PROSPECTS
IN PHARMACEUTICAL SCIENCES

Prospects in Pharmaceutical Sciences
https://prospects.wum.edu.pl/

Review Article

Humulus Species: A Traditional Medicinal Plant and Its Modern Pharmacological Importance

Ghadir A. El-Chaghaby[1], Emre Sevindik[2], Mustafa Sevindik*[3], Oğuzhan Koçer[4], İmran Uysal[5]

[1] *Bioanalysis Laboratory, Regional Center for Food and Feed, Agricultural Research Center, Giza, Egypt*

[2] *Department of Agricultural Biotechnology, Faculty of Agriculture, Aydın Adnan Menderes University, Türkiye*

[3] *Department of Biology, Faculty of Engineering and Natural Sciences, Osmaniye Korkut Ata University, Türkiye.*

[4] *Department of Pharmacy Services, Vocational School of Health Services, Osmaniye Korkut Ata University, Türkiye.*

[5] *Department of Food Processing, Bahçe Vocational School of Higher Education, University of Osmaniye Korkut Ata, Türkiye*

* Correspondence, e-mail: sevindik27@gmail.com

Received: 12.02.2025 / Revised: 10.04.2025 / Accepted: 23.04.2025 / Published online: 06.08.2025

ABSTRACT

The genus *Humulus*, particularly *Humulus lupulus* (hops), has been widely recognized for its historical and traditional uses in various cultures due to its diverse biological activities. This review compiles the general characteristics, traditional uses, essential oil compositions, and pharmacological properties of *Humulus* species, with a focus on their antioxidant, antimicrobial, anti-inflammatory, anticancer, antiviral, and insecticidal activities. The essential oils of *Humulus* species, rich in bioactive compounds such as β-caryophyllene, α-humulene, and β-myrcene, contribute to their broad-spectrum therapeutic effects. These compounds have demonstrated significant potential in reducing oxidative stress, combating microbial infections, alleviating inflammation, and exhibiting cytotoxic effects against cancer cells. Additionally, the traditional uses of *Humulus* species for sleep regulation, digestive health, and hormone balance are supported by modern pharmacological studies. The antioxidant and antimicrobial properties of *Humulus* species highlight their potential as natural sources of antioxidants and alternatives to synthetic antibiotics, particularly in the face of rising antibiotic resistance. Furthermore, the insecticidal and allelopathic effects of these plants suggest their applicability in sustainable agriculture as eco-friendly biopesticides and weed control agents. Despite the promising findings, gaps remain in understanding the pharmacokinetics, bioavailability, and safe dosage ranges of the bioactive compounds in *Humulus* species. Future research should focus on in vivo and clinical studies to validate these effects, explore their potential in functional foods and nutraceuticals, and assess their ecological and environmental impacts for large-scale cultivation. In conclusion, *Humulus* species represent a versatile and valuable natural resource with significant potential in medicine, agriculture, and industry. Continued research efforts are essential to fully unlock their benefits and integrate them into modern therapeutic and industrial applications.

KEYWORDS: Hop, *Humulus* species, complementary medicine, medicinal plants, antioxidant.

1. Introduction

Plants have a history as old as human history and are used for different purposes. Today, plants have an important place in many areas such as nutrition, shelter, heating, religious rituals and medical treatments [1,2]. They are of great importance especially in terms of containing vital nutrients such as food sources, vitamins, minerals and macromolecules [3,4]. In addition, the use of plants is quite common in traditional and complementary medicine practices. Especially in developing countries, natural and herbal treatment methods are widely preferred in addition to modern medical treatments [5,6].

Many scientific studies conducted in recent years have revealed that plants exhibit various biological activities. These activities include antioxidant, antiproliferative, anti-inflammatory, anticancer, antimicrobial, anti-aging, antiallergic, DNA protective and hepatoprotective properties [7-15]. The discovery of such biological activities enables both the development of new treatment approaches in the field of health and the potential pharmaceutical uses of compounds obtained from natural sources [16].

Plants rich in natural compounds contain pharmacologically valuable components, especially essential oils. Essential oils attract attention with their antibacterial, antifungal and antiviral effects, and also have a wide range of use in aromatherapy, cosmetics and food industries [17-20].

In this study, the general characteristics of *Humulus* species, their areas of use, essential oil contents and biological activities reported in the literature were examined and compiled in detail. The evaluation of the biological activities of these species is of great importance in terms of the discovery of new natural resources. In this context, the compilation of studies on the potential health benefits and biological effects of *Humulus* species will shed light on future scientific studies.

2. The Genus Humulus and Its Areas of Usage

The genus *Humulus* belongs to the Cannabaceae family and is commonly known as hops. These perennial herbaceous plants grow rapidly by producing new shoots in the spring and re-grow in the fall thanks to their cold-resistant root systems. Their growth rate is quite high and can reach up to 20-50 cm. The most common of the Humulus species is known as *Humulus lupulus*. Archaeological findings show that pollen belonging to the *Humulus* genus was found in England dating back to 3000 BC. This plant, which was used for various purposes in ancient Egypt, was evaluated in the Roman period for liver diseases, digestive disorders and as a blood purifier. It was recorded that it was used for different medical purposes by the Arab physician Mesue in the 11th century, while in the 13th century, botanist Ibn al-Baytar discovered the sedative effect of hops and the plant was recommended for fever, spleen diseases, diuretic effect and liver detoxification. It is also reported that it is used in traditional Ayurvedic medicine in India. Today, the leaves, flowers, inflorescences, roots and strobili parts of the Humulus plant are used in different areas. While the leaves are consumed as vegetables, they are used in hair care products and as textile dyes. The flower components are used as hair rinse water and textile dyes; the inflorescences are used as protective materials for carrying fragile objects. The roots are used in the production of cattle bedding, yarn, fabric, paper and insulation material. The strobili parts have a wide range of uses. For example, it is used in bread making for yeast production, preservation and flavoring of sausages, bakery products, tobacco, deodorant (antimicrobial and deodorizing), perfume, skin lotions, food oil, antibiotics, sedatives and in the treatment of various health problems. It has been reported that it is used especially against sleep disorders, headache, restlessness, stomach disorders, loss of appetite, tooth and ear pain, neuritis, leprosy, tuberculosis, asbestosis, silicosis, cough, spasms, fever, anxiety, delirium tremens, urinary tract irritation, pain and liver diseases. In addition, hops is one of the main ingredients widely grown in the beer industry to provide aroma and flavor contribution [21-25].

