Review article

Humulus lupulus, Plant of Economic and Therapeutic Importance

Tripti Singh and Ashwani Mathur*

Department of Biotechnology, Jaypee Institute of Information Technology Noida-201309, Uttar Pradesh, India

Curr. Appl. Sci. Technol. 2024, Vol.24 (No. 5), e0258585; https://doi.org/10.55003/cast.2024.258585

Received: 29 May 2023 Revised: 4 December 2023, Accepted: 12 March 2024, Published: 1 May 2024

Abstract

Humulus lupulus, often referred to as "hop," is a plant member of the Cannabaceae family. The plant is dioecious in nature and is a perennial fauna reported for its therapeutic properties. It is used largely in the pharmaceuticals and food industries including breweries. Some of the plant's metabolites have been studied for their application in the treatment of metabolic syndrome. Extensive studies on the plant have established its importance as a product of commercial significance, thereby boosting the economic value of this plant. The present review provides a compact account of the plant's phytocompound profile and the remedial properties of its secondary metabolites. Although this plant can be explored as a high-profit-generating resource due to increased market demand and growing market acceptance, challenges faced in the cultivation of this plant limit its availability as an industrially suitable resource. This review, therefore, aimed to shed light on the function of hop secondary metabolites used in therapeutics, hop plant demography, and the problems associated with the cultivation of hop. Limited land availability and the expanding population create the need to develop a cost-effective strategy for cultivating this plant with enhanced yield.

Keywords

Humulus lupulus;
phytocompounds;
cosmetics;
biocontrol agent;
paper industry;
global market

1. Introduction

The perennial herb *Humulus lupulus* is a member of the order Utrticales and the family Cannabaceae. The vine is commonly called "hop". The plant occurs naturally in wild regions that have a temperate climate. Worldwide, it can be found in North America, Western Asia, and Europe [1]. It is a vine physiologically, having a stem around 6-9 m long while the leaves have a rough surface and are attached to the stem by a heart-shaped long petioles that have 3-5 lobes. It is a dioecious plant species. The dynamics of worldwide trade and the plant's escalating demand have substantially aided the spread of hop-growing regions [1, 2]. The plant has been used for its

*Corresponding author: Tel.: +91-120-2594317
E-mail: ashwani.mathur@jiit.ac.in

medicinal properties and has been reported for the same since ancient times [3]. These are mostly due to the existence of phenolic chemicals produced by the plant that are beneficial in the treatment of ailments including leprosy, obesity, foot odor, and constipation. The plant is also used as a source of blood purifying agent [4]. An extract of *Humulus* species works as a sleep-inducer in combination with other herbal drugs. Similarly, it acts as a sedative in combination with passion flowers [5]. Along with its effect on the nervous system, the plant also exhibits different medicinally significant properties including antioxidant, anti-inflammatory, antiplasmodial, antiviral, antiplatelet and antithrombotic, antifungal, and antibacterial properties [6-13]. Phytochemicals identified and extracted from hops are reported to have therapeutic efficacy for the management of menopausal symptoms like fatigue, hot flashes, night sweats, osteoporosis [14], and the treatment of various types of cancer including glioblastoma, hepatocellular carcinoma, breast, ovarian, pancreatic, colon, thyroid, melanoma, and leukemia [15-17]. Ongoing studies focus on a detailed investigation of the metabolites present in the plant and their application in therapeutics, and the use of the leftovers in other fields, as discussed below.

Figure 1. *Humulus lupulus* plant propagated in soil (JIIT campus premises)

2. Chemistry of Hops

The flower of the *H. lupulus* has lupin glands known to produce secondary metabolites of the plant [18]. Studies of hop phytochemistry have identified substances including proteins, cellulose, lipids, pectins, waxes, resins, polyphenols, essential oils, and others [19-21]. The three significant categories of secondary metabolites secreted by the plant are polyphenols, essential oils, and bitter acids [22].

2.1 Polyphenols

Polyphenols, the largeest group of secondary metabolites produced by plants, are found to be biologically active [23, 24]. The profile and levels of polyphenols found in the plant depends upon various factors such as the variety of the hop and the difference in the climatic conditions at the time of cultivation [12, 24]. Hop polyphenols have been divided into two groups, namely glycosylated and non-glycosylated polyphenols. Flavonoids fall under the category of non-glycosylated polyphenols and are further classified into different groups, as shown in (Figure 2). The cones of the hop have been found to contain about 1000 polyphenolic substances and the cones of dried hop contains approx. 3 to 8 % polyphenols [25].

Some of the secondary metabolites in the plant and their pharmacological properties are shown in Table 1. Extensive work related to compounds such as xanthohumol and their mechanisms in the treatment of cancer were well-studied by Jiang *et al*. [26].

