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## RTA-405

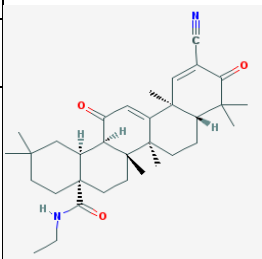
### Evidence Summary

Shows some neuroprotection and carcinogen risk mitigation in animals, but no human studies have been done. Unclear if manufacturer will continue to develop for clinical testing.

**Neuroprotective Benefit:** May partially protect neurons against oxidative stress damage and reduce neuroinflammation. Human studies are needed.

**Aging and related health concerns:** May help mitigate cancer risk following carcinogen exposure based on rodent models. Human studies are needed.

**Safety:** Generally safe and well-tolerated in rodents, but human studies are needed.

<b>Availability:</b> Available from biological chemical suppliers for research, but not for human use.	<b>Dose:</b> Not established	<b>Chemical formula:</b> $C_{33}H_{46}N_2O_3$ <b>MW:</b> 518.742 g/mol  Source: <a href="#">Pubchem</a>
<b>Half life:</b> Not reported	<b>BBB:</b> Yes (animals)	
<b>Clinical trials:</b> None	<b>Observational studies:</b> No human data	

**What is it?** RTA-405 is an orally bioavailable synthetic oleanane triterpenoid, 2-cyano-3,12-dioxooleana-1,9(11)-dien-28-oate-ethyl amide (CDDO-EA). It was developed by Reata Pharmaceuticals as a synthetic activator of the Nrf2 antioxidant pathway. Thus far, it has only been tested in preclinical models primarily for neurodegenerative diseases, cancer, and kidney disease.

**Neuroprotective Benefit:** May partially protect neurons against oxidative stress damage and reduce neuroinflammation. Human studies are needed.

Types of evidence:

- 3 laboratory studies

RTA-405 is capable of reaching the brain following oral administration. In mice fed RTA-405 supplemented chow (200 mg/kg diet), CDDO-EA could be detected in the brain (at  $33.4 \pm 2.1$  nmoles/kg) [1]. There have been no studies testing RTA-405 (CDDO-EA) in humans. Two rodent models of neurodegenerative diseases (Huntington's disease and ALS) showed evidence for neuroprotection (described below).

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function? None

Human research to suggest benefits to patients with dementia: None

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

**Huntington's disease: Potential benefit (mice)**

In a transgenic mouse model (N171-82Q) of Huntington's disease, mice treated with CDDO-EA supplemented chow (200 mg/kg diet) starting prior to onset of symptoms showed increased motor performance, survival ( $155 \pm 4.8$  days control vs.  $189 \pm 4.8$  days CDDO-EA  $P < 0.001$ ) and striatal volume [1]. This suggests RTA-405 can attenuate, but not prevent, neurodegenerative processes.

**Amyotrophic lateral sclerosis: Potential benefit (mice)**

In a transgenic model (G93A SOD1) of ALS, mice treated with CDDO-EA supplemented chow (400 mg/kg diet) showed enhanced motor performance and extended survival (from  $124.05 \pm 3.7$  days to  $144.72 \pm 8.1$  days  $p < 0.001$ ) when given at pre-symptomatic or (from  $40.1 \pm 4.7$  days to  $57.6 \pm 7.6$  days relative to disease onset) at symptomatic stages [2]. At this therapeutically beneficial dose, CDDO-EA induced Nrf2 antioxidant target genes (NQO1, HO-1, GST-3) in brain and spinal cord neurons, and down regulated pro-inflammatory mediators (iNOS, COX-2, FasL, TNF). This suggests the neuroprotective activity of RTA-405 may stem from its ability to activate the Nrf2 pathway in the CNS.

**Brain inflammation (Cerebral malaria): Potential benefit (mice)**

In a mouse model of malaria, the use of CDDO-EA in combination with the anti-malarial drug artesunate prevented the neurological manifestations of cerebral malaria [3]. CDDO-EA did not affect parasite burden but instead prevented BBB leakage and decreased pro-inflammatory cytokines. This suggests that RTA-405 could mitigate neurological impairment in the context of inflammation.

APOE4 interactions: Unknown

**Ageing and related health concerns:** May help mitigate cancer risk following carcinogen exposure based on rodent models. Human studies are needed.

*Types of evidence:*

- Several laboratory studies

**Cancer: Potential minor benefit (mice)**

In mouse models of lung cancer (vinyl carbamate induced), treatment of the mice with CDDO-EA supplemented chow starting 1 week following carcinogen exposure reduced tumor number (by 50%),

tumor size (by 70%), and lesion severity (by 100%) [4; 5]. When treatment was started 8 weeks after carcinogen exposure, CDDO-EA treatment was less effective. In a transgenic metastatic pancreatic cancer model, treatment with CDDO-EA prior to tumor formation did not extend survival [6]. In a colorectal cancer model, CDDO-EA pre-treatment protected against radiation induced tumor formation for at least 100 days in cancer susceptible mice [7]. These studies suggest that RTA-405 may help mitigate the potential for certain carcinogens to cause cancer but is not effective after cancer associated processes have already been initiated.

### Liver disease: Potential benefit (mice)

In a mouse model of chronic liver disease (CCl<sub>4</sub> injections), RTA-405 supplemented chow (200 mg/kg/diet) led to a decrease in fibrotic tissue, maintenance of liver function, and improved survival (from 30% to 80%) [8]. Beneficial effects were dependent on induction of the Nrf2 antioxidant pathway.

**Safety:** Generally safe and well-tolerated in rodents, but human studies are needed.

#### *Types of evidence:*

- Several laboratory studies

**RTA-405 has not been tested in humans.** Most rodent studies indicate that RTA-405 is generally safe and well tolerated without evidence of kidney or liver toxicity. One study in a diabetic rat model showed evidence of renal toxicity, but the lot of RTA-405 used in this study was contaminated with impurities [9]. Two additional studies (one in mice, one in rats) indicated that RTA-405 enhanced renal function with no adverse effects on blood pressure, blood glucose levels, or body weight [10; 11].

A cell culture study indicated that RTA-405 does not decrease the sensitivity of cancer cells to chemotherapy (doxorubin or cisplatin)[12].

### Sources and dosing:

The human equivalent doses for the doses of RTA-405 used in rodent studies are 2.4-4.8 mg/kg/bw.

RTA-405 (CDDO-EA) is manufactured by Reata Pharmaceuticals. CDDO-EA can be purchased for research, but not patient use, through biological chemical suppliers.

### Research underway:

There are no registered ongoing or planned clinical trials for RTA-405.

### Search terms:

Pubmed, Google: RTA-405 + aging, neurodegeneration, neuroprotection, aging, clinical trials, safety, cancer, cardiovascular, inflammation, Nrf2

Websites visited for RTA-405:

- [Pubchem](#)

### References:

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If you have suggestions for drugs, drugs-in-development, supplements, nutraceuticals, or food/drink with neuroprotective properties that warrant in-depth reviews by ADDF's Aging and Alzheimer's Prevention Program, please contact [INFO@alzdiscovery.org](mailto:INFO@alzdiscovery.org). To view our official ratings, visit [Cognitive Vitality's Rating page](#).