MBAA TQ doi:10.1094/TQ-46-2-0416-01

Hops and Health

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ABSTRACT

In Germany, hop was recently recognized as the "Medicinal Plant of the Year." This is reason enough to take a closer look at this ancient, cultured plant, which is predominantly known for its role in beer brewing. This paper discusses the history of hop as a medicinal plant and provides a review of recent research on its health benefits. The hop plant is a valuable and untapped resource for interesting developments in nutraceuticals, dietary supplements, and other health-promoting products. Moreover, raw hop materials are a key to a better understanding of the possible health-related benefits of moderate beer consumption.

Keywords: hop bitter acids, hop polyphenols, hops, medicinal plant

SÍNTESIS

El lúpulo recibió este año en Alemania la distinción de ser "La Planta Medicinal del Año." Aquí se repasa la historia de esta antigua planta medicinal y se reporta sobre las investigaciones recientes con respecto a los beneficios saludables del lúpulo. La planta de lúpulo es un recurso valioso, y poco aprovechado, con usos interesantes en "nutraceuticos," suplementos a la dieta, y otros productos que promueven una vida saludable. Es más, esta materia prima es clave para el mejor entendimiento de los posibles beneficios a la salud como consecuencia de un moderado consumo de cerveza.

Palabras claves: ácidos amargos del lúpulo, lúpulo, plantas medicinalesm, polifenoles del lúpulo

History of Hop as a Medicinal Plant

The Origins of Hops Used in Healing

This section summarizes the origins of hops used in healing as described in *Hops and Health* (3). Long before being discovered as a suitable seasoning for beer, hops were used for medicinal purposes. The early history of the use of hops remains unclear; however, archeologists have found hop seeds in ancient settlements that date back to the New Stone Age. Although archeologists have ruled out a relationship between beer brewing and hops in early human history, they have proposed that medicinal use of hops is the most likely explanation.

Wild forms of the hop plant have been growing in shaded areas of floodplain forests and on the edges of forests and have been collected as medicinal plants for centuries. The first human agricultural use of hops dates back to the 9th century. It is likely that the plant was used as an additive to fermented brews made from cereals, the precursors of beer. The main purpose of this additive was not to improve the taste, but to preserve the brew. Over time, medicinal knowledge was transferred to brewing knowledge, and medieval European monasteries played a key role in the refinement of this information.

One typical example of this historic gain in knowledge was *Physica*, an herbal book from the 12th century written by Hildegard von Bingen, which contains the statement that hops "keep away certain putrefactions from beverages." In today's language, this is equivalent to describing an antimicrobial effect.

Reinheitsgebot and the German Purity Law

During the Middle Ages, hops eventually became the sole flavoring ingredient of beer. This unique status was codified in 1516 in the Bavarian *Reinheitsgebot*, which evolved into the modern Purity Law for beer brewed in Germany. Overall, hops became important in beer brewing by virtue of their antimicrobial properties.

Herbal Books

Reports on the medicinal uses of hops date back to the Middle Ages. The oldest report is found in a book from the 11th century assigned to the Arabic physician Mesue, who described the anti-inflammatory properties of hops. In the 13th century, the Arabic botanist Ibn Al-Baytar emphasized the soothing properties of hops.

Gorgeous herbal books dating from the 1300s through the 1600s delineate various medicinal uses of hops (Fig. 1) as a diuretic and expurgatory for liver and blood and against fevers and spleen disorders. The book *Garden of Health* from 1485 alludes to a hop medication used against ear infections. Most herbal book authors also mention its digestive properties. The use of hops in gynecology was first documented by Hieronymus Bock in 1539.

Hops Used in Folk Medicine

As of the High Middle Ages, at the latest, hops seem to have established themselves in medicinal practice, as well as in folk medicine, not only in Europe, but also in North America. Reports from North America indicate that various native tribes used hops as a remedy against a multitude of afflictions. The Delaware, for example, used them against ear- and toothaches

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Based on a paper presented at the World Brewing Congress 2008, Honolulu, HI, August 2008.

and drank hop tea as a relaxant. The Cherokee employed hops against sleep disorders and the Navajo against coughs and colds. The hop root or a root brew was used by the Dakota as a treatment for bowel complaints and healing wounds, while the Fox used hops as a sleeping agent. Hops were also used in Indian-Ayurvedic medicine as a soothing agent, as well as against stomach complaints and inflammations.

