

REVIEW

Chemical constituents and bioactivities of hops (*Humulus lupulus* L.) and their effects on beer-related microorganisms

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Abstract

The female inflorescence of hops is traditionally used in the brewing industry to impart bitterness, aroma, flavour and longer shelf life to beer, where the bittering acids are the main compounds that enhance the quality of the beer. In recent years, a wide variety of bioactive compounds have been reported to be present in female flowers. Due to the growing consumer interests in natural ingredients, a great deal of research has been carried out in the last few years to find new sources of functional biomolecules. This paper reviews the recent applications of hops in the food, pharmaceutical and cosmetic industries and provides an overview of the bioactive potential of hops. In addition, the analytical techniques of hops compound are reviewed. The biological activities of hops compound such as antibacterial, antifungal, cardioprotective, antioxidant, anti-inflammatory and anticancer are reviewed and the recent effects of hop bittering derivatives on beer-related microbial activity are also presented. It is thus clear that hops have a high potential as bioactive components for use as preservatives in fresh foods to extend shelf life and as cosmetic formulations for skin care products as well as nutraceutical and health implications.

KEYWORDS

analysis technologies, anti-microorganism activities, bioactivities, bitter acids, functional molecules, hops, *humulus lupulus*, pharmacognosy, sedative activity

1 | INTRODUCTION

Beer is one of the oldest and most widespread alcoholic beverages in the world. Moderate beer drinking has positive effects on human intestinal microflora, blood glucose and β -cell function, and has cardiovascular health benefits (de Gaetano et al., 2016; Hernandez-Quiroz et al., 2019). Its intake disrupts the hormonal regulation of the reproductive system in male rats and reduces the apoptosis of interstitial cells (Oczkowski et al., 2019). In addition, beer has some antimutagenic and anticancer effects (González-SanJosé et al., 2017). All such benefits may be related to hops. Hops in beer provide rich aroma and flavour for beer, which is one of the indispensable raw materials in beer brewing. In addition to a wide range of biological activities, hops have sedative and hypnotic nerve activities (Benkherouf et al., 2019; Lelovas et al., 2008). Hops also contain many chemical components, such as resins (α -acid and β -acid), flavonoids, polyphenols, fructose and so on. Among them, flavonoids or polyphenols could prevent osteoporosis and control menopausal symptoms (Karabin et al., 2015). Also, flavonoids might protect against acute liver injury by reducing oxidative stress (Zhou et al., 2018). The polyphenols in hops have good antioxidant activity (Shahidi & Ambigaipalan, 2015), which could prevent the occurrence of human chronic diseases (Sharma, 2014), and extend the shelf life of food, or have the antiproliferative potential for melanoma cell growth (Yanez et al., 2004). For instance, xanthohumol (XN), a specific polyphenol or flavonoid, might act as a potential antitumour-promoting agent, exhibit anti-inflammatory properties by inhibiting the activities of cyclooxygenase-1 and cyclooxygenase-2 (Gerhauser, 2005b; Gerhauser et al., 2002). It may also be a potential anticancer drug that could slow the malignant progression of triple negative breast cancers (TNBC; Kim et al., 2013). In addition, XN, in combination with other inherent compounds in beer, may have antioxidant, antiproliferative and anticancer effects on humans (Henley et al., 2014; Li et al., 2015a, 2015b). Those flavonoids derived from hops have showed good anti-proliferative activity against human cancer cells (Busch et al., 2015). Flavonoids from hops could inhibit the proliferation of three human cancer cell lines (MCF-7, HT-29 and A-2780), especially in inhibiting the growth of human breast cancer cells (MCF-7) and ovarian cancer cells (A2780; Miranda et al., 1999). Polyphenols have shown not only anticancer activity but also other biological activities (Arranz et al., 2012), such as antimutagenesis 34 and inhibition of α -amylase 3S and angiotensin I convertase (Tagashira et al., 1997). The hop flavonoids also showed alleviation of the postmenopausal discomfort (Keiler et al., 2015).

