problems</i>	Type of source	Geographic zone, country	Parts used	Preparation	Administration	References
D53.2 Scorbutic anaemia	OTH	France	R / FR	TEA / DEC	OR	Fournier (1947)
D75.9 Disease of blood and blood-forming organs, unspecified	OTH	Croatia	R	DEC	OR	Gelenčir (1989)
V Mental and behavioural disorders						
F23 Acute and transient psychotic disorders	ETHNPH	Southern Bosnia and Herzegovina and Serbia (W. Balkan), Bulgarian Republic, Romania	AP / R / WP	DEC	OR	Redzic (2010), Ivanova et al. (2004), Tița et al. (2009), Popović et al. (2012)
F30-F39 Mood [affective] disorders	ETHNPH	Greece	AP	TEA	OR	Hanlidou et al. (2004)
F30-F39 Mood [affective] disorders	OTH	Zagori (Greece)	AP / R / WP	DEC	OR	Vokou et al. (1993)
F30-F39 Mood [affective] disorders	ETHNPH	Serbia	R	TEA	OR	Popović et al. (2014)
F43.9 Reaction to severe stress, unspecified	ETHNPH	Serbia	R	TEA	OR	Popović et al. (2014)
F44 Dissociative [conversion] disorders	ETHNPH	Southern Bosnia and Herzegovina and Serbia (W. Balkan), Bulgarian Republic, Romania	AP / R / WP	DEC	OR	Redzic (2010), Ivanova et al. (2004), Tița et al. (2009), Popović et al. (2012)
F44 Dissociative [conversion] disorders	OTH	Germany	R / FR	DEC	OR	Kölbl (1990)
F50 Eating disorders	OTH	Occidental Mediterranean (Italy, France, Spain)	R	LIQ	OR	Panesar et al. (2009)
VI Diseases of the nervous system						

<i>Diseases and Related Health Problems</i>	Type of source	Geographic zone, country	Parts used	Preparation	Administration	References
G40 Epilepsy	ETHNPH	Southern Bosnia and Herzegovina and Serbia (W. Balkan), Bulgaria, Romania	AP / R / WP	DEC	OR	Redzic (2010), Ivanova et al. (2004), Tița et al. (2009), Popović et al. (2012)
G40 Epilepsy	ETHNPH	Serbia	RB / L	TEA	OR	Popović et al. (2014)
G40 Epilepsy	OTH	Germany	R / FR	DEC	OR	Kölbl (1990)
G40 Epilepsy	OTH	France	R	TEA / DEC	OR	Fournier (1947)
G47.0 Disorders of initiating and maintaining sleep [insomnias]	ETHNPH	Serbia	RB / L	TEA	OR	Popović et al. (2014)
Cerebral palsy and other paralytic syndromes (G80-G83)	MODET	Cuenca, Castilla-La Mancha, Spain	AP	CWW	VAP	Fajardo et al. (2007)
IX Diseases of the circulatory system						
Acute rheumatic fever (I00-I02)	OTH	Zagori (Greece)	AP / R / WP	DEC	OR	Vokou et al. (1993)
Hypertensive diseases (I10-I15)	ETHNPH	La Segarra, Catalonia, Spain	AP	DEC	OR	Raja et al. (1997)
Hypertensive diseases (I10-I15)	OTH	Spain	F	DEC	OR	Vanaclocha and Cañigüeral (2003)
Hypertensive diseases (I10-I15)	ETHNPH	Aragonese region, Spain	AP	TEA	OR	Villar et al. (1987)
Hypertensive diseases (I10-I15)	ETHNPH, OTH	Aragonese and Valencian region, Spain	L / F	TEA	OR	Portolés (1952), Mulet (1991), Blanc (2003), Villar (2003), Verde et al. (2008)
Hypertensive diseases (I10-I15)	ETHNPH	Valencian region, Spain	AP	DEC	OR	Mulet (1991)
Other forms of heart disease (I30-I52)	OTH	Zagori (Greece)	AP / R / WP	DEC	OR	Vokou et al. (1993)
Cerebrovascular diseases (I60-I69)	OTH	Catalonia region, Spain	n.d.	n.d.	n.d.	Portolés and Cabo, 1953

