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Hops as a source of biologically active compounds

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Abstract. In recent years, hop, commonly known as the plant used for the production of beer, has attracted increasing interest in the pharmaceutical and cosmetic industries. Secondary metabolites found in hop, such as bitter acids, polyphenols or essential oils, exhibit anti-cancer, anti-inflammatory and antibacterial properties. Moreover, numerous studies confirm estrogenic activity, the ability to lower blood glucose levels and sedative effects of the plant. The paper discusses secondary metabolites in hops divided into groups depending on their chemical structure. Additionally, the biological activity of the metabolites is presented herein. The prospects of using hops for purposes other than brewing are also demonstrated.

Keywords: hop, biological activities, antioxidative effects, antimicrobial effects, anticarcinogenic effects

INTRODUCTION

Hop (*Humulus lupulus* L.) is a climber belonging to the genus Humulus and the Cannabaceae family. Hop is a dioecious perennial. It can be found in the temperate climate zone. Hop reaches height of 7–8 m. Under good conditions, the growth rate of the above-ground parts can reach 30 cm per day. One of the factors affecting flowering is the length of the day. In southernmost areas, the days are too short for the hops to bloom. In turn, in the far north, the climate is unfavourable. Hence, hops only grow in the latitude range of 38° and 51° N and S. In Europe, hops are grown mainly in Germany, the Czech Republic, Poland and Slovenia. In North America, crops are primarily cultivated in the states of Oregon and Washington, while in Asia, in China and Japan. In the southern hemisphere, hops are mainly grown in Australia and New Zealand. As a raw material with a characteristic taste and aroma, this species is predominantly cultivated for the needs of the brewing industry. Due to the content of biologically active compounds, hops are also used in the cosmetics, pharmaceutical and food industries. The most valuable metabolites are found in the lupulin glands, which are mainly formed in female infructescence called cones. Hop harvesting in Poland begins at the end of August and usually lasts until mid-September. The picked cones are immediately dried to a moisture content of approximately 7%–8%. Subsequently, after several days from drying and natural or artificial moistening (up to 10%–11% to reduce crumbling of the hop cones), they are packed in hemp linen or bale wraps, which increases their durability and enables storage for several months.

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USE OF HOP FOR MEDICINAL PURPOSES

Unlike other medicinal plants, such as the valerian root (*Valeriana officinalis* L.), hops do not have a long history of use in traditional European medicine. The taste and aroma of hop were discovered in the Middle Ages; however, at the time, the reports on its medicinal properties were not encouraging. Hildegard of Bingen, the German abbess, herbalist and author of a treatise on the healing power of plants, wrote that hop was of little use to humans, noting however, that following its consumption, men experienced increased melancholy and that its bitterness caused an increase in the shelf life of food products (Bingen, 2005). Thanks to these observations, in Germany, since the 11th century, hops have been exclusively used to improve the taste and extend the shelf life of beer (Ody, 1996). The widespread use of hops in the production of beer has caused a wider interest in this species also in terms of its medicinal purposes. In the 16th century, Paracelsus used hops as a digestive aid, Matthiolus mentioned its diuretic effect and increased bile production, while Bock and Lonicerus praised the use of young hop shoots to cleanse the blood, liver and spleen (Braungart, 1901; Madaus, 1938). According to legend, in

1406, King Wenceslaus IV allowed the inclusion of hop cones in the brewers' coat of arms in recognition of the rejuvenating effect of a cold bath in the brewing sediment formed after the beer brewing process (Fenselau, Talalay, 1973).

In the 19th century, Hecker used hop-flower bitter tonic for medicinal purposes and noted its sedative properties, while Clarus applied female flowers to treat insomnia and gastritis-induced anorexia (Madaus, 1938). One of the most outstanding hop-treated patients was George III, the former King of Great Britain, who, to calm down, rested on pillows filled with hop cones (Braungart, 1901). In the 20th century, in his book on phytotherapy, physician Kahnt recommended the use of hop pillows, teas or extracts for sleep problems related to nervous disorders (Kahnt, 1906). In the interwar period, the use of hop infusions was recommended for hair care, which aimed at protecting against hair loss (Braungart, 1901; Madaus, 1938).

Hops were also extensively utilized in traditional medicine of the Native Americans. The Cherokee used hop as a sedative, analgesic, anti-rheumatic and gynaecological aid to treat problems with the breasts and uterus, while the Delawers applied the plant to treat earache and toothache and employed it as a sleep aid (Hamel, 1975). The Navajo used hop for colds and coughs, and the Dakotas utilised it as an aid enhancing the healing process. It was also effective against gastrointestinal disorders (Moerman, 1971).

In recent decades, the world of science has focused on studying the biological effects of plants used in folk medicine. The acquired knowledge constitutes the basis for the development of new dietary supplements, and even for the design of new drugs, especially in relation to the most common, dangerous diseases of our time, such as cardiovascular disorders, diabetes, Alzheimer's disease and cancer (Higdon, Drake, 2012; Labadie et al., 1989; Sawadogo et al., 2012; Zanoli, Zavatti, 2008). The development of civilisation is associated with the more frequent occurrence of certain diseases, which can be mainly attributed to improper eating habits and a stressful, fast lifestyle (Prins et al., 2015; Eyer, 1980). Organically grown food becomes the privilege of the rich. In contrast, the diets of the poor and middle class increasingly consist of food products filled with synthetic sugars, sensory enhancers, growth hormones and preservatives. The listed substances are undoubtedly associated with the occurrence of diseases such as cardiovascular or neurological disorders as well as cancer (Reganold, Watcher, 2016). Hops have been used for centuries, predominantly as ingredients in beer; however, their medicinal properties, mainly calming ones, are also recognised. Moreover, some dietary supplements with the addition of hops are used in the treatment of sleep disorders (Biendl, Pinzl, 2013). Notably, in vitro and in vivo studies show that some compounds in hop exhibit a broader spectrum of biological activity. They are characterised by strong antioxidant, estrogenic, anti-inflammatory and anti-cancer properties (induction of apoptosis as well as anti-metastatic, anti-proliferative, anti-invasive or anti-angiogenic properties), thanks to which they might potentially become new pharmacological agents in the future (Biendl, Pinzl, 2013; Štulíková et al., 2018).

KEY CHEMICAL COMPOUNDS IN HOPS AND THEIR BIOLOGICAL ACTIVITY

The medicinal properties of hops are attributed to the presence of biologically active compounds belonging to the group of secondary metabolites. Their primary role is to protect the plant from predators, parasites, extreme weather conditions and other threats (Brglez et al., 2016). A large part of our diet consists of plants and their products. Plant-derived substances can be easily added to the diet because they have few or no harmful side effects. In addition, synergistic effects can significantly enhance their action or the action of utilised drugs and therapies (Brglez et al., 2016; Mutlu Altundag et al., 2018). Furthermore, plants and their products, including extracts, can be used to prevent, inhibit the progress of and even treat a variety of widespread diseases. Secondary plant metabolites are characterised by specific reactions depending on the environment (Brglez et al., 2016). The same compound may therefore display antioxidant and proliferative effects in a healthy living cell and pro-oxidative effects in a tumour cell, inducing apoptosis (Brglez et al., 2016) (Table 1).

