Lamiaceae phenols as multifaceted compounds: bioactivity, industrial prospects and role of "positive-stress"

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ABSTRACT

There is a tremendous growing interest both in various industrial sectors and among people worldwide, towards the use of natural compounds from plant origin. The natural compounds obtained from plants have been more and more employed by cosmetic, food and pharmaceutical industries and could represent potential alternatives to synthetic chemicals. In the *Lamiaceae* family there are herbs with enormous socio-economic value, including several species of horticultural and ornamental interest, many used as culinary herbs, and with diversified industrial applications essentially due to their high content in valuable phenolic compounds.

Here, we focus on the wide spectrum of bioactive phenolic compounds in several species in the *Lamiaceae*, which possess known pharmacological properties and are used by humans for therapeutic purposes. We report also other challenging and innovative industrial applications of these compounds as potential alternatives to conventional synthetic chemicals, because natural phenols would have lesser environmental and human health impacts than most of the conventional ingredients used in cosmetic, pesticides and food additives-preservatives industries. Finally, we discuss how an enhanced understanding of the effects of elicitation could be applied to increase and/or modify tissue content of active principles. Chemical or physical elicitors can activate the stress-signaling pathways leading to

enhance the content of bioactive secondary metabolites, thus representing a new perspective for sustainable production of industrial crops.

Highlights

- Phenols are largely used by cosmetic, food, pesticide and pharmaceutical industry
- *Lamiaceae* species are sources of bioactive compounds with multifaceted biological activities
- Phenols from *Lamiaceae* species can be stimulated by eustress ("positive stress").
- Eustress in *Lamiaceae* could represent an effective means for safe antioxidants production.

KEYWORDS: Bioactive compounds, Elicitation, *Labiatae*, Industrial applications, Rosmarinic acid, UV-B, Methyl Jasmonate, Jasmonic Acid, Ozone.

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1. Introduction

Under the constant evolutionary pressure, plants have to deal with the biotic adversities and the sudden weather changes by using their chemical arsenal of secondary metabolites. During evolution, secondary metabolites such as phenols, alkaloids and terpenoids, have been implicated in the successful terrestrial colonization by plants, exhibiting diverse functional roles that are important for plant survival and reproductive fitness. Notably, these compounds act as defense against herbivores, microbes, viruses or competing plants, as a protective layer against solar radiation and as signal compounds to attract pollinating or seed dispersing animals. Plant phenolics merit a special remark among the massive spectra of secondary metabolites, considering their miscellaneous bio-physicochemical properties intrinsically linked to the phenolic functional group (Karabourniotis et al., 2014).

The *Lamiaceae* (formerly *Labiateae*) are a cosmopolitan family with 7136 species in 236 genera. It is the largest family of the order *Lamiales*, and includes Genera with 250 species or even more, such as *Salvia* (959), *Hyptis* (292), *Clorodendrum* (327), *Thymus* (318), *Scutellaria* (461), *Plectratus* (406), *Stachys* (374) and *Nepet*a (252) (The Plant List, 2013). Most species are shrubby or herbaceous and trees are extremely rare (Heywood, 1978). The *Lamiaceae* family has great economic value, as it contains several horticultural species, most of which are used as culinary herbs. *Lamiaceae* species are known to contain pharmacologically active compounds (Venkateshappa and Sreenath, 2013), which have been also exploited by cosmetic, food and pesticides industries (Lee et al., 2011; Kostic-Nikolic et al., 2013; Ramos et al., 2012; Khaled-Khodja et al., 2014). The increasing trend of a global demand in natural plant-derived products has been confirmed by market studies (Bart and Pilz, 2011). Thus, industrial sectors are progressively addressing toward plant-based products as alternatives to products obtained from synthetic chemicals, which could be harmful to both health and environment.

2. Phenolic profile

Generally speaking, the terms phenols and polyphenols could be used to define a major group plant secondary metabolites; they mainly derive from the shikimate and/or the polyketide pathway(s), featuring one or more than one phenolic ring, respectively (Lattanzio et al., 2006). A phenolic function constitutes an amphiphilic moiety with its hydrophobic aromatic nucleus and hydrophilic hydroxy substituent, which can act either as a hydrogen-bond donor or acceptor. Being redox-active compounds, plant phenols can also act either as antioxidant or as pro-oxidant (Quideau et al., 2011). The antioxidant activity of phenolics depends on many factors, such as the number of hydroxyl groups bonded to the aromatic ring, their mutual position and the binding site on the ring (Rice-Evans et al., 1996).

Thus, it is not surprising that plant polyphenols have long been regarded as a pool of bioactive natural products with potential benefits for human health and care. Rosmarinic acid is one of the most abundant phenolic compounds contained in the tissues of several plant species belonging to the *Lamiaceae* (Table 1). During the last decade, about 200 papers concerning rosmarinic acid in this plant family were indexed in Scopus (Elsevier, 2015). This secondary metabolite is a caffeic acid derivative, which is synthesized from the amino acids L-phenyalanine and L-tyrosine via the phenylpropanoid pathway coupled to a tyrosine-derived pathway (Dewanjee et al., 2014). The synthesis and accumulation of this substance are primarily determined by the plant genotype, but they are also strongly influenced by physiological or environmental factors, such as phoenological stage, climate, growing technique, stress conditions (Juliani et al., 2008; Maggini et al., 2014; Kiferle et al., 2011; Kiferle et al., 2013).

Throughout the *Lamiaceae*, high levels of rosmarinic acid are commonly found only within the subfamily *Nepetoideae* (Petersen and Simmonds, 2003). For example, in plants of the genus *Stachys*, which belongs to the subfamily *Lamioideae* (Salmaki et al., 2012), rosmarinic acid was found at concentration close or below the detection limits or was not detected at all (Askun et al., 2013). In addition to rosmarinic acid, several species in the *Lamiaceae* can accumulate large amounts of different phenolic compounds, such as phenolic acids, flavonoids, or phenolic terpenes (Table 2). Some phenolic compounds are present only in *Lamiaceae*, such as carnosic acid, which contribute to the protection of the chloroplast from oxidative damage and displays high antioxidant properties *in vitro* (Birtić et al. 2015). Another exclusive phenolic compound in the *Lamiaceae* is clerodendranoic acid, which was found in *Clerodendranthus spicatus* (Zheng et al., 2012). On the other hand, a lot of bioactive compounds are not unique to the *Lamiaceae* family. For example, *Majorana hortensis* L. contains large concentrations of arbutin (Table 2), which is also present at even higher levels in plants in the *Ericaceae*, *Saxifragaceae* and *Rosaceae* (Rychlińska and Nowak, 2012).

Flavonoids are a widespread class of phenolics having several beneficial effects on human health, and include apigenin and naringenin (Stacks, 2015), luteolin (Lopez-Lazaro, 2009), hesperidin (Lee et al., 2010) and rutin (Chua, 2013). Health benefits have been ascribed also to phenolic acids like chlorogenic acid (Upadhyay and Rao, 2013; Ong et al., 2013), gentisic acid (Khadem and Marles, 2010) and caffeic acid (Duzzo Gamaro et al., 2011). A number of molecules of proven biological activity were found in the *Lamiaceae* as minor constituents; one example is chicoric acid. Although this metabolite is present in a lot of distinct families and species, it was detected also in several basil cultivars at concentrations below 0.3% dry weight (Lee and Scagel, 2013).