<i>Diseases and Related Health Problems</i>	Type of source	Geographic zone, country	Parts used	Preparation	Administration	References
X Diseases of the respiratory system						
J20 Acute bronchitis	ETHNPH, OTH	Albacete, Castilla-La Mancha and Valencian region, Spain	F	TEA	OR	Verde et al. (2008), Rivera et al. (2008), Pellicer (2001)
J20 Acute bronchitis	ETHNPH	Albacete, Castilla-La Mancha, Spain	F	TEA	IVAP	Verde et al. (2008)
J20 Acute bronchitis	OTH	Valencian region, Spain	L	DR	OR	Pellicer (2001)
J31 Chronic rhinitis, nasopharyngitis and pharyngitis	OTH	Germany	R	DEC	OR	Kölbl (1990)
XI Diseases of the digestive system						
K30 Dyspepsia	ETHNPH	Serbia	RB / L	TEA	OR	Popović et al. (2014)
K30 Dyspepsia	ETHNPH	Turkey	F	TEA / DEC	OR	Baser et al. (1994), Raja et al. (1997), Beis et al. (2005), Akbulut and Bayramoglu (2013)
K30 Dyspepsia	ETHNPH	Italy	F	TEA / DEC	OR	Tirillini et al. (2002), Leporatti and Ivancheva (2003)
K30 Dyspepsia	OTH	Italy	R	TEA	OR	Pomini (2000)
K30 Dyspepsia	OTH	Spain	F	TEA / DEC	OR	Vanaclocha and Cañigüeral (2003)
K30 Dyspepsia	OTH	France	R / FR / L	TEA / DEC	OR	Fournier (1947)
K30 Dyspepsia	ETHNPH	Murcia	YL	TEA	OR	Rivera and Obón (1991, 1996)
K30 Dyspepsia	ETHNPH	Mariola, Spain	AP	TEA	OR	Belda et al. (2013)
K52.3 Indeterminate colitis	OTH	Valencian region, Spain	AP	n.d.	n.d.	Portolés and Cabo (1953), Pellicer (2001)

<i>Diseases and Related Health Problems</i>	Type of source	Geographic zone, country	Parts used	Preparation	Administration	References
K52.3 Indeterminate colitis	ETHNPH, OTH	Aragonese and Valencian region, Spain	AP	LIQ	OR	Font Quer (1985), Mulet (1991), Blanc (2003), Ríos and Martínez-Francés (2003, 2008a, 2008b), Barber et al. (2005), Conca and Oltra (2005), Martínez-Francés and Ríos (2005, 2007), Merle et al. (2006).
XII Diseases of the skin and subcutaneous tissue						
L40 Psoriasis	ETHNPH	Turkey	n.d.	n.d.	n.d.	Beis et al. (2005)
L85.3 Xerosis cutis	ETHNPH	Romania	R	DEC	OR	Țița et al. (2009)
L85.3 Xerosis cutis	ETHNPH	Aragonese region, Spain	F	I	OR	Villar et al. (1987)
XIII Diseases of the musculoskeletal system and connective tissue						
Inflammatory polyarthropathies (M05-M14)	ETHNPH	Serbia	WP	n.d.	n.d.	Popović et al. (2012)
Inflammatory polyarthropathies (M05-M14)	ETHNPH	Murcia, Valencian region, Spain	AP	TEA	OR	Obón and Rivera (1991, 1996), Ríos and Martínez-Francés (2003, 2008a, 2008b), Martínez-Francés and Ríos (2005, 2007)
Inflammatory polyarthropathies (M05-M14)	ETHNPH	Serbia	L / F	LIQ	EXT	Popović et al. (2014)
M25.5 Pain in joint	ETHNPH	Serbia	L / F	LIQ	EXT	Popović et al. (2014)
M25.5 Pain in joint	ETHNPH	Serbia	WP	n.d.	n.d.	Popović et al. (2012)
M25.5 Pain in joint	ETHNPH	Murcia, Valencian	AP	TEA	OR	Obón and Rivera (1991, 1996), Ríos and Martínez-

<i>Diseases and Related Health Problems</i>	Type of source	Geographic zone, country	Parts used	Preparation	Administration	References
		region, Spain				Francés (2003, 2008a, 2008b), Martínez-Francés and Ríos (2005, 2007)
XIV Diseases of the genitourinary system						
Renal tubulo-interstitial diseases (N10-N16)	OTH	Zagori (Greece)	AP / R / WP	DEC	OR	Vokou et al. (1993)
Renal tubulo-interstitial diseases (N10-N16)	ETHNPH	Serbia	RB / L	TEA	OR	Popović et al. (2014)
N20 Calculus of kidney and ureter	ETHNPH	Serbia	FR	TEA	OR	Popović et al. (2014)
N20 Calculus of kidney and ureter	OTH	Germany	R / FR	DEC	OR	Kölbl (1990)
N20 Calculus of kidney and ureter	OTH	France	R / FR	TEA / DEC	OR	Fournier (1947)
N21.0 Calculus in bladder	OTH	France	R / FR	TEA / DEC	OR	Fournier (1947)
N21.0 Calculus in bladder	OTH	Germany	R / FR	DEC	OR	Kölbl (1990)
N39.9 Disorder of urinary system, unspecified	OTH	Italy	F / R	TEA	OR	Pomini (2000)
N39.9 Disorder of urinary system, unspecified	ETHNPH	Serbia	RB / L	TEA	OR	Popović et al. (2014)
N39.9 Disorder of urinary system, unspecified	OTH	Zagori (Greece)	AP / R / WP	DEC	OR	Vokou et al. (1993)
N39.9 Disorder of urinary system, unspecified	ETHNPH, OTH	Bulgarian Republic, Romania	R	TEA / DEC	OR	Leporatti and Ivancheva (2003), Ivanova et al. (2004), Tița et al. (2009)
N39.9 Disorder of urinary system, unspecified	ETHNPH, OTH	Valencian region, Spain	AP / RB	TEA	OR	Portolés (1952), Portolés and Cabo (1953), Merle et al. (2006), Verde et al. (2008)