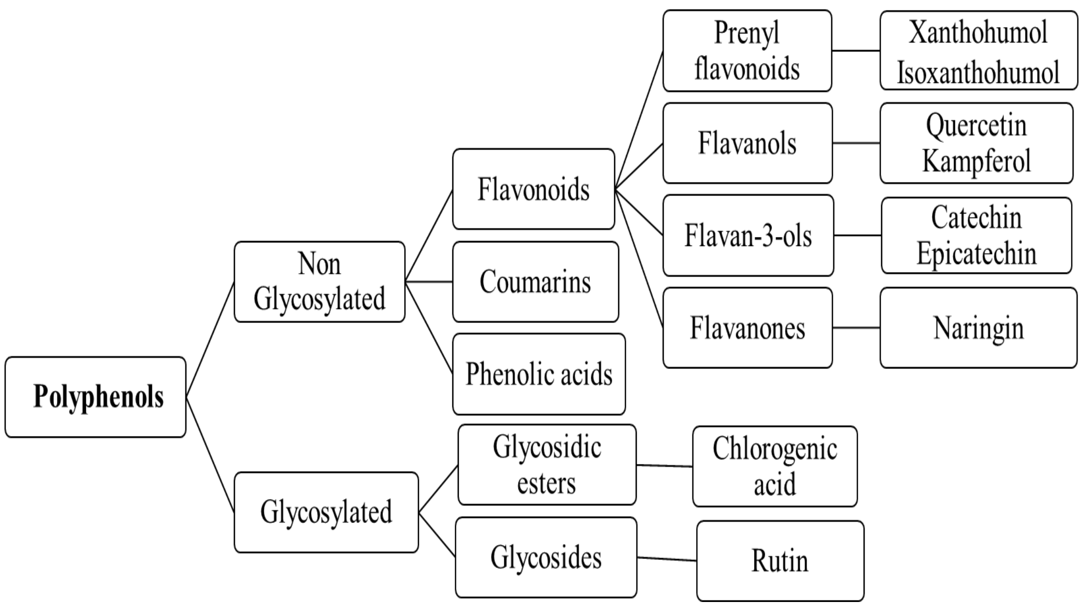
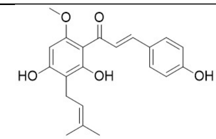
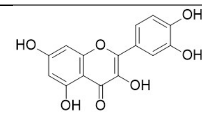
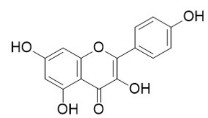
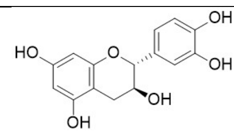
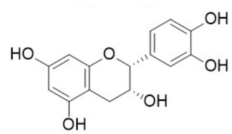
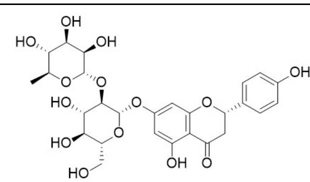


Figure 2. Classification of hop polyphenols

Table 1. Therapeutic applications of hop polyphenols

Class	Compound	Chemical Structure	Use in Therapeutics	References
Prenyl flavonoids	Xanthohumol		DNA synthesis inhibition, cell cycle arrest and apoptosis induction, cancer (ovarian, leukemia, melanoma, breast, thyroid, colon, pancreatic) tumor preventive, anti-inflammatory, antiviral, antiplasmodial, antifungal, antibacterial properties, cardiovascular diseases (atherosclerosis, vasculitis, diabetes) antiplatelet activity, antithrombotic activity, obesity	[26, 27]
Flavanols	Quercetin		Reduces lipid peroxidation, platelet aggregation, and capillary permeability; has anti-carcinogenic, anti-inflammatory, and antiviral properties	[28]
	Kampferol		Increases the body's antioxidant defense against free radicals, lowers the risk of chronic diseases including cancer, and controls apoptosis, angiogenesis, inflammation, and metastasis	[29]
Flavan-3-ols	Catechin		Human chronic disease prevention and intervention, such as for inflammatory bowel disease (IBD)	[30]
	Epicatechin		Reduce blood glucose levels in diabetic patients, antioxidant properties, antiangiogenic	[31]
Flavanones	Naringin		Neurodegenerative diseases (dementia, alzheimer's, Parkinson's), neuro genesis, neuro regeneration, neuroprotection properties, menopause, vasomotor symptoms	[32, 33]

*Structures are drawn using ChemDraw.

2.2 Terpenes

Terpenes are naturally occurring hydrocarbons consisting of five carbon chains known as isoprenes (C_5H_8), which are found in all organisms [34]. The hop has been extensively used in the brewing industry due to the terpenes derived from its cones which comprise 0.5% to 3% of total hop weight. There are three groups of terpenes in essential oils namely, hydrocarbons (60%-80%), oxygenated hydrocarbons (20%-40%) and organosulphur compounds (<1%) [11, 18] (Figure 3). The group's monoterpenes (C_{10}) myrcene, humulene, and sesquiterpenes are the most commonly reported and important terpenes. Table 2 shows the therapeutic applications of various terpenes such as humulene, myrcene, limonene, and other metabolites found in hops.

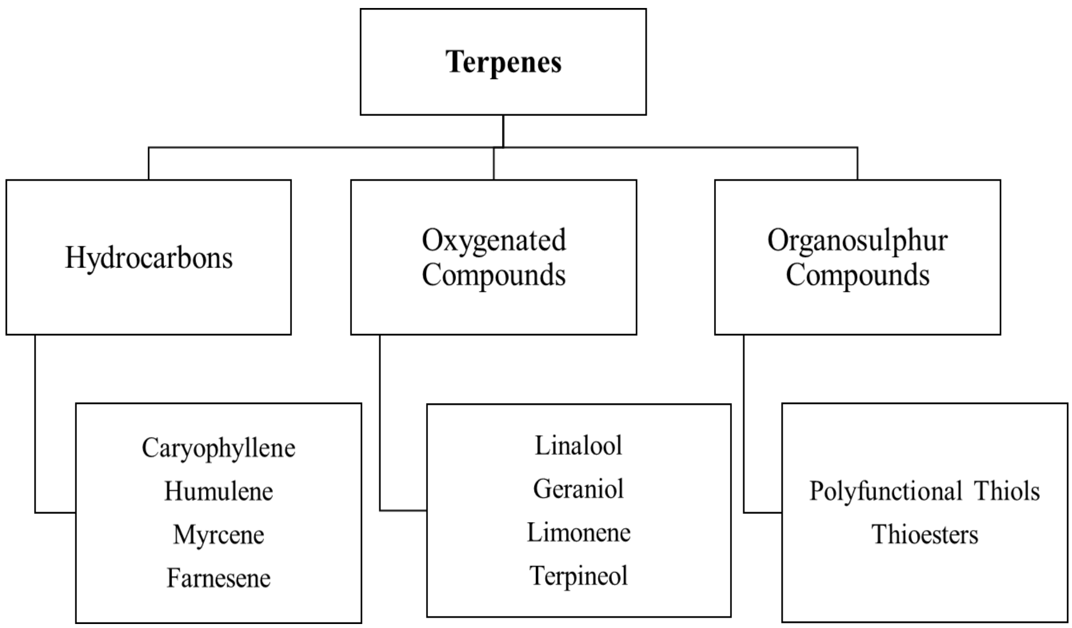


Figure 3. Classification of hop terpenes

2.3 Bitter acids

The potential of *H. lupulus* for use in the brewing industry has been explored broadly. The industry of craft breweries actively incorporates the novel and fresh flavors and aromas of the bitter acids (both alpha and beta bitter acids). This has increased the demand for new *H. lupulus* varieties [2].

