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Review

Hop By-Products: Pharmacological Activities and Potential Application as Cosmetics

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Abstract: Hops (*Humulus lupulus* L.) are known worldwide as a raw material in beer production due their flavor and preservative values. The beneficial properties of the plant have been mostly associated with the female hop inflorescences (cones), which is also the part used in the brewing industry. However, some studies indicate the presence of compounds associated with health benefits in the vegetative parts of hops or small-caliber cones, which discarded in hop collection. Moreover, large quantities of by-products remain in the forms of spent grains and spent hops/hot trub and are produced by breweries raising environmental and economic sustainability concerns. This review focuses on the phytochemicals and biological and pharmacological activities of hop and their potential use in skin care products and also intends to explore the potential of the hop' discarded parts and brewery industry by-products for production in the cosmetics industry.

Keywords: *Humulus lupulus* L.; hop; cosmetic; waste valorization; innovative functional ingredients; antioxidant activity; anti-inflammatory activity; antimicrobial activity

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1. Introduction

The *Humulus lupulus* L. (hop) plant is dioecious (i.e., the male and female flowers usually develop on separate plants); occasional fertile monoecious individual plants have been reported. For brewing beer, viable seeds are undesirable; therefore, only female plants are grown in hops fields to prevent pollination. Female plants are propagated vegetatively, and male plants are culled if plants are grown from seeds. Under natural conditions, the flowers are wind pollinated and the female inflorescence develops to form a strobile (or cone). The strobiles of the female plants are able to develop the lupulin glands that secrete a fine yellow resinous powder. These glands secrete predominantly bitter acids and essential oils, the constituents of which include prenylflavonoids [1,2].

In Europe, there is evidence of the use of *H. lupulus* since prehistoric times. The ancient Romans employed its leaves and inflorescences in some food preparations as well as in textiles and cosmetic products [2]. Afterwards, the use of hop rapidly increased in the Middle Ages, presumably because of their developed utilization in the brewing process. Cultivation of hop began in the mid-ninth century AC in Germany, then spread throughout the Central Europe [3].

According to the latest Food and Agriculture Organization (FAO) estimates, the global area devoted to hop cultivation was around 65,500 ha in 2019, with a production that exceeded 130,000 tons. The European continent contributed decisively to this production, with a volume of almost 68,000 tons, representing 52% of the world hops production [4].

Hop plants are grown almost exclusively for the brewing industry, in which the resins and essential oils from female cones are used for aroma [5]. Female hop flowers, also known as cones or hops, are primarily used in brewing beer; most of the bitter flavor and

characteristic zesty beer aromas arise from hop cones added at various points during wort boiling, secondary fermentation, and the aging process [6]. At harvest, one-third is valuable product (hop cones) and two-thirds is leftover biomass, consisting primarily of leaves, stems, and unremoved hop cones [7].

However, the plant has been well-known for its beneficial properties for human health since ancient times. This is due to the plethora of its bioactive compounds (bitter acids, prenyl chalcones, polyphenols, terpenoids, etc.), which are mainly associated with the female inflorescences [8]. On addition to the application in the brewing industry, hop have for a long time been used for various medicinal purposes [9,10]. The beneficial effects of hop polyphenols in various chronic diseases, such as insomnia, inflammation, diabetes, as well as in menopause and as antifungal, have been scientifically proven in many studies [11,12]. In recent years, the antioxidant and anti-inflammatory activities of hop extracts have attracted attention and have been widely studied [9,13].

In order to fill the void in knowledge, the present review provides insight into the valorization of high-volume brewery by-products as well as of leaves, stems, and small-caliber cones, which are commonly discarded in the hops harvest, and we also explore their potential use in cosmetics.

2. Materials and Methods

PubMed, Web of Science (WOS), and Scopus databases were used to perform this review. The keywords used were "*Humulus lupulus*", "hop", "hops", "hops AND waste", "hops by-products", "hops AND bioactivity", "hops AND antioxidant", "hops AND anti-inflammatory", "hops AND antimicrobial", "hops AND cosmetic". We obtained 638 documents with full text access that were published in the last 10 years: 235 in PubMed, 386 in WOS, and 17 in Scopus. Two documents from 2007 and 2009 were added due their relevance to the review. After elimination of duplicates, the documents were selected based on the title, the abstract, and whenever necessary, by reading the whole document, which resulted in 51 documents, including articles, review articles, book chapters and a monograph.

3. Results and Discussion

3.1. By-Products of H. lupulus

Millions of tons of residues are produced in the brewing process. On other hand, large amounts of vegetal material such as leaves, stems, and small-caliber cones are discarded in the harvest process. The recovery or extraction of high-value bioactive compounds from the by-products or non-used parts of *H. lupulus* in the brewing industry has been a strategy emphasized by the recent literature in order to solve this ecological and economical issue [14–16]. In fact, the by-products and parts of the plant discarded in the hops harvest are a source of potential nutritional and pharmacological compounds that could be used as functional and cosmetic ingredients [17]. The traditional methods using organic solvents have concerns related to the environment and also related to health. Still, new eco-friendly extraction methods should be developed to increase the yield and the selectivity of the compounds [14]. Natural, deep eutectic solvents and emerging extraction technologies such as ultrasound-assisted, microwave-assisted, pressurized liquid, and supercritical fluid extraction are emerging solutions to the sustainable extraction and isolation of natural compounds [2,18].

Many components of the hop by-products of interest are proteins, carbohydrates, fiber, phenolic compounds, vitamins, or minerals that have been explored for applications in the food industry [14,16] but less so for the development of skin care products.

