



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.

Sulforaphane

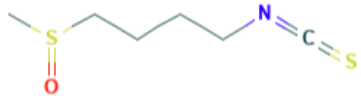
Evidence Summary

Some evidence suggests that sulforaphane may be protective against cancer, but it is not clear it would provide added benefit over eating cruciferous vegetable in a diet.

Neuroprotective Benefit: Preclinical studies suggest that sulforaphane may provide a beneficial impact in Alzheimer's disease, but it is not clear it would do any more than a healthy diet.

Aging and related health concerns: Evidence from multiple meta-analyses suggest that eating cruciferous vegetables may prevent cancer, but there is little evidence sulforaphane supplements will add benefit.

Safety: Multiple clinical studies suggest that sulforaphane is safe with few or no side effects, though no long-term studies have examined safety.

<p>Availability: Found in cruciferous vegetables and available as a supplement</p>	<p>Dose: Many different doses depending on whether broccoli sprout powder (5-10g/day), fresh broccoli (100-250g/day), or stabilized free sulforaphane (60mg/day).</p>	<p>Chemical formula: C₆H₁₁NOS₂ MW: 177.28 g/mol; Source: Pubchem</p> 
<p>Half life: 2.5 hours</p>	<p>BBB: Penetrant (in animals)</p>	
<p>Clinical trials: 0 for Alzheimer's disease; 1 for metabolites in healthy subjects</p>	<p>Observational studies: Many studies for consumption of cruciferous vegetables</p>	

What is it?

Sulforaphane is a naturally occurring isothiocyanate found in cruciferous plants such as broccoli, brussels sprouts, cauliflower, and kale. It is produced by the catalytic breakdown of glucoraphanin by the enzyme myrosinase in response to stress. Myrosinase is denatured by cooking, but gut bacteria can also catalyze the conversion of glucoraphanin to sulforaphane. Sulforaphane is reported to activate the transcription factor NF-E2-related factor 2 (Nrf2) by preventing Keap1 inactivation of Nrf2. Nrf2 activation induces the expression of natural anti-oxidants such as glutathione. Other studies suggest sulforaphane may act as an HDAC inhibitor ([Alumkal et al, 2015](#)). Cruciferous vegetables primarily contain glucoraphanin, which is converted to sulforaphane when ingested.

Neuroprotective Benefit: Preclinical studies suggest that sulforaphane may provide a beneficial impact in Alzheimer's disease, but it is not clear it would do any more than a healthy diet.

Types of evidence:

- 1 pilot open-label study
- 5 preclinical animal studies
- 2 in vitro studies



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

In a pilot open label study in 9 healthy young adults, a 7 day treatment with a broccoli sprout extract containing 100umol of sulforaphane increased blood levels of total glutathione and slightly increased hippocampal glutathione levels (but not in the anterior cingulate cortex or thalamus) ([Sedlak et al, 2017](#)).

Mechanism of action from animal studies

In an animal model of Alzheimer's disease, 4-week daily intake of sulforaphane decreased amyloid, tau, and p-tau levels while increasing HSP70 levels and improving cognition ([Lee et al, 2018](#)). In another Alzheimer's animal model, 5-month treatment of sulforaphane improved cognition, decreased amyloid, and increased expression of the p75 neurotrophic receptor ([Zhang et al, 2017](#)). In a model of intracerebroventricular (ICV) injection of amyloid, 6-day treatment with sulforaphane improved cognition but did not affect amyloid accumulation ([Kim et al, 2013](#)). In a model where animals were given aluminum and galactose to induce amyloid aggregation and cognitive deficits, 80-day treatment with sulforaphane (25mg/kg/day) improved cognition, reduced the number of amyloid plaques, prevented the loss of cholinergic neurons, and prevented the reduction in glutathione activity ([Zhang et al, 2015](#); [Zhang et al, 2014](#)).

Cell culture studies suggest that sulforaphane may induce its neuroprotective effects by upregulating Nrf2 expression and promoting Nrf2 nuclear translocation thereby decreasing amyloid levels, increasing SOD levels, increasing BDNF expression, and reducing inflammatory markers ([Zhao et al, 2018](#); [Kim et al, 2017](#)).

APOE4 interactions:

None reported



Aging and related health concerns: Evidence from multiple meta-analyses suggest that eating cruciferous vegetables may prevent cancer, but there is little evidence sulforaphane supplements will add benefit.

Types of evidence:

- 1 meta-analysis of cruciferous vegetables for cardiovascular disease
- 7 meta-analyses of cruciferous vegetables for cancer
- 1 meta-analysis of cruciferous vegetables for diabetes
- 1 RCT and 2 open-label studies for cardiovascular biomarkers
- 2 RCTs, 1 cross-over trial, and 1 open-label trial for cancer biomarkers
- 4 RCTs and 1 open-label trial for diabetes
- 2 preclinical studies for longevity
- Multiple pre-clinical cancer studies

Longevity

Sulforaphane (0.01%) increased the lifespan of the red flour beetle. 1%-5% of lyophilized broccoli increased the lifespan of the red flour beetle by 20%-33% ([Grunwald et al, 2013](#)). Sulforaphane was also reported to stimulate proteasome activity and autophagy in Hutchinson-Gilford progeria syndrome fibroblasts and promote clearance of progerin ([Gabriel et al, 2015](#)).