A review of colon tumours in rats treated with β -acids showed a significant reduction of 70%–80% (Kuntz et al., 1999; Lamy et al., 2007). Hexahydro β -acids, the β -acid derivatives, could produce an oxidative cellular environment that induces DNA damage and GADD153 gene activation, which in turn triggers apoptosis in HL-60 cells (Liu et al., 2011). The β -acids induced apoptosis by activating the TRAIL signalling pathway in SW480 human colon cancer cell line (TRAIL-sensitive) and its derived TRAIL-resistant metastatic cell line (Lamy et al., 2008, 2011).

In caution, drinking beer might not fully and directly receive such benefits because heavy consumption of beer can lead to alcoholic cirrhosis, therefore, researchers are alternatively looking into the hop ingredients (Pelletier et al., 2002). This paper reviews the recent applications of hop compounds in the food, pharmaceutical and cosmetic industries, and provides an overview of the bioactive potential of hops.

2 | CHEMICAL CONSTITUENTS

The reason that the brewing industry considers hops as a beer additive is mainly because the final beer product after hops addition can provide a longer shelf life, biological stability, much stable foam and pleasant bitter flavour due to its bitter acid content (Cattoor et al., 2013).

2.1 | Botany

It is well known that pellets of hops contribute to the bitterness taste and aroma enrichment in final beer. The source of these pellets is the female cone of plant *Humulus lupulus* (Ntourtoglou et al., 2020). The *Humulus* genus belongs to the family of the *Cannabaceae* (hemp) and the order of *Rosales* (rosids) (Kobus-Cisowska et al., 2019a; The Angiosperm Phylogeny Group, 2003), and used to be described as of *Urticaceae* order (Van Cleemput et al., 2009a, 2009b, 2009c). Except for *Humulus*, the only other genus in this family is *Cannabis*, which has only one representative species of *C. sativa* (Stevens, 1967). Found in Yunnan from southwest China in 1936, the species *H. yunnanensis* was defined as *H. lupulus* (Almaguer et al., 2014; Alonso-Esteban et al., 2019). But two representative species are the common hops (*H. lupulus* L.) and the Japanese hops (*H. japonicus* Zieb. and Zucc.) (Abram et al., 2015). Most probably spread from China, all of these three species are dioecious, herbaceous vines and perennial plants (Murakami et al., 2006). Due to the fact that there is no lupulin glands in *H. japonicus*, the necessity for brewing becomes void (Almaguer et al., 2014).

The bracts and bracteoles have petal-like stipular structures which form the hops cone surrounding the central strig or axis (Figure 1a–e). When the hops have matured, the fine yellow resinous powder called lupulin glands forms in the part of bracteoles base and is weakly attached to the cones (Verzele & De Keukeleire, 1991). The lupulin glands, however, can only be secreted by the female cones (Figure 1f–g). Essential oils and resins are synthesized and accumulated in this main brewing tissue of hops (Stevens, 1967). The compounds that triggered the particular cultivars notes in organoleptic properties of beer are mainly three groups, the volatile secondary metabolites that are made up of hydrocarbons (monoterpenes, sesquiterpenes

and aliphatics), oxygenated compounds such as alcohols, epoxides, esters and ketones, and finally thionated compounds, accumulated in hops cones (Steenackers et al., 2015).

The terpenoid pathway, bitter acid pathway and XN pathway can be found in the paper written by (Nagel et al., 2008) Table 1 shows the main hop polyphenols.

2.2 | Resins and essential oils

The main compounds that are found in cones are resins, proteins, polyphenols, waxes, essential oils, lipids and

