Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

RTA-405

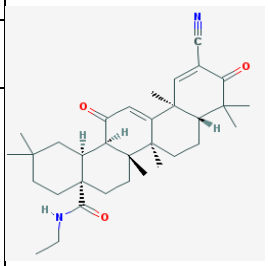
Evidence Summary

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.

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

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 ± 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 ± 4.8 days control vs. 189 ± 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 ± 3.7 days to 144.72 ± 8.1 days p<0.001) when given at pre-symptomatic or (from 40.1 ± 4.7 days to 57.6 ± 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-a3) in brain and spinal cord neurons, and down regulated pro-inflammatory mediators (iNOS, COX-2, FasL, TNFα). 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

Aging 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_4 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, neurodegeration, neuroprotection, aging, clincal trials, safety, cancer, cardiovascular, inflammation, Nrf2

Websites visited for RTA-405:

- Pubchem

References:

1. Stack C, Ho D, Wille E *et al.* (2010) Triterpenoids CDDO-ethyl amide and CDDO-trifluoroethyl amide improve the behavioral phenotype and brain pathology in a transgenic mouse model of Huntington's disease. *Free radical biology & medicine* 49, 147-158.http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2916021/

2. Neymotin A, Calingasan NY, Wille E *et al.* (2011) Neuroprotective effect of Nrf2/ARE Activators, CDDO-ethylamide and CDDO-trifluoroethylamide in a Mouse Model of Amyotrophic Lateral Sclerosis. *Free radical biology & medicine* 51, 88-96.http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3109235/

3. Crowley VM, Ayi K, Lu Z *et al.* (2017) Synthetic oleanane triterpenoids enhance blood brain barrier integrity and improve survival in experimental cerebral malaria. *Malaria Journal* 16, 463.http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5686938/

4. Liby K, Risingsong R, Royce DB *et al.* (2009) Triterpenoids CDDO-methylester or CDDO-ethylamide and rexinoids LG100268 or NRX194204 for prevention and treatment of lung cancer in mice. *Cancer prevention research (Philadelphia, Pa)* 2, 1050-1058.http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2818234/

5. Liby K, Royce DB, Williams CR *et al.* (2007) The Synthetic Triterpenoids CDDO-Methyl Ester and CDDO-Ethyl Amide Prevent Lung Cancer Induced by Vinyl Carbamate in A/J Mice. *Cancer Research* 67, 2414-2419.http://cancerres.aacrjournals.org/content/canres/67/6/2414.full.pdf

6. Liby K, Royce DB, Risingsong R *et al.* (2010) Synthetic triterpenoids prolong survival in a transgenic mouse model of pancreatic cancer. *Cancer prevention research (Philadelphia, Pa)* 3, 1427-1434.http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2988079/

7. Kim SB, Bozeman R, Kaisani A *et al.* (2016) Radiation Promotes Colorectal Cancer Initiation and Progression by Inducing Senescence-Associated Inflammatory Responses. *Oncogene* 35, 3365-3375.http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4837107/

8. Getachew Y, Cusimano FA, Gopal P *et al.* (2016) The Synthetic Triterpenoid RTA 405 (CDDO-EA) Halts Progression of Liver Fibrosis and Reduces Hepatocellular Carcinoma Size Resulting in Increased Survival in an Experimental Model of Chronic Liver Injury. *Toxicological Sciences* 149, 111-120.http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5013822/

9. Zoja C, Corna D, Nava V *et al.* (2013) Analogs of bardoxolone methyl worsen diabetic nephropathy in rats with additional adverse effects. *American Journal of Physiology-Renal Physiology* 304, F808-F819.https://www.physiology.org/doi/abs/10.1152/ajprenal.00376.2012

10. Chin M, Lee C-YI, Chuang J-C *et al.* (2013) Bardoxolone methyl analogs RTA 405 and dh404 are well tolerated and exhibit efficacy in rodent models of Type 2 diabetes and obesity. *American Journal of Physiology-Renal Physiology* 304, F1438-F1446.https://www.physiology.org/doi/abs/10.1152/ajprenal.00387.2012

11. Ding Y, Stidham R, Bumeister R *et al.* (2013) The synthetic triterpenoid, RTA405, increases glomerular filtration rate and reduces angiotensin II-induced contraction of glomerular mesangial cells. *Kidney international* 83, 845-854.http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3600401/

12. Probst BL, McCauley L, Trevino I *et al.* (2015) Cancer Cell Growth Is Differentially Affected by Constitutive Activation of NRF2 by KEAP1 Deletion and Pharmacological Activation of NRF2 by the Synthetic Triterpenoid, RTA 405. *PLoS ONE* 10, e0135257.http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4547720/