Xanthohumol and its Potential Health Benefits
Research Review

INTRODUCTION

The phytochemical xanthohumol (Figure 1) is the most abundant prenylated flavonoid found in the female inflorescences (flowers) of hops (*Humulus lupulus* L.), a plant that has long been used in medicine for various applications and also in the brewing industry. Beer is the major dietary source of xanthohumol, but the amount is very low—at less than 0.2 mg/L.1 Xanthohumol has been extensively studied in recent years, and a wide range of beneficial biological properties in experimental studies have been reported.

![Chemical Structure of Xanthohumol](image)

**Bioavailability.** Xanthohumol has been demonstrated to be bioavailable in vivo and in humans. Male Sprague-Dawley rats received an oral gavage of 1.86, 5.64, and 16.9 mg/kg BW of xanthohumol (corresponding to 20, 60, and 180 mg xanthohumol in humans by using allometric interspecies scaling). The bioavailability was estimated to be 33%, 13%, and 11%, respectively.3 After adult volunteers received a single dose of 20, 60, or 180 mg xanthohumol, the maximum concentrations in plasma were 33 ± 7 mg/L, 48 ± 11 mg/L, and 120 ± 24 mg/L, respectively. The mean half-life of xanthohumol was estimated to be 18-20 hours.4

Scientists from Rutgers and North Carolina State Universities developed a new technology for fortification of edible proteins with phytonutrients. They reported that the bioavailability and bioaccessibility of phytonutrients were enhanced when delivered in an edible protein matrix.5,7 This technology may enhance the bioavailability of xanthohumol.

**BIOLOGICAL PROPERTIES OF XANTHOHUMOL**

**Anti-inflammatory properties.** Xanthohumol exhibits a broad spectrum of anti-inflammatory activity in vitro, suggesting potential in addressing inflammation that is a component of many diseases. For example:

- Excessive nitric oxide (NO) production may cause injuries to host cells and tissues. In RAW264.7 macrophages, xanthohumol (10 μg/mL) significantly inhibits the production of NO by suppressing the expression of inducible NO synthase (iNOS) induced by a combination of lipopolysaccharide (LPS) and interferon-γ (IFN-γ).6
- Excessive interleukin-12 (IL-12) is linked to inflammation or autoimmunity. Xanthohumol inhibits IL-12 production in stimulated macrophages via the down-regulation of NF-κB.9
- Xanthohumol reduces the release of many inflammatory factors, including monocyte chemoattractant protein-1 (MCP-1) and tumor necrosis factor-α (TNF-α) in LPS-stimulated RAW264.7 macrophages and U937 human monocytes.10
- Xanthohumol inhibits LPS-stimulated inflammatory responses in microglial BV2 cells via the Keap1/Nrf2 pathway and up-regulation of the antioxidant enzymes NADPH quinone oxidoreductase (NQO1) and heme oxygenase (HO-1).11

**Effects on risk factors associated with metabolic syndrome.** Metabolic syndrome, a cluster of risk factors including abdominal fat, hyperglycemia, abnormal cholesterol levels, and high blood pressure, may increase the risk of heart disease, stroke, and diabetes.12 Experimental studies suggest that xanthohumol may address these metabolic risk factors:

- Xanthohumol inhibits the differentiation of 3T3-L1 preadipocytes by decreasing adipocyte marker proteins (e.g., PPARγ, C/EBPα, and aP2), and induces apoptosis in mature adipocytes.13-15
- In rats fed a high fat diet, xanthohumol inhibits the increase of body weight, liver weight, and triglyceride levels in the plasma and the liver.16
- In diabetic rats, xanthohumol decreases inflammation and oxidative stress and improves diabetic wound healing.17
- In male Zucker fa/fa rats fed a high fat diet, xanthohumol (16.9 mg/kg BW) significantly lowers body weight and plasma glucose levels.18 The suppression of postprandial hyperglycemia may be due to xanthohumol’s effect in inhibiting the enzyme α-glucosidase.19
- In HepG2 cells, xanthohumol inhibits triglyceride synthesis and decreases apolipoprotein B (ApoB) secretion, suggesting a potential in supporting the treatment of hypertriglyceridemia.20
- Xanthohumol (300 mg/kg BW) reduces plasma cholesterol concentrations, decreases atherosclerotic lesion area, and attenuated plasma MCP-1 in ApoE−/− mice.21

**Antioxidant properties.** Xanthohumol’s antioxidant properties have been observed in various experimental models:

- Xanthohumol displays free-radical-scavenging capacity in oxidative-stress-induced neuronal cells. Also, pretreating
these cells with xanthohumol upregulates phase II cytoprotective genes and the corresponding gene products such as glutathione and HO-1.22

- Xanthohumol protects DNA from benzo(a)pyrene-induced oxidative stress and DNA damage in HepG2 cells and in rat liver tissue.23,24
- In a liver injury rat model, xanthohumol protects against toxic liver injury. The mechanisms are related to the inhibition of lipid peroxidation, hepatic inflammation via decreasing NF-kB activity, and degradation of antioxidant enzymes.25-27

**SELECTIVE KINASE MODULATION**

Activation of protein kinases (e.g., PI3K, GSK3β, MAPK, and I KK) in inflammatory signaling pathways upregulates inflammatory genes and facilitates productions of pro-inflammatory cytokines.28 Xanthohumol has been shown to inhibit signaling pathways (including PI3K/MAPK/NF-κB) in vitro and in vivo models of inflammation.25,29-30 Research from MetaProteomics (Gig Harbor, WA) found that xanthohumol is a selective kinase modulator showing superior kinase inhibition—more potent compared with reduced iso-alpha acids (RAAA) from hops—in cell-free assays and prevents Ik-Ba degradation leading to the inhibition of PGE₂ production in LPS-activated RAW264.7 macrophages (unpublished).

**SUMMARY**

Inflammation and oxidative stress have been connected to various metabolic disorders and chronic diseases. Xanthohumol's anti-inflammatory and antioxidant properties via kinase modulation as observed in many experimental models suggest that xanthohumol has the potential to address inflammation and oxidative stress that is important for managing many metabolic and chronic illnesses in humans (figure below).8-30

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**REFERENCES**


23. Plazzer J, Zegura B, Lah TT, Filipic M. Protective effects of xanthohumol against the genotoxicity of benzo(a)pyrene (BaP), 2-amino-3-methylimidazo[4,5-f]quinoline (IQ) and tert-butylyl hydroperoxide (t-BOOH) in HepG2 human hepatoma cells. Mutat Res. 2007;632:1-6.