3. Biological activities

3.1 Antioxidant activity

All phenolic compounds share a significant antioxidant activity (Table 3). Wojdylo et al. (2007) reported a strong positive correlation between the total phenolics content and the antioxidant activity of *Lamiaceae* plants extracts. In general, antioxidants protect plant cells from damage caused by free radicals, which are developed with the normal cellular metabolism or are due to stressful events, such as excessive UV or visible radiation, exposure to soil or air pollutants, diseases. The antioxidant properties of phenolic compounds can be involved in the following mechanisms: i. scavenging Reactive Oxygen Species and Reactive Nitrogen Specie (ROS/RNS); ii. suppressing ROS/RNS formation by inhibiting some enzymes or chelating trace metals involved in free radical production; iii. up-regulating or protecting the plant antioxidant defense systems (Spaak et al. 2008).

In vitro experiments proved that phenolics are more potent antioxidants than vitamin C, E and carotenoids (Rice-Evans et al., 1996). *In vivo* studies suggested that the normal uptake of phenolics with the dietis failed to provide beneficial effects unless they were used as food additives, shifting the focus from dietary consumption to pharmacological treatment (Chiva-Blancha and Visioli, 2012). The processes of lipid peroxidation, causing damage to fatty acids, tend to decrease membrane fluidity and lead to many other pathological events (Spiteller, 2001). These processes could be reduced by plant phenolics, which are known to be scavengers of various oxygen species (Morton et al., 2000; Gülçin, 2006). Several human, animal orcell studies have suggested that polyphenols may exert beneficial effects on the vascular system via an induction of antioxidant defenses. Vauzour et al.(2010) suggested a mechanism for the action of polyphenols on the vascular function that involves their ability to modulate the levels and activity of nitric oxide synthase (eNOS) and therefore the bioavailability of nitric oxide (NO) to the endothelium. Polyphenols have been shown to protect also neurons against oxidative stress and may act to protect the brain in a number of ways. Regular dietary intake of flavonoids has been associated with the reduction of dementia (Commenges et al., 2000), the preservation of cognitive performance with ageing (Letenneur et al., 2007) and the delay in the onset of Alzheimer’s (Dai et al., 2006) and Parkinson’s (Checkoway et al., 2002) diseases. Thus, polyphenols are likely candidates for direct neuroprotective and neuromodulatory actions, and were demonstrated to be able to permeate across the Blood Brain Barrier BBB (Youdim et al. 2004). A large number of species belonging to the genus *Calamintha*, *Lavandula*, *Mentha*, *Melissa*, *Origanum*, *Rosmarinus*, *Salvia*, *Teucrium* or *Thymus* have traditionally been used for various nervous system disorders due to the presence of polyphenols, particularly rosmarinic acid. Vladimir-Knežević et al. (2014) tested 25 extracts from *Lamiaceae* plants, which all demonstrated moderate to strong antioxidant activities associated with high levels of rosmarinic acid and hydroxycinnamic derivatives.

3.2 Anticancer activity

Generally, phenols protect cells showing an impact on the initial step of cancer development. Scientific results explain the classical epidemiological evidence that there is a correlation between the consumption of fresh vegetables and reduced incidence of some cancers (skin, lung, stomach, esophagus, duodenum, pancreas, liver, breast or colon) (Crowe et al., 2011). In contrast, different epidemiological studies have provided evidence for no or little relationship between fruit and vegetable intake and overall cancer risk (Benetou et al., 2008; Boffetta et al., 2010). Despite this degree of controversy, specific polyphenols may exert protective effects against cancer development (Table 3), particularly in the gastrointestinal tract (Martinez, 2005; Li, 2009).

Polyphenols may exert anticancer effects via a variety of mechanisms, including the modulation of the activity of the mitogen-activated protein kinases (MAPK) and the PI3 Kinase signaling pathway (Ramos, 2008), which are involved in cancer cells proliferation (Wang et al., 2010). Several phenolic acids affect the expression and activity of enzymes (i.e. cyclo-oxygenase 2) involved in the production of inflammatory mediators, which could favor the development of gut disorders like colon cancer (Tsatsanis et al., 2006; Russell and Duthie, 2011). A variety of phenolics, including caffeic and rosmarinic acids, may exert anticancer properties by epigenetic regulation of gene expression (Link et al., 2010). The modulatory roles of these compounds on DNA methylation or histone modifications were associated with silencing or re-expressing genes specifically involved in carcinogenesis.

Plant phenolic extracts or isolated polyphenols were studied using a number of cancer cell lines representing different evolutionary stages of cancer. Evidence that hydroxycinnamic acids, mainly caffeic acid and chlorogenic acid, may have a potential inhibitory effect on cancer invasion and metastasis has been widely reported reported in the scientific literature (Weng and Yen, 2012). The effects of these phenolic acids are manifest on cellular differentiation, proliferation, or apoptosis (Dalbem Rocha et al., 2013). In addition to the anti-proliferative potential of these compounds, the pro-apoptotic activities in several cancer cell lines or animal tumor models have widely known beneficial effects. In fact, cancer cells are characterized by high levels of ROS and hydroxycinnamic acid derivatives could act as pro-oxidants, further increasing ROS production and hence killing the cancer cells (Fan et al., 2009; Esteves et al., 2008). An example of pro-apoptotic behavior was showed by *Majorana hortensis* extracts on human breast cancer cells, where rosmarinic acid exhibited a strong cytotoxic activity (Berdowska et al., 2013).

3.3 Antiatherogenic activity and prevention of metabolic disorders

It has been widely reported that the oxidation of lipids and in particular of LDL is the cause of the development of atherosclerosis and its related diseases such as stroke, thrombosis and cardiovascular disorders. Although phenols act mainly as radical scavengers, they are also able to reduce the clotting of platelets and LDL (Table 3). The extract of *Ocimum canum* (Nyarko et al., 2003) was used in the management of diabetes mellitus through a fast decrease of blood glucose levels in experimental animals. A significant reduction in body weight and lipid accumulation was achieved also using rosemary extracts enriched with carnosic acid; this combination reduced the effects of oxidative stress and prevented cardiovascular complications by counteracting imbalances in lipid metabolism (Vaquero et al, 2012). The beneficial effects of these extracts may be due, at least, by a significant inhibition of gastric lipase and subsequent reduction in fat absorption. Recent evidence has confirmed the potential of rosemary (*Rosmarinus officinalis* L.) for the treatment of both obesity and diabetes mellitus in animal models. The activity of rosemary is mainly due to carnosic acid, carnosol, and rosmarinic acid which exert anti-hyperlipidemic and anti-hyperglycaemic effects (Sedighi et al, 2015) by limiting body fat weight, and improve glucose homeostasis. Further studies are needed to better understand the mechanisms of the protective effects of phenols, as the data available at present concern mainly *in vitro* or animal models, and need to be confirmed in humans. In contrast with medicines, food components like poliphenols have generally a low impact on human physiology. Nevertheless, food macro- and micro-components are ingested throughout the lifetime, so their effect might become important in the long term.