3. Biological Activities

It is known that various natural products possess different biological activities due to the presence of bioactive compounds within their structure [26]. Plants are natural resources of great importance in terms of biological activity [27]. In our study, we have compiled the reported biological activities of *Humulus* species in the literature. Within this scope, it has been observed that the biological activity of *Humulus* species has been investigated through in vitro and in vivo studies utilising extracts such as petroleum ether, ethyl acetate, n-butanol, water, acetic ether, chloroform, benzene, acetone, ethanol, essential oil, methanol, and hydroalcoholic. Table 1 and Figure 1 displays the biological activity study of *Humulus* species.

Table 1. Biological activities of Genus *Humulus* [28-41].

Plant species	Biological activities	Extraction	Country of publication (as reported)
H. lupulus	Antimicrobial, antioxidant, pesticide, antiviral, anticholinesterase, anti-inflammatory, apoptotic, antiplasmodial, anticoagulant	Ethanol, water, essential oil, methanol, hydroalcoholic	Brazil, Czech Republic, Italy, USA, Germany, Poland, Australia
H. scandens	Allelopathic effects, antioxidant, anti-inflammatory, insecticide	Petroleum ether, ethyl acetate, n-butanol, water, acetic ether, chloroform, benzene, acetone, ethanol	China

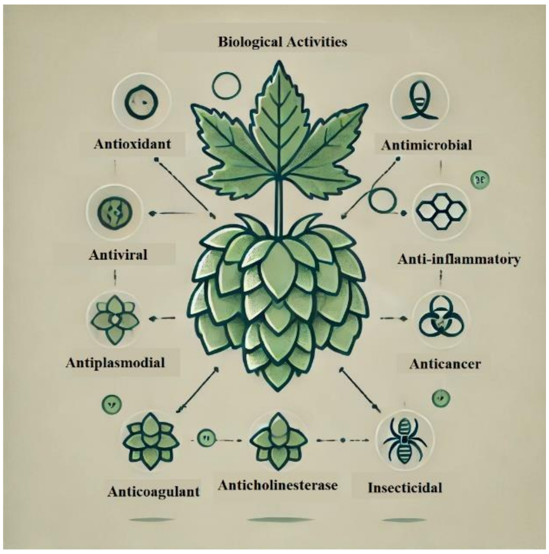

Fig 1. Biological Activities of *Humulus* species

3.1. Antioxidant activity

Free radicals are oxidative compounds formed as a result of metabolic processes in living organisms and when they are not sufficiently neutralized, they lead to oxidative stress [42,43]. Oxidative stress plays a role in the development of many chronic diseases including cancer, neurodegenerative diseases such as Alzheimer's and Parkinson's, and cardiovascular disorders [44,45]. Therefore, natural antioxidants of plant origin are of great interest today [46]. Different extraction methods and analysis techniques have been used in studies on Humulus species (Table 1). In a study conducted in Brazil, DPPH values of ethanol and water extracts of *H. lupulus* were reported as 24.11–43.66 µmol/g, and ABTS values were reported as 58.21–165.13 µmol/g [36]. In a study conducted in Italy with methanol extract, DPPH values were determined as 69–220 µg and ABTS values as 0.63–1.81 µg [37]. In a study from Poland, iron chelation capacity was reported as 55.43–88.76%, while DPPH values were reported as 4.75 mmol/g [33]. In a study conducted in China on H. scandens, DPPH inhibition of n-butanol extract at a concentration of 2.0 mg/mL was determined as 93.6%; the Reducing Power (RP) test was found to be effective in the range of 0.25–2.5 mg/mL [41]. The differences observed between these studies are due to the changes in the solvents used (ethanol, methanol, water, etc.), extract concentrations, analysis methods and parts of the plant used. This situation shows that the contents of bioactive compounds such as phenolic compounds, flavonoids and prenylated flavonoids (e.g. xanthohumol, 8-prenylnaringenin) may vary depending on the extraction method. All these findings show that the antioxidant potential of Humulus species is promising, but further in vivo and clinical studies are needed in terms of pharmacokinetics, bioavailability and dose safety in order to transfer this effect to the clinical level.

3.2. Antimicrobial activity

Microbial diseases have become an important health problem today. The unconscious use of antibiotics has led to the emergence of resistant microorganisms, making treatments difficult [47]. In addition, interest in natural antimicrobial sources has increased due to the potential side effects of synthetic drugs [48]. Studies conducted in this context draw attention to the antimicrobial potential of *Humulus* species (Table 1). In a study conducted in Brazil on *H. lupulus*, it was reported that ethanol and water extracts created an inhibitory zone of up to 35.5 mm against S. aureus; minimum inhibitory concentration (MIC) values were <0.097–7.21 µg/mL and minimum bactericidal concentration (MBC) values were between 0.096–8.65 µg/mL [36]. In another study conducted in Czechia, MIC and MBC values on *B. fragilis, C. perfringens* and *C. difficile* species were reported to be in the range of 15–107 µg/mL [32]. In a study conducted in Italy, it was reported that methanol extract formed zone diameters ranging from 1.78–3.63 mm against microorganisms such as *S. aureus, B. subtilis, E. coli, P. putida, P. fluorescens, P. aeruginosa, C. albicans* and *S. cerevisiae* [37]. In a study conducted in the USA, MIC values of *H. lupulus* against *S. mutans* and other oral streptococci were reported to range from 2–50 µg/mL [28]. These results show that *Humulus* species may be effective against both Gram-positive and Gram-negative bacteria and fungi. However, the antimicrobial activity levels obtained; The extraction method, solvent type and microorganism model used differ. This shows that the methodological diversity in the studies directly affects the results. Flavonoids, phenolic compounds and prenylated contents found in species such as *H. lupulus* are thought to be the main bioactive substances providing antimicrobial effect. However, these effects need to be investigated not only in vitro but also in vivo. In addition, comprehensive toxicological evaluations are needed for these plant compounds to be used in pharmaceutical and food preservation areas. The current literature shows that *Humulus* species can be evaluated as natural preservatives or phytotherapeutic agents, but further studies are needed to better understand this potential at clinical and industrial levels.