Secondary metabolites of hops are mainly obtained from cones produced by female plants. Hop cones contain several groups of compounds: resins and their derivatives, polyphenols, essential oils, proteins, lipids, waxes, cellulose and amino acids (Stevens, 1967; Verzele, 1986) (Fig. 1). All compounds contained in cones, which are soluble in a mixture of ether and methanol, are called resins. Depending on their solubility in hexane, resins are divided into soft and hard. Soft resins, also called bitter acids, dissolve in hexane. Fractions consisting of bitter substances (i.e., soft resins) account for approximately 24% of the dry weight of hop cones; therefore, they are largely responsible for the taste of hop cones, and thus beer (Biendl, Pinzl, 2013). Soft resins are divided into alpha-acids and beta-acids, and hard resins into: α-, β-, δ- and ε-hard resins. In addition to resins, hop cones contain a very diverse group of polyphenols, including prenylated flavonoids and multifidol glucosides, which are almost exclusively present in hops, at least in significant amounts. Prenylated flavonoids show biological activities, which are beneficial to health (Table 2); thus, they can be used as new drugs to treat and prevent many diseases, including cancer (Collins et al., 2014; Pichler et al., 2017; Štulíková et al., 2018). Owing to the biological features of some other polyphenols present in hops and many other plant species, the preparations containing them are often already in the last stages of clinical trials as anti-cancer drugs (Brglez et al., 2016; Niedzwiecki et al., 2016;

Zhou et al., 2016). The properties of hop essential oils are also worth mentioning as potential natural medicinal substances. Unlike polyphenols, the major components of hop essential oils are well-known substances found in most plant essential oils. These compounds play key roles in plant protection mechanisms. Table 2 shows the structures of the discussed biologically active substances.

Bitter acids

Cones are the main source of biologically active compounds in hops because the content of the above metabolites in them is the highest. The presence of bitter acids (soft resins) was also confirmed in male inflorescence; however, their concentrations are considerably lower and similar to those found in the early flowering stages of female plants (De Keukeleire et al., 2003). The presence of bitter acids was also found in hop leaves; however, their content was lower than in cones and was closely related to the variety (De Keukeleire et al., 2003). Hops leaves also contain volatile compounds, but in considerably lower quantities than hop cones (Zanoli, Zavatti, 2008). The soft resins found in lupulin glands are chemically diprenylated (alpha-acids) or triprenylated (beta-acids) phloroglucinol derivatives and their homologues (Chadwick et al., 2006; Okada, Ito, 2001; Steenackers et al., 2015; Zanoli, Zavatti, 2008). They are called bitter acids due to their bitter taste. Soft resins include alpha-acids (humulones), their homologues, the beta fraction consisting of beta-acids (lupulones) and their homologues, as well as uncharacterised soft resins (Hough et al., 1982; Lamy et al., 2007; Palamand, Aldenhoff, 1973; Roberts, Wilson, 2006). The content of hop resins in cones ranges from 15%–30%, of which the majority are soft resins (10%–25%). Hard resins constitute 3%–5%. The alpha-acids include humulone (35%–70%), cohumulone (20%–65%) and adhumulone (10%–15%), while beta acids are a mixture of lupulone (30%–55%), colupulone and adlupulone. Other bitter acids found in small amounts in hop cones include posthumulone/postlupulone, prehumulone/prelupulone and adprehumulone (Zanoli, Zavatti, 2008). The content of alpha and beta acids as well as their homologues can significantly vary depending on the hop variety, climate and growing conditions (Biendl, Pinzl, 2013; Matsui et al., 2016). During beer brewing at high temperatures (100–130 °C) and pH 8–10, alpha-acids isomerise to iso-alpha-acids, giving the beer its characteristic bitter taste (Schurr et al., 2015; Spreng, Hofmann, 2018).

The bitter taste, which promotes digestion, is not the only feature that can be attributed to bitter acids. The calming properties of hops have been recognised for a long time; however, research confirmed that the main component of hops (i.e., alpha-acids) was responsible for these effects, although other fractions, such as beta-acids and essential oils, are also important (Schiller et al., 2006). Consequently, commercially available preparations for insomnia or sleep disorders either consist of hop cones alone or a combination of hops with other sedative herbs, such as valerian (Biendl, Pinzl, 2013).

After World War II, lupulone was used in the treatment of tuberculosis because it showed strong in vitro activity against *Mycobacterium tuberculosis* (Salle et al., 1949). Studies on the bacteriostatic features of hop and its components revealed that bitter acids were particularly effective against Gram-positive bacteria. They work most effectively at low pH in a non-dissociated form. Compared to phenol, the activity of alpha-acids (humulone) and beta-acids (lupulone) is approximately 200 times and 700 times stronger, respectively. The same metabolites show no significant activity against Gram-negative bacteria, and yeast and molds are only minimally inhibited (Lewis et al., 1949; Salle et al., 1949; Schmalreck, Teuber, 1975; Teuber, 1970; Teuber, Schmalreck, 1973). Despite promising results in the treatment of tuberculosis, therapy has been associated with gastrointestinal disorders (Enders, 1951). Adverse effects were caused by the administration of lupulone in high doses; therefore, research on utilising hop components for the treatment of tuberculosis was abandoned with the advent of strong antibiotics in the second half of the last century (Erdmann, 1951, 1952). It is currently estimated that approximately 50% of the world's population carries Helicobacter pylori. In about one-third of infected people, diseases such as gastritis or gastric ulcers can lead to stomach cancer. Studies have shown that beta-acids are effective against these bacteria (Ohsugi et al., 1996).

Since beer is primarily composed of water, it would not be stable without additives. Hops, especially the bitter acids, not only contribute to its flavour, but also stabilise the foam and, more importantly, exhibit strong antibacterial effects. The strong activity, especially of beta-acids, is predominantly attributed to their hydrophobic nature, which facilitates the interactions with microbial cell membranes (Bortoluzzi et al., 2016; Chadwick et al., 2006). On the other hand, the ionophore features of iso-acids are assumed to play key roles in the main mechanism of their antimicrobial activity (Schurr et al., 2015; Teuber, Schmalreck, 1973). There is even research on the use of humulinic acids, which are hydrolysis products of alpha-acids and iso-alpha acids, as tasteless food preservatives (Schurr et al., 2015). Furthermore, the spirit industry has tested bitter acids of hops as natural alternatives to combat bacterial infections during alcoholic fermentation (Rueckle, Senn, 2006).

In addition to their antibacterial and sedative effects, hop resins also exhibit antioxidant, anti-inflammatory and anti-cancer activities (Bortoluzzi et al., 2016; Sandoval-Ramírezi et al., 2017; Villalobos-Delgado et al., 2015). The key mechanism of the chemopreventive effects of hop bitter acids on the induction of apoptosis has been proposed (Chen, Lin, 2004). Subsequent studies confirmed that bit-

Tabela 1. Properties of biologically active substances.