The fact that these uses were also common in Europe, even though an exchange of knowledge on the action of hops had presumably never taken place, is noteworthy. In this respect, one can rate this parallel use as indirect evidence of the effectiveness of hops in medical applications.

Initial Research

Scientific research on hops commenced during the 19th and early 20th centuries and has led to the substantiation of many of the traditional uses of hops. For example, the sedative and sleep-inducing properties of hops have been well documented. Positive gastrointestinal effects also have been studied in detail. The anti-inflammatory activity of hops is well understood and supports the historic use of hops against ear infections. Hops have also been found to contain a phytoestrogen, the herbal equivalent of an estrogen hormone. The rediscovery of the healing properties of hops has evolved from discoveries that were made 1,000 years ago and provides good prospects for the future.

Current Uses

In plant medicine (phytotherapy), hops are recognized, in particular, as a tranquilizer and sleeping agent (1,13,63). Especially in combination with valerian, hops have been found to have a demonstrable effect. There are more than 100 different sleeping pill and tranquilizer formulations for sale in Germany that contain hops. They can be bought in pharmacies, drugstores, and health-food shops. Hop–valerian mixtures are most commonly offered, predominantly in tablet form.

Under the regulations of the U.S. DSHEA Act (Dietary Supplements Health and Education Act of 1994), similar products are widely sold as dietary supplements in the United States. In Canada, hops are classified as safe and effective under the Natural Health Products regulations.

Growing Recognition

Interest in hop as a medicinal plant has grown considerably in recent years. In Germany, hop has been named the "Medicinal Plant of the Year 2007" by the Study Group for the Historical Development of Medicinal Plant Science at the University of Wuerzburg. Hop was also selected as the theme plant of the 2008 Garden Walk at the University of Illinois at Chicago, where research on the plant is ongoing in the UIC/NIH Botanical Center. The basis for this recognition is the increasing number of scientific publications on the beneficial activities of hops and their constituents. During the past 10 years more than 100 papers have been published (Fig. 2).

Beneficial Hop Constituents and Their Activities

Each variety of hops is different as a result of differences in the chemical composition of their constituents (Fig. 3). The essential oil and bitter compounds bestow on hops their characteristic aroma, and brewmasters have individual preferences for the hop varieties they use in different beer styles. At the same time, hop essential oil and bitter compounds exhibit multifaceted medicinal properties.

Polyphenols supplement the vitamins of many fruits and vegetables and are very important for nutrition and health. These phytoconstituents can help prevent cardiovascular disease, osteopo-

