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Origanum spp.: an update of their chemical and biological profiles

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Abstract The purpose of this review is to provide an overview of most recent studies about potential pharmaceutical applications of plants belonging to *Origanum* genus. Oregano is one of the most famous and economically important culinary herbs in the world. The genus *Origanum* includes more than 70 species mainly distributed around the Mediterranean region. The vernacular name "oregano" is attributed to a vast number of species. *O. vulgare* L. is the most variable species of the genus and the most commonly known as oregano in most countries. Today, it is generally accepted that oregano is a characteristic flavour produced by a number of plant species that yield carvacrol-rich essential oils. The genus *Origanum* is characterised by a large morphological and chemical diversity. Because of their several biological activities, such as antimicrobial, expectorant, antispasmodic and carminative, *Origanum* species have been used in traditional medicine to treat various diseases. The botany and chemotaxonomy of the species are thoroughly reported, along with chemical constituents. The in vitro and in vivo effects of *Origanum* extracts are presented and discussed.

Keywords Biological activity · Essential oil · *Origanum* sp. · Phenols · Terpenes

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Abbreviations

5RP7	H-ras transformed rat embryonic fibroblasts
BHA	Butylated hydroxyanisole
BHT	Butylated hydroxytoluene
C6	Rat brain tumour cell line
DPPH	1,1-Diphenyl-2-picrylhydrazil radical
GLUT-2	Glucose transporter-2
HEK293	Human embryonic kidney cells
HeLa	Human cervix carcinoma cell line
HepG2	Hepatocarcinoma cell line
HepG2	Human liver cancer cell line
LoVo	Colon carcinoma cell line
LPL	Lipoprotein lipase
LPS	Lipopolysaccharide
MCF	Minimal fungicidal concentration
MiaPaca-2	Human pancreas carcinoma cell line
MI	Minimal inhibitory concentration
MID	Minimum inhibitory dose
NO	Nitric oxide
PG	Propyl gallate
RAW 264.7	Mouse macrophage cell line
ROS	Reactive oxygen species
TBHQ	*tert*-Butylhdroquinone
Vero	African green monkey kidney epithelium cells

Botany

Oregano belongs to the Lamiaceae family. From an etymological point of view, the name *Origanum* derives from the Greek name ὀρίγανον (origanon), which in turn comes from the words ὄρος (oros = mountain) and γάνος (ganos = brightness), since this plant grows at altitudes of 400–1800 m and in sunny areas (Sakkas and Papadopoulou 2017). The name "oregano" is attributed to several plant taxa of different families and genera, and this reflects the extent of morphological variation the genus exhibits in nature. More than 300 scientific names have been given to the currently recognized *Origanum* species, subspecies, varieties and hybrids. The taxonomic revision by Ietswaart (1980), which is widely recognized today, identifies within the genus *Origanum* three groups, 10 sections, 38 species, six subspecies and 17 hybrids (Skoula and Harborne 2002).

The members of the genus are mainly distributed around the Mediterranean region. It is native to Asia-Tropical, Asia-Temperate, Africa and Europe but it has been introduced in India, west and east coast of North America and Mexico. Four main groups are commonly used for culinary purposes: Greek oregano (*Origanum vulgare* L. ssp. *hirtum* (Link) Ietswaart), Spanish oregano (*Coridothymus capitatus* (L.) Hoffmanns & Link), Turkish oregano (*Origanum onites* L.) and Mexican oregano (*Lippia graveolens* HBK). The most important species is *O. vulgare* with the subspecies *O. vulgare* subsp. L. *vulgare*, *O. vulgare* subsp. L. *glandulosum*, *O. vulgare* subsp. L. *gracile*, *O. vulgare* subsp. *hirtum*, *O. vulgare* subsp. *virens* and *O. vulgare* subsp. *viride* (D'Antuono et al. 2000).

Other species include *O. heracleoticum*, *O. dictamnus*, *O. microphyllum*, *O. scabrum*, *O. onites*, *O. symes*, *O. akhdarense, O. cyrenaicum*, *O. libanoticum*, *O. bargyli, O. dayi, O. ramonense*, *O. elongatum, O. grosii*, *O. floribundum*, *O. petraeum*, *O. punonense*, *O. jordanicum*, *O. acutidens*, *O. solymicum*, *O. bilgeri*, *O. minutiflorum*, *O. boissieri*, *O. saccatum*, *O. hypericifolium*, *O. brevidens*, *O. haussknechtii*, *O. leptocladum*, *O. rotundifolium*, *O. amanum*, *O. micranthum, O. syriacum and O. majorana*. The two most well-known commercial oregano species are the Greek *O. vulgare* subsp. *hirtum* and the Turkish *O. onites* (Sakkas and Papadopoulou 2017).

Within the "vulgare group", Pignatti (1982) includes two species in his *Italian flora*, in agreement with *Flora Europaea*: *O. vulgare* L., widespread throughout the whole country, and *O. heracleoticum* L., typical of southern Italy.

The name oregano corresponds to the characteristic odor originating from the high amounts of the phenol carvacrol in the essential oils of these plants. The quantitative and the qualitative differences in the compositions of the essential oil produced may vary depending on its geographical origin, as different environmental conditions may influence essential oil production, and on its taxonomic identity, as the various oregano species and subspecies have different quality characteristics (Chalchat and Pasquier 1999).

Chemical constituents

Terpenes

Oregano plays a significant role among the culinary herbs as food flavorings in world trade for its volatile oils. Terpenes have been considered as the main active and characteristic compounds of the essential oil of Oregano species. Monocyclic monoterpenes, mainly carvacrol (**1**, Fig. 1) (Skoula and Harborne 2002) and thymol (**2**) (Khoury et al. 2016), are the principal compounds to which the commercial name of oregano is due. Several chemically related compounds such as γ-terpinene (**3**), α-terpinene (**4**), *p*-cymene (**5**), *p*-cymenene (**6**), carvacrol and thymol methyl ethers (**7**,**8**) and acetates (**9**,**10**), terpinen-4-ol (**11**), *p*-cymen-8-ol (**12**), *p*-cymen-7-ol (**13**), thymoquinone (**14**), and thymohydroquinone (**15**) are also present (Ozkan et al. 2010; Skoula and Harborne 2002).

Oregano species are also rich in bicyclic monoterpenes such as thujene (**16**, Fig. 2), sabinene (**17**), camphene (**18**), α-pinene (**19**), β-pinene (**20**), borneol (**21**), *cis*-sabinene hydrate (**22**), *trans*-sabinene hydrate (**23**), *cis*-sabinene hydrate acetate (**24**), *trans*-sabinene hydrate acetate (**25**), *cis*-sabinol (**26**), *trans*-sabinol (**27**), camphor (**28**) and isoborneol (**29**) (Han et al. 2017; Skoula and Harborne 2002).

The acyclic monoterpenes linalool (**30**, Fig. 3), linalyl acetate (**31**), β-myrcene (**32**) and geraniol (**33**) have also been found in *Origanum* spp. (Skoula et al. 1999).