<i>Diseases and Related Health Problems</i>	Type of source	Geographic zone, country	Parts used	Preparation	Administration	References
N91 Absent, scanty and rare menstruation	OTH	Italy	R	TEA	OR	Pomini (2000)
N91 Absent, scanty and rare menstruation	ETHNPH	Serbia	FR	TEA	OR	Popović et al. (2014)
N91.2 Amenorrhoea, unspecified	OTH	France	R / FR	TEA / DEC	OR	Fournier (1947)
N91.2 Amenorrhoea, unspecified	ETHNPH	Jaen, Andalusian region, Spain	AP	TEA	OR	Guzmán (1997)
N91.2 Amenorrhoea, unspecified	OTH	Valencian region, Spain	L	DR	OR	Pellicer (2001)
N91.2 Amenorrhoea, unspecified	OTH	Aragonese region, Spain	AP	TEA	OR	Font Quer (1985)
N91.2 Amenorrhoea, unspecified	ETHNPH	Aragonese region, Spain	AP	TEA	OR	Villar et al. (1987)
N91.2 Amenorrhoea, unspecified	ETHNPH	Castellón, Valencia region	F	LIQ	OR	Mulet (1991)
N91.2 Amenorrhoea, unspecified	OTH	Zagori (Greece)	AP / R / WP	DEC	OR	Vokou et al. (1993)
N94.6 Dysmenorrhoea, unspecified	OTH	France	R / FR	TEA / DEC	OR	Fournier (1947)
N94.6 Dysmenorrhoea, unspecified	ETHNPH, OTH	Murcia and Valencian region, Spain	AP	TEA	OR	Portolés and Cabo (1953), Font Quer (1985), Mulet (1991), Obón and Rivera (1991), Fresquet et al. (1994), Ríos and Martínez-Francés (2003, 2008a, 2008b), Martínez-Francés and Ríos (2005, 2007)
N94.6 Dysmenorrhoea, unspecified	OTH	Zagori (Greece)	AP / R / WP	DEC	OR	Vokou et al. (1993)

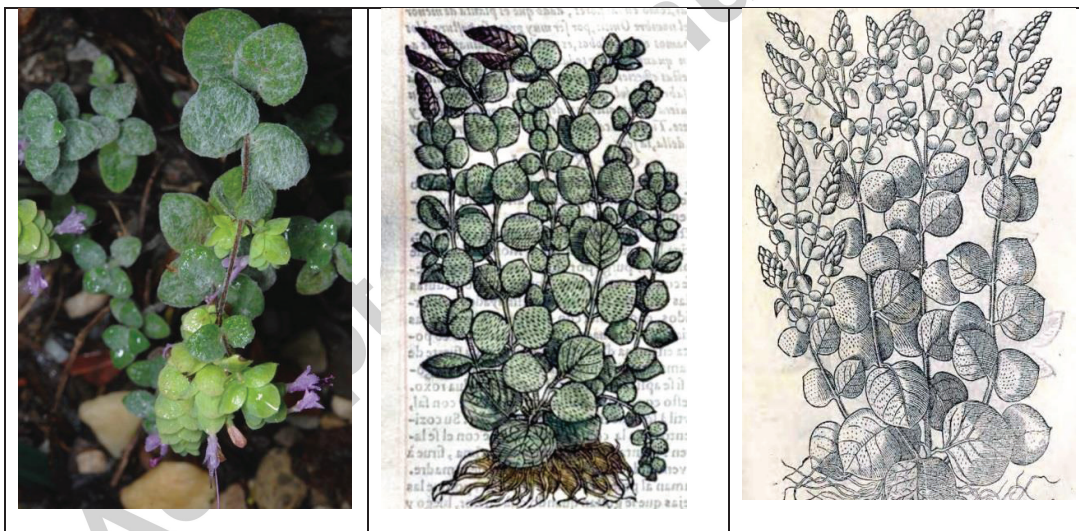
XVIII Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere

