Dittany of Crete: A botanical and ethnopharmacological review

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\textbf{A B S T R A C T}

\textit{Origanum dictamnus} (Lamiaceae family), an endemic plant of the Greek island of Crete, is widely used as a traditional medicine since antiquity, all over Europe. The aim of the present review is to present comprehensive information of the plant's botanical taxonomy and morphology, as well as of the chemical constituents, biological and pharmacological research on \textit{O. dictamnus}, which will be presented and critically evaluated. The paper also highlights particularly interesting aspects and common medicinal uses not previously described in the specific ethnobotanical literature. An increasing number of chemical and pharmacological studies have been reported recently, some of which strongly support its traditional medicinal uses against various illnesses such as sore throat, cough and gastric ulcer. A variety of compounds, including flavonoids, lipids and terpenoids (mainly carvacrol and thymol) have been identified from the plant. Current studies have showed that the extracts, the essential oil, as well as their active principles possess several pharmacological properties, like antimicrobial, antioxidant and anti-ulcer ones. The recent scientific data and the rich historical evidence of its medicinal uses could support further research as well as its use as a safe herbal medicinal product.

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\textsuperscript{b} Abbreviations: AP, aerial parts; B, bracts; L, leaves; F, flowers; NS, not specified; HS, headspace analysis; Ex, CH\textsubscript{3}Cl extract; C, cultivated; W, wild; HC, hydroponic cultivated; P, platypthys; S, stenophyly; MIC, minimal inhibition concentration; ID, inhibition dose; T/C, relative increase of animal survival against a control group; ca, circa.

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1. Introduction

Origanum dictamnus L. (Fig. 1) is a Greek endemic species of the island of Crete, where it grows wild, from sea level up to the high mountains (Fernandes and Heywood, 1972; Ietswaart, 1980). "dittany of Crete", "dictamnos" or "dictamnum", is a plant well known since antiquity for its medicinal applications (wound treatment, "panacea"), which were related to the ancient Greek Gods and mythology (Berendes, 1902; Skrubis, 1979; Thanos, 1994; Baumann, 1996). Nowadays, dittany is still widely used, as a herbal tea plant, as a condiment and in distilleries abroad, holding great commercial value for the local Greek economy (Skoula and Kamenopoulos, 1997; Hanlidou et al., 2004). Because of its wide application as a traditional herbal medicinal product, it receives growing attention from modern pharmacology. There are various examples in recent literature where plant decoctions and the essential oils of *O. dictamnus* are tested for pharmacological effects (Pellecuer et al., 1980; Gergis et al., 1990; Economou et al., 1991; Panizzi et al., 1993; Lagouri and Boskou, 1996; Sivropoulou et al., 1996; Lions et al., 1998; Moller et al., 1999; Economakis et al., 1999; Daferera et al., 2000; Karanika et al., 2001; Economakis et al., 2002; Goun et al., 2002; Couladis et al., 2003; Daferera et al., 2003; Stamatis et al., 2003; Chinou et al., 2007; Kouri et al., 2007; Liolios et al., 2009). Additionally, since it is characterized by the U.S.A. CFR (2009) as a safe spice for consumption, it can be easily applied as a natural additive in food industry, with flavouring, antioxidant or preservative role (Liolios et al., 2009).

The present paper is a brief review of all the historical, ethnomedical, phytochemical and preclinical works published on dittany, until today. It has also been attempted to evaluate particularly interesting applications of the plant, which to our knowledge have not been reported in any scientific review before, in order to provide an original view of its ethnopharmacological importance in Greece and elsewhere.

2. Distribution and taxonomy

*O. dictamnus* L. (syn. = *O. pseudodictamnus* Sieber, *Amaracus dictamnus* (L.) Bentham) is a chasmophyte endemic of Crete. It is a short green white lanate shrub, which stems up to 35 cm. Its stems are ascending and rooting at the bases, yellow or purplish brown, lanate (hairs ca. 2 cm long, branched). Branches of the first order absent or present, in the upper half of the stems, up to 5 pair per stem, 1.5 cm long, not ramified. Leaves up to 15 pairs per stem, lower ones petiolate (petioles up to 1.5 cm long), roundish to oval or ovate, tops obtuse or acute, 15 mm long, 15 mm wide, thin, whitish (green), both sides are lanate (hairs 2 mm long, branched), sessile glands inconspicuous, up to 600 per cm²; margins revolute; veins raised at the underside. Spikes subglobose to cylindrical, 16 cm long, 7 cm wide, nodding. Bracts 8 pairs per spike, roundish to ovate, tops obtuse or acute 9 mm long, 7 mm wide, more or less purple, glabrous or sparcely ciliate. Flowers two per verticilastcer, subsessile. Calyses 1-lipped for c.3/5, 5 mm long, throats sparingly pilose or not, for the rest glabrous; upper lips (sub)entire; lower lips absent or consisting of 2 very small (0.5 mm long) lobes. Corollas two, the lower one 11 mm long, pink, more or less saccate, outside sparsely pilose; upper lip divided into 2. 0.3 mm long lobes; lower lips divided into subequal, 1.5 mm long lobes. Staminal filaments up to 12 and 14 mm long. Styles between the filaments protruding under the upper lips, up to 18 mm long. Roots up to 1 cm in diameter (Ietswaart, 1980). It grows wild inside fissures of calcareous cliffs; usually it prefers shadowy places (Ietswaart, 1980; Turland, 1995) from 300 up to 1500 m above sea level (Ietswaart, 1980). It flowers from June to October (Ietswaart, 1980).

Dittany is widely distributed along Crete with more dense populations on the Western part, while it is doubtfully reported present in Southwest Asiatic Turkey (Ietswaart, 1980; Med-Checklist, 1986; Turland, 1995). Dittany looks a lot like the plant *O. calcaratum* Juss (syn. *O. tournefortii* Aiton, *A. tournefortii* Bentham), from which it differs in its lannate and thinner leaves, its less compact inflorescences and usually subglobose spikes (Ietswaart, 1980). Earlier botanists, classified *Amaracus* (Gleditsch) Bentham as a different genus from *Origanum* and *Majorana* (Rechinger, 1943; Diapoulis, 1949; Kavadas, 1956), while contemporary studies consider that dittany belongs in the genus *Origanum*, sect. *Amaracus* (Gleditsch) Bentham of Lamiaeaceae family (Fernandes and Heywood, 1972; Ietswaart, 1980). According to recent studies by Ietswaart (1980), who monographed genus *Origanum* eight sections can be recognised, which can be arranged in three informal groups. *O. dictamnus* belongs in the third group, which contains plants with unequally lobed calyces, and also have large membranous bracts (Paton, 1994). Section *Amaracus* (Gleditsch) Bentham, is considered to include ancient forms of genus *Origanum*, most of which were created during Pliocene (Ietswaart, 1980, 1982). All the known hybrids of dittany are: *Origanum hybridinum* Miller (*O. dictamnus × O. sipyleum*), *O. amanum × O. dictamnus*, *O. calcaratum × O. dictamnus* (Ietswaart, 1980; Skoula and Harborne, 2002).

