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SALVIA OFFICINALIS L. AND *MELISSA OFFICINALIS* L. - VALUABLE MEDICINAL AND AROMATIC PLANTS

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INTRODUCTION

Lamiaceae family is one of the largest medicinal and aromatic plant families, the species from this family being cultivated all over the world. The species from *Lamiaceae* family are used in the food industry for flavouring and as medicinal herbs, due to the presence of bioactive compounds in their composition (Kontogianni et al., 2013; Risaliti et al., 2019; Zengin et al., 2019).

These active compounds have antibacterial (Stanojević et al., 2010; Pop et al., 2013), antioxidant (Lin et al., 2012; Kamdem et al., 2013), antifungal (Stević et al., 2014) and antitumor effects (de Sousa et al., 2004; De et al., 2012). Considering their pharmacological properties, these plants may be used in the therapy of various diseases, being viable alternatives to synthetic drugs.

Among the genera of the family, *Salvia* and *Melissa* contain species that are intensely studied for their bioactive compounds, which are found in high amounts in their leaves (Duda et al., 2015; Shakeri et al., 2016; Ghorbani and Esmaeilizadeh, 2017).

The genus *Salvia* is one of the largest of the *Lamiaceae* family, that comprises around 900 species which can be found throughout the world in different areas (Russo et al., 2013; Verma et al., 2015; Jiang et al., 2017; Hassiotis, 2018; Mitić et al., 2019). In the European flora, the genus is represented by 36 species, among which *Salvia officinalis* L. (sage) is one of the most representative, being cultivated all over the world, although is native in the Mediterranean region (Hassiotis, 2018; Jokić et al., 2018; Rahmani et al., 2019).

The genus *Melissa* is an important genus belonging to the *Lamiaceae* family, among which *Melissa officinalis* L. (lemon balm) is distributed throughout Europe (Shakeri et al., 2016; Stojanović et al., 2019).

In recent years, many research studies have been conducted to document the traditional uses of *Salvia officinalis* and *Melissa officinalis* and to find new biological effects for these plants. In this review, are presented the pharmacological properties of sage and lemon balm and the bioactive compounds responsible for the therapeutic effects of these plants.

MATERIAL AND METHOD

A systematic and comprehensive research of the current national and international literature was carried out by the use of a set of representative key words, such as *Salvia officinalis*, *Melissa officinalis*, sage, lemon balm, bioactive compounds, pharmacological properties. From the scientific databases accessed 97 studies were used in the present review study.

RESULTS AND DISCUSSION

Bioactive compounds of *Salvia officinalis*

Salvia officinalis contain a wide range of bioactive compounds isolated from its essential oil, butanol fraction, infusion preparation, alcoholic extract, and aqueous extract: phenolic compounds (e.g., flavonoids, tannins, coumarins), alkaloids, glycosidic derivatives (e.g., flavonoid glycosides, cardiac glycosides, saponins), polyacetylenes, steroids, terpenes/terpenoids (e.g., monoterpenoids, diterpenoids, triterpenoids, sesquiterpenoids), carbohydrates, fatty acids, and waxes (Wang et al., 2000; Velickovic et al.., 2003; Capek and Hríbalova, 2004; Lima et al., 2004; Lima et al., 2005; Mitic-Culafic et al., 2005; Seidel, 2006; Lima et al., 2007; Hayouni et al., 2008; Hadri et al., 2010; Badiee et al., 2012; Russo et al., 2013).

The most important compounds of the essential oil prepared from aerial parts of *Salvia officinalis* are borneol, cineole, camphor, thujone, caryophyllene, elemene, ledene, humulene, and pinene (Hayouni et al., 2008; Badiee et al., 2012).

Alcoholic and aqueous extracts of *Salvia officinalis* are rich in flavonoids particularly rosmarinic acid and luteolin-7-glucoside and methanolic extract of sage contain high amount of the phenolic acids such as caffeic acid and 3-caffeoylquinic acid (Lima et al., 2007). In sage infusion extract have been identified several flavonoids (e.g., rosmarinic acid, ellagic acid, chlorogenic acid, epicatechin, epigallocatechin gallate, rutin, quercetin, and luteolin-7-glucoside) and several volatile components (e.g., borneol, cineole, thujone, and camphor)(Lima et al., 2005; Hernandez-Saavedra et al., 2016).

Arabinose, galactose, glucose, mannose, xylose, rhamnose and uronic acids are the most abounding carbohydrates from this plant (Capek and Hríbalova, 2004).

Regarding the part of the plant where the active compounds are in the highest concentration, the most abundant phytochemical in the stem is linalool, the flowers have the highest content of α-pinene and cineole, and bornyl acetate, camphene, camphor, thujone, humulene, and limonene are the most abundant constituents in the leaves (Velickovic et al., 2003).

Pharmacological properties of sage

Salvia officinalis is used in gastronomy in preparation of many foods because of its flavoring and seasoning properties, and in traditional medicine due to the bioactive compounds from its composition.

