



## REVIEW HOPS- BIOACTIVE COMPOUNDS AND THEIR APPLICATIONS

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### ABSTRACT

*Humulus lupulus* L. it's the scientific name of a perennial climbing plant of great importance because of its biocompounds of interest such as: organic acids, polyphenols and essential oils. The female inflorescences (cones) of hops glands secrete mainly lupulin. This is known worldwide as an essential raw material and flavoring agent in beer production. Phytochemical compounds from the plant such as xanthohumol, humulone, and lupulone have been used in trials for cosmetic application. Also the use of the plant has been reported for long time in traditional medicine, due to its properties, anti-inflammatory, antimicrobial, antioxidant among others. This review presents the botanical aspects of the plant as well as its chemical

compounds, traditional uses, and its biological activities for textile, food, medicinal, and cosmetic applications.

**KEYWORDS:** *Humulus lupulus* L., bioactive compounds, resins,  $\alpha$ -acids and  $\beta$ -acids, polyphenols, cosmetics.

### INTRODUCTION

The description of the morphology and taxonomy of the plant denominated by the common name of Hops and with the scientific name of *Humulus lupulus* L. whose genus *Humulus* is a perennial plant belonging to the family *Cannabaceae*, of the order *Rosales*,<sup>[1,2]</sup> are climbers and herbaceous, whose stems curl into any structure to serve as support due to being hairy

derived from the anvil-shaped trichomes or hooks that coat them, the stems are hollow, green or violet in color and generally hexagonal section that grows dextrorhizously around spring and early summer.<sup>[3,4,5]</sup> Their class *Magnoliopsida*, (dicotyledonous) are dioecious, that is, they have female and masculine flowers on different plants that are usually diploid, and are from phylum *Spermatophyta* (angiosperms) of kingdom *Plantae*. The cognomen " *lupulus* ", referring to the shape of the leaves that resemble a heart with 3 to 5 lobes, toothed and with a very rough surface of dark green color and present pubescent on the bottom page, the leaves appear opposite in the nodes that come out of the stipules present in the stem.<sup>[6,7,8,9,10]</sup>

Hops originate in Europe and Western Asia,<sup>[11,12,13]</sup> where it is typically grown in cold climates, of economic and social interest currently with the highest productivity in the United States, Germany China, England, Czech Republic, Slovenia, Australia and France.<sup>[14,15,16]</sup>

Moreover, from the botanical point of view, the male inflorescences have multifloral panicles, small flowers organized in clusters, with a perianth formed by five yellowish green sepals and five short filamentous anthers where they have a groove that stores the resin glands.<sup>[4,17]</sup> The female inflorescences are short spikes that are composed of bracts and bracteoles protecting the flower, when these inflorescences mature, the central axis thickens, the bracts and bracteoles enlarge forming the cones (strobiles) where secretory glands (trichomes) of lupulin develop,<sup>[18,19,20]</sup> which are harvested in early autumn, after their maturation.<sup>[21]</sup> They synthesize and store resins, alpha (humulone) and beta (lupulone) acids and essential oils rich in phenolic terpenes and polyphenols, these are the main compounds responsible for the aroma and flavor, and natural preservation of beer in which this plant is mainly used.<sup>[22,23,24,25,26]</sup>

These compounds are responsible for giving the hops several properties, such as: antiinflammatory, antibacterial, antioxidant and other bioactive effects.<sup>[27]</sup> The species *H. lupulus* presents of importance medicinal, improved by its presence on the European pharmacopoeia of medicines or for the production of herbal infusions or preparations of traditional herbal medicines<sup>[28]</sup> and industrial application,<sup>[13]</sup> with multiple applicability as food (conservation properties), medicinal as herbal medicine to relieve mild symptoms of mental stress and insomnia,<sup>[17]</sup> in the cosmetics industry, and as an alternative source of fiber for the textile industry, among others. However its greatest relevance is in the brewing industry, since 97% of its world production is destined for this industry.<sup>[12, 29, 30]</sup>

## METHODS

This is a literature review, in which a database search is conducted about *Humulus lupulus* L. in order to describe the plant botanically, the main bioactive compounds and chemical profiles, and in addition, also its applications in industries such as food, cosmetics, medicinal and microbiological applications.

Which a search is conducted in databases such as: PubMed, Wiley Online Library, ScienceDirect, b-on, MDPI, Google Scholar and NCBI. The keywords used in Portuguese were *Humulus lupulus*, aplicação cosmética, bioatividade, composição química, atividades biológicas. The keywords used in English were: Hop, secondary metabolites, bioactive compounds, medicinal plants, chemical composition and hops and their applications. This review was carried out about *Humulus lupulus*, L. as to the description of the plant morphologically and botanically, its main chemical components, and finally its bioactivity and applications in industries. The choice of material consisted of three stages. The first stage was reading the titles of the texts, excluding those that were not related to the research theme. The second step was to read the abstracts, selecting the articles that matched the research objectives. The third and final step was to read the studies in full, thus choosing those that fit this review.

