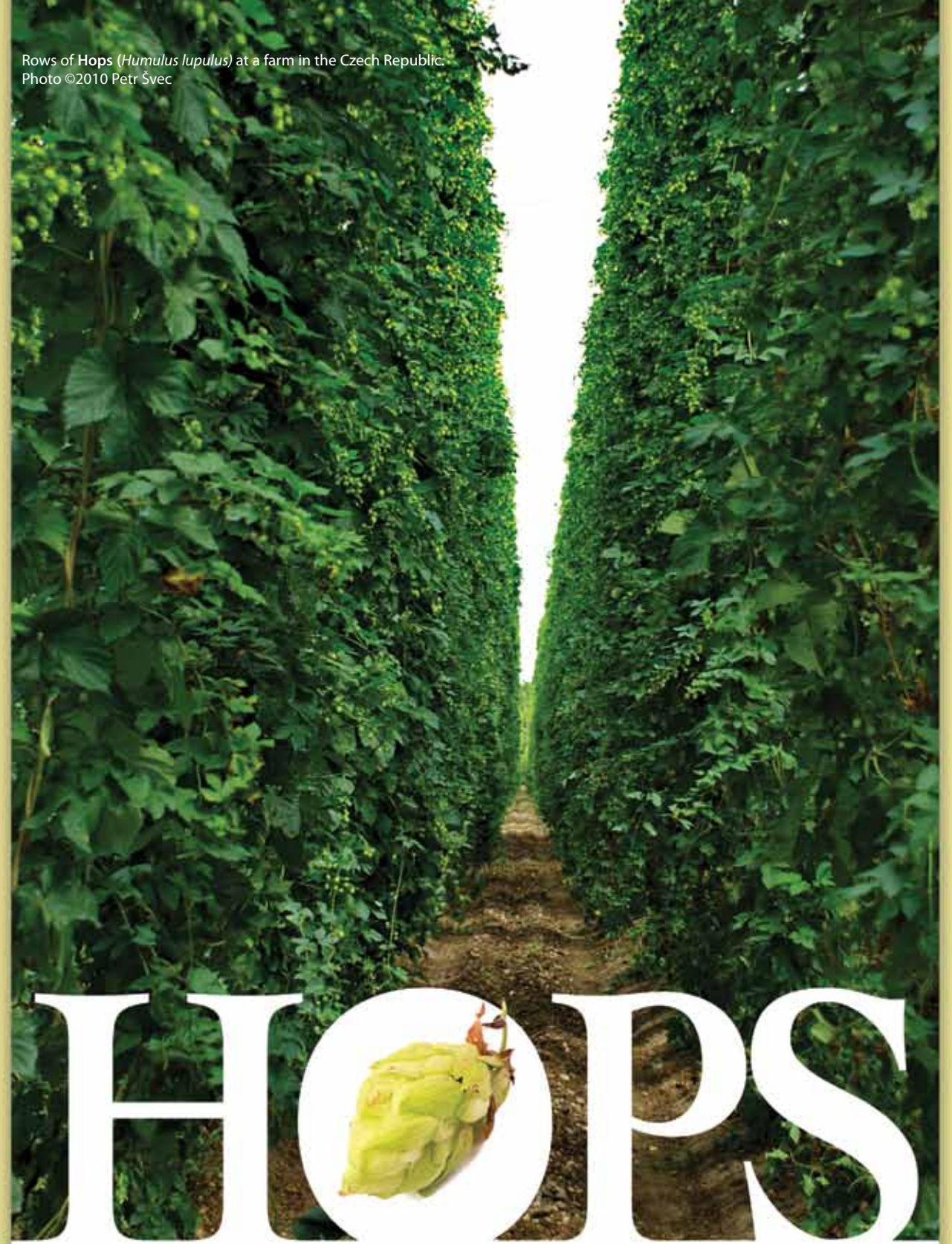


Rows of **Hops** (*Humulus lupulus)* at a farm in the Czech Republic.
Photo ©2010 Petr Švec

HOPS

Humulus lupulus

A Review of its Historic and Medicinal Uses

By Uwe Koetter, PhD, and Martin Biendl, PhD

Introduction

The value of hops in the beer-making process has been undisputed for centuries; the plant's medicinal uses, on the other hand, are less widely known and have many facets. A brief overview of hops and its uses outside beer production are provided below.

Botany

Hop or hops (*Humulus lupulus*) is a climbing vine belonging to the genus *Humulus* in the family Cannabaceae, order Urticacales. Older taxonomists included the genera *Humulus* in the mulberry family (Moraceae).

The genus name *Humulus* has its origin in the Slavic term for hops, *chmele*, which was later Latinized. The species name *lupulus* is a diminutive derived from *lupus*, the Latin word for wolf, based on the plant's habit of climbing on other plants as a wolf does a sheep.[1] Its common name is derived from the Anglo-Saxon *hoppan* (to climb).[2]

Hops is a dioecious perennial plant native to the Northern Hemisphere. It grows vigorously from the end of April to the beginning of July in the temperate climate zone. It is found in shrubbery and at the edge of forests with access to sufficient water, and it reaches a height of up to 7–8 m (23–26 feet). Thus, under good conditions, the growth rate per day of the aerial parts can reach 30 cm (1 foot). The total area covered by the leaves can reach 20 square meters (215 square feet), and the total length of the roots can reach 100 m (328 feet) in one growing season.