The sage extract are strong antioxidant properties. The mainly responsible for the antioxidant activity of many plant extracts, like sage, are the phenolic and flavonoid compounds (e.g., rosmarinic acid, carnosic acid, and salvianolic acid)(Lu and Foo, 2001; Nickavar et al., 2007; Yadav and Mukundan, 2011).

Salvia has beneficial effects on memory disorders, cerebral ischemia, and depression (Perry et al., 2003; Imanshadi and Hosseinzadeh, 2006). *Salvia officinalis* has been used for centuries as restoratives of declining mental functions such as in Alzheimer's disease (Perry et al., 2003; Eidi et al., 2006; Imanshadi and Hosseinzadeh, 2006). Because the neuroprotective effect of sage is mainly due to the rosmarinic acid, it is possible that this natural compound, could be used as a therapeutic agent in the treatment of Alzheimer's disease (Iuvone et al., 2006).

The sage extract demonstrated a strong cytotoxic activity on colorectal cancer (Pedro et al., 2010), human colon carcinoma Caco-2 cells, human prostate carcinoma LNCaP cells and human hepatoma HepG2 cells (Hadri et al. 2010), melanotic melanoma and renal adenocarcinoma cells (Loizzo et al., 2007). The action of *Salvia officinalis* extract to inhibit angiogenesis *in vivo* could be the basis for the development of a new anti-angiogenic drug (Keshavarz et al., 2011).

The sage aqueous extract has significant antibacterial activity against *Bacillus mycoides, Bacillus subtilis, Proteus* sp. and *Enterobacter cloacae* (Stanojevic et al., 2010). Sage essential oil has a good alternative to the traditional antibiotics as well as food preservatives (Rami et al., 2011). The hydroalcoholic extract of *Salvia officinalis* has also growth inhibitory effect on some dental caries causing bacteria such as *Streptococcus mutans, Actinomyces viscosus,* and *Lactobacillus rhamnosus*. Due to its bactericidal effect sage could be a natural remedy for the treatment of diseases affecting mouth and teeth (Kermanshah et al., 2009).

Sage has been used as a traditional remedy against diabetes, its glucose-lowering effects being demonstrated in animal studies (Christensen et al., 2010). *Salvia officinalis* has been also used to treat sweating and menopausal hot flashes, as well as to alleviate the associated menopausal symptoms (Bommer et al., 2011).

Extracts from some sage species have been shown to be effective in the prevention of cardiovascular disease due to, at least in part, prevention of LDL-cholesterol oxidation (Sa et al., 2009).

A study demonstrated the effect of *Salvia officinalis* extract in hyperactive gut disorders such as abdominal colic and diarrhea (Khan et al., 2011).

In a study made by Ninomiya et al. (2004), the sage extract showed inhibitory effect against the pancreatic lipase activity being effective in reducing body weight and obesity.

Bioactive compounds of *Melissa officinalis*

Melissa officinalis contain a wide range of bioactive compounds: hydroxycinnamic acid derivatives (e.g., rosmarinic acid, chlorogenic acid, caffeic acids, metrilic acid, and m-coumaric acid), flavonoids, (e.g., naringin, naringenin, hesperetin, hesperidin, luteolin 7-O-beta-D-glucopyranoside, luteolin 3-O-beta-D-glucuronopyranoside, luteolin, and apigenin 7-O-beta-D-glucopyranoside), tannins, monoterpene glycosides triterpenes, sesquiterpenes (e.g., germacrene and β-caryophyllene), and volatile oils (e.g., citronellal, citral a-geranial, citral b-neral, methyl citronellate, citronellol, geraniol, nerol, ocimene, linalool, β-caryophyllene, β-caryophyllene oxide, and ethric oil)(Heitz et al., 2000; Mikus et al., 2000; Mrlianová et al., 2002; Patora and Klimek, 2002; Patora et al., 2003; Ziakova et al., 2003; Dastmalchi et al., 2008).

The volatile oil represents 0.5-0.1% of the plant by weight, and citronellal, neral, and geranial constitute about 50-70% of this oil. Lemon balm tea contains 10 mg / L essential oil in which citral is 74% and large amounts of polyphenol compounds (Carnat et al., 1998).

The most important compounds of the lemon balm essential oil are citral, citronellal, linalool, geraniol and β-caryophyllene-oxide, but their composition in various climates is different being influencing by many parameters, such as temperature, light intensity, nutrient, plant part age, harvesting time (Shalaby et al., 1995; Moradkhani et al., 2010).

Pharmacological properties of lemon balm

Melissa officinalis has traditionally use for a variety of ailments: depression/anxiety, insomnia,

dyspepsia, bronchitis, asthma, menstrual problems, coughs, fever, hypertension, migraines, shock, gout, vertigo, eczema / skin problems, insect bites/stings, snake bites and skin infections (Mamedov and Craker. 2001; Duke, 2002). Some even believed the plant would remedy baldness (Duke, 2002).

Lemon balm is known as a calming herb. In animal studies, the hydroalcoholic extract showed sedative effects on the central nervous system (Blumenthal et al., 2000; Ulbricht et al., 2005). Lemon balm extract has resulted in a significant improvement in insomnia, irritability, headaches, and heart disease in mentally ill patients (Ulbricht et al., 2005).