Group	Compounds	Properties / application	References
1	*2*	*3*	*4*
Alpha acids (humulones)	Humulone	Sedative effect	Schiller et al., 2006
	Cohumulone	Induction of apoptosis	Chen, Lin, 2004, Van Cleemput et al., 2009
		Inhibition of chemically induced tumor promotion	Saugspier et al., 2012
Beta acids (lupulones)	Lupulone	Calming Sedative effect	Schiller et al., 2006
		Treatment of tuberculosis (Mycobacterium tuberculosis)	Salle et al., 1949
		Treatment of gastritis and ulcers by combating (Helicobacter pylori)	Ohsugi et al., 1996
		Induction of apoptosis	Chen, Lin, 2004, Van Cleemput et al., 2009
		Inhibition of *in vivo* chemically induced tumor promotion and angiogenesis	Saugspier et al., 2012
Prenylflavonoids	Xanthohumol	Antitumor effect	Plazar., 2007
		Bacteriostatic action	Biendl, Pinzl 2013
		Sedative effect	Karabín et al., 2016
		Anti-inflammatory effect	Harikumar et al.., 2009
		Induction of tumor cell apoptosis	Pan et al., 2005; Yang et al., 2007
		Inhibition of cancer angiogenesis and metastasis	Mojzis Et al., 2008
		Limiting endometriosis	Rudzitis-Auth et al., 2012
		Counteracting osteoarthritis	Stracke et al., 2011
		Removal of peroxygen radicals	Yamaguchi et al., 2009
		obesity prevention	Mendes et al. 2008
	Isoxanthohumol	Prevention of osteoporosis	Kondo, 2004
		Prevention of obesity	Yang et al., 2007
		Antimutagenic activity	Ameh et al., 2015
		Anti-angiogenic activity	Ameh et al. 2015
	Xanthohumol C	Antiproliferative effect	Popłoński et al., 2018
		Cytotoxic action	Forino et al., 2016
		Neuroprotective action	Oberbauer et al., 2019
		Antioxidant effect	Forino et al., 2016
	8-prenylnaringenin	Oestrogenic effect	Milligan et al., 2000
		Treatment of menopause	Štulíková et al., 2018
		Antitumor effect	Brunelli et al., 2007
		Anti-angiogenic effect	Brunelli et al., 2007
		Inhibition of the survival and proliferation of estrogen sensitive cells	Brunelli et al., 2007
	6-prenylnaringenin	Oestrogenic effect	Milligan et al., 2000
Flavonols	Quercitin	Reduction of cell viability	Tabrez et al., 2013
		Induction of apoptosis	Sharmila et al., 2014
		chemotherapy in the treatment of chronic lymphocytic leukemia	Spagnuolo et al., 2012
		Epigenetic regulation	Lewandowska et al., 2015
		Anti-inflammatory	Lewandowska et al., 2015
		Reduction of Type I allergic reaction	Segawa et al., 2006

	Kaempferol	Reduction of cell viability and proliferation rate	Lewandowska et al., 2015
		Reduction of Type I allergic reaction	Segawa et al., 2006
Stilbens	Resveratrol	Reducing the viability of breast cancer cells and inducing their apoptosis	Izquierdo-Torres et al., 2017
		PI3K-Akt signaling inactivation	Zeng et al., 2017
		Anti-aging effect	Corrêa et al., 2018
Phenolic acids	Ferrulic acids	Prevention of lipid peroxidation	Ghosh i in, 2017
		Prevention of apoptotic death of healthy cells	Karabín et al., 2016
		Free radical scavenger	Ghosh i in, 2017
		Reduction of the toxicity of carcinogens, ionizing radiation and UV radiation	Bohr et al., 2005
		Treatment of breast cancer	Zhang et al., 2016
		Treatment of diabetes mellitus	Ghosh i in, 2017
		Treatment of Alzheimer's disease	Ghosh i in, 2017
	Curcumin	Food preservative	Yang et al., 2001
		Yellow dye	Yang et al., 2001
Flavanols	(+)-catechin	Antioxidant effect	Biendl, Pinzl, 2013
		Dilation of blood vessels	Biendl, Pinzl, 2013
		Reducing the amount of metastasis by limiting the mobility of cancer cells	Kampa et al., 2007
	(-)-epicatechin	Antioxidant effect	Fresco et al., 2006
		Anti-inflammatory effect	Fresco et al., 2006
		Inhibition of telomerases	Fresco et al., 2006
		Inhibition of cell division of breast and prostate cancer	Kampa et al., 2007
		Anti-aging effect	Corrêa et al., 2018
	(+)-gallocatechin	Antioxidant effect	Fresco et al., 2006
		Anti-inflammatory effect	Fresco et al., 2006
		Inhibition of telomerases	Fresco et al., 2006
		Inhibition of cell division of breast and prostate cancer	Kampa et al., 2007
Multifidol, multifidol glucosides	co-multifidol glucoside	Anti-inflammatory effect	Bohr et al., 2005
	ad-multifidol glucoside		
	n-multifidol glucoside		
	co-iso-multifidol glucoside		
	5 -deprenyllupulonol C	Anti-inflammatory effect	Bohr et al., 2005
		Inhibition of early antigen of Epstein-Barr virus production	Akazawa et al., 2012
	2,4-bis-(4-fluorophenyl acetyl)-phloroglucinol	Induction of cell death and antiproliferation in three types of glioma cells	Lu et al., 2012

Table 1 continued

1	2	3	4
Monoterpenes, sesquiterpenes, aliphatic hydrocarbons	Myrcene	Probable carcinogen Inhibition of the genotoxicity of 2-amino-1-methyl-6-phenyimidazo- [4-5-b] -pyridine and 2-amino-3-methylimidazo- [4,5-f] -quinoline Strong inhibition of tumor necrosis factor (TNF-α) Inhibiting the growth of breast cancer cells Strong repellent of *Rhyzopertha dominica*	Okaru, Lachenmeier, 2017 Mitíć-Culafic et al., 2016 Lee et al., 2015 Lee et al., 2015 Bedini et al., 2015
	Limonene	Strong inhibition of tumor necrosis factor (TNF-α) Strong repellent of *Sitophilus granarius*	Lee et al., 2015 Bedini et al., 2015
	alpha-, beta-pinene	Strong inhibition of tumor necrosis factor (TNF-α) Treatment of non-small cell lung cancer	Lee et al., 2015 Zhang et al., 2015
	Humulene	Corticosteroid action	Ameh et al., 2015
	beta-caryophyllene	Anti-cancer activity	Fidyt et al., 2016
Terpene and sesquiterpene alcohols	Linalool	Inhibition of genotoxicity of 2-amino-1-methyl-6-phenyimidazo- [4-5-b] -pyridine	Mitíć-Culafic et al., 2016
	Caryophyllene oxide	Anti-cancer activity	Fidyt et al., 2016
	2-methyl-3-buten-2-ol	Sedative effect	Hänsel et al., 1980, Biendl, Pinzl, 2013
	farnezol		
Tiols, Sulfides, Polysulfides, Thioesters, Thiophenes	3-mercaptohexan-1-ol (3MH)	Inhibition of oxidation of a strong antioxidant - epigallocatechin gallate Detoxification of the body and prevention of oxidative stress Providing the flavor and aroma of the beer	Unnadkat, Ellias, 2012 Roland et al., 2016, Cibaka et al., 2016 Roland et al., 2016
	3-mercapto hexyl acetate	Providing the flavor and aroma of the beer	Roland et al., 2016, Cibaka et al., 2016
	4-methyl-4-mercaptopentan-2-one (4MMP)		
	3-sulfanyl-4-methyl pentane-1-ol		
	3-sulfanylhexan-1-ol		