3.3. Other activities

It has been reported in the literature that *Humulus* species exhibit various biological activities in addition to their antioxidant and antimicrobial activities. A study conducted in Italy investigated the insecticidal properties of volatile oils obtained from *H. lupulus* against *Sitophilus granarius*. According to the study findings, the LD50/LD90 of adult contact toxicity was reported to be 13.30/40.23 µg/adult [30]. According to a study conducted in Germany, it has been reported that xanthohumol derived from *H. lupulus* exhibits antiviral properties against bovine viral diarrhoea virus, cytomegalovirus, *Herpes simplex* virus type 1 and 2, and human immunodeficiency virus 1 [35]. According to a study conducted in Poland, it has been reported that ethanol and water extracts obtained from *H. lupulus* exhibit higher activity as AChE inhibitors compared to BChE inhibitors [33]. A study conducted in Italy investigated the anti-inflammatory effect of a hydroalcoholic extract obtained from *H. lupulus*. According to the study findings, it has been reported that the concentration-dependent release of IL-8 in human gastric epithelial AGS cells was inhibited [34]. A study conducted in Italy reported the apoptotic effects of extracts obtained from *H. lupulus* on human leukaemia cells (HL60), human neuroblastoma cells (SH-SY5Y), human metastatic adenocarcinoma breast cells (MCF7), and human adenocarcinoma breast cells (MDA) [38]. A study conducted in Australia investigated the antiplasmodial effect of an extract obtained from *H. lupulus* on *Plasmodium falciparum*. According to the study findings, it has been reported that the LC50 had an effect ranging from 8.2-24.0 µM [29]. A study conducted in Poland investigated the anticoagulant effect of an extract obtained from *H. lupulus*. According to the research findings, it has been reported that it inhibits platelet aggregation up to 11% [31]. A study conducted in China investigated the allelopathic effects of petroleum ether, ethyl acetate, and n-butanol extracts obtained from *H. scandens* on *Alternanthera philoxeroides*, a typical invasive species. According to the study's findings, three extracts were reported to inhibit the growth, stem length, node count, leaf count, and leaf size of *A. philoxeroides* seedlings. Additionally, an increase in malondialdehyde (MDA) content was observed in *A. philoxeroides* seedlings, and it was reported that the extracts damaged the leaf membrane system, thereby inhibiting plant growth [40]. In a study conducted in China, the anti-inflammatory effect of acetic ether, chloroform, and water extracts obtained from *H. scandens* was investigated using xylene-induced ear edoema models in mice. According to the study findings, significant reduction in auricular edoema was observed in mice at doses of 1 and 4 g/kg, with inhibitions reported at 51.52% and 50.71%, respectively, at the 4 g/kg dose [41]. A study conducted in China investigated the insecticidal properties of petroleum ether, benzene, chloroform, ethyl acetate, acetone, and ethanol extracts obtained from H. scandens against *Plutella xylostella*. According to the study findings, it has been reported that the acetone extract exhibited the highest potency with a 48-hour adjusted mortality rate of 86.67% [39]. Within this scope, it has been observed in the literature that *Humulus* species possess significant biological activities in terms of reported biological activities.

Studies on the biological activities of *Humulus* species show that these plants attract attention not only with their antioxidant and antimicrobial properties, but also with their various pharmacological and ecological effects. In particular, the fact that insecticidal, antiviral, anti-inflammatory, anticancer, antiplasmodial, anticoagulant and allelopathic effects have been reported in the literature reveals that these species have a wide spectrum of biological effects. It has been determined that the essential oils obtained from the *H. lupulus* species have high insecticidal activity against harmful insects such as *Sitophilus granarius*, indicating that the plant can be evaluated as a biopesticide in agricultural control. In addition, it has been observed that the xanthohumol compound exhibits antiviral effects against various viruses, especially HIV, herpes virus and cytomegalovirus.

It has also been determined that Humulus extracts have potential in terms of neurodegenerative diseases. In particular, the higher AChE inhibitory activity compared to BChE inhibitory activity indicates that this plant may be a promising candidate in the treatment of neurodegenerative diseases such as Alzheimer's. However, apoptotic effects were observed in studies on cancer cells, and cytotoxic activities were reported especially in leukemia and breast cancer cell lines. It is thought that *H. lupulus* extracts, which exhibit antiplasmodial effects against *P. falciparum*, can be evaluated among alternative natural agents in the treatment of malaria. In addition, Humulus extracts, which exhibit anticoagulant effects by inhibiting platelet aggregation, offer significant potential in terms of preventing cardiovascular diseases.

When evaluated from an ecological perspective, the allelopathic effects of the *H. scandens* species are remarkable. In particular, the suppression of the growth of invasive plants such as *Alternanthera philoxeroides* suggests that it may be a natural option for weed control in agricultural ecosystems. In addition, the strong insecticidal effects of *H. scandens* extracts against insects emphasize the importance of phytochemical resources in natural insect control. In conclusion, the broad biological activity profile of *Humulus* species indicates that this plant has a versatile potential for use in food, medicine, cosmetics and agriculture. However, comprehensive toxicological and pharmacokinetic studies are required for a better understanding of these effects at clinical and industrial levels.

