



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.

Silymarin (Milk thistle)

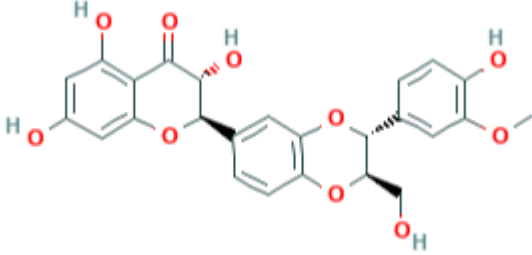
Evidence Summary

Some evidence suggests that silymarin may be effective for liver diseases or metabolic conditions. However, evidence is weak for Alzheimer's disease, and many supplements have high levels of mycotoxins.

Neuroprotective Benefit: Although silymarin is effective in several Alzheimer's animal models, most of the proposed mechanisms of action are similar to approved drugs or drugs that have been ineffective for Alzheimer's.

Aging and related health concerns: Silymarin may be effective for liver diseases or diabetes, though the evidence for other indications is mixed.

Safety: Many clinical trials and consumer use suggest that silymarin is safe; however, most silymarin supplements have high levels of mycotoxins.

<p>Availability: Available as a supplement</p>	<p>Dose: Large variability in doses used, but commonly 200-600mg/day</p>	<p>Molecular Formula: C₂₅H₂₂O₁₀ Molecular weight: 482.4 g/mol Source: PubChem</p>  <p>(Silibinin – main active compound in silymarin)</p>
<p>Half-life: Six hours (oral absorption is ~23-47%)</p>	<p>BBB: Penetrant (for silibinin, in animals)</p>	
<p>Clinical trials: 7 ongoing, mostly for liver disease; many completed trials</p>	<p>Observational studies: 0</p>	

What is it?

Silymarin is the major extract of milk thistle seeds and has been used for many years as a treatment for chronic liver diseases, such as nonalcoholic steatohepatitis, nonalcoholic fatty liver disease (NAFLD) and fibrosis, and acute liver toxicity from drugs and poisons (such as acetaminophen and snake poisons). Silymarin contains several flavonolignans such as silybin A and B, isosilybin A and B, silibinin, silydianin, taxifolin, and silychristin ([Soleimani et al, 2019](#)).

Its primary mechanism of action for diseases of aging is as an antioxidant. However, interest in its use for neurodegenerative diseases (especially Alzheimer's disease) has grown due to its potential impact on the aggregation of amyloid and inhibition of acetylcholinesterase.



There are several reasons for discrepancies in clinical trials testing silymarin. First, silymarin has low bioavailability due to poor water solubility, and, depending on whether it is taken with a meal containing dietary fat, absorption could be affected. Second, there is no standardized silymarin extract (as you get with a single molecular entity when looking at drugs), and different extracts may contain different concentrations of individual components (see Safety section below). Third, different silymarin preparations may contain different levels of toxins which could affect outcomes (see Safety section below).

Silymarin is usually sold as milk thistle in stores, and information is usually found on general health websites as milk thistle.

Neuroprotective benefit: Although silymarin is effective in several Alzheimer's animal models, most of the proposed mechanisms of action are similar to approved drugs or drugs that have been ineffective for Alzheimer's.

Types of evidence:

- One clinical study of tacrine tolerance in Alzheimer's patients
- Several preclinical studies in Alzheimer's, Parkinson's, and ischemia

Human research to suggest prevention of dementia and cognitive aging

None

Clinical research to suggest benefits to patients with dementia or cognitive aging

222 patients were randomized to silymarin (420mg/day) + tacrine (up to 80mg/day) or tacrine alone over seven weeks (tacrine is known to increase liver enzymes in some patients). There were no significant group differences in liver enzymes, side effects, or cognition over the time period ([Allain et al, 1999](#)).

Mechanisms of action from preclinical research

Treatment of Alzheimer's mice with silibinin (a major component of silymarin) (200mg/kg) over eight weeks improved memory performance, reduced oxidative stress (measured by a reduction of malondialdehyde and an increase of superoxide dismutase, nitric oxide, catalase, and glutathione), and reduced apoptosis in the hippocampus ([Bai et al, 2017](#); [Lu et al, 2009](#)). Silibinin was reported to also reduce the level of A β plaques in Alzheimer's mice, possibly by reducing levels of APP and BACE and



increasing the levels of neprilysin – an A β degradation enzyme ([Bai et al, 2019](#)). [Shen et al \(2019\)](#) reported that silibinin and silymarin improved cognition in an Alzheimer's mouse model. They suggested it could be due to an alteration of the gut microbiota, though there is no evidence that changes in the gut microbiota actually improved cognition itself or was just an association with supplementation.