The most common isolated sesquiterpenes are: β-bisabolene (**34**, Fig. 4), β-caryophyllene (**35**),

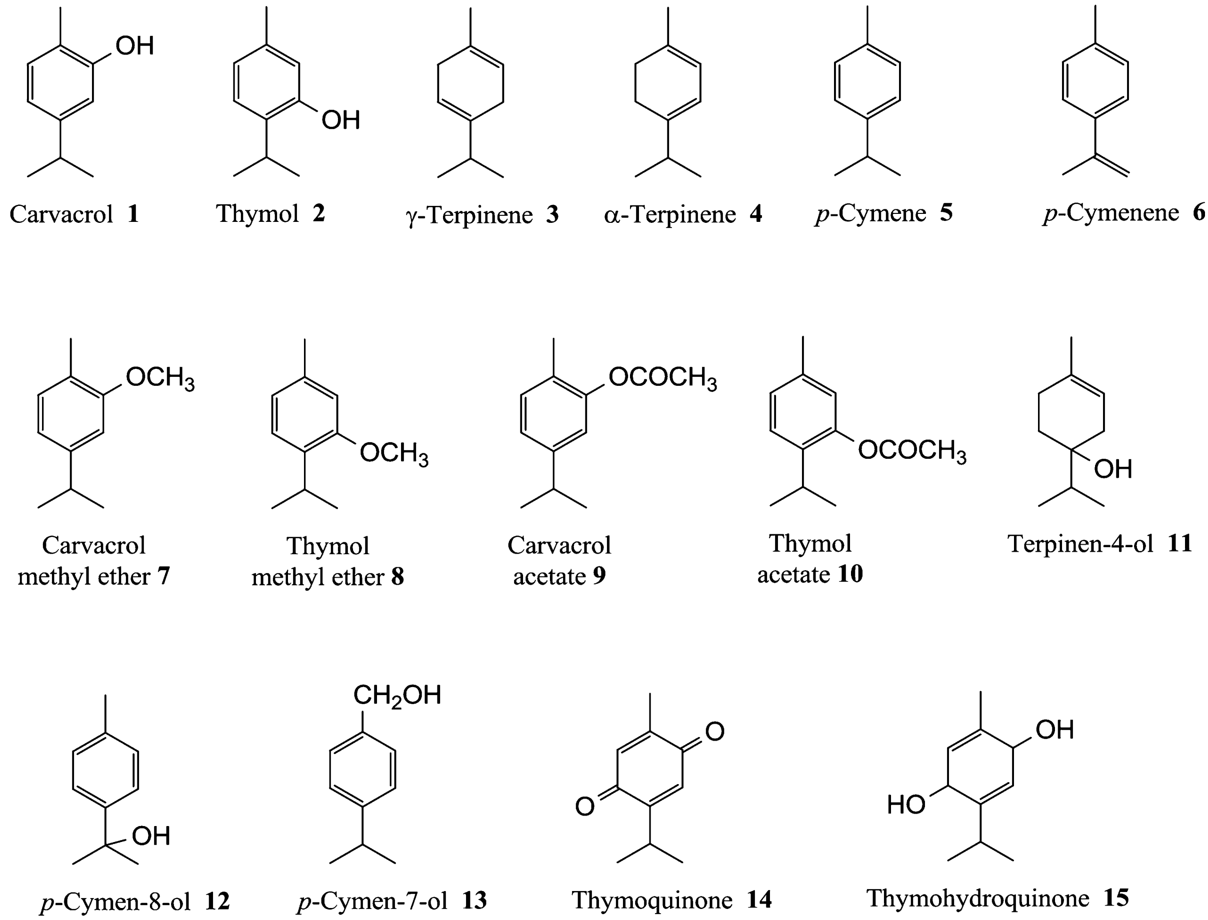


Fig. 1 Most common monocyclic monoterpenes found in *Origanum* spp. (Ozkan et al. 2010; Skoula and Harborne 2002)

aromandrene (**36**), germacrene (**37**), α-humulene (**38**), β-bourbonene (**39**), β-cubebene (**40**), α-muurolene (**41**), γ-muurolene (**42**), α-copaene (**43**), β-caryophyllene oxide (**44**), γ-cadinene (**45**), α-cadinol (**46**), germacrene-D-ol (**47**) and bicyclogermacrene (**48**) (Bisht et al. 2009; Pirigharnaei et al. 2011; Skoula and Harborne 2002).

Diterpenoids have been isolated only from two *Origanum* species, *O. pampaninii* and *O. akhdarense*. Akhdarenol (**49**, Fig. 5), akhdardiol (**50**), akhdartriol, (**51**) and isoakhdartriol (**52**) have been reported (Passannanti et al. 1984; Piozzi et al. 1985 Skoula and Harborne 2002).

Ursolic (**53**, Fig. 5) and oleanolic acids (**54**) are the major triterpenoids that have been found in *Origanum* species, together with β-amyrin (**55**), uvaol (**56**), betulin (**57**) and betulic acid (**58**) (Skoula and Harborne 2002).

Phenols

Hydroquinone (**59**, Fig. 6) is the most common phenol isolated in *Origanum* spp. Hydroquinone monomethyl ether (**60**) and the glucoside arbutin (hydroquinone-*O*-glucoside, **61**) are also reported (Assaf et al. 1987; Ifantis et al. 2012; Lukas et al. 2010).

Among phenolic acids *p*-hydroxybenzoic (**62**, Fig. 6), vanillic (**63**), syringic (**64**) and protocatechuic acids (**65**) have been identified in *Origanum* ssp, together with the hydroxycinnamic acids caffeic (**66**) and cinnamic acids (**67**) and their esterified forms rosmarinic acid (**68**) and chlorogenic acid (**69**) (Skoula and Harborne 2002).

A lot of flavonoids have been identified in many *Origanum* species: apigenin (**70**, Fig. 7), genkwanin (**71**), chrysin (**72**), neglectein (**73**), mosloflavone