## RESULTS

Bioactive compounds have their production greatly influenced by genetics, different soil and climate factors and beyond, such as: growing conditions, location, ripening point during harvest, drying method, and climate and storage conditions.<sup>[31,32]</sup>

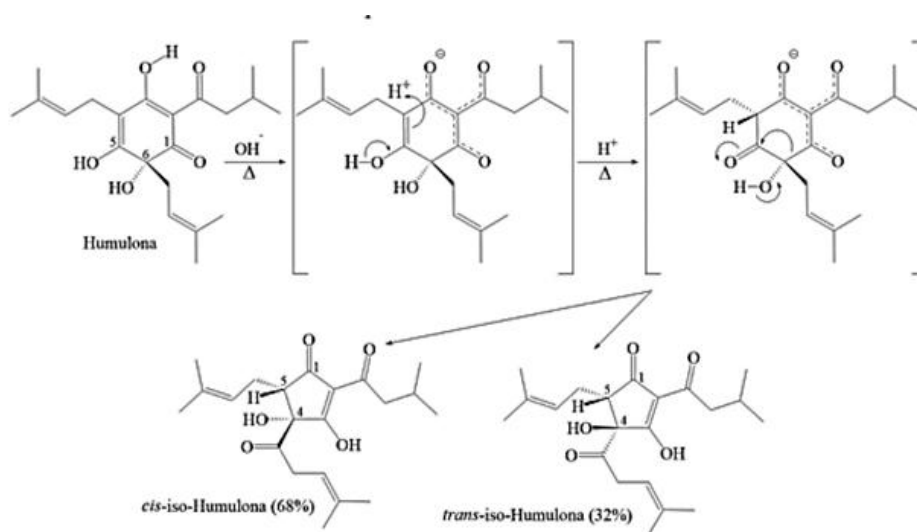
Hops can be the source of a variety of bioactive compounds such as phenolic compounds and organic acids derived from its chemical composition that is complex in which we group the primary metabolites such as ketones, alkanes, sugars, lipids and amino acids<sup>[33,34,35,36,37]</sup> and secondary metabolites produced by the plant as, for example, total resins, essential oils, polyphenols, which also contain chalcones and flavonoids of the type, quercetin, rutin, xanthohumol, phenolic acids, anthocyanins, steroids (prenylflavonoids) of phytoestrogenic substances.<sup>[1,23,38]</sup>

Moving then to the lupulin glands, which constitute a diverse group of compounds with different physicochemical, biological and organoleptic properties,<sup>[39]</sup> one finds all the major compounds that are part of the chemical composition as phenolic compounds: known bitter

compounds such as humulones ( $\alpha$ -acids) and lupulones ( $\beta$ -acids),<sup>[22,40]</sup> terpenes: linalool, myrcene and  $\alpha$ -humulene; and flavonoids: xanthohumol.<sup>[35,41,42]</sup>

Within total resins can be divided into two types: soft and hard resins, and are characterized by their solubility and insolubility in hexane.<sup>[19,42]</sup> Soft resins are formed by two different bitter acids:  $\alpha$ -acids and  $\beta$ -acids (humulones and lupulones, respectively), and hard resins are formed from the oxidation of soft resins.<sup>[1,38,39,43]</sup>

Therefore in the soft resins are part of the  $\alpha$ -acids or humulones,<sup>[44,45]</sup> have weak acid characteristics (pKa of 4.0 to 5.5) and little solubility in water. After undergoing isomerization under high temperature conditions, solubility increases. During isomerization each humulone generates its two diastereoisomers in the form of *cis*-iso-humulone and *trans*-iso-humulone,<sup>[46]</sup> we can see this reaction in Figure 1, which differ in a radical, thus can be *n*-humulones, *co*-humulones and *ad*-humulones, these being the radicals of major importance.<sup>[39,42]</sup>



**Figure 1: Representation of the humulone isomerization reaction in *cis/trans*-iso-humulones.**<sup>[46]</sup>

The  $\beta$ -acids known as lupulones,<sup>[44,47]</sup> are triprenylated analogues of  $\alpha$ -acids also appearing in all three forms of radical (R) substitution as *n*, *co* and *ad* in their chemical structure,<sup>[42]</sup> as we can see in figure 2 and 3, structurally they are very similar, however they are even less soluble in water (pKa of 4.0 to 7.8) due to the absence of a tertiary alcohol group on the aromatic ring. Unlike humulones,  $\beta$ -acids do not undergo isomerization.<sup>[46,48]</sup> The

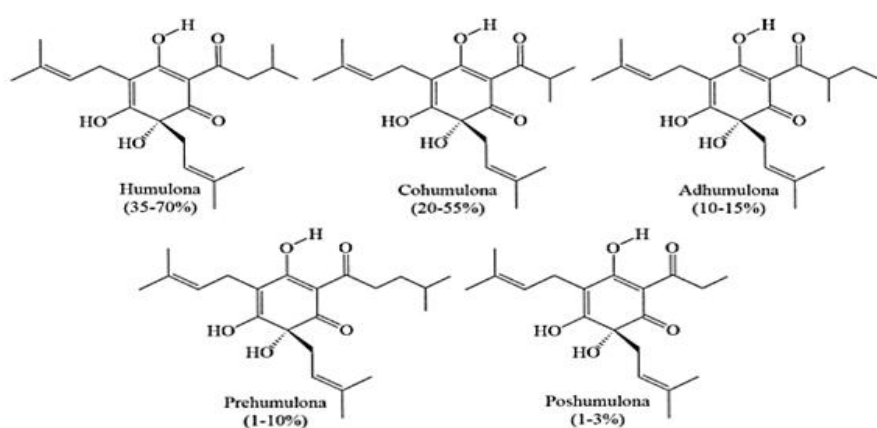
composition of  $\alpha$ -acids and  $\beta$ -acids and their amount in percentage existing in hops, is referred to in table 1 and 2.