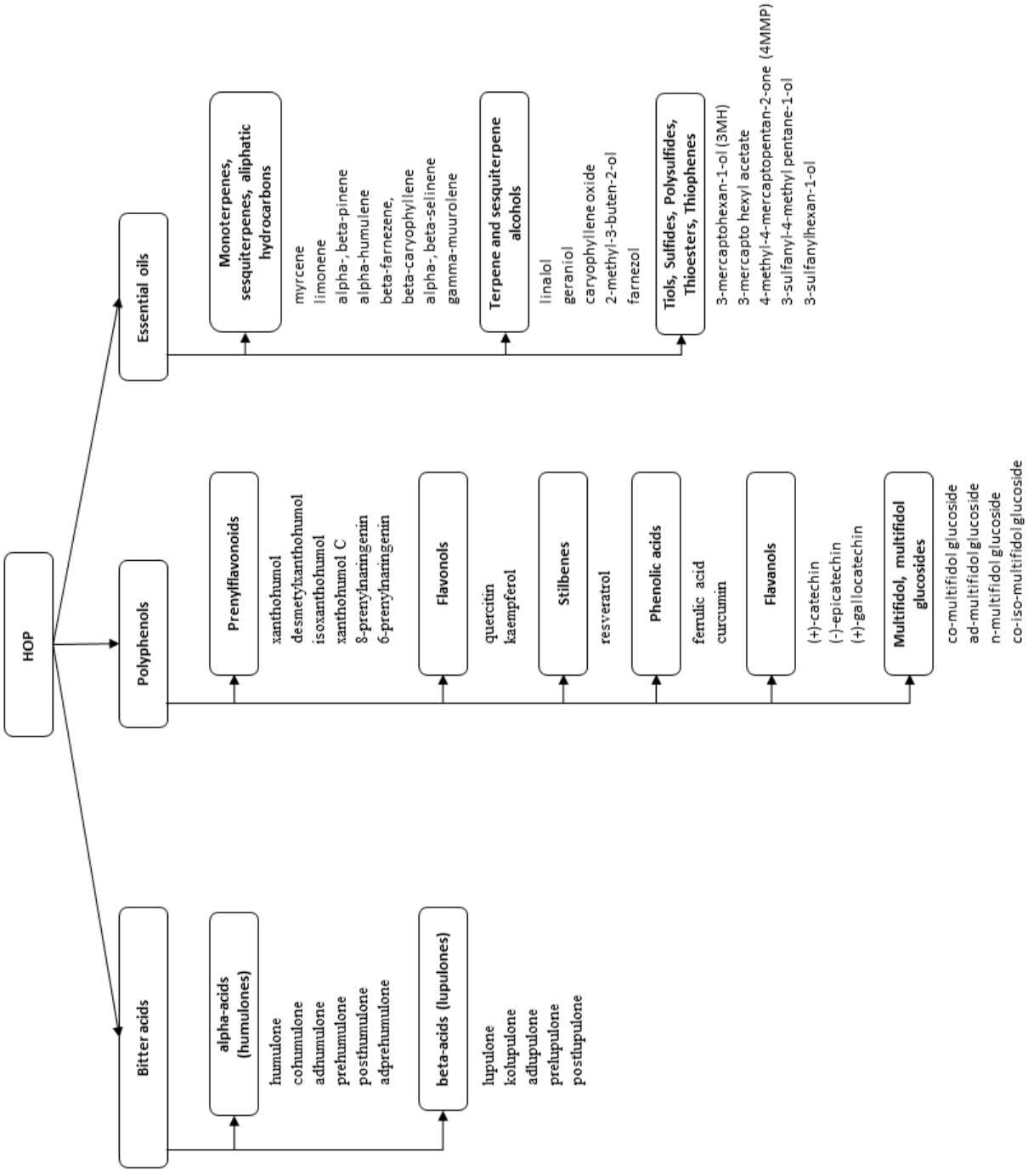
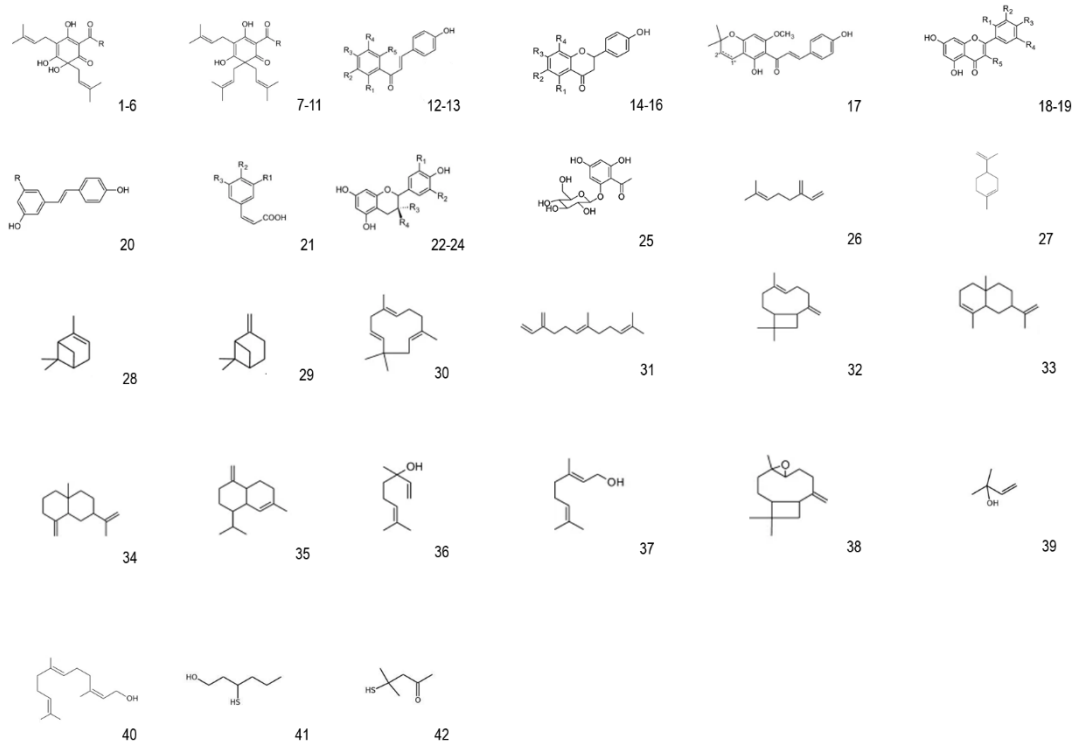


Figure 1. Chemical composition of hop biologically active compounds.

Table 2. Selected biologically active substances in hops.



No.	Compound	R1 (R)	R2	R3	R4	R5
1	*2*	*3*	*4*	*5*	*6*	*7*
	Bitter acids					
1	Humulone	$CH_2CH(CH_3)_2$				
2	Cohumulone	$CH(CH_3)_2$				
3	Adhumulone	$CH(CH)_3CH_2CH_3$				
4	Prehumulone	$CH_2CH_2CH(CH_3)_2$				
5	Posthumulone	CH_2CH_3				
6	Adprehumulone	$(CH_2)_4CH_3$				
7	Lupulone	$CH_2CH(CH_3)_2$				
8	Colupulone	$CH(CH_3)_2$				
9	Adlupulone	$CH(CH)_3CH_2CH_3$				
10	Prelupulone	$CH_2CH_2CH(CH_3)_2$				
11	Postlupulone	CH_2CH_3				
	Prenylflavonoids					
12	Xanthohumol	OCH_3	H	OH	prenyl group	OH
13	Desmethyl xanthohumol	OH	H	OH	prenyl group	OH
14	Isoxanthohumol	OCH_3	H	OH	prenyl group	
15	8-prenylnaringenin	OH	H	OH	prenyl group	
16	6-prenylnaringenin	OH	prenyl group	OH	H	
17	Xanthohumol C	C(1”) = C(2”)				
	Flavonols					
18	Quercitin	H	OH	OH	H	OH
19	Kaempferol	H	H	OH	H	OH
	Stilbenes					
20	Resveratrol	OH				

Table 2 continued

1	2	3	4	5	6	7
	Phenolic acids					
21	Ferrulic acids	OCH_3	OH	H		
	Flavanols					
22	(+)-catechin	OH	H	H	OH	
23	(-)-epicatechin	OH	H	OH	H	
24	(+)-gallocatechin	OH	OH	H	OH	
	Multifidol glucosides					
25	Multifidol glucoside					
	Essential oils					
26	Myrcene					
27	Limonene					
28	alpha-pinene					
29	beta-pinene					
30	alpha-humulene					
31	beta-farnezene					
32	beta-caryophyllene					
33	alpha-selinene					
34	beta-selinene					
35	gamma-muurolene					
36	Linalool					
37	Geraniol					
38	Caryophyllene oxide					
39	2-methyl-3-buten-2-ol					
40	Farnesol					
41	3-mercaptohexan-1-ol (3MH)					
42	4-methyl-4-mercaptopentan--2-one (4MMP)					