In another model of Alzheimer's disease (A β injection into the brain), silibinin reduced hippocampal cell death and attenuated depression and anxiety phenotypes. This was accompanied by an increase in BDNF and TrkB expression and attenuation of autophagy ([Song et al, 2017](#)). Silibinin was also reported to improve cognition in an Alzheimer's mouse model, reduce the levels and activity of acetylcholinesterase in the brain, increase the expression of BDNF, and reduce the levels of soluble and insoluble amyloid. Silibinin also reduced the number of amyloid plaques, increased neuronal spine density, and increased the number of newly generated neurons, microglia, astrocytes, and neuronal precursor cells ([Duan et al, 2015](#)).

Silymarin was also reported to slightly reduce A β plaques, A β oligomers, and insoluble (but not soluble) A β , reduce microglial inflammation, and improve cognition in an Alzheimer's mouse model ([Murata et al, 2010](#)).

The methanol extract of milk thistle seeds (which contains silymarin) was reported to inhibit acetylcholinesterase (IC₅₀ = 110 μ g/mL) and butylcholinesterase (IC₅₀ = 130 μ g/mL) (for context the IC₅₀s for donepezil were 95 μ g/mL and 80 μ g/mL, respectively). The extract improved cognition in a scopolamine model of memory impairment to about the same degree as donepezil ([Nazir et al, 2018](#)). Silibinin was also reported to inhibit A β aggregation *in vitro* ([Yin et al, 2011](#)).

Other neurodegenerative diseases

Silymarin was reported to be neuroprotective and improve neurological outcomes in several models of Parkinson's disease. Reported mechanisms of action for neuroprotection are similar to those in Alzheimer's disease including increasing antioxidant capacity and reducing neuroinflammation ([Ullah and Khan, 2018](#)). Similarly, several studies suggest that silymarin may be beneficial in ischemia animal models, primarily by reducing cell death, reducing inflammation, and reducing oxidative stress ([Akbari-Kordkheyli et al, 2019](#)).

APOE4 Interactions:

None reported.



Aging and related health concerns: Silymarin may be effective for liver diseases or diabetes, though the evidence for other indications is mixed.

Types of evidence:

- Meta-analyses for cardiovascular disease, diabetes, and non-alcoholic fatty liver disease
- Two worm studies for lifespan
- One study in aged rodents, and one study in a model of rodent senescence

Lifespan

[Kumar et al \(2015\)](#) reported that silymarin increased mean lifespan of worms by 10.1% and 24.8% at 25 μ M and 50 μ M, respectively, but had no effect at 100 μ M. It also improved function in a worm model of Alzheimer's disease. [Filippopoulou et al \(2017\)](#) looked at the individual components of silymarin extract and found that the most potent chemical with life-extending properties in worms was 2,3-dehydrosilybin A/B (DHS A/B) which was also effective in a worm model of Alzheimer's.

The impact of oxidative stress in aged rat brains after treatment with silymarin was mixed. In aged rats, the antioxidant capacity against peroxy radicals (ACAP) with a high dose silymarin (400mg/kg/day) was reduced in the hippocampus and increased it in the cortex. Lipid peroxidation results were also mixed with high doses either increasing or decreasing lipid peroxidation depending on the method of measurement used. Low doses (200mg/kg/day) of silymarin generally had no effect. Protein oxidation was reduced at both doses ([Galhardi et al, 2009](#)).

In a mouse model of senescence (injection of D-galactose), six week treatment with silibinin (50mg/kg/day intramuscular injection) improved memory performance, slightly increased the expression of antioxidant proteins, increased autophagy in hippocampal neurons, and downregulated the expression of NF- κ B (though NF- κ B levels were not quantified) ([Wang et al, 2011](#)).

Cardiovascular disease: Potential benefit, though conflicting data (see diabetes and NAFLD below)

[Mohammadi et al \(2018\)](#) conducted a meta-analysis of ten randomized controlled trials comparing silymarin (between 280mg to 600mg of extract) conducted over two to twelve months. In five studies, silymarin was combined with another therapy (standard therapy, insulin, anti-diabetic therapy, lifestyle therapy). Silymarin combined with other treatments reduced LDL-c (non-significant for silymarin alone). Silymarin also increased HDL-c and reduced triglycerides (unfortunately, these measures were not broken out into monotherapy versus combination therapy). Several mechanisms were proposed for silymarin's effect on cardiovascular disease. It may reduce cholesterol synthesis by inhibition of HMG-



CoA, decrease synthesis of triglycerides in the liver, or activate beta-oxidation of fatty acids in mitochondria.

On the other hand, silymarin mostly had no effects on lipid levels in patients with diabetes or NAFLD (see below).