**Table 1 - Composition of  $\alpha$ -acids and percentage of the constituents.**<sup>[3]</sup>

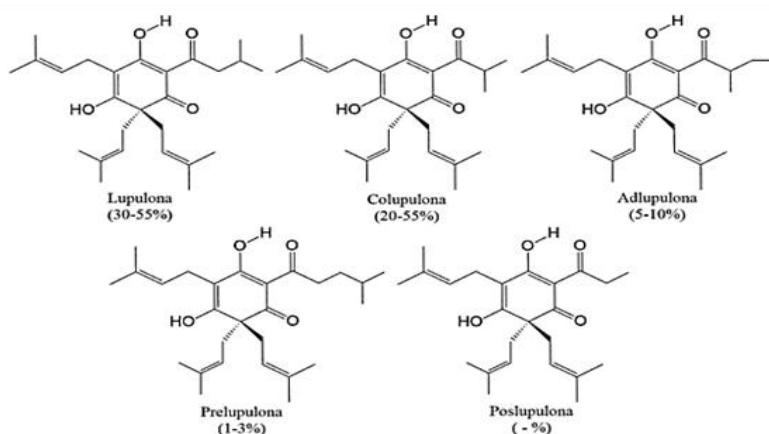
Composition	%
Cohumulone	20 – 55
Prehumulone	1 – 10
Humulone	35 – 70
Adhumulone	10 – 15
Poshumulone	1 – 5

**Table 2 - Composition of  $\beta$ -acids and percentage of the constituents.**<sup>[3]</sup>

Composition	%
Colupulone	20 – 55
Prelupulone	1 – 3
Lupulone	30 – 55
Adlupulone	5 – 10



**Figure 2: Chemical structures of the main  $\alpha$ -acids (humulones) in hops.**<sup>[46]</sup>



**Figure 3: Chemical structures of the main  $\beta$ -acids (lupulones) in hops.**<sup>[46]</sup>

In hops hard resins are soluble in methanol and diethyl ether, but insoluble in hexane, so they are more polar compounds compared to soft resins.<sup>[42,43]</sup> Humulones and lupulones, when they are oxidized, give rise to humulinones and hulupones, two groups of compounds with similar molecular structure to  $\alpha$ -acids and  $\beta$ -acids, except for the presence of an extra hydroxyl group, which make them more polar and more soluble.<sup>[49]</sup> Other phenolic compounds are also part of hard resins such as some prenylated chalcones and flavones and flavanones.<sup>[50]</sup> Xanthohumol is the main prenylflavonoid, which is found solely and exclusively, in hops.<sup>[46,51]</sup> Normally chalcones have a free hydroxyl, which allows isomerization into corresponding flavones.<sup>[37]</sup> Flavones found in hops are isoxanthohumol, 6-prenylnaringenin and 8-prenylnaringenin.<sup>[52]</sup> Still but with less concentration, we have phenolic acids, flavonoids, catechins (flava-3-ols) and proanthocyanidins.<sup>[53]</sup>

Essential oils, compounds that have aromas, obtained from the raw materials of plant origin, by hydrodistillation, play a key role for industries<sup>[46,54]</sup> their components are divided into three major groups: hydrocarbons (aliphatic, monoterpenes and sesquiterpenes), oxygenated (alcohols, terpenes, aldehydes, acids and esters)<sup>[55]</sup> and sulfur (thioesters and cyclic sulfide terpenoids).<sup>[39,42,54]</sup>

Aliphatic hydrocarbons consist of mixtures of isoprene and low amounts of alkanes of varying carbon number (C5-C17).<sup>[56]</sup> The hydrocarbons encompass mainly monoterpenes, are made up of mixtures of acyclic hydrocarbons such as  $\beta$ -myrcene, and sesquiterpenes such as  $\alpha$ -humulene,  $\beta$ -caryophyllene, and  $\beta$ -farnesene, in which, myrcene being the majority compound in the constitution of hop aroma, which has a herbaceous, resinous, green, fresh, and balsamic odor.<sup>[1,57,58,59]</sup>

Within oxygenated compounds are an extremely complex mixture of alcohols, aldehydes, acids, ketones, epoxides and esters (make up on average only 30% of the total hop essential oils).<sup>[1,46]</sup> The oxidation of myrcene gives rise to cyclic compounds such as  $\alpha$ -pinene and  $\beta$ -pinene, and also forms terpenic alcohols such as linalool, nerol, geraniol,  $\alpha$ -terpineol and humulol; aldehydes such as geranial and neral; acids such as 3-methylbutanoic acid and 2-methylpropanoic acid; ketones such as 2-heptanone, carvone, humulenone II and 2-methyl-2-butanoate; epoxides such as humulene epoxide I, humulene epoxide II, humulene diepoxide III, and caryophyllene oxide; saturated esters such as hexanoate, octanoate, and decanoate, unsaturated esters such as 4-decenoate, 4,8- decadienoate, and 8-dodecanoate, terpenic esters the geranyl acetate and geranyl isobutyrate, and branched esters the methyl propanoates,

methyl butanoates, formates, acetates, hexanoates, and heptanoates.<sup>[24,60]</sup> in which linalool is one of the most aromatic components<sup>[61,62]</sup> geraniol is also an important compound, reported as a floral aroma, of hop oils with importance for beer production.<sup>[63,64]</sup>

The sulfur fraction represents a small part of the total essential oils, having a very low flavor threshold. It is a fraction with little biological activity.<sup>[39]</sup> The compounds found we have the thioesters such as 4-mercapto-4-methylpentan-2-one, the thioesters the S-methyl-2-methylthiobutanoate and the organosulfur compounds the dimethyl sulfide, which can be generated due to the thermal degradation of the S-methylcysteine sulfoxide from hops. In general, these compounds impart aromas reminiscent of sulfur and mold, which ultimately detracts from the fragrances.<sup>[46]</sup> On the other hand, some sulfur compounds can have a pleasant aroma as is the case of the thioester S-methyl-2-methyl thiobutanoate and S-methyl thiohexanoate that confers truffle and fruity aromas.<sup>[1,65]</sup>