Numerous studies have reported lemon balm essential oil's antibacterial and antifungal effects (Nascimento et al., 2000; Mimica-Dukic et al., 2004; Ulbricht et al., 2005; Hancianu et al., 2008). The methanol extract of *Melissa officinalis* showed *in vitro* effect against *Helicobacter pylori*, the bacterium that causes ulcers and other gastro-intestinal disorders (Mahady et al., 2005) and the hydro-alcoholic extract of lemon balm showed antibacterial activity against *Klebsiella pneumoniae*, *Staphylococcus aureus,* and *Salmonella choleraesuis* (Nascimento et al., 2000). The lemon balm essential oil has antibacterial effect against *Streptococcus hemolytica* and *Mycobacterium phlei* (Lavender and Franklin, 1996) and against some mold and yeasts, as well as microbes that cause fungal skin infections in humans and animals (Araujo et al., 2003; Mimica-Dukic et al., 2004).

Melissa officinalis has powerful antioxidant effects due to the rosmarinic acid and the benzodioxole present in the extract. The antioxidant effects of these compounds are up to ten times stronger than the effects of those of vitamins B and C. In this way, lemon balm extract can moderate the neurotoxic effects of chemical drugs (Dastmalchi et al., 2008; Ghayoor et al., 2010) and can prevent neurological diseases associated with oxidative stress (Pereira et al., 2009). Due to its ability to inhibit acetylcholinesterase and its antioxidant activity, lemon balm may be used in the prevention and treatment of Alzheimer's disease (Ferreira et al., 2006). Many other studies showed the antioxidant effects of *Melissa officinalis* (Lara et al., 2011; Spiridon et al., 2011; Dias et al., 2012; Martins et al., 2012; Luño et al., 2014; Benedec et al., 2015).

Lemon balm extract has also antiviral effects (Nolkemper et al., 2006; Sanchez-Medina et al., 2007; Mazzanti et al., 2008; Astani et al., 2012; Astani et al., 2014). Some studies have shown that lemon balm is effective against herpes simplex, HIV-1, influenza virus (Blumenthal et al., 2000; Duke, 2002; Ulbricht et al., 2005).

Melissa officinalis essential oil has significant metabolic effects *in vivo*, the terpenoids from its composition inducing hypolipidemic effects by inhibiting liver biosynthesis and formation of cholesterol nucleus in bile (Changizi-Ashtiyani et al., 2013). A study published in 2005 showed that an aqueous extract of dried *Melissa officinalis* leaves decreased serum cholesterol and lipid levels in Swiss albino rats and reduced elevation of enzymes that are markers for liver damage (Bolkent et al., 2005).

Lemon balm essential oil also has anti diabetic properties and improves glucose tolerance and adjusts the expression of the genes involved in hepatic gluconeogenesis. Studies by Chang et al. have shown that daily uptake of *Melissa officinalis* at low doses can cause hypoglycemia by increasing glucose uptake and its metabolism in the liver, as well as by gluconeogenesis inhibition (Chung et al., 2010).

The lemon balm essential oil is also antihistamine and antispasmodic (Leung and Foster, 2003), and has demonstrated their anti-inflammatory (Bounihi et al., 2013) and antitumor effects (de Sousa et al., 2004; de Carvalho et al., 2011; Yoo et al., 2011; Saraydin et al., 2012; Queiroz et al., 2014; Jahanban-Esfahlan et al., 2015; Weidner et al., 2015).

CONCLUSIONS

Salvia officinalis and *Melissa officinalis* are two valuable medicinal plants that have been used since a very long time ago in traditional medicine. Sage and lemon balm extracts have various biological activities such as antioxidant, antibacterial, antiviral, antifungal, antidiabetic, anti-inflammatory, sedative, spasmolytic, digestive and cytotoxic properties, being used for the treatment of a large variety of diseases of the nervous, respiratory, digestive, cardio-vascular and endocrine system. Given their important therapeutic effects, these plants can be used in the development of novel natural drugs to prevent, control, and treat many health problems.

ABSTRACT

Salvia officinalis (sage) and *Melissa officinalis* (lemon balm) are perennial plants that belongs to the *Lamiaceae* family. They are native to Middle East, Mediterranean areas and southern Europe, but today have been naturalized throughout the world. In traditional medicine, sage and lemon balm has use for a variety of ailments including depression, anxiety, insomnia, migraines, vertigo, dyspepsia, bronchitis, asthma, menstrual problems, coughs, fever, hypertension, hyperglycemia, ulcers, diarrhea, rheumatism, inflammation, gout, insect bites/stings, and skin infections. In recent years, due to the increased interest towards herbal-based treatments, many research studies have been conducted to document the traditional uses of *Salvia officinalis* and *Melissa officinalis* and to find new biological effects for these plants. Present review highlights the pharmacological properties of sage and

lemon balm (antioxidant, antibacterial, antiviral, antifungal, antidiabetic, anti-inflammatory, sedative, spasmolytic, digestive and cytotoxic effects) and present the bioactive compounds responsible for the therapeutic effects of these plants.

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