Bocquet et al., 2018; R1 (R), R2, R3, R4, R5 – substituents

ter acids induce apoptosis; however, the full mechanism of this action remains unknown. Nonetheless, it has been established that apoptosis is induced by two pathways, i.e., internal mitochondrial and external ones (Chen, Lin, 2004; Lamy et al., 2008; Van Cleemput et al., 2009). Bitter acids affect the internal pathway by changing the Bcl-2 family of proteins. Moreover, they influence the external pathway by increasing the expression of the p38 protein, which activates the p53 protein and the TRAIL death receptor (Fas and FasL) (Chen, Lin, 2004; Lamy et al., 2011). In addition to the apoptosis-inducing properties, bitter acids have the ability to inhibit chemically induced tumour promotion in vivo as well as angiogenesis (Saugspier et al., 2012). Beta-acids are more active than alpha-acids in inhibiting tumour growth, reducing proliferation and even inhibiting the growth of cancer cells (Biendl, Pinzl, 2013; Karabín et al., 2016; Okada, Ito, 2001; Saugspier et al., 2012; Van Cleemput et al., 2009).

Hops may also find application in the treatment of diabetes (Miura et al., 2005; Shimura et al., 2005; Yajima et al., 2005). Isohumulones contained in hops reduce insulin resistance. Tests on humans with mild type 2 diabetes showed that compared to baseline, isohumulones significantly reduced blood glucose and glycohemoglobin (HbA1c) levels, systolic blood pressure, alanine aminotransferase (GPT), aspartate aminotransferase (GOT) and gamma-GPT after 8 weeks of use (Yajima et al., 2004; Obara et al., 2009).

The latest research on hops includes work on rho iso-alpha-acids (RIAA), which were obtained by modifying hop extracts through isomerisation and hydrogenation. Screening of natural products revealed that RIAAs are among the most active compounds in terms of the anti-inflammatory potential (Desai et al., 2009; Tripp et al., 2005). RIAAs improved the condition of injured joints, which was evidenced by a reduction in the arthritis index and histological score in a mouse model of collagen-induced arthritis (Konda et al., 2009). Furthermore, clinical trials on a proprietary blend of RIAAs, rosemary and oleanolic acid showed significant relief in those diagnosed with osteoarthritis, rheumatoid arthritis or fibromyalgia (Minich et al., 2007).

Research conducted in Japan demonstrated that iso-alpha-acids are among the natural substances, which can alleviate the course of diseases associated with metabolic disorders often classified as the metabolic syndrome. These disorders include impaired kidney, liver and muscle func-

tion, which cause high blood pressure, increased levels of uric acid as well as elevated fats and sugar in the blood. This clinical condition leads to poorer blood circulation and obstruction of the arteries, which can eventually result in coronary heart disease (Biendl, 2009).

Polyphenols

In addition to the aforementioned bitter acids, hop lupulin glands also secrete a mixture of polyphenols, oxidised and cyclic chalcones, and essential oils (Chadwick et al., 2006). One of the key roles of polyphenols in plant organisms is the protection against all kinds of adverse external conditions. Many polyphenols in hops have also been found in other plant species; however, prenylated flavonoids are generally only found in hops. Although polyphenols can be found in all parts of the plant, the concentration of phenolic substances in hop cones is 10 times higher than in the rest of the plant (Abram et al., 2015).

Prenylated flavonoids

Prenylated flavonoids constitute a group of flavonoids with at least one prenyl or geranyl substituent. These substituents change the biological activity of flavonoids, increasing their lipophilicity and enhancing the affinity to biological membranes (Plazar, 2007).

Xanthohumol, constituting more than 1% of the mass of dried hop cones, is the main prenylated flavonoid of hops (Biendl, Pinzl, 2013). Other prenylated flavonoids include desmethylxanthohumol, a xanthohumol isomer – isoxanthohumol, xanthohumol C (dehydrocycloxanthohumol) and the most powerful phytoestrogens, i.e. 8-prenylnaringenin and 6-prenylnaringenin. In vitro and in vivo studies performed on rodents demonstrated that prenylation increased the gastrointestinal uptake of the parent flavonoids and their accumulation in tissues (Cattoor et al., 2010; Konishi et al., 2005; Legette et al., 2012; Mukai and al., 2012, 2013). It has also been shown that the removal of prenylated flavonoids from the blood is slower than the removal of their unprenylated counterparts (Terao, Mukai, 2014).

Numerous studies revealed the enormous potential of xanthohumol as an anti-cancer agent. Its action is not only limited to the prevention of the development of cancer, but also involves limiting all stages of cancer development. In addition, xanthohumol exhibits significant antimicrobial properties. Among five compounds isolated from hops, it was proved to be the most effective against pathogenic fungi, malaria, the hepatitis C virus and HIV-1 virus (Biendl, Pinzl, 2013). Xanthohumol can be used to fight obesity and has calming effects (Karabín et al., 2016; Yang et al., 2007).

Initially, the anti-cancer properties of xanthohumol were attributed to its ability to inhibit the metabolic activation of certain pro-carcinogens, i.e. benzo-α-pyrene (BaP) and 2-amino-3-methyl-3H-imidazo-[4,5-*f*] quinoline (IQ) by cytochrome P450 (Gerhäuser et al., 2002). However, it was later shown that in the rat liver (in vivo), xanthohumol did not inhibit metabolic activation, but protected against the genotoxicity of IQ and BaP, and partially against reactive oxygen species (ROS) as well as the corresponding oxidative DNA damage (Plazar, 2007).

In addition to anti-cancer, sedative and antimicrobial activities, xanthohumol also displays anti-inflammatory properties. This is due to its ability to influence the activity of a complex of enzymes involved in the cellular response to inflammation (IKK). Xanthohumol acts by inhibiting the activation of IKK, which is induced by the tumour necrosis factor (TNF), or by suppressing the translocation of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) by direct interaction with the IKK cysteine residues (Harikumar et al., 2009). In vitro studies also revealed that xanthohumol could induce apoptosis of cancer cells by lowering the expression of the Bcl-2 gene or by activating the caspase cascade, which led to the inhibition of the development of certain types of cancer, including ovarian, breast, colon, prostate, liver and lung cancer as well as leukaemia (Karabín et al., 2016; Pan et al., 2005). The second proposed mechanism of apoptosis induced by xanthohumol is the induction of reactive oxygen species (Yang et al., 2007). It was found that xanthohumol inhibited mitochondrial oxidative phosphorylation, consequently producing reactive oxygen species and inducing cancer cell apoptosis (Zhang et al., 2015). Moreover, xanthohumol is involved in inhibiting cancer angiogenesis and metastasis. Specifically, it has been shown that it inhibits vascular endothelial capillary formation (HMEC-1) (Karabín et al., 2016; Mojzis et al., 2008). Xanthohumol has been demonstrated to be effective not only against cancer, but also against osteoarthritis, diabetes and endometriosis (Nozawa et al., 2005; Rudzitis-Auth et al., 2012; Stracke et al., 2011). It is very effective in removing peroxy radicals, which belong to the most common reactive oxygen species in the body. Utilising both hydrophilic and lipophilic tests of the oxygen radical absorption capacity, it was shown that xanthohumol was more active in this respect than vitamins C and E (Yamaguchi et al., 2009). The use of xanthohumol against certain malaria viruses and protozoa (Plasmodium falciparum) has also been reported in the literature (Buckwold et al., 2004; Frolich et al., 2005; Gerhäuser, 2005). By acting on fat cells (adipocytes), it can also prevent obesity. In vitro studies on murine 3T3-L1 cell lines revealed that the compound inhibited differentiation of preadipocytes and induced apoptosis of mature adipocytes (Mendes et al., 2008).