3.1.1. Brewery By-Products

Generally, in beer production, chemical and biochemical reactions occur and the process involves the main stages of malting, mashing, lautering, boiling, fermenting, conditioning, filtering, and bottling [14]. During this process, spent grains, spent hops/hot trub, and spent

yeast are produced (Figure 1), constituting the main marketable by-products with potential interest for the food, pharmaceutical, cosmetics, agriculture, and chemical industries.

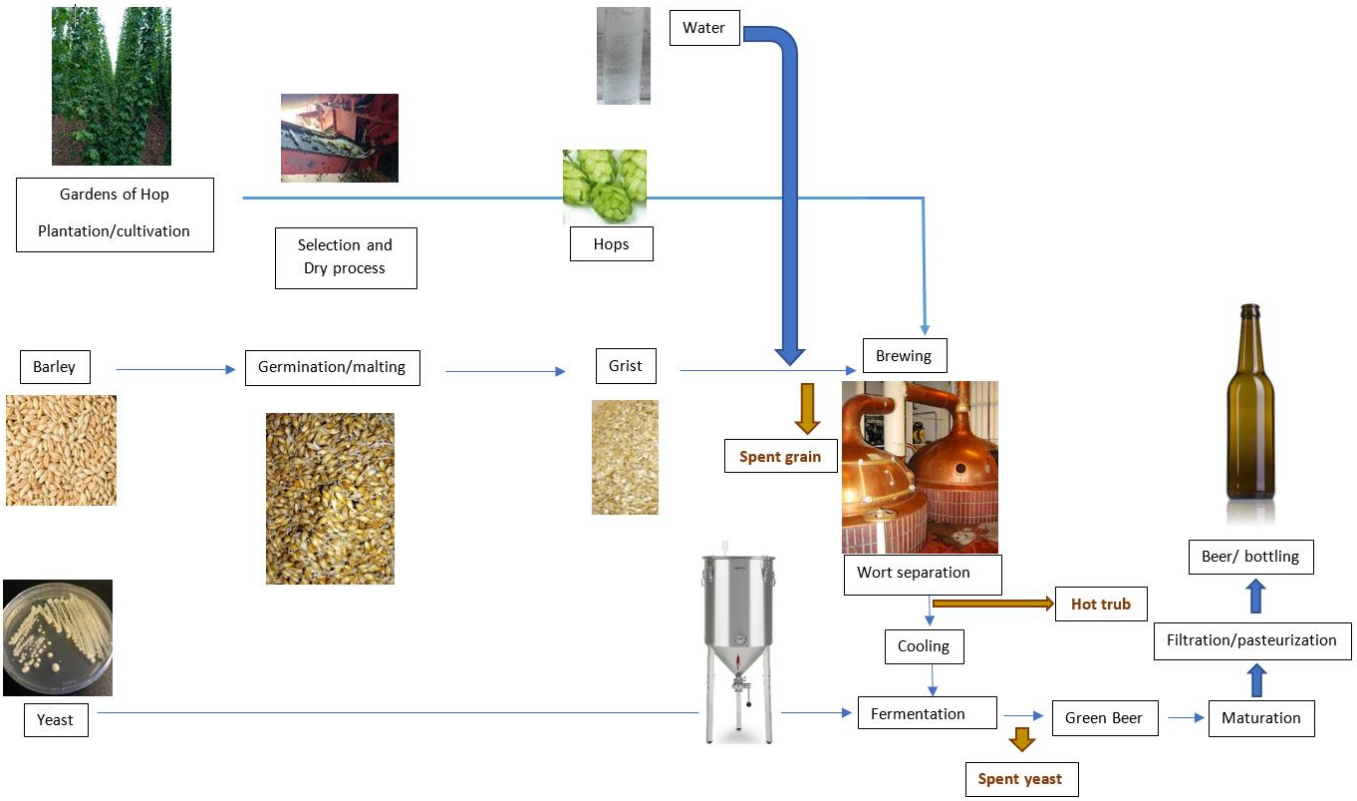

Figure 1. By-products generated in brewing process. Adapted from [14,16].

Spent brewer's grain is formed after the malt mashing process, and in some brewing regimens, some residues of hops are introduced during mashing. Spent brewer's grain is the main solid brewery by-product (accounting for approx. 85% of all residues) which can be used wet and dry as direct animal feed or for further preparation of silage, both used specially for cattle but also for poultry, pigs, goats, and as fish food [14], and less frequently, it is used in human food [19]. Even so, large amounts of spent brewer's grain are discarded despite it being rich in valuable compounds such as proteins (more than 20%), fiber, lipids and fatty acids, carbohydrates, polyphenols (mainly hidroxycinnamic acids), and minerals. In addition to that, it enhances aroma-binding properties and has gelling, emulsifying, and film-forming properties [19].

Approximately 85% of the hops constituents used by beer production become spent hop material. The hot trub are insoluble sediments formed during the wort boiling process [14].

These hops by-products (spent hops or hot trub) have been used as a fertilizer due to the high nitrogen content, as a low-grade fuel, and for animal feed when mixed with spent grain [20].

Although currently the possible markets for spent hops are restricted, hops constitute a by-product rich in interesting compounds such as proteins, lipids, polyphenols, minerals, flavors, carbohydrates, and organic acids [21].

Spent yeast is the second largest by-product from the brewing industry and is obtained after filtration or centrifuging. Originally applied as baker's yeast, currently it is used as fertilizer and as a feedstock for fuel and industrial ethanol production and mixed with spent brewers' grain as a feed material [22].

The chemical composition of spent yeast includes carbohydrates, free amino acids, ash, vitamins and minerals, and fatty acids; it also constitutes an excellent source of high-quality protein [22].

