

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.

Nordihydroguaiaretic acid (NDGA)

Evidence Summary

NDGA has anti-inflammatory, anti-viral, anti-oxidant, and anti-cancer properties and extends lifespan in male mice, but high doses may cause liver and kidney toxicity and no effects have been shown in humans.

Neuroprotective Benefit: Only preclinical evidence exists, which is mixed for mechanisms of action. Brain penetrance is likely low.

Aging and related health concerns: NDGA has anti-inflammatory, anti-viral, and anti-proliferative properties and extends lifespan in mice, but these benefits have not been extended to humans.

Safety: NDGA treatment in cancer patients and in preclinical studies has been associated with kidney and liver toxicity, but low doses may be safer.

What is it? NDGA is produced by the leaves of the creosote bush (*Larrea tridentate*) and constitutes 5-10% of the leaves' dry weight ([Lu et al., 2010](#)). The leaves are shiny with a thick resinous coating, and NDGA represents 80% of all of the phenolic compounds contained in the resin. NDGA and other phenolic compounds act as antimicrobial agents and as protection against herbivores, UV radiation, and water loss in arid climates. Many indigenous tribes of the US have used extracts from this plant to treat diseases like diabetes, cancer, tuberculosis, chicken pox, skin sores, venereal disease, colds, and rheumatism.

NDGA possesses anti-inflammatory, anti-viral, anti-oxidative, and anti-proliferative properties. NDGA inhibits arachidonic acid 5-lipoxygenase, an enzyme that catalyzes the addition of oxygen to arachidonic acid. Inhibition of this enzyme reduces leukotriene and prostaglandin synthesis, leading to a suppression of inflammatory pathways ([Salari et al., 1984](#); [Bhattacharjee et al., 1988](#); [Zhang et al., 2013](#)). LOX inhibitors are currently being investigated as treatment for cancers, coronary artery disease, and asthma. In addition, 4 phenolic hydroxyl groups on NDGA confer strong antioxidant properties ([Lu et al., 2010](#)). Terameprocol (tetra-O-methyl nordihydroguaiaretic acid) is a synthetic derivative of NDGA and is a non-selective lipoxygenase inhibitor.

Neuroprotective Benefit: Only preclinical evidence exists, which is mixed for mechanisms of action. Brain penetrance is likely low.

Types of evidence:

- o clinical trials
- 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 exist and the evidence for neuroprotection is mixed, despite its strong anti-inflammatory and anti-oxidative properties ([Goodman et al., 1994](#); [Hernandez-Damian et al., 2014](#)).

Alzheimer's: MIXED PRECLINICAL DATA. In a mouse model of Alzheimer's disease (Tg2576), consumption of NDGA for 10 months (0.5% NDGA in the diet) significantly decreased A β deposition in

the brain ([Hamaguchi et al., 2009](#)). However, NDGA increased the amount of toxic A β oligomers compared to mice receiving the control diet. This study suggests that NDGA may inhibit the formation of plaques from oligomers, but it does not inhibit the formation of toxic oligomers from A β monomers. In a review that compared different natural phenolic compounds, the authors noted that NDGA would be inappropriate to pursue for Alzheimer's disease because it increases toxic oligomers. Instead, they suggest that rosmarinic acid is the ideal compound, because it inhibited both steps from monomers to toxic oligomers, and oligomers to aggregated A β deposition ([Yamada et al., 2015](#)).

Other studies have shown positive effects on neuroprotection. In wild-type mice, NDGA (1 mg/kg/day, s.c.) for 30 days strongly enhanced glutamate uptake via upregulation of the glutamate transporter EAAT2, leading to reduced excitotoxicity ([Boston-Howes et al., 2008](#)).

There are many studies carried out *in vitro* that also point to mechanisms of action for neuroprotection. NDGA inhibits the acetylcholinesterase ([Szwajgier, 2015](#); [Remya et al., 2013](#)) and prevents A β -induced neuronal injury in a dose-dependent manner by suppressing the A β -induced increase in reactive oxygen species and calcium levels ([Goodman et al., 1994](#)). NDGA also inhibits A β fibril formation and dose-dependently breaks down A β ₄₀ and A β ₄₂ fibrils ([Ono et al., 2002](#)). These partially broken-down fibrils are less toxic in cell culture than intact fibrils. NDGA also inhibits secretion of large soluble fragments of APP ([Kinouchi et al., 1995](#)).