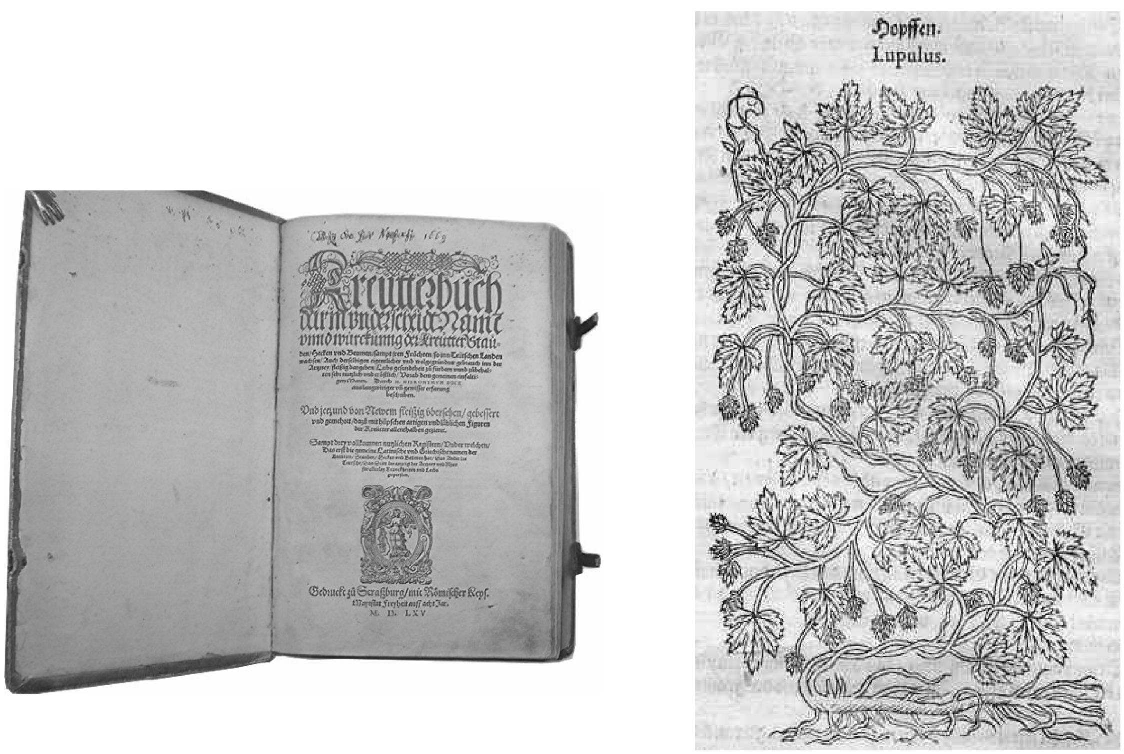

Figure 1. Medieval herbal books contain extensive chapters on hops.

rosis, and cancer (30). Examples of polyphenol-rich foods include green tea, soy beans, and red wine.

Polyphenols contained in hops can be classified into phenolic carboxylic acids (e.g., ferulic acid), flavonols (e.g., quercetin), flavanols (e.g. catechin), and other polyphenolic compounds (Fig. 4 and Table 1). Most are very common in plants, while some are found only in a few plants. Therefore, like bitter substances, some polyphenols are a specific feature of hops. In this instance, the "multifidol" glucosides and prenylflavonoids (xanthohumol, desmethylxanthohumol, and 6- and 8-prenylnaringenin) are involved.

Hop Essential Oil

As previously mentioned, the calming effect of hops is a subject that has long been discussed in-depth among scientists. A connection to the volatile compounds of essential oil has been assumed. Some scientists have concluded that the effect is primarily related to 2-methyl-3-buten-2-ol alcohol (20). This alcohol is contained only in very small amounts in fresh cones; however, its content rises with increased hop storage time (up to 0.15%). There is a simple explanation for this—2-methyl-3-buten-2-ol is a chemical breakdown product of hop bitter substances. There are indications that such conversion could also take place in the human body (31).

The latest results with respect to the underlying mechanism show that the sedative effect of hop essential oil may have been overestimated in the past. In animal tests, a polar hop extract without any essential oil influenced the sleep-inducing hormone melatonin (8). The active hop ingredient could not be identified. In contrast, valerian is known to have an effect on adenosine—another metabolic product that regulates the sleep cycle. Therefore, a combination of hops and valerian is most suitable for treating sleep disorders, as was demonstrated recently in clinical trials with patients suffering from sleep disturbances (12,24).

Bitter Substances: α-Acids and β-Acids

The positive influence of hops on the gastrointestinal tract was known in medieval times. A recent Japanese study has confirmed that a hop extract promotes formation of gastric juices (26), while hop bitters are generally known to assist digestion and stimulate the appetite.

Hops are also very active against inflammation. α-Acids can be used to treat ear inflammation (29,62), an application that has been known since the Middle Ages. Hop bitters are known to abate painful inflammations such as those occurring in rheumatic diseases (22).

Antibiotics are substances that kill bacteria or inhibit their growth, a property of hops that was recognized and taken advantage of during the early Middle Ages. Hops served as a preservative, killing germs that would spoil beer. The antimicrobial activity of hops is mainly due to their bitter compounds (54).