Table 2. Therapeutic uses of terpenes found in hop

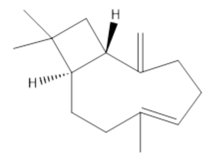
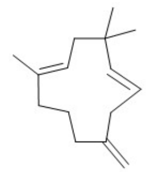
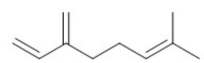
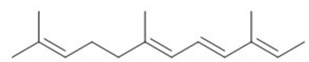
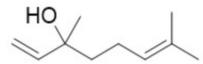
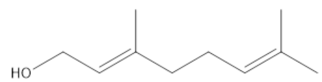
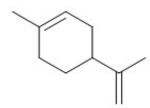
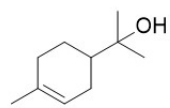
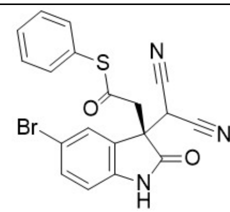
Class	Compounds	Chemical Structure	Use in Therapeutics	References
Hydrocarbons	Caryophyllene		Induces apoptosis, inhibits angiogenesis	[35]
	Humulene		Enhances mucosal integrity	[36]
	Myrcene		Antioxidant, anti-aging, anti-inflammatory, analgesic, and antioxidant properties	[37]
	Farnesene		Anti-inflammatory, anti-allergy properties.	[38]

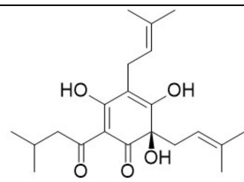
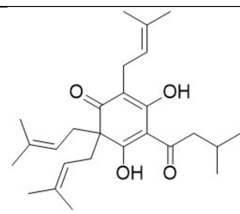
Table 2. Therapeutic uses of terpenes found in hop (continued)

Class	Compounds	Chemical Structure	Use in Therapeutics	References
Oxygenated Compounds	Linalool		Anticancer, neuroprotective, antimicrobial, anti-stress anxiolytic, antidepressant	[39]
	Geraniol		Antioxidant and anti-inflammatory properties	[40]
	Limonene		Antiviral, anti-inflammatory, antinociceptive, antioxidant, anticancer, antidiabetic, antihyperalgesic	[41]
	Terpineol		Antioxidant, anticancer, anticonvulsant, anti-ulcer, antihypertensive, anti-nociceptive	[42]
Organosulfur Compounds	Thioesters		SARS-CoV-2 Mpro inhibitors	[43]

*Structures are drawn using ChemDraw.

The proportions of alpha and beta acids are largely influenced by the variety of hop plants and their conditions of growth [44]. The alpha acids predominantly contain humulone accounting for 35-70% of total alpha acids, followed by co-humulone at 20-65% of the total, and ad-humulone which is 10-15% of the total alpha acids. As for the beta acids, co-lupulone, ad-lupulone, and lupulone constitute 30-55% of total beta acids. Chemical changes of these bitter acids under various conditions of biosynthesis, isomerization, oxidation, and degradation have been extensively studied [44, 45]. Some researchers have explored the role of bitter acids as aseptic additives in the form of antibiotics for food preservation [46], and the bitter acids have been applied in other fields apart from the brewing industry. Some of the other types of applications are depicted in Table 3.

Table 3. Therapeutic uses of bitter acids from hop

Compound	Structure	Therapeutic Uses	References
Humulone		Anti-tumor effects, anti-inflammatory, antioxidants	[46, 47]
Bitter acids		Antiproliferative activities, antioxidant, prevention of inflammation, antidepressant and sedative activities	[48-52]

*Structures are drawn using ChemDraw.

3. Cosmetic Industries

Bioactive ingredients have shown promising effects by enhancing skin-conditioning properties. The formulations consisting of hop cone extract are helpful in the treatment of oily hair and dandruff due to its antifungal and antiseborrheic activities. The use of hop extracts decreases the brittleness of the hairs and helps them give nourishment and shine, thus increasing strength and preventing loss [53]. Hops have been used in bath lotions in combination with other compounds present in the lotion [54]. Vogt *et al*. [53] focused on supercritical CO_2 extraction techniques for the formulation of shower gels. The safety of *H. lupulus* plant extract for use as an herbal foundation for various cosmetic products was evaluated by the Cosmetic Ingredient Review (CIR) Expert Panel. The panel evaluated the safety of plant extracts and their uses as an antibacterial and hair conditioners, as well as the aroma of hop essential oil. Their report concluded that hop extract and oil were safe for use in cosmetics [55]. Table 4 shows the different parts of the plant that have been explored for cosmetic use. In facial products, the plant parts are used as calming agents due to their richness in tannins, which reduce inflammation, thus promoting detoxification [56].

