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REVIEW ARTICLE

HUMULUS LUPULUS L. (HOPS) – A VALUABLE SOURCE OF COMPOUNDS WITH BIOACTIVE EFFECTS FOR FUTURE THERAPIES

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Summary

Hops are a well-known source of resins, essential oils and polyphenolic substances, such as proanthocyanidins or prenylflavonoids with significant representatives of xanthohumol, isoxanthohumol, and 8-prenylnaringenine, and represent an essential ingredient in beer production. Recently, however, many additional bioactive effects of hop compounds have been investigated.

A systematic review of the structure-function relationship between the individual hop-derived compounds and their bio-activity has been lacking. In this review we summarize some recent findings in this area from reports from our as well as other studies. It shows multiple bio-medical effects of the individual hop derived compounds, which can act individually, or in a synergistic manner.

The hops can serve as a source of bio-active compounds in phyto-medicine and as such, more attention and detailed studies are warranted to utilize the broad spectrum of effects of individual compounds in future treatments.

Key words: Humulus lupulus L.; hops; hop resins; hop oils; hop polyphenols; bioactive effects

INTRODUCTION

Humulus lupulus L., more precisely flowers (cones) of the female plant represent one of the most important raw materials for brewing, because of their bitter and aromatic properties. In addition, hops have been used in cosmetic and pharmaceutical industries, especially for their antimicrobial and antiviral effects. The fact, that hops were originally used and added to beer for its antimicrobial activity as a preservative, classifies this plant as a natural source of compounds with biological effects.

An increasing number of pathogenic strains of bacteria (and viruses) resistant to different types of antimicrobials poses a major medical problem. Secondary metabolites of hops have been described

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as potent antimicrobial agents against a wide range of microorganisms. The importance of this plant was supported by the "Medicinal Plant of the Year 2007" award granted by the Study Group for the Historical Development of Medicinal Plant Science at the University of Würzburg, Germany, or by the selection of hops as the 2008 theme plant by the University of Illinois, Chicago, USA. An increasing number of scientific publications on the beneficial properties of hops further underscores their importance and is the main reason for such recognition [1].

Yellow lupulin glands within hop cones contain resins (α-acids and β-acids) and essential oils, which give bitter taste and characteristic aroma to beer. In addition, the matrix of hop cones contains a wide spectrum of polyphenolic compounds, such as phenolic acids and proanthocyanidins, or prenylated chalcones, which are generated in the lupulin glands [2]. The purpose of this review is to summarize biological activities of all three main groups of hop secondary metabolites (resins, essential oils and polyphenols), i.e. functional metabolites formed in the hop cone during maturation, including their antibacterial, antifungal and antiviral activities with their future therapeutic potential (Table 1).

THE HISTORY OF HOPS

Hops were known as a wild plant already during the antique times. Historical findings lead to the conclusion that their origin was in Asia, more specifically in the fertile Mesopotamia, the lowlands of Caucasus and southern Siberia [3]. From the botanical point of view, however, the hop plants are thought to have originated in China, because China is the only country in the world where all three species of hops (*H. Lupulus, H. Japanicus, H. Yunnanensis*) are naturally found [4-6]. Hops have been grown as a cultivated plant from the beginning of our age. Records showing hops being used for seasoning and preserving of beer by Slavic tribes come from at least 1500 to 1000 years BC. Other nations started using hops for brewing since the 13th century (A.D.). Until the 12th century (A.D.) however, hops were obtained probably only by collecting of wild plants [3].

Very soon people discovered healing effects of hops, which then found their way into the traditional medicine. Hops were used, according to an old herbarium for medical treatment of various conditions, such as leprosy, bad smell of feet, liver diseases, constipation, sleeping disorders and for purification of blood [7,8]. Records from the 7th and 9th (A.D.) centuries show, that the earliest predecessors of hop gardens were founded under monastic administration, where the hops were grown for their medicinal properties together with other herbs [9]. Even at that time, hop extracts were recognized for their anti-inflammatory and anti septic effects as decoctions prepared from hops were used to treat poorly healing injuries.

