Editorial

C. Gerhäuser (above) and N. Frank (left)

Xanthohumol, a new all-rounder?

It is well accepted that in the fight against common diseases, prevention strategies are in the long term better than therapy. Nutrition plays a prominent role both as a risk factor but also as a measure to prevent diseases such as cancer or coronary heart diseases. This concept is gaining increasing importance among the general public, as evident in the rising sales figures for "healthy" or "health-promoting" food supplements. Epidemiological studies have demonstrated that a well-balanced diet is one of the best means to remain healthy. The crucial question remains: which food in the diet is "good" and which is "bad"? Scientifically we are used to regarding this question analytically, *i.e.* we investigate the biological or potential medical effects of individual food components to propose food recommendations based on the experimental results obtained, or to modify food production if necessary. The overall goal is to bring about a positive effect on health.

This Special Issue summarizes known and novel properties of xanthohumol, a prenylated chalcone derived from the hop (*Humulus lupulus* L.). In the hop, the yellow compound (Greek: xantho = yellow) is found in high quantities in the lupulin glands of the female inflorescence. Xanthohumol also occurs in the Chinese medicinal plant *Sophora flavescens* Ait. (Jung *et al.*, *Arch. Pharm. Res*. 2005, *28*, 534–540), but it is part of our diet mainly in the form of beer or mixed beer drinks. Due to the thermal conversion of xanthohumol to the isoflavanone isoxanthohumol during the brewing process, the concentration of xanthohumol in beer, however, is very low (approximately 0.1 mg/l in German lager beer).

Since the 1990s, interest in health-promoting activities of hop-derived constituents, including prenyl flavonoids and hop bitter acids, has increased constantly, and scientific investigations have been initialized worldwide. As an example, in 1997 a Japanese group reported that xanthohumol was able to inhibit the activity of diacylglycerol acyltransferase, an enzyme that catalyses the acyl residue transfer from acyl-CoA to diacylglycerol to form triacylglycerols (triglycerides) (Tabata *et al.*, *Phytochemistry* 1997, *46*, 683–687). Accumulation of triglycerides is linked to high risk conditions of fatty liver, obesity, and hypertriglyceridemia, leading to atherosclerosis, diabetes, metabolic disorders and functional depression of some organs. Around the same time, another Japanese group described xanthohumol and the bitter acid humulone as novel inhibitors of osteoporosis based on the potential to prevent bone resorption in a model system (Tobe *et al.*, *Biosci. Biotechno.l Biochem.* 1997, *61*, 158–159). Potential anticancer activities of prenylated flavonoids including xanthohumol were first described by John Buhler *et al.* at Oregon State University (Corvallis, USA), who investigated antiproliferative and cytotoxic effects in three cancer cell lines (Miranda *et al.*, *Food Chem. Toxicol.* 1999, *37*, 271–285). They also described the inhibition of cytochrome P450 enzymes which play an important role in the metabolic activation of certain procarcinogens (Henderson *et al.*, *Xenobiotica* 2000, *30*, 235–251). In 2002, we identified xanthohumol as a broad-spectrum cancer chemopreventive agent acting by multiple mechanisms relevant for the prevention of carcinogenesis in the initiation, promotion and progression phase. Subsequently, we demonstrated its chemopreventive efficacy in a mouse mammary organ culture model (Gerhäuser *et al.*, *Mol. Cancer Ther.* 2002, *1*, 959–969). Quite recently, xanthohumol was shown to potentially influence two other major human diseases, *i.e.* AIDS and malaria, at least in vitro. It prevented cytopathogenic effects of the human immunodeficiency virus HIV-1 and inhibited the proliferation of the malarial pathogen *Plasmodium falciparum* (reviewed by Gerhäuser, this issue).

In the contributions to this Issue, the range of biological effects of xanthohumol is broadened even further. Radovic *et al.* describe that xanthohumol stimulates iodide uptake in a cell culture model of normal, non-transformed rat thyrocytes at nanomolar concentrations, and might be an interesting candidate for more efficient radioiodide therapy. Poly(ADP-ribose)polymerase (PARP) cleavage, activation of caspases-3, -7, -8, and -9 and downregulation of Bcl-2 protein expression were found to contribute to apoptosis induction and antiproliferative mechanisms in cultured human colon cancer cells (Pan *et al.*). Intracellular targets of xanthohumol for cell growth inhibiting effects were investigated by Lust *et al.* in B-chronic lymphocytic leukemia cells. Induction of apoptosis and PARP cleavage was not linked to changes in Akt, Erk, p38MAPK and JNK phosphorylation. In addition to these mechanistic investigations in cell culture, the metabolism of xanthohumol by a series of nine human recombinant UDP-glucuronosyltransferases and five sulfotransferases was studied by Ruefer *et*

al. They identified three mono-glucuronides as well as three mono-sulfates as important metabolites that can be formed in the liver as well as in the gastrointestinal tract. Berwanger *et al.* succeeded in generating and isolating radioactive-labelled xanthohumol using a biosynthetic labelling method in hop cones. The labelled compound will be a valuable tool for future investigations, *e.g.* of whole body distribution.

Safety after long-term application is a very important issue for compounds intended for the prevention of chronic diseases. Hussong *et al.* demonstrated weak hepatotoxicity when xanthohumol was applied as a daily dose of 1000 mg/kg per day to female Sprague Dawley rats. At a 10-fold lower concentration, however, xanthohumol did not show any toxic effects and did not influence rat fertility when given either for four weeks prior to or during mating, gestation and nursing. Although antimicrobial effects of xanthohumol have been described before (reviewed by Gerhäuser), it did not change the diversity of the faecal microbial community in the sub-chronically treated animals (Hanske *et al.*).

Beer is the only dietary source of xanthohumol, but the average content of xanthohumol in beer is probably too low to achieve a measurable health-promoting effect. Therefore, it is an interesting technological problem to increase the content of xanthohumol in beer by modifying the brewing process. One solution is described by Wunderlich *et al.* in this Issue.

The various and quite diverse effects of xanthohumol make the presentation of its biological activities particularly interesting, and we hope to provide with this Special Issue additional input to the discussion of potential health-promoting effects of xanthohumol. All the knowledge of xanthohumol combined suggests that it is a substance with a very broad spectrum of activities and various preventive mechanisms. Further investigations in experimental animal models need to demonstrate whether these multiple effects are relevant *in vivo.* Also, molecular intracellular targets of xanthohumol will be the subject of future studies to further characterize the preventive and therapeutic potential of this interesting natural product.

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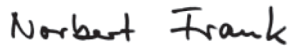

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