When the plant reaches a certain height, it starts to blossom. A second trigger for the advent of blossoming is the length of the day. Too far south the days are too short for hops to blossom; too far north the climate is adverse. Hence, hops grows only at certain latitudes (38º- to 51º- latitude). This explains why hops cultivation in North America is primarily done in areas like Oregon and Washington. Although Northern California has a history of hops cultivation (e.g., Hopland, CA), today the 3 important regions are Idaho with 10%, Oregon with 15%, and Washington with 75% of the annual harvest. The National Hop Report, released in December 2009, found that production in those regions increased from 60 million pounds in 2007 to 95 million pounds in 2009.[3]

In Europe, hops is cultivated in Germany, Great Britain, Poland, and Czech Republic. In Asia, cultivation takes place in certain areas of China and to a limited extent in Japan. For the southern hemisphere, cultivation of hops occurs in Australia from 37º- to 43º- and in New Zealand from 41º- to 42º-latitude.

Only the female hop flowers are cultivated in order to

Hops *Humulus lupulus.* Photo ©2010 Steven Foster

Table 1: Hop products used worldwide

Hop products	Percentage
Hop strobiles (raw, dried)	5%
Hop pellets (cut, milled and homogenized)	60%
Hop extracts (produced with ethanol or supercritical carbon dioxide)	25%
Modified hop products	10%

Adapted from Biendl and Pinzl (2008)[8]

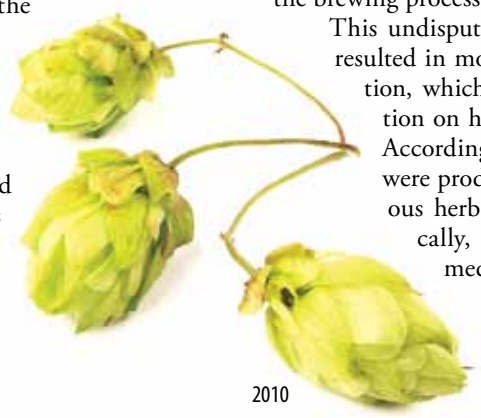
prevent the ripening of fruits (nuts), which are heavy and of no commercial value. In breeding programs, male plants are essential.

Many female flowers form an inflorescence, called strobiles, which consist of membranous stipules and bracts that are attached to a zigzag, hairy axis. Each small branch of the axis bears a bract, represented only by its pair of stipules, which subtends either 4 or 6 bracts, each enclosing a flower or fruit. The stipules and bracts resemble one another closely but are actually numerous shining glands. When separated, these constitute the drug lupulin.[4] The bracts and stipules of the hop contain polyphenols; the odor and taste of the drug is due mainly to the very complex secretion contained in the lupulin glands.

The ideal time for harvesting is August to September in the Northern Hemisphere, while it is February south of the equator. The entire aerial part of the plant is cut and transported to a processing unit, which separates the inflorescences from the rest of the aerial parts. The roots and rhizome remain in the ground, where they begin another vigorous growing season the next year. The rootstock itself can reach an age of 50 years.

After harvesting, the inflorescences are dried immediately to a water content of about 10% for stability reasons. Also, depending on the environmental conditions, hops is kept under constant refrigeration during some or all steps from harvest to final product. The bitter principles are known to break down rapidly during storage and, unless refrigerated, their concentration decreases by 50 to 70% in only 6 months.[5] One study has shown that after 9 months of storage, hops retained only around 15% of its original activity.[6] The alpha and beta acids are sensitive to oxygen. The alpha acids undergo the most intense degradation right after harvest, leveling off during storage. An increase of 10°C doubles the loss, but other factors like the hops variety and even the environmental conditions during the growing season have an effect on alpha acid levels and its decrease during storage.[7]

Besides the limited stability of the dried inflorescences, they are non-homogeneous and have a low bulk density. Consequently, today only 5% of the total annual harvest is used without further processing (raw). About 60% of the inflorescences are converted into pellets. The hop flowers are cut, milled, homogenized, and pressed into granules. The granules are stored and shipped in a method that protects them from air and light, increasing their stability significantly. Such granulation also increases the density of the hops by a factor of up to 10 times, improving costs of transport.



Twenty-five percent of the harvested hop strobiles are extracted with ethanol or supercritical carbon dioxide to obtain as many alpha-acids as possible. Since ethanol and carbon dioxide are naturally occurring during the brewing process, the use of these solvents is of no concern.

When brewing is not done according to the German purity law for beer, the addition of modified hops is possible at the end of the process. During the beer brewing process, compounds of hops undergo isomerization. The substances have been identified and it is known that these isomers can be formed by catalytic modification outside of the brewery. About 10% of the annual hops strobile harvest is used for this purpose today. (See Table 1.[8])

From the immense biomass production, the inflorescences (strobiles) are the only part of the hops plant that is used. Except for some use of young shoots, eaten in salads, there is no human use for the stems, leaves, rhizomes, and roots. The above-ground (aerial) parts are composted and used for fertilization of the fields. The under-ground parts (roots, rhizomes) remain in the ground for the next growing season.