Another example of such treatment applications is the use of heated hops as a poultice [10] for pneumonia or treatment of fevers using decoctions from hops [11]. Alcoholic extracts of hops have been also used in Chinese medicine for treatment of pulmonary tuberculosis, or acute bacterial dysentery and have been also a part of Ayurvedic treatments [12]. Some recent studies have shown that alcoholic extracts from hops possess a strong spasmolytic effect on smooth muscle and thus are effective in conditions characterized by tension of visceral smooth muscles, including nervous colitis, nervous dyspepsia, palpitations, nervous or irritable coughs, and asthma[13,14].

PHYTOGEOGRAPHY AND BOTANY OF HOPS

Wild hops, which grow in wet areas close to rivers, are widespread on large areas of Europe, Asia and North America [15].

Today, the production of cultivated common hops is concentrated in moist temperate climate areas, with much of the world's production occurring near the 48th parallel North. Hop yards are an integral part of the countryside around Europe, North and South Americas, South Africa, Australia and New Zealand. The cultivar plants are grown typically on large flat areas with acidic soil. Currently the biggest producers of hops include Germany, USA, China and Czech Republic (the production in 2014 was 25 338, 38 499, 6 887and 6 202 tons, respectively) [16].

When technological aspects or medical effects of hops derived products are discussed, it should be noted that these products are derived only from cones of female plants. *Humulus lupulus* L. is a dioecious twining perennial creeper from *Cannabaceae* family[17], which also includes the genera *Cannabis* (hemp) and *Celtis* (hackberries). The leaves are positioned on the stalk in the opposite manner on 7

Table 1. List of antibacterial, antifungal and antiviral activities of hop compounds

Hop compounds	Microorganism tested	activity +/-	Reference No.
RESINS (soft)		+	38
	Candida albicans	+	38
	Trichophyton mentagrophytes var. interdigidale	+	38
	Fusarium	+	38
	Mucor	+	38
	Lactobacillus spp	+	39-42
	Pediococcus spp	+	39-42
	Streptococcus mutans	+	39-42
	Streptococcus sanguis	+	39-42
	Streptococcus salivarius	+	39-42
	Clostridium perfringens	+	39-42
	Staphylococcus aureus	+	39-42
	Micrococcus	+	39-42
	Clostridium difficile	+	39-42
	Clostridium botulinum	+	39-42
	Helicobacter pylori	+	39-42
	Bacillus subtilis	+	39-42
	Listeria monocytes	+	43, 44
	Mycobacterium tuberculosis	+	45
OILS			
	Bacillus subtilis	+	44
	Staphylococcus aureus	+	44
	Trichophyton mentagrophytes var. interdigitale	+	44
	Escherichia coli	-	44
	Candida albicans	-	44
POLYPHENOLS			
	Staphylococcus aureus	+	38
	Streptococcus mutans	+	40
	bovine viral diarrhea virus (BVDV)	+	42
	surrogate model of hepatitis C virus (HCV)		42
	human immunodeficiency virus (HIV)	-	42
	influenza A virus (FLU-A)	-	42
	influenza B virus (FLU-B)	-	42
	rhinovirus (Rhino)	+	42
	respiratory syncytial virus (RSV)	-	42
	yellow fever virus (YFV)	-	42
	cytomegalovirus (CMV)	+	42
	hepatitis B virus (HBV)	+	42
	herpes simplex virus type 1 (HSV-1)	+	42
	herpes simplex virus type 2 (HSV-2)	+	42

to 12 cm long leafstalks and are heart-shaped with coarsely toothed edges. The female flowers (often called cones) consist of short green spikelets (called hop cones, seed cones or strobiles) and secrete a fine yellow resinous powder from structures called lupulin glands. Lupulin glands synthesize the resins and essential oil [18, 19], which give the characteristic bitter taste and aroma to beers, but also stabilize the foam and final product [20]. Special vacuoles of the external system of lupulin glands represent rich reservoirs of brewing and pharmacologically important substances, which are often called secondary metabolites.

Male plants are characterized by little yellow flowers and are important for breeding of new varieties. Otherwise, male plants are removed from hop fields to prevent fertilization of female plants and production of seeds [21].

The demands of beer consumers on sensorial specificity lead to breeding and development of hundreds of varieties of hops, which differ substantially in the content and chemical profile of hop oils and bitter acids (and related polyphenols) [5, 22]. Based on genetic markers, hop varieties can be divided into four groups: hops of the European origin of the Saaz group, hops of the European origin of the Fuggle group, hops of the American origin and hops of mixed origin [23] (Figure 1) New hop varieties are bred by crossing of a different genetic material to achieve desired characteristics, such as high yield, disease resistance and content and composition of resins and oils. For example, the twelve registered Czech varieties are positioned virtually across the entire genetic spectrum of hop varieties (Figure1).