3. Morphology and anatomy

The leaf of *O. dictamnus* is nearly rounded, densely covered with branched non-glandular hairs, which lend to it a velvety appearance. They are more numerous on the lower brighter leaf side. They consist of many cells and they seem to have a protective role. The branching of non-glandular hairs, while it is frequent for *O. dictam-
nus, it rarely occurs in the other species of the genus such as *O. vulgare, O. onites* (Bosabalidis, 2002).

The leaf also bears glandular hairs, in lesser numbers than the non-glandular hairs. Glandular hairs are divided in two categories: capitate and peltate glandular hairs. Capitate hairs consist of one head, one basal cell and one to five stalk cells between them. Peltate hairs are bigger than capitates ones, short and voluminous. They are composed of a large basal cell, a flattened stalk cell and a multicellular head (the number of cells differ depending on the member of the family, and is 8 cells for *O. dictamus*). Both categories have secretory role. Their head cell stores the precious essential oil of the plant (Bosabalidis and Tsekos, 1982). The transversal section of the leaf is typical for Lamiaceae family plants, different only at the length and width of the palisade parenchyma cells and the density of chloroplasts. The density of the glandular hairs of *O. dictamus* is less than in the other plants of the Lamiaceae family. This is in agreement with the great density of non-glandular hairs and closely connected with the harsh environmental conditions in the natural growing environment of the plant (Bosabalidis and Tsekos, 1982; Bosabalidis and Papadopoulos, 1983; Bosabalidis, 2002, 1990, 1987a,b; Vrachnakis, 2003).

### 4. Mythology and history

According to ancient mythology the plant was dedicated to the ancient Cretan goddess Diktytnna and thus was named dittany. The goddess or nymph Diktynna was in later times matched with Artemis (Diana) and became Artemis-Diktynna, famous as the goddess of the forest, the hunt, the mountains, the springs and the rivers. Greek Mythology tells us that Minos, the famous Cretan king of the Minoan civilization, fell in love with her, chased her, and in order to avoid him she fell into the sea, near the cape of Psakos (known today as Spatha), but she was saved by the fish-nets of local fishermen, so they gave her the name Diktytnna from the Greek word “Diktis” (=net).

Moreover, both Artemis and dittany were believed to magically cure arrow wounds. This relationship explains why Artemis is often represented with an *O. dictamus* crown on her head (Skoula and Kamenopoulos, 1997). Excavations in Knossos palace (near Heraklion city, Crete), Zakros (east coast of Crete, south of Palaikastro), and the Royal palace of Mycenae as well as in the palace of Pylos (North East and South Peloponnesse respectively), revealed seeds of different kinds of aromatic plants, like *O. dictamus*, *Artemisia absinthium* (common wormwood), *Salvia triloba* and others. This proves the existence of ancient laboratories, which produced essences and cosmetics using aromatic plants as raw materials. Especially between 1700 and 1450 BC, the so-called “naturalistic period”, the Minoan civilization for the first time in the history of mankind used plants for decorating pottery and murals. Some of the mankind are so realistic that the species of the plant can be identified. Among the plants depicted we can recognise dittany (Diapoulis, 1980).

Besides, the plant relates to Roman goddess of hunting Artemis-Diana, so it was named “Artemidia”. For both cases the link between goddess Artemis and dittany was probably due to the fact that both the plant and the goddess assisted childbirth. Before Zeus (Jupiter) arrived in the Aegean Sea, Cretan goddess “Lithia” or “Elethia” was dedicated to childbirth, but she was later on also connected to Artemis. Euripides (ca. 480–406 BC), one of the three great tragedians in classical Athens, in his tragedy “Hippolytus” states that goddess Lithia (Artemis-Diana) wears a crown made of a plant, which according to later scholars (Schwartz, 1891) could have been dittany (Scholia in Euripidem, Argumentum Hippolyti, 73.46).

Since ancient times, dittany was considered as “panacea”, which means a drug against every illness. So it was thoroughly used for stomach disorders, gastric ulcers, for the digestive system in general, spleen problems, against rheumatism, to facilitate childbirth and against gynaecological disorders. The marvellous power of this plant has been extolled by at least twenty-four writers from antiquity up to the fourth century. Homer (9th century BC) (Ilid, 11.843–847) reported that a bitter root was used as a cure against gastric ulcers and bleeding (Homer, 1920, 1924), which in later times has been identified as dittany (Berendes, 1888, 1900). Hippocrates (5th–4th century BC) (De natura muliebri, 32.1; de mulierium affectibus i–iii, 46.6; de exsectiones foetus, 4.11) the father of medicine, used it on Cos island, against gall bladder ailments, tuberculosis and in poultices for wounds; it has also been stated that it could induce abortion (Hippocrates, Med., et Corpus HippocrATICUM, 1853). The most interesting reference to the medicinal power of *O. dictamus* came from Aristotile (4th century BC) (Historia Animalium 9.7.1), who stated that when wild goats of Mount Ida (Crete) were struck by poisoned arrows, they ate aerial parts of *O. dictamus*, which had the effect of causing the arrows to leave their bodies and of healing their wounds (Aristotle, 1994, 2000). Theophrastus (4th–3rd century BC) (Historia plantarum, 9.16.1) repeated his master’s (Aristotle) previous statement but with scepticism (Theophrastus, 2007). This story was retold even until the seventeenth century, when it inspired the making of a quite famous engraving (Fig. 2). The engraving is found in the work of the Flemish travel-writer O. Dapper “Description exacete dei iles de l’Archipelago” (Amsterdam, 1703), who repeated the previously mentioned story (Baumann, 1891). This story was retold even until the seventeenth century, when it inspired the making of a quite famous engraving (Fig. 2). The engraving is found in the work of the Flemish travel-writer O. Dapper “Description exacete dei iles de l’Archipelago” (Amsterdam, 1703), who repeated the previously mentioned story (Baumann, 1996; Thanos, 1994; Skrubis, 1979; Berendes, 1902).

Latin writers Cicero (2nd–1st century BC) in his work “De Natura Deorum” (2.126) (Cicero Tullius, 1917) and Virgil (1st century BC) in “Aeneid” (12.412) attributed many virtues to *O. dictamus* (Virgilius, 1903). Specifically in the work of the famous poet Virgil, it can be seen Aphrodite, the ancient goddess of love, showing her lavish care for the Trojan hero Aeneas using the Cretan *O. dictamus* to heal his wounds (Fig. 3) (Hunt, 2005). Dittany was also
mentioned by the Latin writers Pliny (Gaius Plinius secundus, 1st century AD) in "Naturalis Historia" (8.44) (Plinius Secundus, 1685; Plinius Secundus, 1906) and Celsus (Aulus Cornelius Celsus, 1st century BC) in "De Medicina" (5.25.13), who suggested that we need four sips of NH$_3$ or water solution of the plant in order to have the desired effects (Celsus, 1971). Later on, the Greeks Plutarch (1st–2nd century AD) (Plutarch, 1954) and Dioscorides (1st century AD) in his work "De Materia Medica" (Codex Vindobonensis) (Fig. 4) attributed to dittany similar properties with Aristotle (Wellmann, 1958; Gunther, 1959; Dioscurides, 1970, 2010). Finally, Galen, the famous Greek physician, who is considered to be the “father of Pharmacy” Galen (2nd century AD) in his works: “De compositione medicamentorum” and “De antidotis”, attributed to dittany healing, as well as anti-rheumatism and abortion properties (Galeni, 1827).