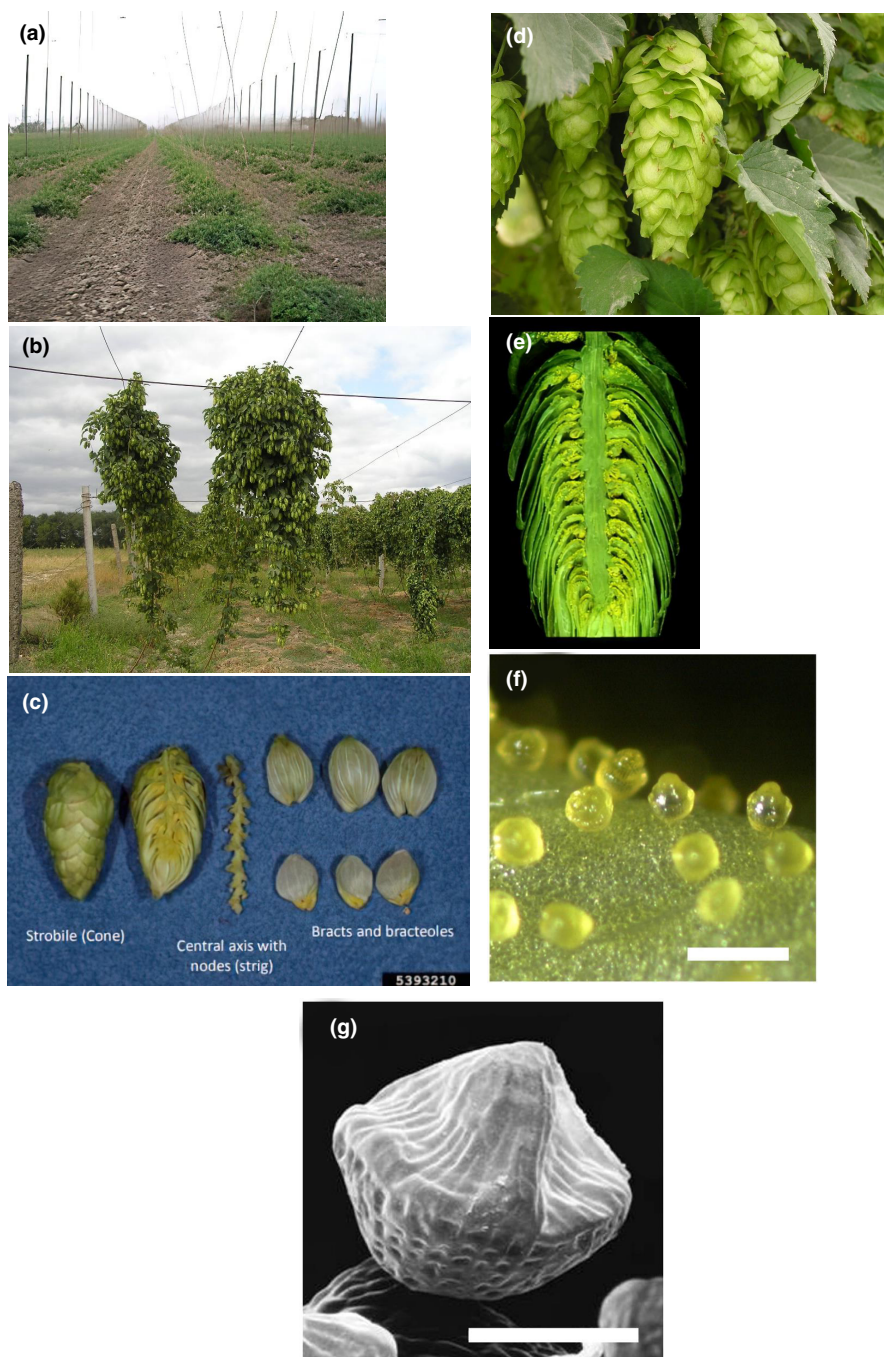


FIGURE 1 Hop and its cones morphology. (a) Spring growth of hop plants; (Gent et al., 2008) (b) Trellising of hops, which growing very tall on a supported stock, photo courtesy of Dr Nie; (c) Female hop strobiles (cones), section view of hop cones, central axis with nodes (strig), and Bracts and bracteoles, from left to right respectively; (Aron, Ting, and Ryder 2012) (d) Cones of hop cultivar Tsingtao flower, photo courtesy of Dr Nie; (e) Longitudinal section of a hop cone showing lupulin glands at the base of bracteoles, photo courtesy of Oregon State University. (f) A light microscopy image of ripe lupulin glands, Bar = 500 mm; (Nagel et al., 2008) (g) Scanning electron micrograph of a ripe lupulin gland showing the peaked appearance of the filled subcuticular sac, Bar = 100 mm. (Nagel et al., 2008)