Table 4. Plant part explored in cosmetics [55]

Plant Part	Use in Cosmetics
Whole Plant	Antimicrobial agent; fragrance ingredient, hair, and skin-conditioning agent, skin protectant
Cone	Antimicrobial, antiperspirant, hair conditioning
Flower	Skin-conditioning agent – miscellaneous
Stem	Skin protectant

4. Hop Bine Fibers in Paper Industry

The stems or vines or bines of the hop plant can be used to make excellent strings or bands to bind grain. Furthermore, paper can be manufactured from these plant parts [57]. Earlier, A. O. Taylor of England procured a patent for his process of conversion of hop vines into paper, as depicted in Figure 4 [57]. Also, the fibers obtained through the same process as depicted in Figure 4 could be used in the preparation of rope. In other words, bines can therefore be used as an inexpensive alternative source of renewable lignocellulosic biomass. Hop bine is being processed in the Pacific Northwest at a rate of 85,000 MT annually for the production of paper, making it a main source of cellulosic fiber. The rise in cultivation area may therefore indicate that it is an important source of fibre for its use in producing paper and other bio-based products [58]. Recent research has shown that hop fiber carbohydrate content is high (about 58%), which is similar to the fiber content in other cellulosic materials along with lignin and can be used as bioenergy feedstocks. Also, hop fibers morphologically resemble those of hardwood, having a length of 0.85 mm with a width of 16.5 µm. The potential of hop fiber as a multipurpose agri-material suitable for various industries and the production of bio-based products have been evaluated in recent research, and it was found that the flexibility of hop-made paper was e 61% greater than those made from industrial hemp [58].

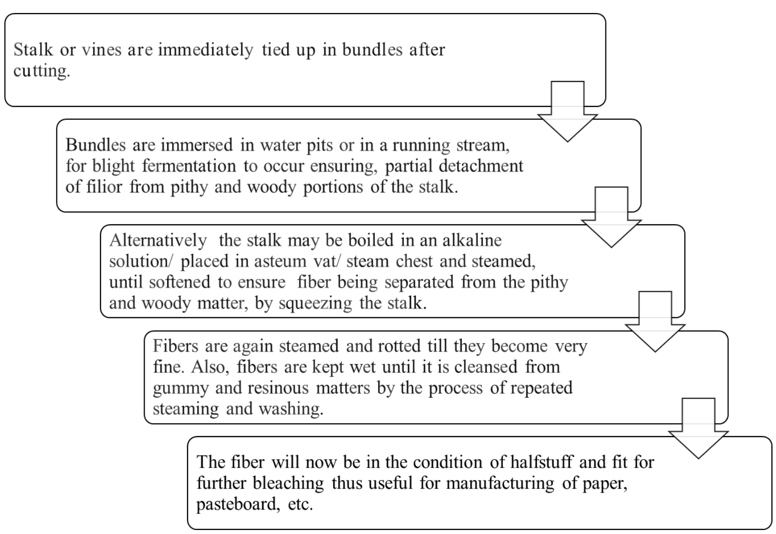


Figure 4. Schematic representation of the process of paper-making

5. Hops as Biocontrol Agents

Searching for alternatives to conventional pesticides used against crop pathogens is quite difficult and challenging. The potential of *H. lupulus* as a controlling agent of pests has been tested as well. Natural bioactive substances obtained from hop extracts, mainly essential oils, were used as an alternative and effective control method for fighting against American foulbrood (AFB) and varroosis diseases caused by *Paenibacillus* larvae, a flagellated gram-positive bacterium, and ectoparasitic mite *Varroa destructor*, respectively [59, 60].

The effects of the secondary metabolites by the plant and their efficiency against pests/pathogens are depicted in Table 5. The results exhibit hop as a rich source of secondary metabolites that have the potential to be low-cost and eco-friendly insect pest repellents in diverse fields. The hop secondary metabolites may find application in the protection of stored foods, or in the control of certain pests that damage crops. However, more studies need to be performed to screen the responsible compounds and ascertain their functions against specific pathogens/pests before thay can be declared as biocontrol agents.

Table 5. Hop as a biocontrol agent against certain pests and pathogens

Secondary Metabolite	Name of Pest/Pathogen	Acute Toxicity (LC_{50})/ Minimum Bactericidal Concentration (MBC)	References
Essential Oils	*Aedes albopictus*	330.855 (µL L^{-1})	[61]
	Physella acuta	118.653 (µL L^{-1})	[61]
	Cloeon dipterum L.	219.787 (µL L^{-1})	[61]
Residual hydrolats	*Varroa destructor*	Victoria (16.1 µL/mL), Mapuche (30.1 µL/mL), Spalt (114.3 µL/mL), Cascade (117.9 µL/mL)	[62]
Methanolic /Ethanolic extract	*Paenibacillus larvae*	Cascade (0.69-2.75 mg/kg) Spalt (1.38-5.5 mg/kg) Victoria (5.5-11 mg/kg)	[62]
Essential Oils (Myrcene/limonene)	*Rhyzopertha dominica*	RD_{50} = 0.27 µM cm^{-2}	[61]
	Sitophilus granarius	RD_{50} = 0.89 µM cm^{-2}	[61, 63]
Desmethylxanthohumol and co-humulone	*Zymoseptoria tritici*	half-maximal inhibitory concentration (0.2 and 0.11 g L^{-1})	[64]

6. Challenges for Cultivation

Growing hop from seeds is quite challenging due to the dormant nature of seeds and poor germination rates. Various studies have evaluated physical and chemical methods to increase the germination efficiency of seeds [65]. Vegetative propagation is the most common method of cultivation of crops, but recent studies have shown that this method has not been highly successful in developing healthy, vigorous plants [66]. Pests and pathogens such as spider mites and aphids, and diseases like Downy mildew [67] and Powdery mildew [68] compromise the production of hop. In addition to these diseases, viroids such as the hop stunt viroid (HSVd), citrus bark cracking viroid (CBCVd), and apple fruit crinkle viroid (AFCVd) can negatively impact the hop plant [69]. The Japanese beetle (*Popillia japonica* Newman) feeds on the leaves of the plant, decreasing the plant's photosynthetic activity [70]. Overall, the cultivation of the plant requires in-depth knowledge and application of various cultivation practices to develop a well-designed structure, and an understanding of plant growth and maintenance that includes well-timed pruning and careful hop-bine training, is also essential [70]. Recently, beer was made using a hydroponic system that required a minimal amount of substrate for roots [71].

