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.

Xanthohumol

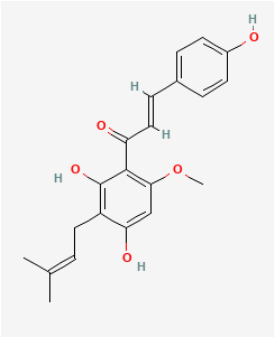
Evidence Summary

Xanthohumol appears to have antioxidant, anti-inflammatory, and neuroprotective benefits based on studies in rodents. However, studies in humans are currently limited.

Neuroprotective Benefit: Xanthohumol treatment has restored cognitive function in numerous rodent models of Alzheimer's disease and cognitive dysfunction. However, no studies have tested the neuroprotective effects of xanthohumol in humans.

Aging and related health concerns: Adjuvant treatment with xanthohumol decreased mortality and plasma IL-6 levels in critically ill COVID-19 patients. Xanthohumol increased lifespan in flies and improved metabolic health in rodent models.

Safety: Xanthohumol treatment is well tolerated based on 2 small short-term clinical trials. Larger, longer-duration intervention trials are needed to fully establish safety.

Availability: OTC and naturally occurring in hops	**Dose**: not established	**Chemical formula:** $C_{21}H_{22}O_5$ **MW**: 354.4  Source: PubChem
Half-life: 18-20 hours	**BBB**: low penetrance	
Clinical trials: The largest trial testing xanthohumol to date enrolled 50 critically ill patients with COVID-19.	**Observational studies**: none available	

What is it?

Xanthohumol is a flavonoid found in flowers of hops (*Humulus lupulus*) and is present in beers and refreshment drinks. Preclinical studies have suggested that it may have anti-cancer properties, including inhibition of carcinogenesis and inhibition of cancer cell division (Gerhauser, 2005; Plazar et al., 2007). Xanthohumol also has antioxidant and anti-inflammatory actions (reviewed in Piekara and Piasecka-Kwiatkowska, 2024). Aside from cancer, xanthohumol has been tested extensively in rodent models of cognitive dysfunction and neurodegeneration (Liu et al., 2022; Liu et al., 2024; Rancan et al., 2017). Ongoing clinical trials are testing the effects of xanthohumol in Crohn's disease, metabolism, immune function, viral infections, and septic shock (ClinicalTrials.gov).

Neuroprotective Benefit: Xanthohumol treatment has restored cognitive function in numerous rodent models of Alzheimer's disease and cognitive dysfunction. However, no studies have tested the neuroprotective effects of xanthohumol in humans.

Types of evidence:

- 0 clinical trials
- 0 observational studies
- Numerous laboratory studies

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

No studies have tested whether xanthohumol treatment may prevent dementia or age-related cognitive decline.

Human research to suggest benefits to patients with dementia:

No studies have tested xanthohumol treatment in patients with dementia.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

In a mouse model of Alzheimer's disease (APP/PS1 mice), xanthohumol treatment (5 mg/kg, oral gavage every other day) for 90 days reduced cognitive dysfunction, measured by the Morris water maze, while restoring the composition and function of gut microbiota (Liu et al., 2022).

Xanthohumol treatment (5 mg/kg, oral gavage every other day) for 90 days reduced cognitive dysfunction measured by the Morris water maze in 6-month old APP/PS1 mice, but the treatment did not prevent cognitive impairment when given to 2-month old APP/PS1 mice (Liu et al., 2024). The effects of xanthohumol treatment on urinary metabolomics varied across the two age groups of APP/PS1 mice.

In an Alzheimer's mouse model (APP/PS1 mice), xanthohumol treatment (0.5 or 5 mg/kg, orally) improved spatial learning and memory (measured by the Morris water maze) by increasing the number of newborn neurons in the subgranular zone and dentate gyrus of the hippocampus (Liu et al., 2025).

In a rat model of diabetes (high-fat diet with streptozotocin injection), xanthohumol treatment (50 mg/kg/day, orally) for 4 weeks rescued cognitive deficits (measured by fear memory), restored hippocampal dendritic spine density, increased synaptic plasticity (measured by LTP), inhibited oxidative stress (decreased MDA, increased GSH), and decreased blood glucose levels (Ma et al., 2021).

In a mouse model of cognitive decline (ovariectomy-induced estrogen deprivation), xanthohumol treatment (25 mg/kg, i.p., every 2 days) reversed cognitive decline measured by the Morris water maze (Liu et al., 2023).

