Xanthohumol and its Potential Health Benefits

Brief Research Review

INTRODUCTION

The phytochemical xanthohumol (XNT; **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 XNT, but the amount is very low; at less than 0.2 mg/L.[1] XNT has been extensively studied in recent years, and a wide range of beneficial biological properties in experimental studies have been reported.

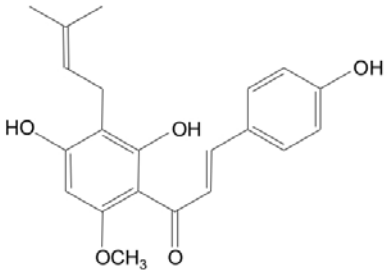


Figure 1. Chemical structure of XNT.

Bioavailability. The oral bioavailability of XNT is very low (<1%).[2] Without special processing, absorption of XNT after oral administration would be very poor. Research has shown that a special XNT capsule (featuring a self-emulsifying isotropic mixture of XNT powder, oleic acid, Tween 80, and propylene glycol) enhanced the bioavailability of XNT.[3,4] After adult volunteers received a single dose of 20, 60, or 180 mg XNT, 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 XNT was estimated to be 18-20 hours.[4]

Enhanced Bioavailability with XNT ProMatrix™. 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 is featured in XNT ProMatrix, a proprietary delivery form of XNT that utilizes edible protein matrix to enhance the bioavailability of XNT.

A double-blind, randomized, crossover study was conducted at the Functional Medicine Research Center (Gig Harbor, WA) to evaluate XNT ProMatrix. Volunteers (n=6) consumed 13.4 mg XNT ProMatrix and a control XNT (with 1-week washout period in between). Fasting plasma concentrations of XNT and its metabolites were measured at baseline and up to 6 hours after consumption. The Schuirmann's two one-side equivalence test indicated that the two tested products were not bioequivalent.

Compared with the control XNT, XNT ProMatrix exhibited increased plasma concentrations over time (**Figure 2**). According to the area-under-curve (AUC) data, plasma levels of XNT and its metabolites were 81% greater after consumption of XNT ProMatrix than a control XNT (**Figure 3**).

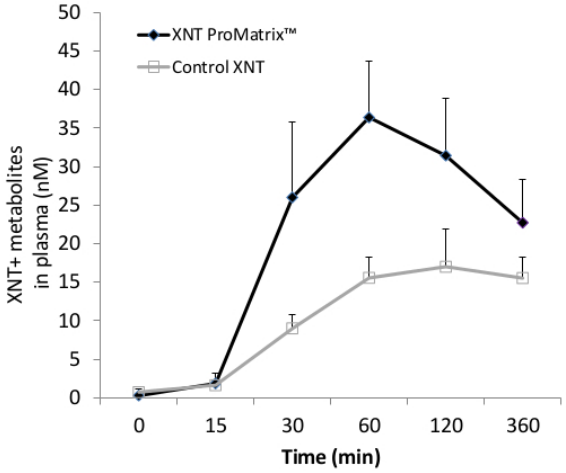


Figure 2. Plasma levels (mean ± SEM) of XNT and its metabolites from baseline to 6 hours after consumption of XNT ProMatrix or a control XNT.

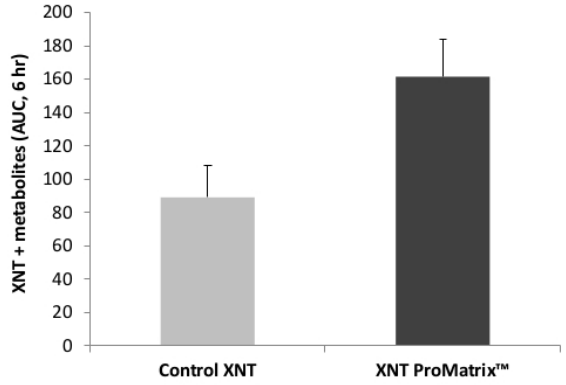


Figure 3. Area-under-curve data over 6 hours after consumption of XNT ProMatrix or a control XNT.