This diverse genomic spectrum together with the diversity of associated characteristics of the hop varieties listed above make it highly likely, that the profiles of biologically active compounds are also different among the individual varieties of hops. Indeed, some already available chemotaxonomic studies of hops support this notion.

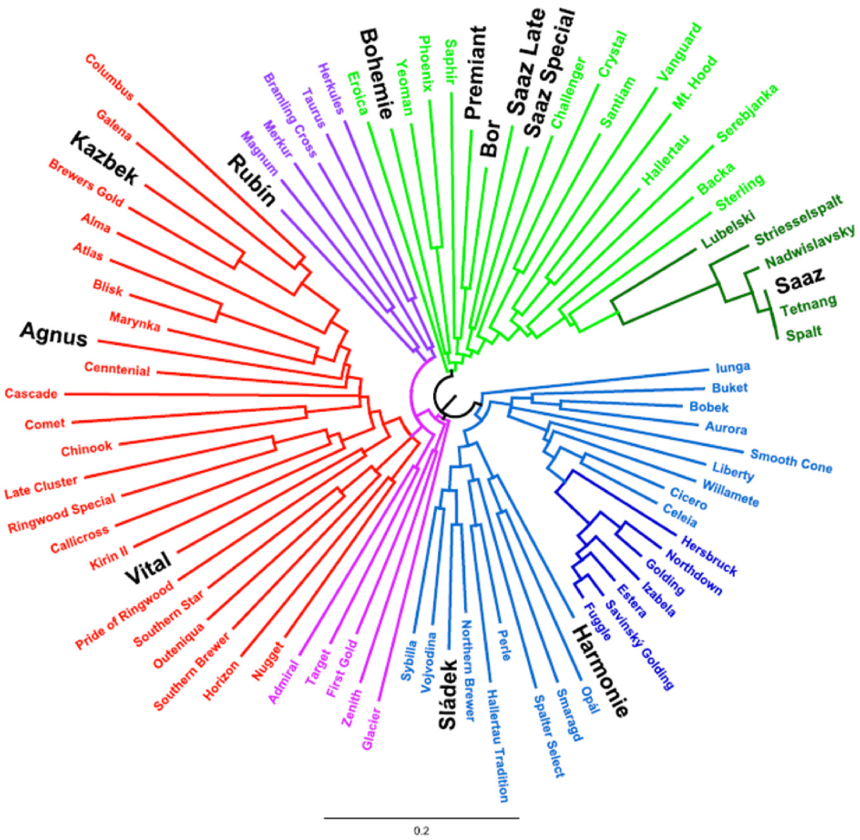

Figure 1. Dendrogram of the genetic distances of 85 world hop varieties based on 238 polymorphic molecular markers. *Green* - hops of the European origin of the Saaz group, *blue* - hops of the European origin of the Fuggle group, *red* - hops of the American origin, *purple* – hops of mixed origin, *black* - Czech registered varieties [23].

Li et al., *2006* [24] published a comprehensive study about structural identification and distribution of proanthocyanidins in 13 different hops species. They established the correlation between the profiles and the geographic origin of hops. Our studies have also proven the dependence of proanthocyanidin composition on hop variety (Saaz, Premiant, Sladek and Agnus) using a newly developed method based on ultra-high performance liquid chromatography [25]. Our new method provided profiles of proanthocyanidins, whose partial identification was based on accurate mass (<5 ppm) of their pseudomolecular [M–H]- ions. This approach could not provide an exact compound structure; however, it was possible to establish the type of monomer units, from which the proanthocyanidin oligomers were composed. In this way, (epi)catechin, (epi)gallocatechin and (epi)afzelechin differing in mass can be distinguished from each other, whereas isomer pairs such as catechin and epicatechin or gallocatechin and epigallocatechin provide identical MS signals, but they differ in their retention times. In the profiles, proanthocyanidins were considered and statistically evaluated. The results obtained from crop of 2011and 2012 corresponded to each other. Catechin was the most abundant flavan-3-ol monomer in Saaz, Sladek and Premiant hops (15.4–18.2%), which is in contrast to the Agnus variety, where the major monomer was epicatechin (9.0%). It is worth mentioning, that our method was capable of detecting low amounts of (epi)afzelechin incorporated in proanthocyanidin. Interestingly, (epi)afzelechin was only identified in the dimer formed by (epi)catechin and (epi)afzelechin.

