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.

Ursolic Acid

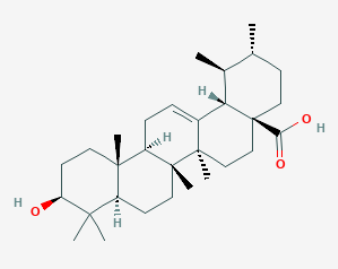
Evidence Summary

Ursolic acid has promising antioxidative, anti-inflammatory, and anti-cancer actions, but bioavailability is low and clinical evidence is sparse. Strategies to improve its bioavailability are underway.

Neuroprotective Benefit: Antioxidative and anti-inflammatory effects of ursolic acid are observed in preclinical models of cognitive impairment, Alzheimer's, Parkinson's, brain injury, and others, but no clinical evidence in humans exist to date.

Aging and related health concerns: Clinical evidence is limited, but ample preclinical evidence suggests benefits for cancer, atherosclerosis, cardiovascular disease, diabetes, arthritis, and others. For clinical utility, improved bioavailability is likely needed.

Safety: Long-term safety is unknown; based on a few short-term trials, ursolic acid liposome can cause adverse events such as liver enzyme elevation and abdominal distension. Rat toxicity studies suggest the NOAEL for ursolic acid is above 1,000 mg/kg/day.

Availability: OTC, supplement	**Dose**: Dose is not established. In people with metabolic syndrome, a daily dose of 150 mg (oral) was tested.	**Chemical formula:** $C_{30}H_{48}O_3$ **MW**: 456.7  Source: PubChem
Half life: 4 hours	**BBB**: penetrant, based on rodent studies	
Clinical trials: Several small studies have been carried out (e.g., a trial of 24 people with metabolic syndrome, a trial of 21 people with advanced solid tumors, and a few others).	**Observational studies**: none	

What is it? Ursolic acid is a pentacyclic triterpenoid that is present in many fruits and herbs, such as apple peels, cranberry juices, grape skins, holy basil, rosemary, thyme, oregano, sage, lemon balm, marjoram, and other herbs. Ursolic acid has been studied mostly in preclinical studies for its diverse pharmacological effects including protection from cancer and neurodegenerative diseases (Habtemariam, 2019). While ursolic acid does not scavenge reactive oxygen species, it has antioxidant effects through upregulation of antioxidant defenses. It also has anti-inflammatory activities. Ursolic acid also modulates the monoaminergic system by inhibiting the monoamine oxidase A and dopamine-β hydroxylase, potentially increasing the availability of monoamines (e.g., dopamine, norepinephrine) in the synaptic cleft (Ramos-Hryb et al., 2017).

Neuroprotective Benefit: Antioxidative and anti-inflammatory effects of ursolic acid are observed in preclinical models of cognitive impairment, Alzheimer's, Parkinson's, brain injury, and others, but no clinical evidence in humans exist to date.

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:
Numerous preclinical studies have been carried out that reported anti-inflammatory and antioxidant effects of ursolic acid (Habtemariam, 2019). Ursolic acid increases antioxidant defenses and decreases oxidative stress and other cellular stresses like mitochondrial stress and ER stress. The anti-inflammatory actions of ursolic acid may be mediated, in part, through inhibition of NF-kB signaling pathways.

Cognitive impairment models: In a mouse model of cognitive impairment induced by a high fat diet, ursolic acid treatment (10 mg/kg/day, oral, dissolved in distilled water containing 0.1% Tween-80) for 20 weeks significantly improved behavioral performance as measured by the step-through test and the Morris water maze task (Lu et al., 2011). These results were accompanied by the inhibition of ER stress and IκB kinase β/NF-κB-mediated inflammatory signaling and the restoration of insulin signaling and the PI3K/Akt/mTOR pathway. Ursolic acid administration also increased memory-related protein expression [p-mTOR(S2448), p-S6K(T389), p-S6K(T432/S424), p-CaMKII(T286), PSD-95] and reduced the expression of inflammatory markers (CD11b, GFAP, IL2, TNF-α, COX2, iNOS) in the hippocampus.