Already at very beginning of the 20th century, menstrual disorders were observed in women picking hops. This was associated with the potential estrogenic activity of hops (Biendl, Pinzl, 2007). In 1953, it was confirmed that hops indeed exhibited this kind of activity (Brucker,

1960). Many years later, it was discovered that the compound with estrogenic activity was 8-prenylnaringenin, which displayed 10% of the binding activity of 17-beta-estradiol, while structurally similar flavonoids showed over 100-fold lower potency (Milligan et al., 1999, 2000). The precursor of this compound is xanthohumol, which is converted into isoxanthohumol by spontaneous cyclisation during the process of wort brewing. In the further stage, 8-prenylnaringenin is formed from isoxanthohumol with the participation of the intestinal microflora or cytochrome P450 enzymes. Even at high doses (750 mg), 8-prenylnaringenin has been shown to be well tolerated, rapidly absorbed and stable in the body (Rad et al., 2006). Clinical trials confirm that it is a promising new therapeutic for the treatment of menopause (Štulíková et al., 2018). Only the long-term safety of this phytoestrogen and its side effects remain to be clarified, although studies performed on rats show that a standardised hop extract containing 0.42% of 8-prenylnaringenin did not stimulate the growth of methylnitrosourea-induced breast cancer cells (Štulíková et al., 2018; Keiler et al., 2017). According to some reports, in contrast to hormone replacement therapy, the use of hop polyphenols is a safer and more effective treatment for postmenopausal women (Erkkola et al., 2010; Sandoval-Ramírez et al., 2017).

During the clinical trials preceding the launch of the commercially available MenoHop® preparation, which is a hops extract enriched with 8-prenylnaringenin, a significant reduction in menopausal discomfort was demonstrated after 6 weeks of therapy in menopausal women assessed by the Kupperman index and a simplified patient questionnaire. In the case of other preparations such as Gynomunal® and Esvegyne®, which are vaginal gels with the addition of hops, improved comfort in terms of vaginal dryness, itching, burning, inflammation and rash was shown after 30 days of therapy (Morali et al., 2006). Similarly to isoxanthohumol, 8-prenylnaringenin exhibits various anti-cancer effects, including strong anti-angiogenic properties as well as inhibition of survival and proliferation of estrogen-sensitive cells by disrupting the PI3K pathway (Brunelli et al., 2007). Moreover, xanthohumol and 8-prenylnaringenin turned out to be potent inhibitors of NF-κB activation in microglial cell lines, thus confirming the ability to modulate immune responses in the nervous system (Karabín et al., 2016).

The concentration of isoxanthohumol in beer is on average 3 mg per litre. Isoxanthohumol is particularly effective in counteracting bone density loss caused by osteoporosis. This discovery was a result of experiments carried out on mice in a laboratory of one of Japanese breweries (Kondo, 2004). Recently, isoxanthohumol and xanthohumol have been proven to display in vitro activity against obesity (Yang et al., 2007). The addition of isomerised hop extracts to a high-fat diet of the C57BL/6N mouse cell line inhibited the animal weight gain and adipose tissue gain (Ayabe et al., 2018; Miranda et al., 2016). Although the anti-cancer activity of isoxanthohumol turned out to be lower than that of xanthohumol, it has been shown that the former displays stronger anti-mutagenic and anti-angiogenic effects, and even shows limited estrogenic activity (Ameh et al., 2015).

In 1997, xanthohumol C was detected in hop extracts (Stevens et al., 1997). However, its anti-proliferative, cytotoxic, neuroprotective and antioxidant activity has only been demonstrated in recent years (Forino et al., 2016; Oberbauer et al., 2013; Popłoński et al., 2018). Recent studies show that xanthohumol C is a stronger inhibitor of human breast cancer cell lines (MCF-7) than xanthohumol. Xanthohumol C causes changes in the endoplasmic reticulum of cancer cells, affecting the intercellular adhesion process, while xanthohumol affects the cell cycle and DNA replication (Roehrer et al., 2019)

In 2008, it was proved that hop prenylated flavonoids, including xanthohumol, isoxanthohumol, 8-prenylnaringenin and 6-prenylnaringenin, induced a caspase-independent form of cell death (Delmulle et al., 2008).

Flavonols

Flavonols are another group of flavonoids. The best-known flavonols are quercetin and kaempferol. Both compounds are commonly present in plants. In the literature, quercetin and kaempferol are considered to be some of the most powerful antioxidants (Karabín et al., 2016). Plants, including hops, contain flavonols mainly in the form of glycosides (Manach et al., 2004). Their bioavailability depends on the glycoside part. Unfortunately, the least bioavailable form of quercetin, i.e. rutin, is most commonly found in hops (Biendl, Pinzl, 2013; Manach et al., 2004). In vitro and in vivo studies have shown that quercetin reduces cell survival, decreases the level of proteins involved in cell division and induces apoptosis (Sharmila et al., 2014; Tabrez et al., 2013). Apoptosis can be partly induced by hyperacetylation of histones H3 and H4 in lung cancer and leukaemia cells, and also by modulating the expression and activity of the Mcl-1 anti-apoptotic proteins belonging to the Bcl-2 family (Lewandowska et al., 2015; Spagnuolo et al., 2012). Similarly to quercetin, kaemferol is also capable of inducing hyperacetylation of the histone H3 complex in human liver and colon cancer cell lines, thus reducing the cell viability as well as the proliferation factor (Lewandowska et al., 2015). Quercetin can also be used in chemotherapy, where the synergistic effect resulting from the combination with fludarabine is used. This combination further enhances the effects of established chemotherapy drugs in the treatment of chronic lymphocytic leukaemia (Spagnuolo et al., 2012). A characteristic feature of the carcinogenesis process is the relatively long period between initiation and the development of a clinical form of a cancer, which offers many opportunities for early intervention. Induction of phase II enzymes is an effective

method of protecting the cell from the effects of both reactive metabolites of carcinogenic compounds and reactive oxygen species. This could be the basis for using this method as a chemopreventive strategy in cancer prevention as well as for general chemoprotection. Quercetin and kaempferol are examples of such chemopreventive compounds due to their ability to activate the phase II enzymes (Karabín et al., 2016).

In addition, quercetin, probably as a result of its lipophilicity, has the ability to penetrate the cell and nuclear membrane, and therefore may be involved in epigenetic regulation (Lewandowska et al., 2015). Quercetin also exhibits anti-inflammatory effects by inhibiting cyclooxygenase (COX-2) involved in the development of inflammatory processes (Lewandowska et al., 2015). It has also been demonstrated that aqueous hop extracts containing quercetin and kaempferol glucosides have the ability to inhibit the release of histamine and thus to reduce type I allergic reactions (Segawa et al., 2006).