TABLE 1 Constituents of the hop polyphenol fraction

	Classification	Name	Description
Hop Polyphenols	Flavonols	Quercetin	Quercetin was one the main compounds identified and quantified in hop shoot extracts (Maietti et al., 2017)
		Kaempferol	Kaempferol is member of a flavonoid subclass mentioned as flavonols and is found in hops (Rajendran et al., 2014)
		Myricetin	Regarding the hop plant, myricetin is one of the dominant flavonols (Dušek et al., 2021)
		Flavonol glycosides	The flavonol glycosides, is mostly related to the aglycones quercetin and kaempferol but with different carbohydrate residues (Sägesser & Deinzer, 1996)
		Rutin	Rutin is a UV-B-absorbing secondary plant metabolite synthesized in higher plants, mosses and ferns in order to protect them from the harmful effects of UV-B radiation and disease (Fabjan et al., 2003)
	Flavan-3-ols	Astragalin	Astragalin significantly inhibited the mRNA expression of all inflammatory mediators (Kou et al., 2008)
		Catechin	(+)–Catechin and (–)-epicatechin are compounds of great importance in different industrial sectors. These are widely used as functional ingredients not only in functional foods, dietary supplements and nutraceuticals to promote consumers health, prevent various diseases and extend the product shelf life but also in different pharmaceutical and cosmetic formulations (Alonso-Esteban et al., 2019)
		Epicatechin	
		Flavanol dimers	Flavanol dimers linked through a methylene bridge and related unsymmetrical diaromatic methylene have been recently described as natural substances from <i>Glycosmis montana</i> , <i>Agrimonia pilosa</i> or produced by fermentation of cacao liquor (Boyer & Ducrot, 2005)
		Oligomeric flavanols	Flavanols are biologically active molecules that have a wide range of effects and are known as very strong antioxidants that can scavenge various forms of free radicals (Fernandes et al., 2012)
	Phenolic carboxylic acids	Polymers(tannins)	Tannins are universally present in plants and represent the fourth most abundant group of secondary metabolites after cellulose, hemicellulose and lignins (Sharma, 2019)
		Ferulic Acid	Ferulic acid (FA) is a type of aromatic acid compound that mainly exists in the cell walls of grass, plants, nuts, etc. During wine making and beer brewing, these phenolic acids can be released from the grape and malt into the juice and wort respectively (Xu et al., 2020)
	Other polyphenols	Prenylflavanoids	Prenylflavanoids are present in human fluids (plasma and urine) mainly as glucuronidated and sulphated metabolites (Quifer-Rada et al., 2017)
		Multifidol glucosides	co-, ad-, n- and co-iso-multifidol glucosides, which are phloroglucinol derivatives with prenyl side chains, have been found in hops (Stevens et al., 1998; Chadwick et al., 2004; Stevens et al., 2002; Taylor et al., 2003)
		Resveratrol	Resveratrol is a phytoalexin produced by a variety of plants in response to stress, injury or fungal infection (Jerkovic & Collin, 2007)

cellulose. The resins in the hops make up between 10% and 30% of the dry matter of the cone, soft resins account for 9%–27.5% of the dry matter and hard resins for 1.5%–2.5% of the dry matter, and together they make up the resins in the hops. The bitter acids that are derived from hops are accountable for imparting the taste of bitterness in beers, and the α -acids, or humulones, along with β -acids,

or lupulones, are derivatives of prenylated phloroglucinol which belongs to the hop-derived bitter acids (Van Cleemput et al., 2009a, 2009b, 2009c; Yan et al., 2019).

The α - and β -acids represent a great portion of the dry constituents of hop cones and they are associated with flavour and bitterness of beer, besides playing an important role in plant properties, including antimicrobial potential

(Afonso et al., 2021). The α -acids isomerized to iso- α -acids under high temperature conditions. Iso- α -acids are considered the main agents of beer bitterness, also exhibiting antibacterial activity, mainly against Gram-positive bacteria (Astray et al., 2020). Furthermore, the β -acids constitute approximately 10% of the hop dry weight and play a potential role in plant characteristic flavour and antimicrobial activity (Arruda et al., 2021). In addition, an experiment proved the involvement of a functional metabolon of membrane-bound prenyltransferases in bitter acid biosynthesis in hop (Li et al., 2015a, 2015b). Table 2 shows the main hop bitter acids.