7. Global Market

The global annual net worth of the hop plant trade is approximately $500 million (US). The commercial-scale production of this species and its products span in a broad area that includes North America, the whole of Europe, East Asia, as well as Australia and New Zealand [2].

The US is the world's largest hop producing country at 39%, followed by Germany at 38%. China, with 6%, comes in third place, and the Czech Republic in fourth place with 5% [72]. The rest of the world accounts for almost 4% of hop production (Table 6). Data obtained from Barth Report [72] (Table 7) states that Europe was the major producer of hop with an area of 31405 hectares in the year 2018. It was followed by the United States with 23255 hectares, and China being third in the list with 2608 hectares [73]. Table 7 also shows that South Africa had a production area of 427, followed by Canada with 350 and Argentina with 160 hectares, respectively, while Japan was at last with a hop production area of 106 hectares.

Table 6. Global hop production share worldwide in 2020 by leading country

S. No.	Country	Global Hop Production Share (Percentage)
1	United States	39%
2	Germany	38%
3	China	6%
4	Czech Republic	5%
5	United Kingdom	1%
6	Rest of Europe	7%
7	Rest of the World	4%

* *H. lupulus* Growers of America Statistical Report 2020, page 23 [72]

Table 7. Area of hop production worldwide by leading country/region in 2018 in hectares

S. No.	Country	Production Area (Hectares)
1	European Union	31405
2	United States	23255
3	China	2608
4	Australia	652
5	New Zealand	531
6	South Africa	427
7	Canada	350
8	Argentina	160

*The Barth Report [73]

Table 8 shows the trend in hop acreage worldwide from 1998 to 2019 in hectares [73]. According to Table 8, in 1998, the average hop acreage was 60,000, while in 2008, it was 57,500. However, there was a downfall in the year 2013. A constant increase in the hop acreage can be seen in the years from 2013 to 2019 worldwide [74]. The tremendous growth in the hop acreage worldwide can be attributed to the discovery of various novel metabolic properties of hop, and its wide use in the brewing industry.

Table 8. Trend in hop acreage worldwide from 1998 to 2019 in hectares

S.No.	Year	Acreage (Hectares)
1	1998	60111
2	2003	53500
3	2008	57297
4	2013	46246
5	2018	60383
6	2019	61559

*The Barth Report, 2019 / 20 [74]

8. Conclusions

Humulus lupulus, a medicinal and commercial plant of high value, is the focus of scientific interest. The plant is exclusively used in the brewing industries as a flavor enhancer in alcoholic beverages. However, demographic and environmental variations often restrict the cultivation of this dioecious plant. The season specific harvesting of cones from the female plant further elevates the economic demand and market cost of the hop plant. Recent studies have provided a cost effective solution by cultivating the plant using hydroponic cultivation techniques, which can improve the growth rate. However, the effect of such techniques on phytochemical composition and morphological properties needs to be explored. Optimization studies may provide cost-effective solutions that can overcome problems of the yield consistency of the compounds in the plant extract and their role in biotherapeutic applications.

References

[1] Biancardi, E. and Wagner, T. 1989. ll luppolo da birra in Italia. *Annali dell'Istituto Sperimentale per le Colture Industriali*, 21, 1-59. (in Italian)

[2] McCallum, J.L., Nabuurs, M.H., Gallant, S.T., Kirby, C.W. and Mills, A.A.S., 2019. Phytochemical characterization of wild hops (*Humulus lupulus* ssp. lupuloides) germplasm resources from the maritimes region of Canada. *Frontiers in Plant Science*, 10, https://doi.org/10.3389/fpls.2019.01438.

[3] Zanoli, P. and Zavatti, M., 2008. Pharmacognostic and pharmacological profile of *Humulus lupulus* L. *Journal of Ethnopharmacology*, 116(3), 383-396.

[4] Karabín, M., Hudcová, T., Jelínek, L. and Dostálek, P., 2016. Biologically Active Compounds from Hops and Prospects for Their Use. *Comprehensive Reviews in Food Science and Food Safety*, 15(3), 542-567.

[5] Brattström, A., 2009. *Humulus Lupulus* (hops), is there any evidence for central nervous effects related to sleep? *Acta Horticulturae*, 848, 173-178,

[6] Tagashira, M., Watanabe, M. and Uemitsu, N., 1995. Antioxidative activity of hop bitter acids and their analogues. *Bioscience, Biotechnology, and Biochemistry*, 59(4), 740-742.

[7] Yamamoto, K., Wang, J., Yamamoto, S. and Tobe, H., 2000. Suppression of cyclooxygenase-2 gene transcription by humulon of beer hop extract studied with reference to glucocorticoid. *FEBS Letters*, 465(2-3), 103-106.

[8] Liu, M., Hansen, P.E., Wang, G., Qiu, L., Dong, J., Yin, H., Qian, Z., Yang, M. and Miao, J., 2015. Pharmacological profile of xanthohumol, a prenylated flavonoid from hops (*Humulus lupulus*). *Molecules*, 20(1), 754-779.

[9] Lin, M., Xiang, D., Chen, X. and Huo, H., 2019. Role of Characteristic Components of Humulus lupulus in Promoting Human Health. *Journal of Agricultural and Food Chemistry*, 67(30), 8291-8302.

[10] Simpson, W.J. and Smith, A.R., 1992. Factors affecting antibacterial activity of hop compounds and their derivatives. *The Journal of Applied Bacteriology*, 72(4), 327-334.

[11] Hrnčič, M.K., Španinger, E., Košir, I.J., Knez, Ž. and Bren, U., 2019. Hop compounds: extraction techniques, chemical analyses, antioxidative, antimicrobial, and anticarcinogenic effects. *Nutrients*, 11(2), https://doi.org/10.3390/nu11020257.

[12] Muzykiewicz, A., Nowak, A., Zielonka-Brzezicka, J., Florkowska, K., Duchnik, W. and Klimowicz, A., 2019. Comparison of antioxidant activity of extracts of hop leaves harvested in different years. *Herba Polonica*, 65(3), 1-9.