Hops appear to be particularly promising as a treatment for tuberculosis. First accounts of its usage in such an application

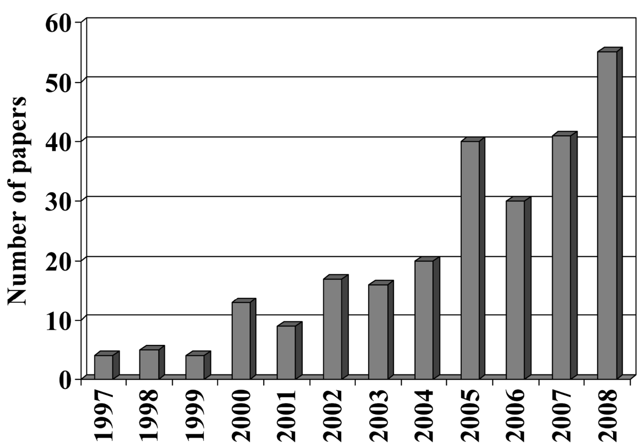

Figure 2. Number of scientific articles published on hops and health from 1997 through 2008.

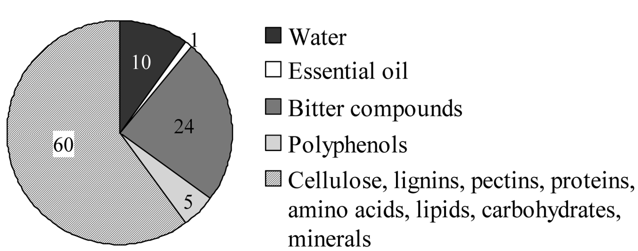

Figure 3. Fractions of air-dried hop cones (composition in percentages; average of different commercial varieties).

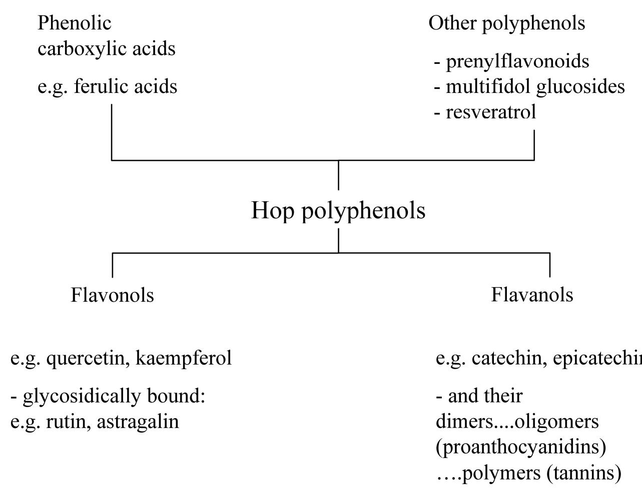

Figure 4. Components of the hop polyphenol fraction.

Table 1. Maximum polyphenolic compound contents in air-dried hop cones (10% water)

Component	Content (%)
Total	
Flavanols	7
Prenylflavonoids	1.3
Flavonols	0.5
Phenolic carboxylic acids	0.05
Individual	
Xanthohumol	1.1
Co-multifidol glucoside	0.3
Catechin	0.2
Quercetin	0.2
Kaempferol	0.1
Desmethylxanthohumol	0.1
6-Prenylnaringenin	0.03
8-Prenylnaringenin	0.01
Ferulic acid	0.01
Resveratrol	<0.01

were published as early as the 1950s, triggered by the observation that workers in breweries had a decreased susceptibility to tuberculosis compared with workers in other industries. Here the crucial active ingredients are the hop β-acids (46).

An estimated 50% of the global population is infected with *Helicobacter pylori*. About one-third of infected individuals experience diseases such as gastritis or gastric ulcer, which can lead to stomach cancer. The β-acids in hops have proven to be effective against these bacteria (42). Hop α- and β-acids are also effective against athlete's foot fungi, and they inhibit the growth of bacteria associated with acne and neurodermatitis. In addition, hop essential oil shows similar activities (28).

Interestingly even the sugar industry has taken advantage of hops as a natural antibiotic. β-Acids are applied during the processing of sugar beets. In addition, the ethanol industry is testing hop bitter compounds as natural alternatives to control bacterial infections in alcoholic fermentation (48).