3.4 Antimicrobial activities

Among phenolics, the volatile compounds, which constitute essential oils, are generally major active ingredients against bacterial infections (Table 3). In most *Lamiaceae* herbs, carvacrol (in oregano and rosemary), thymol (in thyme *Thymus vulgaris* L.) and eugenol (in clove *Syzygium;* Shan et al., 2005) are the main essential oil constituents (Bassolè and Juliani, 2012; Kulisic et al., 2004). In the case of carvacrol, the presence of one hydroxyl group and its relative position in the phenolic ring enable antimicrobial activity and can explain its high antimicrobial feature compared to other plant essential oil components(Velasco, and Williams, 2011; Dorman and Deans, 2000). The molecular structure and position of functional groups are responsible for the strong ability of essential oils to dissolve and accumulate in cell membranes causing their destabilization. Essential oils interact with processes associated with the phospholipid bilayer, including electron transport, ion gradients, protein translocation, phosphorylation, and other enzyme-dependent reactions (Dorman and Deans, 2000), affecting the permeability of bacterial membranes (Lambert et al., 2001). In a similar way, the presence of phenolic acids in the gut could inhibit the growth of several pathogenic intestinal bacteria. In particular, it was observed that dihydroxylated forms of phenols could efficiently destabilize the outer membrane of Salmonella.

Analogous properties of phenolic constituents of essential oils in *Lamiaceae* family are confirmed also against fungal infections (Zabkaet al., 2014). Essential oils from oregano and thyme are the best potent inhibitors of fungal pathogens, because of the presence of carvacrol and thymol as main constituents which might disrupt the fungal cell membrane. Antifungal properties of these compounds were attributed to their ability to block ATP and ergosterol synthesis (Zabka et al., 2014). The antiviral activity of essential oils was tested against many enveloped RNA and DNA viruses, such as herpes simplex virus type 1 and type 2 (DNA viruses), dengue virus type 2 (RNA virus), and influenza virus (RNA virus). Essential oils extracted from oregano were also tested against non-enveloped RNA and DNA viruses, such as adenovirus type 3 (DNA virus), poliovirus (RNA virus), and coxsackievirus B1 (RNA virus) (Aktharet et al., 2014). It has been reported that flavonoids, essential oils, different derivatives of caffeic acid and tannins can block viral surface ligands or host cell receptors and inactivate HSV (Ansari, 2014). In particular, anti-HIV-1 effects were ascribed to rosmarinic acid contained in *Teucrium polium* L., *Ziziphorac linopoides* Lam. or *Salvia rhytidea* Benth from *Lamiaceae* family (Swarup et al., 2007; Osakabe et al., 2004).

It should be noted that some essential oils are potentially toxic. Phenolic constituents such as carvacrol and thymol exerted weak mutagenic effects on bacteria according to the Ames test, and eugenol resulted genotoxic by inducing chromosomal aberration and endoreduplications in lung V79 cells (Bakkali et al., 2008). Moreover, eugenol and isoeugenol may cause allergic reactions (Shaaban et al., 2012). Therefore, essential oils containing these components should be handled carefully to avoid any adverse effects.

3.5 Bioavailability

Quantifying bioavailability means to define the fraction of an ingested compound that reaches the systemic circulation and the specific sites where it can exert its biological action (Porrini and Riso, 2008). The compounds that reach our cells and tissues are chemically and biologically different from their original form taken from diet. The increase of phenolics concentration in blood is transitional and reflects the uptake of the compounds from the food matrix. Therefore, this increase can have only a minor effect on the bioactivity of phenolics. On the contrary, only a regular and constant intake, even in low amounts, can significantly increase the concentrations both at plasma and cellular level (Scalbert and Williamson, 2000). On the basis of scientific literature, the relative bioavailability of some hydroxycinnamic acids is chlorogenic<caffeic<ferulic<*p*-coumaric (Zhao and Moghadasian, 2010). Most of the studies on phenolics bioavailability (Chiva-Blanch and Visioli, 2012) have focused on their absorption in the small intestine. It has been estimated that at most only one tenth of the total phenolics intake is absorbed in the small intestine; the main part is metabolized by the colon microbiota, then it can be either reabsorbed (Crozier et al., 2009; Selma et al., 2009) or eliminated (Monagas et al., 2010). It has been reported that in the colon, 3-hydroxyphenylpropionic (9–24% of the initial dose) and benzoic acids were the main microbial metabolites of caffeic acid and of its esters chlorogenic acid and caftaric acid (Williamson and Clifford, 2010). In the small intestine, and mostly in the liver, the simple aglycones derived from phenols undergo further structural modifications by various conjugation processes, including methylation, sulfation and glucuronidation, which facilitate their biliary and urinary discharge (Day et al. 2000).

4. Non-culinary uses of *Lamiaceae*

Many species in the *Lamiaceae* family have recently showed potential pioneering use in pharmaceutical, food, pesticide and cosmetic industries, due to the remarkably diverse range of properties of their phenolic constituents, that makes them unique and promising natural products (Table 4). Moreover, in a context where consumers demand safe natural products because synthetic chemical are perceived as potentially toxic, the exploration of naturally occurring ingredients from plants has received great interest from research and industry, due to the potential to provide quality and safety benefits, with a reduced impact on human health and on environment (Lucera et al., 2012).

4.1 Cosmetic industry

The field of skin care products and cosmetics shows a marked interest in the natural cosmetic segment. The skin is extensively exposed to stressful environmental factors such as pollutants and UV radiation, which produce a large number of aggressive oxidants that damage cell membranes (Binic et al., 2013). Therefore, the selection of protective substances among natural compounds is a good method for developing skin-care agents. Rosmarinic acid has been proposed to act both as a photo-protective agent against UV, being a free radical scavenger, and as an endogenous trigger of body's defence mechanisms, by regulating tyrosinase activity and stimulating melanin production (Sánchez-Campillo et al., 2009; Lee et al., 2011). In a recent study, the extracts of *Rosmarinus* species have been suggested to contain an anti-acne ingredient for cosmetics (Lee et al, 2011) because they possess strong anti-inflammatory and anti-*Staphylococcus aureus* activities. Additionally, this genus exhibited high UVA and UVB adsorption ability, which made it a good natural source to develop experimental sun blocks. Furthermore, *R. officinalis* L. extracts have been reported to have good antielastase activity (Baylac and Racine, 2004). *Lamiaceae* extracts have displayed also depigmentation properties through various mechanisms. For example deoxyarbutin, a natural derivative of hydroquinone and naturally present in *Origanum majorana* L. leaves, acts as a potent inhibitor of tyrosinase (Boissy et al., 2005) contributing to a skin-lightening effect *in vivo*. On the other hand, origanoside from *O. vulgare* inhibits melanin synthesis by reducing the activity of cellular DOPA (dihydroxyphenyl-alanine oxidase) through the down-regulation of two transcription factors (Zhu and Gao, 2008) linked to skin pigmentation disorders.

4.2 Additives and preservatives for food industry

There is a growing interest in the food industry area to replace synthetic antioxidants and additives, such as butylated hydroxytoluene (BHT) and butylated hydroxyanisole (BHA), which are strongly suspected to have carginogenic and toxic effects on humans (Göktürk Baydar et al., 2007). The results of two recent studies performed on six different species, all belonging to *Lamiaceae* family (i.e. *Micromeria myrtifolia*, *Calamintha origanifolia*, *Ajuga iva*, *Marrubium vulgare*, *Mentha pulegium* and *Teucrium polium*) demonstrate that these plant species could be considered potential alternatives to synthetic food additives for their antioxidant properties (Formisano et al., 2014; Khaled-Khodja et al., 2014). All the extracts of these plants exhibit also anti-microbial properties, and are perceived by consumers as low health risk antimicrobial agents compared with the synthetic ones (Anwar-Mohamed and El-Kadi, 2007).The use of natural antibacterial compounds extracted from species in the *Lamiaceae*, such as thyme, rosemary, oregano and marjoram is reported in the literature to improve the shelf life of meat- and fish-based products (Mastromatteo et al., Uçak et al., 2011; Busatta et al., 2007; Busatta et al., 2008).