3.1.2. Non-Recovered Parts of *H. lupulus*

As only the hop cones have been used in the beer making industry, hop leaves are an agricultural by-product currently discarded as waste (like the stems and small-caliber cones that are discarded in the hop harvest process) [6].

Leaf sampling from wild-growing hop plants is a far simpler task than collecting cones, which are located up to 10 m off the ground in heavily wooded and overgrown areas and are only present late in the growing season. Additionally, male hop plants do not generate cones. Hop leaves are composed of flavanol glycosides (quercetin and kaempferol derivatives) ranging in total concentration from 0.28% to 2.77% dw (quercetin-3-*O*-rutinoside equivalents), although the total values are highly dependent on the phenological development stage, sampling date, and physical location [6]. The work of Macchioni et al. [4] showed the presence of significant quantities of soluble polyphenolic compounds and antioxidant pigments in the non-phenolic fraction of hop leaves.

3.2. Bioactivity of H. lupulus

3.2.1. Antioxidant Effects

Hop flavonoids xanthohumol, quercetin, and kaempferol are most responsible for the antioxidant properties of hop [9]. The total phenolic and antioxidant activities of hop extracts are generally determined by well-established methods.

The *H. lupulus* extracts have been explored for a range of biological effects, including antioxidant ability. Studies compiling such criteria are summarized in Table 1.

Acetone extract of cones cultivated in the Czech Republic showed good in vitro antioxidant and anti-adipocyte effects and are dependent on different polyphenols that vary with the time and year of harvest. Concerning individual compounds, the highest percentage of antioxidant capacity, determined with the DPPH radical method among compounds present in hop cones, was demonstrated for procyanidin B2, while xanthohumol showed the highest anti-NO production activity and isorhamnetin showed the best anti-adipocyte differentiation effects [11].

The Cascade variety of hop was also investigated by antioxidant activity using DPPH and ORAC methods. In detail, the study was performed to measure the impact of copper-based fungicides on the antioxidant quality of polar hops extracts (Cascade var.) observed no differences between hops treatments with copper (II) hydroxide [23].

Phenolic-enriched extracts obtained from pellets were also investigated for antioxidant effect by Wu at al. (2020). Ethanolic extracts have shown better antioxidant effects than hot water extracts in DPPH, TEAC, and reducing power assays, which were attributed to higher total phenolic and/or flavonoid compounds [13]. Similar conclusions have been drawn after antioxidant experiments with three Poland hop cultivars. The cones of Magnum demonstrated higher antioxidant activity, which is consistent with the higher phenolic acids and flavonol contents [24].

Table 1. Antioxidant activities of hop extracts.

Hop Variety/Part of Plant	Solvent Extraction (Compounds)	Methods/Studied Effects	Results of Assay	Ref.
Saaz hops/cones	Acetone/water (70:30, *v*/*v*) (polyphenols)	In vitro DPPH	DPPH (% of inhibition) = 45–60 (at 25 µg/mL)	[11]
Cascade var./cones	Aqueous ethanol (80:20 *v*/*v*)	In vitro DPPH ORAC	DPPH (µmol Trolox/g extract): 1.47 ± 0.11 (control), 1.50 ± 0.11 (low copper), 1.52 ± 0.14 (high copper) ORAC (µmol Trolox/g extract): 501.4 ± 45.69 (control), 490.7 ± 61.79 (low copper) and 491.3 ± 33.03 (high copper)	[23]
Pellets/cones	Hops hot water (HWE); Hops ethanol (HEE) (polyphenols, flavonoids)	In vitro DPPH TEAC RP	DPPH, IC_{50} (µg mL^{-1}): 93.12 (95% HEE) TEAC, IC_{50} (µg mL^{-1}): 948.55 (55% HEE); 956.43 (95% HEE); RP, %: 8.78 (55% HEE)	[13]
Magnum var. (M), Lubelski var. (L), and Marynka var. (Ma)/cones	Hot water and aqueous ethanol (60:40) (*v*/*v*) extracts (Phenolic acids, epicatechin and rutin)	In vitro Chelating activity DPPH ABTS	Chelating activity (%): ~90 for M ethanol extract at 2000 ppm DPPH (EC_{50}, µg/mL): 0.31, 0.38 and 0.44 for L, Ma, and L water extracts, respectively ABTS (EC_{50}, µg/mL): 0.92, 0.93, and 0.99 for M, L and Ma ethanol extracts, respectively	[24]
Aurora var. and Hallertauer Magnum var./leaves and cones	Ethanol extracts	In vitro DPPH FRAP	DPPH (IC_{50} mg/mL): ~0.01–0.043 (leaves); ~0.005–0.017 (cones) FRAP (mL µgferric ions): 0.055–0.2 (leaves); 0.05–0.33 (cones)	[25]
Young hop shoots	Methanol (flavonol glycosides)	In vitro DPPH Photochemiluminescence assay (PCL-ACL)	DPPH: 0.3–0.5 mg Trolox equivalents/g PC–L-ACL: 1.1–0.7 mg Trolox equivalents/g	[26]
Brewing spent grains (BSGs), Brewing spent hops (BSH)	Spent grains (phenolic acids), Spent hop (phenolic acids)	In vitro FRAP DPPH ABTS	FRAP, DPPH, ABTS (EC_{50}, g/L) BSG-IRA: 7.00, 23.09 and 8.52, respectively BSG-BSA: 5.18, 11.61 and 4.67, respectively BSH-IRA: 7.28, 12.35 and 5.40, respectively BSH-BSA: 6.11, 9.14 and 4.38, respectively	[21]

