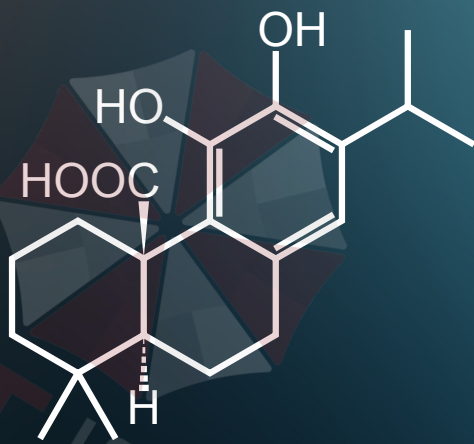




Carnosic Acid

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History

Carnosic acid (CA) is a naturally occurring compound, with the most well-known sources being *Rosmarinus officinalis* (Rosemary) and *Salvia officinalis* (common sage). The leaves of the plants contain around 2% carnosic acid in dry mass. More specifically, it is located in the chloroplasts of the plants trichome cells, which form little hairs in the plants surface. There are several plant derived derivatives of CA which are produced through the same metabolic pathways like CA with similar properties, for example rosmarinic acid.

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.

Carnosic acid is a bitter-tasting, yellow powder and can be isolated from plants by solvent extraction using hexane and/or ethanol or high-pressure extraction using supercritical carbon dioxide.¹ Carnosolic acid can be oxidized by atmospheric oxygen to form the unstable hydroxycarnosolic acid, which converts to carnosol.

Structure of Carnosol

In addition to its antioxidant properties, carnosic acid also has antimicrobial activity, for example against the common pathogen *Staphylococcus aureus*. This is attributed to an inhibition of nucleic acid biosynthesis in

bacteria.¹ In animal studies, carnosolic acid also showed chemoprotective effects against different carcinogens.

Carnosic acid is used as a fat-soluble antioxidant, preservative and flavoring agent in foods such as meat products, oils and fats, flour, milk powder, fish products, sauces, and in animal feed.² In a report from June 2008, the European Food Safety Authority (EFSA) certified the safety of carnosic acid for use in food. In the United States, rosemary oil, which contains up to 30% carnosic acid and carnosol, has been classified as Generally Recognized As Safe (GRAS) since 1965 (FEMA) and 1970 (FDA), respectively, and can be used in food.

Cell Culture Experiments

Most research on CA originates from cell culture experiment in cancer cell lines.

Initial studies showed an effect of CA effect on 3 types of cultured colorectal cancer cells: Caco-2, HT29 and LoVo. They revealed a dose-dependent reduction in the viability of these cells treated with CA with IC50 values within the range of 24–96 mM. Cellular death followed the induction of apoptosis and inhibition of cell migration and adhesion. This effect was accompanied by a downregulation of the expression of a variety of known cellular regulators.³

A group of Korean researchers showed a decrease in the viability of human colon cancer HCT116 cells treated with CA (20 to 100 mM). It triggered HCT116 cells apoptosis via generation of reactive oxygen species.⁴ The same team demonstrated that CA could slow down the rapidity of colon cancer formation associated with high body fat. In fact, they discovered that treatment with CA at 1 and 10 mM for 48 h attenuated the proliferation of HT-29 colon adenocarcinoma cells co-cultured with adipocytes by inducing cell cycle arrest and apoptosis.⁵ These early results gave reason to believe that CA might be a suitable treatment to certain human cancer entities.

Due to the positive effect on cells of colorectal cancer, more studies followed focusing on other common cancer cell types such as liver cancer^{6,7} renal cancer⁸ brain cancer⁹ and leukemia.^{10,11}

On the other hand, pretreatment with CA can protect and counteract the toxic effect of some carcinogenic agents. A dose-

dependent protective effect of CA pretreatment on cell toxicity induced by aflatoxin in liver cells was demonstrated. When cells were pre-treated with relatively low doses of CA (20 or 30 mM) for 24h prior to aflatoxin, it decreased reactive oxygen species level and cell death. This study highlighted the preventive effect of this molecule, which can play a dual role as a preventive and curative herbal drug against some type of cancer, although it is not clear when CA prevents the formation of reactive oxygen species and when it promotes it.¹²

Additional information on the topic of the anti-cancer activity of CA stems from experiments focusing on the potential of CA to inhibit the formation of new blood vessels (angiogenesis).¹³ Malignant tumors depend on this process in order to grow above sizes of 1 cm. Many inhibitors of angiogenesis are available on the international market to fight a variety of cancer in a clinical setting, e.g. the antibody Bevacizumab. CA was in fact shown to suppress the formation of new blood vessels in cell models with umbilical cord cells.¹⁴ This activity could contribute to the prevention of angiogenesis-related disorders including cancer and neurodegenerative diseases.

CA could be proposed and taken into consideration for the prevention and/or for the treatment of prostate cancer, but current results remain insufficient and need to be more elaborated.¹⁵

It was discovered that CA treatment has the ability to block the formation of fat tissue in cultured adipocytes.¹⁶ This seems

to be connected to a lower level of fats in the cells.^{17,18} These findings led to the believe that CA might be an effective agent to reduce body weight in humans.

Animal Studies

Bioavailability and toxicity in rats

6h 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 24h was 15.6 %.¹⁹ CA is absorbed into the bloodstream after oral administration and its traces were found in intestine, liver and muscle tissue of abdomen and legs. In another study the authors also investigated the bioavailability of CA and similar compounds in rosemary extract and detected all the metabolites 25min after oral administration in rats.²⁰ 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. A 30-day oral toxicity study of CA on Wistar rats and measured an acute oral lethal dose (LD50) in the range of 7100 mg/kg of body weight.²¹ 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 CA.