Antimicrobial packaging technology is a novel approach of food active packaging, where the environment interacts with the product to extend its shelf life and reduce at the same time the growth rate of microorganisms. Ramos et al. (2012) reported that the antimicrobial active film prepared by incorporating thymol and carvacrol in polypropylene, increased the stabilization against thermo-oxidative degradation and showed a potent inhibition of bacterial growth. The use of antimicrobial cellulose-based packaging films incorporated with cinnamaldehyde and eugenol was effective to inhibit a wide spectrum of food pathogenic and spoilage microorganisms (Sanla-Ead et al., 2012). The use of edible films enriched with natural bioactive compounds, important for both functional and antimicrobial properties, could represent an "appetizing" novelty for food industry, which could allow increasing at the same time the shelf-life and the nutraceutical value of the food products.

4.3 Pesticides industry

Many plants produce biologically active secondary metabolites as part of their constitutive defensive arsenal that could be used as insecticides and fungicides. The use of natural products as biopesticides can be a valid alternative to replace existing synthetic products that are considered toxic for human health and environment. Besides, the risk of developing resistance in pathogens and the high cost–benefit ratio of synthetic pesticides has forced industry towards alternative investigations (Miresmailli and Isman, 2014).

The most cited family having insecticidal and fungicidal activity, as reported by Boulogne et al. (2012) is the *Lamiaceae* and the most important genera are: *Teucrium*, *Pycnanthemum*, *Thymus*, *Satureja*, *Origanum*, *Micromeria*, *Mentha*, *Monarda,* and *Ocimum*. Within these genera, carvacrol, thymol and eugenol are the main bioactive phenolic compounds, which were proved to be very effective and suitable for the development of botanical pesticides. A potent antifungal efficacy of thymol and eugenol against *Fusarium*, *Aspergillus* and *Penicillium* was reported by Zabka et al. (2014). The antifungal and antiaflatoxigenic properties of *Thymus vulgaris* essential oil were evaluated upon *Aspergillus flavus in vitro*, as thymol was capable of controlling the growth of *A. flavus* and its aflatoxins production. The fungicide effect was expressed at a thymol concentration of 250 mg/mL, while the production of both B1 and B2 aflatoxins was completely inhibited at a concentration of 150 mg/mL (Kohiyama, 2015).

Origanum oil, rich in carvacrol and thymol, was tested against phytonematodes and exhibited nematicidal activity, being effective to control these difficult to eradicate crop pests due to limited availability of chemical nematicides (Ntalli et al., 2010). By-products from the hydrodistillation of *Rosmarinus officinalis* could represent an affordable and valuable source of natural crop protectants. In fact the solid residues are known to still contain rosmarinic acid, carnosol, rosmanol, carnosic acid (Navarrete et al., 2011). Santana-Méridas et al. (2014) reported in rosemary by-products, a strong antifeedant activity against *Leptinotarsa decemlineata*, *Spodettera littoralis* and *Myzus persicae* along with limited phytotoxic effects on lettuce and tomato plants. A striking application for botanical pesticides is the use of nanotechnological carrier systems that may enhance the target specificity, optimizing the action of bioactive compounds and minimizing adverse environmental impacts (Oliveira et al., 2014). For example, the antimicrobial nanoclay film containing thymol can be easily dispersed and the amount of active ingredient used can be minimized (Lim et al., 2010; Wattanasatcha et al., 2012), thus this product could be exploited to control *Varroa destructor*, which infests honeybee colonies (Glenn et al., 2010).

4.4 Pharmaceutical industry

Investigation on plant phenols concerns different pharmacological applications, due to the mutual behavior-role of these substances. Phenolics act as antioxidants that are capable of quenching toxic free radicals, inhibiting the oxidative damage process and, at the same time, they are capable to generate toxic quinonoid species and to act as pro-oxidants under certain conditions (Quideau et al., 2011). In particular, phenols as novel anticancer agents represent a very promising research area for developing new drugs. A clinical trial demonstrated that rosmarinic acid could contribute to the treatment of allergies and asthma by its free radical scavenging action and the suppression of both allergic immunoglobulin production and inflammatory responses by polymorphonuclear leukocytes (Stansbury, 2014). Moreover, phenol compounds might be employed in the development of novel therapeutic agents against fungal and bacterial diseases facing the development of resistance by pathogenic microorganisms. Pinto et al. (2013) recently found that the treatment of dermatomycosis and common fungal infections, such as *Candida* and *Aspergillus*, were effectively controlled using topical applications of essential oils of *Thymus villosus* subsp. *Lusitanicus*. The essential oils of other species of thyme could also represent an interesting alternative to synthetic drugs, and may be used in combination with conventional antibiotics against multidrug-resistant bacteria (Nabavia et al., 2015). Moreover, with the globalization we assist to the resurgence of tuberculosis and the extracts of *Thymus sipthorpii* and *Satureja aintabensis* with high levels of rosmarinic acid, were effective against *Mycobacterium tuberculosis*, representing a natural anti-tuberculosis agent (Askun et al., 2013).

5. Elicitation to increase phenols production

Secondary metabolites biosynthesis in plants depends on environmental stresses and the accumulation of these substances can be stimulated by elicitors (Baenas et al., 2014). Elicitors are biological, chemical or physical agents that switch on both the enzymatic activity against stress and the signaling pathways that potentially and realistically lead to an enhanced concentration of valuable phytochemicals. In fact, by the application of an eustress ("positive stress") and the induction of a stress response, the plants can be actively and suitably stimulated to produce the desired chemicals, providing a beneficial outcome for industrial purpose (Wargent and Jordan, 2013; Gorelick and Bernstein, 2014).Plants need to grow and must also defend and protect themselves from adverse environmental conditions, facing the dilemma "growth *versus* defense" reviewed recently by Karabourniotis et al. (2014). The primary metabolism is linked to biomass accumulation while the secondary metabolism is linked to defence and involves the slowdown or interruption of growth (Lucchesini and Mensuali, 2010). Considering the growth and the secondary metabolite biosynthesis as a two-stage-specific strategy (Murthy et al., 2014), elicitation could be introduced in the plant cultivation protocols: in the first stage the plants could be grown under optimal conditions, then the synthesis of secondary metabolites could be stimulated by the application of an eustress, to enhance the production of the desired phytochemicals.

For this reason we report on recent attempts regarding *Lamiaceae* elicitation by chemical elicitors such as jasmonic acid (JA) and its methyl ester, methyl jasmonate (MeJA), or by the physical elicitors UV-B and ozone (O_3). We selected these elicitors because they demonstrated to have an immediate effect to enhance the production of phenols even with short term treatments, whitout affecting the biomass production. Additional advantages of these elicitors can be ascribed to their easy use and the simple equipment necessary for growing the plants in greenhouses or in growth-chambers for industrial production.