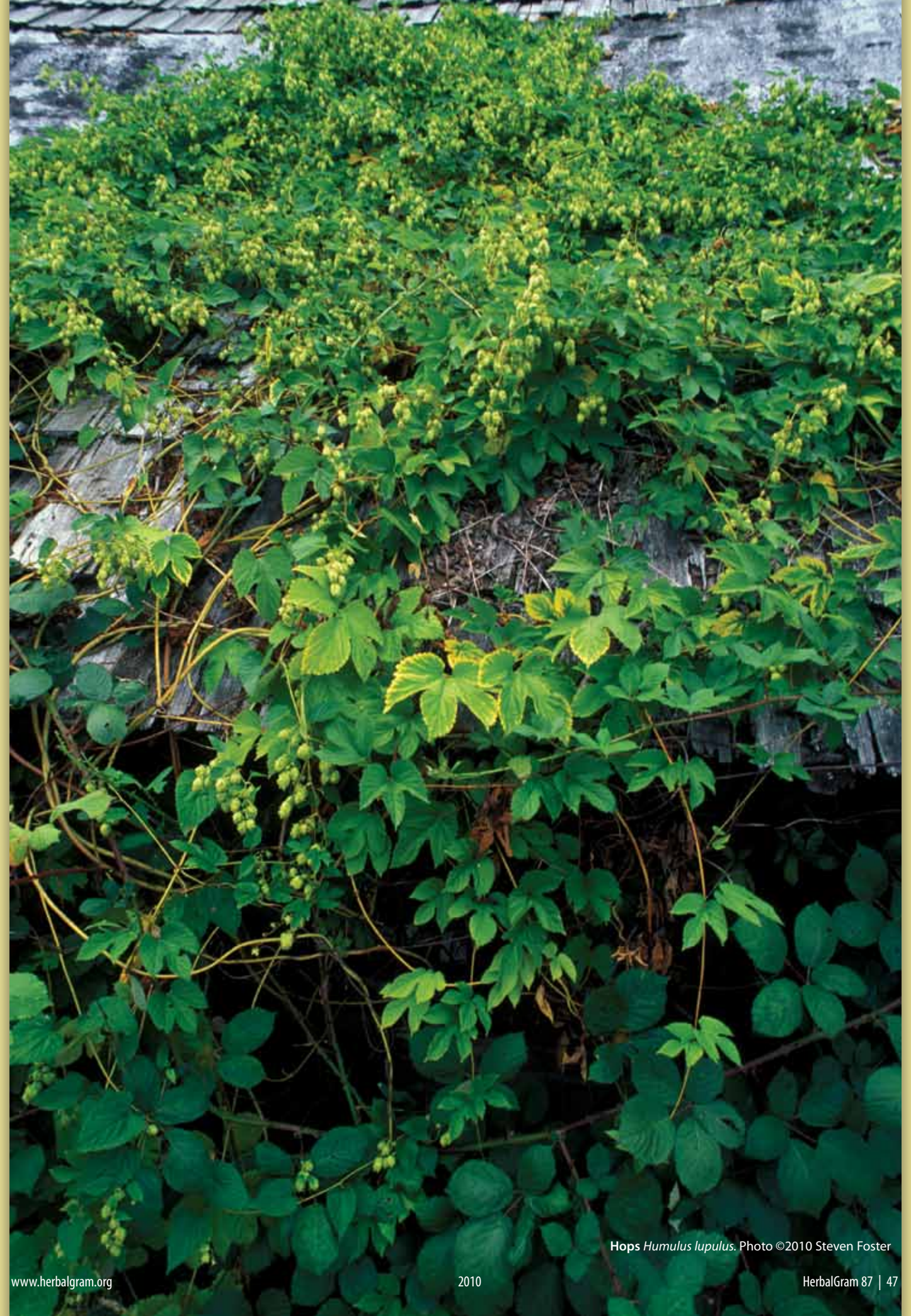
Historic Use

Unlike other well-established medicinal plants like valerian (*Valeriana officinalis,* Valerianaceae), hops does not have a 2000-plus-year history of traditional medicinal use within European herbal medicine. The historic use of hops is interesting as its technical properties—use as flavor and for the preservation of beer—were discovered in the mid ages, but reports of its medicinal use from that time were not very encouraging. Hildegard von Bingen, the noted German abbess, herbalist, and author (1098–1179), wrote in *Physica*, a text on observations of nature and creatures and their virtues, that hops has little use for humans, noting that it "increases melancholy in men." However, she notes that "its bitterness fends off decomposition of beverages and increases shelf life."[9]

With these antimicrobial properties and its ideal flavor, in the region of Germany from the 11th century on, hops replaced all other substances that were formerly used to attempt to improve the taste and increase the storage time of beer.[10] The *Reinheitsgebot* (the German beer purity law) was formulated in 1516, which stated that beer could be made only of malt, hops, and water. (Yeast, an obviously essential ingredient to create the fermentation process, was not known at that time, nor the chemical processes that take place during the brewing process.)

This undisputed benefit of hops in brewing probably resulted in more widespread recognition and distribution, which in turn may have increased the attention on hops for additional (e.g., medicinal) uses. According to Wiesner (1883), so-called herb-beers were produced in the years 1300–1500, with various herbs added for medicinal purposes.[11] Basically, beer was the base, which delivered the medicinal properties of the added plants.

Paracelsus (1493–1541) used hops as a digestive aid, and Matthiolus (1501–



Hops *Humulus lupulus.* Photo ©2010 Steven Foster

1577) mentioned its diuretic and bile-increasing effects. These authors did not specify plant parts used. Bock (1498–1554) and Lonicerus (1528–1586) praised the use of the young hops shoots for cleaning the blood, liver, and spleen.[1,11]

The use of hops flowers was described by Hecker in 1814, who mentioned its strong tonic features as a bitter (Amarum) and noted its calming properties (without having the effects of a strong sleep aid). Clarus (1864) used the female flowers to treat anorexia due to gastritis and sleeplessness. Other authors of that time, including Osiander (1824), Stephenson and Churchill (1834), and Maton (1860), reported on the sleep-promoting properties of the female inflorescences.[1]

One of the most prominent patients treated with hops was Georg III, King of the United Kingdom (1738–1820), who was supposedly bedded on pillows filled with hops to calm him.[11] The physician Kahnt (1905), in his book on phytotherapy, recommended the use of hop pillows,* hop teas, or hop extracts for sleeping problems associated with nervous disturbances.[12] It was believed that hops acted through its strong and heavy odor, causing somnolence.[13]