There is information in the literature on the molecular mechanisms of action of some of the main bioactive compounds contained in Humulus species. For example, ß-caryophyllene binds to CB2 (cannabinoid 2) receptors as a selective agonist and thus exhibits anti-inflammatory and analgesic effects. The interaction with this receptor acts by suppressing the release of inflammatory cytokines in the immune system.

Another important compound, xanthohumol, inhibits various cellular pathways such as NF-κB, PI3K/Akt, and MAPK signaling pathways, exhibiting apoptosis, anticancer, and antioxidant effects. It is also stated that xanthohumol has hormonal balancing effects due to its interaction with estrogen receptors.

The effects of these compounds occur not only at the level of interaction with target proteins, but also through the regulation of gene expression. However, most of these mechanisms are based on cell culture studies; therefore, advanced in vivo and clinical studies are needed.

4. Limitations and Critical Considerations of Existing Studies

Although numerous studies have demonstrated the biological activities of Humulus species, certain methodological limitations should be taken into account when interpreting their results. First, the variability in extraction methods—including solvent polarity (e.g., ethanol, methanol, water, petroleum ether)—can lead to significant differences in the composition and concentration of bioactive compounds, thereby affecting the observed pharmacological effects. Additionally, discrepancies in dosage levels, extraction yields, and experimental models (e.g., in vitro vs. in vivo systems) complicate direct comparisons between studies. Most studies employed in vitro assays such as DPPH, ABTS, and MIC, which, while useful for initial screening, may not fully represent the biological efficacy in living organisms due to differences in absorption, metabolism, and bioavailability. Furthermore, many of the existing studies lack standardization in terms of extraction protocols and biological testing, which limits the reproducibility and generalizability of the findings. Toxicological data are also sparse, and little is known about the long-term safety and effective dosage ranges of the bioactive compounds present in Humulus species. Future research should aim to address these gaps by employing standardized methodologies, conducting dose-response studies, and expanding into in vivo and clinical research to validate the therapeutic potential suggested by in vitro findings.

5. Essential Oil Contents

Plants synthesise numerous biologically active secondary metabolites within their systems. Bioactive compounds are compounds that do not possess nutritional properties but are medically significant [49,50]. Within this context, the identification of compounds present in plants is crucial. In our study, a compilation of chemical compounds found within the *Humulus* species has been presented based on existing literature (Table 2). The chemical compounds of the plant were identified by utilising both the aerial parts and stem segments.

According to the studies conducted, it has been reported that the main components of the volatile oil content of the *H. lupulus* species are ß-caryophyllene

(4.52-29%),α-bergamotene (0.15-4.36%), α-humulene (3-37.14%), β-farnesene (0.75-20.60%), γ-muurolene (0.84-18.5%), α-muurulene (3.0%) β-selinene (1.79-17.87%), α-selinene (0.88-9.95%), σ-cadinene (1.60-18.5%), β-bisabolol (9.6-15.0%), α- zingiberene (5.6%), myrcene (6.1-45.3%), γ-elemene(14%), β-myrcene (10.99–89.32%), trans-β-farnesene (10.59%), γ-cadinene (5.5-21.7%), α- pinene (37.4%), β- pinene (41.6%), α-copaene (14%) and β-bisabolene (29%) [51-58]. It has been reported that the main components of the volatile oil content of the *H. scandens* species are dibutyl phthalate (14.77%),n-hexadecanoic acid (6.29-13.99%), 9,12,15-octadecatrienoic acid, (Z,Z,Z)- (12.33%), 9,12-octadecadienoic acid (Z,Z)- (11.79%), methyl palmitate (11.8%), stigmasta-3,5-diene (8.75%), (Z,Z)-octadeca-9, 12-dienoic acid (7.62%), 9,12-octadecadienoic acid (Z,Z)-methyl ester (6.13%), stigmastane-3,6-dione,(5à) (6.73%), á-sitosterol (5.63%), β-caryophyllene (49.37-97.03%), β-myrcene (2.3-15.1%), (E)-β-farnesene (96.4%), δ-cadinene (78.7%) and caryophyllene epoxide (53.1%) [40, 59, 60]. Within this context, it has been observed that the most abundant compounds in *Humulus* species are β-caryophyllene, β-myrcene, myrcene, α-humulene, (E)-β-farnesene, δ-cadinene, and caryophyllene epoxide. The most abundant type in terms of concentration is β-caryophyllene, accounting for 97.03%.

The chemical composition of essential oils in *Humulus* species has been extensively studied with literature data, revealing various bioactive compounds with potential pharmacological and industrial applications. The major components identified in *H. lupulus* include β-caryophyllene, β-myrcene, α-humulene, (E)-β-farnesene, δ-cadinene, and caryophyllene epoxide; β-caryophyllene is the most abundant, reaching concentrations as high as 97.03% in *H. scandens*. These compounds are known for their important biological activities, including anti-inflammatory, antimicrobial, antioxidant, and insecticidal properties [61, 62], contributing to the wide-ranging medical and commercial uses of *Humulus* species. Among these, β-caryophyllene is particularly notable for its dual role as both a flavoring agent and a bioactive compound with anti-inflammatory and analgesic properties, and functions as a cannabinoid receptor agonist. Similarly, α-humulene and β-myrcene have been reported to exhibit anti-inflammatory, sedative, and antioxidant effects [63, 64], which may explain the traditional use of *Humulus species* in herbal medicine. Furthermore, caryophyllene epoxide, a known antimicrobial agent, enhances the potential of these plants as natural preservatives in the food and pharmaceutical industries.

Unique components such as dibutyl phthalate, n-hexadecanoic acid, and stigmastane derivatives have been identified in *H. scandens*, further diversifying its potential applications. The presence of fatty acid derivatives and sterols suggests that *H. scandens* may have additional nutritional and pharmacological benefits, especially in cardiovascular and metabolic health.

