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Molecules of Interest

Carnosic acid

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ABSTRACT

Carnosic acid (salvin), which possesses antioxidative and antimicrobial properties, is increasingly exploited within the food, nutritional health and cosmetics industries. Since its first extraction from a *Salvia* species (~70 years ago) and its identification (~50 years ago), numerous articles and patents (~400) have been published on specific food and medicinal applications of *Rosmarinus* and *Salvia* plant extracts abundant in carnosic acid. In contrast, relevant biochemical, physiological or molecular studies *in planta* have remained rare. In this overview, recent advances in understanding of carnosic acid distribution, biosynthesis, accumulation and role *in planta*, and its applications are summarised. We also discuss the deficiencies in our understanding of the relevant biochemical processes, and suggest the molecular targets of carnosic acid. Finally, future perspectives and studies related to its potential roles are highlighted.

1. Introduction

Well before its chemical structure (Fig. 1; **1**) was elucidated, carnosic acid (salvin) (**1**) and similar compounds of the ferruginol type were extracted from sage *Salvia carnosa* Dougl. as a 'bitter principle' (White and Jenkins, 1942). At that time, probably due to oxidation processes, only a derivative of carnosic acid (**1**) could be isolated and named carnosol (**2**) (pikrosalvin).

Carnosic acid (**1**) was first discovered by Linde in *Salvia officinalis* L. (Linde, 1964). Later, Wenkert et al. (1965) found carnosic acid (**1**) at much higher levels (~3% on weight basis of air-dried leaves) in *Rosmarinus officinalis* L. leaves (Wenkert et al., 1965). Since then, rosemary cultivars highly abundant in carnosic acid (**1**) (4–10% on weight basis of air-dried leaves) were developed, including VAU3, Daregal, Farinole, 4 English, Severn Seas, Miss Jessops Upright, 1 English, Lighthorne culinary (Wellwood and Cole, 2004). The molecule has also been found in other *Salvia* species and other genera of the Lamiaceae (Luis, 1991). Apart from the influence of the genetic background, contents in carnosic acid (**1**) may also be modulated by growth conditions (Tounekti and Munné-Bosch, 2012). Recently, Tounekti and Munné-Bosch (2012) have reviewed certain aspects of phenolic diterpene biology, with a particular focus on the physiological, rather than trans-genetic, approaches, to enhancing and improving the phenolic diterpene levels and composition in *Salvia* and *Rosmarinus* plants and plant extracts. For instance, authors reported that the English climate favours the production of carnosic acid more than the warmer, more arid environmental conditions found in Mediterranean countries where rosemary and sage are typically found. Furthermore, rosemary plants subjected to enhanced levels of UV-B radiation display higher yields of carnosic acid than non-treated plants. Moreover, water, salinity, intense light, and heat stress seem to negatively affect carnosic acid concentrations. Although stress conditions alone seem to decrease levels in carnosic acid (**1**), when applied together with supplements, they result in high yields in phenolic diterpenes. This was confirmed when low amounts of fertilizer or kinetin were supplemented to plants upon saline stress (Tounekti and Munné-Bosch, 2012). Carnosic acid (**1**) is a phenolic diterpene with a formula $C_{20}H_{28}O_4$. It belongs to the largest class of over 50,000 plant secondary metabolites termed terpenoids, also known as isoprenoids or terpenes (Hill and Connoly, 2013). Because carnosic acid (**1**) contains a phenolic group, it is often classified among polyphenols. Yet, its cellular distribution, biosynthetic pathway, solubility properties and roles substantially differ from the majority of polyphenolic classes and rather resemble terpenoids such as tocopherols and carotenoids.

Despite the great interest that this molecule, as part of plant extracts, has received for industrial applications, surprisingly few studies have been conducted into its biology. This overview aims

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to bring together what is known and to highlight deficiencies in our basic knowledge of carnosic acid.

2. Taxonomic, morphological and (sub)cellular distribution of carnosic acid

Mediterranean plants are exposed to a combination of environmental stress conditions, including low water availability, high light, temperature fluctuations, and nutrient deprivation. Such stresses may lead to an imbalance between antioxidant defences and the amount of ROS, resulting in oxidative stress. Besides a number of compounds that have been recognised to protect the chloroplasts from oxidative damage, including carotenoids, α-tocopherol, ascorbate, and glutathione, some plants have evolved carnosic acid, which displays high antioxidant properties *in vitro* and may play a part in the arsenal of antioxidative compounds that contribute to the protection of the chloroplast from oxidative damage. To date, carnosic acid (**1**) has been identified in only a few species, all exclusive of the Lamiaceae (Luis, 1991; Brieskorn and Dumling, 1969; Luis and Johnson, 2005; Bruno et al., 1991; Hossain et al., 2010; Achour et al., 2012; Djarmati et al., 1991) (Fig. 2). To the best of our knowledge, only seven out of 70 genera of the Mentheae tribe contain carnosic acid: *Salvia* (Brieskorn and Dumling, 1969), *Rosmarinus* (Luis and Johnson, 2005), *Lepechinia* (Bruno et al., 1991), *Oreganum* (Hossain et al., 2010) and *Thymus* (Achour et al., 2012). It may be present in *Hyssopus* where one of its possible derivatives, rosmanol-9-ethyl ether (**7**), was identified (Djarmati et al., 1991). Carnosic acid (**1**) also occurs as a minor compound in one genus of the Ocimeae tribe, *Ocimum* (Jayasinghe et al., 2003). Species belonging to the above genera all differ in carnosic acid (**1**) content. Presently, *R. officinalis* is considered to be the most abundant source of carnosic acid, followed by a number of *Salvia* species. Considerable intra-genus and intra-species variations remain regarding carnosic acid (**1**) content. In *Salvia*, 50 out of 62 screened species contained carnosic acid (**1**) with concentrations ranging from 0.1 to 21.8 mg g^{-1} DW

