



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.

Tauroursodeoxycholic Acid (TUDCA)

Evidence Summary

TUDCA prevents neurodegeneration in preclinical models and improves insulin sensitivity and cholesterol in clinical populations; it is regarded as safe, but no data exist for long-term treatment.

Neuroprotective Benefit: Promising for neuroprotection and potentially for AD therapy, but all evidence is currently based on preclinical work.

Aging and related health concerns: Effects in healthy adults are unknown, but TUDCA increases insulin sensitivity, decreases total (and HDL) cholesterol, and reduces inflammation.

Safety: TUDCA is safe and well-tolerated in patients with liver transplants, liver cirrhosis, and other diseases, but no clinical data exist for treatments longer than 1 year.



What is it? Tauroursodeoxycholic acid (TUDCA) is a water-soluble bile salt naturally occurring in the body. When bile salts reach the intestines, they can be metabolized by bacteria into ursodeoxycholic acid (UDCA). TUDCA is formed when taurine binds to UDCA. TUDCA is used to treat cholestasis, a condition in which bile fails to flow from the liver to the duodenum. TUDCA, UDCA, and other soluble bile salts can counteract the toxicity of regular bile acids when the latter are backed up in the liver. TUDCA is also used to treat cholesterol gallstones, dissolving them to a size in which they may be passed.

Neuroprotective Benefit: Promising for neuroprotection and potentially for AD therapy, but all evidence is currently based on preclinical work.

Types of evidence:

- Numerous laboratory studies

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

Human research to suggest benefits to patients with dementia: None available.

Mechanisms of action for neuroprotection identified from laboratory and clinical research: Only preclinical studies have been carried out.

The most compelling study for neuroprotection is one in an Alzheimer's mouse model (APP/PS1) where the treatment was started after pathology was present (7 months old). TUDCA treatment (500 mg/kg, i.p., every 3 days) for 3 months significantly decreased A β deposition (A β 40 and A β 42) in the frontal cortex and hippocampus ([Dionisio et al., 2015](#)). The amyloidogenic processing of amyloid precursor protein was also reduced, indicating that TUDCA interferes with A β production. TUDCA also decreased glial activation and proinflammatory cytokine RNA expression (TNF α), while partially rescuing synaptic loss. Thus, even when started after disease onset, TUDCA was able to attenuate A β production and deposition, tau pathology, glial activation, and loss of synaptic function. Most of these effects are likely related to the activation of the Akt/GSK3 β signaling pathway. Only a trend to improved spatial memory was found in TUDCA-treated APP/PS1 mice, likely because these mice already had extensive cognitive deficits. Several studies have shown in the same mouse model that when TUDCA diet (0.4% mixed in food) is started at 2 months of age (before significant amyloid deposits) and continued for 6 months,



deficits in spatial, recognition, and contextual memory can be prevented ([Nunes et al., 2012](#); [Lo et al., 2013](#)). These actions were mediated in part through modulation of the γ -secretase activity. This same treatment paradigm also prevented the decrease in PSD95 expression, suggesting a neuroprotective role of TUDCA at the synaptic level ([Ramalho et al., 2013](#)).

Other potential mechanisms of action for neuroprotection have been reported. An *in vitro* study has shown that TUDCA can directly suppress A β -induced disruption of the mitochondrial membrane structure, which correlates with mitochondrial health ([Rodrigues et al., 2001](#)). A study from a cell culture model of Alzheimer's reported that TUDCA reduces p53-induced apoptosis and modulates expression of the anti-apoptotic Bcl2 family ([Ramalho et al., 2006](#)). TUDCA also downregulates the expression of connective tissue growth factor (CTGF), which is present in the vicinity of A β plaques and neurofibrillary tangles and influences γ -secretase activity ([Lo et al., 2013](#)).

Studies in mouse models of Huntington's disease also reported neuroprotection with TUDCA. TUDCA increased neuronal survival, preserved mitochondria, and decreased huntingtin inclusions in the mouse striatum while reducing cognitive and sensorimotor deficits ([Keene et al., 2001](#); [2002](#)). The authors noted that "TUDCA can be administered orally or i.v., are accessible to the brain and other organs, and exhibit essentially no toxicity".

APOE4 interactions: Unknown.

Aging and related health concerns: Effects in healthy adults are unknown, but TUDCA increases insulin sensitivity, decreases total (and HDL) cholesterol, and reduces inflammation.

Types of evidence:

- 7 clinical trials, 5 in liver disease, 1 in insulin resistance, and 1 in ALS
- Numerous laboratory studies

Liver disease: IMPROVED. Randomized controlled trials have shown that TUDCA treatment improves liver function in patients with liver cirrhosis ([Pan et al., 2013](#)), HCV-related chronic hepatitis ([Crosignani et al., 1998](#)), and cholestasis ([Ma et al., 2016](#)), a condition in which bile fails to flow from the liver to the duodenum. These studies have shown that TUDCA drastically lowers serum liver enzymes that are markers of liver inflammation (ALT, AST, and ALP). TUDCA effects on cholestasis are strong and it is used as a reference drug for these effects.