The supplement to the *Edinburgh New Dispensatory* (1829) states the observation that inhabitants from London were less subject to bladder stones since they had been accustomed to adding hops to their beer.[14]

Other historic uses of hops include the preparation of remedies against hair loss. Washing the head with beer was believed to increase hair growth.[11] According to a personal note from Stieber to Madaus (1938), an infusion prepared from hops is an ideal hair care product.[1] Braungart (1906) cites Strufs, who recommended washing the hair daily with a freshly-prepared hops tea to prevent hair loss, as well as Herzfeld, according to whom hops oil was said to restore even to the bald the beauty of full hair. Unfortunately, the authors do not provide details about the formulation used.[11]

For an overall rejuvenating effect, people formerly bathed in cold brewery-sludge, which contained about 30% hops extracts. According to legend, King Wenceslas IV in 1406 permitted the incorporation of the hops cone into the coat of arms of the brewers in recognition of the rejuvenating effects of the cold brewery sludge bath.[15]

Outside of Europe, other cultures have also demonstrated traditional medicinal uses for hops. For instance, in the Arabic world, Mesue the Younger (d. 1015) wrote that hops helps in the purification of blood, aids in reducing fever and purging yellow bile, and that it has proposed anti-inflammatory properties.[8,11,16] Avicenna (980–1037) discussed hops as one of many herbs in his book *al-Qanun fi'l-tibb*.[17] Ibn-Al Baitar (1188–1248), an Arab scientist, botanist, pharmacist, and physician, described digestive and calming properties of hops.[16]

In North American traditional medicines, the Cherokee used hops as a sedative, anti-rheumatic, analgesic, gynecological aid for breast and womb problems, and kidney and urinary aid for 'gravel' and inflamed kidneys.[18] The Delaware used hops against earache and toothache. The Navajo used it for coughs and cold, and the Dakota for wound healing and against gastrointestinal disturbances.[19] For relaxation and as a sleep aid, it was used by the Delaware and the Fox.[19]

In Indian-Ayurvedic medicine, hops has been recommended for restlessness associated with nervous tension, headache, and indigestion;[20] its actions are reported as sedative, hypnotic, and antibacterial.[21]

According to an inventory of medicinal plants used in different countries, commissioned by the World Health Organization (WHO) in 1978, the use of hops was also established in Asia in China, Japan, and Korea, in addition to the before-mentioned India.[22]

A summary of the indications generally noted for hops since the beginning of the last century are listed in Table 2.[23,24]

Table 2: Traditional Medicinal Indications of Hops and Plant Parts Used

Indications	Plant parts employed
Sedative, hypnotic effects	Hops, hops preparations and combinations with other plants, hops fragrance (sleep pillows), hops tea, lupulin
Mild pain-reducing effects	Lupulin
Amarum aromaticum-like effects	Lupulin, hops bitter acids, hops glands
Anti-diabetic effects	Hops, hops shoots
Beneficial effects on the urinary tract (cystitis, prostatitis, incontinence, diuretic effects)	Hops, hops shoots, syrup made from hops or hops shoots
Anaphrodisiac effects	Lupulin
Effects on skin conditions and against baldness	Hops herb, hops tea, hops juice

Hops for Sleeplessness

Lupulin

One of the most widely known and studied medicinal properties of hops is its ability to induce sleep. Lupulin, the fine yellow resinous substance of the female flowers from hops, was first isolated by the French pharmacist Planche in 1813.[25] Reports on systematic chemical investigation of lupulin can be found in the United States as early as 1820. Ives, a physician, reported from his own experience that it frequently induced sleep and "quiets great nervous irritation."[26] Planche praised its aromatic, tonic, and narcotic (sleep-promoting) virtues. In many cases, it provokes sleep and appeases excessive nervous

*A 3-arm pilot study was conducted in 2001, investigating the effects of sleep pillows on sleep architecture in 30 patients. The pillows were of 3 sizes and filled with a proprietary combination of herbs, including hops, lemon balm leaves (*Melissa officinalis*, Lamiaceae), lavender (*Lavandula angustifolia*, Lamiaceae), orange flowers (*Citrus aurantium*, Rutaceae), and macela flowers (*Achyrocline satureioides*, Asteraceae). The larger pillows showed a trend towards improvement of sleep parameters using polysomnography. [Ref: Füssel A, Wolf A, Büter B, Schrader E, Brattström A. Effizienter Einsatz von Schlafkissen bei Personen mit nicht-organischen Schlafstörungen--eine Pilotuntersuchung. *Forsch Komplementarmed Klass Naturheilkd.* 2001;8(5):299-304.]

Hops *Humulus lupulus.* Photo ©2010 Steven Foster

irritation, but without causing constipation.[14] This was a great advantage compared to the effective treatment with opium (the dried latex of *Papaver somniferum*, Papaveraceae).

Fresh lupulin consists of various compounds, mainly bitter acids, volatile oils, and polyphenols. The aromatic odor of the hops strobiles is due to a volatile oil, present in a yield of about 0.3-1.0%. Active compounds thought to be responsible for its medicinal effects include 15-30% resins (such as humulon, lupulon, and its derivatives 2-methyl-3-butenol), tannins, and flavonoids, as well as essential oils (with its main constituents myrcene, alpha-humulene and beta-caryophyllene, and farnesene).[24]

Despite the early praise by Ives, little work was published on hops' value for sleep in subsequent years. Nevertheless, hops has been consistently employed in combination products with other sleep-promoting herbal preparations. In amounts of 0.3 g and up to 1 g several times a day, lupulin was used against incontinence, to reduce sexual desire (anaphrodisiac), and to treat excessive irritability or sensibility to stimulation of the sexual organs (erethismus genitalis), to treat sleeplessness, and to work against nervousness, migraine headache, and sluggish digestion.[25]