In a mouse model of cognitive deficits induced by chronic restraint stress, ursolic acid (5, 10 mg/kg oral gavage), metformin, and gliclazide (antidiabetic) administered alone or in combination for 30 days significantly restored cognitive performance, improved insulin sensitivity, decreased serum corticosterone levels, and decreased levels of a proinflammatory biomarker (TNF-α)(Mourya et al., 2018). Moreover, combination of metformin (150 mg/kg) and ursolic acid (10 mg/kg) produced enhanced improvement in insulin sensitivity and cognitive impairment as compared to each alone.

In a mouse model of cognitive deficits induced by LPS, ursolic acid treatment (10 or 20 mg/kg/day, oral gavage, dissolved in distilled water containing 0.1% Tween-80) for 12 weeks significantly improved cognitive deficits as measured by open field, step-through passive avoidance, and Morris water maze tasks (Wang et al., 2011). These effects were attributed to the decreased production of pro-inflammatory markers including COX-2, iNOS, TNF-α, IL-1β, IL-2 and IL-6. Ursolic acid markedly inhibited

the LPS-induced IκBα phosphorylation and degradation, NF-κB p65 nuclear translocation, and p38 activation.

In senescent mice (D-gal-induced neurotoxicity) with memory impairment, ursolic acid treatment (10 mg/kg/day, oral gavage, dissolved in distilled water containing 0.1% Tween-80) for 2 weeks markedly reversed the learning and memory impairment (Lu et al., 2007). Ursolic acid increased the activity of antioxidant enzymes while reducing lipid peroxidation. Ursolic acid also inhibited the activation of caspase-3 induced by D-gal and increased the level of growth-associated protein GAP43.

In a mouse model of memory impairment (induced by 5Gy irradiation), ursolic acid treatment (25 mg/kg/day) started 1 hour after irradiation and continued for 30 days greatly improved acute irradiation-induced deficits in contextual learning and memory and in novel object recognition memory although it exacerbated radiation-induced disruption of neurogenesis in the subgranular zone (Tang et al., 2017).

In a mouse model of drug (domoic acid)-induced cognitive deficits, ursolic acid treatment (100 mg/kg/day in distilled water containing 0.1% Tween-80, oral gavage) for 3 weeks attenuated mitochondrial dysfunction and cognitive deficits through promoting Akt phosphorylation and FoxO1 nuclear exclusion in the hippocampus (Wu et al., 2013).

Alzheimer's disease models: In mice intracerebroventricularly injected with Aβ25-35, administration of ursolic acid (14, 28, 56 mg/kg) improved memory as measured by the shortened escape latency and time to the target quadrants on the Morris water maze (Li et al., 2020). Ursolic acid treatment also significantly decreased the level of Aβ25–35 deposition. Ursolic acid at the 56 mg/kg dose was most effective at scavenging Aβ25–35, while microglial activation (Iba1 expression) was increased in a dose-dependent manner.

In a different study of mice intracerebroventricularly injected with Aβ25-35, ursolic acid treatment (10, 20, 40 mg/kg, oral gavage) for 11 days significantly reversed the Aβ25-35-induced learning and memory deficits (Liang et al., 2016). Ursolic acid attenuated the accumulation of oxidative stress (measured by malondialdehyde) and depletion of the endogenous antioxidant glutathione in the hippocampus. Ursolic acid also significantly suppressed the upregulation of inflammatory markers (IL-1β, IL-6, and tumor necrosis-α factor) in the hippocampus of Aβ25-35-treated mice.

In vitro studies also suggest that ursolic acid is neuroprotective. In PC12 cells exposed to Aβ25-35, ursolic acid inhibited the expression of iNOS and COX-2, inhibited the nuclear translocation of the p65 subunit of NF-κB and phosphorylation of IκB-α, and reduced ERK1/2, p-38, and JNK phosphorylation (Yoon et al., 2014). A similar study in PC12 cells exposed to Aβ25-35 reported that ursolic acid suppressed the generation of reactive oxygen species, attenuated DNA fragmentation, and attenuated Aβ-induced apoptosis in a dose-dependent manner (Hong et al., 2012).

Other *in vitro* studies have found that ursolic acid has inhibitory action on BACE1 (the amyloid precursor protein-cleaving enzyme that generates Aβ) and acetylcholinesterase (the enzyme that degrades the neurotransmitter acetylcholine)(Ramos-Hryb et al., 2017).