Overall, the essential oil composition of *Humulus* species supports their broad-spectrum biological activities and industrial benefits. The high concentration of terpenes, sesquiterpenes, and fatty acid derivatives indicates a promising potential for pharmaceutical, food, cosmetic, and agricultural applications. However, further studies are needed to investigate the synergistic effects of these compounds and fully elucidate their mechanisms of action in biological systems.

Table 2. Compounds of *Humulus* species

Plant species	Country of publication (as reported)	Used Parts	Compounds (%)
H. lupulus	Poland, Lithuania, Netherlands, Brazil, Argentina, Germany, Czech Republic	Aerial parts	β-caryophyllene (4.52-29), α-bergamotene (0.15-4.36), α-humulene (3-37.14), β-farnesene (0.75-20.60), γ-muurolene (0.84-18.5), α-muurulene (3.0) β-selinene (1.79-17.87), α-selinene (0.88-9.95), σ-cadinene (1.60-18.5), β- bisabolol (9.6-15.0), α-zingiberene (5.6), myrcene (6.1-45.3), γ-elemene(14), β-myrcene (10.99–89.32), trans-β-farnesene (10.59), γ-cadinene (5.5-21.7), α- pinene (37.4), β- pinene (41.6), α-copaene (14), β-bisabolene (29)
H. scandens	China	Stem, Aerial parts	Dibutyl phthalate (14.77), n-Hexadecanoic acid (6.29-13.99), 9,12,15-octadecatrienoic acid, (Z,Z,Z)- (12.33), 9,12-octadecadienoic acid (Z,Z)- (11.79), methyl palmitate (11.8), stigmasta-3,5-diene (8.75), (Z,Z)-octadeca-9, 12-dienoic acid (7.62), 9,12-octadecadienoic acid (Z,Z)-methyl ester (6.13), stigmastane-3,6-dione,(5à) (6.73), á-sitosterol (5.63), β-caryophyllene (49.37-97.03), β-myrcene (2.3-15.1), (E)-β-farnesene (96.4), δ-cadinene (78.7), caryophyllene epoxide (53.1)

6. Possible side effects of *Humulus* species

Previous studies have predominantly focused on the beneficial effects of medicinal and aromatic plants. However, it is imperative to acknowledge that these plants may induce unexpected adverse effects in humans and animals. A review of the literature revealed that *Humulus* species, particularly *H. lupulus* and *H. scandes*, are of significant interest. Notably, *H. lupulus* exhibits pharmacologically important adverse effects. It has been reported to cause allergic reactions, bronchial irritation, dry cough, and dyspnea in individuals with compromised immune systems [65-66]. Furthermore, hops used in alcohol production have been associated with respiratory disorders in workers due to increased total IgE levels [67]. In addition to these findings, *H. lupulus* has been implicated in dermatological effects [68].

7. Conclusions

The genus *Humulus*, particularly *Humulus lupulus* (hops), has long been valued in traditional medicine systems and is now increasingly supported by modern pharmacological research. This review demonstrates that *Humulus* species possess significant biological activities, including antioxidant, antimicrobial, anti-inflammatory, anticancer, antiviral, and insecticidal effects. These effects are largely attributed to key bioactive compounds such as β-caryophyllene, α-humulene, and xanthohumol, which have been shown to interact with molecular targets including cannabinoid receptors and inflammatory signaling pathways.

To clearly summarize the most impactful findings:

- Humulus species contain essential oils and flavonoids that exhibit strong antioxidant activity, helping to mitigate oxidative stress.
- Antimicrobial effects against resistant pathogens suggest potential for alternative natural antibiotics and preservatives.
- Insecticidal and allelopathic activities support their role in eco-friendly agricultural applications.
- Molecular mechanisms, particularly for β-caryophyllene and xanthohumol, involve anti-inflammatory and pro-apoptotic pathways.
- Traditional uses in areas such as sleep regulation and digestive support are increasingly validated by scientific evidence.

Despite these promising findings, important research gaps remain. In particular, more in vivo and clinical studies are required to confirm efficacy and determine safe dosage ranges. Standardization of extraction methods, and deeper investigation into bioavailability and pharmacokinetics, are essential to advance the therapeutic application of Humulus species. Additionally, future research should explore their incorporation into functional foods and nutraceutical products, and assess their large-scale cultivation from an ecological perspective.

In conclusion, Humulus species represent a promising natural resource with multifaceted applications in medicine, food, and agriculture. Strategic and interdisciplinary research efforts are needed to fully realize their potential in modern therapeutic and industrial contexts.

Author Contributions: This is a paragraph specifying the individual contributions to the article. The following statements should be used: Conceptualization, X.X. and Y.Y.; methodology, X.X.; validation, X.X., Y.Y. and Z.Z.; investigation, X.X.; resources, X.X.; data curation, X.X.; writing—original draft preparation, X.X.; writing—review and editing, X.X.; visualization, X.X.; supervision, X.X.; project administration, X.X.; funding acquisition, Y.Y. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Acknowledgments: None