Phenolic compounds are classified as simple phenols or polyphenols based on the number of phenols in the molecule,<sup>[66]</sup> the dry weight ranges from 3% to 6% of hop cones, with the exception of prenylflavonoids which are secreted by the lupulin glands.<sup>[39,44,67]</sup> Polyphenols are a broad group of biologically active secondary metabolites, which can be divided into 4 groups flavonoids, flavan-3-ols, phenolic carboxylic acids and other polyphenolic compounds such as prenylflavonoids, stilbenes and tannins.<sup>[39,68,69]</sup> Flavonoids are secondary metabolites that are rich in quercetin, kaempferol, morin and myricetin are the major ones present, being considered among the most abundant in the plant kingdom that are natural of great interest, in the form of glycosides, where D-glucose and L-ramnose are the most frequent sugar groups.<sup>[70,71,72,73]</sup> The flavonoids that consist of the majority of secondary metabolites, in which we find anthocyanins, flavonols, isoflavones, among other compounds, which also confer antioxidant, antitumor, and anti-inflammatory activity, among others.<sup>[74]</sup> Humol, isoxanthohumol, desmethyl xanthohumol, and 6- and 8-prenylnaringenin, constitute the main prenylflavonoids in hops,<sup>[1,39,75]</sup> less abundant bioactives, but important for the health of the plant itself.<sup>[76]</sup> Flavan-3-ols can be synthesized from the reduction of a flavan-3,4-diol, such as leucoanthocyanidin by the action of the enzyme dihydroflavonol 4-reductase, or else after the reduction of an anthocyanidin by the action of anthocyanidin reductase.<sup>[37,75]</sup> The flavan-3-ols monomers most commonly found in hops are catechin and epicatechin, which form oligomers or polymers that are called proanthocyanidins or condensed tannins.<sup>[1,75,77]</sup> The

most abundant phenolic carboxylic acids are caffeic acid, ferulic acid and sinapic acid,<sup>[39]</sup> stilbene in hops is found in trans and cis-resveratrol.<sup>[78,79,80,81]</sup>

To complete, we can verify the amount in percentage of chemical compounds existing in hops, referred to in table 3.

**Table 3 - Chemical composition of hops.**<sup>[170]</sup>

Composition	%
$\alpha$ -acids	4 – 10
$\beta$ -Acids	3 – 6
Proteins	12 – 24
Tannins	2 – 6
Essential oils	0.5 – 2
Total resins	12 – 21

### Compounds Bioactivity Applications

The properties of *Humulus lupulus* L. besides being known as a raw material mainly in the production of beer that provides the flavor and aroma, have also been used for production in industries such as cosmetic products, food, textiles and for a long time for the manufacture of formulations for medicinal purposes,<sup>[4,82,83]</sup> by revealing health benefits such as their antioxidant potential, their antimicrobial activity, which inhibit the growth of a broad spectrum of microorganisms, and biological properties of high importance.<sup>[39,84]</sup> The hop plant, has shown a wide range of pharmacological properties, such as anti-inflammatory effect antimicrobial antioxidant activity, sedative and neuro pharmacological properties, estrogenic properties of the phytoestrogen 8-prenylnaringenin., chemopreventive activity, antiallergic properties, has pesticidal activity, are due to its high content, which has a content of relevant bioactive substances, such as bitter acids and polyphenols, essential oils and the resins.<sup>[20,38,85,86,87]</sup>

Also its bioactive compounds such as  $\beta$ -acids humulone and lupulone, cohumulone and the prenylflavonoid xanthohumol possess properties with strong antimicrobial, antifungal, anti-inflammatory antioxidant and anticancer activity and other bioactive properties.<sup>[88,89,90,91]</sup> And the  $\alpha$ -acids, antioxidant and antimicrobial substances, both for drug formulation and food preservative.<sup>[87]</sup> We can see a summary of the components and their properties in table 4.

**Table 4: Summary of the properties of hops and their components**

<i>Humulus lupulus L.</i>				
Properties	Components			References
Anti-inflammatory; Antioxidant; Antimicrobial; Anticancer; Preservatives; Sedatives; Treatment of obesity	Resins:	$\alpha$ -acids	humulone, cohumulone, adhumulone, prehumulone, posthumulone	[69,87,91,93,109,172]
		$\beta$ -acids	lupulone, colupulone, adlupulone, prelupulone, postlupulone	
Antimicrobial; Anticancer; Antidiabetic; Pesticide; Food products; flavorings; Anti-catabolic; Chemopreventives; preservatives	Essencial oils:	Terpenes, Hydrocarbons, Oxygenates	myrcene, terpene alcohols, sesquiterpenes	[38,99,115,116,127]
Phytoestrogen; Osteoporosis; Chemopreventives; Anticancer; Antidiabetic; Anticoagulants; Anticholinesterase; Antimicrobial; Anti-aging; dyes; Antiallergic	Polyphenols :	Flavonoids, Flavan-3-ols, Carboxylic-phenolic acids, Prenylflavonoids	xanthohumol, 6-prenylnaringenin, 8-prenylnaringenin, catechins, tannins, proanthocyanidins	[13,41,86,91,96,104,110,137]

Currently, Hops is a species well known to society by tradicional medicine and over the years due to its multiple uses, as a medicinal plant it is used for various purposes, anti-inflammatory, antibacterial and antioxidants in which these properties come from lupulin.<sup>[92]</sup>

Lupulin, which have anti-inflammatory, sedative and for anxiety activities, in the form of herbal tea, infusions, liquid/alcoholic extracts, tinctures and powder have traditionally, been used in the treatment of insomnia, as for example formerly the dried flowers were used to stuff pillows.<sup>[93]</sup> The European Commission approved its use for the treatment of anxiety and insomnia<sup>[94]</sup> and tuberculo-static properties,<sup>[95,96]</sup> in addition to these, it is attributed anaphrodisiac, antimycotic properties.<sup>[97]</sup>

