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Relevance of carnosic acid to the treatment of several health disorders: Molecular targets and mechanisms

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ABSTRACT

Carnosic acid is a phenolic diterperne compound found in abundance in sage and rosemary, which are both widely used in traditional medicine. Research over the past decade indicates that carnosic acid has multiple bioactive properties including antioxidant, anti-inflammatory and anticancer activities among others. This review summarizes the current *in vitro* and *in vivo* data about the efficacy of carnosic acid in the prevention or treatment of various experimental health disorders. The analysis of the literature allows an insight into the participation of numerous signaling pathways modulated by carnosic acid, into its synergistic potential and, thus, into the divergence in cellular mechanisms of action of this molecule.

Contents

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1. Introduction

Currently, research on bioactive substances of plant or animal origin earned a growing interest in numerous industrial sectors, including cosmetics, pharmaceutics and food processing. Notably, plants are rich source of biomolecules generally well tolerated by the human body. Many of these biomolecules served as natural remedies since ancient times. The enormous technical progress, discoveries and innovations, which promoted industrialization, helped pharmaceutical companies to identify natural substances obtained from plants and to determine their therapeutic potential. The term "medicinal plant" characterizes species that contain active compounds, which belong mainly to the category of secondary metabolites (polyphenols, essential oils) known for their medicinal properties. However, caution should be taken as to what part of the plant to use, since they can differ in characteristics and contain more than one active compound in different proportions. Therefore, plant usage requires a real knowledge to avoid any risk of poisoning.

Carnosic acid (CA) was discovered first by Linde in *Salvia officinalis* L. [1], then by Wenkert et al. [2] in *Rosmarinus officinalis L* leaves. Despite the fact that sage and rosemary are hailed since ancient times for their therapeutic properties, the exploration of the mechanisms of CA action began only in the early 2000s. Over the last decade, several research teams studied the pharmacological properties of CA, demonstrating that this molecule may have clinical applications for various human diseases. Indeed, studies using rosemary extract showed that its properties are closely related to its phenolic constituents, especially the most abundant compounds, carnosic acid and rosmarinic acid. On the other hand, consumption of the whole plant leads to the ingestion of products other than the active ingredient sought. This requires the extraction and purification of the active compound in order to reveal its effects, to know the dose administered and to avoid the risk of overdose that can lead to toxicity.

Carnosic acid ($C_{20}H_{28}O_4$, Fig. 1), a phenolic diterpene that belongs to the terpene class of secondary metabolites [3], is localized in rosemary leaves, more precisely in chloroplasts of trichome cells. The stability of this molecule remains discussed because it can give rise even *in planta* to several dehydrogenation derivatives such as carnosol, rosmanol and isorosmanol. In plants subjected to intense solar radiation and high drought, CA may be transformed into methyl derivatives. This clearly demonstrates that this molecule exerts a dual protective role in rosemary plant against environmental constraints by capturing free radicals in chloroplasts and by preserving the stability of cell membranes [4].

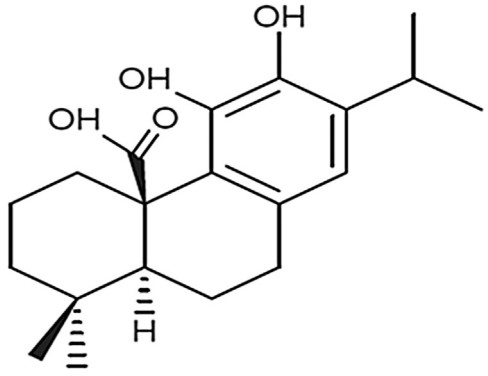

Fig 1. Carnosic acid.

Detection of the anticancer activity of CA was among the first research work carried out. CA exerted an antiproliferative action in leukemic cells without induction of apoptotic or necrotic cell death [5]. This study demonstrated that CA could cooperate synergistically with other natural anticancer compounds, such as vitamin D and retinoic acid metabolites, to potentiate anticancer effects. Later on, consequent studies of CA in the field of oncology took a considerable place both *in vivo* and *in vitro*. However, studies in other health areas demonstrate that CA is clearly promiscuous molecule that is useful in the treatment of many other human diseases.

In this review, we will focus on the biological effects of vegetable extracts rich in CA or pure CA that were demonstrated by different research teams. We will assess efficacy of CA in various physiological assays and clinical trials published till now.

2. Methods

In order to explore available information about CA beneficial effects for the treatment/prevention of various diseases, we have collected data published between August 2001 and April 2016 in the Pubmed database using the following appropriate combinations of MeSH (Medical Subject Heading) terms: carnosic acid, carnosic acid antioxidant, carnosic acid cancer, carnosic acid brain, carnosic acid obesity, carnosic acid breast, carnosic acid liver, rosemary carnosic acid.

3. Bioavailability and toxicity of carnosic acid

At present, there are only two studies on bioavailability of carnosic acid. First, it was reported that 6 h after oral administration in rats (64.3 ± 5.8 mg/kg), the bioavailability of CA in its free form was 40.1%, and its excretion in the feces after 24 h was $15.6 \pm 8.2\%$ [6]. CA is absorbed into the bloodstream after oral administration and its traces were found in the rat intestine, liver and muscle tissue of abdomen and legs [6]. In another study, Romo Vaquero et al. [7] also investigated the bioavailability of CA and other diterpenoids found in rosemary extract and detected all the metabolites 25 min after oral administration in rats. CA was pronouncedly present in the intestine, liver, and plasma with some quantities of CA and its metabolites even in the brain, translating their potential health benefits in these tissues.

Wang et al. [8] evaluated the acute and 30-day oral toxicity of CA on Wistar rats and defined acute oral lethal dose (LD50) in the range of 7100 mg/kg of body weight. In rats treated chronically with a high-dose of CA, they observed slight reduction in the body weight gain compared to control group and revealed only weak pathological changes in the heart, liver, and kidney. These observations reflect low toxicity profile of the molecule.

4. Anti-cancer effect of carnosic acid

4.1. Carnosic acid and colorectal cancer

The relevance of the current studies to the oncology is based on the inhibition of the *in vitro* viability of different cell lines