Blood-brain-barrier penetration: LOW. NDGA has low blood-brain-barrier penetration and poor central nervous system activity ([Remya et al., 2013](#)). Newly designed NDGA derivatives have been shown to possess better blood-brain-barrier permeability with acetylcholinesterase inhibiting properties, along with good adsorption, distribution, metabolism, and excretion (ADME) profiles. These compounds may hold greater promise for neuroprotection if they do not increase toxic A β oligomers.

APOE4 interactions: None available.

Aging and related health concerns: NDGA has anti-inflammatory, anti-viral, and anti-proliferative properties and extends lifespan in mice, but these benefits have not been extended to humans.

Types of evidence:

- 3 clinical trials, 1 in prostate cancer, 1 in leukemia, and 1 in people with actinic keratosis (precancerous skin lesions)
- Numerous laboratory studies, including lifespan studies in mice

Lifespan: BENEFIT IN MALE MICE. No evidence in humans yet. The National Institute on Aging Interventions Testing Program (NIA ITP) was designed to test compounds such as NDGA that are purported to extend lifespan and/or delay onset of age-related diseases. This collaborative program uses 1) parallel studies in males and females at 3 different sites, 2) genetically heterogeneous mice to guard against conclusions based on a single inbred genotype, and 3) enough samples to provide statistical power.

In male mice, NDGA treatment started at 6 months of age (800, 2500, or 5000 mg/kg-diet, or ppm) significantly increased the median survival by 8-10% ([Harrison et al., 2014](#)). These results are consistent with a previous NIA ITP study ([Strong et al., 2008](#)), but some of the benefit may be explained by an artifact of unusually short survival of male controls at 2 out of 3 sites.

The 2008 study did not show extension of lifespan in female mice ([Strong et al., 2008](#)). The 2014 follow-up tested whether this sex difference was due to differences in pharmacodynamics. A higher dose (5000 ppm) was used in an attempt to increase blood NDGA levels to see whether these would increase female lifespan ([Harrison et al., 2014](#)). The blood level was increased to a value similar to that in males receiving 2500 ppm NDGA, a dose most effective at increasing lifespan in males, but there was no evidence for an increase in lifespan in female mice. Thus the lack of benefit in females appears to not be due to altered pharmacodynamics.

A 2016 follow-up to the 2014 NIH ITP study reported that while NDGA increased median lifespan in male mice, there was no effect on maximal lifespan at any dose tested, in males or in females ([Strong et al., 2016](#)). Thus, positive effects on lifespan in males may be limited to the middle portion of the lifespan. Interestingly, in this study, they found that neuromuscular performance was improved in both males (2500 ppm) and females (5000 ppm). On the rotarod test, grip duration of male mice treated with NDGA was indistinguishable from young mice and significantly higher than that of old controls. The ability to remain on the rotarod was significantly increased in both males and females at 22 months of age. The NIH ITP continues to examine the effects of NDGA on lifespan as well as on age-sensitive physiological traits. Because cancer is often the cause of death for rodents, the anti-proliferative properties of NDGA may produce greater lifespan extension in rodents than humans. In humans, the risks (toxicity discussed below) may outweigh the benefits.

In a Huntington's disease mouse model, NDGA treatment (12 mg/kg/day, i.p., 5 times a week) started at 30 days old extended their survival by 19% (105 days in vehicle-treated and 125 days in NDGA-



treated)([Lee et al., 2011](#)). NDGA treatment also reduced oxidation (lipid peroxidation), improved ATP generation, restored mitochondrial function (membrane potential), and blocked the apoptotic pathway (prevented cleavage of pro-caspase 9). Only male mice were included in this study and it's unknown whether similar benefits could be experienced by females.