Hop is also noted for its use in herbal medicine due to its compounds, such as in the area of medicine, irritation, delirium, excitability and restlessness associated with tension headaches, depressive symptoms, and digestive disorders, such as gastrointestinal spasm and treating

indigestion, and bacterial infections, in the form of infusions to relieve pain, swelling, wound suppurations and skin lesions.<sup>[22,98,99,100,101]</sup>

Medicinally the phenolic compounds in hops show great potential, which is being increasingly explored. The most active compounds known so far as the bitter acids are the main phytochemical components responsible for the medicinal value of hop resins, exhibiting strong biological activities and benefits to human health, the prenylflavonoids the xanthohumol, are considered some of the phytoestrogens, which have shown interesting biological effects in that they have been shown to have the prevention or treatment of menopausal symptoms, heat waves (postmenopausal) and osteoporosis,<sup>[39,86,102,103,104]</sup> also for application in cancer prevention programs with chemopreventive activity in in vitro assays and showed that the prenylated flavonoid (xanthohumol) inhibits the development of prostate cancer,<sup>[13,105]</sup> colorectal and liver cancer<sup>[106]</sup> and antiviral effect against HIV-1 and inhibition of replication of *Plasmodium falciparum*, the causative agent of malaria. Among such compounds, we also have the flavonoid 8-prenylnaringenin, the demethylated isoxanthohumol derivative, is also a potent phytoestrogen used for relief of symptoms caused by menopause, also as a dietary supplement, besides presenting antidiabetic action.<sup>[13,107,108]</sup> Studies in administration of hop-derived extracts has also been shown to reduce body weight and fat mass and improve glucose homeostasis in humans, with the inclusion in the diet of bitter extract of *Humulus lupulus* results in both gastric and duodenal delivery of a suppressed energy intake and modified the release of hormones involved in appetite and glycemic regulation, providing a potential “bitter brake” on energy intake in healthy-weight males, and control and treatment of obesity.<sup>[109]</sup>

Flavonoids have also shown health benefits, shown to have antiallergic, anticoagulant, platelet antiaggregant properties and take on anticholinesterase activity (therapeutic in Alzheimer's disease),<sup>[41,110]</sup> estrogenic activity,<sup>[111]</sup> anticancer<sup>[112]</sup> and diuretic action.<sup>[113]</sup>

In addition to the aromatic characteristics, hop essential oils and bitter acids also possess biological properties such as terpenoids and phenylpropanoids are attributed various pharmaceutical and biological activities such as antibacterial, antifungal, anticancer, anti mutagenic, antidiabetic, antiviral.<sup>[114,115]</sup> These extracts show high antibacterial potential for Gram-positive bacteria, such as *Staphylococcus aureus*, and a mild to moderate activity against some Gram-negative bacteria. Hop oil alters the membrane properties of bacteria and is active against plant pathogenic bacteria, and can even be employed as a natural

pesticide,<sup>[90,116]</sup> also shows antimicrobial activity against fungi and viruses,<sup>[71,72,117,118,119]</sup> this suitability is due to substances such as xanthohumol, 6-prenylnaringenin, and prenylated flavonoids.<sup>[85]</sup> Their antibacterial activity is attributed to alpha-acids and beta-acids, mainly for Gram-positive bacteria. The  $\alpha$ -acids or humulones are used as precursors of iso- $\alpha$ -acids, which inhibit the growth of Gram-positive bacteria, such as *Lactobacillus*, *Propionibacterium acnes*, *Staphylococcus aureus*, *Staphylococcus epidermitis*, *Bacillus*, *Corynebacterium diphtheriae*, *Sarcina lutea*, *Streptococcus spp.*<sup>[108,120]</sup> In addition to antibacterial activity, it has also demonstrated anti-cancer activity<sup>[121]</sup> and possesses a blockade in the development of several complex diseases, such as metabolic syndrome.<sup>[39]</sup> The importance of  $\beta$ -acids such as lupulone is associated with the biological activity of these molecules for their antioxidant and antimicrobial actions.<sup>[46,48]</sup>

Considering the properties exhibited by hop extracts and essential oils, in recent years these have been used in different food products, such as in the production of frozen desserts, gelatines, bonbons, puddings and baked sweets, and also in some non-alcoholic beverages as a flavoring in mineral waters.<sup>[122]</sup> Hop cones, on the other hand, are considered a natural source of food flavoring for cereals, spices, gravy, and also for alcoholic beverages other than beer.<sup>[38]</sup> The young leaves, shoot tips and flowers make a good addition in salads and soups<sup>[122,123,124,125,126]</sup> and as preserving agents in fresh meats and meat products, where plant extracts prevent their oxidative and microbial deterioration, increasing their shelf life and safety and conferring functional properties,<sup>[38,127]</sup> it is also used to extend the shelf life of beverages.<sup>[91]</sup>

In the textile industry, as its stems are rich in fiber,<sup>[91]</sup> it has been used for many centuries for fodder, textile fiber that serves to manufacture the coarse cloth, produce coarse cloths, paper, baskets and wicker items.<sup>[44,123,125,128,129]</sup>

Essential oils are used in the tobacco industry as a flavoring agent.<sup>[38]</sup> Hops are also widely used as an ornamental,<sup>[130]</sup> as for example the female cones, once dried, are used in decoration because, as they are similar to pinecones, they look very good in dried flower arrangements and wreaths<sup>[131]</sup> and also because they are climbers because of their vigorous growth, it is ideal to put on trellises or near trees, as it is also very used to divide large gardens because of its beautiful foliage.<sup>[125,132]</sup>