Cardiovascular disease

In a 12-week study in individuals with a 10-year CVD risk profile between 10-20%, 400g of high-glucoraphanin broccoli did not change biomarkers of CVD risk compared to a 400g pea control ([Armah et al, 2013](#)). In an RCT of 40 hypertensive patients, 4-week treatment with dried broccoli sprouts did not change lipid profiles, flow-mediated dilation, or blood pressure ([Christiansen et al, 2010](#)). In a small study of 12 patients, 100g/day of fresh broccoli sprouts decreased LDL levels in men and increased HDL levels in women after 1 week ([Murashima et al, 2004](#)).

Observational meta-analyses for intake (highest vs. lowest) of cruciferous vegetable for cardiovascular disease

- Coronary heart disease (7 studies – RR = 1.01; 95%CI 0.90-1.13) ([Aune et al, 2017](#))
- Total stroke (4 studies – RR = 0.97; 95%CI 0.78-1.20) ([Aune et al, 2017](#))
- Cardiovascular disease (8 studies – RR = 0.88; 95%CI 0.73-1.05) ([Aune et al, 2017](#))



Cancer

In an open label study of 20 patients with recurrent prostate cancer, 20 weeks of treatment with 200 μmoles/day of sulforaphane-rich extracts decreased PSA levels > 50% in only one patient with 7 others having smaller declines. However, the study did report an increase in PSA doubling time (a biomarker of prostate cancer progression) ([Alumkal et al, 2015](#)). In an RCT in 78 patients with increasing PSA levels after radical prostatectomy, 6-month treatment with 60mg of stabilized free sulforaphane did not meet the primary endpoint of a change in the log PSA slope from month 0 to month 6. However, mean increases in PSA levels between month 6 and month 0 were lower in the sulforaphane group and PSA doubling time increased 86% (28.9 months in sulforaphane, 15.5 months in placebo). Additionally, more individuals in the sulforaphane group had stabilized or lower PSA levels at 6 months (56% vs. 28%) ([Cipolla et al, 2015](#)).

Sulforaphane conjugates with glutathione for transport across the intestines. *GSTM1* enzymatic activity catalyzes the conjugation and cleavage of sulforaphane and glutathione in the plasma. An RCT in 22 male volunteers reported no changes in PSA levels after 6 months comparing broccoli and pea intake. However, there were gene expression changes in prostate biopsies in men eating broccoli with a functional *GSTM1* allele compared to men without – an effect not seen in individuals eating peas – suggesting that individuals with a functional *GSTM1* allele might process and excrete sulforaphane differently ([Traka et al, 2008](#)). Epidemiology studies suggest that *GSTM1* null subjects may have less benefit from sulforaphane than *GSTM1* positive subjects, but there is some conflicting data ([Gasper et al, 2005](#)).

In two 10-day crossover studies in smokers (n=27 and n=20), 250g/day of steamed broccoli was reported to decrease DNA oxidation in blood mononuclear cells, increase resistance to DNA strand breaks, and decrease oxidized DNA bases with no changes to activity of DNA repair enzymes, HDAC activity, or serum IGF-1 levels; all measures were compared to baseline ([Conzatti et al, 2015](#)).

Nrf2 is considered an oncogene, and its expression is upregulated in certain cancers. Despite the fact that sulforaphane increases Nrf2 expression, sulforaphane is considered to be protective in cancer. Cancers where Nrf2 does not act as an oncogene include prostate and breast cancer. In cancers where Nrf2 is an oncogene, such as non-small cell lung carcinomas, sulforaphane is suggested to act through different mechanisms. *In vitro* studies suggest that sulforaphane enhances resistance to anti-cancer drugs, such as paclitaxel, and thus should not be used when undergoing chemotherapy ([Briones-Herrera et al, 2018](#)). In another cancer model where Nrf2 is reported to be an oncogene, K-ras-driven lung



cancer, sulforaphane treatment increased tumor number and size and tumor cell proliferation ([Tao et al, 2018](#)).

Preclinical studies suggest that sulforaphane's cancer prevention activities are through an upregulation of Nrf2 which then induces the expression of anti-oxidants such as glutathione. Its anti-cancer activities are thought to be modulated by inhibitory activity against HDACs (in fact, other cancer drugs being developed are HDAC inhibitors) ([Ullah, 2015](#)). HDAC inhibitors are reported to induce growth arrest, apoptosis, and ROS facilitated cell death in cancer cells.