Table 1. *Cont.*

Hop Variety/Part of Plant	Solvent Extraction (Compounds)	Methods/Studied Effects	Results of Assay	Ref.
Cones	Aqueous ethanol (60:40) *v*/*v* (Proanthocyanidins, flavonoid glycosides, xanthohumol)	In vitro DPPH •OH- O_2•$^-$ DNA oxidative damage In vivo TBARS, SOD and GSH-Px activity in mouse liver	DPPH, •OH-, O_2•$^-$ (IC_{50} (μg mL^{-1}): 6.7, 34.0, and 690.0, respectively DNA oxidation damage: inhibited by extract TBARS (nmol mg^{-1} protein): 8.73 (HPE200), 6.20 (HPE400), 5.93 (HPE800) SOD (U mg^{-1} protein): 630.9 (HPE200), 658.9 (HPE400), 686.6 (HPE800) GSH-Px (U mg^{-1} protein): 657.1 (HPE200), 822.0 (HPE400), 838.3 (HPE800)	[27]
Cones	Supercritical hop CO_2-extract (Humulone, lupulone)	In vitro Irradiated human primary keratinocytes (HPKs)	↓ formation of ROS-induced dichlorofluorescein IC_{50} (μg/mL) = 29.43	[28]
Chinook var., Centennial var., Comet var., Columbus var., Cascade var./Leaves	Ethanol (oven drying (OD) at 45 °C and freeze-drying (FD))	In vitro DPPH ABTS	DPPH (EC_{50}, μg/mL) = 103–291 μg mL^{-1} (Chinook var. FD and Columbus var. OD, respectively) ABTS (EC_{50}, μg/mL): 1.15–15.6 μg mL^{-1} (Columbus var. FD and Comet var. OD, respectively)	[4]
Hop by-products	Water and aqueous ethanol (30:70) (*v*/*v*)	In vitro DPPH, FRAP, ABTS keratinocytes HaCaT cells	Spent malt: DPPH (μmol TE/g): 10.24 ± 1.35 (ethanol extract, Maior); ABTS (μmol TE/g): 21.72 ± 2.16 (ethanol extract, Alter); FRAP (μmol TE/g): 67.71 ± 1.44 (Water extract, Ego) Spent hops: DPPH (μmol TE/g): 7.579 ± 0.436 (ethanol extract, Ego); ABTS (μmol TE/g): 8.26 ± 1.32 (water extract, Ego); FRAP (μmol TE/g): 102.66 ± 3.99 (water extract, Ego) Spent yeast: DPPH (μmol TE/g): 58.68 ± 11.57 (ethanol extract, Ubi); ABTS (μmol TE/g): 51.31 ± 3.05 (water extract, Triplo malto); FRAP (μmol TE/g): 136.72 ± 2.91 (water extract, ubi) HaCaT cells: decrease mitochondrial activity; reduction of intracellular ROS formation	[29]

ABTS—2.20-azino-bis-(3-ethylbenzothiazoline-6-sulphonic acid) radical scavenging assay; BSGs—brewing spent grains; BSH—brewing spent hop; BSA—Belgian strong ale beers; DPPH—2.2-diphenyl-1-picrylhydrazyl radical scavenging assay; EC_{50}—Half-maximal effective concentration; FRAP—ferric reducing antioxidant power; FD—freeze-drying; GSH-Px—gglutathione peroxidase; HPKs—human primary keratinocytes; HWE—hops water extract; HEE—hops ethanol extract; IC_{50}—Half-maximal inhibitory concentration; IRA—brewing of imperial red ale beer; PCL-ACL—photochemiluminescence assay; TBARS—thiobarbituric acid reactive substances assay; SOD—superoxide dismutase; •OH—hydroxyl radical scavenging assay; O_2•$^-$ superoxide radical scavenging assay; ORAC—oxygen radical absorbance capacity; OD—oven-drying; RP—reducing power; ROS—reactive oxygen species; TE—Trolox equivalent; TEAC—Trolox equivalent absorbance capacity; TPA—12-OTetradecanoylphorbol-13-acetate; ↓—decrease.

Despite most studies being carried out on cones, there are some experiments performed with the non-recovered parts of *H. lupulus* and with brewery by-products. In more detail, hop young shoots from northern regions of Italy, composed of quercetin and kaempferol glycosides, have been studied in terms of antioxidant activity by means of PCL-ACL and DPPH assays. Vicchio hop shoot samples had the greatest number of antioxidants, followed by Santa Maria in Punta and Cologna. In addition, the data regarding antioxidant activity have a good correlation with the total flavonol content (r2 of 0.9577) [26].

The antioxidant properties of hop leaf were investigated for ethanolic extracts, concluding that the antioxidant activity was lower for leaves than for hop cones [25]. An antioxidant study performed on the leaves of four varieties of hop showed the best antioxidant activities for freeze-dried extracts of Chinook var. and Columbus varieties and for oven-dried extracts of Columbus and Comet varieties [4].

On the other hand, the brewing by-products, spent grains, and spent hops have shown high antioxidant activity and the authors attributed the effect to the content of the phenolic compounds, mainly in Belgian strong ale samples [21].

Hop cones extracts rich in polyphenols, such as proanthocyanidins, flavonoid glycosides, and xanthohumol, have demonstrated important in vitro and in vivo protection from oxidation and from mutagenesis, with similar effects to green tea polyphenols [27].