In a 1967 pilot study with capsules containing 250 mg of lupulin, none of the 15 volunteers indicated that the capsules had a sleep-promoting effect during 5 days of use, although dizziness was reported in the morning by some of the participants. The conclusion of the author was that the volatile oil present in the lupulin had probably caused the effect, as anecdotal evidence suggests that it would have been the only compound that could have made hop pickers sleepy. In a second trial with bitter acids equivalent to 5 bottles of beer, again no special sleep-promoting effect was reported.[27]

Possible Mechanisms of Action

There have been numerous reports demonstrating that preparations of hops have sedative-like activity in frogs, pigeons, mice, goldfish, and golden carp. However, a full understanding of the biochemical mechanism and the conclusive identification of compounds responsible for such activity have not yet been achieved.[28]

Animal studies testing the possible tranquilizing effect of hops were published by Dreser (1887),[29] Staven-Gronberg (1927),[30] Steidle (1931),[31] Rusicki and Sikorski (1937),[32] Grumbach (1957),[33] and others. Bravo et al (1974) showed a significant decrease in spontaneous activity after intraperitoneal application.[34] During these early studies, no specific sedative principle was found.

However, in 1983, a volatile alcohol, 2-methyl-3-buten-2-ol (dimethylvinyl carbinol), was isolated from hops and is believed to account for at least part of the plant's sedative properties.[35] Interestingly, the amount of this substance increases during storage.[36] It may be a degradation product of hop bitter acids, and it may be formed after ingestion as well.[37] Nevertheless, researchers were very cautious about the clinical relevance of the results of their animal studies.[38]

Recent *in vitro* experiments on sedative activ-

ity indicated activity on the melatonin receptor. Melatonin, a hormone secreted by the pineal gland in humans, through binding to its receptor, is responsible for maintaining the diurnal circadian rhythm in vertebrates.[39]

Hops extracts had significant hypothermic effects *in vivo* in male mice analog melatonin.[40] This effect was antagonized with the competitive melatonin receptor antagonist luzindole. The data suggest that potential sleep-inducing effects of hops extract are possibly centrally mediated through activation of melatonin receptors.

Other *in vitro* and *in vivo* research points towards involvement of the GABA-$_A$ receptor.[41] The fraction containing beta-acids of a lipophilic CO_2 hops extract was investigated in a benzodiazepine receptor-binding assay. Hops beta-acids affected the plateau of the GABA currents dose dependently without mediating this effect via the benzodiazepine receptor.

Another study examined the effects of beer, hop oils, and fragrance components on the GABA-$_A$ response using the *Xenopus oocyte* expression system and an electrophysiological method.[42] The 2 hops oils alpha-humulene and mycrene caused only a small potentiation of the GABA-$_A$ receptor response. However, these compounds did not work as agonists. More pronounced were the effects of fragrances, which caused a potentiation of the GABA-$_A$ receptor response.

In mice, the sedating activity of hops could be attributed to alpha-bitter acids as the most active constituents. Beta-bitter acids and the volatile oil contributed to the activity in ethanolic and carbon dioxide extracts of hops. Spontaneous locomotor activity was reduced, ketamine-induced sleeping time increased, and body temperature was reduced, thus confirming a central sedating effect.[43]

Most promising are the results from Butterweck et al. (2007), as they provide direction for future isolation and structure elucidation work. With the mode of action potentially linked to melatonin, structural analog substances or precursors may now be identified in hops.[44]

Hops *Humulus lupulus*. Photo ©2010 Steven Foster

Clinical Support for its Efficacy as a Sedative

Positive monographs for hops on the treatment of sleep disturbances are published by the German Commission E[45] and the Scientific Committee of European Experts of the European Scientific Cooperative on Phytotherapy (ESCOP).[46] Both have extensively reviewed literature to form a consensus opinion on indication, method of administration, and posology (dosage, duration of use, etc.).

No pharmacodynamic data are available for hops as a single herb; hops has been investigated pharmacodynamically as part of fixed combinations containing other herbal ingredients (e.g., valerian root). In all studies, the study medication showed an effect, which differentiated from that of placebo. For example, Müller-Limmroth et al. (1977) showed that under artificially disturbed sleep, the study medication (containing hops and valerian root extracts [Seda-Kneipp®, Kneipp, Germany] alters brainwaves monitored by EEG in a manner different from placebo.[47] The EEG changes indicated better sleep as deep sleep and REM sleep increased objectively.

Brattström[48] and Schellenberg et al.[49] demonstrated that a proprietary fixed combination containing hops and valerian root extracts (manufactured by Zeller AG, Switzerland) affects the central nervous system within an hour. This confirms the historically established dose regimen to be taken around 1 hour before bedtime. The effect measured by Schellenberg (2004) is meaningful in regard to the proposed indication as artificially-aroused patients show an increase in alpha-1-power, a wavelength which indicates relaxation. Also beta-2-power,

which indicates higher alertness and mental activity, is reduced.

In a recent randomized, double-blind, placebo-controlled, three-arm, parallel group trial, the effects of hops in combination with valerian were compared with just valerian. In this trial, 30 patients (16 women, 14 men) with non-organic insomnia received a hops-valerian combination (Ze 91019, Max Zeller Söhne AG, Switzerland), placebo, or just valerian for 4 weeks. Polysomnographic recordings were obtained at home with a portable recording device twice at baseline and after 4 weeks of use. Sleep latency (the time required to fall asleep) was reduced when hops was added to the valerian formulation.