Multiple sclerosis models: In mice with drug (cuprizone)-induced demyelination, ursolic acid in drinking water (1 mg/mL) for 6 weeks decreased the extent of demyelination and enhanced myelin stain intensity (i.e., myelin basic protein levels) within the corpus callosum and protected oligodendrocyte lineage cells (i.e., Olig2+ cells)(Honarvar et al., 2019). Ursolic acid treatment also improved spatial recognition memory, as measured by the Y-maze.

In rats injected with ethidium bromide (i.c.v. route) into the hippocampus, ursolic acid treatment (5 mg/kg, oral) for 14 days attenuated neuroinflammation (measured by pro-inflammatory cytokines, TNF-α and IL-6) in the prefrontal cortex (Garabadu et al., 2020). Ursolic acid also significantly attenuated astrogliosis (measured by GFAP and Iba-1) in the rat prefrontal cortex. Ursolic acid also significantly attenuated the decrease in mitochondrial function, integrity, and respiratory control rate, while reducing mitochondria-dependent apoptosis in the rat prefrontal cortex. Levels of cytochrome c, caspase-9, and caspase-3 were reduced with ursolic acid.

Parkinson's disease models: In a rat model of Parkinson's disease (rotenone-injected), ursolic acid treatment (5 and 10 mg/kg, orally) ameliorated motor deficits (measured by the rotarod test and the open field test), attributed to the protection of dopaminergic neurons from degeneration (Peshattiwar et al., 2020). Ursolic acid treatment also significantly improved cognitive function, as measured by the Barnes maze test. Rotenone-induced oxidative stress and inflammation were significantly diminished by ursolic acid. Ursolic acid treatment restored levels of catalase, reduced glutathione, and superoxide dismutase, while significantly decreasing lipid peroxidation. Ursolic acid also significantly decreased TNF-α levels in the mid-brain. And ursolic acid promoted mitochondrial biogenesis, as measured by increased mitochondrial complex I gene expression.

In a mouse model of Parkinson's (MPTP-treated), ursolic acid treatment (25 mg/kg, orally) for 21 days significantly improved behavioral deficits, restored altered dopamine levels, and protected dopaminergic neurons (Rai et al., 2016). These improvements were accompanied by reductions in oxidative stress (measured by MDA and nitric oxide levels).

Brain injury models: In a mouse model of traumatic brain injury, ursolic acid treatment (50-150 mg/kg) reduced brain edema and neurological deficits (Ding et al., 2017). Ursolic acid increased nuclear translocation of the antioxidant transcription factor Nrf2, and also increased the expression of Akt.

In a mouse model of spinal cord injury, ursolic acid (100 or 200 mg/kg) administered 1 hour after the injury and daily thereafter promoted recovery of motor functions and axonal regrowth while suppressing proinflammatory cytokines such as IL-6 and TNF-α and activating MAPK and PI3K/Akt mTOR pathways (Sahu et al., 2018).

In a mouse model of cerebral ischemia (induced by middle cerebral artery occlusion), ursolic acid treatment (130 mg/kg, i.p.) 24 hours after the stroke led to a significant reduction in infarct size coupled with a reduced level of lipid peroxidation (measured by MDA), which was coupled with the induction of Nrf2 and HO-1 (Li et al., 2013). Ursolic acid also suppressed neuroinflammation (levels of TLR4 and NF-κB) after the stroke.

APOE4 interactions: Unknown.

Aging and related health concerns: Clinical evidence is limited, but ample preclinical evidence suggests benefits for cancer, atherosclerosis, cardiovascular disease, diabetes, arthritis, and others. For clinical utility, improved bioavailability is likely needed.

Types of evidence:

- 2 clinical trials
- Numerous laboratory studies

Lifespan: NO BENEFIT IN MICE, BUT EXTENDED IN FLIES AND WORMS
Ursolic acid was one of the therapies tested in the National Institute on Aging Interventions Testing Program (NIA ITP; see list of compounds here) for evaluating lifespan extension in mice. Ursolic acid

treatment (2,000 ppm in food) started at 10 months of age, however, did not affect lifespan in mice (Harrison et al., 2019).