<i>Diseases and Related Health Problems</i>	Type of source	Geographic zone, country	Parts used	Preparation	Administration	References
classified						
R05 Cough	ETHNPH, OTH	Romania	R / RB	DEC	OR	Țița et al. (2009)
R14 Flatulence and related conditions	OTH	France	R / FR	TEA / DEC	OR	Fournier (1947)
R14 Flatulence and related conditions	ETHNPH	Valencian region, Spain	AP	n.d.	n.d.	Portolés and Cabo (1953)
R14 Flatulence and related conditions	OTH	Spain	F	DEC	OR	Vanaclocha and Cañigüeral (2003)
R14 Flatulence and related conditions	ETHNPH, OTH	Valencian region, Spain	F	TEA	OR	Mulet (1991), Stübing and Peris (1998)
R14 Flatulence and related conditions	OTH	Valencian region, Spain	AP	TEA	OR	Stübing and Peris (1998)
R14 Flatulence and related conditions	ETHNPH	Greece, Serbia, Bulgarian Republic	L / RB / WP	TEA	OR	Souleles (1989), Ivanova et al. (2004), Hanlidou et al. (2004), Popović et al. (2010)
R14 Flatulence and related conditions	OTH	N and C Spain	L / RB / WP	TEA	OR	Font Quer (1985), Souleles (1989), Ivanova et al. (2004), Hanlidou et al. (2004), Popović et al. (2010)
R14 Flatulence and related conditions	ETHNPH, OTH	Valencian region, Spain	AP	TEA	OR	Mulet (1991), Conca and Oltra (2005), Martínez-Francés (2006)
R17 Unspecified jaundice	OTH	Bulgarian Republic	RB	n.d.	n.d.	Ivanova et al. (2004)
R45 Symptoms and signs involving emotional state	ETHNPH	Serbia	RB / L	TEA	OR	Popović et al. (2014)
R45 Symptoms and signs involving emotional state	ETHNPH	Serbia	R	TEA	OR	Popović et al. (2014)
R45.3 Demoralization and apathy	ETHNPH	Mariola, Spain	AP	TEA	OR	Belda et al. (2013)
R45.3 Demoralization and	ETHNPH	Greece	AP	TEA	OR	Hanlidou et al. (2004)

<i>Diseases and Related Health Problems</i>	Type of source	Geographic zone, country	Parts used	Preparation	Administration	References
apathy						
R45.3 Demoralization and apathy	OTH	Greece	AP / R / WP	DEC	OR	Vokou et al. (1993)
R50.9 Fever, unspecified	OTH	Italy	R	TEA	OR	Pomini (2000)
R50.9 Fever, unspecified	OTH	Germany	R	DEC	OR	Kölbl (1990)
R50.9 Fever, unspecified	OTH	Turkey	F	n.d.	n.d.	Beis et al. (2005)
R50.9 Fever, unspecified	ETHNPH	Serbia	WP	n.d.	n.d.	Popović et al. (2012)
R50.9 Fever, unspecified	ETHNPH	Serbia	R	TEA	OR	Popović et al. (2014)
R50.9 Fever, unspecified	ETHNPH	Romania	R	DEC	OR	Tița et al. (2009)
R50.9 Fever, unspecified	ETHNPH	Murcia region, Spain	AP	TEA	OR	Obón and Rivera (1996)
R50.9 Fever, unspecified	OTH	France	R / FR	TEA / DEC	OR	Fournier (1947)
R52 Pain, not elsewhere classified	ETHNPH	Murcia region, Spain	AP	TEA	OR	Obón and Rivera (1991, 1996)
R56 Convulsions, not elsewhere classified	ETHNPH	Serbia	RB / L	TEA	OR	Popović et al. (2014)
R56 Convulsions, not elsewhere classified	OTH	Germany	R / FR	DEC	OR	Kölbl (1990)
R63.0 Anorexia	OTH	Western Mediterranean (Italy, France, Spain)	R	LIQ	OR	Panesar et al. (2009)
XIX Injury, poisoning and certain other consequences of external causes						
T63 Toxic effect of contact with venomous animals	ETHNPH	Romania	R	DEC	OR	Tița et al. (2009)

<i>Diseases and Related Health Problems</i>	Type of source	Geographic zone, country	Parts used	Preparation	Administration	References
T01.9 Multiple open wounds, unspecified	ETHNPH	Murcia region, Spain	AP	DEC	OR	Obón and Rivera (1991)
XXI Factors influencing health status and contact with health services						
Z29.1 Prophylactic immunotherapy	ETHNPH	Serbia	WP	n.d.	n.d.	Popović et al. (2012)

Fig. 1. The image of “Dictamnus” Upper: *Origanum dictamnus* L. (Photo: D. Rivera), Cretan dittany (Laguna 1555), Cretan dittany (Matthioli 1565). Middle: *Ballota pseudodictamnus* (L.) Benth. (Photo: D. Rivera), False dittany (Laguna 1555), False dittany (Matthioli 1565) Lower: *Dictamnus albus* L. (Photo: D. Rivera), White dittany (Tournefort 1700), White dittany (Matthioli 1565).