No adverse events were reported for any of the patients in the 3 groups, which underlined the safety of the products used in this trial. Safety laboratories data at baseline and at the end of the treatment period were within the normal physiological range. In combination with valerian, hops reduced sleep latency significantly.[50]

Sleep improvements with a hops-valerian combination (Ze 91019, Max Zeller Söhne AG, Switzerland) are also associated with improved quality of life. In a recent randomized, placebo controlled trial, the treatment appeared safe and did not produce rebound insomnia upon discontinuation during the study.[51]

Hops "Bitters" for Digestive Complaints

The *British Herbal Pharmacopoeia*[52] notes the use of hops as a "bitter," while the monograph from the World Health Organization (WHO) provides details associated with this action, i.e., treatment of dyspepsia and lack of appetite.[53]

In Japan, hops is used for activation of gastric function. However, there are actually few reports about the effect of hops on gastric function. In a rat model it was shown that intra-oral but not intra-gastric administration increased gastric secretion.[54]

In North America, Belgium, and England, hops has been used to aromatize liquors, which serve well as aperitifs and digestifs due to their reputation for increasing appetite as well as digestion. These liquors were quite popular in the United States in the last century.

Preparation of these so-called hop bitters is a delicate business, as too little hops may taste good but possess nothing of the beneficial effects of hops. Adding a greater amount of hops may be effective, but the taste of concentrated hops is not considered pleasant by many.

Estrogenic Activity Associated with Hops

Circumstantial evidence over many years, including menstrual disturbances reported to be common among female hops-pickers, linked hops with potential estrogenic activity.[16] In 1953, Koch and Heim found estrogenic activity without being able to elucidate a corresponding substance.[55] When commercial hops extracts, essential oil, alpha- and beta- bitter acids, hops resins, and fractions thereof were examined using the uterine weight assay in immature female mice, no estrogenic activity was detected.[15] Further studies to confirm this activity experimentally were inconclusive or contradictory due to methodology of inadequate sensitivity.

The estrogenic principle in hops extract is 8-prenylnaringenin (8-PN)[56] with 10% of the binding activity of 17-beta-estradiol, while structurally related hops flavonoids had more than 100 times lesser potency.[57] However, the effects of whole extracts are much smaller, and the direction of activity is unclear. While whole hops extract (50% ethanol)

Table 3 Reduction of Sleep Latency by Hops and Valerian (median values)

	N	Baseline	N	End of treatment	Difference
Hops and valerian	10	56.5 min	9	12.0 min	44.5 min
Valerian	10	45.9 min	10	23.8 min	22.1 min
Placebo	10	64.2 min	8	69.7 min	5.5 min

Adapted from Koetter et al. (2007)[50]

Table 4: Summary of Indications for Hops in Well-Regarded Monographs

Reference	Hop Strobile Indications
German Commission E Monographs	Mood disturbances such as restlessness, anxiety, and sleep disturbances
British Herbal Pharmacopoeia	Action: Sedative, bitter
ESCOP Monographs	Tenseness, restlessness and sleep disorders
WHO Monographs Vol 3	Uses described in pharmacopeias and well established documents: As a sedative for the treatment of nervous tension and insomnia. Treatment of dyspepsia and lack of appetite Uses described in traditional medicine: Treatment of abdominal cramps, anemia, bacterial infections, dermatitis, diarrhea, dysmenorrhea, leukorrhea, migraine and edema. As an analgesic, anthelminthic, antipyretic, aphrodisiac, carminative, depurative, digestant, diuretic, diaphoretic and tonic.
HMPC Community Herbal Monographs	Traditional herbal medicinal product for relief of mild symptoms of mental stress and to aid sleep

in one *in vitro* study stimulated cell proliferation in estrogen-dependent T47D breast cancer cells,[58] hops extract in another *in vitro* study inhibited serum-stimulated growth of T47D cells.[59] In an *in vivo* study with ovariectomized adult rats, the primary outcome measure, uterus weight gain, indicated that hops did not have an estrogenic effect on the uterus, and none of the secondary outcome measures were positive, confirming the safety of hops.[60]

It bears emphasis that the estrogenic principle in hops (8-PN) is formed spontaneously from the chalcone desmethylxanthohumol. Hence, it is not typically present in relevant concentrations in most hops extracts, e.g., either in beer or in medications. The concentrations of 8-PN are generally too low in such preparations to produce a measureable effect in humans.[61] While 8-PN may be formed in the intestine,[62] absorption should be reduced significantly by intestinal and hepatic metabolism.[63] From the long-established use of hops extracts, one can safely assume that drinking a beer or taking hops as a sleep aid is without any known toxicological problems. The components of potential toxicological concern are present in only minor quantities in the typical extracts consumed in beer or as sleep medication.[64]

Numerous studies have been conducted to investigate the effects of 8-PN. These trials were recently thoroughly reviewed.[65] One potential use of 8-PN could be an alternative option for reducing hot flashes in menopausal women.[66] In an animal model, it reverses the ovariectomy-induced rise in skin temperature.[67]

The development of 8-PN-enriched hops extracts for the relief of menopausal symptoms (MenoHop® from Biodynamics, Ostend, Belgium) is fairly recent. A randomized, double-blind, placebo-controlled study over 12 weeks with 67 menopausal women showed a significant reduction in menopausal discomforts and complaints assessed by the Kupperman index and by a simplified patients' questionnaire in the treatment group after 6 weeks ($p = 0.023$) compared to placebo, but not after 12 weeks ($p = 0.086$).[68] Furthermore, no dose-response relationship could be established. A higher dose appeared less active.