BIOLOGICAL PROPERTIES OF XNT

Anti-inflammatory properties. XNT exhibits a broad spectrum of anti-inflammatory activity in vitro, suggesting its potential in helping to nutritionally address conditions associated with inflammation. For example:

- Excessive nitric oxide (NO) production may cause injuries to host cells and tissues. In RAW264.7 macrophages, XNT (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).[8]

- Excessive interleukin-12 (IL-12) is linked to inflammation or autoimmunity. XNT inhibits IL-12 production in stimulated macrophages via the down-regulation of NF-κB.[9]

- XNT 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]

- XNT 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 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 XNT may reduce related metabolic risk markers:

- XNT 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, XNT inhibits the increase of body weight, liver weight, and triglyceride levels in the plasma and the liver.[16]

- In diabetic rats, XNT decreases inflammation and oxidative stress and improves diabetic wound healing.[17]

- In male Zucker fa/fa rats fed a high fat diet, XNT (16.9 mg/kg BW) significantly lowers body weight and plasma glucose levels.[18] The suppression of postprandial hyperglycemia may be due to XNT's effect in inhibiting the enzyme α-glucosidase.[19]

- In HepG2 cells, XNT inhibits triglyceride synthesis and decreases apolipoprotein B (ApoB) secretion, suggesting a potential in treating hypertriglyceridemia.[20]

- XNT (300 mg/kg BW) reduces plasma cholesterol concentrations, decreases atherosclerotic lesion area, and attenuated plasma MCP-1 in $ApoE^{-/-}$ mice.[21]

Antioxidant properties. XNT's antioxidant properties have been observed in various experimental models:

- XNT displays free-radical-scavenging capacity in oxidative-stress-induced neuronal cells. Also, pretreating these cells with XNT upregulates phase II cytoprotective genes and the corresponding gene products such as glutathione and HO-1.[22]

- XNT protects DNA from benzo(a)pyrene-induced oxidative stress and DNA damage in HepG2 cells and in rat liver tissue.[23,24]

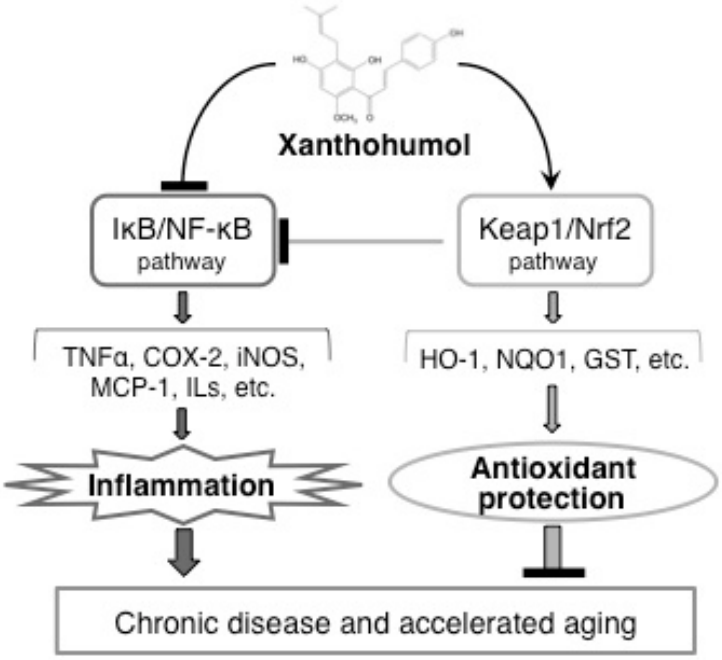
- In a liver injury rat model, XNT protects against toxic liver injury. The mechanisms are related to the inhibition of lipid peroxidation, hepatic inflammation via decreasing NF-κB activity, and degradation of antioxidant enzymes.[25-27]

SELECTIVE KINASE MODULATION

Activation of protein kinases (e.g., PI3K, GSK3β, MAPK and IKK) in inflammatory signaling pathways upregulates inflammatory genes and facilitates productions of pro-inflammatory cytokines.[28] XNT has been shown to inhibit signaling pathways (including PI3K/MAPK/NF-κB) in in vitro and in vivo models of inflammation.[25,28-30] Research from MetaProteomics (Gig Harbor, WA) found that XNT is a selective kinase modulator showing superior kinase inhibition in cell-free assays and prevents Iκ-Bα degradation leading to the inhibition of PGE_2 production in LPS-activated RAW264.7 macrophages (unpublished).

SUMMARY

Inflammation and oxidative stress have been associated with various metabolic disorders and chronic diseases. XNT's anti-inflammatory and antioxidant properties via kinase modulation as observed in many experimental models suggest that XNT may have the potential to help manage many metabolic pathways related to chronic conditions (**figure below**).[8-30]



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