5.1 Chemical elicitation of phenols

Both JA and MeJA are important signaling compounds in the process of elicitation leading to the hyperproduction of various secondary metabolites**.** The jasmonates can be applied to plants using different methods, for example as a gas in an enclosed environment, or dissolved in a nutrient solution to be used in hydroponic growing system, or simply dissolved in a solution and sprayed on the plant (Rohwer and Erwin, 2008). These compounds effectively strongly affected the phenolic biosynthesis in different plant tissues and under various growing conditions (Table 5). *Coleus forskohlii* hairy root culture elicited with 0.1 mM MeJA exhibited a strong increase (3.4 fold) of rosmarinic acid (Li et al., 2005). The concentration of 0.1 mM MeJA also enhanced the level of rosmarinic acid in *Coleus blumei* but only by 21% (Bauer et al., 2009). In cell suspensions of *Agastache rugosa* the application of 50 mM MeJA determined a significant enhancement (4.7-fold) of rosmarinic acid. Also the genes directly involved in the biosynthesis of rosmarinic acid were upregulated after MeJA treatment, suggesting a positive correlation between transcription and metabolites production in the phenylpropanoid pathways (Kim et al., 2013). Many experiments have been carried out on *Salvia miltiorrhiza* to elicit the production of secondary metabolites. Xiao et al. (2009) tested 0.1 mM MeJA on hairy root culture and found that the treatment enhanced the accumulation of phenolic acids like rosmarinic acid (1.9-fold) and lithospermic acid B (6.6-fold). The transcriptional machinery involved in the biosynthesis of rosmarinic acid was also coordinately induced, with the genes encoding ammonia-lyase, cinnamic acid 4-hydroxylase, tyrosine aminotransferase, 4-hydroxyphenylpyruvate reductase and 4-hydroxyphenylpyruvate dioxygenase displaying a rapid increase. In another study *Salvia miltiorrhiza* roots elicited with 0.2 mM MeJA showed increased levels of salvianolic acid to 79.3%, caffeic acid to 14.9%, rosmarinic acid to 59.5% (Wang et al., 2012).

Regarding cells suspensions cultures, Szabo et al. (1999) and Krzyzanowska et al. (2012) tested the elicitation of rosmarinic acid with 100 µM of MeJA on *Coleus blumei* and *Mentha x piperita*, respectively. In *Coleus blumei* MeJA stimulated rosmarinic acid accumulation (33%) when applied as a gas and not when added directly to the culture medium. In *Mentha x piperita* the highest rosmarinic acid accumulation (117.95 mg g-1 DW, that is 12% DW) was reported promptly after 24 h after MeJA treatment, however the cellular material showed a decrease in biomass accumulation. In cell suspension cultures of *Lavandula vera*, exposure to 50 µM MeJA increased the level of bioactive rosmarinic acid about 2.5 fold (Georgiev et al., 2007).

The effect of a high concentration of MeJA (0.5mM) on the production of secondary metabolites was reported for *Ocimum basilicum* (Kim et al., 2006; Li et al., 2007). Rosmarinic acid, eugenol and caffeic acid levels were increased by about 50%, 55% and 300% respectively (Kim et al., 2006). Moreover, the antioxidant activity of basil extract after treatment was 2.3 fold enhanced. In order to understand the signaling effect of MeJA on sweet basil, Li et al. (2007) used suppression subtractive hybridization library (SSH) to identify the MeJA up-regulated genes. Among the 576 cDNA clones screened from the forward SSH cDNA library, 28 were found to be up-regulated by the MeJA treatment. Sequencing of these cDNA clones revealed six transcripts displaying high similarities to the known enzymes and peptides: lipoxygenase (LOX), cinnamic acid 4-hydroxylase (C4H), prephenate dehydrogenase (PDH), polyphenol oxidase (PPO), acid phosphatase (APase), and pentatricopeptide repeat (PPR), all of which play an important role in the synthesis of secondary metabolites in sweet basil. The same dose of MeJA (0.5 mM) was used in combination with 1.0 mM spermine in *Ocimum basilicum* grown in hydroponic system and the rosmarinic acid concentration increased about 40% compared to the control (Koca and Karaman, 2015).

In *Salvia miltiorrhiza*, two genes involved in the rosmarinic acid biosynthesis pathway, cinnamate 4-hydroxylase (SmC4H) and tyrosine aminotransferase (SmTAT) where up-regulated by MeJA and further expression analysis revealed that the transcript levels of these genes were enhanced by other signaling components of defense/stress pathways, such as ABA, SA and UV-B (Huang et al., 2008a;

2008b). JA was also an effective elicitor to increase the secondary metabolites production in suspension cultures of *Lavandula officinalis* (Stehfest et al., 2004).

5.2 Physical elicitation of phenols

UV-B radiation (wavelength range 280–320 nm), has been proved an effective elicitor for the biosynthesis of phenolic metabolites in *Lamiaceae* species (Table 6). Naturally, the accumulation of the UV-B absorbing pigments such as phenols alleviates the harmful effects of UV-B light on plants. Peppermint plants (*Menthapiperita* L.) exposed to 7.1 kJm^{-2} day^{-1} UV-B exhibited an enhancement of phenolic compounds such as eriocitrin, hesperidin and kaempferol 7-O-rutinoside (Dolzhenko et al., 2010).

Irradiation of UV-B on basil (*Ocimum basilicum*) tissues led to a strong increase of phenylpropanoids (eugenol and methyl eugenol) as well as terpenoids (Bertoli et al., 2013; Bertoiget al., 2013) and the induction of these secondary metabolites was found to be higher in the older leaves (Johnson et al., 1999). Sakalauskaite et al. (2012) studied the effect on total phenolic compounds in sweet basil cv. Thai using different doses of UV-B. The plants after one week of 2 kJ m^{-2} day^{-1} or 4 kJ m^{-2} day^{-1} UV-B doses showed a significant increase in total phenols. In *Nepeta cataria* L., *Melissa officinalis* L. and *Salvia officinalis* L., UV-B induction of polyphenols accumulation was most effective using low-dose irradiation (1 kJ m^{-2} d^{-1}) under controlled greenhouse cultivation (Manukyan et al., 2013). Rosmarinic and carnosic acids in *Rosmarinus officinalis* L. plants after 14 days of UV-B exposure were induced by both dosages (5.4 and 31 kJ m^{-2} d^{-1}), but the most effective was the highest dose which provided2.3- and 1.8-fold increase, respectively(Luis et al., 2007). In a controlled environmental condition, exposure of basil plants to UV-B over a period of two weeks for 3 h or 1h stimulated the synthesis of eugenol (Xianmin et al., 2009; Ioannidis et al., 2002).UV-B can promote the production of chrysin in *Scutellaria baicalensis* L. (Tang et al., 2014). This compound was not detected in the control, but the use of different UV-B light intensities (12.1 μW/cm or 34.5 μW/cm) activated its biosynthesis.

Ozone is well-known as a tropospheric pollutant, having a strong oxidative potential that causes negative effects on plant metabolism, physiology and growth. Pellegrini et al. (2013) reported that a single O_3 exposure (200 ppb, 5 h) determined the activation of programmed cell death (PCD) in *Melissa officinalis*, which resembles the hypersensitive response and a realistic ozone concentration showed a marked activation of photoprotective mechanisms (Döring et al., 2014). In fact, ozone fumigation of *M. officinalis* shoot cultures can mediate the stimulation of secondary metabolites involved in plant-pathogen interactions, as Tonelli et al. (2015) recently reported. At the base of this type of elicitation there are the activation of the enzymes involved in phenolic metabolism, the development of cellular barriers involving polymerization of cinnamyl alcohols and the increase of antioxidant capacity. In ozone-treated *M. officinalis* a positive correlation was found among the enzymatic activities of PAL (phenylalanine ammonia-lyase), the first enzyme in the formation of phenolic compounds, and RAS (rosmarinic acid synthase), the specific enzyme leading to rosmarinic acid synthesis, and the transcript levels of genes encoding enzymes involved in phenylpropanoid and rosmarinic acid pathways (Döring et al., 2013). Thus, the fumigation of medicinal plants containing phenolic ingredients with important pharmaceutical properties deserves attention.