The thermal isomerization of the α -acids (humulone, cohumulone and adhumulone) to the iso- α -acids (isohumulone, isocohumulone and isoadhumulone) via an acyloin-type ring contraction. Conversion of each α -acid results in two epimeric iso- α -acids, distinguished as *trans*- and *cis*-iso- α -acid (Salfer et al., 2020). Consequently, six major iso- α -acids are present in beer, that is, the *trans*- and *cis*-isomers of isocohumulone, isohumulone and isoadhumulone. At most 50%–60% of α -acids could be yielded to iso- α -acids as isomerization form during wort boiling, and the ratio even changes during the different brewing processes (Bastgen et al., 2020). Poor isomerization of the α -acid is attributed to the limited solubility of the α -acid in the wort, incomplete isomerization during boiling, and depletion of the α -acid and iso- α -acid due to the formation of adsorption on the trub (Jaskula et al., 2008). The fundamental mechanism of the α -acids isomerized to iso- α -acids has been revealed in 1971 (De Keukeleire & Verzele,

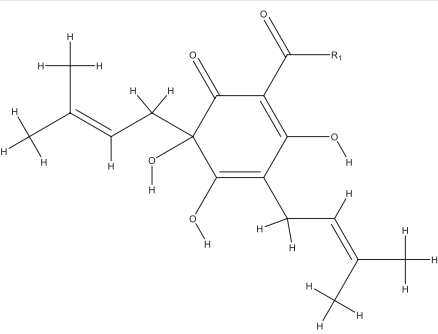
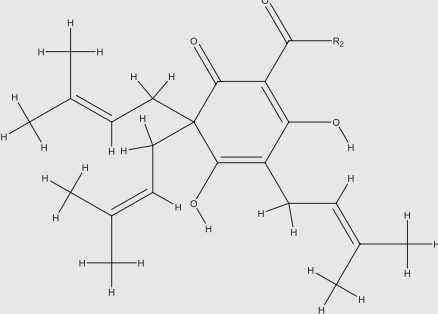
1971) and a detailed reaction mechanism has been provided by Jaskula-Goiris et al. (2010) (Figure 2).

The β -acids cannot isomerize in the same way as the α -acids. The most important property of β -acids that determines their behaviour in the course of the brewing process is oxidation initiated by airborne oxygen. Hop β -acids are sensitive to oxidation reactions initialized by air (Krofta et al., 2019), and the oxidation of hop β -acids occurs during natural ageing (Ano et al., 2020). The anti-depressant activity of hops extracts can be hypothetically explained by the mechanism of lupulones (β -acids) activating the Ca^{2+} channels (Schulz et al., 2018). Recently, Hao et al. (2020) reviewed that there are total 39 bitter derivatives of α - (15), iso- α - (15), β -acids (9) (including various trace and minor oxidized hop acid products) found in beer and model solutions.

2.3 | Methods to analyse aroma compounds

There are various ways to analyse the hops volatile aroma compounds. The important features of each sample preparation technique has been summarized in Table 3, apart from that, the hydrodistillation (Pistelli et al., 2018), gas chromatography with quadrupole accurate mass time-of-flight mass spectrometry (Yan et al., 2018), gas chromatography with accurate mass time-of-flight mass spectrometry (Yan et al., 2019), capillary zone electrophoresis with

TABLE 2 The structure of main hop bitter acids (Caballero et al., 2012; Sanz et al., 2019; Zeković et al., 2007)

Acids	Structure	R	Synonym
α -acids		$\text{R}_1 = \text{CH}_2\text{CH}(\text{CH}_3)_2$	Humulone
		$\text{R}_1 = \text{CH}(\text{CH}_3)_2$	Cohumulone
		$\text{R}_1 = \text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3$	Adhumulone
		$\text{R}_1 = (\text{CH}_2)_2\text{CH}(\text{CH}_3)_2$	Prehumulone
		$\text{R}_1 = \text{CH}_2\text{CH}_3$	Posthumulone
β -acids		$\text{R}_2 = \text{CH}_2\text{CH}(\text{CH}_3)_2$	Lupulone
		$\text{R}_2 = \text{CH}(\text{CH}_3)_2$	Columulone
		$\text{R}_2 = \text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3$	Adlumulone
		$\text{R}_2 = (\text{CH}_2)_2\text{CH}(\text{CH}_3)_2$	Prelumulone
		$\text{R}_2 = \text{CH}_2\text{CH}_3$	Postlumulone