In Drosophila flies, ursolic acid (50 µM/L, dissolved in dimethyl sulfoxide in food) significantly lengthened health and life span of males, while improving energy metabolism (Saats et al., 2019). The health-promoting effect of ursolic acid, demonstrated by a significant increase in climbing activity, was mediated by an upregulation of srl expression, the Drosophila orthologue of mammalian peroxisome proliferator-activated receptor-gamma coactivator 1α (PGC1α), an important regulator of energy homeostasis and mitochondrial function. Srl upregulation led to a metabolic shift in the flies without reducing fecundity or gut integrity. Ursolic acid treatment also affected the flies' microbiota.

In *C. elegans* worms, ursolic acid treatment (25 µM) increased mean lifespan by 31.3% (Negi et al., 2017). Ursolic acid uptake by worms resulted in reduced fat storage and attenuation of reactive oxygen species. Ursolic acid also reduced toxic protein aggregation in transgenic polyglutamine (polyQ) *C. elegans* by inducing c-Jun-NH2-terminal kinase (JNK1) activation.

In a related study in *C. elegans*, mean lifespan was 14.60 ± 0.5 days on 0 µM ursolic acid and 19.34 ± 0.4 days on 25 µM ursolic acid ($p < 0.0001$; 32.48% increase)(Negi et al., 2016). In heat shock stress (35 °C), all wild-type control worms died within 300 minutes, whereas the ursolic acid supplemented (25 µM) worms remained alive, with spontaneous movement and pharyngeal pumping. In an oxidative stress tolerance experiment (induced by the toxic agent paraquat), ursolic acid (25 µM) pre-treated worms demonstrated significant tolerance over control worms.

Arthritis: POTENTIAL BENEFIT BASED ON RODENT MODELS
In mouse models, ursolic acid treatment ameliorates autoimmune arthritis, acute inflammation, and chronic arthritis (induced by zymosan)(Habtemariam S, 2019).

Atherosclerosis: POTENTIAL BENEFIT BASED ON PRECLINICAL MODELS
In a mouse model of atherosclerosis (LDLR-/- mice fed a high-fat diet), ursolic acid treatment (0.05%) for 20 weeks resulted in reduced atherosclerotic lesion size by 19% (Nguyen et al., 2018). However, ursolic acid treatment did not affect plasma lipids or blood glucose levels nor white blood cell and monocyte counts. Ursolic acid prevented the reduced activity of MKP-1, a negative feedback effector that represses MAPK-mediated pro-inflammatory signaling pathways and cytokine secretion. In the same mouse model, ursolic acid treatment (50 mg/kg in 0.1% DMSO, i.p.) for 11 weeks significantly reduced atherosclerotic lesion size, accompanied by increased macrophage autophagy (Leng et al., 2016).

Increased macrophage autophagy, in turn, led to suppression of IL-1β secretion, promotion of cholesterol efflux, and attenuation of atherosclerosis in mice. Also in the same mouse model, dietary supplementation of ursolic acid (0.2%) for 11 weeks resulted in a 53% reduction in lesion formation (Ullevig et al., 2011).

In another mouse model of atherosclerosis (APOE-/- mice fed an atherogenic diet), ursolic acid treatment (100 mg/kg/day, intragastric gavage) for 12 weeks significantly attenuated atherosclerotic plaque formation and shrunk necrotic core areas, while also decreasing levels of LOX-1 (the main endothelial receptor for atherogenic ox-LDL), which is mediated by ROS/NF-κB signaling pathways (Li et al., 2018). Ursolic acid also inhibited NF-κB-mediated LOX-1 expression *in vitro*.

In quails fed a high-fat diet, ursolic acid treatment prevented the changes in serum lipid profiles and antioxidant status (Jiang et al., 2016). *In vitro* studies (in human umbilical vein endothelial cells), ursolic acid treatment induced autophagy, enhanced SIRT1 expression, and decreased acetylation of lysine residue on Atg5.

Cancer: CLINICAL BENEFIT INCONCLUSIVE; BENEFIT IN PRECLINICAL MODELS
In a phase I clinical study of 21 patients with advanced solid tumors, ursolic acid liposome treatment (56, 74, and 98 mg/m^2) was given for 14 days in a 21-day treatment cycle (repeated 3 times) (Qian et al., 2015). However, only 5 patients completed at least 2 cycles, and therefore evaluation of antitumor efficacy was limited. Three (60%) subjects achieved stable disease. One of these subjects had advanced renal carcinoma and had no significant change in the lesion after 2 cycles of treatment with 56 mg/m^2 ursolic acid liposome treatment. Another patient that had advanced hepatocellular carcinoma had no significant change in the lesion after 2 cycles of treatment with the 74 mg/m^2 dose. And one patient had advanced lung cancer in which the lesion shrunk from 9.6 to 7.5 cm after 2 cycles of treatment with the 98 mg/m^2 dose. Two additional subjects, 1 with primary non-Hodgkin lymphoma and the other with breast cancer, showed progressive disease after 2-cycle treatment with the 74 mg/m^2 ursolic acid liposome dose. No complete responses or partial responses were observed. A larger, well-controlled trial would be needed to investigate whether ursolic acid treatment is beneficial in people with advanced solid tumors.