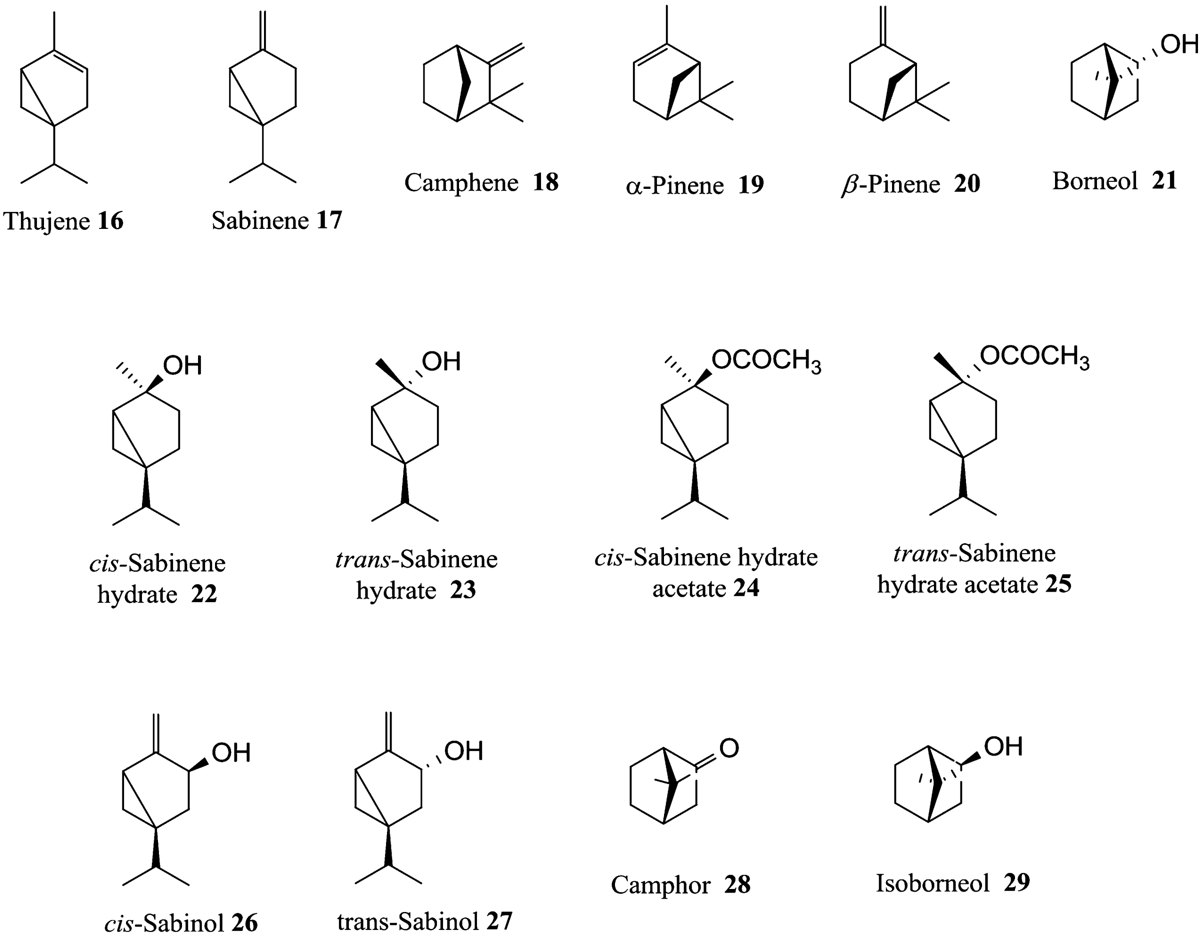


Fig. 2 Most common bicyclic monoterpenes isolated in *Origanum* spp. (Han et al. 2017; Skoula and Harborne 2002)

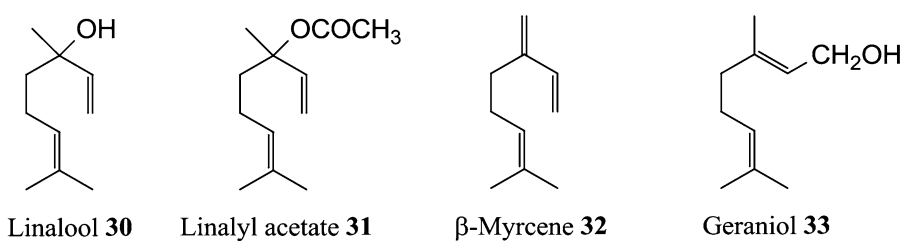


Fig. 3 Most common acyclic monoterpenes found in *Origanum* spp. (Skoula et al. 1999)

(**74**), apigenin 7-*O*-glucuronide (**75**), isovitexin (**76**), acacetin (**77**), apigenin-7,4′-dimethylether (**78**), cirsimaritin (**79**), luteolin (**80**), cinaroside (**81**), luteolin-7-*O*-glucuronide (**82**), luteolin-7-*O*-rutinoside (**83**), isoorientin (**84**), chrysoeriol (**85**), chrysoeriol-7-*O*-glucuronide (**86**), thymusin (**87**), thymonin (**88**), 6-hydroxyluteolin-7,3′-dimethylether (**89**), 6-hydroxyluteolin-7,3′,4′-trimethylether (**90**), kaempferol (**91**), penduletin (**92**), quercetin (**93**), desmethylnobiletin (**94**), galangin (**95**), axillarin (**96**), naringenin (**97**), chrysosplenol-D (**98**), retusin (**99**), taxifolin (**100**), eriodictyol (**101**), eriodictiol-7-*O*-glucoside (**102**), aromadendrin (**103**) (Cavero et al. 2006; Ifantis et al. 2012; Nagy et al. 2011; Radušienė et al. 2008; Skoula and Harborne 2002; Skoula et al. 2008).

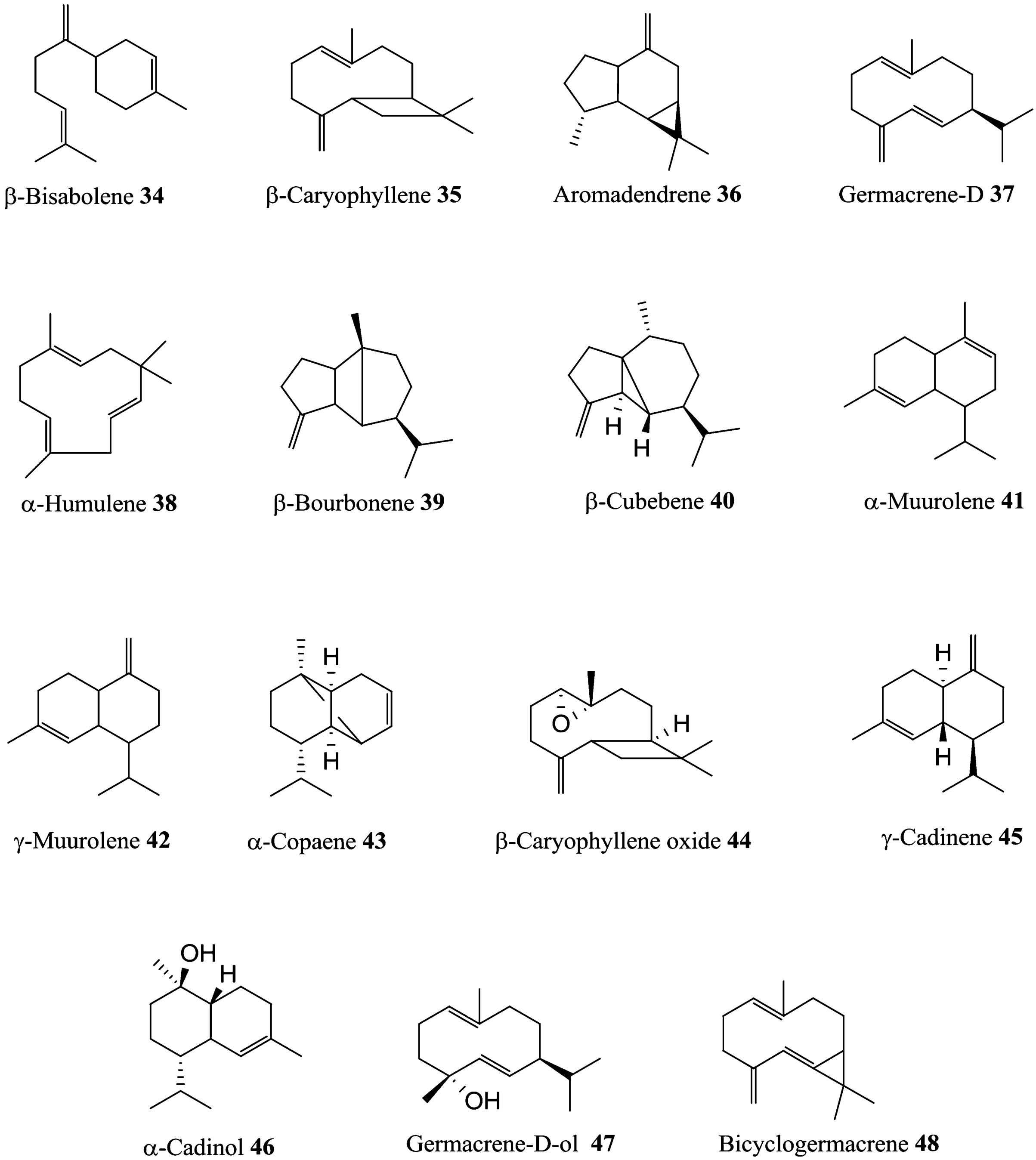


Fig. 4 Most common sesquiterpenes found in *Origanum* spp. (Bisht et al. 2009; Pirigharnaei et al. 2011; Skoula and Harborne 2002)