Cancer. MIXED. In a phase II open-label study of prostate cancer patients, NDGA (2000 mg/day, orally) did not induce significant declines in PSA levels in a pre-planned interim analysis of 12 patients ([Friedlander et al., 2012](#)). The authors suggested that there was low bioavailability of NDGA and routes that bypass the gastrointestinal tract (parenteral; e.g., intravenous, intramuscular, etc.) may be more promising to avoid first-pass hepatic metabolism. However, other studies reported that NDGA is detoxified in the liver (via glucuronidation) and parenteral administration is not ideal ([Lambert et al., 2002](#)). In a double-blind randomized controlled trial of 113 patients with actinic keratosis (precancerous growth on skin), application of an NDGA cream for 14-28 days reduced actinic keratosis by 66% ([Olsen et al., 1991](#)).

In chemotherapy (trastuzumab)-resistant breast cancer cell lines, NDGA promoted cell death and inhibited insulin-like growth factor-1 (IGF-1) and HER2 signaling, with reduced downstream PI3 kinase/Akt signaling ([Rowe et al., 2008](#)). Additionally, a combination treatment with NDGA and chemotherapy suppressed proliferation and survival of resistant cells to a greater degree than either drug alone, suggesting that NDGA increases trastuzumab efficacy. This combination treatment may be therapeutic for HER2-overexpressing breast cancers that have developed treatment resistance. Many other cell culture studies have shown that NDGA suppresses growth of lung cancer, pancreatic cancer, and cervical cancer ([Lu et al., 2010](#)).

Potential mechanisms of action for anti-tumor activities include inhibition of the specificity protein 1 (Sp1)-regulated proteins such as cyclin-dependent kinase 1, survivin, and VEGF, which in turn, lead to inhibition of cell cycle, increased apoptosis, and decreased angiogenesis ([Smolewski 2008](#)). In contrast, NDGA exerts antioxidant and protective effects in non-tumor cells by modulating the nuclear factor erythroid 2-related factor 2 (Nrf2)/antioxidant response element (ARE) antioxidant pathway ([Hernandez-Damian et al., 2014](#)).

Weight: DECREASED. The 2014 NIH ITP study reported that both males and females receiving NDGA had reduced body weight ([Harrison et al., 2014](#)). The high dose (5000 ppm) reduced body weight in female mice by 14, 22, and 23% at 12, 18, and 24 months, respectively. In males, a smaller reduction in

body weight (by 3-6%) was observed with the same dose. The magnitude of weight loss did not correlate with longevity.

Anti-viral: BENEFIT. NDGA may have anti-viral properties; *in vitro* studies have shown that it inhibits HIV₁, HSV, HPV, and the influenza virus by suppressing the Sp1-regulated transcription of these viruses ([Craig et al., 2000](#); [Hwu et al., 2008](#); [Uchide et al., 2005](#)).

Safety: NDGA treatment in cancer patients and in preclinical studies has been associated with kidney and liver toxicity, but low doses may be safer.

Types of evidence:

- 4 clinical trials in cancer patients, 2 in phase II and 2 in phase I
- Several laboratory studies

Toxicity: In 1943, NDGA was approved as a food antioxidant by the Meat Inspection Division of the US War Food Administration. It was utilized in the US as a preservative for fats and butter until it was shown to induce cystic nephropathy in rats. In 1968, it was removed from the FDA's list of generally-regarded-as-safe (GRAS) agents. However, products derived from the creosote bush remained on the over-the-counter, dietary-supplement market. Although consumption of low doses of such products appear to be harmless, high doses have been associated with dermatitis, kidney toxicity, biliary toxicity, and liver toxicity in humans, including fulminant liver failure and renal cell carcinoma ([Alderman S et al., 1994](#); [Obermeyer et al., 1995](#); [Lambert et al., 2002](#); [Meyers RO et al., 2009](#); [Lu et al., 2010](#)). In mice, LD₅₀ was 75 mg/kg, i.p., and there was a dose-dependent increase in serum alanine aminotransferase levels, suggesting liver damage ([Lambert et al., 2002](#)).