6. Conclusions

Secondary metabolites are present in all higher plants, usually in a high structural diversity. A large number of plant species belonging to the *Lamiaceae* family are a source of a wide variety of phenolic compounds, such as phenolic acids, flavonoids or phenolic terpenes. These compounds are widely recognized to be pharmacologically active and recently have been exploited in other important sectors like cosmetic, food and pesticide industries. They are promising ingredients to develop novel products due to their biological activity and their environmental friendly sustainability.

The compounds of botanical origin are perceived by consumers as low health risk substances and recently we assist to a tremendous growing interest in the substitution of synthetic compounds by natural ones. One of the most effective environmental friendly approaches employs compounds of botanical origin as pesticides for different species, taking advantage of biodiversity to develop a simple and sustainable strategy for pest management.

Moreover, by-products from the hydrodistillation of *Lamiaceae* plants could represent an affordable and valuable source of natural crop protectant as well as antioxidants for food industry. However, further investigation is still required to use these compounds/extracts in the food industry, regarding in particular their stability. Similar concerns apply to drugs based on *Lamiaceae* ingredients in the pharmaceutical industry, because often research is conducted on *in-vitro* systems, and lacks the essential knowledge of *in vivo* mechanisms of action.

Phenols biosynthesis in plants is influenced by environmental stresses, and the accumulation of these compounds can be artificially stimulated by the use of elicitors as eustresses. Thus, elicitation may be exploitable in the context of sustainable contribution towards secondary metabolism alteration, to provide a beneficial outcome for industrial purpose.

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List of table captions

Table 1. Plant species in the *Labiatae* family containing rosmarinic acid as the main phenolic compound at concentration above 0.5% dry weight.

Table 2. Main phenolic compounds found along with rosmarinic acid in plant species belonging to the *Lamiaceae* family.

Table 3. Main biological activity of phenolic compounds found in plant species belonging to the *Lamiaceae* family.

Table 4. Ingredients from Lamiaceae for pioneering industrial applications

Table 5. JA and MeJA-elicited phenolic secondary metabolites in various *Lamiaceae* species.

Table 6. Effect of UV-B doses on production of secondary metabolites in *Lamiaceae* specie.

Table 1

Genus	Species	Organ	References
Ballota	*Acetabulosa (L.) Benth*	Aerial part	Askun et al., 2013
Melissa	*Officinalis L.*	Leaf	Zgórka and Glowniak, 2001
Mentha	*Piperita L.*	Not specified	Generalić Mekinić et al., 2014
Mentha	*Spicata L.*	Herb	Kivilompolo and Hyötyläinen, 2007
Mentha	*Canadensis L.*	Leaf and branch	Shan et al., 2005
Micromeria	*Juliana (L.) Benth ex Reich*	Aerial part	Askun et al., 2013
Nepeta	*Cataria*	Leaf	Kraujalis et al., 2011
Nepeta	*Bulgaricum*	Leaf	Kraujalis et al., 2011
Nepeta	*Transcaucasica*	Leaf	Kraujalis et al., 2011
Ocimum	*Basilicum*	Leaf	Kiferle et al., 2013
Ocimum	*Basilicum*	Flower	Kiferle et al., 2013
Ocimum	*Basilicum*	Root	Kiferle et al., 2013
Ocimum	*Basilicum*	Stem	Kiferle et al., 2013
Origanum	*Vulgare L.*	Herb	Kivilompolo and Hyötyläinen, 2007
Origanum	*Vulgare L.*	Leaf	Shan et al., 2005
Origanum	*Indercedens*	Leaf	Pizzale et al., 2002

Prunella	*Vulgaris L.*	Spike	Lamaison et al.,1991
Rosmarinus	*Officinalis L.*	Leaf	Zgórka and Glowniak, 2001
Rosmarinus	*Officinalis L.*	Leaf and branch	Shan et al., 2005
Salvia.	*Officinalis L*	Leaf	Zgórka and Glowniak, 2001
Salvia.	*Officinalis L*	Leaf and branch	Shan et al., 2005
Satureja	*Aintabensis P.H. Davis*	Aerial part	Askun et al., 2013
Satureja	*Hortensis L.*	Herb	Zgórka and Glowniak, 2001; Exarchou et al., 2002
Thymus	*Serpyllum L.*	Not specified	Generalić Mekinić et al., 2014
Thymus	*Sibthorpii Benth*	Aerial part	Askun et al., 2013
Thymus	*Vulgaris L.*	Leaf and branch	Shan et al., 2005

Table 2

Genus	**Species**	**Organ**	**Phenolic compound**	**References**
Ballota	*Acetabulosa (L.) Benth*	Aerial part	Chlorogenic acid	Askun et al., 2013
Lavandula	*Officinalis Chaix*	Flower	Gentisic acid	Zgórka and Glowniak, 2001
Majorana	*Hortensis*	Herb	Arbutin	Rychlińska and Nowak, 2012; ukas et al., 2010; Fecka and Turek, 2008
Melissa	Officinalis L.	Herb	Caffeic acid	Wojdylo et al., 2007
Mentha	*X Piperita (L.)*	Leaf	Eriocitrin c)	Dorman et al., 2009 (M. x dalmatica in M&M)
Micromeria	*Juliana (L.) Benth ex Reich*	Aerial part	Hesperidin, Rutin, Chlorogenic acid	Askun et al., 2013
Origanum	*Vulgare L.*	Herb	Caffeic acid	Wojdylo et al., 2007
Origanum	*Indercedens*	Flower	Carvacrol c)	Pizzale et al., 2002
Origanum	*Onites*	Flower	Carvacrol c)	Pizzale et al., 2002
Rosmarinus	*Officinalis L.*	Leaf and branch	Epirosmanol, carnosol, carnosic acid	Shan et al., 2005
Satureja	*Aintabensis P.H. Davis*	Aerial part	Hesperidin, Naringenin, Naringin, Luteolin	Askun et al., 2013
Stachys	*Tmolea Baiss*	Aerial part	Chlorogenic acid, Apigenin b)	Askun et al., 2013

Stachys	*Thirkei C. Koch*	Aerial part	Chlorogenic acid, Caffeic acid	Askun et al., 2013
Thymus	*Sibthorpii Benth*	Aerial part	Chlorogenic acid, Luteolin	Askun et al., 2013
Thymus	*Vulgaris L.*	Leaf and branch	Thymol	Shan et al., 2005

a) concentration higher than 0.5% dry weight
b) rosmarinic acid not found
c) similar or higher amount than rosmarinic acid