In young mice, xanthohumol treatment (30 mg/kg/day) for 8 weeks improved cognitive flexibility; however, this improvement was associated with the young control mice on a phytoestrogen-deficient diet performing as poorly as the old mice and the xanthohumol supplementation reversing this deficit (Zamzow et al., 2014). Xanthohumol treatment had no significant effects on learning in old mice.

In a mouse model of accelerated aging (SAMP8 mice), xanthohumol treatment (1 or 5 mg/kg/day) significantly reduced brain levels of pro-inflammatory (TNF-α, IL-1β) and pro-apoptotic (AIF, BAD, BAX) while restoring synaptic markers (synaptophysin, synapsin)(Rancan et al., 2017).

In a cell culture model of Alzheimer's disease (murine neuroblastoma N2a cells stably expressing human Swedish mutant amyloid precursor protein [N2a/APP]), xanthohumol treatment inhibited Aβ accumulation and APP processing and ameliorated tau hyperphosphorylation (via PP2A, GSK3β pathways)(Huang et al., 2018). Reduction in tau hyperphosphorylation with xanthohumol was also observed in HEK293/Tau cells.

APOE4 interactions:

Xanthohumol treatment has shown APOE isoform-dependent effects on cognitive performance in a mouse model of high-fat diet (Kundu et al., 2022). No studies in humans have evaluated whether xanthohumol treatment affects APOE4 carriers differently from non-carriers.

Aging and related health concerns: Adjuvant treatment with xanthohumol decreased mortality and plasma IL-6 levels in critically ill COVID-19 patients. Xanthohumol increased lifespan in flies and improved metabolic health in rodent models.

Types of evidence:

- 5 clinical trials
- Numerous laboratory studies

COVID-19: DECREASED MORTALITY, LENGTH OF MECHANICAL VENTILATION, AND PLASMA IL-6

The severity of clinical symptoms of COVID-19 has been associated with the degree of inflammatory response to SARS-CoV2, including cytokine storms (reviewed in Hojyo et al., 2020). In a double-blind

randomized controlled trial of 50 critically ill COVID-19 patients, adjuvant treatment with xanthohumol (1.5 mg/kg body weight, 3 times daily, enterally; Hop-RXn™, BioActive-Tech Ltd., Lublin, Poland; http://xanthohumol.com.pl/) for 7 days significantly decreased mortality rate (20% vs 48% in control group; $p<0.05$) as well as plasma IL-6 levels ($p<0.05$), D-dimer levels (marker of blood clotting; $p<0.05$), and the neutrophil-to-lymphocyte ratio (marker of severity of inflammation and poor clinical outcome; $p<0.01$) compared to the control group that received standard treatment with placebo (0.9% NaCl, 3 mL, enterally 3 times daily)(Dabrowski et al., 2023). The xanthohumol treatment also improved the oxygenation index and reduced the length of mechanical ventilation (completed within 7 days in 14 patients receiving xanthohumol and 4 patients in the control group). The standard treatment included remdesivir (Veclury, Ireland) at an initial dose of 200 mg/day followed by 100 mg/day for 5-7 days, vitamin D3 at a dose of 4000 U per day, corticosteroid therapy with dexamethasone (Dexaven, GmbH Arzneimittel, Germany) at a dose of 8 mg/day for 10 days, and anticoagulant therapy with enoxaparin (Clexane, Sanofi-Aventis, France). All patients also received a continuous infusion of insulin to maintain plasma glucose concentrations between 100 and 160 mg/dL. All patients treated with xanthohumol who survived were discharged from the ICU to the pulmonology or rehabilitation ward and then discharged home in good clinical condition. None of the patients in the control group were discharged directly home but instead were discharged to another pulmonology hospital followed by another hospital.

Evidence from ex vivo studies: DECREASED DNA DAMAGE AND INFLAMMATION

In a randomized controlled crossover trial of 22 healthy non-smokers, consuming a drink containing xanthohumol (12 mg/day; TA-XAN Company) for 14 days resulted in a decrease in oxidatively damaged purines and DNA damage in lymphocytes along with a decrease in urinary markers of oxidative stress (8OHdG, 8-OG) (Ferk et al., 2016). Lymphocytes after consumption of the xanthohumol drink were resistant to carcinogen-induced DNA damage (induced by benzo(a)pyrene, 2-amino-3-methylimidazo[4,5-f]quinoline, or nitrosamine) (Pichler et al., 2017). Protection from carcinogen-induced DNA damage occurred concurrently with induction of α-GST, which catalyzes detoxification of harmful substances within cells.