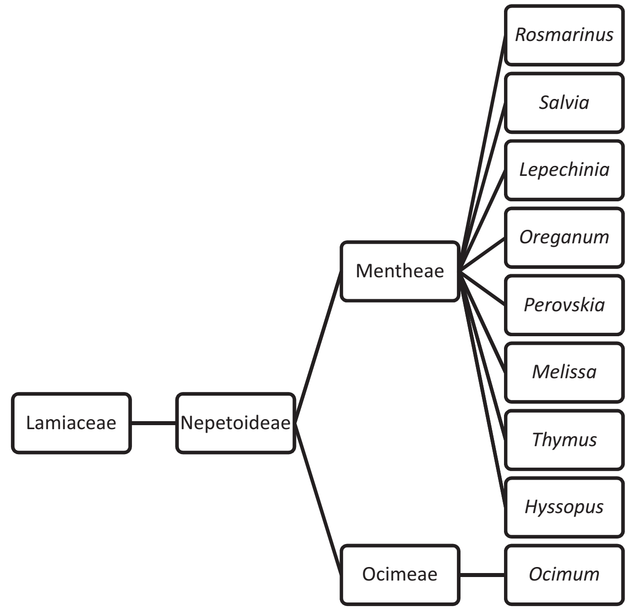

Fig. 2. Occurrence of carnosic acid (**1**) in the plant kingdom, exclusively in the Lamiaceae.

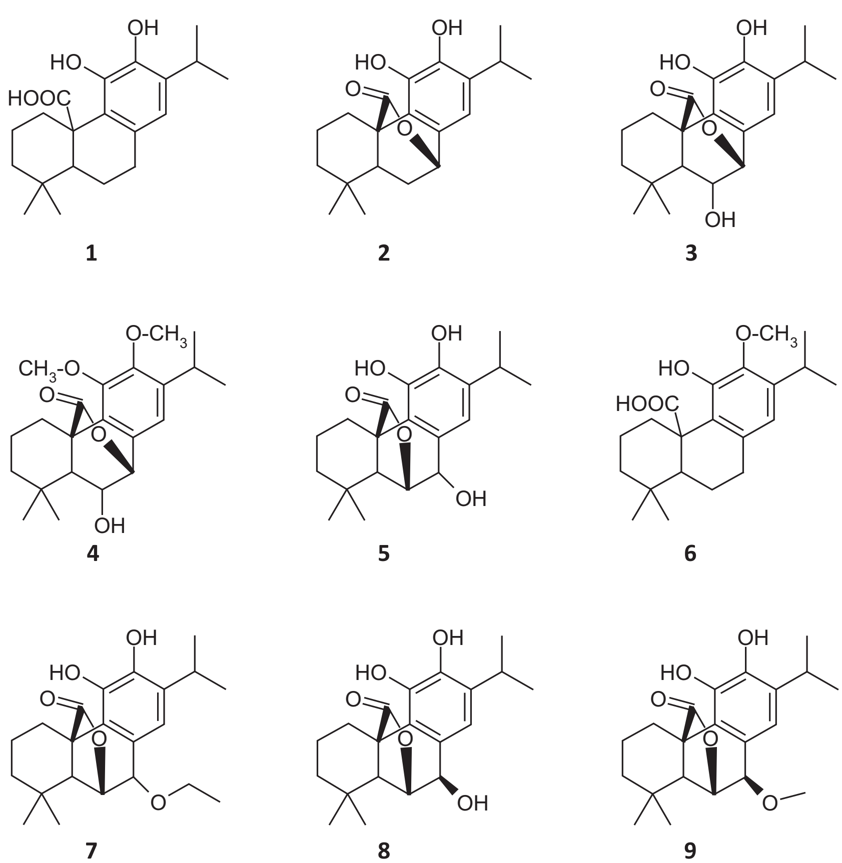

Fig. 1. Structures of carnosic acid (**1**) and of phenolic diterpenes similar to carnosic acid (**1**): **1** carnosic acid; **2** carnosol; **3** isorosmanol; **4** 11,12-di-*O*-methylisorosmanol; **5** rosmanol; **6** 12-*O*-methylcarnosic acid; **7** rosmanol-9-ethyl ether; **8** epirosmanol; **9** 7-methyl-epirosmanol.