Stilbenes

One of the best-known polyphenols from the stilbene group is resveratrol. Numerous in vitro and in vivo studies have shown its anti-inflammatory and anti-tumour effects. In various types of cancer, resveratrol inhibits tumour formation and growth, angiogenesis as well as metastasis. It also induces apoptosis. One of the possible mechanisms of resveratrol's anticancer activity, at least in breast cancer cells, is to induce the expression of the SERCA3 gene, which is necessary to maintain intracellular homeostasis (Ca^{2+}). This reduces the viability of breast cancer cells and induces their apoptosis (Izquierdo-Torres et al., 2017). Resveratrol inactivates PI3K-Akt signalling by regulating the bone morphogenetic protein 7 (BMP7) gene (Zeng et al., 2017). In addition, resveratrol prevents or improves the condition of patients with cardiovascular diseases (Brglez et al., 2016; Park, Pezzuto, 2015). It is also perceived as an anti-aging agent (Corrêa et al., 2018). Thus, resveratrol has become a component of many patented solutions for therapeutic, cosmetic and nutraceutical applications (Park, Pezzuto, 2015).

Phenolic acids

Hop cones contain ferulic acid, which belongs to the hydroxycinnamic acids (hydroxycinnamates) of the phenolic acids class. Ferulic acid exhibits various health-promoting effects. It prevents lipid peroxidation, apoptotic death of healthy cells and is an efficacious scavenger of free radicals (Ghosh et al., 2017; Karabín et al., 2016). It slows down the process iso-alpha-acid degradation, consequently partially preventing beer spoilage (Spreng, Hofmann, 2018). Unlike numerous polyphenols, free ferulic acid is very effectively absorbed (Manach et al., 2004; Ghosh et al., 2017).

Ferulic acid decreases the toxicity of carcinogens and ionising radiation, and is a strong UV radiation absorbent (Bohr et al., 2005; Ghosh et al., 2017). In conjunction with various enzymes, it shows anti-inflammatory, anti-apoptotic and anti-tumour effects. It has been proven that it decreases the viability of cells and reduces the formation of cancer cell colonies, suppressing cell migration and invasion (Ghosh et al., 2017). Zhang et al. (2016) utilised ferulic acid for the treatment of breast cancer. Owing to its anti-diabetic, hepatoprotective, cardioprotective and neuroprotective properties, ferulic acid can also be used in the treatment of diseases such as diabetes, Alzheimer's disease and cardiomyopathic disorders (Ghosh et al., 2017). In comparison to flavonoids, which exhibit strong antibacterial properties, ferulic acid shows weaker activity; however, it can still be effectively used against several species of Gram-positive bacteria, such as Staphylococcus aureus and Listeria monocytogenes, as well as against some Gram-negative bacteria, including Pseudomonas aeruginosa (Karabín et al., 2016). The ferulic acid dimer, i.e. curcumin, also displays some important biological properties. It is widely used as a food preservative and as a dye for foods, drugs and cosmetics (Yang et al., 2001).

Flavanols

Considering their quantity, flavanols are the second group of biologically active compounds in hop cones after prenylflavonoids (Biendl, Pinzl, 2013). The amount of (+)-catechin, which has also been detected in hawthorn leaves and fruits, is the highest. It exhibits antioxidant and vasodilating properties, which is why it is used in herbal preparations aimed at strengthening the cardiovascular functions (Biendl, Pinzl, 2013). Other flavanols, which abundantly occur in hop cones are (-)-epicatechin and (+)-gallocatechin (Karabín et al., 2016). The above catechins are also important constituents of tea, particularly green tea. In studies concerning prostate and breast cancers, catechin and epicatechin were confirmed to display antioxidant and anti-inflammatory activities. The effectiveness of the compounds in the suppression of telomerase was also determined (Fresco et al., 2006). Similarly to other polyphenols, depending on the dose and the length of therapy, they reduce the division of breast and prostate cancer cells (Kampa et al., 2007). Epicatechin limits the growth of various types of cancer cells and exerts neuroprotective effects by suppressing apoptosis of the PC12 cells (Kampa et al., 2007). Both epicatechin and resveratrol display anti-aging effects (Corrêa et al., 2018). Catechin significantly restricts the formation of intestinal tumours and suppresses the activity of the focal adhesion kinase (FAK), consequently decreasing the number of metastases by limiting the mobility of cancer cells (Kampa et al., 2007). Polymers, such as proanthocyanidins and tannins, are also classed as flavanols. Naturally, these compounds do not occur in plants

individually, they are most often found as mixtures. The interactions in mixtures may strengthen the effects of individual components. Studies have shown that in the case of hop plants, a mixture of hop proanthocyanidins displays stronger antioxidant effects than individual flavanols and proanthocyanidins (Biendl, Pinzl, 2013).

Multifidol and multifidol glucosides

Kosasi and co-workers gave multifidol its name because they found 2-methylbutyryl, which belongs to phloroglucinols, in the latex of the Jatropha multifida shrub. 2-Methylbutyryl is used in folk medicine to treat infected wounds, skin infections and scabies (Kosasi et al., 1989). Four acylphloroglucinolcopyranosides have been identified in hop extracts: co-multifidol glucoside (1-(2-methylpropanoyl)phloroglucinol pyranoside), ad-multifidol glucoside (multifidol glucoside), n-multifidol glucoside (1-(3-methylbutyryl)phloroglucinol) and co-iso-multifidol glucoside (5-(2-methylpropanoyl)phloroglucinol) (Bohr et al., 2005). The discovered phloroglucinols display anti-inflammatory activity (Bohr et al., 2005). The acyl side chains of the identified phloroglucinols are identical to iso-alpha-acids found in hops. Their presence suggests that they are intermediates in the biosynthesis of bitter acids in hops (Bohr et al., 2005). Several years later, another phloroglucinol was isolated from hops, namely 5-deprenylolupulonol C, which suppresses the generation of the Epstein–Barr virus early antigen (EBV-EA) in infected patients (Akazawa et al., 2012). Research on phloroglucinol derivatives from hops confirms their significant anti-tumour potential. A phloroglucinol derivative 2,4-bis(4-phlorophenylacetyl) phloroglucinol induces concentration-dependent cell death and anti-proliferation in three types of glioblastoma cells, but not in primary human astrocytes (Lu et al., 2012).

Essential oils

Essential oils in a plant are responsible for its characteristic aroma. Similarly to bitter acids in hop cones, these oils are secreted by the lupulin glands. Essential oils can be divided into three groups according to their chemical structures. The first hydrocarbon group includes monoterpenes, sesquiterpenes and aliphatic hydrocarbons. The second group consists of oxidised compounds, such as terpene and sesquiterpene alcohols. The last, third group are sulfur-containing compounds. They include thiols, sulfides, polysulfides, thioesters, thiophenes and terpene derivatives. Among hop essential oils, beta-myrcene, alpha-humulene, beta-caryophyllene, caryophyllene oxide and humulene II epoxide are the most abundant (47–89%) (Kaškonas et al., 2016). Considering the division of essential oils into three groups, most of the hydrocarbon fraction consists of the monoterpenes of myrcene, limonene, alpha- and beta-pinene, as well as sesquiterpenes, namely alpha-humulene, beta-farnesene, beta-caryophyllene, alpha- and beta-selinene and gamma-muurolene (Biendl, Pinzl, 2013; Karabín et al., 2016). During the maturation of cones, oxidation processes result in the formation of oxidised fractions containing linalool, geraniol, caryophyllene oxide, 2-methyl-3-buten-2-ol and derivatives of farnesol (Biendl, Pinzl, 2013; Karabín et al., 2016).

