

*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.*

## Oxaloacetate

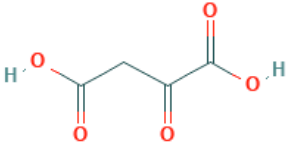
### Evidence Summary

There is little evidence that oxaloacetate will be beneficial for most diseases except possibly stroke or traumatic brain injury.

**Neuroprotective Benefit:** There is little evidence that oxaloacetate will be beneficial for Alzheimer's disease, except possibly at high doses.

**Aging and related health concerns:** Despite one *C. elegans* lifespan study, there is little evidence suggesting that oxaloacetate will be beneficial for age-related diseases.

**Safety:** Oxaloacetate is probably safe, but there are few human studies.

<b>Availability:</b> Available as a supplement.	<b>Dose:</b> 1g twice per day is being used in Alzheimer's clinical trials	<b>Chemical formula:</b> C <sub>4</sub> H <sub>4</sub> O <sub>5</sub> <b>MW:</b> 132.07 g/mol  Source: <a href="#">Pubchem</a>
<b>Half life:</b> Unknown, but likely very short	<b>BBB:</b> Probably penetrant	
<b>Clinical trials:</b> One ongoing for Alzheimer's disease	<b>Observational studies:</b> None	



### What is it?

Oxaloacetate (OAA) is a small molecule intermediate involved in many biochemical reactions including gluconeogenesis, the glyoxylate cycle, glyoxylate degradation, anaerobic respiration, the Krebs cycle, aspartate biosynthesis, and degradation of glutamate ([Cash, 2009](#)).

From the perspective of Alzheimer's disease, there are two potential mechanisms by which OAA may be beneficial. As an intermediate of the Krebs cycle, it may increase mitochondrial respiration. Additionally, it may reduce glutamate toxicity through glutamate oxaloacetate transaminase (GOT). GOT converts glutamate and OAA to L-aspartate and alpha-ketoglutarate. Therefore, by administering OAA, glutamate is reduced in the periphery and this reduction acts as a glutamate 'sink', pulling excess glutamate from the brain and preventing glutamate toxicity.

**Neuroprotective Benefit:** There is little evidence that oxaloacetate will be beneficial for Alzheimer's disease, except possibly at high doses.

#### Types of evidence:

- One PK and one FDG-PET clinical study in Alzheimer's patients
- One clinical study in Parkinson's patients
- Five preclinical studies

#### Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function?

None

#### Human research to suggest benefits to patients with dementia:

[Swerdlow et al \(2016\)](#) treated 6 Alzheimer's patients with 100mg of OAA twice per day (bid) for 28 days. On day one there was a transient (~30 min) increase in plasma OAA levels with no increase 28 days later. The authors concluded that 100mg OAA bid was too low a dose to see an increase over background serum levels of OAA.

The Trial of Oxaloacetate in Alzheimer's Disease (TOAD) trial is an open label trial comparing the effects of 500mg OAA bid to 1000mg OAA bid in 21 Alzheimer's patients over 28 days. An interim analysis found a greater increase in hippocampal FDG-PET signal in the 1000mg bid group compared to the 500mg bid group from baseline (2.5% vs. 0.3% increase for the 1000mg and 500mg groups, respectively) ([Vidoni et al, 2018](#)).



Human research to suggest benefits to patients with Parkinson's disease:

One RCT tested the effects of 100mg OAA/100mg ascorbic acid per day in 33 Parkinson's patients over 4 months. There were no significant differences in any outcomes ([NCT01741701](#)).

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

[Wilkins et al \(2014\)](#) reported that two-week treatment with OAA increased markers of mitochondrial biogenesis (p-AMPK, PGC1 $\alpha$  mRNA and nuclear translocation). There were no changes in COX2 or SIRT1; however, markers of inflammation (NF-kB and CCL11) decreased while neurogenesis increased. OAA also increased p-mTOR and p-CREB. *In vitro*, OAA increased the NAD/NADH ratio and SIRT1 expression ([Wilkins et al, 2016](#)).