Beside a basic description of found compounds, we used a more comprehensive interpretation of the obtained profiles such as multivariate statistical methods PCA and cluster analysis. Using PCA, hop samples were grouped into the "varietal clouds". Also, the PCA results showed that the hop cultivars differed in the content and proportions of oligomeric proanthocyanidins. In addition to this, a considerable influence of the above mentioned non-varietal types of behaviour summarized in the term growing locality was observed. Also, the result of the cluster analysis showed that hops were clearly grouped depending on their variety. Except of the two Premiant hop samples, the greatest distance was observed between the traditional Saaz fine aroma variety and the other three tested hybrid varieties. To summarize our results, we were able to distinguish 4 varieties from 24 localities using just the proanthocyanidin profiles of 40 different hop samples.

Subsequently we improved this method by using high-resolution mass spectrometry. In that study the identification of hop varieties based on the specificity of groups of proanthocyanidins was performed using 50 hop samples from the 2014 crop. Five varieties (Saaz, Sladek, Premiant, Kazbek and Agnus) were clearly distinguished based on the proanthocyanidin profiles, which even correlated to their genetic relatedness [26].

Finally, we performed an analysis and distinguished four important Czech varieties (Agnus, Premiant, Saaz, and Sládek) of hops in 59 samples using contents of α- and β- bitter acids and linalool (an important representative of hop oil) [27]. By using a new method based on sample preparation by a fluidized-bed extraction followed by GC-MS determination of linalool, we managed to obtain results in a 3D projection. Except for one Saaz sample, we obtained four clearly separated clusters corresponding to the four tested hop varieties.

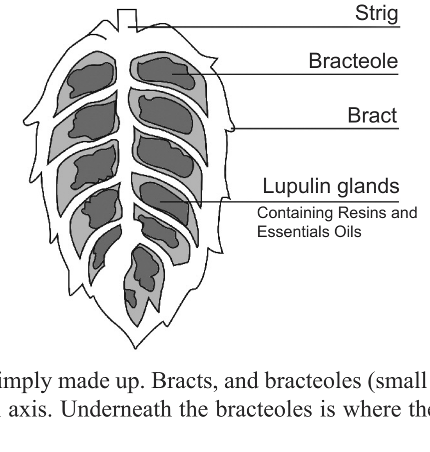

Figure 2. Anatomy of hops. The cone is very simply made up. Bracts, and bracteoles (small bracts) are leaf like structures that surround the entire cone, attaching to a central axis. Underneath the bracteoles is where the magic of the hop plant is found, the lupulin glands (draw by Olsovsky, 2016).

MORPHOLOGY OF HOP CONES

As mentioned above, flowers of female hop plants form hop cones that appear as side arms developing along a stem. These hop cones are made of a string, bracts, bracteoles and lupulin glands (Figure 2). Unlike a smooth stem, a string, which is the continuation of the stem, is corrugated. The corrugation varies considerably and according to the structure of the string it is possible to distinguish three groups of hops [28]. Strings with dense corrugations give compactness to the cone, which is a useful feature for breeding new varieties. Stipular bracts and seed-bearing bracteoles are leaf like structures that are attached to a central axis or a string surrounding the entire cone [29]. The bracts are pointed at the tip, the bracteoles are rounded. The bracts perform as protective organs and contain few lupulin glands whereas the bracteoles are winged organs containing a wealth of lupulin glands, particularly at the bottom in a pocket-like fold. The lupulin glands form tiny yellow sacs found at the base of the petals of the hop cone.

Organisms, predominantly plants, fungi and bacteria, produce and excrete a broad spectrum of mostly low-molecular-weight chemicals called secondary metabolites. Compared to primary metabolites (i.e. amino acids, fatty acids, carbohydrates, nucleotides, proteins, lipids, polysaccharides, DNA), secondary metabolites occur in a significantly higher diversity and their role has been intensely discussed since the beginning of the 20th century, when scientists finally began to explore this issue. In hops, lupulin glands produce characteristic hop secondary metabolites (resins, essential oils, and prenylflavonoids) during their maturation, while these metabolites are placed on the bracteoles of the cone [30]. Commercial value of hops is evaluated according to the content of resins (α-bitter acids), which are responsible for the bitterness of beers. The second measure of hops quality is the content and composition of hop oils, which contribute to the flavour and aroma of beers.