The most important ingredient in hop oil is the monoterpene myrcene. It exhibits two distinct properties. According to the International Agency for Research on Cancer (IARC), myrcene is considered a potential human carcinogen; however, this fact requires further evaluation (Okaru, Lachenmeier, 2017). On the other hand, both myrcene and linalool significantly inhibit the genotoxicity of 2-amino-1-methyl-6-phenylimidazo-[4-5-b]-pyridine, and only myrcene, though less efficiently, inhibits the toxicity of 2-amino-3-methylimidazo-[4,5-f]-quinolines (Mitíć-Culafíc et al., 2016). Beta-myrcene is also a potent inhibitor of the tumour necrosis factor (TNF-α). It has been demonstrated to exhibit more potent activity than alpha-pinene and d-limonene (Lee et al., 2015). Moreover, beta-myrcene also inhibits the TNF-α-induced growth of MDA-MB-231 breast cancer cells (Lee et al., 2015). Most studies emphasise the positive health effects of myrcene, not its carcinogenic properties; therefore, it cannot be excluded as a potential anti-cancer drug. Myrcene is also a strong repellent (RD50 = 0.27 A mu M cm^{-2}) against Rhyzopertha dominica insects, while limonene can be used as a repellent against Sitophilus granarius (Bedini et al., 2015). This enables the utilisation of post-production brewing waste as an insect repellent in food warehouses (Bedini et al., 2015). One of the components of essential oils, which is responsible for the hop aroma, is the monoterpene beta-pinene, also found in rosemary, parsley, dill and rose (Ameh et al., 2015). Both alpha-pinene and beta-pinene have been shown to display significant synergistic effects when combined with Paclitaxel® in the treatment of non-small cell lung cancer (Zhang et al., 2015). Among the sesquiterpenes found in the essential oils of hops, caryophyllene is the most important compound with health-promoting activity. In vitro studies have shown that caryophyllene and its oxide exhibit significant anti-cancer activity, influencing the growth and proliferation of various cancer cells (Fidyt et al., 2016). In particular, beta-caryophyllene oxide has been demonstrated to modulate several key pathways of cancer development, including the MAPK, PI3K / AKT / mTOR / S6K1 and STAT3 pathways (Fidyt et al., 2016). Since beta-caryophyllene only activates the type 2 cannabinoid receptor (CB2) and not type 1 (CB1), it has been applied as a new natural pain reliever. In addition, both compounds increase the effectiveness of standard drugs by increasing their concentration in cancer cells (Fidyt et al., 2016). Humulene, which belongs to the same group of sesquiterpenes as alpha-humulene and alpha-caryophyllene, is responsible for the characteristic hop aroma of beer, but also displays mild corticosteroid effects (Ameh et al., 2015).

In the group of oxidised compounds, 2-methyl-3-buten-2-ol (dimethylvinyl carbinol), the concentration of which increases during hop storage, is responsible for the calming effects of hop essential oils (Biendl, Pinzl, 2013; Hänsel et al., 1980). It has shown activity with respect to the melatonin receptor. Melatonin is a hormone secreted by the pineal gland in humans. It is responsible for maintaining the circadian rhythm in vertebrates through binding to its receptor (Abourashed et al., 2004). Despite the confirmed sedative properties of hops, no clinical doses have been proposed for pure hop preparations. In 2007, a clinical trial compared the effects of the valerian root alone and its combination with hops. In patients with diagnosed insomnia, after 4 weeks of therapy based on conducted polysomnographic studies, it was found that following the addition of hops to the valerian preparation, the time required to fall asleep was shortened, which significantly improved the quality of the patients' lives (Koetter et al., 2007).

The third group of compounds in essential oils includes sulfur-containing substances and accounts for less than 1% of hop essential oils. They affect the aroma of hops, but can also exhibit biological activity (Peppard, 1981). Thiols, such as 3-mercaptohexan-1-ol (3MH), 3-mercaptohexyl acetate, 4-methyl-4-mercaptopentan-2-one (4MMP), 3-sulfanyl-4-methylpentan-1-ol and 3-sulfanylhexan-1-ol, have been extensively investigated in the field of oenology as compounds that give wine the desirable aromas of rhubarb, citrus, passion fruit or blackcurrant (Roland et al., 2016; Cibaka et al., 2016). In addition to releasing pleasant aromas, 3-mercaptohexane-1-ol inhibits the oxidation of epigallocatechin gallate (EGCG), a potent antioxidant found mainly in green tea. This ensures the necessary stability of EGCG, which is essential to maintain its beneficial biological activity (Unnadkat, Elias, 2012). More than 99% of 3-mercaptohexan-1-ol (3MH) found in hops are its precursors, namely S-cysteinylated and S-glutathionylated conjugates (Roland et al., 2016). Considering that free glutathione, which is a potent antioxidant, can be released from S-glutathionylated conjugates, human consumption of thiol precursors from hops may significantly contribute to detoxification of the body, thus preventing oxidative stress and diseases such as cancer. Hence, sulfur-containing compounds found in hop essential oils may be beneficial in three different ways. Some of them are carriers of aroma and flavour; therefore, following aromatherapy, they may significantly affect our mental and physical state. Others prevent the oxidation or degradation of important biologically active molecules, such as EGCG. Some sulfur-containing compounds can release glutathione again, thus contributing to the detoxification of the body, particularly from the numerous carcinogens around us. Finally, even compounds which are not biologically active on their own may still produce synergistic effects and consequently enhance the health-promoting effects of other more active substances found in hops or even provide new effects that none of these compounds induce individually.

CONCLUSION

The increasing knowledge of the healing properties of hops has resulted in the growing interest in the use of the plant in applications other than beer production. Scientific and clinical discoveries indicate that hops may be used more widely in the future, both in the fields of medicine and nutrition. This may lead to the development of new hop varieties with a high content of pharmaceutically valuable substances.

The optimal dietary pattern in modern nutritional science is considered not only at the level of providing the body with essential nutrients, but also in terms of preventing diseases. As a plant rich in biologically active compounds, hops fits this model perfectly. The health-promoting benefits are currently mainly achieved through the consumption of beer; however, in the near future, hop extracts may be added to products to create functional foods. Modern brewing technologies increasingly endeavour to reduce the production of waste as well as to generate useful substances from brewing by-products. The extraction of phytochemicals from the food industry waste should not only contribute to the reduction of the negative environmental impact, but also to the sustainable development of the brewing industry. Large quantities of valuable compounds found in waste may also be inexpensive sources of natural antioxidants and antimicrobials for various applications in the food industry. The extracts of phenolic compounds with high antioxidant activities may also be obtained from brewery waste produced during the regeneration of polyvinylpolypyrrolidone (PVPP) resins used for beer clarification (Mastanjević et al., 2018).

Some hop extracts, particularly those with sedative and estrogenic effects, are already in common use. Others may potentially be used, since in vitro studies indicate that many secondary hop metabolites show significant biological activity. Nonetheless, in vivo studies using physiologically achievable concentrations to confirm these effects are still relatively rare. The current research problem not the confirmation whether these compounds actually affect enzymatic activity or cellular processes, but rather whether the active substances reach the target cells in adequate concentrations and form to achieve the desired effects. Metabolic changes that follow the consumption of a given substance can significantly affect its absorption. Except catechins, most polyphenols, including prenylated flavonoids, are poorly absorbed (Brglez et al., 2016; Konishi et al., 2005; Mukai et al., 2013) and therefore are characterised by low bioavailability. It is possible to improve their absorption by nanoencapsulation (Santos et al., 2013; Siddiqui et al., 2015; Tabrez et al., 2013) or in the case of quercetin, by oligoglycosylation (Murota et al., 2010).

In conclusion, the utilisation of bioactive compounds in hops in pharmacotherapy requires further in vitro and in vivo studies. The latter are particularly important for preventing potential high-dose toxicity and improving the

tolerability of already established drugs as well as for identifying potential synergistic effects.

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