Flavanols

A mixture of very long-chain hop flavanols has been found to be capable of fighting a broad spectrum of bacteria. Therefore, it could be useful in alleviating symptoms caused by a multitude of bacterial infections. Confirmation of its effectiveness against caries has been proven in tests carried out in a dental clinic in Japan (52). Animal tests at a Japanese medical university provided evidence of the effect of hop flavanols against infection with *H. pylori*, the cause of stomach and intestinal ulcers (58).

Flavonols

The flavonol quercetin is widespread in the plant world and is also present in hops. Of all the polyphenols described in the literature, it is one of the most potent antioxidants (30). Antioxidant compounds protect cells against the damaging effects of reactive oxygen species. An imbalance between antioxidants and reactive oxygen species results in oxidative stress, leading to cellular damage. Oxidative stress has been linked to cancer, aging, atherosclerosis, inflammation, and neurodegenerative diseases such as Parkinson's and Alzheimer's. In addition to quercetin, hops also contain kaempferol, which is chemically very closely related. Neither of these compounds occurs in free form; both are bonded to sugar (glycosides). Typical representatives are rutin (quercetin-3-rutinoside) and astragalin (kaempferol-3-glucoside). Researchers at a Japanese brewery discovered that an aqueous hop extract made up of quercetin and kaempferol bonded to sugar may be effective in alleviating allergy symptoms. This effect has already been confirmed by a double-blind, placebo-controlled clinical trial (49).

Multifidols

So far, only a very few plants containing multifidols have been identified. They were recently discovered in hops as part of a doctoral thesis at the University of Saarbruecken in Germany. Their chemical structure is similar to that of hop α- and β-acids. Co-, n- and ad-homologues were also found. In contrast to bitter substances, multifidols do not occur in free form but are, like many other polyphenols, glycosidically bound (to the sugar glucose). Hop multifidols demonstrate anti-inflammatory activity in vitro (4).

Resveratrol

Resveratrol has become well known as the main polyphenol found in wine. An especially high concentration is found in the skins and pips of red grapes. When Belgian chemists also found this polyphenol in various hop varieties, it came as a surprise to many. However, concentrations measured were very low (23).

Xanthohumol

Recent research has revealed that xanthohumol, a polyphenolic constituent of the lupulin glands, has a multitude of activities (19,55). The xanthohumol content in hops varies from year to year and between different varieties (2).

In 1999, an American research group at Oregon State University described the anticancer activity of xanthohumol for the first time. This activity has been confirmed at many other institutions as well (e.g., the German Cancer Research Centre in Heidelberg). Up to now, the data were mainly generated from experiments with cell lines and isolated organs. Research in animals is ongoing. Especially promising is the potential of xanthohumol used for cancer chemoprevention, i.e., the use of agents with the objective of inhibiting the development of cancer before actual tumor growth occurs (18).

Xanthohumol exhibits this activity through different pathways (17). On the one hand, it can deactivate certain carcinogenic compounds. These compounds are generated, for example, when meat is heated for a prolonged time. Xanthohumol also induces certain enzymes in the body that contribute to detoxification. In addition it has antioxidative properties, which means it can scavenge cell-damaging free radicals from the body. Xanthohumol also inhibits the growth of tumor cells or induces tumor cell death (9). Furthermore, it can inhibit the formation of new blood vessels that would enhance tumor growth (10). Xanthohumol has been shown to inhibit colon, breast, ovarian, and prostate carcinoma (11) and to be effective against leukemia (36). Hop bitter compounds could be useful in fighting cancer as well because they also inhibit the growth of tumor cells (21) and generation of new blood vessels (50,53) and induce cell death (27).

Moreover, in vivo trials on mice have shown xanthohumol activity against diabetes (38). Xanthohumol can also protect against infections—in vitro testing has shown growth inhibitory effects on herpes simplex, hepatitis C, and HIV-1 viruses (15). Xanthohumol has also been demonstrated to be active in vitro against malarial parasites (14).

8-Prenylnaringenin

As far back at the mid-1900s, research was performed to determine whether hops have estrogen-like effects. A hormone-like compound was isolated from hops for the first time in 1953. It was discovered, that hops contain a phytoestrogen, a plant form of the hormone estrogen. For many years thereafter, researchers tried to elucidate the chemical structure of the corresponding compound. In 1999 they identified this constituent in hops as 8-prenylnaringenin (8PN) (32).