In a follow-up study that tested pure xanthohumol (12 mg/day) for 14 days in 10 people in a parallel design study, decreased DNA damage in lymphocytes was confirmed (Ferk et al., 2016). However, other biomarkers reflecting redox-, lipid-, and glucose metabolism were not altered with xanthohumol (oxidized LDL, total cholesterol, HDL-C, LDL-C, MDA, progesterone, 17β-estradiol, blood glucose, triglycerol, FRAP, ORAC, urea, and CRP in plasma).

In a single-blind placebo-controlled crossover trial of 14 healthy adults, consuming a beverage containing 0.125 mg of xanthohumol resulted in a suppression of inflammation by peripheral blood mononuclear cells (measured by induction of IL-1β, IL-6, and sCD14 protein release) in response to Gram-positive bacteria (induced ex vivo by lipoteichoic acid) (Jung et al., 2022). The suppression of the inflammatory response appeared to occur through mechanisms involving the interaction of CD14 and TLR2. Given the ex vivo nature of the study, whether or not these effects will be observed in people infected with bacteria remains to be seen.

In a single-blind placebo-controlled crossover trial of 9 healthy women, consuming a beverage containing 0.125 mg of xanthohumol resulted in a suppression of inflammatory cytokine release by peripheral blood mononuclear cells (measured by IL-1β, IL-6, and TNF-α) in response to Gram-negative bacteria (induced ex vivo by LPS) (Jung et al., 2022). Similar to the study described above, because of the ex vivo nature of the study, it is not clear how these effects will translate to those in people infected with Gram-negative bacteria.

Evidence from preclinical studies: INCREASED LIFESPAN IN FLIES; IMPROVED METABOLIC HEALTH; DECREASED INFLAMMATION

Numerous preclinical studies have reported anti-cancer effects of xanthohumol in models of breast cancer and lung cancer (Sun et al., 2017; Li et al., 2022; Siahmazgi et al., 2023). Preclinical studies have shown that xanthohumol treatment inhibits carcinogenesis and cancer cell division (Gerhauser, 2005; Plazar et al., 2007).

In a rat model of diabetes (high-fat diet with streptozotocin injection), xanthohumol treatment (50 mg/kg/day, orally) for 4 weeks decreased blood glucose levels (Ma et al., 2021).

In a mouse model of osteoporosis (induced by D-galactose), xanthohumol treatment (30 or 90 mg/kg, orally, 6 days per week) for 12 weeks significantly improved bone quality, and mitigated bone loss primarily by inhibition of AKT/mTOR/p70S6K activation (Xia et al., 2025). In vitro studies showed that xanthohumol promoted autophagosome flux toward autolysosome and binding assays identified mTOR as a direct target of xanthohumol. Xanthohumol treatment also decreased oxidative stress (decreased MDA levels and increased GSH).

Xanthohumol treatment appears to improve metabolic dysfunction-associated steatotic liver disease, in part, through reduction in de novo lipogenesis and better glucose control (Gomez-Zorita et al., 2024). In

rodent models of obesity, xanthohumol treatment reduces body weight and white adipose depots, while improving metabolic indices such as dyslipidemia, insulin resistance, and fatty liver. These findings in rodents have not been confirmed in humans.

In Drosophila flies, xanthohumol supplementation (0.5 mg/mL mixed in diet) extended the mean lifespan by 14.89%, improved locomotor activity (climbing activity), and increased antioxidant enzyme activities (SOD1, SOD2, catalase) (Wongchum and Dechakhamphu, 2021). Xanthohumol treatment also improved the recovery from cold and heat shock, starvation stress, and acetic acid-induced stress. The 50% survival time was 54 days with xanthohumol treatment compared to 47 days in control flies. In a paraquat challenge test, xanthohumol supplementation (0.5 mg/mL) increased maximum survival time to 32 hours compared to 20 hours in control flies ($p<0.01$)). In a hydrogen peroxide challenge test, xanthohumol supplementation (0.5 mg/mL) increased maximum survival time to 24 hours compared to 16 hours in control flies ($p<0.01$).

