

Review Article

HUMULUS SPECIES: A TRADITIONAL MEDICINAL PLANT AND ITS MODERN PHARMACOLOGICAL IMPORTANCE

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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.

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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 was 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 also 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 display the biological activity studies of *Humulus* species.

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

Plant species	Biological activities	Extraction	Country of publication (as reported)
<i>H. lupulus</i>	Antimicrobial, antioxidant, pesticide, antiviral, anticholinesterase, anti-inflammatory, apoptotic, antiparasitodal, anticoagulant	Ethanol, water, essential oil, methanol, hydroalcoholic	Brazil, Czech Republic, Italy, USA, Germany, Poland, Australia
<i>H. scandens</i>	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 scavenging values of ethanol and water extracts of *H. lupulus* were reported as 24.11-43.66 $\mu\text{mol/g}$, and ABTS scavenging values were reported as 58.21-165.13 $\mu\text{mol/g}$ [36]. In a study conducted in Italy with methanol extract, DPPH scavenging values were determined as 69-220 μg and ABTS scavenging 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 $\mu\text{g/mL}$ and minimum bactericidal concentration (MBC) values were between 0.096-8.65 $\mu\text{g/mL}$ [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 $\mu\text{g/mL}$ [32]. In a study conducted in Italy, it was reported that methanol extract formed zone diameters ranging 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 2-50 $\mu\text{g/mL}$ [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 $\mu\text{g/adult}$ [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 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, 8-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- κ B, 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.

Table 2. Compounds of *Humulus* species [40, 51-60].

Plant species	Country of publication (as reported)	Used Parts	Compounds (%)
<i>H. lupulus</i>	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-murolene (0.84-18.5), α-murolene (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)
<i>H. scandens</i>	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, (5α) (6.73), β-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)

According to the studies conducted, it has been reported that the main components of the volatile oil of the *H. lupulus* species are β-caryophyllene (4.52-29%), α-bergamotene (0.15-4.36%), α-humulene (3-37.14%), β-farnesene (0.75-20.60%), γ-murolene (0.84-18.5%), α-murolene (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, (5α) (6.73%), β-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.

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. scandens*, 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 increasing 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 B-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 B-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.

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