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Sevindik, M., Akgul, H., Pehlivan, M. and Selamoglu, Z., Fresen Environ Bull, 2017, vol. 26, no. 7, pp. 4757-4763.
2. Mohammed, F. S., Günal, S., Şabik, A. E., Akgül, H. and Sevindik, M., Kahramanmaraş Sütçü İmam Üniversitesi Tarım ve Doğa Dergisi, 2020, vol. 23, no. 5, pp. 1114-1118.
3. Korkmaz, N., Dayangaç, A., Sevindik, M., Journal of Faculty of Pharmacy of Ankara University, 2021, vol. 45, no. 3, pp. 554-564.
4. Mohammed, F. S., Korkmaz, N., Doğan, M., Şabik, A. E., & Sevindik, M. (2021a). Some medicinal properties of Glycyrrhiza glabra (Licorice). Journal of Faculty of Pharmacy of Ankara University, 45(3), 524-534.
5. Alinkina, E. S., Vorobyova, A. K., Misharina, T. A., Fatkullina, L. D., Burlakova, E. B., & Khokhlov, A. N. (2012). Cytogerontological studies of biological activity of oregano essential oil. Moscow University biological sciences bulletin, 67, 52-57.
6. Sevindik, M., Uygun, A. E., Uysal, I., & Sabik, A. E. (2025). A Comprehensive Review on the Biological Activities, Usage Areas, Chemical and Phenolic Compositions of Lycium barbarum Used in Traditional Medicine Practices. Science and Technology Indonesia, 10(1):173-182
7. Mohammed, F. S., Akgul, H., Sevindik, M., & Khaled, B. M. T. (2018). Phenolic content and biological activities of Rhus coriaria var. zebaria. Fresenius Environmental Bulletin, 27(8), 5694-5702.
8. Sevindik, M., Gürgen, A., Krupodorova, T., Uysal, İ., & Koçer, O. (2024). A hybrid artificial neural network and multi-objective genetic algorithm approach to optimize extraction conditions of Mentha longifolia and biological activities. Scientific Reports, 14(1), 31403.
9. Sevindik, M., Uysal, İ., Sevindik, E., Krupodorova, T., Koçer, O., & Ünal, O. (2024). Citrullus colocynthis (Bitter-apple): a comprehensive review on general properties, biological activities, phenolic and chemical contents. Notulae Scientia Biologicae, 16(4), 12202-12202.
10. Mohammed, F. S., Karakaş, M., Akgül, H., & Sevindik, M. (2019). Medicinal properties of Allium calocephalum collected from Gara Mountain (Iraq). Fresen Environ Bull, 28(10), 7419-7426.
11. Sim, L. Y., Abd Rani, N. Z., & Husain, K. (2019). Lamiaceae: An insight on their anti-allergic potential and its mechanisms of action. Frontiers in pharmacology, 10, 677.
12. Uysal, I., Sevindik, M., Dogan, M., Mohammed, F. S., Seğmenoğlu, M. S., & Pehlivan, M. (2024). Biological Activities, Phenolic Contents and Chemical Compositions of Essential Oils and Different Extracts of Origanum laevigatum. Pharmaceutical Chemistry Journal, 58(8), 1289-1297.
13. Gürgen, A., Sevindik, M., Krupodorova, T., Uysal, I., & Unal, O. (2024). Biological activities of Hypericum spectabile extract optimized using artificial neural network combined with genetic algorithm application. BMC biotechnology, 24(1), 83.
14. Mohammed, F. S., Pehlivan, M., Sevindik, E., Akgul, H., Sevindik, M., Bozgeyik, I., & Yumrutas, O. (2021b). Pharmacological properties of edible Asparagus acutifolius and Asparagus officinalis collected from North Iraq and Turkey (Hatay). Acta Alimentaria, 50(1), 136-143.
15. Unal, O., Eraslan, E. C., Uysal, I., Mohammed, F. S., Sevindik, M., & Akgul, H. (2022). Biological activities and

phenolic contents of Rumex scutatus collected from Turkey. Fresenius Environmental Bulletin, 31(7), 7341-7346.

16. Ayenew, K. D., & Wasihun, Y. (2023). Hepatoprotective effect of methanol extract of Agave americana leaves on paracetamol induced hepatotoxicity in Wistar albino rats. BMC Complementary Medicine and Therapies, 23(1), 1-8.

17. Laha, A., Sarkar, A., Chakraborty, P., Panja, A. S., & Bandopadhyay, R. (2023). Efficacy screening of prospective anti-allergic drug candidates: An in silico study. Current Bioinformatics, 18(2), 143-153.

18. Yazar, M., Sevindik, M., Polat, A. O., Koçer, O., Karatepe, H. K., & Uysal, İ. (2024). General properties, biosynthesis, pharmacological properties, biological activities and daily uses of luteolin. Prospects in Pharmaceutical Sciences, 22(4), 146-154.

19. Uysal, I., Koçer, O., Mohammed, F. S., Lekesiz, Ö., Doğan, M., Şabik, A. E., Sevindik, E., Gerçeker, F.O., & Sevindik, M. (2023). Pharmacological and Nutritional Properties: Genus Salvia. Advances in Pharmacology and Pharmacy, 11(2): 140-155

20. Mohammed, F. S., Sevindik, M., Uysal, İ., Çesko, C., & Koraqi, H. (2024). Chemical Composition, Biological Activities, Uses, Nutritional and Mineral Contents of Cumin (Cuminum cyminum). Measurement: Food, 100157.

21. Moir, M. (2000). Hops—a millennium review. Journal of the American Society of Brewing Chemists, 58(4), 131-146.

22. Zanoli, P., Zavatti, M. (2008). Pharmacognostic and pharmacological profile of Humulus lupulus L. Journal of ethnopharmacology, 116(3), 383-396.

23. Dostálek, P., Karabín, M., Jelínek, L. (2017). Hop phytochemicals and their potential role in metabolic syndrome prevention and therapy. Molecules, 22(10), 1761.

24. Girisa, S., Saikia, Q., Bordoloi, D., Banik, K., Monisha, J., Daimary, U. D., Kunnumakkara, A. B. (2021). Xanthohumol from Hop: Hope for cancer prevention and treatment. IUBMB life, 73(8), 1016-1044.

25. Korpelainen, H., Pietiläinen, M. (2021). Hop (Humulus lupulus L.): Traditional and present use, and future potential. Economic botany, 1-21.

26. Mohammed, F. S., Günal, S., Pehlivan, M., Doğan, M., Sevindik, M., & Akgül, H. (2020b). Phenolic content, antioxidant and antimicrobial potential of endemic Ferulago platycarpa. Gazi University Journal of Science, 33(4), 670-677.

27. Mohammed, F. S., Kına, E., Sevindik, M., Doğan, M., & Pehlivan, M. (2021c). Antioxidant and antimicrobial activities of ethanol extract of Helianthemum salicifolium (Cistaceae). Indian Journal of Natural Products and Resources (IJNPR)[Formerly Natural Product Radiance (NPR)], 12(3), 459-462.