Many studies have tested the anticancer effects of ursolic acid in preclinical models of various cancers. Ursolic acid modulates cellular transcription factors, growth factor receptors, inflammatory cytokines, and other molecular targets that regulate proliferation, apoptosis, metastasis, autophagy, and angiogenesis in cancer tissue (Chan et al., 2019).

Breast cancer: In a mouse model of breast cancer, ursolic acid decreased tumor cell proliferation by modulating Akt/mTOR signaling and inducing apoptosis (Chan et al., 2019).

In breast cancer cells, ursolic acid induces apoptosis, autophagy, and cell cycle arrest by suppressing cell proliferation, angiogenesis, and metastasis (Chan et al., 2019). Ursolic acid induces apoptosis by 1) downregulating Bcl-2 activity, 2) activating the mitochondrial death pathway through activation of caspase-8 and -3 and cleavage of poly(ADP-ribose) polymerase, and 3) suppressing the expression of foxhead box protein M1. Other mechanisms include: autophagy cell death and endoplasmic reticulum stress via upregulation of myeloid cell leukemia sequence 1 and MAPK1/3, inhibition of cell proliferation and inflammation, as well as induction of autophagy and apoptosis via the glycogen synthase kinase and Bcl-2/caspase-3 signaling pathways, and suppression of cell migration and metastasis by inhibition of JNK, mTOR, and Akt signaling, and by downregulation of matrix metalloproteinase-2 and urokinase-type plasminogen activator.

In breast cancer cells, ursolic acid with the chemotherapeutic agent doxorubicin showed synergistic effects (Zong et al., 2019). Ursolic acid increased the amount of doxorubicin entering the cell to accumulate in nuclei, decrease the efflux ratio, and decrease the content of intracellular alanine, lactate, pyruvate, glucose, α-ketoglutarate, glutamate, glutamine, aspartate, serine, and glycine. Ursolic acid appears to reverse multidrug resistance through inhibition of P-glycoprotein function and disruption of energy metabolism including amino acids.

Colorectal cancer: In several mouse models of colorectal cancer (orthotopic nude mice implanted with HCT116 cells, HCT116 xenografted mice, and HT-29 xenografted mice), ursolic acid treatment inhibited tumor growth and metastasis (Chan et al., 2019).

In colorectal cancer cell lines, ursolic acid modulates transcription factors and kinases, and triggers apoptosis, cell cycle arrest, anti-angiogenesis, and antimetastatic activity (Chan et al., 2019). Molecular targets of ursolic acid-induced apoptosis include: upregulation of caspase-3, -8 and -9; activation of the PI3K and MAPK/extracellular signal-regulated kinase signaling pathways; inhibition of the epidermal growth factor regulator and/or MAPK pathway; downregulation of Bcl-2, Bcl-xL, and survivin; activation of reactive oxygen species; JNK-mediated upregulation of death receptors 4 and 5; activation of the COX2 pathway; upregulation of p53, NFkB, Bax, and p21 followed by activation of caspase-3 and -9; multiple signaling pathways including cytochrome c/caspase; and via upregulation of microRNA-4500 and inhibition of activators of STAT3. Other effects include induction of autophagy cell death via the JNK pathway; inhibition of cell proliferation through cell-cycle arrest; inhibition of angiogenesis through

suppression of multiple signaling pathways including VEGF-A, basic fibroblast growth factor, sonic hedgehog, STAT3, Akt, and p70S6; and inhibition of angiogenesis by downregulation of HIF-1α accumulation.