Hops are used in the cosmetic industry due to its bioactivity and diversification of application, which are marketed through perfumes, shampoos, lotions and creams.<sup>[3]</sup> Hop cones are incorporated into formulations, as an ingredient for example of fragrance of some perfumes, particularly in spicy and oriental perfumes types "Spicy", "Oriental",<sup>[133]</sup> "Chypre" and "Fougère",<sup>[123,134]</sup> shampoos, as a product for reducing hair loss or hair growth, dandruff on hair bath lotions and creams, for the treatment of oiliness due to its alleged skin softening properties, with its essential oil are used to give a pleasant odor to astringent skin lotions.<sup>[38,44,97]</sup> Due to its antifungal and antiseborrheic properties<sup>[91]</sup> and for its antioxidant, anti-inflammatory and antimicrobial properties, highlights the effects of hop extract on acne-causing bacteria and can be used as an alternative for skin treatment.<sup>[135]</sup> And in the case of the xanthohumol compound, one of the flavonoids isolated from the Hop plant, resulted effective in improving skin structure and firmness, which implies, a greater protective effect on elastin, collagen and fibrillin<sup>[136]</sup> and has already been determined to exert a protective effect on liver cells against oxidative stress resulting from aging.<sup>[137]</sup>

## DISCUSSION

Accordingly, several studies on the hop plant and phytochemicals with the extracts have been conducted to investigate and identify compounds of pharmacological importance, such as polyphenols (flavanones, chalcones), essential oils and the resins,<sup>[39,44]</sup> which have demonstrated antioxidant, anti-inflammatory, antimicrobial and anticarcinogenic activity.<sup>[66,69]</sup>

The studies by Pearson and Smith confirm that hops is an herbaceous and perennial plant, i.e. it has a long life span.<sup>[138]</sup> Matsui and his team point out that because it is a climbing plant, hops grow under a system of that intertwine on any support and can reach a height of 6-8 meters.<sup>[21]</sup>

Some primary metabolites have been found in hops by Stevens in 1967 who observed many ketones and alkanes identified in hops.<sup>[139]</sup> Faivre and Farag highlighted the presence of some sugars such as glucose, fructose, raffinose and maltose.<sup>[34,35]</sup> Within lipids, in hops was found sitosterol derivatives by the authors Chadwick *et al.*<sup>[33]</sup> In amino acids, Tanaka *et al.* managed to purify tryptophan, from hop bracts.<sup>[36]</sup>

Referring to secondary metabolism, hops consist mainly of terpenoids which are also present in the essential oil as well as various phenolic compounds.<sup>[75]</sup> Some studies done have

identified predominant phenolic compounds in hop extracts in which showed the presence of luteolin, rutin, ferulic acid, catechin kaempferol, quercetin, gallic acid and coumaric acid.<sup>[26,140]</sup>

Yan and collaborators found that female plants have cones, with glands producing a resin, called lupulin rich cells that secrete secondary metabolites such as polyphenols, alpha and beta acids, and terpenoids, and are harvested in early fall, after their maturation.<sup>[141]</sup> Maliar and his researchers further add that the major groups of secondary metabolites secreted by hops have bioactivity in sedative properties related to sleep disturbance and phytoestrogens related to menopause.<sup>[142]</sup>

In further research on hydrocarbons in essential oils, Kobus-Cisowska and his partners point out that the essential oils produced by lupulin glands contain mostly hydrocarbons in their composition, representing a percentage of 70% and 30% of oxygen. They also describe that these hydrocarbons are divided into aliphatic hydrocarbons, monoterpenes and sesquiterpenes.<sup>[85]</sup> Among the monoterpenes are the myrcenes, which in Chapman studied the essential oil of hops, comparing its aroma with other essential oils, and found that the presence of myrcene had a characteristic aroma of hops.<sup>[143]</sup>

Both Nuutinen and Tyskiewicz and co-workers also mention that the essential oil in the terpene class found in hops is rich in  $\beta$ -myrcene can be used in medicine, since this compound has anti-inflammatory and anticatabolic activities for the treatment of osteoarthritis that can slow it down.<sup>[99,144]</sup>

And the sesquiterpenes that stand out the caryophyllene, humulene and farnesene from hops They were verified by Paventi, who investigated the complex composition of hop essential oils collected from different localities and identified hundreds of compounds with significant differences in the composition of the main terpenes,  $\alpha$ -humulene stands out in some samples.<sup>[54]</sup> Also according to Shellhammer, hop varieties that have large amounts of sesquiterpenes such as  $\beta$ -caryophyllene,  $\alpha$ -humulene and their respective epoxides provide pleasant aromas for beer.<sup>[145]</sup> In parallel recently studies with the spontaneous hop in all Italy shown that they can have different aromatic composition, but although this composition was not interesting for beer productions can be very important source of pharmacologic compounds.<sup>[146]</sup> While a research conducted with Chen group with isolated  $\alpha$ -humulene, presented that this compound is a monocyclic terpene that contains antineoplastic activity

through the essential oils, moreover, this compound also showed cytotoxic activity in hepatocellular carcinoma cells, causing mitochondrial apoptosis of these cells.<sup>[147]</sup> About farnesene, according to Lv and companions it is used in pharmaceutical industries, in the biofuel industry and also in the production of rubber and tires.<sup>[148]</sup> With that, the biological activity of farnesene was tested by Stanojevic and researchers on some bacterial strains, where it demonstrated efficacy on the bacteria *Listeria monocytogenes* and on *Staphylococcus aureus*.<sup>[149]</sup> Another study done by Paventi *et al.* for pest control with the essential oil and terpenes of hops the three most abundant components,  $\alpha$ -humulene,  $\beta$ -myrcene and  $\beta$ -caryophyllene, against *Sitophilus granarius* which were sensed by the antennae of this insect and induced repellent activity.<sup>[54]</sup>