28. Bhattacharya, S., Virani, S., Zavro, M., Haas, G. J. (2003). Inhibition ofStreptococcus mutans and Other Oral streptococci by hop (Humulus lupulus L.) constituents. Economic Botany, 57(1), 118-125.

29. Frölich, S., Schubert, C., Bienzle, U., Jenett-Siems, K. (2005). In vitro antiplasmodial activity of prenylated chalcone derivatives of hops (Humulus lupulus) and their interaction with haemin. Journal of Antimicrobial Chemotherapy, 55(6), 883-887.

30. Gerhäuser, C. (2005). Broad spectrum antiinfective potential of xanthohumol from hop (Humulus lupulus L.) in comparison with activities of other hop constituents and xanthohumol metabolites. Molecular nutrition & food research, 49(9), 827-831.

31. Luzak, B., Golanski, J., Przygodzki, T., Boncler, M., Sosnowska, D., Oszmianski, J., Rozalski, M. (2016). Extract from spent hop (Humulus lupulus L.) reduces blood platelet aggregation and improves anticoagulant activity of human endothelial cells in vitro. Journal of functional Foods, 22, 257-269.

32. Cermak, P., Olsovska, J., Mikyska, A., Dusek, M., Kadleckova, Z., Vanicek, J., Bostik, P. (2017). Strong antimicrobial activity of xanthohumol and other derivatives from hops (Humulus lupulus L.) on gut anaerobic bacteria. Apmis, 125(11), 1033-1038.

33. Kobus-Cisowska, J., Szymanowska-Powałowska, D., Szczepaniak, O., Kmiecik, D., Przeor, M., Gramza-Michałowska, A., Szulc, P. (2019). Composition and in vitro effects of cultivars of Humulus lupulus L. hops on cholinesterase activity and microbial growth. Nutrients, 11(6), 1377.

34. Sangiovanni, E., Fumagalli, M., Santagostini, L., Forino, M., Piazza, S., Colombo, E., Dell'Agli, M. (2019). A bio-guided assessment of the anti-inflammatory activity of hop extracts (Humulus lupulus L. cv. Cascade) in human gastric epithelial cells. Journal of Functional Foods, 57, 95-102.

35. Paventi, G., de Acutis, L., De Cristofaro, A., Pistillo, M., Germinara, G. S., Rotundo, G. (2020). Biological activity of Humulus lupulus (L.) essential oil and its main components against Sitophilus granarius (L.). Biomolecules, 10(8), 1108.

36. Arruda, T. R., Pinheiro, P. F., Silva, P. I. and Bernardes, P. C., LWT, 2021, vol. 141, pp. 110905.

37. Macchioni, V., Carbone, K., Cataldo, A., Fraschini, R., Bellucci, S. (2021). Lactic acid-based deep natural eutectic solvents for the extraction of bioactive metabolites of Humulus lupulus L.: Supramolecular organization, phytochemical profiling and biological activity. Separation and Purification Technology, 264, 118039.

38. Ovidi, E., Laghezza Masci, V., Taddei, A. R., Torresi, J., Tomassi, W., Iannone, M., Garzoli, S. (2022). Hemp (Cannabis sativa L., kompolti cv.) and hop (Humulus lupulus L., chinook cv.) essential oil and hydrolate: HS-GC-MS chemical investigation and apoptotic activity evaluation. Pharmaceuticals, 15(8), 976.

39. Sun, T., Wang, F., Wang, J., Wang, L., Sun, Y. (2012). Insecticidal activity of different solvent extracts and partitioned extracts from Humulus scandens. Journal of Plant Resources and Environment, 21(2), 64-67.

40. Wang, L., Liu, Y., Zhu, X., Zhang, Z., Huang, X. (2021). Identify potential allelochemicals from Humulus scandens (Lour.) Merr. root extracts that induce allelopathy on Alternanthera philoxeroides (Mart.) Griseb. Scientific reports, 11(1), 1-8.

41. Zhang, D., Tan, L. H., Feng, Y. J., Yao, L., Yan, X. W., Cao, W. G. (2021). Evaluation of antioxidant, anti-inflammatory activity and identification of active compounds of Humulus scandens. South African Journal of Botany, 141, 126-132.

42. Krupodorova, T., & Sevindik, M. (2020). Antioxidant

potential and some mineral contents of wild edible mushroom Ramaria stricta. AgroLife Scientific Journal, 9(1), 186-191.

43. Bal, C., Sevindik, M., Akgul, H., & Selamoglu, Z. (2019). Oxidative stress index and antioxidant capacity of Lepista nuda collected from Gaziantep/Turkey. Sigma Journal of Engineering and Natural Sciences, 37(1), 1-5.

44. Selamoglu, Z., Sevindik, M., Bal, C., Ozaltun, B., Sen, İ., & Pasdaran, A. (2020). Antioxidant, antimicrobial and DNA protection activities of phenolic content of Tricholoma virgatum (Fr.) P. Kumm. Biointerface Research in Applied Chemistry, 10 (3), 5500-5506

45. Saridogan, B. G. O., Islek, C., Baba, H., Akata, I., & Sevindik, M. (2021). Antioxidant antimicrobial oxidant and elements contents of Xylaria polymorpha and X. hypoxylon (Xylariaceae). Fresenius Environmental Bulletin, 30(5), 5400-5404.

46. Eraslan, E. C., Altuntas, D., Baba, H., Bal, C., Akgül, H., Akata, I., & Sevindik, M. (2021). Some biological activities and element contents of ethanol extract of wild edible mushroom Morchella esculenta. Sigma Journal of Engineering and Natural Sciences, 39(1), 24-28.

47. Sevindik, M. (2021). Anticancer, antimicrobial, antioxidant and DNA protective potential of mushroom Leucopaxillus gentianeus (Quél.) Kotl. Indian Journal of Experimental Biology (IJEB), 59(05), 310-315.