[13] Carbone, K. and Gervasi, F., 2022. An updated review of the genus *Humulus*: A valuable source of bioactive compounds for health and disease prevention. *Plants*, 11(24), http://doi.org/10.3390/plants11243434.

[14] Van Cleemput, M.V., Cattoor, K., De Bosscher, K., Haegeman, G., De Keukeleire, D. and Heyerick, A. 2009. Hop (*Humulus lupulus*)-derived bitter acids as multipotent bioactive compounds. *Journal of Natural Products*, 72(6), 1220-1230.

[15] Miranda, C.L., Stevens, J.F., Helmrich, A., Henderson, M.C., Rodriguez, R.J., Yang, Y.-H., Deinzer, M.L., Barnes, D.W. and Buhler, D.R., 1999. Antiproliferative and cytotoxic effects of

prenylated flavonoids from hops (*Humulus lupulus*) in human cancer cell lines. *Food and Chemical Toxicology*, 37(4), 271-285.
[16] Shimamura, M., Hazato, T., Ashino, H., Yamamoto, Y., Iwasaki, E., Tobe, H., Yamamoto, K. and Yamamoto, S., 2001. Inhibition of angiogenesis by humulone, a bitter acid from beer hop. *Biochemical and Biophysical Research Communications*, 289(1), 220-224.
[17] Chen, W.-J. and Lin, J.-K., 2004. Mechanisms of cancer chemoprevention by hop bitter acids (beer aroma) through induction of apoptosis mediated by Fas and caspase cascades. *Journal of Agricultural and Food Chemistry*, 52(1), 55-64.
[18] Krofta, K., Hervert, J., Mikyška, A. and Dušek, M., 2019. Hop beta acids - from cones to beer. *Acta Horticulturae*, 1236, 15-22.
[19] Tursun, E., Li, Z. and Aisa A.J., 2021. Isolation and identification of soft resins from *Humulus lupulus* L. *Industrial Crops and Products*, 172, https://doi.org/10.1016/j.indcrop.2021.114014.
[20] Forino, M., Pace, S., Chianese, G., Santagostini, L., Werner, M., Weinigel, C., Rummler, S., Fico, G., Werz, O. and Taglialatela-Scafati, O., 2016. Humudifucol and bioactive prenylated polyphenols from hops (*Humulus lupulus* cv. "Cascade"). *Journal of Natural Products*, 79(3), 590-597.
[21] Lin, M., Xiang, D., Chen, X. and Huo, H., 2019. Role of characteristic components of humulus lupulus in promoting human health. *Journal of Agricultural and Food Chemistry*, 67(30), 8291-8302.
[22] Helmja, K., Vaher, M., Püssa, T., Kamsol, K., Orav, A. and Kaljurand, M., 2007. Bioactive components of the hop strobilus: Comparison of different extraction methods by capillary electrophoretic and chromatographic methods. *Journal of Chromatography A*, 1155(2), 222-229.
[23] Steenackers, B., De Cooman, L. and De Vos, D., 2015. Chemical transformations of characteristic hop secondary metabolites in relation to beer properties and the brewing process: a review. *Food Chemistry*, 172, 742-756.
[24] Almaguer, C., Schönberger, C., Gastl, M., Arendt, E.K. and Becker, T., 2014. Humulus lupulus—A story that begs to be told. A review. *Journal of the Institute of Brewing*, 120(4), 289-314.
[25] Dostálek, P., Karabín, M. and Jelínek, L., 2017. Hop phytochemicals and their potential role in metabolic syndrome prevention and therapy. *Molecules*, 22(10), http://doi.org/10.3390/molecules22101761.
[26] Jiang, C.-H., Sun, T.-L., Xiang, D.-X., Wei, S.-S. and Li, W.-Q., 2018. Anticancer activity and mechanism of xanthohumol: A prenylated flavonoid from hops (*Humulus lupulu*s L.). *Frontiers in Pharmacology*, 9, https://doi.org/10.3389/fphar.2018.00530.
[27] Elrod, S.M., 2018. Xanthohumol and the medicinal benefits of beer. In: R.R. Watson, V.R. Preedy and S. Zibadi, eds. *Polyphenols: Mechanisms of Action in Human Health and Disease*. 2nd ed. Cambridge: Academic Press, pp. 19-32.
[28] Li, Y., Yao, J., Han, C., Yang, J., Chaudhry, M.T., Wang, S., Liu, H. and Yin, Y., 2016. Quercetin, inflammation and immunity. *Nutrients*, 8(3), https://doi.org/10.3390/nu8030167.
[29] Chen, A.Y. and Chen, Y.C., 2013. A review of the dietary flavonoid, kaempferol on human health and cancer chemoprevention. *Food Chemistry*, 138(4), 2099-2107.
[30] Fan, F.-Y., Sang, L.-X. and Jiang, M., 2017. Catechins and their therapeutic benefits to ınflammatory bowel disease. *Molecules*, 22(3), https://doi.org/10.3390/molecules22030484.
[31] Abdulkhaleq, L.A., Assi, M.A., Noor, M.H.M., Abdullah, R., Saad, M.Z. and Taufiq-Yap, Y.H., 2017. Therapeutic uses of epicatechin in diabetes and cancer. *Veterinary World*, 10(8), 869-872.
[32] Oberbauer, E., Urmann, C., Steffenhagen, C., Bieler, L., Brunner, D., Furtner, T., Humpel C., Bäumer, B., Bandtlow, C., Couillard-Despres, S., Rivera, J.F., Riepl, H. and Aigner, L., 2013. Chroman-like cyclic prenylflavonoids promote neuronal differentiation and neurite outgrowth and are neuroprotective. *The Journal of Nutritional Biochemistry*, 24(11), 1953-1962.