During the middle ages, dittany was recorded in the code of Charlemagne (8th–9th century AD) about 795 AD “...diptramnum, sinape, satureiam, sissimbrium, mentam, mentastrum...” (chapter LXX.) (Fig. 5). Linnaeus (18th century AD) fully identified O. dictamnus botanically much later in “Species Plantarum” (1753 AD) (Fig. 6) (Linnean Herbarium, 2003). Dittany was also widely used in monasteries since the Middle Age, in the famous liqueur’s Benedictine and Trappistines monks, respectively. Even in our days, dittany is used in distilleries. Vermouth (Cinzano) for example is flavoured with this very aromatic plant (Baumann, 1996; Plimakis, 1997).

Ditanny has been referred very often in Greek literature and poetry as a plant symbol of Crete and Greece (Nobel prize owner Elytis, 1972).

5. Ancient and common names and their origin

Various names have been attributed to dittany in the ancient world (Table 1), among them the name dictamnos, which survives...
till our days, probably derived from “Dicti” + “thamnos” (Skrubis, 1979). “Dicti” comes from the name of Cretan mountain “Knossia Dicti”, where Zeus (Jupiter) was raised up by the goat Amalthia, and it was dedicated to him and “thamnos” means shrub in Greek. Today, this mountain is called Yucta and O. dictamnus is known to grow wild in great quantities. Another view on dittany’s name originated from the ancient Cretan goddess or nymph “Dictyna” as it has been mentioned referred in Mythology and history (Part 4) (Skoula and Kamenopoulos, 1997). Ancient names like “veloulko”, “velotoko” probably derive from the magical ability of the plant to heal arrow wounds (Gennadios, 1914) (“velos” = arrow in Greek); which O. dictamnus was strongly believed to possess.

Nowadays, the plant is widely known across the world by various vernacular names (Table 1). Among those, the name “erontas”, attributed to dittany by the local people of Crete, presents great interest because it probably derives from “Erotas”, the ancient Greek god of love. Like the edelweiss (Leontopodium alpinum L.) O. dictamnus was offered to girls as an expression of love. Dittany grows wild, high in the mountains, in places difficult to be reached, thus it was believed that someone had to be fully in love in order to climb and gather the plant to be offered (Fragaki, 1969; Plimakis, 1997).

Additionally, the name of the genus “Origanum”, according to some researchers has its roots in the Greek words “oros” (mountain) + “ganos” (from “ganimai-ganousthai”, which means becoming bright or being happy). This name probably originates from and is closely associated with the high mountains the natural growing environment of Origanum plants in the Mediterranean (Panou-Fillotheou et al., 1997).

The name of dittany “stamatochorto”, which in Greek means “stopping herb” originates from the Greek words “stamato” (=to stop) and “horto” (=herb), and probably derives from the property of dittany to stop bleeding. Furthermore the name “stoma-chorto”, literally meaning “herb for the stomach”, originates from the words “stomach” and “horto” and refers to its healing property to cure stomach ache. Additionally, the word “stomatohorto” originates from the words “stoma” (=mouth) and “horto” and refers to the plant’s property to refresh the mouth (Plimakis, 1997; Skoula and Kamenopoulos, 1997). Other names like “malariochorto”, which means in Greek hairy herb, and “gerondas” (=old man) refer instead to the plant morphology as its aerial parts are covered by dense white hairs (Skoula and Kamenopoulos, 1997).

6. Ethnobotany, collection and cultivation

The herb of dittany consists of the dried or fresh aerial parts of O. dictamnus, which are collected during the early summer period. More specifically, wild dittany is collected while in full bloom. During its entire blooming period 2–4 different harvestings can take place. The first in the end of May, the second two months later after the name-celebration of Prophet Elias at the 20th of July, when the plant is “full of essential oil”, and the third in the end of August. According to other folkloric sources the best time for harvesting is supposed to be after the 17th of July (name-celebration of Saint Marina) (Fragaki, 1969).

Dittany is a species with significant commercial interest since it is widely used for herbal teas, not only in the local markets of

Table 1
Botanical synonyms, vernacular and ancient names of dittany.

<table>
<thead>
<tr>
<th>Scientific names</th>
<th>Synonyms</th>
<th>Ancient names</th>
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<tbody>
<tr>
<td>Origanum dictamnus Linnaeus</td>
<td>Majorana dictamnus (Linnaeus) Kosteletzký</td>
<td>Greeks: artemidia, baetion, dordakion (dorcidiunum), ekvoion (elbium), okytokos velotoko, veluolako, veluxo, (Wellmann, 1958, Gunther, 1959)</td>
</tr>
<tr>
<td>Family: Lamiaceae [Labiatae]</td>
<td>Amaracus dictamnus (Linnaeus) Bentham, Dictamus creticus J. Hill, Origanum saxatile Salisbury</td>
<td>Romans: ustilago rustica (Gunther, 1959)</td>
</tr>
<tr>
<td></td>
<td>Origanum tomentosum Moench, Origanum pseudodictamnus Sieber, Majorana tomentosa Stokes, Origanum pseudodictamnus Sieber, Origanum dictamnifolium Saint-Lager</td>
<td></td>
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the island of Crete but all around Greece in traditional or modern shops and open-air market stalls (Skoula and Kamenopoulos, 1997; Hanlidou et al., 2004). In the past, the demand for plant material was covered only by the collection of wild populations, a fact which lead to their rapid decrease and extinction from several areas of the island (Skoula and Kamenopoulos, 1997).