Diabetes: Potential benefit

[Voroneanu et al \(2016\)](#) conducted a meta-analysis of five RCTs (n=270) of silymarin (45 day to 6-month treatment) versus placebo with or without standard of care treatments. Silymarin significantly reduced HbA1c and fasting glucose, but had no effect on total cholesterol, triglycerides, or HDL-c. One study looked at diabetics with nephropathy and found no effect on kidney function. Two studies looked at potential side effects and reported that silymarin was associated with an increase in gastrointestinal side effects and headaches.

Another meta-analysis of seven partially overlapping studies (n=370; ranging in length from 45 days to 12 months) testing the effect of silymarin (200-600mg) with or without standard therapy reported that silymarin reduced fasting blood glucose, HbA1c, and insulin levels. Silymarin had no effect on total cholesterol or triglycerides, but it reduced LDL-c and increased HDL-c levels. Silymarin treatment also significantly reduced levels of oxidation (MDA levels: -1.98nmol/mL, p=0.02) ([Hadi et al, 2018](#)).

Non-alcoholic fatty liver disease (NAFLD): Potential benefit

[Zhong et al \(2017\)](#) conducted a meta-analysis of eight RCTs (n=587) testing silymarin (doses ranging from 70mg 3x/day to 280mg 4x/day) with studies ranging from 8-24 weeks. They reported that silymarin monotherapy reduced liver enzymes while silymarin in combination with other therapies did not (though this could be because the other drugs in combination were effective on their own). There were no effects on triglycerides or total cholesterol.

Cancer

Silymarin has been reported to have anti-cancer effects in preclinical studies. *In vitro* studies suggest silymarin may be anti-proliferative and anti-angiogenic in several different cancer cell lines ([Hosseiniabadi et al, 2019](#)).

Some clinical studies suggest that silymarin in combination with several other supplements may be beneficial for brain metastases or prostate cancer, and one study in patients with pediatric acute lymphoblastic leukemia showed a slight reduction in hepatotoxicity. However, no studies suggest that



silymarin alone is beneficial in cancer patients (though very few have been conducted), and there is no evidence that silymarin is more effective than current cancer drugs ([Hosseinabadi et al, 2019](#)).

Safety: Many clinical trials and much consumer use suggest that silymarin is safe; however, most silymarin supplements have high levels of mycotoxins.

Types of evidence:

- One review of clinical trials
- Two studies on mycotoxin levels

A review of clinical trials testing silymarin (various doses, most common being 140mg three times per day) reported that silymarin was relatively safe with the most common side effect being gastrointestinal discomfort ([Soleimani et al, 2019](#)). Silymarin has also been reported to increase the incidence of headaches. However, silymarin is, in general, relatively safe.

One potential concern with all plant-based supplements is the possibility of contamination with mycotoxins. In a study of multiple plant-based supplements (milk thistle (i.e. silymarin), red clover, flax seed, soy, green barley, nettle, goji berries, and yucca), the highest mycotoxin concentrations were found in milk thistle supplements (up to 37 mg/kg). Thirty-two samples were tested, and the number of samples with the highest number of co-occurring mycotoxins (12-16) were milk thistle, occurring in almost 60% of those tested ([Veprikova et al, 2015](#)).

Another study examined the quality and purity of 26 different silymarin supplements from the United States and the Czech Republic. The quantities of the different constituents of the silymarin extracts varied from sample to sample. All samples tested contained mycotoxins, but these too varied from sample to sample. For the most common mycotoxins (T-2 toxin + HT-2) the percentage range of recommended daily tolerable intake from silymarin supplements in the United States ranged from 5%-78% and for the Czech Republic ranged from 0%-318%. Some of the supplements also contained pesticides, though these were generally less abundant than mycotoxins.

The authors suggest that the variability in concentrations of different components of silymarin supplements and the potential levels of toxins in these supplements could be one of the reasons for the variability in clinical trial results and consumer outcomes ([Fenclova et al, 2019](#)).



Drug interactions:

Silymarin inhibits several enzymes at higher concentrations. One review noted that silybin may increase exposure of talinolol and domperidone but decrease exposure of indinavir and metronidazole ([Xie et al, 2019](#)). [Drugs.com](#) reports interactions with the anti-viral drugs indinavir and simeprevir.

Sources and dosing:

Silymarin is available from any supplement store. Doses in clinical studies vary widely, but most use doses in the range of 200-600mg/day.

Research underway:

Seven clinical trials are ongoing, most related to [liver disease](#).

Search terms:

Silymarin + Alzheimer, Parkinson, ischemia, lifespan, atherosclerosis, cardiovascular, neuropathy, [meta-analysis], mycotoxins

Websites visited:

- [Clinicaltrials.gov](#)
- [Pubmed](#)

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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](#).