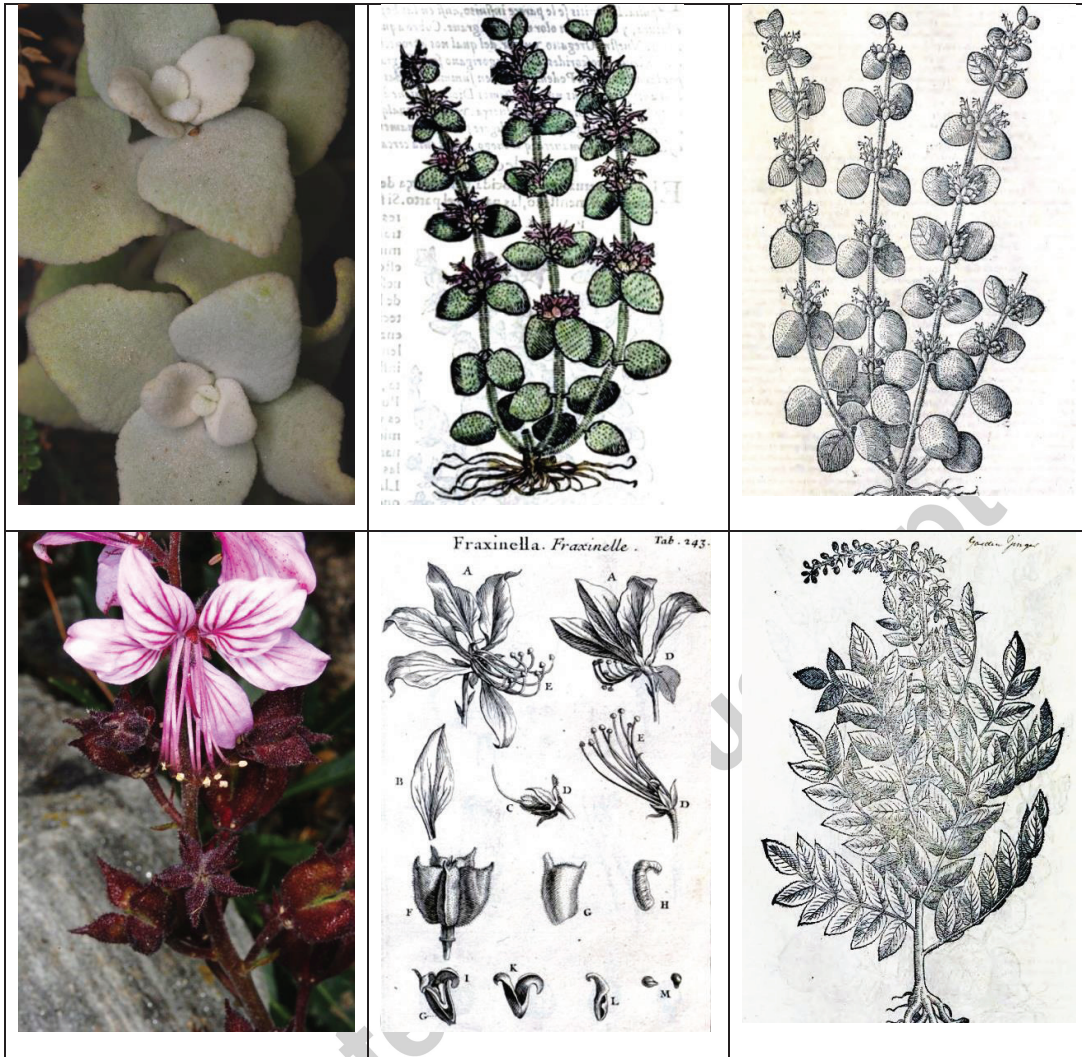


Fig. 2 Holotype of *Dictamnus albus* L. at the Hortus Cliffortianus in the Natural History Museum of London (Image: NHM 2015).



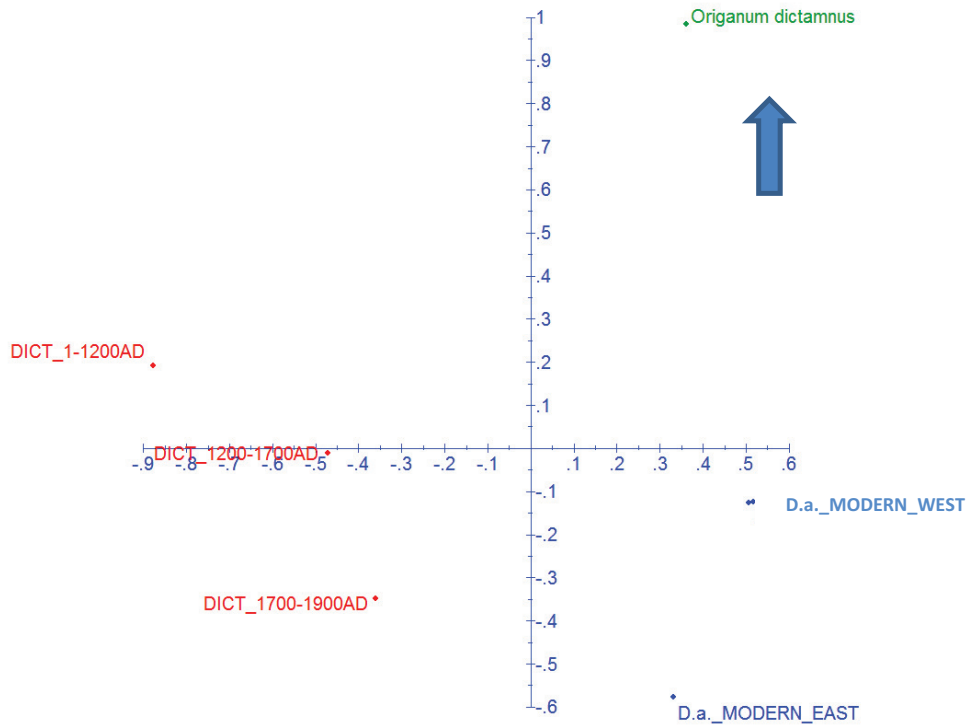
Fig. 3 Fruiting plants of *Dictamnus albus* (left) and *Dictamnus hispanicus* (right), living in two close populations in Ciudad Real (Spain), with clearly different ecology and without hybridizations between both. Note the different shape of the leaves and leaflets, also the density of glands in the fruit.