Prostate cancer: In a mouse model of prostate cancer (DU145 xenograft nude mice), ursolic acid treatment (200 mg/kg) for 6 weeks inhibited the growth of prostate cancer cells without any significant effect on body weight (Shanmugam et al., 2011). Ursolic acid treatment led to a substantial decrease in VEGF expression and an increase in caspase-3 expression, suggesting anti-angiogenic and pro-apoptotic actions. In a different mouse model of prostate cancer (LNCaP prostate tumor xenografted athymic nude mice), ursolic acid treatment (20 or 40 mg/kg, i.p., 5 days/week) for 3 weeks significantly inhibited tumor growth, which was associated with inhibition of cell proliferation, induction of apoptosis of tumor cells, and decreased expression of PI3K downstream factors (e.g., p-Akt and p-mTOR) in tumor xenograft tissues (Meng et al., 2015).

In prostate cancer cell culture, ursolic acid induced apoptosis by decreasing levels of Bcl-2, Bcl-xl, and survivin, and activating caspase-3 (Meng et al., 2015). Treatment with ursolic acid also inhibited the expression of PI3K, phosphorylation of Akt, and phosphorylation of mTOR.

Other cancers: Ursolic acid has shown benefit in other cancer cell lines, including endometrial, pancreatic, lung, ovarian, bladder, gastric, and liver carcinoma (Chan et al., 2019). Ursolic acid appears to exert anti-cancer effects by targeting multiple proinflammatory transcription factors, cell cycle proteins, growth factors, kinases, cytokines, chemokines, adhesion molecules, and inflammatory enzymes (Shanmugam et al., 2013). These targets can potentially mediate the chemopreventive and therapeutic effects of ursolic acid by inhibiting the initiation, proliferation, and metastasis of cancer.

Cardiovascular disease: DECREASED LDL AND TRIGLYCERIDES IN A RAT MODEL
In a rat model of hypertension (DSS insulin resistant rats), ursolic acid treatment (60 mg/kg, i.p.) for 6 weeks prevented the development of hypertension, an effect that was attributed to a potent diuretic-natriuretic-saluretic activity, decreased heart rate (by 32%), decreased LDL and triglycerides (by more than two-fold), antioxidant effects (GPx increase by 10%; SOD increase by 22%), and decreased blood glucose (by 50%)(Somova et al., 2003).

Diabetes/Metabolism: IMPROVED GLUCOSE AND INSULIN IN METABOLIC SYNDROME
In a double-blind randomized controlled trial of 24 people with untreated metabolic syndrome, ursolic acid treatment (150 mg orally, once daily before breakfast) for 12 weeks resulted in remission of

metabolic syndrome in 50% of patients, with significant improvements in body weight (75.7 ± 11.5 vs. 71 ± 11 kg; p=0.002), body mass index (29.9 + 3.6 vs. 24.9 ± 1.2 kg/m^2; p=0.049), waist circumference (93 ± 8.9 vs. 83 + 8.6 cm; p=0.008), fasting glucose (6.0 ± 0.5 vs. 4.7 ± 0.4 mmol/L; p=0.002), and insulin sensitivity (3.1 ± 1.1 vs. 4.2 ± 1.2; p=0.003)(Ramirez-Rodriguez et al., 2017). However, there were no significant treatment effects in lipid profile (triglycerides, total cholesterol, HDL-c) and blood pressure (diastolic or systolic). No significant differences were seen in inflammation biomarkers (IL-6 and CRP) before and after the intervention.

In mice with diabetes-induced nephropathy, ursolic acid treatment (25 mg/kg, oral gavage) for 60 days increased body weight, reduced kidney/body weight index, protected kidney cells, alleviated inflammation (TNF-α, IL-1β, IL-6 and IL-18 levels), and decreased kidney cell damage (Li et al., 2018). Ursolic acid also suppressed TLR4, myeloid differentiation factor 88, and NFkB protein expression in these mice. Inhibition of TLR4 mediated the anti-inflammatory actions of ursolic acid.

In rats with diabetic cardiomyopathy (induced by streptozotocin injection), ursolic acid treatment (35 mg/kg, intragastric) for 8 weeks improved cardiac structure and function by attenuating oxidative stress (measured by MDA and SOD), inflammation (TNF-α, MCP-1 and TGF-β1), and myocardial interstitial fibrosis (Wang et al., 2018).