Chaparral (extract of the creosote bush) has been reported to be hepatotoxic at doses of crude herb from 1.5-3.5 g/day. Chaparral tea has traditionally been prepared with 1 teaspoon of chaparral leaves or flowers steeped in 1 pint of water for 15 minutes ([drugs.com](#)).

Clinical studies: In a phase II clinical trial in prostate cancer patients, NDGA (2000 mg/day orally) was generally well-tolerated, but some adverse events included nausea/vomiting, diarrhea, syncope, and elevated liver function tests ([Friedlander et al., 2012](#)). In a phase I study in glioma patients, hypoxia and kidney inflammation (interstitial nephritis) were noted at 2200 mg/day of terameprocol (i.v.), but the drug was well-tolerated at 1700 mg/day (i.v.) ([Grossman et al., 2012](#)). In a phase I study in leukemia patients, terameprocol treatment (1000, 1500, 2200 mg, i.v., 3 times per week for 2 weeks every 21 days)

was associated with nausea, headache, increased liver enzymes, pruritus (severe itching of the skin), and low blood sodium levels ([Tibes et al., 2015](#)).

Drug interactions: Drug interactions are not well-documented. Some information is available for Chaparral, the aqueous extract of the creosote bush which contains NDGA ([drugs.com](#)). Because NDGA inhibits platelet aggregation, there is a potential increased risk for bleeding in people taking anticoagulants, antiplatelet drugs, or supplements with these properties. An increased risk for toxicity is expected in people taking renal or hepatotoxic medications. NDGA blocks the activity of cytochrome P450 (enzyme that metabolizes many medications), and therefore may increase the risk for toxicity from medications that are substrates of this enzyme.

Sources and dosing: NDGA is produced by the leaves of the creosote bush (*Larrea tridentate*) and constitutes 5-10% of the leaves' dry weight ([Lu et al., 2010](#)). Although the pure form of NDGA is not available commercially, Chaparral (extract of the creosote bush) is sold as herbal supplements, in aqueous extract, tea bags, capsules, and tablets. Terameprocol, a synthetic derivative of NDGA, is under development by Erimos Pharmaceuticals LLC for the potential treatment of cancer, though no clinical trials are currently underway. In the clinic, NDGA and terameprocol have been used in cancer patients and given short-term or parallel to chemotherapy cycles at 2000 mg/day (oral) for NDGA ([Friedlander et al., 2012](#)) and 750-2200 mg/day (i.v.) for Terameprocol ([Grossman et al., 2012](#); [Tibes et al., 2015](#)). The optimal dose used in mouse lifespan studies was 2500 mg/kg of diet (ppm). Assuming that the mice consumed 10-15 g of chow per 100 g of body weight daily ([Huerkamp and Dowdy, 2008](#)), it is roughly estimated that the mice consumed ~250 mg/kg/day of NDGA. The human equivalent dose after taking into account differential body surface area is 20.3 mg/kg/day (or 1.22 g daily for a person weighing 60 kg), which is a dose only slightly lower than those associated with hepatotoxicity in humans. Chaparral tea has traditionally been prepared with 1 teaspoon of chaparral leaves or flowers steeped in 1 pint of water for 15 minutes ([drugs.com](#)). Chaparral has been reported to be hepatotoxic at doses of crude herb from 1.5-3.5 g/day.

Research underway: No clinical trials are underway on [clinicaltrials.gov](#) for NDGA or for terameprocol. A few prostate cancer trials using NDGA have been terminated because they ran out of the drug ([NCT00313534](#)) or found no significant clinical changes in their interim analysis ([NCT00678015](#)). One major hurdle with NDGA for neuroprotection is that it has low blood-brain-barrier penetration and poor central nervous system (CNS) activity, making it a poor candidate for CNS indications ([Remya et al., 2013](#)). New NDGA derivatives have been designed that have better blood-brain-barrier penetration

with good ADME profiles. It is unknown whether these derivatives increase toxic A β oligomers like NDGA, and even if not, safety and toxicity will need to be redefined.

Search terms:

Pubmed, Google: nordihydroguaiaretic acid, NDGA, and masoprocol

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

Clinicaltrials.gov: nordihydroguaiaretic acid, NDGA, and masoprocol

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