The collectors of wild dittany were organised groups of local people called “Erontades”, “Atitanologi”, “Botanologi”, or “Mazoc-tades”, which travelled across the island in order to collect enough plant material. The often climbing accidents, which occurred during the collection and the increasing demand for plant material, drove the locals towards the cultivation of the plant since 1920. Nowadays, the cultivated plants are the main source of plant material used. Wild populations are under legal protection as a vulnerable species under the Revised Appendix 1 of the Bern Convention (2002). The populations within Samaria Gorge National Park are protected by law against collecting (Turland, 1995) as well. The systematic cultivation of O. dictamnus in several villages of Crete like Kato Poros and Argiroupoli started around 1920. In the beginning the local farmers, cultivated the plant in pots and in rocky places, but since 1928, when the cultivation spread all over Crete they also tried cultivation in small fields close to the areas of the wild plant populations. After 1935, there was a rapid increase in its cultivation reaching a peak of 10 tonnes/year of total production. During the war cultivation was inhibited. Right after the end of the German occupation cultivation started again in the villages of Heracleion estate by about 370 farmers in an area 500 acres and production reached 50 tonnes/year. The first farmers’ partnership for the production and trade of dittany was created around 1956 for the production and trade of dittany was created around 1956 and during 1964 there is a noted export of 24 tonnes of dried dittany from Heracleion port (Plimakis, 1997). The production of dittany reached its peak from 1980 to 1990 and is now in decline. In 1991–2000 a portion of 85% of the product was exported (mainly to Italy, France, Germany and Japan), while 15% of the total production was absorbed by the Greek market. Abroad, main users of the product are distillery industries. At present, the intensive cultivation of O. dictamnus has ceased and production has dropped to minimum levels with the price fluctuating between 5.0 and 5.90 €/kg. Only a few farmers still harvest O. dictamnus today and they do so mainly from wild populations as this offers them an additional income, albeit low. Of the several reasons for the drop in dittany cultivation, the most important is the lack of a properly organized marketing system for such a crop (Skoula and Kamenopoulos, 1997). The production of dittany, were sparse and mostly based on the local the farmers’ experience. It is proposed that dittany can be cultivated in the same field for up to 4 years, but according to the farmers’ long standing experience, it would be much preferable, to replant every October. February and March are supposed to be the best period for planting of the new dittany plants, while irrigation depends on the dryness of the soil. Farmers distinguish different types of plant cultivars such as (i) the “black” (green, less hairy, narrow leaved) and (ii) “white” (hairy, large leaved). These types of cultivars occur in several locations and they have not yet been related to environmental conditions. Especially the “black” (narrow leaved) type is more aromatic, yields more biomass per plant and requires more harvesting since it is woodier, although it is more susceptible to pests during storage (Skoula and Kamenopoulos, 1997).

Several efforts for hydroponic cultivation of dittany have been made (mainly Nutrient Film Technique), with successful results (Economakis, 1992, 1993). Nowadays, there is a systematic cultivation in several villages especially in Heracleion estate.

After harvesting, dittany is usually dried under mild conditions, in order not to harm the volatile constituents of its essential oil. Usually the plant is left to dry in shadowy, well aired, dry places, in hanging little bunches or spread on grids. According to the local farmers drying should not be done in plastic bags or containers because the product is blackened. During drying the containing water decreases under the 10% of the total, while plant weight decreases to the 2/3 of its initial weight (Plimakis, 1997).

7. Phytochemistry

7.1. Chemical analysis of plant extracts

The lipid composition, of the dried and the fresh leaves of O. dictamnus L. has been identified by Komaitis et al. (1988) and Revintsi-Moraiti et al. (1985), as well as a variety of non-polar components such as fatty acids, lipids, sterols and essential oil.

A vast number of polyphenolic components, flavonoids and coumarins have also been isolated and identified from the methanol extract of aerial parts of the plant (Harvala and Skaltsa, 1986; Skaltsa and Harvala, 1987). Generally the extracts of O. dictamnus with polar solvents contain higher amounts of phenolic compounds than the ones with non-polar solvents. The total phenol content of the O. dictamnus water, methanol, ethanol and acetone extract has been identified as 21.7, 13.8, 7.7, 6.7 (meq/100g) by Moller et al. (1998).

From the aqueous extract of O. dictamnus the following phenolic compounds have been identified: 7-O-coumaric acid (13.9%), ferulic acid (0.34%), hydrated catechin (0.5%) or catechin (0.22%) (Proestos et al., 2006, 2008).

Recently, from the polar extracts of the aerial parts of cultivated O. dictamnus one new depside has been isolated, to which was given the trivial name salvinolic acid P, in addition to the known depsides rosmarinic acid and rosmarinic acid methylster, two monoterpenes: thymoquinone and thymoquinol 2-O-$\beta$-glucopyranoside; two simple phenolic acids: oregiisin A and E-caffeic acid; six flavonoids: apigenin, kaempferol, quercetin, eriodictyol, taxifolin, narigin; and two alicyclic derivatives: 12-hydroxy jasmonic acid and its 12-O-$\beta$-d-glucoside (Chatzopoulou et al., 2010).

Exploring the chemotaxonomic differences of genus Amaracus Piozzi et al. (1986) isolated the following triterpenes from the aerial parts of Amaracus dictamus Bentham (syn. Originatum dictamus L.): oleanolic and the rare 21e-OH oleanolic acid, ursolic acid and a new 21a-OH ursolic acid and also ouvaol. During this study no diterpenic components were found in the acetone extract, a fact which was in contrast with previous findings of the same group for Amaracus akhdeirensis and A. pampinanii (Lamiaceae). The results of the above studies are summarized in Table 2.

7.2. Chemical analysis of essential oil

The plants belonging to the Lamiaceae family are well known for the production of essential oils (EOs). Essential oils are normally formed in special cells or groups of cells like the glandular hairs already described for O. dictamnus by Bosabaliadis and Tsekos (1982). They are aromatic, oily mixtures of volatile components with characteristic odour and taste. They usually consist of a great number of different components, up to 150, with various chemical formulas. Steam distillation is a cheap and commonly used method for producing EOs on commercial basis, while extraction by means of liquid carbon dioxide under low temperature and high pressure is rarely used because it is more expensive (eventhough it produces a more natural organoleptic profile) (Burt, 2004). The majority of the data considering the chemical composition of O. dictamnus EOs refer to the first method of extraction and usually for the produc-
The composition of the EOs they use the aerial parts of the plant (Table 3) are used.

The so-called character of the essential oil is defined from its major components. For O. dictamnus the major components of its essential oil are the monoterpenes: carvacrol, γ-terpinene and sometimes thymoquinone following the extraction technique. Skoula et al., 1999, 2003, Daferera et al., 2000, Figueredo et al., 2006, Economakis et al., 2003, Daferera et al., 2003, Daferera et al., 2000, Piozzi et al., 1994, Schaden and Hesse, 1976, Berendes, 1902, Fournier, 1947, Carcaris et al., 1953, Economakis et al., 2005, Revinthi-Moraiti et al., 1985, Komaitis et al. (1988). In most cases, carvacrol proved as the major component of the studied oils (Fig. 7), with p-cymene, γ-terpinene and sometimes thymoquinone following in amounts (Table 3). In only one case of cultivated O. dictamnus, thymol (isomer of carvacrol), has been revealed, as the dominant volatile constituent of its essential oil, while carvacrol was totally absent (Daferera et al., 2000). The monoterpenes p-cymene and γ-terpinene are the precursors of carvacrol and its isomer thymol in Origanum and Thymus species (Skoula et al., 1999). Although the composition of EOs can differ between different harvesting seasons and between geographical sources, the sum of the amounts of these four compounds defines the character of the essential oil since in almost all the specimens it ranges between 62 and 100% (Table 3). This is an observation proven true for most Greek oregano plants derived from different geographical regions (Kokkinis et al., 1997). Hydroponic cultivations in Crete under different conditions also revealed carvacrol as main compound (33.5–89.0%) (Economakis et al., 1999, 2002, 2003).