The polyphenols are mainly concentrated in the green parts of the hop cone (string, bracts and bracteoles) but the distribution of individual groups of polyphenols in each of these parts varies as well. Most of tannins in the hop cone could be found in the string and stem, as opposed to their very low content in the hop leaves.

Generally, hop cones are frequently used in phytomedicine, e.g. as bitter tonics, sedatives or hypnotics, and for supporting healthy digestion. In addition, they have also been used to treat cancer and ulcerations. Hop teas are used as a mild sedative and remedy for insomnia. A poultice of hops is used to topically treat sores and skin injuries and to relieve muscle spasms or neural pain [31, 32].

CHEMISTRY AND BIOACTIVE EFFECTS OF HOPS COMPOUNDS

Hop resins

Hop resins, which are soluble in methanol and diethyl ether, are subdivided into hard and soft resins based on their further solubility [3, 19, 29].

Hard resins are insoluble in hexan. It is generally accepted that hard resins are mainly composed of oxidation products of soft resins (α- or β-acids), which are produced during maturation, postharvest processing and storage of hop cones. Natural hard resins contain xanthohumol, which is the most abundant prenylated chalcone present in hops and is composed of β-hard resins [3]. *Almaguer et al, 2011*[33] showed that hard resins could be effectively separated by using modern analytic techniques. In this study, it was possible to further purify hard resin extract through the development of novel fractionation techniques. The δ-resins and ε-resins were obtained by this purification process, and from each resin it was possible to further retrieve 11 fractions.

Soft resins (or bitter acids) are soluble in hexan and include α-bitter-acids (α-acids), ß-bitter-acids (ß-acids), also referred to as humulones and lupulones, respectively, and uncharacterized soft resins. Dried hop cones contain from 2% to 17% of α-acids and from 2% to 10% of β-acids, depending on the variety of hops.

The α-acids represent a mixture of chemical analogues, including humulone, cohumulone and adhumulone. Similarly the ß-acids are a mixture of lupulone, colupulone and adlupulone. The chemistry and properties of α-acids are well studied and known - they are main compounds of hops with preservative effects in beer. The α-acids isomerize at higher temperatures in aqueous conditions into more soluble iso-α-acids (Figure 3) [20]. Hop α-acids have also been reported to exert a wide range of effects utilized in phytomedicine, both *in vitro* and *in vivo*. They exhibit a potential anticancer activity

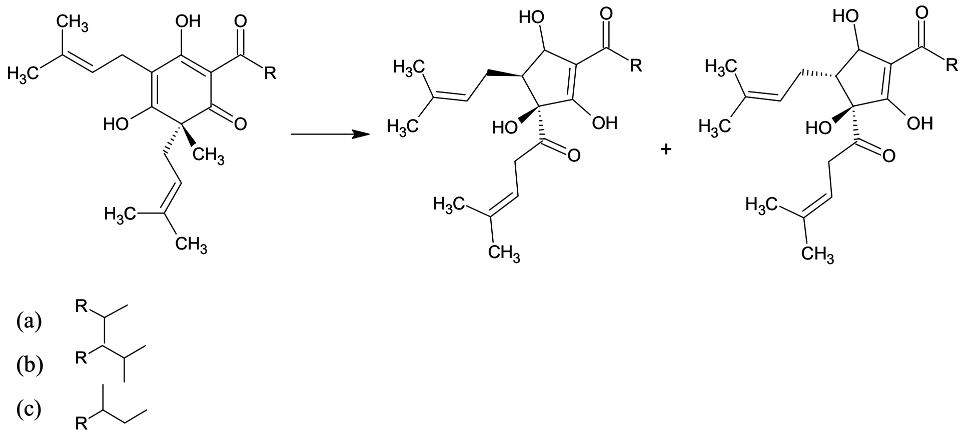

Figure 3. Conversion of the humulones to the *cis*- and *trans*-isohumulones, (a) cohumulone, (b) humulone, (c) adhumuone (by authors).