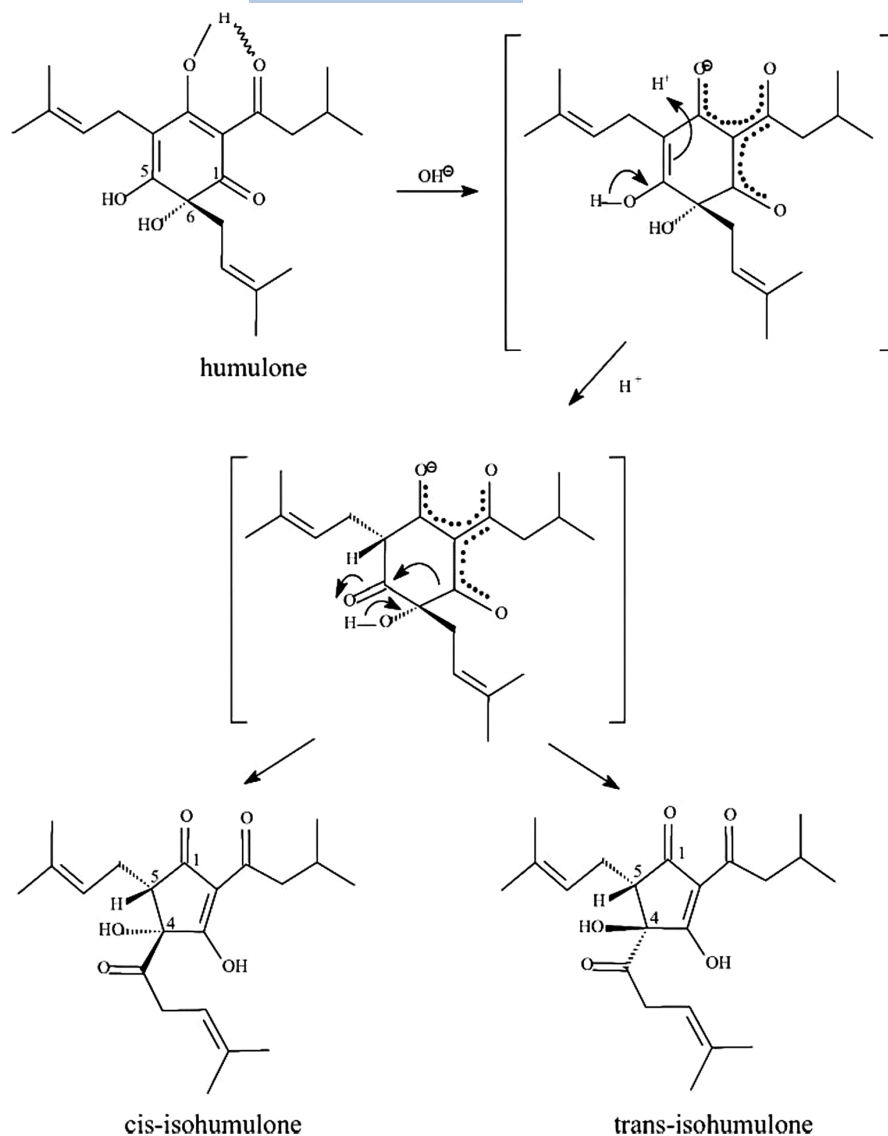


FIGURE 2 Detail reaction mechanism of the α -acids isomerization into iso- α -acids. (Jaskula-Goiris et al., 2010)

direct absorption ultraviolet detection (Duarte et al., 2020), simultaneous headspace gas chromatography-mass spectrometry ion mobility spectrometry (Brendel et al., 2020), ultra-microscale-fractionation technique coupling ultra-performance liquid chromatography mass spectrometry (McCallum et al., 2020) and pulsed electric field (Ntourtoglou et al., 2020) have been applied in hops aroma analyses.