Biological activities

Origanum, widely used in food industry and traditional medicine in many countries, is an important medicinal and aromatic plant. Several studies dealt with the chemical composition of *Origanum* spp. essential oils, which have been applied as a flavouring for sauces and soups, meat and fish. *Origanum* species have been used as a folk remedy for the treatment of different diseases such as diarrhoea,

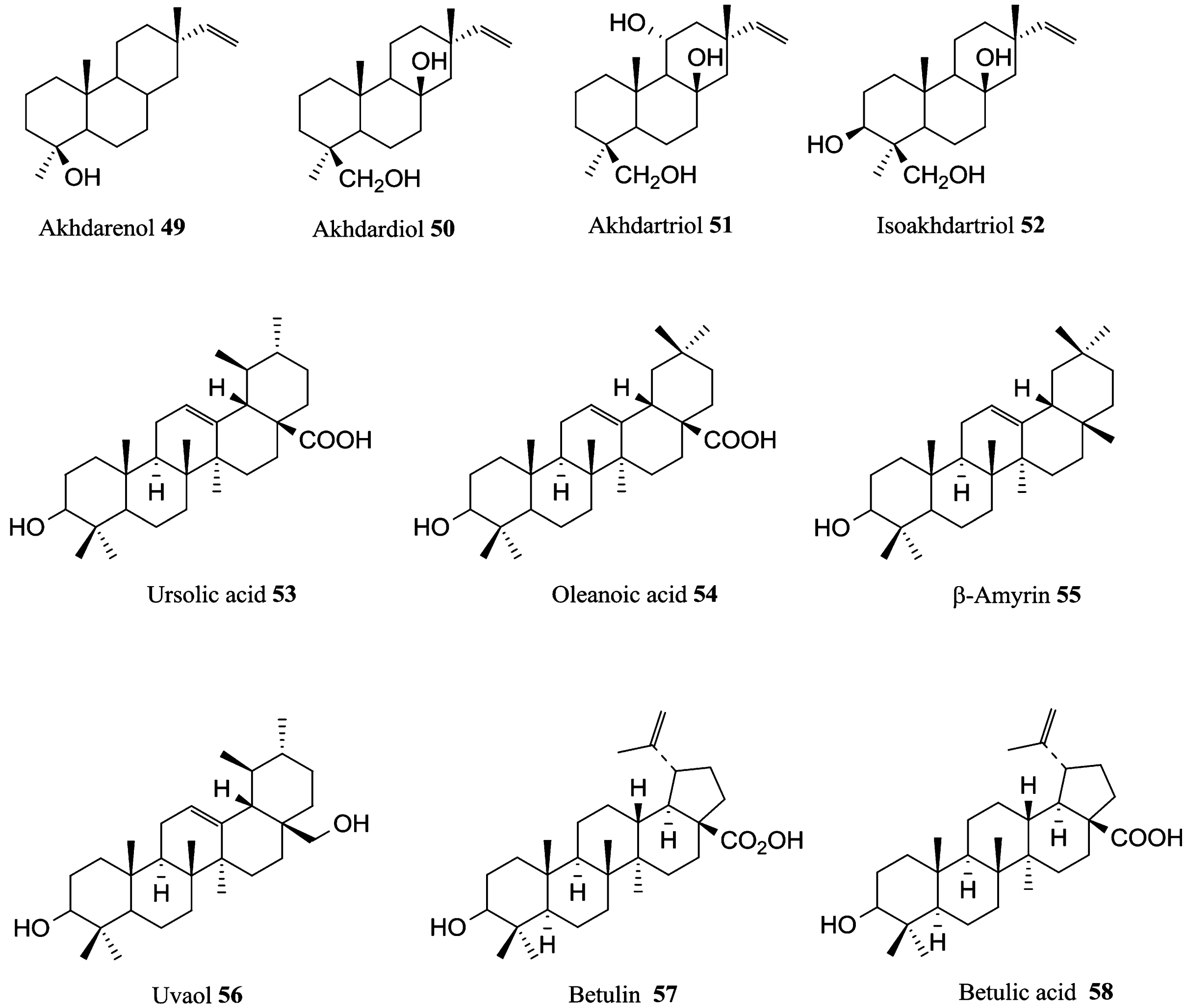
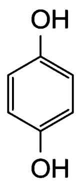


Fig. 5 Most common diterpenes (**49**–**52**) and triterpenes (**53**–**58**) identified in *Origanum* spp. (Passannanti et al. 1984; Piozzi et al. 1985; Skoula and Harborne 2002)

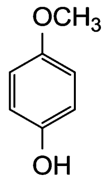
rheumatism, indigestion, headache, muscle pains and asthma (Erenler et al. 2017). This genus exhibits also interesting antimicrobial activity against foodborne bacteria and fungi (Busatta et al. 2008). The different biological properties demonstrated for *Origanum* spp. are here reported and summarized in Table 1.

Antimicrobial activity

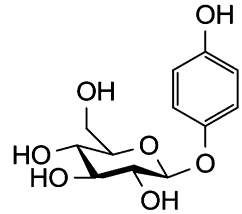
Over the past years, due to the emergence of drug-resistant pathogens, the potential antimicrobial properties of medicinal plants and their metabolites have attracted much interest. The development of new antimicrobials from plants is a possible action against drug-resistance problem (Sakkas et al. 2016). The antimicrobial properties of many plants, particularly plant oils and extracts, are attributed to their ability to synthesize aromatic substances, most of which are phenols or oxygen-substituted derivatives (Sakkas and Papadopoulou 2017). Sakkas and coworkers (2016) investigated the antimicrobial activity of five plant essential oils, among which Spanish oregano oil (*Thymus capitatus* L., Labiatae), on multidrug resistant Gram-negative bacteria: *Acinetobacter baumannii*, *Escherichia coli*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*. The obtained results showed that *Origanum* oil was ineffective on *P. aeruginosa* while exerted antibacterial activity