3.2.2. Anti-Inflammatory Effects

Table 2 describes the anti-inflammatory effects of hop and spent hops extracts. When the inflammatory response occurs, excess NO production accelerates the formation of superoxide to damage tissues and DNA and further cause diseases. Therefore, scavenging NO is beneficial to decrease the damage. A cellular assay performed in murine macrophage J774.1 cells by Inui et al. showed anti-NO production activity of cones extract and also anti-adipocyte differentiation effects in murine pre-adipocyte 3T3-L1 cells (at 75 μg/mL for both assays). Moreover, xanthohumol and isorhamnetin were indicated as important compounds in those effects [11].

During the inflammatory response, pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), IL-1β, and IL-6 are released and involved in the development of inflammatory and pathological diseases [2]. Therefore, the inhibition of pro-inflammatory cytokines is a method to improve inflammatory symptoms. Phenolic-enriched hot water extract and ethanol extract of hops pellets have been investigated for anti-inflammatory activities, and both have demonstrated the in vitro capacity to decrease NO production. Moreover, the hot water extract decreased the pro-inflammatory cytokines TNF-α and IL-6 secretion, while the ethanol extract decreased IL-1β and IL-6 secretion [13].

Table 2. Anti-inflammatory activities of hop extracts.

Hop Variety/Part of Plant	Solvent Extraction (Compounds)	Methods/Studied Effects	Results of Assay	Ref.
Cones	Acetone/water (70:30, *v*/*v*) (polyphenols)	In vitro Anti-NO murine macrophage J774.1 cells Anti-adipocyte differentiation (Murine pre-adipocyte 3T3-L1 cells)	Anti-NO production activity (%) = 20–60 (at 75 µg/mL), anti-adipocyte differentiation (%) = 15–70 (at 75 µg/mL)	[11]
Pellets/Cones	Hops hot water (HWE); Hops ethanol (HEE) (polyphenols)	In vitro NO production Pro-inflammatory cytokine secretion	↓ NO production: 20 and 40 µg mL^{-1} (HEE) Pro-inflammatory cytokine secretion ↓ TNF-α: up to 400 µg mL^{-1} (HWE) ↓ IL-1β: 5 to 40 µg mL^{-1} (HEE) ↓ IL-6: 50 to 400 µg mL^{-1} (HWE); 5 to 40 µg mL^{-1} HEE)	[13]
META060/Hops extract	Reduced iso-α acid	In vitro Endothelial and monocyte cell models	Inhibited cell adhesion (10 µg/mL) Inhibited expression of IL-6, IL-8, MCP-1, RANTES, IL-1β, IL-10, MIP-1α, and MMP-9 (1–20 µg/mL)	[30]
Hallertauer Magnum var./Cones	Hexane and methanol (phloroglucinol derivatives, xanthohumol, flavanones, flavonol glycosides, triterpenoids)	In vivo TPA-Induced Inflammation in mice	Anti-inflammatory activity similar to indomethacin: ID_{50} = 0.13–1.06 µmol/ear (All studied compounds except astragallin and quercitrin) ID_{50} = 0.91 µmol/ear (indomethacin)	[31]
Cascade var./Cones	Methanol/water (80:20) (*v*/*v*) and acetone (prenylated compounds)	In vitro Pro-inflammatory enzymes, microsomal mPGES-1 5-LO	5-LO cell-free (IC_{50}, µM) = 2.1 (xanthohumol); 5.9 (4-hydroxycolupulone) 5-LO cell-based (IC_{50}, µM) = 2.9 (xanthohumol); >10 (4-hydroxycolupulone) mPGES-1 (residual activity at 10 µM) = 32.3 (xanthohumol); 32.8 (4-hydroxycolupulone)	[32]
Cones	Supercritical hops CO_2-extract (humulone, lupulone)	In vitro Irradiated human primary keratinocytes (HPKs)	↓ IL-6 expression: IC_{50}: 0.8 µg/mL	[28]
Spent hops	Basal diet supplemented with 1% spent hops	Randomized, controlled trial in pigs	↓ Expression of pro-inflammatory genes: IL1β, IL8, and TNF	[33]

HPKs—human primary keratinocytes; HWE—hops water extract; HEE—hops ethanol extract; IC_{50}—half-maximal inhibitory concentration; ID_{50}—inhibitory dose; IL—interleukin; 5-LO—5-lipoxygenase; mPGES-1—microsomal prostaglandin E2 synthase; MCP-1—monocyte chemoattractant protein-1; MIP-1α—macrophage inflammatory protein 1α; MMP-9—matrix metallopeptidase 9; NO—nitric oxide; RANTES—regulated on activation, normal T cell expressed and secreted; TPA—12-OTetradecanoylphorbol-13-acetate; TNF-α—tumor necrosis factor α; ↓—decrease.

META060, a reduced iso-α acid derived from an extract of *H. lupulus*, showed anti-inflammatory effects in endothelial and monocyte cell models. In detail, it was effective for inhibiting TNF-α-induced expression of many inflammatory factors such as IL-1β, MCP-1, RANTES in HAECs, and THP-1 cells. In addition to that, META060 inhibited expression and activity of MMP-9 [30]. A randomized, controlled trial aimed to determine the effect of spent hops on the expression of pro-inflammatory genes in the intestine of pigs showed the reduction of the mRNA concentrations of IL1β and IL8 in the duodenum, of IL1β and IL8 in the ileum, and of IL1β and TNF in the colon in pigs fed with spent hops [33].

The potential anti-inflammatory activity of a hop cone CO_2 extract composed of 50% humulone and lupulone was determined. After solar irradiation of human primary keratinocytes, the extract showed a reduction in IL-6 expression with an IC_{50} of 0.8 μg/mL [28].