In vitro studies have reported that ursolic acid improves insulin signaling by enhancing the insulin receptor β subunit phosphorylation and Akt (Mancha-Ramirez and Slaga, 2016). Ursolic acid also promotes glucose uptake from the bloodstream into peripheral tissues through upregulation of GLUT4. Another mechanism by which ursolic acid is suggested to aid in lowering blood glucose levels is by lowering endogenous glucose production through gluconeogenesis inhibition.

Muscle strength: POTENTIAL BENEFIT
In a randomized placebo-controlled trial of 16 healthy young adult men, resistance training with ursolic acid treatment (3 capsules each containing 150 mg daily, i.e., 450 mg/day) for 8 weeks significantly reduced body fat percentage, despite body weight, body mass index, lean body mass, glucose, and insulin levels remaining unchanged (Bang et al., 2014). The group that received ursolic acid treatment also had significantly increased levels of IGF-1 and irisin, as well as significantly increased maximal right and left extension ($p<0.01$), right flexion ($p<0.05$), and left flexion ($p<0.001$) compared to baseline levels. However, the underlying molecular mechanisms mediating the increase in IGF-1, irisin, and muscle strength with ursolic acid treatment require further investigation.

Safety: Long-term safety is unknown; based on a few short-term trials, ursolic acid liposome can cause adverse events such as liver enzyme elevation and abdominal distension. Rat toxicity studies suggest the NOAEL for ursolic acid is above 1,000 mg/kg/day.

Types of evidence:

- 2 clinical trials
- 1 review article
- Several rodent toxicity studies

Because of the lack of large, long-term, randomized controlled clinical trials testing ursolic acid, long-term safety is unknown. In one phase 1 clinical study of 21 patients with advanced solid tumors, an ursolic acid liposome treatment (56, 74, and 98 mg/m^2) for 14 days in a 21-day treatment cycle did not result in adverse events at or above grade 3 (Qian et al., 2015).

Multiple-dose pharmacokinetic analysis suggested ursolic acid liposome does not accumulate in the body. All hematological parameters and results of electrocardiography and routine stool tests were normal. Only 1 patient experienced grade 1 microscopic hematuria, while 2 subjects developed grade 1 proteinuria after 2 cycles of treatment with ursolic acid liposome (74 mg/m^2). Immune function tests showed no significant differences in CD4/CD8 on the 14th day compared to baseline. Significant differences in the NK cells were also not observed. In addition, 3 (14%) subjects treated with 56 mg/m^2 ursolic acid liposome developed a low-grade fever (grade 1) but then recovered after 2 hours without any treatment. Three (14%) subjects treated with 56, 74, and 98 mg/m^2 ursolic acid liposome experienced grade 2 liver disease biomarker (GGT) elevation. Two (10%) subjects treated with 56 and 74 mg/m^2 ursolic acid liposome experienced grade 1 abdominal distention. Finally, 1 (5%) patient had grade 2 liver enzyme (ALT) elevation. Other mild symptoms including liver enzyme (AST) and triglyceride elevation, pruritus, arthralgia, and hypokalemia were also observed. The most frequent adverse events included pyrexia, GGT elevation, and abdominal distention.

In rat toxicity studies, administration of ursolic acid at doses up to 1,000 mg/kg/day (oral gavage, in a mixture of 0.1% Tween 80 and 0.5% hydroxypropyl methylcellulose) for a duration of up to 90 days did not cause any deaths, abnormal body weights, or abnormal pathology (Geerlofs et al., 2020). In addition, no toxicological changes were observed in behavior, neurotoxicity, coagulation, hematology, or clinical chemistry. Therefore, the NOAEL for UA is predicted to be higher than 1,000 mg/kg/day.

In a related rat toxicity study, ursolic acid at doses up to 1,000 mg/kg/day (oral gavage, in a mixture of 0.1% Tween 80 and 0.5% hydroxypropyl methylcellulose) for 15 days did not result in any significant toxicological changes in maternal or fetal rats as measured by body weight, organ weights, food consumption, gross pathology, sex organs, maternal behavioral performance, and fetal behavioral performance.

In rats, ursolic acid dose of 80 mg/kg resulted in about 0.6% oral bioavailability, and the half-life was around 4.3 hours (Mancha-Ramirez and Slaga, 2016). Ursolic acid was detected in kidney tissue after oral administration of 0.2% ursolic acid in the diet over a period of 11 weeks.