2.4 | Main aroma compounds

Almost all temperate regions have grown hops in the world (Kobus-Cisowska et al., 2019b). A large number of hops varieties are applied commercially with distinct odour characteristics. Factors such as geographical location, climate and agronomical mainly affect the volatile composition of hops (Ceh et al., 2007; International Hops

Growers' Convention, 2019; Kishimoto et al., 2008; Mozy et al., 2009).

The hops can endow beer a complex and desirable feature, and a highly diverse group of terpenes, terpene alcohols and esters forms the main constituents, and become an economically important crop for the brewing industry (Gonçalves et al., 2014). The monoterpene myrcene together with the α -humulene and β -caryophyllene are the predominant components in mass terms (Liu et al., 2017). They can remain in final beer through late boiling stage of beer brewing (Lermusieau et al., 2001; Takoi et al., 2010).

Although in smaller amounts, other chemical groups are also present, such as sulphur compounds, aldehydes, alcohols, esters, ketones, lactones, phenols, carboxylic acids, furans and terpenoids. Hops can vest some crucial aroma and flavours such as fruity, vegetative, caramelized, woody, earthy, floral, spicy and smoked characteristics. (Table 4).

TABLE 3 The typical methods of hops compound analyses

Method	Advantages	Disadvantages	Representative hops varieties used in the method	References ^a
Steam distillation	Simplest method for isolation of essential oil; operator time required shorter than solvent extraction; produces enough hops oil for further separation; high concentration of sulphur compounds than vacuum distillation or CO ₂ extracts due to high temperature	Affect the amounts of oxidation products, and oxidation	Nugget, Hallertauer Triplloid, Cascade, Chinook, Cluster, Saaz, Tettnang, Willamette	Eyres and Dufour (2009), Likens and Nickerson (1967), Nickerson and Van Engel (1992), Wright and Connery (1951)
Simultaneous distillation extraction	Evaporated oils directly and continuously collected in organic solvents pentane, which combines distillation with liquid–liquid solvent extraction	Raised temperature during distillation can make artefact formation become true; the Maillard or Strecker reaction might format sugars and free amino acids into additional, nongenuine aroma compounds or the amount of the genuine aroma compound may increase in food samples; formation of esters or acetyls is also possible; important food aroma compounds like furaneol, are known to be discriminated	Late Cluster	Engel et al. (1999), Nickerson and Likens (1966), Pickenhagen et al. (1981), Richter et al. (2017), Schieberle (1995), Weurman et al. (1970)
Liquid–liquid extraction	α - and β -acids declined in time has been frozen in the hops aging process, so that the brewing character of the hops at the time of extraction has been preserved	Aged hops were not extracted with liquid CO ₂ because of many of the UV active hops acid degradation products accumulated	Northern Brewer, Bullion Comet, Wye Norihdown, Wye Target, Wye Saxon	D R J Laws et al. (1977), Derek R J Laws et al. (1977), Grimmert and Peppard (1983), Priest et al. (1991)
Direct thermal desorption	The yield of essential oil is higher than simultaneous distillation extraction method because of the sample preparation has the minimum loss; Hops varietal characterization for the varieties can be analysed; Suitable for analysis of individual cone and large numbers of hops samples, each sample need only 1g; no need of other solvents or other time-consuming sample preparation; directly coupled to GC/MS	This complex sample preparation for volatile analysis is frequently connected with a risk of indefinable analyse loss	Nugget, Galena, Willamette, Cluster	Aberl and Coelhan (2012a), Eri et al. (2000), Esteban et al. (1993), Esteban et al. (1996), Graham et al. (2010), Robson et al. (2018)
Direct microwave desorption	Improved from direct thermal desorption method, 60 s sample preparation, requires 0.3 g of plant with no usage of solvent	–	–	Abolghasemi and Piryaee (2020)

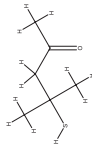
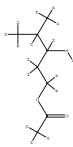
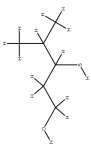
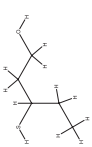
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TABLE 3 (Continued)