Compounds obtained from cones of the Cascade var. of hop exerted marked effects on key enzymes of eicosanoid biosynthesis. In detail, xanthohumol and 4-hydroxycolupulone showed a capacity to inhibit in vitro the pro-inflammatory target enzymes prostaglandin E2 synthase (mPGES)-1 and 5-lipoxygenase (5-LO) [32]. Xanthohumol showed an effective inhibition of 5-LO with an IC_{50} of 2.9 μM, and together with 4-hydroxycolupulone, were the two most active compounds in inhibiting mPGES-1. The phenolic compounds isolated from an extract of the Magnum var. of hops, i.e., phloroglucinol derivatives, xanthohumol, flavanones, flavonol glycosides, and triterpenoids, have shown important anti-inflammatory activity in TPA-induced inflammation in a mouse model. In fact, almost all of the isolated compounds showed anti-inflammatory activities (ID_{50} = 0.13–1.06 μmol/ear) similar to or higher than indomethacin (ID_{50} = 0.91 μmol/ear), which was used as positive control [31].

3.2.3. Antimicrobial Effects

Antimicrobial effects have been described for the hop plants and its components (Table 3). In detail, a hops CO_2 extract was proved to be effective against bacteria responsible for acne, such as *Propionibacterium acnes* (*P. acnes*) and *Staphylococcus aureus* (*S. aureus*), including MRSA (methicillin-resistant strains), and also *Bacillus anthracis*, *Bacillus subtilis*, *Corynebacterium diphteriae*, *Sarcina lutea* and *Lactobacillus brevis*. In addition to that, a gel formulation with 0.3% hops extract (*w*/*w*) showed antibacterial activity superior to that of the placebo gel [28].

S. aureus and *Staphylococcus epidermidis* were sensitive mainly to aqueous extracts of the cones of Magnum, Lubelski, and Marynka varieties [24]. Low values of minimal inhibitory concentrations (MICs) against *S. aureus* of ethanol extracts from different countries of hop cones of cv. 'Aurora' and cv. 'H. Magnum' showed high antimicrobial activities [25].

A hydroalcoholic extract obtained from female inflorescences (hops) of *H. lupulus* has shown the inhibition bacterial capacity by diffusion methods. In detail, from the Gram-positive bacterial strains tested, the larger inhibition area was observed against *B. subtilis* (~8mm), similar to the positive control vancomycin (30 μg) and for *S. aureus* (~4.5mm for the extract; ~6mm for the same positive control). A similar effect was observed for *E. coli* (gram negative bacteria) with ~4.5mm of the inhibition zone against ~14mm rifampicin used as positive control [34].

Table 3. Antimicrobial activities of hop extracts.

Hop Variety/Part of Plant	Solvent Extraction (Compounds)	Methods/Studied Effects	Results of Assay	Ref.
Magnum var., Lubelski var., Marynka var./Cones	Ethanol/water (40%); Water, 85 °C (chlorogenic acid, *o*-coumaric, *p*-coumaric, cinnamic, and syringic acid, epicatechin, rutin, quercetin and kaempferol)	In vitro Well-diffusion method	*Staphylococcus aureus* ATCC 25923 Inhibition growth area [mm] = 18, 27, 39 (water extracts of Lubelski, Marynka, and Magnum varieties, respectively) *Staphylococcus aureus* clinical isolates Inhibition growth area [mm] = 11, 22, 28 (water extracts of Lubelski, Marynka, and Magnum varieties, respectively) *Staphylococcus epidermidis* ATCC 12228 Inhibition growth area [mm] = 12, 31, 34 (water extracts of Lubelski, Marynka, and Magnum varieties, respectively) *Staphylococcus epidermidis* clinical isolates Inhibition growth area [mm] = 8, 26, 25 (water extracts of Lubelski, Marynka, and Magnum varieties, respectively)	[24]
Cones	Supercritical hops CO_2-extract (humulone, lupulone)	In vitro Broth microdilution method	*P. acnes* MIC = 3.1 µg/mL Inhibition growth area gel= 5.5 mm *S. aureus* MIC = 9.4 µg/mL Inhibition growth area gel = 3 mm	[28]
Cones	Ethanol/water (70:20) (*v*/*v*)	In vitro Disc diffusion method	*B. subtilis* Inhibition growth = ~8mm *S. aureus* and *E. coli* Inhibition growth = ~4.5mm (for both)	[34]
Cones/prenylated phenolic compound	Hydro-ethanolic	In vitro Antibacterial; Antiparasitic	*Corynebacterium, Enterococcus, Mycobacterium, Staphylococcus* and *Streptococcus* strains MICs = 39–156 µg/mL *T. brucei* IC_{50} = <1 to 11 µg/mL	[35]
Aurora var. and Hallertauer Magnum var./Leaves and cones	Ethanol	In vitro Broth microdilution method	*S. aureus* MIC = 0.0013–0.0029 mg/mL (cones); 0.22–0.44 mg/mL (leaves) *E. coli* MIC = 0.19–0.43 mg/mL (cones); 0.16–0.44 mg/mL (leaves)	[25]

