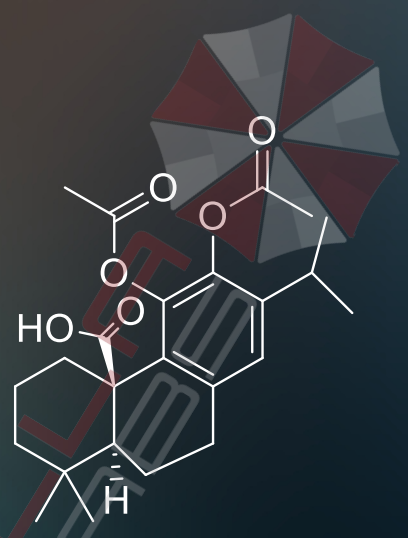
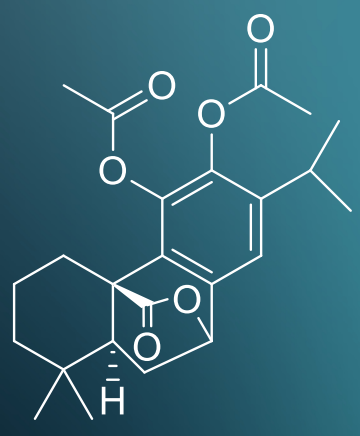



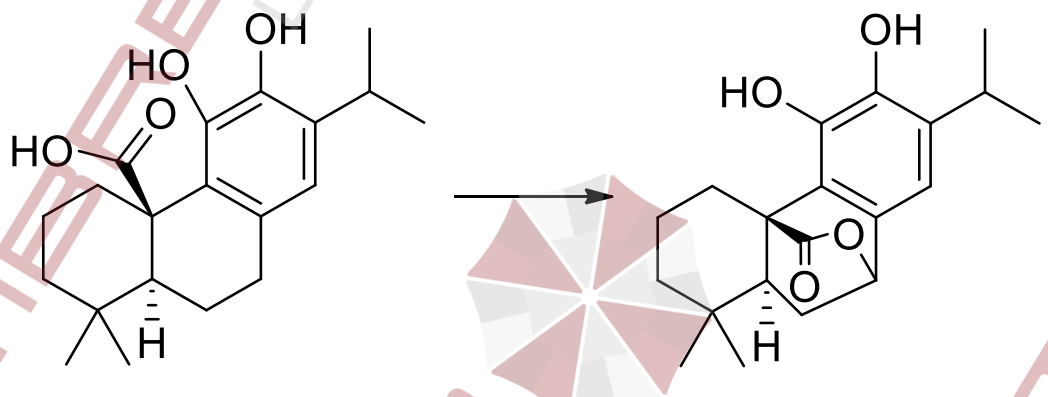
Enhancing Carnosic Acid's Promise: Preclinical Advances with diAcCA and Diacetyl Carnosol in Neurodegenerative Disorders

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History

Diacetyl carnosic acid (diAcCA) is a chemically modified form of carnosic acid (CA), which is a natural compound found in plants of the family Lamiaceae such as rosemary (Salvia rosmarinus) and sage (Salvia officinalis). Carnosic acid was discovered in 1962 and a few years later its antioxidative properties had been described. The compound partitions readily into biological membranes because of its hydrophobic backbone, allowing it to intercept lipid radicals and inhibit lipid peroxidation. Carnosic acid is chemically labile and undergoes oxidation to carnosol and related quinone derivatives when exposed to heat, light or oxygen.

In mammalian systems it activates the Keap1–Nrf2 axis, upregulating phase II detoxifying enzymes and broad cytoprotective gene programs, which is seen as generally health promoting in animals and humans. It also modulates NF-κB signaling, reducing proinflammatory cytokine production. Antimicrobial, neuroprotective, and metabolic regulatory activities have been documented across in vitro and in vivo models. Ongoing research focuses on improving its stability and bioavailability through encapsulation strategies and prodrug design.



Conversion of carnosic acid to carnosol

In 2025 diAcCa was first described as a modified form of CA, which is designed to increase its stability against oxidative breakdown. When absorbed into body fluids, the acetyl moieties can be cleaved off by enzymes in blood and tissue to liberate CA inside the body. Hence, diAcCa can also be seen as a further development compared to CA.

Diacetyl carnosol (NO.20), also known as picrosalvin diacetate, is a close analoge of diAcCA and will also be included in the scope of this review, since NO.20 is a likely metabolite of diAcCA and that both have largely comparable effects. It was first mentioned in a 2022 research paper.