### 8. Biological activities

#### 8.1. Biological activities of O. dictamnus extracts

#### 8.1.1. Antimicrobial activity

The water extracts of O. dictamnus and other plants from Lamiaceae family have been tested vs. the yeast *Yarrowia lipolytica*. Dittany and rosemary extracts (concentration of 5 g extract/L) presented the greater lag time and the greater inhibition activity against *Yarrowia lipolytica* compared to all the other extracts (Karanika et al., 2001). The traditionally known use of the plant against gastric ulcers (Fourrier, 1947, Berendes, 1902) was proved by *in vitro* tests. The aqueous 70%/methanol extract was tested against one reference strain of *Helicobacter pylori* and 15 clinical isolates of *H. pylori* (from antral biopsies). O. *dictamnus* and its close relatives, *O. vulgare* and *O. majorana* proved very active against the used *Helicobacter* strains. The minimal inhibition concentration (MIC) was also identified for the extract (around 2.50 mg/ml for all but one strain) (Stamatis et al., 2003).

Moreover the methanol extract has been proved active against the Gram-negative clinical strains *Acinetobacter haemolyticus, Empedobacter brevis, Pseudomonas aeruginosa* and *Klebsiella Pneumonia* (Chatzopoulos et al., 2010).

#### 8.1.2. Antioxidative activity

Studies conducted by the Umezawa method for various plants of Lamiaceae family and among them *O. dictamnus*, have shown that

<table>
<thead>
<tr>
<th>Lipids</th>
<th>Plant part</th>
<th>Extract</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipid composition (w/w% of plant material)</td>
<td>Dried leaves</td>
<td>CHCl&lt;sub&gt;3&lt;/sub&gt;/MeOH (2:1), CHCl&lt;sub&gt;3&lt;/sub&gt;</td>
<td>Proestos et al. (2006, 2008)</td>
</tr>
<tr>
<td>Total lipids: 9.72%, non-polar lipids 7.68% (81% of total lipids), polar lipids 1.85% (19% of total lipids)</td>
<td>Fresh leaves</td>
<td>CHCl&lt;sub&gt;3&lt;/sub&gt;/MeOH (2:1), CHCl&lt;sub&gt;3&lt;/sub&gt;</td>
<td>Komaitis et al. (1988)</td>
</tr>
<tr>
<td>Total lipids: 20%, non-polar lipids: 13.6% (68% of total lipids), polar lipids 6.38% (32% of total lipids)</td>
<td>Fresh, dried leaves</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipid components identified</td>
<td>Aerial parts</td>
<td>Acetone</td>
<td>Piozzi et al. (1986)</td>
</tr>
<tr>
<td>Sterols, steryl esters, fatty acids, free fatty acids (palmitic, oleic, linoleic), waxes, traces of triglyceride, sulpholipids, cerebrosides, mono-, di- and poly-digalactosyl diglycerides, phosphatidylyl-ethanolamine, -serine, -glycerol, -inositol, -choline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phosphatidic acid</td>
<td>Aerial parts</td>
<td>CHCl&lt;sub&gt;3&lt;/sub&gt;/MeOH (2:1), CHCl&lt;sub&gt;3&lt;/sub&gt;</td>
<td>Komaitis et al. (1988)</td>
</tr>
<tr>
<td>Oleanolic, ursolic acid, uvaol, 21 α-OH oleanolic acid, 21 α-OH ursolic acid</td>
<td>Aerial parts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triterpenes</td>
<td>Aerial parts</td>
<td>MeOH (ethyl acetate fraction)</td>
<td>Skaltsa and Harvala (1986, 1987)</td>
</tr>
<tr>
<td>Polyphenols</td>
<td>Aerial parts</td>
<td>MeOH (butanol fraction)</td>
<td>Komaitis et al. (1988)</td>
</tr>
<tr>
<td>π-Coumaric acid (13.9%), ferulic acid (0.34%), hydrated catechin (0.5%), catechin (0.22%), eriodictyol, apigenin, luteolin, quercetin, iso-orientin, vitexin, iso-vitexin, vicenin-2, aesculin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thymoquinone, thymoquinol</td>
<td>Aerial parts</td>
<td>MeOH</td>
<td>Chatzopoulos et al. (2010)</td>
</tr>
<tr>
<td>2-O-β-D-glucopyranoside, E-caffeic acid, salvianolic acid F, apigenin, kaempferol, quercetin, eriodictyol, taxifolin, narigenin, 12-hydroxyjasmonic acid (alicyclic derivative)</td>
<td>Aerial parts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rosmarinic acid, rosmarinic acid methyl ester, oregubisin A, 12-O-β-D-hydroxyjasmonyl-glucopyranoside (alicyclic derivative)</td>
<td>Aerial parts</td>
<td>MeOH/H&lt;sub&gt;2&lt;/sub&gt;O (5:1)</td>
<td></td>
</tr>
</tbody>
</table>

### Table 2

Overview of chemical constituents isolated from different part of dittany.

Studies conducted by the Umezawa method for various plants of Lamiaceae family and among them *O. dictamnus*, have shown that...
Table 3
Major constituents of studied essential oils from dittany.