Insulin sensitivity: INCREASED. In a randomized controlled trial of 20 obese men and women with insulin resistance, TUDCA treatment (1750 mg/day) for 4 weeks resulted in a 30% increase in insulin sensitivity in the liver and muscle ([Kars et al., 2010](#)). Although TUDCA is reported to decrease ER stress, markers of ER stress were not altered in these subjects (from adipose tissue biopsy). Thus, the specific cellular mechanisms responsible for the increased insulin sensitivity are unclear. It is also unknown whether TUDCA is protective in healthy adults without insulin resistance.

Cholesterol: DECREASED. In a small dose-response study in 24 primary biliary cirrhosis patients, higher doses of TUDCA treatment (1000 or 1500 mg/day) for 6 months decreased both total and HDL cholesterol compared to baseline, while the low dose (500 mg/day) showed no change ([Crosignani et al., 1996](#)). Change ratios for total cholesterol were 1.01, 0.94, and 0.89 for 500, 1000, and 1500 mg, respectively. Change ratios for HDL cholesterol were 1.04, 0.81, and 0.81 for 500, 1000, and 1500 mg, respectively. There were no placebo controls in this study. The changes in cholesterol levels may be explained by the improvement of cholestasis and also by a decrease in cholesterol absorption. It is unknown whether TUDCA would have similar effects in people without liver disease.

Inflammation: DECREASED IN MICE. In a mouse model of neuroinflammation (LPS injection), TUDCA treatment reduced the production of nitrites by microglial cells and astrocytes by inhibiting the NFkB pathway ([Yanguas-Casas et al., 2014](#)). A triple anti-inflammatory effect on glial cells was observed: 1) reduced glial cell activation, 2) reduced microglial cell migratory capacity, and 3) reduced expression of chemoattractants (e.g., MCP1) and vascular adhesion proteins (e.g., VCAM1) that are required for microglial migration and blood monocyte invasion to the brain inflammation site.

Safety: TUDCA is safe and well-tolerated in patients with liver transplants, liver cirrhosis, and other diseases, but no clinical data exist for treatments longer than 1 year.

Types of evidence:

- 1 Cochrane meta-analysis in people receiving liver transplants
- 4 RCTs, 3 in liver cirrhosis, and 1 in ALS
- Numerous laboratory studies

A Cochrane meta-analysis of 7 randomized controlled trials in liver-transplanted patients reported that bile acids including TUDCA were safe and well-tolerated ([Chen and Gluud, 2005](#)). Of the 4 trials that reported adverse events, diarrhea was the only adverse event reported and occurred in only 2 trials.



There were no significant differences in adverse events between those receiving standard immunosuppressants versus those receiving bile acids in addition. Other trials in liver cirrhosis (up to 6 months) and ALS (1 year) have also reported that TUDCA is well-tolerated with diarrhea being the only side effect ([Elia et al., 2016](#); [Ma et al., 2016](#); [Pan et al., 2013](#); [Crosignani et al., 1996](#)).

Drug interactions: Unknown. In human liver cell culture, TUDCA and UDCA reduced cell death induced by alcohol when administered at the same time ([Henzel et al., 2004](#)). However, when TUDCA or UDCA was administered before ethanol insult, damage to liver cells was exacerbated. The mechanisms driving these opposing effects are unclear. It is also unknown whether these effects extend to humans.

Sources and dosing: TUDCA is available as a dietary supplement in capsule form. No studies or websites have directly compared efficacy, purity, or safety of the different brands. Doses used in clinical studies vary widely. As low as 10-13 mg per day has been shown to improve liver regeneration rates in people with chronic liver disease ([Panella et al., 1995](#)). Doses of 750 mg daily have been used in patients with liver cirrhosis ([Ma et al., 2016](#); [Pan et al., 2013](#)).

The dose used in mouse models of Alzheimer's and Huntington's disease that provided neuroprotection was 500 mg/kg (i.p.) every 3 days, or a diet containing 0.4% TUDCA (roughly estimated at 12 mg/day, or 400 mg/kg/day) ([Dionisio et al., 2015](#); [Lo et al., 2013](#); [Keene et al., 2002](#)). The human equivalent oral dose after taking into account differential body surface area is 32.5 mg/kg/day (or 1951 mg daily for a person weighing 60 kg).

Research underway: Clinical trials are underway to test the efficacy of TUDCA in type 1 diabetes ([NCT02218619](#)) and in HIV patients with insulin resistance ([NCT01877551](#)). These trials are scheduled to be completed in late 2018.

Search terms:

Pubmed, Google: Tauroursodeoxycholic Acid, TUDCA

- + meta-analysis, + clinical trial, + dementia, + Alzheimer's, + cognitive, + lifespan, + cardiovascular, + neuropathy, + safety, + ApoE4

Clinicaltrials.gov: Tauroursodeoxycholic Acid, TUDCA



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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. To view our official ratings, visit [Cognitive Vitality's Rating page](#).