In a rat model where either amyloid or TNF $\alpha$  were injected into the brain, peripheral treatment of OAA prevented the reduction of long-term potentiation (LTP) ([Zhang et al, 2017](#)). In rodent models of hemorrhagic and ischemic stroke, OAA improved neurologic performance, blood brain barrier integrity, long-term potentiation, and reduced lesion size ([Boyko et al, 2012](#); [Marosi et al, 2009](#); [Nagy et al, 2009](#)).

The hypothesized mechanism for neuroprotection using OAA is to reduce glutamate neurotoxicity through glutamate oxaloacetate transaminase (GOT). GOT converts glutamate and OAA to L-aspartate and alpha-ketoglutarate. Therefore, by administering OAA, glutamate is reduced in the periphery and this reduction acts as a glutamate 'sink', pulling excess glutamate from the brain.

APOE<sub>4</sub>

No information

**Ageing and related health concerns:** Despite one *C. elegans* lifespan study, there is little evidence suggesting that oxaloacetate will be beneficial for age-related diseases.

Types of evidence:

- *Two lifespan studies, one in worms and one in mice*
- *Once cancer preclinical study*
- *One open-label study in diabetes*

Lifespan

One study in worms suggested that OAA increased median lifespan by 25% and maximal lifespan by 13%. These increases required signaling through AMPK-FOXO ([Williams et al, 2009](#)). OAA was tested in



the NIA's Interventions Testing Program and did not increase lifespan in mice. However, OAA was ground into chow at an intended concentration of 2200ppm. OAA broke down in the food, and at different time points it was estimated the food did not contain more than 250-560ppm of OAA during the lifespan study. Therefore, due to the steep reductions in expected dosing, conclusions cannot be drawn from this experiment ([Strong et al, 2013](#)).

### Cancer

One study reported that OAA reduced tumor size in glioma-implanted rodents and increased survival, especially when co-administered with a glioma chemotherapeutic ([Ruban et al, 2012](#)). Similar to the neuroprotective studies above, the benefits of OAA treatment were thought to be due to a reduction in peripheral glutamate.

### Diabetes

One open label study suggested that OAA was effective in most patients with type 1 and type 2 diabetes. The paper is from 1968 and the quality of the data is low (no specific outcome measures of OAA's effects, just whether it was effective or ineffective) ([Yoshikawa, 1968](#)).

**Safety:** Oxaloacetate is probably safe, but there are few human studies.

### Types of evidence:

- *Two small clinical studies*

One small study in Parkinson's patients suggested that OAA increased the risk of gastrointestinal symptoms and possible worsening of Parkinson's symptoms and insomnia. However, the study is too small to draw conclusions ([NCT01741701](#)). One small, open-label study reported no side effects, though the data was poor ([Yoshikawa, 1968](#)).

### **Drug interactions:**

There is little clinical work completed and drug interactions are unknown.

### **Sources and dosing:**

OAA is unstable, and a thermally stabilized drug should be used. The ongoing TOAD study is using 500 or 1000mg OAA

#### Research underway:

One open-label clinical study of oxaloacetate for Alzheimer's disease was recently completed. Results of FDG-PET data were presented above. Cognitive data should be out soon ([NCT02593318](#)).

#### Search terms:

Pubmed:

oxaloacetate (title/abstract) + lifespan, aging, Alzheimer, cardiovascular, cancer, neuropathy, hypotension

Websites visited for

- Clinicaltrials.gov (oxaloacetate)
- Drugs.com
- DrugBank.ca
- Pubchem

***Disclaimer:** Cognitive Vitality Reports® do not provide, and should not be used for, medical advice, diagnosis, or treatment. You should consult with your healthcare providers when making decisions regarding your health. Your use of these reports constitutes your agreement to the [Terms & Conditions](#).*

*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](#).*