<table>
<thead>
<tr>
<th>Components</th>
<th>Plant part studied</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-Thujene</td>
<td></td>
<td></td>
</tr>
<tr>
<td>α-Pinene</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Camphene</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cymene</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sabinene</td>
<td></td>
<td></td>
</tr>
<tr>
<td>γ-Terpinene</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thymoquinone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thymohydroquinone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linalool</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thymol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carvacrol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>α-Copaene</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Germacrene</td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-Caryophyllene</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sum*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| 4.45 | 7.50 | 71.86 | 83.8 | AP(C) | Harvala et al. (1987) |
| 13.49 | 11.41 | 62.44 | 87.3 | AP(C) | Sivropoulou et al. (1996) |
| 0.24 | 0.34 | 1.17 | 22.90 | 6.25 | 5.45 | 3.16 | 32.6 | LW | Daferera et al. (2000, 2002, 2003) |
| 3.40 | 2.96 | 3.50 | 48.15 | 7.41 | 2.93 | 13.00 | 2.85 | 1.99 | 0.58 | 53.9 | LW | Figueredo et al. (2006) |
| 3.77 | 2.61 | 2.42 | 40.47 | 8.68 | 5.16 | 16.94 | 5.57 | 1.10 | 0.31 | 51.2 | FW | Chorianopoulos et al. (2004) |
| 10.1 | 7.9 | 78.0 |       |       |       |       |       |       |       |       |       |
| 15.1 | 5.4 | 72.1 | 92.6 | AP(W) | Economakis et al. (1999, 2002, 2005) |
| 20.3 | 3.9 | 64.1 | 88.3 | AP(W) II | Economakis et al. (1999, 2002, 2005) |
| 2.9 | 3.5 | 5.2 | 70.0 | 72.9 | AP(W) | Economakis et al. (1999, 2002, 2005) |
| 1.22 |       |       |       |       | 91.3 | 72.70 | 81.8 | B(HC) I | Economakis et al. (1999, 2002, 2005) |
| 2.02 |       |       |       |       | 0.10 | 87.10 | 87.2 | R(HC) I | Economakis et al. (1999, 2002, 2005) |
| 2.00 |       |       |       |       | 0.16 | 89.0 | 89.2 | R(HC) I | Economakis et al. (1999, 2002, 2005) |
| 26.44 |       |       |       |       | 0.32 | 63.87 | 90.6 | R(HC) I | Economakis et al. (1999, 2002, 2005) |
| 18.68 | 0.28 |       |       |       | 0.29 | 73.41 | 92.4 | R(HC) I | Economakis et al. (1999, 2002, 2005) |
| 11.13 |       |       |       |       | 10.83 | 60.04 | 82.0 | R(HC) I | Economakis et al. (1999, 2002, 2005) |
| 17.5 | 10.1 |       |       |       | 10.1 | 54.5 | 72.0 | R(HCP) | Economakis et al. (1999, 2002, 2005) |
| 20.2 | 4.7 | 3.9 | 85.8 | 85.8 | R(HCS) | Economakis et al. (1999, 2002, 2005) |
| 5.5 | 2.2 | 1.9 | 79.9 | 85.4 | R(HCS) | Economakis et al. (1999, 2002, 2005) |
| 3.11 |       |       |       |       | 0.10 | 67.87 | 87.3 | B(HC) | Economakis et al. (1999, 2002, 2005) |
| 3.81 |       |       |       |       | 2.46 | 60.94 | 68.0 | B(H) | Economakis et al. (1999, 2002, 2005) |
| 6.63 | 7.68 | 1.43 | 53.60 | 55.0 | I(HC) | Economakis et al. (1999, 2002, 2005) |
| 5.64 | 6.98 | 1.88 | 45.60 | 47.5 | I(HC) | Economakis et al. (1999, 2002, 2005) |
| 41.46 | 10.80 | 0.28 | 63.87 | 105.6 | I(HC) | Economakis et al. (1999, 2002, 2005) |
| 42.41 | 13.59 | 0.24 | 73.41 | 116.1 | I(HC) | Economakis et al. (1999, 2002, 2005) |
| 42.18 | 12.59 | 0.36 | 60.04 | 102.6 | I(HC) | Economakis et al. (1999, 2002, 2005) |
| 45.5 | 10.9 | 3.42 |       | 79.7 | I(HCP) | Economakis et al. (1999, 2002, 2005) |
| 45.3 | 11.6 |       |       | 58.7 | I(HCP) | Economakis et al. (1999, 2002, 2005) |
| 15.1 |       |       |       | 78.8 | I(HCP) | Economakis et al. (1999, 2002, 2005) |
| 27.8 | 2.1 | 61.3 | 89.1 | I(HCS) | Economakis et al. (1999, 2002, 2005) |
| 14.1 | 1.5 | 69.7 | 83.8 | I(HCS) | Economakis et al. (1999, 2002, 2005) |
| 4.17 | 5.67 | 6.55 | 46.30 | 52.9 | L(W) | Liolios et al. (2009) |
| 8.78 | 14.1 |       |       | 51.7 |       |       |       |       |       |       |       |       |       |
| 10.1 | 9.20 | 42.9 | 3.88 | 62.2 | AP(C) |       |       |       |       |       |       |       |       |
its methanol extract has antioxidant action similar with \(\alpha\)-tocopherol (Couladis et al., 2003).

Extracts of dittany of different polarities have been tested: (i) with electron spin resonance (ESR) spectrometry (16.5 µl extract/ml corresponding to 0.413 mg of dried spice/ml), for their efficiencies as scavengers of free radicals and (ii) by measurement of oxygen depletion (12.5 mg dried spice/ml) in a methyl linoleate emulsion, for their efficiencies as chain breaking antioxidants. The water extracts showed high efficiency for both tests. The methanol extract was of medium efficiency, whereas the acetone extract showed less activity in both assays. The methanol and water extract are rich in phenolic derivatives, contrary to the acetone extracts and that is why they have greater efficiency as antioxidants (Moller et al., 1999). These results are of great importance for the food industry, because they open a new possibility, where natural products like dittany, would potentially replace synthetic antioxidants (Economou et al., 1991). On the other hand Lionis et al. (1998) did not report any significant antioxidant effect for the water extract of dittany by the lipid peroxidation assay when tested in cultured lung cells exposed to iron and ozon. Although more scientific data are needed concerning the antioxidant ability of the polar dittany extracts, the water extracts in general, seems to have the highest antioxidative ability. Thus the herbal tea of dittany, which is a water extract, would be very beneficial for consumers.

The non-polar extracts of dittany have also been tested with positive results. The cyclohexane extract has reported antioxidant efficiency as well as the ability to suppress the mutagenicity of Trp-P-Z, a common dietary carcinogen. Also, in the unsaponified fraction of dittany all the four known tocopherols (\(\alpha\), \(\beta\), \(\gamma\) and \(\delta\)-tocopherols) have been determined, and especially the concentration especially of \(\gamma\)-tocopherol was significantly higher. Total tocopherol content ranged from 288 to 672 ppm (Lagouri and Boskou, 1996).

A recent study (Kouri et al., 2007) comparing the antioxidant scavenging activity against DPPH, between the non-polar and the polar extracts of \(O.\) dictamus (0.1 ml of extract), showed that the most polar ethanol extract (EtOHs) presented the highest activity, followed by the DE (diethyl ether) and the EAc (ethyl acetate) extract, while the PE (petroleum ether) extract exerted a weak activity. In the same study when the authors tested the protective effect of each extract against the accelerated oxidation of oil they found the opposite results, with EtOHs extract presenting no protective effect, while PE, DE and EAc extracts protected the cot-nosed oil significantly. The polar extract although rich in active antioxidative compounds, like phenolic acids and flavonoid glycosides, could not incorporate them in the oil due to their hydrophobic characteristics.

8.1.3. Cytotoxic activity

Based on preliminary bio-assays for the isolation of potentially cytotoxic compounds various extracts of \(O.\) dictamus were submitted to pharmacological investigations. The dichloromethane residue showed an important \textit{in vitro} cytotoxic activity, while ethanol and water extracts proved almost inactive. The bioassay-directed fractionation of the dichloromethane extract led to the isolation and characterization of ursolic acid. The initial dichloromethane extract was tested according to NCI procedures and proved to be active \textit{in vitro} ID\(_{50}\) = 8 and 14 µg/ml against P388 (murine leukemia) and human bronchial epidermoid cancer NSCLC-N6 (non-small cell lung cancer) cell lines respectively. Ursolic acid exhibited a high activity in vitro against the same cell lines (ID\(_{50}\) = 3.5 and 9 µg/ml). Afterwards
in vivo experiments on murine ascite leukemia P388 exhibited a marginal anti-leukemia activity (T/C=125% at 50 mg/kg). All in vivo tests were conducted on nude mice (Chinou et al., 2007). Ursolic acid isolated from Origanum vulgare ssp. hirtum (common oregano) is also known for its anti-thrombus activity (Goun et al., 2002; Sivropoulou et al., 1996).