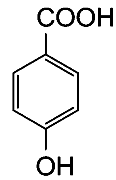
Hydroquinone **59**



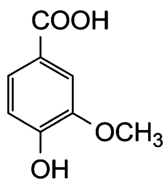
Hydroquinone monomethyl ether **60**



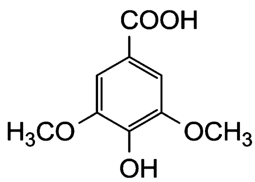
Arbutin **61**



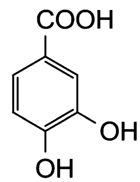
p-Hydroxybenzoic acid **62**



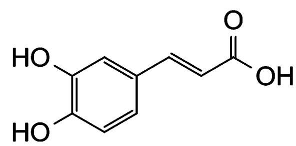
Vanillic acid **63**



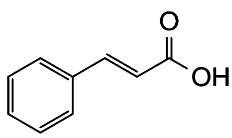
Syringic acid **64**



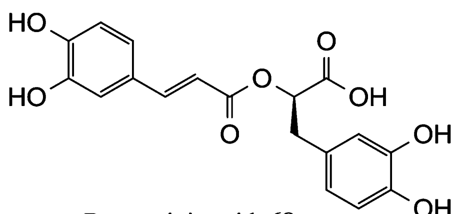
Protocatechuic acid **65**



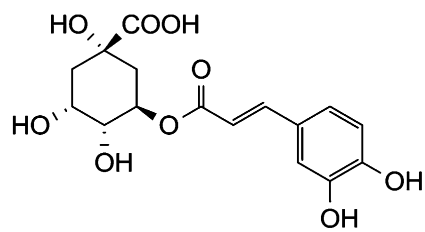
Caffeic acid **66**



Cinnamic acid **67**



Rosmarinic acid **68**



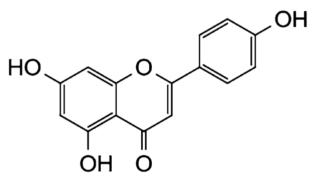
Chlorogenic acid **69**

Fig. 6 Most common phenols found in *Origanum* spp.

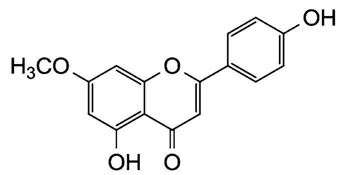
against the other strains with minimum inhibitory concentration (MIC) and minimum bactericidal concentration values ranging from 0.25 to 4% (v/v). The possible mechanism of action of the *Origanum* oil, but in general for all essential oils, is based on the ability to disrupt the bacterial cell wall and the cytoplasmic membrane for the presence of phenolics that can penetrate into the phospholipids layer of the bacterial cell wall, bind to proteins and block their normal functions.

Harmati and coworkers (2017) evaluated the in vivo therapeutic efficiency against *Helicobacter pylori* infection of a mixture of *Satureja hortensis* and *O. vulgare* subsp. *hirtum* essential oils. This study was done in order to develop novel therapeutic agents against *H. pylori* infections because it can cause many gastrointestinal and extra-gastrointestinal disorders and is a major risk factor for gastric carcinoma and MALT lymphoma. The results of this study demonstrated that this essential oil mixture would be a highly effective therapeutic agent against *H. pylori* than the individual oils.

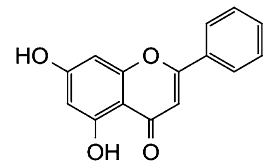
The essential oils of the aerial parts of three *Origanum* species, *O. libanoticum*, *O. ehrenbergii* and *O. syriacum* were investigated for their antimicrobial activity against *Candida albicans* and six pathogenic bacteria (*Escherichia coli*, *Pseudomonas aeruginosa*, *Enterococcus faecalis*, *Salmonella enteritidis*, *Staphylococcus aureus*, *Bacillus subtilis* subsp. *spizizenii*). The *O. syriacum* and *O. ehrenbergii* essential oil showed significant microbial inhibition for *Bacillus spizizenii*, *Escherichia coli*, and *Enterococcus faecalis* (MIC value equal to 0.4 mg/ml), and *Staphylococcus aureus* (MIC 0.4 and 0.6 mg/ml, respectively). Both



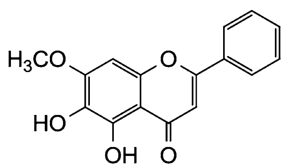
Apigenin **70**



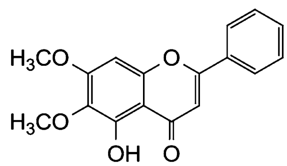
Genkwanin **71**



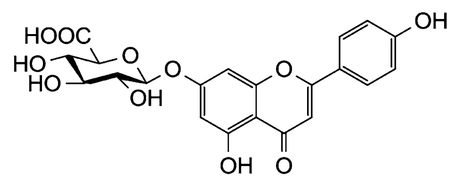
Chrysin **72**



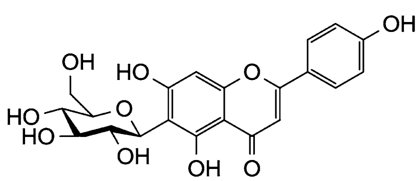
Neglectein **73**



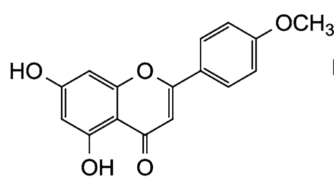
Mosloflavone **74**



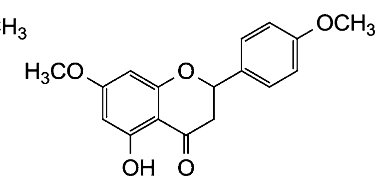
Apigenin 7-*O*-glucuronide **75**



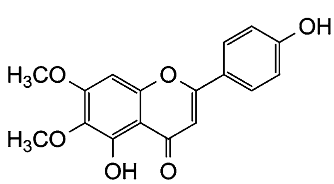
Isovitexin **76**



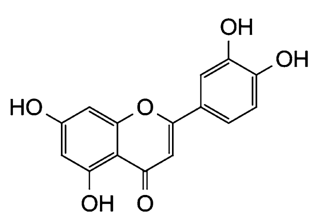
Acacetin **77**



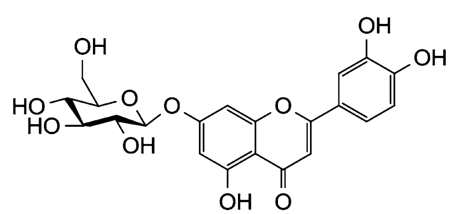
Apigenin-7,4'-dimethylether **78**



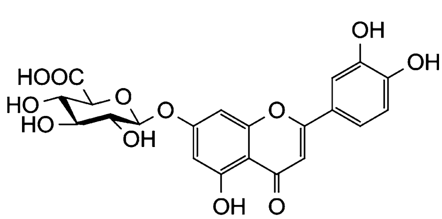
Cirsimaritin **79**



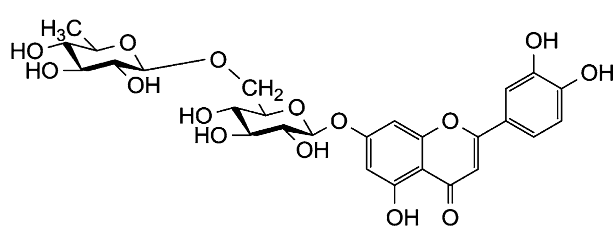
Luteolin **80**



Cinaroside **81**

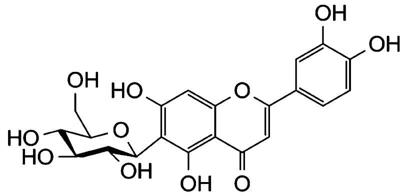


Luteolin 7-*O*-glucuronide **82**

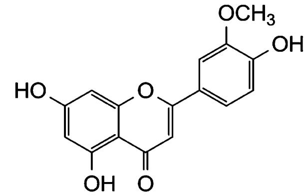


Luteolin 7-*O*-rutinoside **83**

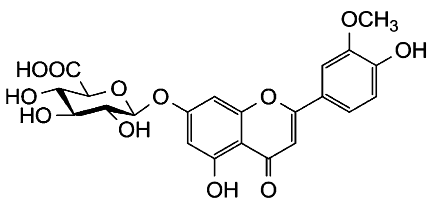
Fig. 7 Flavonoids found in *Origanum* spp. (Cavero et al. 2006; Ifantis et al. 2012; Nagy et al. 2011; Radušienė et al. 2008; Skoula and Harborne 2002; Skoula et al. 2008)