Table 3

Class of phenolic	Compound	Biological activity	mechanism of action	Species/extract/compound	Reference
Phenolic acids	Caffeic and chlorogenic acids	Neuroprotective Hepatoprotective Antibacterial Antioxidant Antiinflammatory Anticancer	Effects on DNA methylation, histone modifications regulation miRNA expression	compound	Link et al, 2010;
			Cytotoxicity against breast cancer cells	compound	Berdowska et al. 2013
			Inhibition by binding the pro-inflammatory gut cyclo-oxygenase 2	compound	Gülçin, 2006
			Antioxidant capacity and modulation of the production of prostanoids	compound	Russell and Duthie 2011
			Uptake in the intestine and antioxidant capacity	compound	Sato et al. 2011
			Acetylcholinesterase (AChE) inhibition and antioxidant activities	*M. officinalis* and other Lamiaceae	Wojdylo et al., 2007
			Inhibition of Gram-negative (*Campylobacter coli, Escherichia coli and Salmonella Infantis*) and Gram positive (*Bacillus. cereus, Listeria monocytogenes* and *Staphylococcus aureus*) bacterial strains	*S. officinalis* and other Lamiaceae	Generalić Mekinić et al. 2014
			Inhibition in glioma secretion; protective effects on brain damage, sensory-motor functional deficit, brain edema, and BBB damage	compound	Lee et al. 2012
			Scavenger against free radical production after hypoxia and reperfusion of the gut	compound	Sato et al. 2011;
	Rosmarinic acid	Anticancer Neuroprotectie Antiatherogenic Antibacterial Antiviral Antidiabetic	Anti *Mycobacterium tuberculosis*	*B. acetabulosa* *T. sibthorpii* *S. aintabensis*	Askun et al., 2013
			Hepatoprotective effect by lowering of xanthine oxidase in oxidative stress	*T. vulgaris*	Gavarić et al. 2015
			Skin-care by tyrosinase-inhibition activity and anti-*S. aureus*	*O. majorana* and other Lamiaceae	Lee et al. 2011

			High potential to decrease diabetes mellitus and allergy by inhibiting α-glucosidase activity	*P. frutescens*	Zhu et al. 2014
			Increase of the activity of human immunodeficiency virus (HIV) and inhibition of viral replication in human lymphocyte MT-4 cells without cellular toxicity	*S. miltiorrhiza* *O. basilicum* *P. frutescens* *Dracocephalum moldavica*	Kim et al. 2015
Flavones	Luteolin	Anticancer; Antibacterial Antioxidant¸ Antiinflatory	Acetylcholinesterase (AChE) inhibition and antioxidant activities	*M. officinalis* and other Lamiaceae	Wojdylo et al., 2007
			Decrease of H_2O_2 involved in the apoptotic process	*T. vulgaris* *O. vulgaris*	Ramos, 2008
			Cytotoxicity against breast cancer cells	compound	Berdowska et al. 2013
			Skin-care by tyrosinase-inhibition activity and anti-*Staphylococcus aureus*	*O. majorana* and other Lamiaceae	Lee et al. 2011
			Therapeutic potential in controlling the proliferation of MDR cancers	compound	Rao et al., 2011
			Reduction Keratinocyte proliferation skin human keratinocyte cell line HaCaT in psoriatic deseases	compound	Weng et al., 2014
	Apigenin	Anti-metastasis, Antiangiogenesis, Antibacterial Antimutagenic Antiinflammatory	Antimutagenic potential against the mutagens ethyl methanesulfonate (EMS) and acridine (AC) in a eukaryotic cell system *Saccharomyces cerevisiae* RS112	*M. longifolia*	Gulluce et al. 2012
			Growth inhibitory responses due to inhibition of class I histone deacetylases (HDACs) in prostate cancer cells	compound	Pandey et al.2012
			Induction of AMPK activation, connected with several tumor suppressors, in human keratinocytes.	compound	Tong et al. 2012
			Overcome of multidrug resistance in otherwise refractory tumors by inhibition of overexpressed ATP-binding cassette (ABC) transporters in multidrug-[illegible]	compound	Saeed et al. 2015
Flavanos	Hesperidin	Antinociceptiv; Antimycobacterial;	Decrease of the H_2O_2 involved in the apoptotic process	*T. vulgaris* *O. vulgaris*	Ramos, 2008

		Antioxidant; Antiinflammatory	Anti *Mycobacterium tuberculosis*	*S. aintabensis*	Askun et al., 2013
	Naringin	Antioxidant Antimycobacterial Antibacterial Antifungal	Antibacterial (*Escherichia coli* ATCC 25922, *Klebsiella pneumoniae* FMC 5, *Staphylococcus aureus* COWAN 1, *Bacillus megaterium* DSM 3), antifungal (*Candida albicans* FMC 17, *Candida glabrata* ATCC 66032) and radical scavenging activities.	*N. italica* *Sideritis montana*	Emre et al. 2011
	Naringenin	Neuroprotective Antiatherogenic	Neuroprotection by suppressing the oxidative stress responsive transcription factor, the Nuclear Factor -κB-induced neuroinflammation.	compound	Raza et al. 2013
	Eriotricin	Antioxidant Antiulcer activity	Preservation of the mucosal integrity against ethanol-induced gastric diseases	*C. officinalis*	Monforte et al., 2012
			Strong antioxidant potential and influence on the glutathione metabolite system	*M. piperita*	Riachi and De Maria,
Flavonols	Rutin	Antioxidant Antibacterial	Induction of topoisomerase IV-mediated DNA cleavage and growth inhibition in *E. coli* in combination with anti-pseudomonal drugs	compound	Jayaraman et al. 2010
			Induction of damages linked to oxidation diseases of membrane integrity, which affects pH homeostasis and equilibrium of inorganic ion, in *Pseudomonas aeruginosa* and *Staphylococcus aureus*	*M. officialis* *S. officialis* *M. piperita* *O. vulgaris*	Lambert et al., 2001
Terpenois	Thymol	Antiaflatoxigenic Antioxidant	Control of the growth of *Aspergillus flavus* and its production of aflatoxins	*T. vulgaris*	Kohiyama et al. 2015
			Protection of gastric mucosa from damage induced by alcohol, protection against the constriction of small arteries and neutrophil infiltration in lymphatic vessels by the downregulation of matrix metalloproteinase-9	compound	Chauhan et al. 2015
	Carvacrol	Antibacterial Antiaflatoxigenic Antifungal Antioxidant	Control of the growth of *A. flavus* and its production of aflatoxins	*T. vulgaris*	Kohiyama et al., 2015
			Anti-inflammatory potential (inhibition of inducible cyclooxygenase 2, COX-2, isoform)	compound	Landa et al. 2009
			Antimicrobial activity against planktonic cells of *Salmonella* Saintpaul observed during biofilm	compound	Uchida et al. 2015

Carnosic acid; Carnosol	Antiangiogenic Antioxidant Antidiabetic Antiatherogenic	Inhibition of the growth of bacterial strains and radical scavenger	*R. officinalis*	Jordán et al. 2012
		Inhibition the invasion of B16/F10 mouse melanoma cells by suppressing metalloproteinase-9	*R. officinalis*	Weng and Yen, 2012
		Growth inhibitory effect, exerted on proliferative endothelial and tumor cells due to induction of apoptosis	*R. officinalis*	Lo´pez-Jime´nez e al. 2013
		Control of the growth of *A. flavus* and its production of aflatoxins	*T. vulgaris*	Kohiyama et al. 2015
Eugenol	Antimicrobial Antinociceptive Antiaflatoxenic Antifungal	Benefic effects against neurogenic and inflammatory pains	*O. gratissimum*	Paula-Freire et al., 2013
		Topical anti-inflammatory effect with edema inhibition	*O. gratissimum* *O. basilicum*	Okoye et al. 2014