Vaginal application of a gel with hops manufactured by Polichem SA, Lugano, Switzerland (Brand names: Gynomunal®, Germany; Esvegyne®, Italy) was tested in an open, non-controlled study with 100 postmenopausal women for 30 days. The results showed a marked effect on vaginal dryness and associated symptoms. Dryness, itching, burning, dyspareunia, inflammation, and rashes improved. The study and an additional pilot study by the same group confirm a good safety profile for the intended use. The study was not designed to distinguish between the effects of hops and other ingredients like hyaloronic acid, liposomes, and vitamin E, which were all components of the gel.[69]

In a very recent randomized, double-blind, placebo-controlled, cross-over pilot study, time-specific estimates of treatment efficacy indicate significant reductions for Kupperman index ($p = 0.02$) and visual analog scale ($p = 0.03$) and marginally significant reduction of menopause rating scale ($p = 0.06$) after 16 weeks.[70] Whereas the first treatment period of the cross-over study resulted in similar reductions in menopausal discomforts in both groups, results from the second period suggest superiority of the standardized hops extract (MenoHop) over placebo.

Other Potential Medicinal Uses of Hops

Considerable work has been done investigating the antibiotic, antiseptic and tuberculocidal properties of hops and its constituents. Hop bitter acids have proven to be especially effective against gram-positive bacteria. They work best at low pH in not dissociated form.[71-75] In comparison to phenol, alpha-acids (humulone) and beta-acids (lupulone) are about 200 times and 700 times more potent, respectively. Against gram-negative bacteria, the same substances are without considerable effect, and yeast and molds are minimally inhibited.[24]

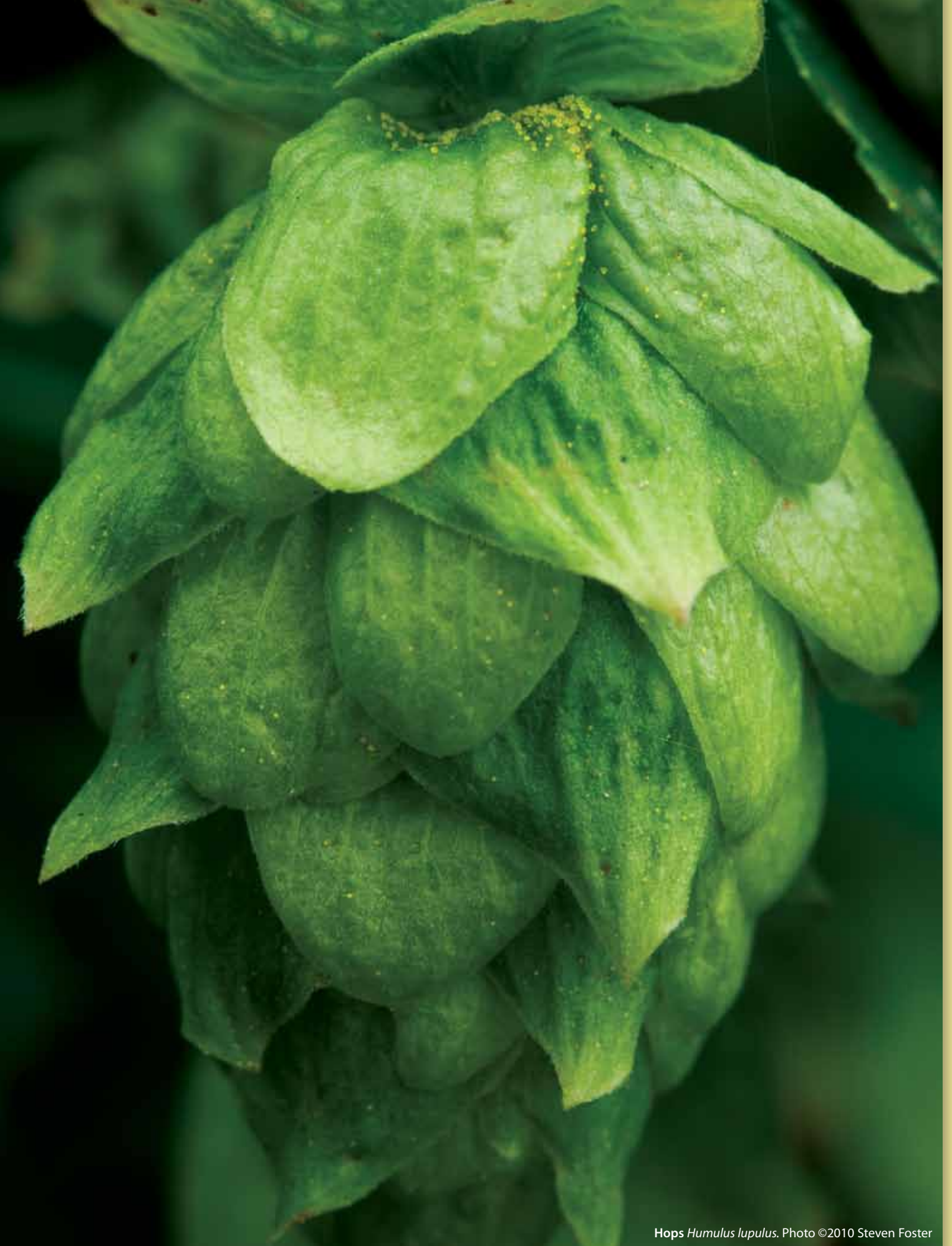
Lupulone was tested as a treatment for tuberculosis, as it has the highest *in vitro* effect against *Mycobacterium tuberculosis* of all the hops constituents.[72] Enders (1950) reduced tubercular infection in mice treated with lupulone.[76] However, Chin (1949) did not see this effect in his investigations.[77] When given to men, preliminary results were promising, although the treatment was associated with gastrointestinal disturbances.[76] In a clinical trial, treatment was impaired by side effects of the single substance given in high doses.[78,79]

Statistics in England from the first half of the last century showed that mortality from tuberculosis in brewery workers was 30% of the average.[76,80] In Bavaria, in the same period, the incidence rate of tuberculosis was 4 times lower in brewery workers than in other professions. However, the result could have been due to general better health of these workers.[81] With the advent of potent antibacterial substances in the second half of the last century, research relating to hops constituents for tuberculosis did not progress further.