Xanthohumol inhibits proinflammatory pathways by inhibition of farnesoid X receptor activity and NF-κB-dependent inhibition of proinflammatory gene expression, such as IL-1β, IL-6, TNF-α, and interferon gamma (Gao et al., 2009; Luescher et al., 2017; Nozawa 2005).

Safety: Xanthohumol treatment is well tolerated based on 2 small short-term clinical trials. Larger, longer-duration intervention trials are needed to fully establish safety.

Types of evidence:

- 2 clinical trials
- Numerous laboratory studies

In a phase I triple-masked placebo-controlled trial of 30 healthy adults (21-50 years old), xanthohumol treatment (24 mg/day in a single capsule, taken with the first daily meal each day) for 8 weeks was safe and well-tolerated (Langley et al., 2021). There were no study discontinuations due to adverse events or serious adverse events. There were no clinically relevant between-group differences in laboratory biomarkers (hepatic and renal function, electrolytes, fasting glucose, and blood counts), vital signs (heart rate, blood pressure), body weight, or health-related quality of life. Mean albumin concentration increased slightly in the placebo group and decreased slightly in the xanthohumol group, leading to a small statistically significant difference ($p=0.04$); however, the means for both groups remained within the clinically normal reference range. Both groups achieved greater than 80% adherence and adherence

was significantly higher in the xanthohumol group (96.1% of capsules consumed over 8 weeks) than in the placebo group (87.2%).

In a double-blind randomized controlled trial of 50 critically ill COVID-19 patients, adjuvant treatment with xanthohumol (1.5 mg/kg body weight, 3 times daily, enterally; Hop-RXn™, BioActive-Tech Ltd., Lublin, Poland; http://xanthohumol.com.pl/) for 7 days was well-tolerated with no reported adverse effects (Dabrowski et al., 2023).

In mice, a high dose of xanthohumol treatment (1000 mg/kg body weight) for 3 weeks did not significantly affect body weight or food intake (Dorn et al., 2010). Based on histopathological examination, there were no signs of xanthohumol-induced toxicity in the liver, kidney, colon, lung, heart, spleen and thymus. Biochemical serum analysis suggested normal organ function. Xanthohumol treatment did not affect hepatic glycogen content CYP2E1 and CYP1A2 expression levels, but CYP3A11 mRNA was reduced by approximately 30%.

In a mouse model of cognitive decline (ovariectomy-induced estrogen deprivation), xanthohumol treatment at the highest dose (50 mg/kg, i.p., every 2 days) resulted in significant body weight loss (Liu et al., 2023).

Drug interactions: Drug interactions with xanthohumol have not been documented.

Sources and dosing:

Xanthohumol levels vary significantly across different types of beer, ranging from 0.001 mg/L to up to 3 mg/L (Paszkot et al., 2021). One clinical trial combined xanthohumol with rice protein because rice protein has been shown to increase the bioavailability of xanthohumol and its metabolites in humans (Langley et al., 2021).

Dosage of xanthohumol has not been established for any indication. The low bioavailability of xanthohumol has been a hurdle for its clinical development (Gomez-Zorita et al., 2024). Xanthohumol absorption is limited, and it also spontaneously cyclizes to isoxanthohumol in the low pH environment of the stomach (Buckett et al., 2023). To enhance its absorption and its biological activities while protecting it from the acidic stomach, micellar formulations and other formulations have been tested. In a double-blind randomized controlled crossover study of 5 healthy adults, the oral bioavailability of micellar

xanthohumol was significantly higher than native xanthohumol (Buckett et al., 2023). A single micellar xanthohumol dose of 43 mg resulted in a 5-fold higher area under the plasma concentration-time curve of its metabolite, xanthohumol-7-O-glucuronide, with its maximum plasma concentration greater than 20-fold higher compared to a single 43 mg dose of native xanthohumol.

Research underway:

There are 6 ongoing clinical trials testing xanthohumol (ClinicalTrials.gov). Two studies are investigating the effects of xanthohumol on the immune system (NCT06286644; NCT06745102), one study is testing whether it attenuates viral infections (NCT06286657), one study is testing its safety and tolerability in people with Crohn's disease (NCT04590508), one study is testing it as an adjuvant for the treatment of septic shock (NCT06225258), and one study is examining its metabolism in healthy people (NCT03735420).

Search terms:

Pubmed, Google: xanthohumol

- + clinical trial, + meta-analysis, + cognitive, + APOE4

Websites visited for xanthohumol:

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

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