by inhibiting cell proliferation and angiogenesis [34, 35], by inducing apoptosis [36], and by increas-ing the expression of cytochrome P450 detoxification enzymes [37]. Furthermore, hop bitter acids are effective against inflammatory [36] and metabolic disorders [33], which makes them potentially attractive candidates for treatment of *diabetes mellitus*, cardiovascular diseases and metabolic syndrome. The bitter acids were reported to exert antifungal activity against *Candida albicans*, *Trichophyton mentagrophytes* var. *interdigidale*, *Fusarium* and *Mucor* species [38]. The antibacterial activity of hop acids has been investigated for many years especially for purposes of preservation. Their antimicrobial applications utilize their antiprotozoal, anticlostridial and antiviral effects. Specifically the Gram-positive species, such as *Lactobacillus* spp., *Pediococcus* spp., *Streptococcus mutans*, *S. sanguis, S. salivarius*, *Staphylococcus aureus*, *Micrococcus, Clostridium difficile, C. botulinum, C. perfringens*, *Helicobacter pylori and Bacillus subtilis* have been investigated in these studies [39-42]. The bitter acids from hop plants have also an antimicrobial activity against *Lactobacillus* brevis and monovalent cations enhanced the antibacterial activity of trans-isohumulone. Growth of *Listeria monocytes* was found to be inhibited in culture media and in certain foods by four different hop extracts containing varying concentrations of α– and β-acids [14,43]. *Serkani et al., 2012* [44] showed antimy-cobacterial effects of different concentrations of hop ethanolic extract. They reported a remarkable inhibitory effect on both the rifampin sensitive and resistant isolates of *Mycobacterium tuberculosis*.

While the properties and effects of α-acids are well understood and described, much less infor-mation is available about β-acids in this regard. The β-acids, which are prenylated phloroglucinol derivatives, do not contain a tertiary alcoholic group on the aromatic nucleus and therefore they are not capable of isomerization (Figure 4). The presence of another isoprenyl side chain causes that the mole-cule as a whole exhibits a hydrophobic character. Therefore, the β-acids are much less soluble in water compared to the α-acids. Poor solubility of the β-acids in water causes that they are normally lost during the brewing process during wort boiling [45-47].

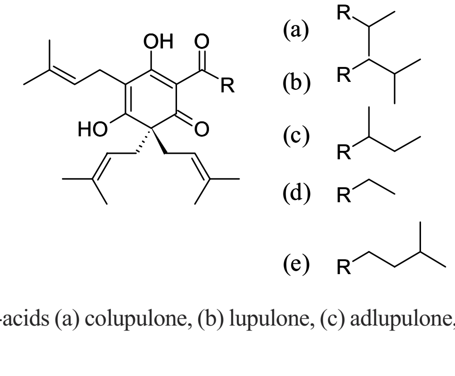

Figure 4. Skeletal formula of the β-acids (a) colupulone, (b) lupulone, (c) adlupulone, (d) postlupulone, (e) prelupulone (by authors).

Hence they generally received much less attention of scientists. But recently in studies employing high-tech methods both their structure and transformation products were described [48,49]. Antimicrobial effects of the β-acids ensue from the presence of three isopropenyl nonpolar chains that make the entire molecule highly hydrophobic and thus their antibacterial activity is greater in acidic environments, which suppress their dissociation [50]. In our recent study [51] we tested green, non-dried hops homogenate for their antimicrobial activity against the causative agent of gastric ulcer disease, bacteria *Helicobacter pylori*. The results obtained from a large collection of 33 strains of H. pylori isolated from clinical specimens from patients of the University Hospital Motol and Thomayer Hospital in Prague, as well as from the DSM collection of organisms (DSM No. 21031), show that inhibitory effects are very strong and measured values approximate the effects of antibiotics. The differences in the measured values of minimal inhibitory concentration (MIC) are very small and are in the range of one order of magnitude. Whole hops have a considerably greater effect than pure α-acids or β-acids. Thus the effect of whole hops is an example of a cumulative, synergic effect of substances contained in fresh crushed hops capable of inhibiting nearby *H. pylori* cells. Our results thus form a basis for further research on a hops homogenate as a potential source of components having anti-infective effects. Furthermore our results have proven greater inhibitory effects of the β-acids compared to those of the α-acids. This result is consistent with the literature regarding the effectiveness of α- and β- acids on fungi and protozoa [42].