Phytoestrogens can help prevent cardiovascular disease and cancer. Of special interest is their positive effect on the symptoms of menopause. Related to this is the potential prevention of osteoporosis (loss of bone density) by phytoestrogens. Osteoporosis is triggered by a decrease in endogenous estrogen levels. The loss of naturally occurring estrogen can be replaced by phytoestrogens such as 8PN. Experiments have been conducted to elucidate the efficacy of 8PN for osteoporosis and symptoms of menopause (6,33,43,47). The content of 8PN in hops is very low; however, it can be isolated and concentrated for use as a natural remedy.

In addition to estrogenic activity, 8PN also demonstrates an appreciable cancer inhibition activity. In fertilized hen's eggs, it reduced formation of new blood vessels (angiogenesis), thus potentially counteracting the growth of tumors (44).

Future of Hop as a Medicinal Plant

All of these recent scientific findings open new options for the use of hops in medicine, as well as nutrition.

Medicine

The use of hop extracts in new applications (e.g., for infectious or inflammatory conditions) is just as conceivable as the development of individual hop compounds (e.g., 8PN) for use in drugs. This could lead to selective breeding of new hop varieties with particularly high contents of pharmaceutically active ingredients (pharmaceutical hops).

Nutrition

In modern nutritional science, the composition of food is also viewed in terms of prevention of diseases. With its beneficial components, hop joins the ranks of plant-based foods that can be beneficial for human health. Currently the health benefits of hops are still mainly achieved through beer consumption, although this could change soon. It is conceivable that special hop extracts could be developed and added to foods to create a line of functional foods. A few new specialty hop extracts (e.g., xanthohumol-enriched extracts) are already available as dietary supplements in health-food shops and drugstores.

Beer and Health

Beer contains a multitude of nutritionally valuable substances, primarily minerals, B group vitamins, and polyphenols, originating largely from malt. However, bitter substances, as well as some polyphenolic compounds, are exclusively introduced into beer by hops (Table 2). Some of these hop components pass into the beer unchanged. Among them are the polyphenols bonded to sugar, such as rutin, astragalin, and multifidol glucosides (their respective beneficial properties were described earlier). Other components originating exclusively from hops are converted during brewing.

Isoxanthohumol

Conventional beers contain up to approx. 3 mg of isoxanthohumol per L, depending on hopping (quantity added and hop product used) and the brewing process employed. This compound is formed from the xanthohumol in the hops during wort boiling (45).

The efficacies of xanthohumol and isoxanthohumol have been compared in many pharmacological studies. In most tests, xanthohumol was found to be more potent than isoxanthohumol. Experiments with harmful substances formed when boiling meat and triggering cancer in humans due to their mutagenicity (ability to alter the genotype) were an exception. Isoxanthohumol effectively inhibited the damage caused by such compounds (e.g., 2-amino-3-methylimidazoquinoline) in vitro at concentrations lower than those of xanthohumol (34). The isomerized form, thus, can also be ascribed as having potential cancer chemopreventive properties, although its effectiveness compared with xanthohumol must be classified as being lower (17).

Isoxanthohumol seems to be particularly effective against the decrease in bone density caused by osteoporosis. This finding was the result of experiments with mice conducted in the research laboratory of a Japanese brewery. In the first instance, hopped beer, surprisingly, had a clearly superior effect compared with unhopped beer. Isoxanthohumol was identified as the active constituent of the hopped beer (25). Recently, isoxanthohumol and xanthohumol were also found to have activity in vitro against obesity (61).

As a result of the chemical reaction during wort boiling, significantly higher quantities of isoxanthohumol compared with xanthohumol are found in beer: 1 L of beer contains up to 3 mg of isoxanthohumol, although sometimes only 0.1 mg of xanthohumol or less. If at all, dark, strongly hopped beers such as stout and porter can contain somewhat more than 1 mg of xanthohumol per L (56). By modifying the brewing process and using special hop products, it is possible to raise xanthohumol levels in beer (57).