***Drug interactions**:* Drug interactions with ursolic acid have not been well-studied.

Sources and dosing: Ursolic acid is available over the counter as a supplement. It is also present in food, such as apple peel, cranberry juice, grape skin, holy basil, rosemary, thyme, oregano, sage, and other herbs. Rosemary and sage have the highest content of ursolic acid, 3.0% and 1.8%, respectively (Chan et al., 2019). Apple skin contains 1.4% ursolic acid.

Derivatives: Ursolic acid has limited water solubility, and therefore, low bioavailability. Several efforts are ongoing to synthesize derivatives of ursolic acid to improve solubility and therapeutic potential (Ramos-Hryb et al., 2017). Various ursolic acid analogues have been synthesized through modification at positions C2-OH, C3-OH, and C17-CO2H (Hussain et al., 2017). The C-17 amide and amino analogs of ursolic acid possessed greater anticancer activity compared to the parent compound, ursolic acid. Other studies suggest that structural modifications of ursolic acid –OH groups at C3 and at C28 are critical factors influencing its cytotoxic activity (Chan et al., 2019). Amides and esters are the most common semisynthetic derivatives of ursolic acid. For example, the cytotoxicity of the 3β-amino derivative was 20-fold stronger than that of the corresponding 3α-amino derivative against HL-60, HeLa, BGC and Bel-7402 cancer cell lines. Ursolic acid can also be conjugated with other anticancer drugs to enhance the anticancer activities.

Nanotechnology: There are also strategies being developed to improve the bioavailability of ursolic acid through use of cyclodextrins, liposomes, preparation of ursolic acid nanoparticles, nanomicelles, and nano-microspheres (Hussain et al., 2017). Nanotechnology allows hydrophobic drugs to increase their solubility and bioavailability as well as minimize toxicity and sustain the release of drugs (Zou et al., 2019). Liposomes, chitosan, polymers, and mesoporous silica nanoparticles have been used to load ursolic acid. Modification of ursolic acid liposomes using polyethylene glycol resulted in liposomes that

possessed higher stability and slower release rate (Zhao et al., 2015). Another study of folate-targeted ursolic acid stealth liposome showed that cancer cells endocytosed more targeted liposomes than non-targeted PEGylated liposome (Zou et al., 2019). A study encapsulating ursolic acid in chitosan modified liposomes revealed that they could release ursolic acid more efficiently at an acidic pH 5.0 than pH 7.4. In addition, these chitosan ursolic acid liposomes showed high anti-proliferative activity in cancer cells as well as in tumor-bearing mice (Wang et al., 2017).

Polymeric materials have been used to enhance pharmacodynamic effects of poor solubility drugs. In gastric cancer cells, polymeric encapsulation of ursolic acid showed greater cell apoptosis compared to free ursolic acid by inhibiting COX-2 and activating caspase-3 (Zhang et al., 2013).

Mesoporous silica nanoparticles also show promise for drug delivery. A prodrug delivery system of ursolic acid based on mesoporous silica showed that it is more efficient in inhibiting cancer cell proliferation measured by cellular uptake, cellular metabolic activity (MTT) assay, cell cycle arrest, and cell apoptosis assays (Zou et al., 2019). This formulation also has high drug encapsulation capacity, cellular uptake, and sustained release of ursolic acid.

Research underway: There are currently 2 ongoing clinical studies testing ursolic acid. One is a study of bioavailability of curcumin and ursolic acid (NCT04421716), and the other is testing the synergism of curcumin and ursolic acid in prostate cancer patients (NCT04403568). There are also several programs funded by the National Institute of Health that are evaluating ursolic acid for prevention of prostate cancer and prostate inflammation, treatment of multiple sclerosis, and prevention of skin cancer.

Search terms:

Pubmed, Google: ursolic acid

- + cognitive, + Alzheimer, + ApoE4, + neuropathy, + atherosclerosis, + diabetes, + inflammation, + cancer, + toxicity

Websites visited for ursolic acid:

- Clinicaltrials.gov
- Examine.com
- DrugAge
- Geroprotectors (0)
- Drugs.com (0)
- WebMD.com (0)
- PubChem
- DrugBank.ca
- Labdoor.com (0)
- ConsumerLab.com (0)
- Cafepharma (0)
- Pharmapro.com (0)