8.2. Biological activities of O. dictamnus essential oil

8.2.1. Antimicrobial activity

The essential oils extracted from the plants of the Lamiaceae family contain phenolic compounds, which are well known for their antimicrobial activities (Sivropoulou et al., 1996; Panizzi et al., 1993; Gergis et al., 1990; Pellecuer et al., 1980). Plants belonging to the genus Origanum are generally well known for the production of essential oils rich in phenolic compounds, like thymol and its isomer carvacrol. The essential oil of O. dictamnus is located in the aerial parts of the plant i.e. bracts, leaves and flowers. There are controversial studies whether the essential oil from the bracts has stronger antimicrobial effect than the one from the leaves. According to current data, the antimicrobial action seems to depend upon the concentration of carvacrol, the percentage of which is also dependant on the method of cultivation. Two different antimicrobial studies have been conducted against Staphylococcus aureus, S. epidermidis, S. hominis: the first one has shown stronger antimicrobial effect for the essential oil of the leaves while the second has shown stronger antimicrobial activity for the essential oil of the bracts (Economakis et al., 1999, 2002).

A recent study (Liolios et al., 2009) determined the antimicrobial activities of the oils from wild and cultivated plants as well as of the pure substances carvacrol, thymol and their mixtures carvacrol/thymol (6:1) carvacrol/c-terpinene, before and after liposomal encapsulation by the diffusion technique (disc method). The tests were conducted against four Gram positive bacteria: Staphylococcus aureus, S. epidermidis, S. mutans and S. viridans, four Gram negative bacteria: Pseudomonas aeruginosa, Escherichia coli, E. cloacae and Klebsiella pneumoniae, three human pathogenic fungi: Candida albicans, C. tropicalis and C. glabrata, as well as against the food-pathogen Listeria monocytogenes. The essential oils from both assayed species (wild and cultivated specimen) showed comparable activities against all tested microbial strains. Pure compounds (carvacrol, thymol), proved more active than the oil, and their antimicrobial activities were significantly increased after their encapsulation in liposomes. Thymol exhibited stronger activity than carvacrol, against most microbial types while no inhibition was found in controls, consisting of empty liposomes. Despite the fact that only a small quantity of carvacrol was encapsulated in liposomes it showed equal or improved activity than the pure compound at higher concentrations.

A dose-dependent inhibition against the mycelial growth of Penicillium digitatum and conidial germination was observed by O. dictamnus essential oil. Mycelial growth was totally inhibited at 300 μg/ml, while complete inhibition of germination was observed at the concentration of 250 μg/ml (Daferera et al., 2000). A dose-dependent inhibition of mycelial growth was also observed for Botrytis cinerea and Fusarium sp. The concentrations needed for the total inhibition of the mycelia growth were 200 and 250 μg/mL respectively. Additionally, the colony forming ability of the bacterial pathogen of tomatoes, Clavibacter michiganensis subsp. michiganensis, was inhibited by 100 μg/mL of O. dictamnus essential oil. (Daferera et al., 2003).

The essential oil of O. dictamnus, shows antimicrobial action against the phytopathogenic bacteria for potato tubers Erwinia carotovora. This activity is also due to carvacrol (Vokou et al., 1993).

Antimicrobial activity of major essential oil compounds: carvacrol and thymol. Carvacrol and thymol (the isomeric phenol of carvacrol), seem to possess strong antimicrobial activity, whereas their biosynthetic precursors: γ-terpinene and p-cymene are inactive. The bacteria which showed positive results were: Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, Bacillus subtilis, Rhizobium leguminosarum and Salmonella typhimurium. Both carvacrol and thymol were inactive against P. aeruginosa. (Sivropoulou et al., 1996; Panizzi et al., 1993). Carvacrol in particular seems to possess strong antibacterial activity against Bacillus cereus, a spore forming food born pathogen bacteria (Ulte et al., 1998) and it has also shown antifungal activity against Rhizopus (9 species), Mucor (4 species), and Aspergillus (7 species) (Thompson, 1989). A dose-dependent inhibition of the mycelial growth of Penicillium digitatum was observed for carvacrol and thymol. The following values were reported for carvacrol and thymol for the concentration causing 50% inhibition of radial growth (ED50): carvacrol ED50 = 47 μg/mL, thymol ED50 = 79 μg/mL. For minimal inhibitory concentration (MIC) the values reported were, carvacrol MIC = 160 μg/mL and thymol MIC = 200 μg/mL (Daferera et al., 2000). A similar previous study reported for carvacrol MIC = 125 μg/mL (Caccioni and Guzzardi, 1994).

Inhibition of DNA synthesis by Carvacrol. Carvacrol has also been assessed using a cell proliferation assay using mouse myoblast cell line, CO25, bearing a mutated human N-ras oncogene. In vitro cytotoxicity of carvacrol reported was IC50 = 60 μg, while for the inhibition of DNS synthesis the dose was 10 μg/mL (Zeytinoglu et al., 2003).

8.2.2. Insecticidal effect

The essential oil of O. dictamnus, shows insecticidal effect against Drosophila auraria. The essential oil was lethal for the 37–40% of the adult flies’ population after 24 h of exposure thought their food. After 48 h of exposure to the essential oil the eggs failed to hatch in a percentage less than 10–40% of the whole. Several kinds of malformation were observed to the dead and surviving larvae and pupae, which indicates the strong toxic effect of the essential oil during the insect’s development (Konstantopoulou et al., 1992).

8.3. Therapeutic uses

8.3.1. Known traditional uses (not supported by in vivo experimental data)

Nowadays, as in the past, dittany is widely used in Crete as a traditional medicine. The aeroial parts of the plants are being used in various preparations against almost every illness and for the maintenance of good health. The following data refer to the most common uses of these preparations according to the local villagers and ethnographic literature (Plimakis, 1997; Skoula and Kamnopoulo, 1997; Havakis, 1978; Fragaki, 1969; Steinmetz, 1954).

Infusion: 20–30 g of plant material in 0.5–1 L hot water. Uses: tonic, anti-convulsion, against tonsillitis, cold, cough and sore throats, diuretic, digestive, spasmylytic, against stomach and kidney discomforts. It has also been recommended traditionally, against liver diseases, diabetes and obesity.

Infusion/chewed crude plant parts: against gingivitis and toothache and as emmenagogue and assisting childbirth (induction delivery). Moreover it is considered as an abortifacient while it is also lessens the abdominal pains (Skoula and Kamnopoulo, 1997).

Decoction: 1.5–5 g of dried/fresh dittany in 250 ml (about one glass) of boiling water. The plant should not be left for long into the boiling water because its valuable components are destroyed. The decoction called ‘brastari’ in Crete should be used within 24 h, glass) of boiling water. The plant should not be left for long into the boiling water because its valuable components are destroyed. The decoction called ‘brastari’ in Crete should be used within 24 h, otherwise it is proved as useless. Dosage 2 cups per day. Uses: headaches, neuralgia, gingivitis and toothaches, tonsillitis and sore
throat, common cold and against cough. The decocation also has been used for digestion against stomach-aches, as diuretic against nephralgia and against arthritis. Finally it is considered to induce menstruation.