Fig. 4 Results of the Factorial Analysis of Principal Coordinates based on the main groups of medicinal uses. Axis 1: Eigenvalue 0.27 Inertia 37.1%, Axis 2: Eigenvalue 0.21 Inertia 29.3%, Axis 3: Eigenvalue 0.1 Inertia 14.29%, Axis 4: Eigenvalue 0.06 Inertia 8.94%, Axis 5: Eigenvalue 0.06 Inertia 8.06%. Above: Axis 1 vs. 2. Below: Axis 1 vs. 3.

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Factorial analysis: Axes 1 / 2



Factorial analysis: Axes 1 / 3

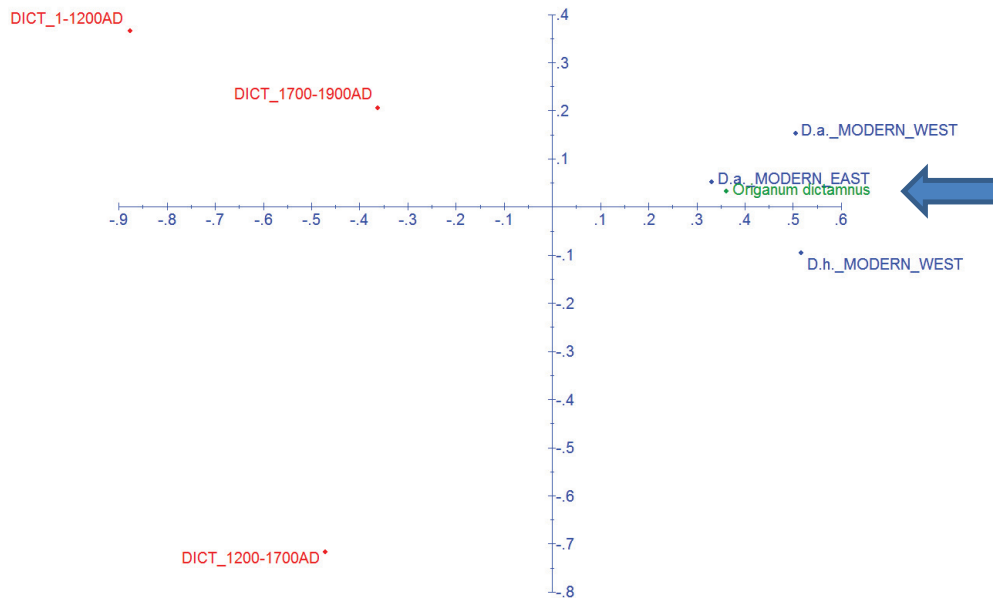


Fig. 5 “*Dictamnus*” hierarchical tree which describe the relationships between long-term traditional medicinal uses divided in three periods, modern uses of *Dictamnus albus* in Western Europe and Eastern Europe, modern uses of *D. hispanicus* and *Origanum dictamnus*, based on the common agglomerative

heuristic. For updating dissimilarity during the tree construction the Ward criterion was adopted. Abbreviations: D.a. *Dictamnus albus*, D.h. *Dictamnus hispanicus*.