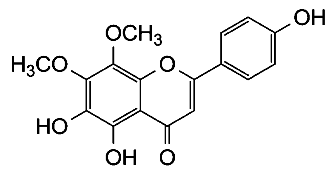
Isoorientin **84**



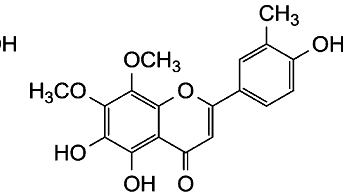
Chrysoeriol **85**



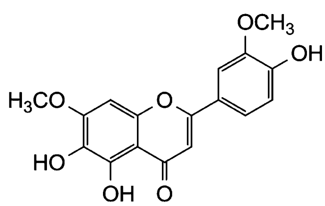
Chrysoeriol-7-*O*-gluroconide **86**



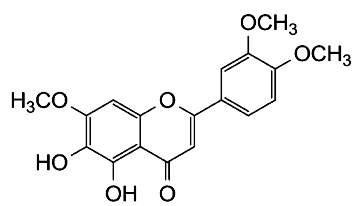
Thymusin **87**



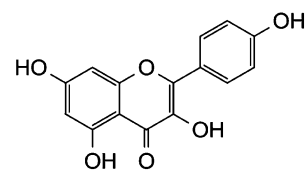
Thymonin **88**



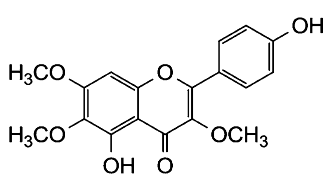
6-hydroxyluteolin-7,3'-dimethylether **89**



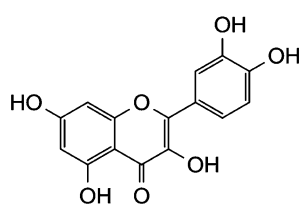
6-hydroxyluteolin-7,3',4'-trimethylether **90**



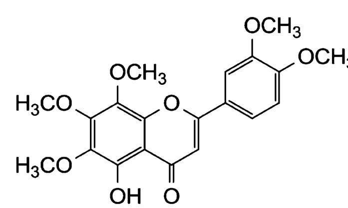
Kaempferol **91**



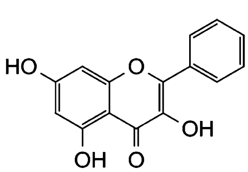
Penduletin **92**



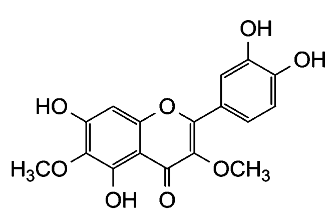
Quercetin **93**



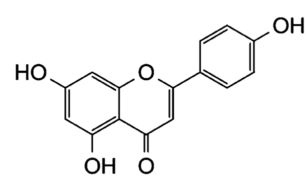
Desmethylnobiletin **94**



Galangin **95**

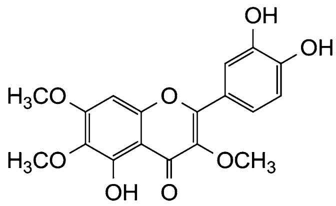


Axillarin **96**

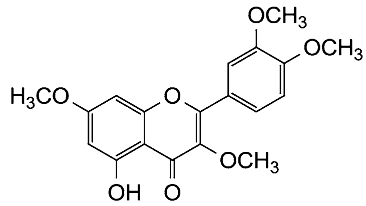


Naringenin **97**

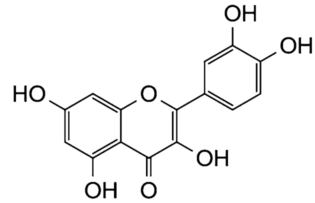
Fig. 7 continued



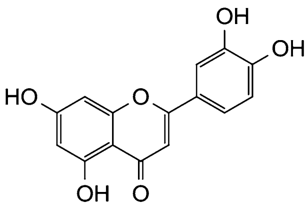
Chrysosplenol-D **98**



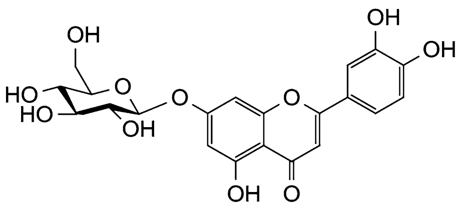
Retusin **99**



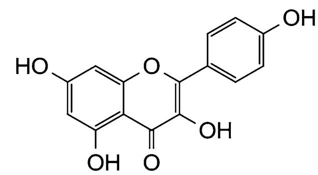
Taxifolin **100**



Eriodictyol **101**



Eriodictyol-7-*O*-glucoside **102**



Aromadendrin **103**

Fig. 7 continued

essential oils were not effective against the other three bacteria (MIC ≥ 2 mg/ml). The comparison of the chemical composition of the essential oils indicated that the antimicrobial activity of *O. syriacum* and *O. ehrenbergii* essential oils is mainly due to the presence of the phenolic monoterpenes thymol and carvacrol (Al Hafi et al. 2016).

De Martino and coworkers (2009) examined the composition of the essential oils of three *O. vulgare* L. ssp. *hirtum* populations growing wild in Campania (Southern Italy) and their antimicrobial activity on ten selected microorganisms: *Bacillus cereus*, *Bacillus subtilis*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus faecalis*, *Escherichia coli*, *Proteus mirabilis*, *Proteus vulgaris*, *Pseudomonas aeruginosa*, *Salmonella typhi Ty2*. The essential oils were mainly effective against the Gram-positive pathogens, above all *S. epidermidis*. Among Gram-negative bacteria, only *E. coli* was affected by the oils. The different activity exerted by the three populations was mainly related to their phenolic components, such as thymol, carvacrol and carvacrol methyl ether, and to the synergistic presence of minor active constituents, such as γ-terpinene and *p*-cymene.

Tepe and coworkers (2016) reported the traditional use, phytochemistry and pharmacology of *O. onites*. In this review was reported that extracts and essential oils exhibited a broad spectrum of antimicrobial activity against Gram-negative and Gram-positive bacteria and fungi. Antimicrobial activity of this species has been attributed mainly to the presence of carvacrol and thymol.