Hop oils

The *hop oil* fraction is a complex mixture of volatile aromatic compounds, which are considered "essential", because they give hops their characteristic smell. The total content of essential oils is 0.5–3% [20]. Over time over 1000 different compounds in the hop oil fraction were identified [19]. Currently, three main chemical groups of oils are recognized, in which hydrocarbons and oxygenated compounds predom-inate and sulfur-containing components are represented to lesser extent [53]. Structures of the main members of the hop oils group are shown in Figure 5.

Several studies determined the correlation of hydrocarbon fraction patterns with hop variety and growing locality [54-57].

Hydrocarbons are classified as aliphatic hydrocarbons (pentane, octane, isoprene, undecane, dodecane, etc.), monoterpenes (β-myrcene, limonene, p-cymene, α-pinene, β-pinene) and sesquiterpenes (α-farnasene, β-farnesene, α-humulene, β-caryophyllene, etc.) [53, 58]. These compounds are very volatile and they easily undergo oxidation and polymerization. The main component β-myrcene generally accounts for 30-60% of the total oil content, depending

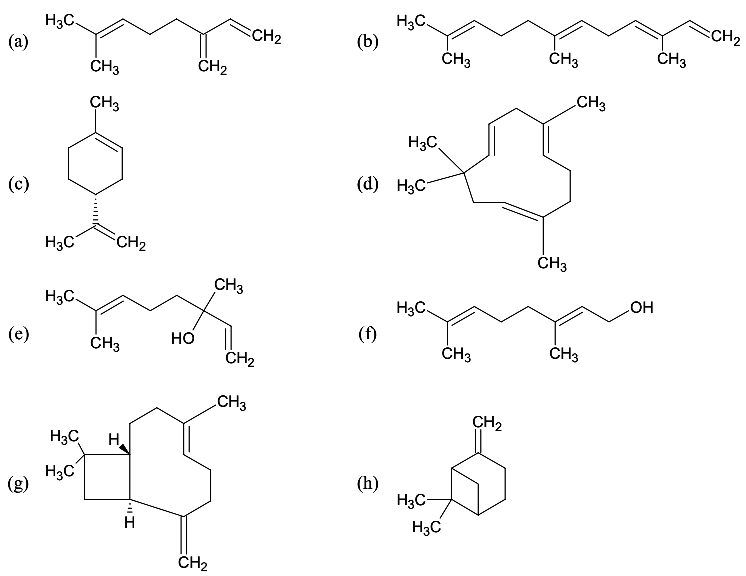

Figure 5. Skeletal formula of the hop terpenes (a) β-myrcene, (b) β-farnesene, (c) limonene, (d) humulene, (e) linalool, (f) geraniol, (g) β-caryophyllene, (h) β-pinene (by authors).

on the individual variety, and is responsible for the pungent smell to fresh hops [59]. However, it is readily oxidized and lost after harvest.

The most important sesquiterpenes are α-humulene, β-caryophyllene and β-farnesene, where the last one was first isolated from the most famous Czech variety of hops – the Saaz [60, 61]. The α-humulene, which is generally present in large quantities in older traditional aromatic hops (18-25% of the oil), undergoes transformation reactions to form epoxides and other oxidation products that contribute to the beer aroma [62, 63].

The composition of the oxygenated fraction is more complex compared to the hydrocarbon one. The substances found are classified into a group of alcohols, aldehydes, acids, ketones, epoxides and esters [58]. The major constituents of the alcohol fraction are 2-methylbutanol and linalool, with lower amounts of geraniol, nerolidol, nerol and terpineol [18]. The most abundant and also best known representative of this group is the terpene alcohol linalool, which is a hydration product of β-myrcene [64].

Essential oils from hops have been examined for their sedative effects and their potential in the treatment of sleep disorders [65]. Results on the antimi crobial activity of hop oils have been published as well [43] in which the isolated hop oils showed activity against the Gram-positive bacteria (*B. subtilis* and *S. aureus*) and fungi (*T. mentagrophytes* var. interdigitale), but exhibited almost no activity against Gram-negative bacteria (*Escherichia coli*) and yeast (*C. albicans*).