Table 4

Industrial segment	Species/extract/compounds	Activity / Property	Target product	References
Cosmetics	Rosmarinic acid	Induction of melanogenesis	Sun block	(Sanchez-Campillo et al., 2009)
		Photoprotective: high UV-A and UV-B adsorption ability		(Lee et al., 2011;)
	Rosmarinus spp.	Anti-staphylococcus aureus and anti-inflammatory activities	Anti-acne skin agent	(Lee et al., 2011)
	R. officinalis	Anti-elastase activity	Skin aging	(Baylac and Racine, 2004)
	Deoxyarbutin in *O. majorana*	Inhibitor of tyrosinase, depigmentation property	Skin lightening	(Boissy et al., 2005)
	Lavandula angustifolia	Anti-collagenase activities	Skin aging	(Thring et al., 2009)
Food	*Ajugaiva*; *M. vulgare*; *M. pulegium*	Anti-microbial	Food preservatives	(Khaled-Khodja et al., 2014)
	M. myrtifolia; C. origanifolia;	Anti-oxidant	Food additivies	(Formisano et al., 2014)
	Thymol and carvacrol	Stabilization against thermo oxydative degradation	Active films for packaging	(Ramos et al., 2012)
	Eugenol	Antimicrobial		(Sanla-Ead et al., 2012)
	Thymus spp., *Rosmarinus* spp. and *Origanum* spp.	Antibacterial properties	Food preservatives in fish and meat products	(Mastromatteo et al., 2011; Busatta et al., 2007; Busatta et al., 2008)
Pesticide	Thymol and eugenol	Fungicidal against *Fusarium*, *Aspergillus* and *Pennicilium*	Fungicide	(Zabka et al., 2014)
	Thymol in *T. vulgaris* essential oil	Antiaflatoxigenic activity		(Kohiyama et al., 2015)
	Carvacrol and thymol in Origanum oil	Nematicidal activity	Nematicide	(Ntalli et al., 2010)
	Rosmarinic acid, carnosol, cornosic acid in *R. officinalis*	Antifeedant activity	Insecticide	(Navarrete et al., 2011; Santana-Mèridas et al., 2014)
	Thymol	Antimicrobial	Nano-clay films	(Glen et al., 2010; Wattanasatcha et al., 2012)
Pharmacological	Rosmarinic acid	Suppression of allergic immunoglobulin	Anti-allergies drug	(Stansbury et al., 2014)

	Suppression of polymorphonuclear leukocytes	Anti-asthma drug	
T. villosus subsp. *Lusitanicus*	Anti-microbial agaist *Candida* and *Aspergillus*	Anti-dermatomycosis drug	(Pinto et al., 2013)
Thymus spp. essential oil	Anti-microbial against multidrugs-resistant bacteria	Antibiotics	(Nabavia et al., 2015)
T. sipthorpii and *S. aintabensis*	Anti-bacterial activity against *M. tuberculosis*	Antituberculosis drug	(Askun et al., 2013)

Table 5

Species	Tissue type	Elicitor and concentration	Target compound	Fold induction	Reference
Coleus blumei	Cell suspension cultures	MeJA: 100 µM	Rosmarinic acid	3.3%	Szabo et al., 1999
Ocimum basilicum	Leaves	MeJA: 0.5mM	Phenolic compounds	Total phenolics: 57% Rosmarinic acid: 47% Caffeic acid: 3.8 fold	Kim et al., 2006
Mentha x piperita	Cells suspensions cultures	MeJA: 100µM	Rosmarinic acid	1.5 fold	Krzyzanowska et al., 2012
Ocimum basilicum	Hairy root culture	JA 100µM, 250µM, 500µM	Rosmarinic acid		Bais et al., 2002
Salvia miltiorrhiza	Roots	MeJA: 0.2mM	Salvianolic acids, caffeic acid and rosmarinic acid	Total salvianolic acids: 79.3% Caffeic acid: 14.9% Rosmarinic acid: 59.5% Salvianolic acid B: 93.2%	Wang etal., 2012
Ocimum basilicum	Leaves	MeJA: 0.5mM	Phenolic compounds	Rosmarinic acid: 55% Caffeic acid: 300%	Li et al., 2007
Salvia miltiorrhiza	Hairy root culture	MeJA: 0.1mM	Phenolic acids	Rosmarinic acid: 1.9 fold	Xiao et al., 2009

				Lithospermic acid B: 6.6 fold	
Ocimum basilicum	Microponic	MeJA+spermine (Spm): 0.5 mM+1.0 mM	Phenolic compounds	Total phenolics: 40% Rosmarinic acid: 64%	Koca and Karaman, 2015
Lavandula officinalis.	Cell suspension cultures.	JA: 50 μM,	Rosmarinic acid	PLEASE ADD	Stehfest et al., 2004
Agastache rugosa Kuntze	InVitro Cell suspension cultures	MeJA: 50 mM	Rosmarinic acid	4.7 fold	Kim et al., 2013
Coleus forskohlii	InVitro Hairy root culture	MeJA: 0.1 mM	Rosmarinic acid	3.4 fold	Li et al., 2005
Lavandula vera MM	Cell suspension cultures	MeJA: 50 μM	Rosmarinic acid	2.4 fold	Georgiev et al., 2007
Coleus blumei	Hairy root culture	MeJA:100 μM	Rosmarinic acid	21%	Bauer et al., 2009

Table 6

Species	Organ/Tissue	Elicited compounds	UV-B intensity	UV-B exposure time	Reference
Ocimum basilicum L. cv. Thai	3-4 leaf pair stage	Total phenolic	2 kJ m^{-2} day^{-1} and 4 kJ m^{-2} day^{-1}	7 days	Sakalauskaite et al., 2012
Nepeta cataria L. var. citriodora	Young plants	Essential oils and polyphenols	1 kJ m^{-2} d^{-1}	10 h/day for 7 days	Manukyan, 2013
Melissa officinalis L.	Young plants	Essential oils and polyphenols	1 kJ m^{-2} d^{-1}	10 h/day for 7 days	Manukyan, 2013
Salvia officinalis L.	Young plants	Essential oils and polyphenols	1 kJ m^{-2} d^{-1}	10 h/day for 7 days	Manukyan., 2013
Rosmarinus officinalis L.	Mature leaves	Rosmarinic and carnosic acids	5.4 and 31 kJ m^{-2} d^{-1}	14 days	Luis et al., 2007
Ocimum basilicum L.	3 and 4 leaf-pair stage	Phenyl propanoid, eugenol	222.6 μW/m^2	3 h /day for 14 days	Xianmin et al., 2009
Mentha × *piperita* L.	A few days before full bloom	Flavonoids eriocitrin, hesperidin and kaempferol 7-O-rutinoside	7.1 kJm^{-2} day^{-1}	3 h	Dolzhenko et al., 2010
Ocimum basilicum	Two leaf stage	Phenylpropanoids, eugenol and methyl-eugenol	Two Philips 20 - W/12 UV-B fluorescent tubes	2.5 h for 14 days	Johnson et al., 1999
Ocimum basilicum	Mature leaves	Monoterpenes trans-ocimene linalool, 1-8 cineole, eugenol,	Normal daily dose on summer's day in the Mediterranean	1 h/day for 15 days	Ioannidis et al., 2002
Scutellaria baicalensis Georgi	Leaves and roots	Flavonoids	12.1 μW/cm and 34.5 μW/cm	8h/day for 15 days	Tang et al., 2014
Ocimum sanctum L.	Oil glands	β-caryophyllene, germacrene-D, ethyl linoleolate, β-elemene, camphenol	ambient +1.8$kJm^{-2}day^{-1}$	3h/day for 40 days	Kumari and Agrawal, 2011
Mentha piperita	Six weeks plants	Total phenols	7. 1 kJm^{-2} day^{-1} UV_{BE}	15 min/day for 18 days	Maffei and Scannerini, 2000