Already in the study on oxygenates demonstrated at the time 1981 by Sharpe and Laws that hop essential oils there are 70 esters, 60 aldehydes and ketones, 50 alcohols, 30 oxygenated heterocyclic compounds and 25 acids.<sup>[150]</sup> About the oxygenated compounds found in hop essential oils, in which the authors Takoi realized studies on the biotransformation of monoterpenic alcohols from hops such as linalool which contains a floral-fruity aroma, geraniol with rose and geranium aroma,  $\beta$ -citronellol from lemon and lime, nerol is sweet, citrus and rose aroma and  $\alpha$ -terpineol is oily with an anise and mint aroma, and their contribution is important to the flavor and aroma of beer, they also reported that there is a synergism between too much linalool and the terpenes geraniol and  $\beta$ -citronellol, which leads to certain varieties of hops having a citrusy, characteristic aroma of this plant.<sup>[151]</sup>

The class of secondary metabolites found in hops, are flavonoids, according to studies conducted by researchers and Karabin, these phenolic substances that act as antioxidants, antimicrobials and confer coloring characteristics, also have proven biological benefits, act in the elimination of free radicals and have estrogenic agents.<sup>[96]</sup>

The polyphenols that have flavan structure, such as flavan-3-ols, flavonols and tannins, condensates found in hops there was a study by Li and Deinzer who isolated new oligomers of proanthocyanidins from different hop cultivars, including galocatechin derivatives, the concentration of compounds may vary depending on the geographical origin and their nature may affect the proanthocyanidin profiles of hops.<sup>[152]</sup> They also exhibit active antimicrobial activity and exert inhibitory actions against a wide range of Grampositive bacteria including *Staphylococcus aureus*, *Lactobacillus acidophilus*, *Actinomyces naeslundii*, *Streptococcus mutans* and *Colistridium perfringens* and against Gram negative bacteria such as *Prevotella*

*oralis*, *Prevotella melaninogenica*, *Fusarium nucleatum* and *Escherichia coli* as stated in the study by Karabín *et al.*<sup>[39]</sup>

Recent investigations on anti-inflammatory, antimicrobial and anticancer properties, Wang and collaborators report, that the phenolic compound, which is part of the flavonoids, a prenylflavonoid from hops, xanthohumol has shown a feature of enormous importance that has drawn attention, which is its chemopreventive activity, exhibiting inhibitory mechanisms in the early stage preventing the progression of carcinogenesis. It also acts as a broad-spectrum anti-infective agent that inhibits the replication of microorganisms mainly Gram-positive bacteria, including species of *Staphylococcus*, *Bacillus spp*, *Micrococcus spp*, *Mycobacterium spp* and *Streptomyces spp*, with its antibacterial activity is one of the best properties presented by hops.<sup>[153]</sup> Stompor and Zarowska also studied the antimicrobial activity of structural analogues of xanthohumol present in hops and observed the inhibition of *S. aureus* by only 4 of the 11 compounds tested, while for *E. coli*, none of the compounds showed activity.<sup>[154]</sup> And Zanoli & Zavatti on the anti-infective properties, of hop constituents who described xanthohumol, as an inhibitor of Gram-positive bacteria such as *Staphylococcus aureus* and *Streptococcus mutans*, viruses such as cytomegalovirus, herpes simplex virus type 1 and type 2 and human immunodeficiency virus, prevents the growth of fungi such as *Trichophyton spp* and against the protozoa of malaria, *Plasmodium falciparum*.<sup>[44]</sup> We can also prove in Karabin studies antifungal activities that include the ability of xanthohumol and 6-prenylnaringenin to inhibit the growth of the dermatolytic fungi *Trichophyton mentagrophytes* and *Trichophyton rubrum*.<sup>[39]</sup>

This study by Yan, demonstrates *in vitro* and *in vivo* antifungal activity of isoxanthohumol, an isoprene flavonoid from hops, against *Botrytis cinerea*, which can be used as a potential botanical fungicide for the management of phytopathogenic fungi.<sup>[27]</sup> Recent research by Krajnović and other authors, also with xanthohumol, has shown that this compound found in hops exhibited antimetastatic power *in vitro*.<sup>[155]</sup> Another recent study by Caban also proved that hops are a good anti-inflammatory against macrophages due to being rich in flavonoids.<sup>[156]</sup>

While its derivatives 8-prenylnaringenin and isoxanthohumol show potent phytoestrogenic actions, so that they have been indicated by some researchers in chemopreventive diets.<sup>[111]</sup> Developed a study where, after extraction and separation of the chemical components of hops, they isolated and identified a potent phytoestrogen, 8- prenylnaringenin, structurally

related to flavonoids, which has a higher estrogenic activity than other plant estrogens already studied. Aghamiri and collaborators studied hops, finding that it is a plant rich in phytoestrogenic activity, and since 1953, hops has been studied and presented as estrogenically active by the compound 8-prenylnaringenin, and may, develop good performance in prevention of osteoporosis, menopause or cancer, in which in-vitro research confirms the phytoestrogenic power, thus increasing the commercialization of hops.<sup>[157]</sup> We can point out that Stulíková and other researchers have cited that hops can be an extra treatment outlet for hormone replacement.<sup>[158]</sup> Also Xanthohumol was used in studies in vivo and in vitro with good and promising results as protective effects against iron-induced memory impairment.<sup>[159]</sup>

Regarding  $\alpha$ -acids and  $\beta$ -acids, Tanigushi and researchers describe cohumulone, n-humulone and adhumulone as constituents of  $\alpha$ -acids. On the other hand, lupulone, colupulone and adlupulone correspond to the  $\beta$ -acids fraction. These acids present anticancer, anti-inflammatory and antioxidant activities.<sup>[160]</sup> Hops have also captured attention with their antibacterial properties, recent studies have shown that the  $\alpha$ -acids and  $\beta$ -acids point to beneficial effects, as proven in the study Wang and co-workers report that the acids present in hop resins have been identified as strong antibiotics against Gram-positive bacteria showing anti-inflammatory effects.<sup>[153]</sup> Blanco and contributors, complement that the bitter acids in hops comprise a percentage between 5-20% and also exert an antimicrobial power against Gram-positive bacteria, and limited action against Gram-negative bacteria.<sup>[161]</sup> Also Abram evaluated the antimicrobial and antioxidant properties of  $\alpha$  and  $\beta$  acids from cones and leaves, respectively DPPH radical scavenging and antibacterial activities against *S. aureus* which showed good results.<sup>[95]</sup>