Hop polyphenols

Polyphenols is a common name for secondary metabolites of hops, which contain more than one phenolic hydroxyl group. Hop polyphenols comprise up to 4% of total weight of dried hop cones. Basic classification of polyphenols involve groups of flavonols (quercetin, kaempferol, flavonol glycosides, rutin, astragalin), flavan-3-ols (catechin, epicatechin, flavanol dimers, oligomers and polymers, so called tannins), phenolic carboxylic acids (ferulic acid), and other polyphenols (prenylflavonoids, resveratrol, etc.). More than 80% of hop polyphenols contain higher molecular compounds such as catechin tanning agents and tannins (tannic acids), which give astringency to preparations made from hops. Amongst other functions polyphenols protect plants from predators, or entice insects for pollination due to their color [66-68]. Approximately 2,0% of hop polyphenols consist of monomer substances such as phenolic carbonic acids as well as flavonoids and their glycosides [66-68].

The most important group of polyphenols consists of prenylflavonoids (prenylated chalcones), xanthohumol and related compounds. Xanthohumol, in particular, has been examined for its potential anticancer effects [1, 69].

Compared to hop acids the antimicrobial activity of polyphenolic substances of hops has been only poorly studied. On the other hand, their estrogenic activity and cancer-related bioactivity are broadly described. Polyphenolic substances belonging to prenylflavonoids (xanthohumol, iso-xanthohumol, 6-prenylnaringenin and 8-prenylnaringenin) have health-promoting and protective effects against many civilization-related diseases [69-71]. Xanthohumol has been characterized as a "broadspectrum" cancer chemopreventive agent in *in vitro* studies, while 8-prenylnaringenin has been described as the most potent phytoestrogen known to date [72,73]. These biological activities suggest that prenylflavonoids from hops have a large potential for applications in cancer prevention programs and in the prevention or treatment of (post)menopausal 'hot flashes' and osteoporosis [34]. Nevertheless, xanthohumol has also a broad spectrum of anti-infective effects against Gram-positive bacteria [38,40] (*S. aureus*, *S. mutans*) and viruses. *Buckwold et al., 2004* [43] investigated both crude extracts and also purified hop components for antiviral activity against bovine viral diarrhea virus (BVDV) as a surrogate model of hepatitis C virus (HCV), human immunodeficiency virus (HIV), influenza A virus (FLU-A), influenza B virus (FLU-B), rhinovirus (Rhino), respiratory syncytial virus (RSV), yellow fever virus (YFV), cytomegalovirus (CMV), hepatitis B virus (HBV), and herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2). All extracts failed to prevent replication of HIV, FLU-A, FLU-B, RSV and YFV. The xanthohumol-enriched hop extract displayed a weak to moderate antiviral activities against BVDV, Rhino and HSV-1. Pure iso-α-acids demonstrated low to moderate antiviral activities against both BVDV and CMV. No antiviral activity was detected using β-acids or hop oil extracts. Ultrapure preparations (>99% pure) were used to show that xanthohumol accounted for the antiviral activity observed in the xanthohumol-enriched hop extract against BVDV, HSV-1 and HSV 2. Xanthohumol was also found to be a more potent antiviral agent against these viruses than the isomer iso-xanthohumol. With rhinovirus, the opposite trend was observed with iso-xanthohumol showing an antiviral activity superior to that observed with xanthohumol. Xanthohumol also showed an activity against CMV, suggesting that it might have a gen-eralized antiviral activity against herpetic viruses. In this case, a superior antiviral activity against CMV was obser-ved with the xanthohumol isomer. In sum-mary, iso-α-acids and xanthohumol were shown to have low-to-moderate antiviral activities against several viruses.

CONCLUSION

Taken together, compounds isolated from *Humulus lupulus* L. exert a broad variety of bioactivity, such as: anti-inflammatory effects, antimi crobial effects, antioxidant effects, antiproliferative effects, cytochrome P450 effects, glucose metabolism effects, hormonal effects, lipid effects and sedative/hypnotic effects.

Because of all these interesting properties of hops, research in this area is highly desirable, because of the possibility to use the hop-derived compounds as naturally occurring phyto-drugs. Furthermore, better knowledge can be utilized in hop breeding programs allowing for target enrichment of new cultivars in the desired compounds.

ACKNOWLEDGEMENT

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