Table 3. *Cont.*

Hop Variety/Part of Plant	Solvent Extraction (Compounds)	Methods/Studied Effects	Results of Assay	Ref.
Hop/Isoxanthohumol	Ethanol	In vitro Mycelium growth inhibition method	Antifungal activity: 37.01~51.52% (*H. lupulus* at 500 µg/mL) EC_{50} = 4.32, 14.52 and 16.50 µg/mL (Isoxanthohumol agains *B. cinerea*, *S. sclerotiorum* and *F. graminearum*, respectively)	[12]
Cones	Hydro-ethanolic (rutin, syringic acid)	In vitro Anti-influenza activity	Antiviral effect during the 1 h infection PR8, NWS, and ULSTER strains (46%, 50%, and 29% of inhibition, respectively). Antiviral effect after the infection pH1N1, PR8, and ULSTER titer (75%, 44% and 29% reduction, respectively).	[36]
Purified hop fractions	(α-bitter acids, β-bitter acids and xanthohumol)	In vitro Standard testing protocols EUCAST	Antibacterial effect: xanthohumol MICs = 4–7.5 mg/L β-bitter acids MICs = 0.5–15 mg/L α-bitter acids MICs = 30–60 mg/L	[37]
Aerial parts	Supercritical carbon dioxide ($scCO_2$) extracts and 75% ethanol extracts (cohumulinic acid, dehydrocohumulinic acid, hulupone, lupulone)	In vitro CellTiter-Glo® LuminescencenAssay	*E. coli* $scCO_2$ extracts are more active than the ethanol extracts	[38]
Hallertauer Magnum var./Cones	Supercritical hops extract	In vitro Agar-dilution assay	MICs = 6.25 and 25 µg/mL *(Corynebacterium xerosis* and *S. epidermidis*, respectively)	[39]
Hop bract polyphenols (HBP)	Mouthrinse containing 0.1% HBP	Randomized, controlled trial Patient hygiene Performance score	Reduction amount of plaque score ($p < 0.001$) Reduction the number of *Mutans streptococci* in the plaque samples ($p < 0.05$)	[40]
Hallertauer Magnum var./Cones	Hops and zinc ricinoleate	Clinical study ASTM method E 1207-87 in 42 human volunteers	Malodor score: 6.28 (±0.70) (control) to: 1.80 (±0.71) (8 h of extract application), 1.82 (±0.74) (12 h of extract application), 2.24 (±0.77) (24 h of extract application)	[39]

EC_{50}—Half-maximal effective concentration; EUCAST—European Committee on Antimicrobial Susceptibility Testing; HBP—hops bract polyphenols; MIC—minimum inhibitory concentration; NWS—A/NWS/33 H1N1; pH1N1—pandemic A/California/04/09 H1N1; PR8—human A/Puerto Rico/8/34 H1N1; ULSTER—avian Parrot/Ulster/73 H7N1.

In another study, the antibacterial properties of the *H. lupulus* were tested against *Escherichia coli* (*E. coli*), a standard model for bacteria studies. The extracts were tested on bacterial cells starting from a concentration of 40 mg/mL with a serial two-fold dilution. In detail, hops leaf supercritical carbon dioxide ($scCO_2$) extracts inhibited the growth of bacterial cells more than 75% while ethanol extracts never exceeded 60% of growth inhibition. In addition to that, the $scCO_2$ extraction of hop leaves could be used to obtain innovative functional ingredients by valorizing low-value agro-waste [38]. In these extracts, cohumulinic acid, dehydrocohumulinic acid, hulupone, and lupulone are the more representative compounds that may play an important role in the antibacterial effect. In fact, Weber et al. identified hops bitter acids α- and β-acids and their derivatives as important antimicrobial agents, probably due to their highly hydrophobic character that induces leakage of the bacterial membrane [28].

Essential oils have been described as potent antimicrobial agents. In fact, Jeliazkova et al. [41] reported that *E. coli* and *S. aureus* were strongly inhibited by essential oil fractions of hops after 0 to 30 min.

Mizobuchi reported that xanthohumol and 6-isopentenylnaringenin can inhibit the growth of *S. aureus* with an MIC value of 6.25 μg/mL, while that of isoxanthohumol is 50.0 μg/mL. According to Bocquet et al., it was possible to demonstrate that desmethylxanthohumol in *H. lupulus* has antifungal activity against *Zymoseptoria tritici* (MIC value of 0.63 g/L) [42]. Additionally, it was found that xanthohumol can inhibit the growth of three *Fusarium* species, with MIC values from 0.015 to 0.100 mg/mL [43]. Additionally, Yin-Fang Yan showed in his work that ethanolic extracts of *H. lupulus* showed moderate antifungal activity against pathogenic fungi, while isoxanthohumol, an isoprene flavonoid from *H. lupulus*, showed high antifungal activity, in particular against *B. cinerea*. The study suggests isoxanthohumol as a potential botanical fungicide for the management of phytopathogenic fungi [12].

The results of Bocquet and co-workers also showed an inhibition close to 100% at the MIC for the selected MRSA clinical isolate. In addition, it was also demonstrated that a previous formation of the biofilm does not prevent hops compounds from acting on bacteria. In both cases, desmethylxanthohumol and lupulone seem to be more effective than xanthohumol, with an inhibition of the biofilm formation and a biofilm destruction at sub-inhibitory concentrations [35].

According to Sotto et al. the hydroalcoholic extract from *H. lupulus* (female inflorescences) have the ability to directly counteract viral replication and viral protein synthesis and indirectly increase host cell defense due to its phenolic content [36].

In 2018, Bogdanova and co-workers showed that a purified fractions of hop composed by α-bitter acids (humulones), β-bitter acids (lupulones), and xanthohumol were effective against reference strains of Gram-positive bacteria and also against their methicillin- and vancomycin-resistant variants, although no effect was detected against Gram-negative bacterial strains. Xanthohumol was the hop fraction with more antimicrobial activity. Hop compounds have antimicrobial effects at concentrations lower than the determined MICs, with the biggest effect from α-bitter acids on enterococci [37].

3.3. H. lupulus and By-Products as Cosmetics

Herbal products and/or it active compounds have been used as ingredients for cosmetics formulations [44]. Recent scientific studies confirm the use of hop extracts for treating acne, loose skin, stretch marks and sagging, preventing skin aging, and as hair cosmetics [2,45,46].