Iso-α-acids

Iso-α-acids, the main bittering substances in beer, are formed during wort boiling by isomerization of α-acids. A number of investigations conducted in Japan have concluded that iso-α-acids are among those natural substances that might be able to mitigate the course of diseases associated with metabolic disorders (often classified as metabolic syndrome). These disorders include impairment of organ and cell functions (kidney, liver, fat, and muscle cells), resulting in symptoms such as high blood pressure and elevated uric acid and blood fat and sugar values. This clinical condition results in inferior blood circulation, occlusion of blood vessels (arteries), and, thus, ultimately myocardial infarction or stroke. All sorts of metabolic disorders within the metabolic syndrome interact and may influence and reinforce one another.

The positive influence of iso-α-acids on metabolism has been proven in several tests conducted with rats and mice (35,37,51, 60). Investigations into the effect against type 2 diabetes (adult-onset diabetes) are the most advanced. This disease is characterized by elevated glucose levels in the blood (blood sugar) due to decreased effectiveness of endogenous insulin (insulin resistance). Very promising possibilities for preventing these symptoms became apparent through in vitro experiments and subsequent animal tests. These possibilities were confirmed in a clinical pilot study of 20 males and females (40–65 years old) with adult-onset diabetes who were divided into two groups. One group was given a placebo, while iso-α-acids (two times, 80 mg/day) were administered to the other group. Compared with the control group, daily intake of iso-α-acids resulted in significant decreases in blood sugar levels and blood pressure after 8 weeks (59). Japanese researchers have announced further investigations aimed at treating metabolic syndrome and insulin resistance through the use of isohumulones in beer.

Some scientific reports on the potential cancer-preventive activities of beer have been published. Inhibition of colonic and mammary carcinogenesis in rats has been reported (39,40). In these experiments freeze-dried beer proved to be active. Iso-α-acids were tentatively identified as the active constituents (41). These studies were also carried out in Japan. In vitro tests conducted at the German Cancer Research Centre in Heidelberg confirmed the cancer chemopreventive potential of iso-α-acids and might help in understanding the abovementioned activity of beer (5).

Table 2. Maximum polyphenolic compound contents contributed exclusively by hops in commercial beers

Component	Content (mg/L)
Isoxanthohumol	3.4
Xanthohumol	1.2
Rutin (quercetin-3-rutinoside)	1.8
6-Prenylnaringenin	0.56
Co-multifidol glucoside	0.3
8-Prenylnaringenin	0.24

Depending on bitterness, iso-α-acid concentrations in beer vary from 5 to 40 mg/L or even higher. At concentrations greater than 1 mg/L, beer contains a few more constituents, introduced exclusively by hops, that are relevant to cancer prevention: rutin, isoxanthohumol, and xanthohumol (dark beers) (16).

Beneficial Effects of Moderate Beer Consumption

According to long-term studies, moderate, regular consumption of alcoholic beverages can help prevent sclerosis of blood vessels (atherosclerosis) and, thus, mitigate the risk of myocardial infarction or stroke. This is attributed to the fact that alcohol raises the concentration of good cholesterol in the blood and, in addition, has a blood-thinning effect. Higher blood flow through the vessels has a positive effect on many tissues and organs.

Scientific investigations were initially carried out during the 1980s in countries where a lot of red wine is consumed (e.g., France, Italy, and Spain). In the meantime, it has been proven that the same results can be found in population groups that prefer beer. For this reason, beer and red wine are now regarded as equal by most scientists. It goes without saying that this positive assessment of alcoholic beverages applies only when consumption is moderate.

Other investigations have established that moderate beer consumption can lower the incidence of gastrointestinal inflammation and slow down development of kidney stones and gallstones. Likewise, moderate beer consumption has been proven to lower the risks of suffering from dementia, Alzheimer's, and Parkinson's diseases, as well as having preventive effects against osteoporosis, diabetes type 2, and weight gain (in females) (7).

The nutritionally valuable constituents found in hops play a major part in the positive assessment of beer. As a result of recent findings, the discussion about beer and health is focusing more and more on raw hop materials.

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