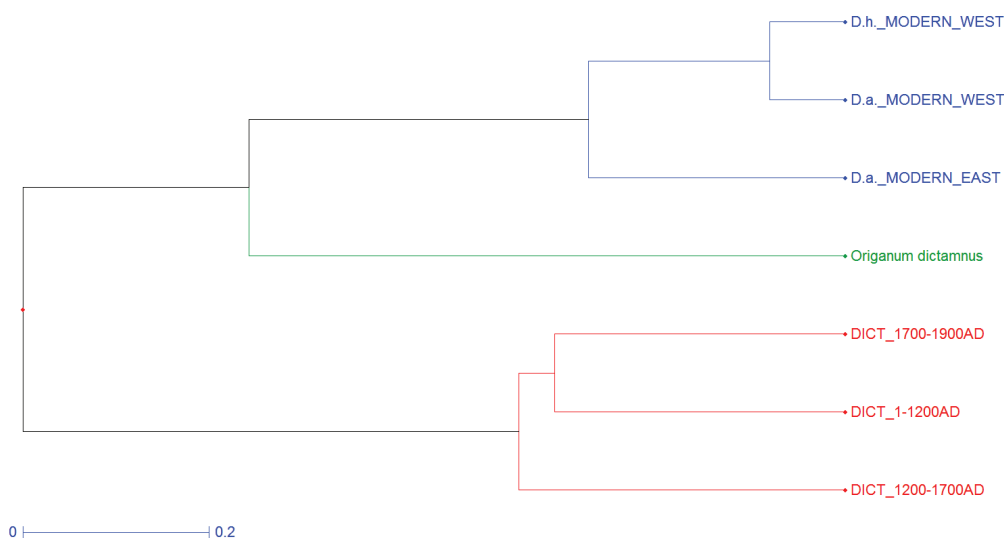


Fig. 6 “*Dictamnus*” complex Weighted Neighbor-Joining tree which uses the criterion of relative neighborhood, weighted average for dissimilarity updating, and adjustment to an additive tree distance. A bootstrap value is given to each edge that indicates the occurrence frequency of this edge in the 20 000 bootstrapped trees. Bootstrap values range between 0 and 100. Abbreviations: D.a. *Dictamnus albus*, D.h. *Dictamnus hispanicus*.

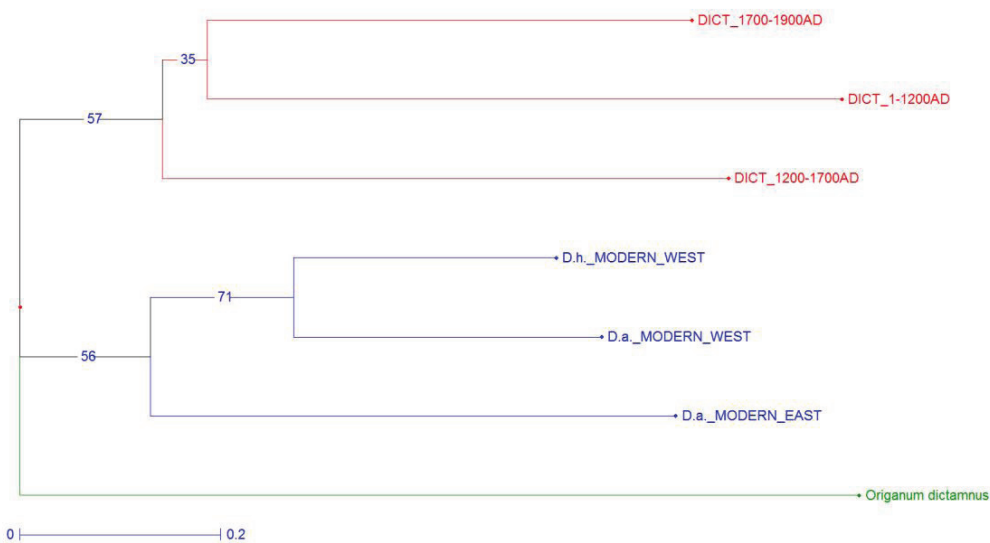


Fig. 7 Overlapping medicinal uses of *Dictamnus* (Rutaceae) in Europe.