Mechanism of Action

Like CA, it is assumed that diAcCA and NO.20 exert their effects by activating the transcription factor Nrf2, which leads to a variety of protective downstream effects, such as increased production of enzymes that fight reactive oxygen species. There may be more factors contributing to the effects of CA, diAcCA and NO.20, but currently research data on the subject is limited.

Preclinical Trials

Studies in Cell Culture

A study investigated the neuroprotective effect of diacetyl carnosol on H2O2-induced neurotoxicity in human brain cells (SH-SY5Y) and its possible mechanism. It was found that NO.20 pre-treatment (1 µM for 1 h) had cytoprotective effects and

weakened H2O2-induced damage in brain cells by reducing apoptotic rate and reactive oxygen species production. In addition, NO.20 inhibited H2O2-induced mitochondrial dysfunctions. NO.20 also downregulated the harmful compound malondialdehyde and upregulated the cytoprotective glutathione. Furthermore, NO.20 pretreatment caused the nuclear translocation of the transcription factor NF-E2-related factor 2 (Nrf2), increasing heme oxygenase-1 (HO-1) expression in SH-SY5Y cells. Notably, the study found that silencing Nrf2 suppressed the NO.20-induced HO-1 expression and abolished the neuroprotective effect of NO.20. These results demonstrate that NO.20 protects SH-SY5Y cells from H2O2-induced neurotoxicity by activating the Nrf2/HO-1 pathway.[1]

Studies in Animals

CA has been investigated for applications in neurodegenerative diseases such as Alzheimer's for decades.[2] A research group has therefore also investigated the effects of the further modified NO.20 as well. The study found NO.20 converted to CA in the stomach prior to absorption into the bloodstream, and exhibited improved stability and bioavailability as well as comparable pharmacokinetics (PK) and efficacy to CA. To test the efficacy of NO.20 in AD transgenic mice which received the drug for 3 months, the study employed behavioural and immunohistochemical studies. Notably, in addition to amyloid plaques and tau tangles, a hallmark of human AD is synapse loss, a major correlate to cognitive decline.

Treatment with NO.20 reduced inflammation in brain cells, amyloid plaque formation, and Alzheimer typical protein aggregates. In toxicity studies, NO.20 was as safe or safer than CA, which is listed by the FDA as "generally regarded as safe", indicating NO.20 is suitable for human clinical trials in AD.[3]

The last currently available study worked on exploring a more detailed view of the underlying mechanism of NO.20 in animals as approximation for human physiology. In this particular study, the focus was placed in the anti-depressant effects of NO.20, which were known from CA as well.[4] However, its anti-depressant effects and underlying mechanisms remain mostly unclear and are likely complex. NO.20 was supplied to chronically stressed mice as well as to brain cell culture. Results showed that NO.20 did also affect the inflammatory HMBG1 protein. High mobility group box 1 protein (HMGB1)-mediated inflammatory responses and associated neurofunctional impairments play a crucial role in the pathogenesis of depression.

The study also showed that stressed mice exhibited reduced signs of depression if they received NO.20 in oral form at doses between 10 and 40 mg/kg.[5]

Clinical Trials

There are no clinical trials with diAcCA.

Conclusion

diAcCA and NO.20 are rationally designed prodrugs that increase the oral bioavailability of CA (and carnosol respectively) by around 30%, which was shown by one study in mice in case of diAcCA. The effects and applicable fields are identical to CA, namely treatment of neurodegenerative disorders, depression and general health due to its anti-oxidative properties.

A further study demonstrated that NO.20 is partially converted to carnosol in the stomach, at least in mice. This shows that this prodrug is not ideal and could be developed further, as it would be

better if the conversion to CA was later during the metabolic process, ideally after absorption into the bloodstream or after cellular uptake.

Overall, there are only 3 preclinical studies that investigate specifically diAcCA and NO.20 in total, showing the low availability of information about both compounds.

Human data is not yet available; next steps would be formal toxicology and early-phase clinical trials if the developers pursue translation into human use. Extrapolated dosing from mouse data would result in human doses ranging from ~50-500 mg/day orally (for both NO.20 and diAcCA).

Further Reading

- Abietane diterpenes with antibiotic activity from the flowers of Salvia canariensis. Reaction of galdosol with diazomethane (1989)

- Sage extract rich in phenolic diterpenes inhibits ultraviolet-induced erythema in vivo (2007)

- The Diterpenoids from the Genus Hyptis (Lamiaceae) (2009)

References

[1] Luo Q, Hu W, Yu H, Zhang R, Chen X. 11,12-Diacetyl-carnosol Protects SH-SY5Y Cells from Hydrogen Peroxide Damage through the Nrf2/HO-1 Pathway. *Evid Based Complement Alternat Med.* 2022;2022:4376812. doi: 10.1155/2022/4376812.

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