The main prenylflavonoid in hops, xanthohumol, has a high scavenging capacity against peroxyl radicals, which are among the most commonly reactive oxygen species in the body. Using both hydrophilic and lipophilic oxygen radical absorbance capacity tests, xanthohumol is more potent than vitamin C and vitamin E.[82] Due to its strong antioxidant activity, a number of potential health benefits are attributed to the substance. Mostly in *in vitro* tests it has shown antiproliferative,[83] anticarcinogenic,[84] antigenotoxic,[64] anti-inflammatory effects,[84] and decrease of plasma glucose, lipid levels, and weight of white adipose tissue in diabetic mice.[85] Recent research has begun testing xanthohumol against certain viruses[86] and the malaria protozoa (*Plasmodium falciparum*).[87,88] Special enriched xanthohumol extracts have been developed for health benefits in xanthohumol-enriched beers.[89]

Hop derived compounds[90] have also shown potential benefits in treatment of diabetes.[91,92,93] Following the discovery that isohumulones reduce insulin resistance, a double-blind, placebo-controlled pilot study showed that isohumulones (isom-

Hops *Humulus lupulus*. Photo ©2010 Steven Foster



Hops *Humulus lupulus*. Photo ©2010 Steven Foster

Lupulin glands on the Hops *Humulus lupulus*.
Photo ©2010 Hopsteiner

erized hop extract purchased from English Hop Products Co. Ltd, Kent, UK) significantly decreased blood glucose and hemoglobin A1c levels after 8 weeks. Twenty volunteers with mild type 2 diabetes were included in this study. Ten men and 10 women (ages 45-65 years) were randomized, receiving either placebo or a capsule containing 100 mg of isohumulones twice a day for 12 weeks. Results after 8 weeks showed a significant decrease for blood glucose, HbA1c, systolic blood pressure, GPT, GOT and gamma-GPT versus baseline. In the placebo group, only blood glucose levels improved versus baseline.[94]

In a follow-up study with 94 subjects, ingestion of isohumulones (isomerized hop extract obtained from Botanix Limited, Kent UK) had beneficial effects in diabetes and obesity. The volunteers with prediabetes received either placebo, 16 mg, 32 mg, or 48 mg of isohumulones for 12 weeks. After treatment, fasting blood glucose was decreased in the 32 mg and 48 mg groups after 4 weeks but did not change in the placebo group. HbA1c was also significantly decreased after 4 weeks in the 16 mg group and after 8 weeks in the 32 mg and 48 mg groups. Body mass index was significantly decreased in the 48 mg group compared with the placebo group at 12 weeks. The decrease in total fat area was also significantly greater in the 48 mg group than in the placebo group at 12 weeks.[95]

Other recent developments include research on modified hops extracts, which have undergone isomerization and hydrogenation. These so-called rho iso-alpha acids have anti-inflammatory potential. In a screening of natural products, hop-derived substances called MgRIAA obtained from Metagenics (Gig Harbor, WA), commercial hop materials from Betatech Hops Products (Washington DC), an experimental extract from BetaTech, and META060 supplied by Hopsteiner (New York, NY) were found to be among the most active in terms of anti-inflammatory potential.[96,97] These rho iso-alpha acids ameliorated joint damage as evidenced by significant reduction of the arthritis index and histology score in a murine model of collagen-induced arthritis.[98] Bone and cartilage degradation were reduced by META060.[99] Additionally, clinical research on a proprietary blend of rho iso-alpha acids, rosemary, and oleanolic acid (Kaprex®, Metagenics Inc. Gig Harbor, WA) demonstrated significant relief for people diagnosed with osteoarthritis, rheumatoid arthritis, or fibromalgia.[100] And rho iso-alpha acids from hops and proanthocyanidins from *Acacia nilotica* (Fabaceae), both supplied by Metagenics, Inc., have been shown to modulate insulin signaling *in vitro*. In a 12-week, double-blind, placebo controlled trial, completed by 91 individuals, effects on serum glucose, insulin, and lipids were investigated with the combination of the 2 ingredients. Daily supplementation with 300 mg rho iso-alpha acids and 1500 mg proanthocyanidins, in addition to lifestyle modification including dietary alteration, reduced serum triglyceride, triglyceride:HDL ratio, and fasting insulin significantly more than diet and lifestyle modification alone in patients with features of metabolic syndrome.[101]

Conclusion

With increased understanding of the medicinal properties of hops, its use beyond beer is increasing. Scientific and clinical findings point to the possibility of hops' becoming even more widely used in the future—both in medicine as well as in nutrition. New uses as food for health are just as conceivable as the processing of individual hops components in pure form for use as dietary supplements and medicines. HG

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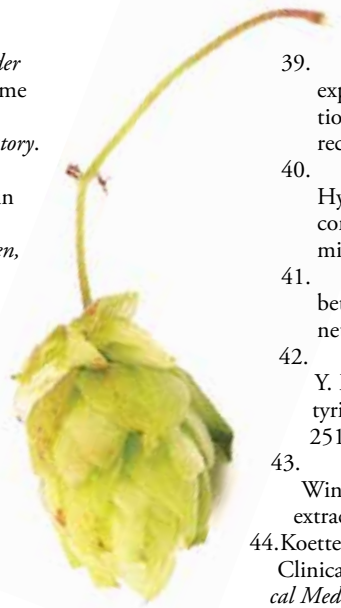

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