Tincture: made with 15–30 g of dried or fresh herb in 1 L wine or “raki” (traditional Cretan drink) or 25% ethanol dilution. Uses: similar to the decocation.

Cutaneous use (used externally): compresses, powder, plant parts crushed with water. Uses: anti-septic, anti-inflammatory, anti-bleeding, cicatrizing, against bruises, carbuncles and ulcerations, against bad breath and sore throat, for wound healing and against headaches. Compresses on the underbelly are said to induce childbirth. It is also recorded as anti-epileptic.

Additionally a recent ethnopharmacological study, considering the herbs traded in the local markets of Thessaloniki, the following therapeutic uses for the aerial parts of the herb were reported, applied either by infusion or as an external application (cutaneous use as a compress or by washing): endocrinial disorders – diabetes, gastrointestinal disorders – liver disorders, spasmodytic, stomach ulcer, metabolic disorders – cholesterol, neuropyschiatric disorders – brain stimulant, headache, skin disorders – antiseptic, sanative, urogenital system – diuretic, dysmenorrhoea, other – antibiotic activities, aphrodisiac, stimulant (Hanlidou et al., 2004).

8.3.2. Safety and Pharmacology

According to the U.S.A. CFR (2009) O. dictamnus is characterised as safe for consumption spice. This means that it can be used as a natural flavouring substance or adjuvant may as long as: (a) it is used in the minimum quantity required to produce its intended physical or technical effect and in accordance with all the principles of good manufacturing practice and (b) it is used in the appropriate forms (plant parts, fluid and solid extracts, concentrates, absolutes, oils, gums, balsams, resins, oleoresins, waxes, and distillates) alone or in combination with other flavouring substances and adjuvants also generally recognized as safe for food use.

Especially the essential oil of O. dictamnus can be added as flavouring in alcoholic beverages, usually around 21.00 ppm and max 55.00 ppm (De Vincenzi et al., 2004; Fenaroli and Burdock, 2004). Additionally, when it was given to rats, through in vivo experiments, it was found to induce glutathione of S-transferase (GST) in some tissues. This particular enzyme is considered to have protective role against chemical mutagens (Lam and Zheng, 1991). Absorption kinetics and metabolism of the major component of the oil, carvacrol after per os administration in rats, rabbits and dogs has been previously reported (Austgulen et al., 1987; Williams, 1959; Schroder and Vollmer, 1932), while the same parameters have been studied for thymol (Austgulen et al., 1987; Takada et al., 1979; Williams, 1959; Robbins, 1934) showing considerable similarities between them.

8.3.3. Mutagenicity

There are no data considering the mutagenicity effect of the plant extracts or its essential oil. The data considering carvacrol in the Ames test is somewhat ambiguous. Carvacrol was marginally more toxic to the repair-deficient E. coli strain than to its repair proficient counterpart. It also increased the relevant numbers in the Ames test strain TA100, regardless of methanolic activation, but not to a level considered significant.

The positive results in SOS chromotest at high doses probably reflect some secondary effect caused by the toxicity of this compound. In conclusion, the genotoxic potential of carvacrol is very weak, although the possibility of its action at DNA level cannot be excluded, because of the nuclear fragmentation that was observed (Stammati et al., 1999).

9. Conclusions

This review on the endemic plant of Crete O. dictamnus known as dittany, attempts to shed light on the therapeutic potential of the herbal tea as traditional herbal medicinal product, as well as its commercial applications in distilleries and production of aromatic wine – liqueurs (Benedictine), since antiquity (Skoula and Kamenopoulos, 1997; Raumann, 1996). The historical records for dittany’s various medicinal properties date back to ancient Greece, while nowadays it is still in use mainly as herbal tea, a well-known traditional medicine against various illnesses i.e. sore throat and cough, stomach ulcer, cholesterol, as well as for its believed activities as: spasmodytic, brain stimulant, antiseptic, diuretic, antibacterial activities and aphrodisiac (Hanlidou et al., 2004; Plimakis, 1997). Some of those therapeutic uses can be linked to specific ingredients, since their medicinal properties have been individually proven through international literature (Fourrier, 1947; Berendes, 1902; Skoula and Kamenopoulos, 1997).

Especially the traditional use of dittany’s herbal tea against gastro- ulcers (Fourrier, 1947; Berendes, 1902), was studied through in vitro assays on its aqueous 70% extract, chemically comparable to the herbal tea, which was found active against Helicobacter pylori (Stamatis et al., 2003). The above results could possibly be linked to the high phenolic content of the water extracts of the leaves of the plant, and/or especially to its content in depsides, which have been recently isolated and determined (Chatzopoulos et al., 2010).

The published strong antimicrobial activities of the essential oil of dittany (Liolios et al., 2009; Daferera et al., 2003, 2000; Economakis et al., 2002, 1999) could be linked to its high content in carvacrol, and its isomer thymol, two phenols well known for such activity (Daferera et al., 2000; Ultre et al., 1998; Sivropoulou et al., 1996; Caccioni and Guizzardi, 1994; Panizzi et al., 1993; Thompson, 1989). The strong in vitro activity of the oil against the food-pathogen Listeria monocytogenes has also been shown (Liolios et al., 2009). Moreover, the recently published strong antimicrobial activity of the polyphenols isolated from the polar extracts against the Gram-negative clinical strains: Acinetobacter haemolyticus, Empedobacter brevis, Pseudomonas aeruginosa and Klebsiella pneumonia (Chatzopoulos et al., 2010) could also be linked to its traditional medicinal uses against sore throat, toothache, gingivitis, tonsillitis. Dittany as a natural source of essential oil and pheno- lics components has attracted many investigators to evaluate their activity as antioxidants or free radical scavengers (Kouri et al., 2003; Couladis et al., 2003; Moller et al., 1999; Lagouri and Boskou, 1996; Economou et al., 1991). It is clear according to published results that the EO and the extracts of the plant maybe considered as potential natural antioxidant. Additionally, the antibacterial and antioxidant activity of O. dictamnus make it a potential safe food additive as flavour agent with numerous potential applications, in the field of food, cosmetic and pharmaceutical industry as well as food preservative.

Finally, it is noteworthy, that although the famous wound-healing activity of the herb has never been studied or proved experimentally, it is still in use, according to all references through centuries, from antiquity (Minoan civilisation, Hippocrates and Aristotle), till our days for the same indication, based on this long-standing traditional practise.

In conclusion, the recent scientific data and the rich histori- cal evidence concerning the various applications of O. dictamnus could support its ethnomedicinal importance as well as its uses as a safe herbal medicinal product, while it remains essential to document the existing traditional medical experience in combination with further relevant in vitro/in vivo pharmacological assays.
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