Waller and coworkers (2016) evaluated the anti-*Sporothrix* spp. activity of the essential oil of *O. majorana* Linn. (marjoram) against 18 fungal isolates of *Sporothrix brasiliensis* from humans, dogs and cats, and a standard strain of *Sporothrixs chenckii*. The resistance of *Sporothrix* spp. to itraconazole has been recently evidenced and it is a great problem for the public health (Rodrigues et al. 2014). No significant difference was observed between the MIC values, while *O. majorana* presented better MFC values than itraconazole. All tested strains were susceptible to the essential oil: fungistatic activity occurred at concentrations ≤ 2.25–9 mg/ml, while fungicidal activity was observed between 2.25 and 18 mg/ml (Waller et al. 2016).

O. vulgare essential oil showed antifungal activity against the six *Candida* strains tested by Brochot and coworkers (Brochot et al. 2017) with MICs ranging from 0.01 to 0.05% v/v and minimal fungicidal concentrations from 0.02 to 0.05% v/v.

Table 1 Main biological activities of *Origanum* spp.

Species	Extracts/fractions/compounds	Biological activities		References
		In vitro models	In vivo models (animals)	
O. acutidens (Hand.-Mazz.) Ietswaart	Water extract	Antioxidant		Aras et al. (2017)
O. dictamnus L.	Essential oil	Antimicrobial, antioxidant, antiproliferative		Marrelli et al. (2016)
O. ehrenbergii Boiss.	Essential oil	Antimicrobial		Al Hafi et al. (2016)
O. heracleoticum L.	Ethanolic extract	Antioxidant		Conforti et al. (2011b)
O. libanoticum Boiss.	Essential oil	Antimicrobial, antioxidant		Al Hafi et al. (2016), Marrelli et al. (2016)
O. majorana L.	Essential oil	Antifungal		Nardoni et al. (2015), Waller et al. (2016)
	Aqueous extract		Antidiabetic	Soliman et al. (2016)
O. microphyllum (Bentham) Vogel	Essential oil	Antimicrobial, antioxidant		Marrelli et al. (2016)
O. onites L.	Extracts and essential oil	Antimicrobial, antioxidant		Tepe et al. (2016)
	Essential oil	Antiproliferative		Tepe et al. (2016)
			Antidiabetic	Lermioglu et al. (1997), Tepe et al. (2016)
O. rotundifolium Boiss.	Essential oil	Antioxidant		zbek et al. (2017)
	Extracts and isolated vitexin	Antiproliferative		Erenler et al. (2017)
O. syriacum L.	Essential oil	Antimicrobial		Al Hafi et al. (2016)
O. vulgare L.	Essential oil	Antifungal, antibacterial, antioxidant		Brochot et al. (2017), Csarov et al. (2016), Han et al. (2017), Miller et al. (2015), Nardoni et al. (2015); Sharifzadeh and Shokri (2016), Texeira et al. (2013)
	Water extract	Antioxidant		Texeira et al. (2013)
	Ethanolic extract	Antioxidant, antibacterial		Nile et al. (2017), Texeira et al. (2013)
O. vulgare L. ssp. *hirtum*	Mixture of the essential oil with *S. hortensis* L.		Antimicrobial	Harmati et al. (2017)
	Essential oil	Antimicrobial		De Martino et al. (2009)
	Essential oil and isolated carvacrol, thymol, citral and limonene	Cytotoxic		Elshafie et al. (2017)
	Ethyl acetate extract		Antidiabetic	Vujicic et al. (2016)
O. vulgare L. ssp. *virens*	Methanolic extract	Antioxidant		Gonalves et al. (2017)
O. vulgare L. ssp. *viridulum* (Martin-Donos) Nyman	Hydroalcoholic extract	Antioxidant, antiproliferative		Conforti et al. (2011a), Marrelli et al.(2015)

Sharifzadeh and Shokri (2016) evaluated the antifungal activity of essential oils from Iranian plants against fluconazole-resistant and fluconazole-susceptible *Candida albicans*. *O. vulgare* was one of the most active tested essential oils, showing the lower MIC value against *C. albicans*. The oil of Iranian *O. vulgare* is rich in monoterpene phenols, especially thymol. The antifungal mechanism of thymol is not well understood although it has been hypothesized that it causes membrane and cell wall disruption with deterioration of the yeasts. A significant activity against *Candida albicans* of the essential oil from *O. vulgare* was also reported by Miller and coworkers (Miller et al. 2015).

Císarová and coworkers (2016) assessed the antifungal activity of 15 essential oils (EOs) against three fungi of the genus *Aspergillus*. The best antifungal activity, using the micro-atmosphere method was found for *O. vulgare* (MID of 31.5 µl/l air) against all tested strains together with other EOs.

O. majorana and *O. vulgare* essential oils were assayed against clinical animal isolates of *Microsporum canis*, *Trichophyton mentagrophytes*, *T. erinacei*, *T. terrestre* and *Microsporum gypseum*, main causative agents of zoonotic and/or environmental dermatophytoses in humans (Nardoni et al. 2015). *O. vulgare* was the most effective essential oil (MIC range 0.025–0.5%).

Also the essential oils of the three *Origanum* species, *O. dictamnus*, *O. libanoticum* and *O. microphyllum* from Greece were subjected to screening for their possible antimicrobial activity. The oils showed an interesting activity mainly against the Gram (+) pathogens, while among Gram (–) bacteria only *Escherichia coli* was affected by *O. dictamnus* and *O. microphyllum* essential oils (Marrelli et al. 2016).

Antioxidant activity

Free oxygen radicals, called reactive oxygen species (ROS), comprising hydroxyl radical, superoxide and singlet oxygen, can yield cellular harm leading to cancer, cardiovascular diseases and Parkinson and Alzheimer's disease (Valko et al. 2007). Some compounds such as butylated hydroxytoluene (BHT), propyl gallate (PG), butylated hydroxyanisole (BHA), tert-butylhdroquinone (TBHQ) are commonly used as synthetic antioxidants. However, due to the toxicity of these chemicals, demand for natural antioxidants has increased. ROS could be scavenged by compounds present in fruits and vegetables. Therefore, plant extracts containing antioxidant compounds are important for pharmacology and food industry (Balasundram et al. 2006; Miguel 2010).

The study of Teixeira and coworkers (2013) suggests that the hot water extract of *O. vulgare* of Portuguese origin has strong antioxidant capacity. Additionally, *O. vulgare* ethanolic extract and particularly the essential oil revealed antibacterial properties. In this context, *O. vulgare* extracts and essential oil have strong potential to be used as alternatives to synthetic chemicals in industries whereas oxidation and microbial contamination are serious problems.

Nile and coworkers (2017) evaluated the phenolic content, antioxidant and antitumor activities of commonly used medicinal herbs from a Unani system of medicine using four different extraction methods. Among these medicinal herbs, *O. vulgare* showed the highest level of antioxidant activity using ethanol as solvent of extraction and maceration as extraction technique.

Han and coworkers (2017) evaluated the differences in chemical compositions and antioxidant activities of the essential oils from different parts of oregano (*O. vulgare* L.) collected in Huanggang City, Tuanfeng County, Hubei Province, China. The results showed that the contents of carvacrol and thymol in essential oil from the leaves-flowers were close to 50% while the total percentage of two components just was only 4.35% from the underground parts (roots). However, the results of the antioxidant activity tests showed that the essential oils from the underground parts were similar to those from the aerial parts. This suggests that the antioxidant capacities of the root oils are not just dependent on the content of phenolic compounds.