A study carried out by Di Lodovico to prove the antibacterial activity and the ability to inhibit biofilm formation, of a hop extract used against strains of bacteria involved in the multidrug-resistant skin diseases of *Staphylococcus aureus*, *Staphylococcus epidermidis* and *Cutibacterium acnes*, the extract exhibited a good antimicrobial action, which was able to inhibit biofilm formation<sup>[162]</sup> and can be used as an alternative for skin treatment.

A study conducted by Weber evaluated the antioxidant, anti-inflammatory, and antibacterial potential of a hop extract with 50% humulone and lupulone, where it was shown to be a treatment option for acne-prone skin in cosmetic products.<sup>[135]</sup> Also, Yang conducted a study

for election of natural products for use as cosmetic ingredients, a variety of *H. lupulus* with tyrosinase inhibitory activity, suggesting as a whitening ingredient in cosmetic products.<sup>[163]</sup>

According to Duke, (1983) in Europe, hops are used in the cosmetic industry in perfumes, shampoos, lotions and creams, and also in the flavoring of tobacco and mineral waters, with its essential oil. Further in the cosmetic industry, where hops are used in shampoos and shower lotions.<sup>[122]</sup> Astray *et al.* refer to research where they used supercritical CO<sub>2</sub> extracts of hop cones in order to formulate shower gels, and the results showed that their addition improved various skin properties due to their bioactive ingredient content. Also, hair cosmetic formulations containing hop cone extracts exhibited compounds for hair grease and dandruff treatments characterized by their antifungal and antiseborrheic properties, which reduce hair brittleness, nourish, provide shine, increase hair strength, and prevent hair loss.<sup>[38]</sup> Essential oils such as myrcene, linalool and geraniol are the most important *H. lupulus* aromatic compounds that have added to perfumes and deodorants, but have also been useful for their preservative qualities.<sup>[120]</sup>

In the food part we cannot fail to mention the production of beer using the ingredient hops, according to Sanz and collaborators, currently, more than 90% of the world production of hops is destined for the brewing industry.<sup>[164]</sup> As Yan and his research group state that *Humulus lupulus* L. of different varieties have the possibility to impart distinctive characteristics of both flavor and aroma to beer, due to the difference in the content of chemical components accumulated in each variety, depending on the concentrations of alpha and beta acids.<sup>[141]</sup> The composition and Characterization of *Humulus lupulus* glycosides in volatile fraction is an emerging area of study, this compounds are determinants of the free volatiles in the different varieties and determinants to the beer aroma in the brewing industry.<sup>[165]</sup> The antimicrobial and antioxidant activities of hop cones, leaves and seeds have already been studied as food preservatives,<sup>[166]</sup> the bitter acids in hops are also used as aseptic supplements in food preservation. The FDA (US Food and Drug Administration) and FSIS (Department of Agricultural Food Safety and Inspection Services) have authorized  $\beta$ -acids such as lupulone, co-lupulone, ad-lupulone as safe antimicrobials in meat products weighing between 4-5 mg/kg. Also  $\beta$ -acids have been used in the sugar industry, replacing formalin, which can control microbial growth and reduce the amount of dextran during sugar extraction.<sup>[167]</sup> Hops have long been used as a sedative and sleeping aid in beverages, Franco

*et al.* and Rossini *et al.* evaluated the sedative effect of hops in non-alcoholic beers, taking into consideration the quality of sleep in the study population after beer consumption.<sup>[168,169]</sup>

## CONCLUSION

After the detailed literature review, it was observed that hops, as a whole, have a wide range of applications due to their potential active ingredients and bioactivities.

There are several works that report hops as a plant of diverse bioactive properties and its compounds. Since ancient times in traditional medicine, mainly for the treatment of sleep disorders the cones of the plant were used as sedatives. Hops is also used in cosmetic preparations as a flavoring agent in perfumes, shower gels, hair cosmetics even can be used for topical applications. We know that *Humulus lupulus* L. is known worldwide as a raw material and essential flavoring in beer production, or flavouring sweet wines.<sup>[17]</sup> It can also be used in the textile industry, as food, and for decoration.

Several of the plant compounds such as acyclic hydrocarbons like  $\beta$ -myrcene, and sesquiterpenes like  $\alpha$ -humulene,  $\beta$ -caryophyllene, and  $\beta$ -farnesene, xanthohumol, 8-prenylnaringenin, polyphenols, essential oil, resins, and alpha and beta acids, are considered compounds with bioactive properties such as estrogenic, antiallergic, antiinflammatory, antimicrobial, and antioxidant properties among other activities.<sup>[170,171]</sup> New approach as metabolomic methods can clarify and used as tools to understand the compounds<sup>[172]</sup> and their activity and possibilities of used in new applications in health, medicine and well-being.

Thus, it is necessary to conduct further studies regarding the cosmetic application because it is little reported, nonetheless the utilization of nanoparticles for development of formulations to prevent oxidation as pharmaceuticals application instead of food use, was reported by Lela and co-workers in 2022. Although its use still is mostly for the brewing industry.<sup>[173]</sup>

The use in cosmetics can be further studied because hops have a lot of potential of its active compounds and bioactivity, which should, however, be studied for future work.

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