Sulforaphane was reported to induce cell cycle arrest or apoptosis *in vitro* in prostate cancer cells, colon cancer cells, breast cancer cells, acute lymphoblastic leukemia (ALL) cancer cells, bladder cancer cells, ovarian cancer cells, salivary gland adenoid cystic cancer cells, glioblastoma cells, adenocarcinoma cells, and others. *In vivo* studies have reported a reduction in tumor growth in ALL, bladder cancer, osteocarcinoma, breast cancer, and other models ([Ullah, 2015](#); [Briones-Herrera et al, 2018](#); [Jaman and Sayeed, 2018](#)).

Observational meta-analyses for intake (highest vs. lowest) of cruciferous vegetables for cancer

- Total cancer (5 studies – RR = 0.84; 95%CI 0.72-0.97) ([Aune et al, 2017](#))
- Renal cell carcinoma (12 studies – RR = 0.81; 95%CI 0.72-0.91) ([Zhao and Zhao, 2013](#)).
- Colorectal neoplasms (33 studies – OR = 0.84; 95%CI 0.72-0.98); broccoli specifically (10 studies – OR 0.80; 95%CI 0.65-0.99); by GSTM1/GSTT1 genotype, only GSTT1 null individuals significant (8 studies – 0.78; 95%CI 0.64-0.95) ([Tse and Eslick, 2014](#)).
- Pancreatic cancer (9 studies – OR = 0.78; 95%CI 0.64-0.91) ([Li et al, 2015](#)).
- Ovarian cancer (8 studies – RR = 0.89; 95%CI 0.81-0.99) ([Hu et al, 2015](#)).
- Breast cancer recurrence (2 studies – HR = 0.98; 95%CI 0.81-1.11) ([Peng et al, 2017](#)).
- Non-Hodgkin lymphoma (3 studies – RR = 0.84; 95%CI 0.71-1.00) ([Sergentanis et al, 2018](#)).

Diabetes

In RCTs in diabetic patients (~70), 4 week treatment of 10g/day broccoli sprout powder decreased insulin levels, HOMA-IR, oxidized LDL, fasting blood glucose, triglycerides, oxidative stress, and hsCRP ([Bahadoran et al, 2012](#); [Bahadoran et al, 2011](#); [Bahadoran et al, 2012](#); [Mirmiran et al, 2012](#)). All the studies were conducted in one lab and may have been the same study population. Another 12-week study reported reductions in fasting blood glucose and HbA1c levels in obese patients with dysregulated type 2 diabetes ([Axelsson et al, 2017](#)).



Observational meta-analyses for intake (highest vs. lowest) of cruciferous vegetables for diabetes

- Type 2 diabetes (3 studies – RR = 0.82; 95%CI 0.67-0.99) ([Wang et al, 2016](#)).

Liver abnormalities

52 males with a fatty liver were given broccoli sprout extract containing 30mg glucoraphanin or placebo for two months. Levels of ALT were slightly reduced in the glucoraphanin group (54IU/L before vs. 48.5IU/L after) as were GGT levels (51.5IU/L before vs. 50.0IU/L after) but not AST levels. The placebo group's levels did not significantly change. Unfortunately, the glucoraphanin group and placebo group were not directly compared, and looking at the graphs, individual responses greatly varied ([Kikuchi et al, 2015](#)).

Safety: Multiple clinical studies suggest that sulforaphane is safe with few or no side effects, though no long-term studies have examined safety.

Types of evidence:

- Multiple clinical trials

Sulforaphane used at the doses above is generally safe, with only minor GI discomfort reported. However, most studies report side effects are balance between the placebo and drug group. The longest study reported was 8 months, so long-term safety of sulforaphane is not known ([Cipolla et al, 2015](#)).

Sources and Dosing:

Glucoraphanin (the precursor of sulforaphane) is present in cruciferous vegetables. It is higher in broccoli sprouts (~1153mg/100g dry weight) than in full grown broccoli (~44-171mg/100g dry weight). Sulforaphane supplements commonly contain broccoli seeds (which have the highest concentration of sulforaphane) or broccoli sprouts.

Many different doses depending on whether broccoli sprout powder (5-10g/day), fresh broccoli (100-250g/day), or stabilized free sulforaphane (60mg/day).

Drug interactions:

There are no clear drug interactions with sulforaphane.

Research underway:

There are currently [20 clinical trials](#) ongoing using sulforaphane. Most of the studies are looking at cancer or autism.

Search terms:

sulforaphane + (all clinical trials)

sulforaphane + alzheimer

broccoli + alzheimer

sulforaphane + cancer (meta-analysis, systematic review, review), longevity, aging

cruciferous vegetable + cancer (meta-analysis)

cruciferous vegetables + Alzheimer

Websites visited:

- Treato (0)
- Drugs.com (0)
- DrugAge (0)
- DrugBank.ca
- Geroprotectors (0)
- Cafepharm.com (0)
- Labdoor.com (0)

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