Gonçalves and coworkers (2017) evaluated the antioxidant properties of the methanolic extracts from *O. vulgare* subsp. *virens*. The extract exhibited a good DPPH and ABTS scavenging capacities, as well as ferric reducing ability. This extract also showed a high total phenolic content and although HPLC-DAD analysis revealed rosmarinic acid as the main compound, other chemicals seem to be involved in the antioxidant activity.

Hydroalcoholic extract from non-cultivated *O. vulgare* L. subsp. *viridulum* (Martin-Donos) Nyman, traditionally consumed by Calabrian people (Southern Italy), demonstrated a strong antioxidant activity against DPPH radical (Conforti et al. 2011a). The same extract showed weak antioxidant activity using the β-carotene bleaching method (Marrelli et al. 2015) and weak activity in the inhibition of nitric oxide (NO) production in the LPS-stimulated RAW 264.7 mouse macrophage cell line (Conforti et al. 2011a). The ethanolic extract of the aerial parts of *O. heracleoticum* L. showed a significant radical scavenging activity using the 1,1-Diphenyl-2-picrylhydrazil radical (DPPH) test and an interesting antioxidant activity with the β-carotene bleaching test. The test for the inhibition of NO production, performed using the murine monocytic macrophage RAW 264.7 cell line, showed that the extract had significant activity (Conforti et al. 2011b).

The essential oils of the three *Origanum* species, *O. dictamnus*, *O. libanoticum* and *O. microphyllum*, were subjected to screening for their possible antioxidant activity by means of two spectrophotometric methods (DPPH and FRAP tests). The essential oils revealed poor antiradical activity, and only the oil from *O. dictamnus* exerted a weak capacity to scavenge free radicals (Marrelli et al. 2016).

O. onites also exhibited strong antioxidant activity using different tests and extracts obtained from several solvents (Tepe et al. 2016).

Aras and coworkers (2017) evaluated the antioxidant activity of the leaves of *O. acutidens* by using DPPH, FRAP and CUPRAC methods. Obtained results confirmed that the water extract of this species had effective DPPH radical scavenging activity.

An antioxidant potential has been also reported for the essential oil of *O. rotundifolium*, whose activity was measured by scavenging of ABTS, H_2O_2 and superoxide radical (Özbek et al. 2017).

Antiproliferative activity

Natural products play a leading role in the discovery and the development of drugs for the treatment of human diseases. The anticancer activity observed for a number of traditional medicines and natural products has been supported by scientific validation. Moreover, natural products, being a complex mixture of chemical compounds may target multiple vulnerabilities of cancer cells, without toxicity to the noncancerous cells (Ovadje et al. 2015).

Oregano (*O. vulgare* L. subsp. *viridulum*) showed a selective antiproliferative activity on epatocarcinoma cell line HepG2. The same sample showed also weak activity against breast cancer cells MCF-7 (Marrelli et al. 2015).

Also the cytotoxic properties of the essential oil of *O. vulgare* subsp *hirtum,* together with its main constituents (carvacrol, thymol, citral and limonene), has been tested on hepatocarcinoma HepG2 cells. This essential oil was effective in inhibiting cell viability in a dose depending mode and, interestingly, it showed lower cytotoxicity against the non tumor cell line HEK293 (Elshafie et al. 2017).

The essential oils from *O. dictamnus*, *O. libanoticum* and *O. microphyllum* were tested against two human cancer cell lines: colon carcinoma cell line LoVo and hepatocarcinoma cell line HepG2. All samples reduced cell viability in a dose-dependent manner. The essential oil *O. dictamnus*, at the highest concentration (100 mg/ml), was statistically the most inhibitory against both cell lines, particularly colon carcinoma cell line, causing a 58.39% of inhibition after 24 h of incubation. At the same concentration (100 mg/ml), the essential oils of *O. microphyllum* and *O. libanoticum* caused 47.12 and 48.15% of inhibition, respectively (Marrelli et al. 2016).

The extract of *O. rotundifolium* and some isolated compounds were tested for their antiproliferative activity against various cell lines (C6, HeLa and Vero cells). Vitexin revealed the highest activity on all cells lines. The extract activity was better than the single compound, probably as a consequence of synergic effect of different phytochemicals (Erenler et al. 2017).

The essential oil of *O. onites* has been studied for its antiproliferative, antiangiogenic and cytoprotective properties on different cell lines, among which H-ras transformed rat embryonic fibroblasts 5RP7 and hepatoma cells HepG2. The oil inhibited cell viability and induced apoptosis of 5RP7 cells. When compared, the oil was found less cytotoxic on HepG2 cells than carvacrol and thymol, and protected cells against H_2O_2-induced toxicity (Tepe et al. 2016).

The study of García-Risco and coworkers (2017) demonstrated that *O. majorana* has no effects on the growth of pancreatic human tumor-derived cell line MiaPaca-2 cells.

Antidiabetic activity

Diabetes mellitus is a metabolic disease caused by defect in insulin action or secretion. Diabetes is frequently associated with an increased risk of stroke, coronary heart disease, hypertension, renal failure and dyslipidemia (Olokoba et al. 2012). Because of the abundance of antioxidants and potential health benefits, plant extracts are attractive candidates for diabetes treatment (Kooti et al. 2016).

The study of Soliman and coworkers (2016) investigated the effects of the aqueous extract of *O. majoranum* leaves on dyslipidemia, hypoglycemia and hyperinsulinemia induced in a rat model of type 2 diabetes. The results showed that the administration of *O. majoranum* extract improved and normalized dyslipidemia recorded in type 2 diabetic rats and reduced glucose and insulin levels. It was demonstrated that the extract induced up-regulation in the expression of genes involved in carbohydrate and lipid metabolism such as adiponectin, glucose transporter-2 (GLUT-2) and lipoprotein lipase (LPL). Moreover, the extract was able to normalize histopathological changes occurred in liver and kidney of diabetic rats.

It has been also reported that *O. onites* L. essential oil long-term use might be effective in preventing or at least in retarding the development of some complications of diabetes mellitus through large reductions in aspartate aminotransferase (AST), urea, and cholesterol levels (Lermioglu et al. 1997; Tepe et al. 2016).

As *Origanum* species contain antioxidant and anti-inflammatory molecules, Vujicic and coworkers investigated the activity of *O. vulgare* L. ssp. *hirtum* for the treatment of Type 1 diabetes (Vujicic et al. 2016). This study demonstrated that the ethyl acetate extract was able to prevent Type 1 diabetes development *via* attenuation of proinflammatory M1/Th1/Th17 response, and through shifting macrophage population toward protective M2 form. The methanolic oregano extract showed very specific effects on IL-17-producing T lymphocytes (Vujicic et al. 2015), while ethyl acetate extract exerted a wide range of immunomodulatory effects that could be useful for reducing islet-directed inflammation (Vujicic et al. 2016).

Conclusion

Actually, there is an increasing interest in herbal products worldwide. The pharmacological properties of many bioactive ingredients and their potential health benefits in the treatment of a number of diseases have been deeply investigated. Several drugs have been marketed through the exploration of ethnopharmacology and traditional medicine.

The present review summarizes information regarding *Origanum* species, with particular attention to chemical constituents and biological activities. These data strongly supports the view that different species belonging to *Origanum* genus could have potential beneficial therapeutic actions in the management of various pathological conditions, such as bacterial and fungal infections, diabetes and cancer.

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