



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



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ARTICLE INFO

Article history:

Received 30 April 2015

Received in revised form

15 December 2015

Accepted 16 December 2015

Available online 22 January 2016

Keywords:

Bioactive compounds

Elicitation

Labiatae

Industrial applications

Rosmarinic acid

UV-B

Methyl Jasmonate

Jasmonic Acid

Ozone

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.

This review focuses 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. It also reports 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, the review considers 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.

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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 propagative ability. Notably, these compounds act as defense against phytophages, viruses or as a tool for interplant competition, as a protective layer against solar radiation and as signal for pollination or seed dispersion. 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 *Labiatae*) is 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 *Nepeta* (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; 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 denote a major group of plant secondary metabolites, bearing at least one phenolic ring in their molecule; they mainly derive from the shikimate pathway (Lattanzio, 2006). A phenolic ring is made of a hydrophobic aromatic nucleus and a hydrophilic hydroxy group, which can be involved in hydrogen-bond formation. Being redox-active compounds, plant phenols can also act either as antioxidants or as pro-oxidants (Quideau et al., 2011). The antioxidant behavior of phenolic compounds depends on the number of hydroxy substituents, their mutual position and the binding site on the aromatic ring (Rice-Evans et al., 1996).

Thus, due to their high content of phenolics, the *Lamiaceae* have ever been considered as a source of valuable natural substances for health care. Rosmarinic acid is among the main 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-phenylalanine 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 phenological stage, climate, growing technique, stress conditions (Juliani et al., 2008; Maggini et al., 2014; Kiferle et al., 2011, 2013).

Throughout the *Lamiaceae*, high levels of rosmarinic acid are commonly found only within the subfamily *Nepetoideae* (Petersen and Simmonds, 2003). For example, in the genus *Stachys* in 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 high levels of different phenolics, such as phenolic acids, flavonoids, or phenolic terpenes (Table 2). Some phenolic compounds are present only in *Lamiaceae*, such as carnosic acid, which prevents the oxidative damage of the chloroplast and displays high antioxidant properties *in vitro* (Birtić et al., 2015). Another exclusive phenolic compound in the *Lamiaceae* is clerodendranic 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 group of bioactive phenolic secondary metabolites, which include apigenin and naringenin (Stacks, 2015), luteolin (López-Lázaro, 2009), hesperidin (Lee et al., 2010) and rutin (Chua, 2013). Health benefits have been ascribed also to phenolic acids like chlorogenic acid (Upadhyay and Mohan 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 (*Ocimum basilicum* L.) cultivars at concentrations below 0.3% dry weight (Lee and Scigel, 2013).

3. Biological activities

3.1. Antioxidant activity

All phenolic compounds of *Lamiaceae* plants share a significant antioxidant activity of extracts (Wojdyło et al., 2007) (Table 3). 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 and diseases. The antioxidant properties of phenolic compounds can be involved in scavenging reactive oxygen species and reactive nitrogen species (ROS/RNS), inhibiting ROS/RNS formation by suppressing enzymes or metals associated with free radical production and up-regulating or defending the plant antioxidant systems (Spaak et al., 2008).

In vitro experiments proved that phenolics are more efficient antioxidants than vitamin C, E and carotenoids (Rice-Evans et al., 1996). *In vivo* studies suggested that the normal uptake of phenolics with the diet failed to provide beneficial effects unless

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