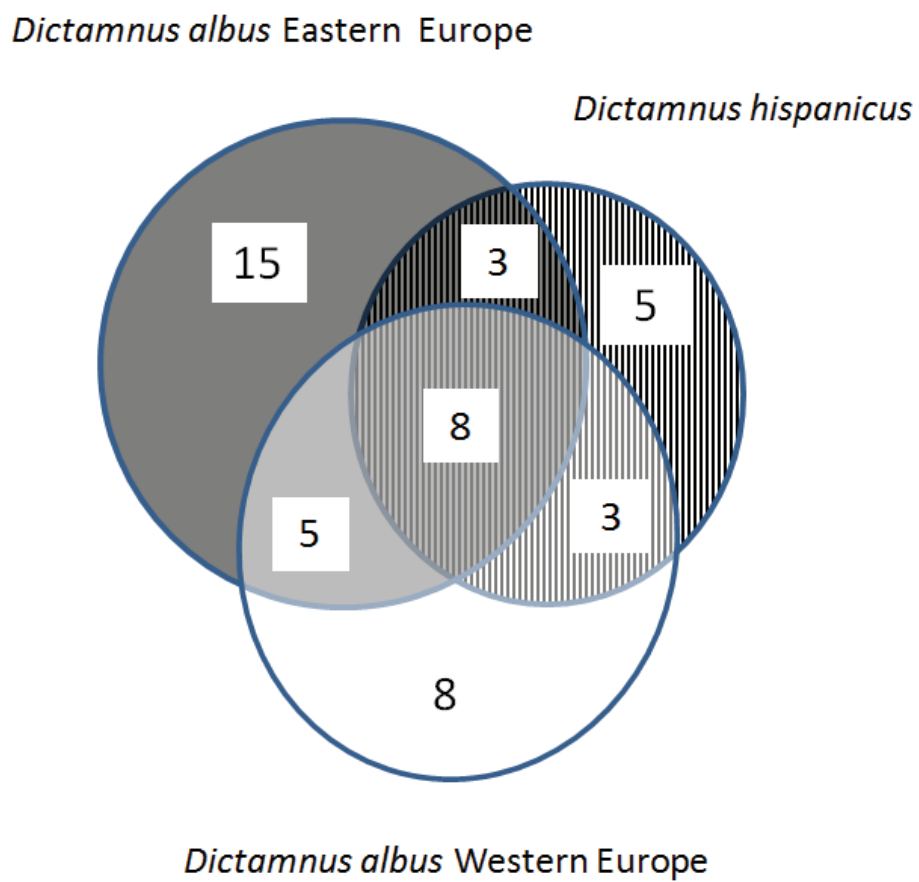


Fig. 8 *Dictamnus* (Rutaceae) most relevant uses in modern records of Western Europe.

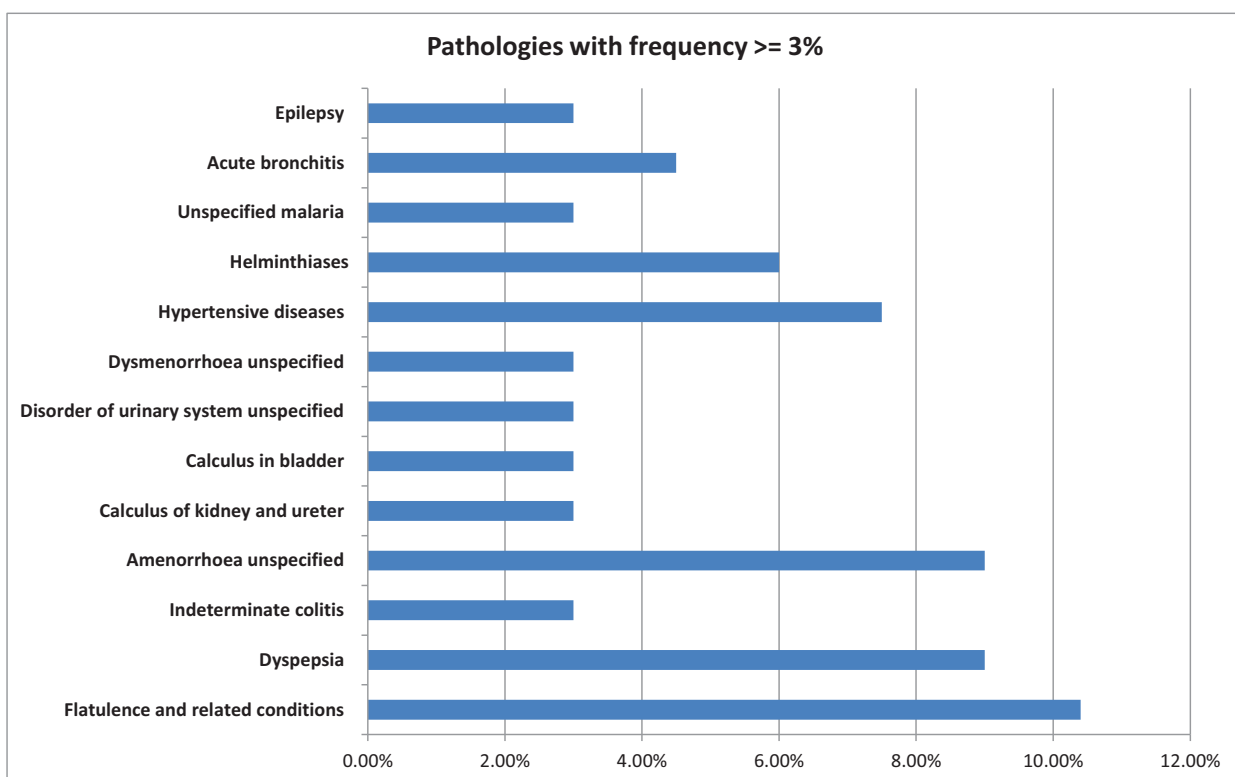


Fig. 9 Phototoxic effects (left) of furanocoumarins present in *Dictamnus hispanicus* and protections usually used by collectors to avoid them (right).



Accepted manuscript

Dictamnus albus L.
Type at the Natural History
Museum (London)



Relationships exclusively based on the analysis of medicinal uses.