48. Mohammed, F. S., Uysal, I., & Sevindik, M. (2023). A Review on Antiviral Plants Effective Against Different Virus Types. Prospects in Pharmaceutical Sciences, 21(2), 1-21.

49. Bal, C., Akgul, H., Sevindik, M., Akata, I., & Yumrutas, O. (2017). Determination of the anti-oxidative activities of six mushrooms. Fresenius Envir Bull, 26(10), 6246-6252.

50. Islek, C., Saridogan, B. G. O., Sevindik, M., & Akata, I. (2021). Biological activities and heavy metal contents of some Pholiota species. Fresenius Environmental Bulletin, 30(6), 6109-6114.

51. Katsiotis, S. T., Langezaal, C. R., Scheffer, J. J. C., Verpoorte, R. (1989). Comparative study of the essential oils from hops of various Humulus lupulus L. cultivars. Flavour and fragrance journal, 4(4), 187-191.

52. Malizia, R. A., Molli, J. S., Cardell, D. A., Grau, R. J. (1999). Essential oil of hop cones (Humulus lupulus L.). Journal of Essential Oil Research, 11(1), 13-15.

53. Patzak, J., Matoušek, J., Krofta, K., Svoboda, P. (2001). Hop latent viroid (HLVd)-caused pathogenesis: effects of HLVd infection on lupulin composition of meristem culture-derived Humulus lupulus. Biologia plantarum, 44(4), 579-585.

54. Bernotienë, G., Nivinskienë, O., Butkienë, R., Mockutë, D. (2004). Chemical composition of essential oils of hops (Humulus lupulus L.) growing wild in Aukstaitija. Chemija, 15(2), 31-36.

55. Jirovetz, L., Bail, S., Buchbauer, G., Denkova, Z., Slavchev, A., Stoyanova, A., Geissler, M. (2006). Antimicrobial testings, gas chromatographic analysis and olfactory evaluation of an essential oil of hop cones (Humulus lupulus L.) from Bavaria and some of its main compounds. Scientia Pharmaceutica, 74(4), 189.

56. Ligor, M., Stankevičius, M., Wenda-Piesik, A., Obelevičius, K., Ragažinskienė, O., Stanius, Ž., Buszewski, B. (2014). Comparative gas chromatographic–mass spectrometric evaluation of hop (Humulus lupulus L.) essential oils and extracts obtained using different sample preparation methods. Food analytical methods, 7(7), 1433-1442.

57. Tyśkiewicz, K., Gieysztor, R., Konkol, M., Szałas, J., Rój, E. (2018). Essential oils from Humulus lupulus scCO2 extract by hydrodistillation and microwave-assisted hydrodistillation. Molecules, 23(11), 2866.

58. da Rosa Almeida, A., Maciel, M. V. D. O. B., Cardoso Gasparini Gandolpho, B., Machado, M. H., Teixeira, G. L., Bertoldi, F. C., Barreto, P. L. M. (2021). Brazilian grown cascade hop (Humulus Lupulus L.): LC-ESI-MS-MS and GC-MS analysis of chemical composition and antioxidant activity of extracts and essential oils. Journal of the American Society of Brewing Chemists, 79(2), 156-166.

59. Jın F., Zhao L., Zhang Y., Wu J., Peng X. (2014). Analysis of Volatile Chemical Constituents of Dried and Fresh Humulus scandens in Guizhou by HS-SPMEGC-MS. China Pharmacy, 25(31), 2931-2934.

60. Peng, X., Shao, J., Liu, B., Zhang, F., Jin, F., Wu, J. (2014). Volatile oil composition and content in different parts of fresh Guizhou Humulus scandens. Guizhou Agricultural Sciences, 42(4), 178-181.

61. Fidyt, K., Fiedorowicz, A., Strządała, L., & Szumny, A. (2016). β-caryophyllene and β-caryophyllene oxide—natural compounds of anticancer and analgesic properties. Cancer medicine, 5(10), 3007-3017.

62. Francomano, F., Caruso, A., Barbarossa, A., Fazio, A., La Torre, C., Ceramella, J., ... & Sinicropi, M. S. (2019). β-Caryophyllene: a sesquiterpene with countless biological properties. Applied sciences, 9(24), 5420.

63. de Lacerda Leite, G. M., de Oliveira Barbosa, M., Lopes, M. J. P., de Araújo Delmondes, G., Bezerra, D. S., Araújo, I. M., ... & Kerntof, M. R. (2021). Pharmacological and toxicological activities of α-humulene and its isomers: A systematic review. Trends in Food Science & Technology, 115, 255-274.

64. Surendran, S., Qassadi, F., Surendran, G., Lilley, D., & Heinrich, M. (2021). Myrcene—what are the potential health benefits of this flavouring and aroma agent?. Frontiers in nutrition, 8, 699666.

65. Meznar, B., Kajba, S. (1990). Bronchial responsiveness in hops processing workers. Plucne Bolesti: Casopis Udruzenja Pneumoftiziologa Jugoslavije= the Journal of Yugoslav Association of Phthisiology and Pneumology, *42*(1-2), 27-29.

66. Skórska, C., Mackiewicz, B., Góra, A., Golec, M., Dutkiewicz, J. (2003). Health effects of inhalation exposure to organic dust in hops farmers. In Annales Universitatis Mariae Curie-Sklodowska. Sectio D: Medicina, 58(1), 459-465.

67. Godnic-Cvar, J., Zuskin, E., Mustajbegovic, J., Schachter, E. N., Kanceljak, B., Macan, J., Ebling, Z. (1999). Respiratory and immunological findings in brewery workers. American journal of industrial medicine, 35(1), 68-75.

68. Spiewak, R., Dutkiewicz, J. (2002). Occupational airborne and hand dermatitis to hop [Humulus lupulus] with non-occupational relapses. Annals of Agricultural and Environmental Medicine, 9(2).