As previous described, hop cones and also other parts of the plant or brewery by-products have been described as enriched in antioxidant, anti-inflammatory and antimicrobial compounds, with these properties being crucial for skincare formulations [44]. Other properties such as antioxidant protective effects in keratinocytes models, in vitro and cellular tyrosinase inhibition, intracellular melanin inhibition, and anti-odor and anti-acne effects, have been reported.

In detail, trehalose, a polysaccharide that could be used as bio-protectant in cosmetic formulations, has been recovered from spent hops [18]. Moreover, the improvement in the mitochondrial activity and the prevention of oxidative stress of spent hops extracts and yeast extracts was proved in an in vitro assay in keratinocytes HaCaT [29].

The antimicrobial effects of hop and their constituents against oral pathogens such as *Streptococcus mutans*, *S. salivarius*, *S. sanguinis*, *Porphyromonas gingivalis*, *Lactobacilli* and also *Candida albicans* have also been described [47].

A randomized controlled trial performed with 29 healthy male volunteers showed the inhibitory effects of a mouthrinse containing 0.1% hops bract polyphenols. In fact, a significant reduction in the mean amount of plaque was verified after volunteers used the mouthrinse [40].

The deodorant effect of hops extracts has been demonstrated in in vitro and in vivo studies. In detail, antibacterial activity of a *H. lupulus* extract against *Corynebacterium xerosis* and *Staphylococcus epidermidis* showed minimum inhibitory concentration values of 6.25 and 25 μg/mL in an agar-dilution assay. The in vivo axillary deodorant effect was evaluated with the ASTM method E 1207-87 Standard Practice for the Sensory Evaluation of Axillary Deodorancy of a hops/zinc ricinoleate-containing formulation. The mean malodor score dropped from 6.28 (±0.70) to 1.80 (±0.71), 1.82 (±0.74), and 2.24 after 8 h, 12 h, and 24 of the application, respectively [39].

In a recent study, a gel formulation with 0.3% hops extract (*w*/*w*) showed antibacterial activity in the agar-diffusion test against *P. acnes* and *S. aureus* (inhibition zone values: 5.5 mm and 3 mm, respectively). Therefore, hops extract might be an alternative treatment option for acne-prone skin [28]. A formulation of shower gels based on CO_2 extracts of hop cones was created, and its skin-conditioning properties were attributed to their bioactive compounds [48].

Weber et al. performed an in vitro assay on a human primary keratinocytes (HPKs) model with a supercritical hops CO_2 extract rich in hops bitter acids α- and β-acids. The extract was shown to be able to reduce the formation ROS induced in a concentration-dependent manner, and with similar effect to the flavonoid luteolin. In adition to that, the extract showed strong inhibitory effects in reducing pro-inflammatory cytokine IL-6 production, with an effect comparable to the positive control luteolin [28].

Another described effect of hops is their tyrosinase inhibition ability, which makes them promising whitening agents for the cosmetics industry. A study performed by Liu et al., showed a tyrosinase inhibition of hops-enriched tannins extract with a comparable effect to kojic acid, recognized as stronger tyrosinase inhibitor (IC_{50} = 76.52 ± 6.56 μM and 49.54 ± 2.08 μM, respecytively) [49]. In cellular assays, the tannin extract showed intracellular tyrosinase inhibition and intracellular melanin inhibition in a dose-dependent manner (70% and 35% for 10 μM, respectivelly). Another study showed the in vitro depigmenting effect of xanthohumol, a prenylated flavonoid of hops. In fact, low micromolar concentrations of xanthohumol were able to inhibit melanogenesis in human melanocytes by targeting melanin export and also by melanin degradation [50].

Although the limited scientific data related to the application of hop ingredients in skin products, the properties described for hop plant extracts or brewery by-products and also for their active compounds makes hop a promising ingredient for skincare cosmetics. However, some studies suggest occupational dermatitis related to hop harvesting, and there are some questions about oral animal ingestion. This point must also be better explored before proposing any extract or component as a cosmetics ingredient [47,51].

In this context, the extracts or isolated compounds must fulfil the Cosmetics Regulation related to the safety of cosmetics ingredients (EC 1223/2009) and also the Directive 2004/24/EC if the natural ingredients are used as herbal medicinal products. The regulations cover the choice of the ingredients, manufacturing (according to Good Manufacturing Practices), and product commercialization. The Cosmetics Regulation ensures the equality and immediate access to the market and the free circulation throughout the European Union. Additionally, define the 'responsible person' comprising a person or company who

places the cosmetic product on the market and is responsible for that product ensures the safety of the product and compliance with the Cosmetics Regulation requirements.

4. Conclusions

In hop cultivation as a brewery industry raw material, just the hop cones are the valuable product, leaving about two-thirds of the crop as almost unexploited biomass. On the other hand, applying the high-volume brewery by-products to develop new innovative products would be useful for waste management and the environment. Hop plant and brewery by-products are sources of bioactive compounds with proved antioxidant, anti-inflammatory, and antimicrobial activities. In addition, extracts of hop have been proposed as whitening, anti-odor, and anti-acne agents. Polar extracts obtained by hop or their by-products are rich in polyphenols (e.g., phenolic acids, phloroglucinol derivatives, flavanones, flavonol glycosides and terpenes), while supercritical carbon dioxide extracts contain mainly hop bitter acids (α- and β-acids). These compounds, along with those present in essential oils, have been the most associated with the described effects. However, this review showed that the beneficial effects of hop plants and their by-products have been mainly assessed in in vitro experiments, emphasizing the need to be tested in animal models and further with randomized, double-blind and placebo-controlled studies.

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