[33] Abdi, F., Mobedi, H. and Roozbeh, N., 2016. Hops for menopausal vasomotor symptoms: Mechanisms of action. *Journal of Menopausal Medicine*, 22(2), 62-64.
[34] Aldred, E.M., Buck, C. and Vall, K., 2009, Terpenes. In: E.M. Aldred, C. Buck and K. Vall, eds. *Pharmacology*. Edinburgh: Churchill Livingstone, pp.167-174.
[35] Dahham, S.S., Tabana, Y., Asif, M., Ahmed, M., Babu, D., Hassan, L.E., Ahamed, M.B.K., Sandai, D., Barakat, K., Siraki, A. and Majid, A.M.S.A., 2021. β-caryophyllene induces apoptosis and inhibits angiogenesis in colorectal cancer models. *International Journal of Molecular Sciences*, 22(19), https://doi.org/10.3390/ijms221910550.
[36] Yeo, D., Hwang, S.-J., Song, Y.-S. and Lee, H.-J., 2021. Humulene inhibits acute gastric mucosal injury by enhancing mucosal integrity. *Antioxidants* 10(5), https://doi.org/10.3390/antiox10050761.
[37] Surendran, S., Qassadi, F., Surendran, G., Lilley, D. and Heinrich, M., 2021. Myrcene-what are the potential health benefits of this flavouring and aroma agent? *Frontiers in Nutrition*, 8, https://doi.org/10.3389/fnut.2021.699666.
[38] Scott, R.P.W., 2005. *Essential oils*. In: P. Worsfold, A. Townshend and C. Poole, eds. *Encyclopedia of Analytical Science*. 2nd ed. Amsterdam: Elsevier, pp-554-561.
[39] An, Q., Ren. J.-N., Li, X., Fan G., Qu, S.-S., Song, Y., Li, Y. and Pan S.-Y., 2021. Recent updates on bioactive properties of linalool. *Food and Function*, 12(21), 10370-10389.
[40] Mączka, W., Wińska, K. and Grabarczyk, M., 2020. One hundred faces of geraniol. *Molecules*, 25(14), https://doi.org/10.3390/molecules25143303.
[41] Vieira, A.J., Beserra, F.P., Souza, M.C., Totti, B.M. and Rozza, A.L., 2018. Limonene: Aroma of innovation in health and disease. *Chemico-biological Interactions*, 283, 97-106.
[42] Khaleel, C., Tabanca, N. and Buchbauer, G., 2018. α-Terpineol, a natural monoterpene: A review of its biological properties. *Open Chemistry*, 16(1), 349-361.
[43] Pillaiyar, T., Flury, P., Krüger, N., Su, H., Schäkel, L., Barbosa Da Silva, E., Eppler, O., Kronenberger, T., Nie, T., Luedtke, S., Rocha, C., Sylvester, K., Petry, M.R.I., McKerrow, J.H., Poso, A., Pöhlmann, S., Gütschow, M., O'Donoghue, A.J., Xu, Y., Müller, C.E. and Laufer, S.A., 2022. Small-molecule thioesters as sars-cov-2 main protease inhibitors: enzyme inhibition, structure-activity relationships, antiviral activity, and x-ray structure determination. *Journal of Medicinal Chemistry*, 65(13), 9376-9395.
[44] Goese, M., Kammhuber, K., Bacher, A., Zenk, M.H. and Eisenreich, W., 1999. Biosynthesis of bitter acids in hops. A (13)C-NMR and (2)H-NMR study on the building blocks of humulone. *European Journal of Biochemistry*, 263(2), 447-454.
[45] Verzele, M., 1986. 100 years of hop chemistry and its relevance to brewing. *Journal of Institute of Brewing*, 92(1), 32-48.
[46] Zhang, G., Zhang, N., Yang, A., Huang, J., Ren, X., Xian, Mo. and Zou, H., 2021. Hop bitter acids: resources, biosynthesis, and applications. *Applied Microbiology and Biotechnology*, 105, 4343-4356.
[47] Yasukawa, K., Takeuchi, M. and Takido, M., 1995. Humulon, a bitter in the hop, inhibits tumor promotion by 12-O-tetradecanoylphorbol-13-acetate in two-stage carcinogenesis in mouse skin. *Oncology*, 52(2), 156-158.
[48] Machado, J.C., Faria, M.A., Melo, A. and Ferreira I.M.P.L.V.O., 2017. Antiproliferative effect of beer and hop compounds against human colorectal adenocarcinome Caco-2 cells. *Journal of Functional Foods*, 36, 255-261.
[49] Önder, F.C., Ay, M., Türkoğlu, S.A., Köçkar, F.T. and Çelik, A., 2016. Antiproliferative activity of Humulus lupulus extracts on human hepatoma (Hep3B), colon (HT-29) cancer cells and proteases, tyrosinase, β-lactamase enzyme inhibition studies. *Journal of Enzyme Inhibition and Medicinal Chemistry*, 31(1), 90-98.
[50] Ano, Y., Ohya, R., Yamazaki, T., Takahashi, C., Taniguchi, Y., Kondo, K., Takashima, A., Uchida, K. and Nakayama, H., 2020. Hop bitter acids containing a β-carbonyl moiety prevent

