Mini Review

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Carnosic Acid and its Derivatives: Diterpenes of Biological Interest

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ABSTRACT

Carnosic acid and its oxidized derivatives are phenolic abietane diterpenes found abundantly within members of the botanical family Lamiaceae, such as Salvia and Rosmarinus. Related scientific literature indicates these compounds have numerous bioactive properties. In this review, we present an overview of significant advances described in the latest literature concerning therapeutic applications of carnosic acid and its derivatives.

Keywords: Carnosic Acid; Carnosol; Cancer; Rheumatoid Arthritis; Biological Activities

Mini-Review

Carnosic Acid (CA) and its major oxidized derivative, carnosol, are phenolic abietane diterpenes present in various species of the *Lamiaceae* family, such as *Salvia* and *Rosmarinus*. The unstable nature of the carnosic acid molecule tends to oxidize easily and produce derivatives such as carnosol, rosmanol and isorosmanol [1]. For this reason, CA concentrations vary greatly in medicinal plants throughout the year. The highest amounts of CA are found during winter, probably due to higher precipitations, while their concentration is lower in summer [2]. The most common procedure to obtain these compounds is through isolation from the natural source [3]. However, several synthetic routes have been published. Tada *et al*. [4] have described a semi-synthetic process to obtain CA and carnosol from natural pisiferic acid, and some minor diterpenes such as rosmanol and 7-methoxyrosmanol have been efficiently obtained from carnosic acid [5]. CA and related diterpenes exhibit a wide variety of interesting biological properties, which have awaken interest within the medical and pharmacological communities. Diverse studies have demonstrated its antibacterial, antioxidant, antidiabetic, antitumor, leishmanicidal, and antiplasmodial properties, as well as neuroprotective and inhibitory effects for Human Immunodeficiency Virus (HIV) infection [6,7]. The anticancer activity of these compounds is of special interest given the significant increase in the number of cancer patients because of aging and growth of world population.

CA related compounds have shown these effects both *in vitro* and *in vivo*, including the inhibition of angiogenesis, proliferation and cancerous cells migration [8]. Rosmanol induced apoptosis in COLO 205 human colorectal adenocarcinoma cells with an IC_{50}=42 μM [9]. Carnosol, on the other hand, inhibits breast and prostate cancers by binding to estrogenic and androgenic receptors respectively [10,11]. Additionally, several studies on CA prove its ability to cooperate with and enhance the effects of some drugs like tamoxifen [12] and trastuzumab [13], inhibiting breast cancer progression and increasing the sensitivity of glioma cancer cells to temozolomide [14]. Carnosol protects skin cells from Ultraviolet B radiation and inhibits melanoma growth [15], while CA improves the anticancer effects of carmustine and lomustine in melanoma, both *in vitro* and *in vivo* [16,17]. Rheumatoid Arthritis (RA) is a systemic autoimmune disease, characterized mainly by chronic inflammation of the joints, which is associated with progressive disability and premature death. CA and carnosol display significant *in vivo* dose-dependent anti-inflammatory and anti-nociceptive effects [18]. Xia *et al*. [19] demonstrated that the administration of CA to db/db mice reduced the risk of systemic

inflammatory condition through the suppression of the production of pro-inflammatory cytokines [20]. In a recent study conducted by Ishitobi *et al*. [21], CA demonstrated its potential as an agent for osteoarthritis prevention as well, reducing cartilage degeneration in articular chondrocytes through upregulation of hemeoxygenase-1.

It is estimated that the number of people living with Alzheimer's Disease (AD) will triple by year 2050. AD has been characterized by the accumulation of extracellular amyloid-β plaques in an early stage followed by the formation of intracellular neurofibrillary tangled inclusions [22]. The ingestion of CA (30 mg $kg^{-1}d^{-1}$) daily for 7 weeks can inhibit the intracellular oligomerization of exogenous Aβ42/43 monomer in C57BL/6 mice, which may have potential in the prevention of Aβ-involved diseases, particularly Alzheimer's disease [23]. On the other hand, CA inhibits triglyceride accumulation in ob/ob mice [24]. Zhao *et al*. [25] demonstrated that CA could dose-dependently ameliorate obesity and metabolic syndrome induced by a high-fat diet in C57BL/6J mice. The mechanism of action is simple, the inflammation and lipogenesis is supressed through Myristoylated Alanine-Rich C-Kinase Substrate (MARCKS) regulation [26]. In the present review, emphasis is placed on the therapeutic applications of CA and its oxidized derivatives. We believe that the information compiled in this minireview article will update scientists with recent findings on the biological activities of phenolic abietane diterpenes and help them improve their available information for further studies. Future goals in this field of research include the development of efficient methods to isolate these natural compounds and new synthesis strategies. Furthermore, it is essential to perform bioavailability studies and begin targeted clinical studies.

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