Cancer studies in animals

The previously mentioned Korean

team tested the effect of CA in a mice model of colitis as well as in a model of colon cancer. Compared to untreated animals, mice treated with CA have shown a reduction in the number of colon tumors and a decrease in circulating concentrations of biomolecules responsible for inflammation and cell-proliferation.⁵

In mice with leukemia, CA was found to have a synergistic effect with existing treatments for this disease, meaning that treatment outcomes were better if CA was added to the existing treatment.²² Considering these results, the authors deduced that CA has a potent anti-tumor effect against different cell lines of leukemia.

Non-cancer disease models

Additional studies in rats have investigated whether CA can prevent damage to liver cells. At doses around 60 mg/kg, CA was indeed able to normalize the signs of liver damage mediated by several classes of toxins.²³⁻²⁵ Individual studies pointed towards the conclusion that CA might enhance the body's own antioxidant defense system. Similar anti-oxidative properties of CA have also been identified in heart muscle cells of mice.²⁶

Due to its anti-oxidative properties, CA has been theorized to benefit in Alzheimer's disease, as oxidative and inflammatory processes play a role in the pathogenesis of Alzheimer's disease. In 2011 beneficial effect of CA in experimental rat model of Alzheimer disease was reported for the first time. It was

demonstrated that CA at a dose of 3 mg/kg protected neurons from cellular death, and this in turn prevented beta- amyloid-induced neurodegeneration.²⁷ Another group of researchers confirmed these results and explored the effect of CA, administered at the same dose of 3 mg/kg, on memory and behavioural alteration. They demonstrated that CA could ameliorate the spatial and learning memory deficits.²⁸

CA can also be used as anti-oxidative agent, meaning it can potentially protect cells from harmful reactive oxygen species. A group investigated the properties in 2008 and found that CA can indeed have neuroprotective effects which are connected to a lower burden of oxidative damage.²⁹ Mechanistic studies suggest that CA exerts this properties by the activation of other genes and a dose of 3 mg/kg showed sufficient effect to reliably activate these genes in mice.^{30,31} In general, CA seems to be able to induce the expression of a variety of genes in neurons, which can protect the neuron from damage.³²⁻³⁴

There is limited experimental evidence in animal models that CA might be beneficial in the treatment of Parkinson's disease³⁵ retinal changes³⁶ and skin inflammation.³⁷⁻³⁹

Additional potential applications of CA include treatment of viral infections⁴⁰ and attenuation of cis-platin induced nephrotoxicity.⁴¹

Obesity

In mice and rats, there are several studies indicating that the extract

from rosemary or sage (both rich on CA) can reduce the uptake of lipids and reduce body weight when fed in a fat-rich diet.^{42,43} It also leads to a reduction of metabolic parameters indicating a lower level of inflammation markers and energy metabolism.⁴⁴ Additionally, CA has an effective on the digestive enzymes that are responsible for the digestion of fats and their absorption in the GI tract.⁴⁵ An increase in glucose tolerance was also observed, which makes CA a potential supplement for type-2 diabetics.⁴⁶⁻⁴⁸

The majority of experimental studies designed to evaluate the anti-obesity effect of rosemary extract demonstrated that this molecule can be a promising agent to attenuate metabolic disorders by regulating fatty acid metabolism, hepatic fat accumulation, glucose tolerance and various other manifestations.

Metabolism of CA in rats

The maximum blood concentration of CA after ingestion in rats was found at 136 min, while half-life was 93 min. After 1 day, almost no CA was excreted in the urine, but significant amounts were present on the feces. The compound is converted into metabolites in the blood, although the exact molecular identity of these metabolites is unknown.¹⁹

The ingestion of higher doses of CA (90 mg/kg) does lead to a limitation of uptake in the gut and intestinal tract. High effective doses of CA are hence to be expected to be found in stomach,

small and large intestine. It was shown that these organs are also protected by CA from toxin induced lesions, probably due to the anti-oxidative effects of CA.⁴⁹ Interestingly, synthetic analogs of CA were able to prevent gastric lesions as well.⁵⁰

Conclusion

Much evidence of the beneficial effect of CA for the treatment of various health disorders has been published. However, the best evidence stems from studies in rats and mice, as no studies with human subjects have been published.

The mechanisms of CA in cell culture and animal models include the inhibition of oxidative stress, the attenuation of inflammation and cancer. In the latter case, CA can attenuate tumor progression via apoptosis induced by ROS generation and caspase activation. The results demonstrate clearly that CA could be a potent candidate for the treatment of renal cancer and other forms of cancer. Indeed, CA on various types of carcinomas may induce apoptosis, cell cycle arrest, autophagy, and inhibition of cellular proliferation. In each case, different signalling pathways are involved. Typical oral experimental doses of CA range between 20 – 80 mg/kg in mice and rats, which roughly translates to human daily doses of 100-1000 mg. Ingestion of CA before food intake may reduce fat absorption in the GI tract and prevent unwanted weight gain as well, hence a general supplementation to prevent obesity associated

diseases may also be a useful application of CA.

In conclusion the experimental results are a good start on the way to the use of CA in the prevention or treatment of several forms of cancer. Generally, this molecule appears to exert its antitumor action by inhibiting cell viability via induction of apoptosis, as well as a general protection of health through anti-oxidative mechanisms.

However, most of the studies did not go beyond the in vitro experimentation. This constitutes the biggest limitation. Further research and preclinical studies are required to fully elucidate and to understand the potential of CA as a preventive or therapeutic agent against various human carcinomas.

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