inflammation-induced cognitive decline via the vagus nerve and noradrenergic system. *Scientific Report*, 10, https://doi.org/10.1038/s41598-020-77034-w.
[51] Schiller, H., Forster, A., Vonhoff, C., Hegger, M., Biller, A. and Winterhoff, H., 2006. Sedating effects of Humulus lupulus L. extracts. *Phytomedicine*, 13(8), 535-541.
[52] Negri, G., Santi, D.D. and Tabach, R., 2010. Bitter acids from hydroethanolic extracts of *Humulus lupulus* L., Cannabaceae, used as anxiolytic. *Revista Brasileira de Farmacognosia*, 20(6), 850-859 .
[53] Vogt, O., Sikora, E. and Ogonowski, J., 2014. The effect of selected supercritical CO_2 plant extract addition on user properties of shower gels. *Polish Journal of Chemical Technology*, 16(4), 51-54.
[54] Cieśliński, M. and Idowski, P., 2003. Application of common hop in medicine and cosmetology. *Polish Journal of Cosmetology*, 6, 188-192.
[55] Cosmetic Ingredient Review, 2017. *Safety Assessment of Humulus Lupulus (Hops)-Extract and Oil as Used in Cosmetics.* [Online] Available at: https://www.cir-safety.org/supplementaldoc/safety-assessment-humulus-lupulus-hops-extract-and-oil-used-cosmetics-0.
[56] Thomas, K., 2024. *Hops for Anti-Wrinkles*. [online] Available at: https://www.naturalorganicskincare.com/collections/hops-benefits-in-products-for-the-face.
[57] Possemiers, S., Verstraete, W. and de Wiele, T.V., 2008. Estrogenicity of beer: The role of intestinal bacteria in the activation of the beer flavonoid isoxanthohumol. In: V.R. Preedy, eds. *Beer in Health and Disease Prevention*. London: Academic Press, pp. 523-539.
[58] Haunreiter, K.J., Dichiara, A. and Gustafson, R., 2021. Structural and chemical characterization of hop bine fibers and their applications in the paper industry, *Industrial Crops and Products*, 174, https://doi.org/10.1016/j.indcrop.2021.114217.
[59] Anderson, D.L. and Trueman, J.W.H., 2000. *Varroa jacobsoni* (Acari: Varroidae) is more than one species. *Experimental and Applied Acarology*, 24(3), 165-189.
[60] Iglesias, A., Martinez, P.G., Ramirez, C., Mitton, G., Arcerito, F.R.M., Fangio, M.F., Churio, M.S., Fuselli, S., Fanovich, A., Eguaras, M. and Maggi, M., 2021.Valorization of hop leaves for development of eco-friendly bee pesticides. *Apidologie*, 52, 186-198.
[61] Bedini, S., Flamini, G., Girardi, J., Cosci, F. and Conti, B., 2015. Not just for beer: evaluation of spent hops (*Humulus lupulus* L.) as a source of eco-friendly repellents for insect pests of stored foods. *Journal of Pest Science*, 88, 583-592.
[62] Iglesias, A.E., Fuentes, G., Mitton, G., Ramos, F., Brasesco, C., Manzo, R., Orallo, D., Gende, L., Eguaras, M., Ramirez, C., Fanovich, A. and Maggi, M., 2022. Hydrolats from *Humulus lupulus* and their potential activity as an organic control for *Varroa destructor*. *Plants*, 11(23), https://doi.org/10.3390/plants11233329.
[63] Paventi, G., de Acutis, L., De Cristofaro, A., Pistillo, M., Germinara, G.S. and Rotundo, G., 2020. Biological activity of *Humulus lupulus* (L.) essential oil and ıts main components against *Sitophilus granarius* (L.). Biomolecules, 10(8), https://doi.org/10.3390/biom10081108.
[64] Bocquet, L., Rivière, C., Dermont, C., Samaillie, J., Hilbert, J.L., Halama, P., Siah, A. and Sahpaz, S., 2018. Antifungal activity of hop extracts and compounds against the wheat pathogen *Zymoseptoria tritici*. *Industrial Crops and Products*, 122, 290-297.
[65] Liberatore, C.M., Giulia M., Rodolfi, M., Tommaso G., Fabbri, A. and Chiancone, B., 2018. Chemical and physical pre-treatments to improve in vitro seed germination of *Humulus lupulus* L., cv. Columbus. *Scientia Horticulturae*, 235, 86-94.
[66] Marceddu, R., Carrubba, A. and Sarno, M., 2020. Cultivation trials of hop (*Humulus lupulus* L.) in semi-arid environments. *Heliyon*, 6(10), https://doi.org/10.1016/j.heliyon.2020.e05114.
[67] Neve, R.A. 1991. *Hops*. London: Chapman and Hall.
[68] Gent, D.H., Nelson, M.E., Grove, G.G., Mahaffee, W.F., Turechek, W.W. and Woods, J.L., 2012. Association of spring pruning practices with severity of powdery mildew and downy mildew on hop. *Plant Disease*, 96, 1343-1351.

[69] Matoušek, J., Siglová, K., Jakše, J., Radišek, S., Brass, J.R.J., Tsushima, T., Guček, T., Duraisamy, G.S., Sano, T. and Steger, G., 2017. Propagation and some physiological effects of Citrus bark cracking viroid and apple fruit crinkle viroid in multiple infected hop (*Humulus lupulus* L.). *Journal of Plant Physiology*, 213, 166-177.
[70] Rossini, F., Virga, G., Loreti, P., Iacuzzi, N., Ruggeri, R. and Provenzano, M.E., 2021. Hops (*Humulus lupulus* L.) as a novel multipurpose crop for the mediterranean region of Europe: Challenges and opportunities of their cultivation. *Agriculture*, 11(6), https://doi.org/10.3390/agriculture11060484.
[71] Noronha, P.M., 2022. Cheers to the first beer made entirely from ındoor hops. *Nature*, 609(7928), https://doi.org/10.1038/d41586-022-02965-5.
[72] America Statistical Report, 2020. *Global Hop production share worldwide in 2020 by leading country, 2020.* [online] Available at: https://www.statista.com/statistics/757766/global-hop-production-area-by-country/.
[73] Barth Report, 2020. *Area of Hop production worldwide by leading country/region in 2018 (in hectares),2020*. [online] Available at: https://www.barthhaas.com/fileadmin/user_upload/news/2019-07-23/19-07-23_en.pdf.
[74] Barth Report, 2020. *Trend in the Hop Acreage Worldwide from 1998 to 2019 (in hectares), 2020,* [online] Available at: https://www.statista.com/statistics/270273/global-hop-acreage/.