Method	Advantages	Disadvantages	Representative hops varieties used in the method	References ^a
Static headspace	A high number of samples can be analysed in a relative short time; quick and simple sample preparation and easy to automate	Difficult to obtain quantitative data	Saaz, Cluster, Hallertau Perle, Pacific Gem, Sticklebrast, Tettnang Hallertauer	Jorge and Trugo (2003), Wu et al. (1998)
Headspace solid phase micro-extraction	Hydrophobic and volatile analyses can be handled simply and reproducibly; solvent-free; the ratios between two important constituents, which are two sesquiterpenes, α -humulene and β -caryophyllene, can be monitored to characterize hops	Difficult to obtain quantitative data due to strong analyte–matrix interactions; the extraction time increased because the high molecular weight volatiles have a slow evaporation speed (can increase the extraction temperature to promote evaporation rate)	Cascade, Aurora, Celeia, Magnum Savinjski Golding, Sybilla, Lubelski, Pulaswki, Magnat, Marynka	Charry-Parra et al. (2011), Field et al. (1996), Gonçalves et al. (2014), Jelen et al. (1998), Kataoka et al. (2000), Kovačević and Kač (2001), Matich et al. (1996), Pistelli et al. (2018), Prosen and Zupančič-Kralj (1999), Rocha et al. (2001), Van Opstaele et al. (2010), Wolfe (2012), Zhang and Pawliszyn (1993)
Dynamic headspace	The qualitative evaluation of flavour compounds has a better result than Static Headspace; sample clean-up is not necessary before GC analysis	The requirement to trap the volatiles need some special equipment; the low sensitivity is a problem, but using Headspace solid phase micro-extraction instead can eliminate this issue	Magnum	Aberl and Coelho (2012b), Barani et al. (2006), Salanță et al. (2012), Steinhaus et al. (2003)
Stir bar sorptive extraction	Quantification of terpenoids is accurate; the limits of detection and quantification are lower than other conventional methodology; Due to the polymeric coating of this method is much larger than solid phase micro-extraction method, the sensitivities is much higher	Many factors can affect the extraction since the basis of volatile extraction technique is the equilibrium of analyses between sample solution and poly-(dimethylsiloxane) solid phase; this method cannot effectively extract polar compounds so that acids, short carbon chain alcohols, and ethyl acetate, were not quantified	Citra, Simcoe, Hallertau Mitelfruh, Saaz, Cascade, Centennial, Chinook, East Kent Goldings	Baltussen et al. (1999), Bicchietti et al. (2002), Fang and Qian (2006), Fang and Qian (2012), Juan-García et al. (2004), Kishimoto et al. (2005), Kishimoto et al. (2020), Sharp et al. (2016)

^aThe definition and technology of those methods can be found in References column.

TABLE 4 The main flavour chemical compounds that are derived from hops

Principal odour	Compound ⁱ	Chemical Structure	Compound type	Odour descriptors	Representative source (hops varieties and others)	References
Fruity ^a	4-Methyl-4-sulfanylpentan-2-one		Sulphur compounds	Grape fruit, mango, black currant, box tree	Nelson Sauvin	Buettner and Schieberle (1999), Buettner and Schieberle, (2001b), Takoi et al. (2009)
	3-sulfanyl-4-methylpentyl acetate		Sulphur compounds	Grape fruit	Nelson Sauvin, Tomahawk	Gros et al. (2011), Takazumi et al. (2017), Takoi et al. (2009)
	3-sulfanyl-4-methylpentan-1-ol		Sulphur compounds	Grape fruit, rhubarb	Nelson Sauvin, Hallertau Blanc	Cibaka et al. (2015), Cibaka et al. (2016), Takoi et al. (2009)
	(S- glutathione) 3-sulfanylhexan-1-ol		Sulphur compounds	Passion fruit, grape fruit	Sorachi Ace, Cascade, Nelson Sauvin, Amarillo, Citra, Hallertau Blanc, Polaris, Saaz	Chenot et al. (2019), Cibaka et al. (2015), Engel and Tressl (1991), Gros et al. (2012), Ochial et al. (2015), Takoi et al. (2009), Tominaga and Dubourdieu (2000)
	3-sulfanylpentan-1-ol		Sulphur compounds	Grape fruit, citrus zest	Nelson Sauvin	Takoi et al. (2009), Thibon et al. (2010)
Hexanal	Hexanal		Aldehydes	Apple, pear, strawberry, raspberry, blackcurrant, cherry, plum, apricot, kiwi, table grapes, grape fruit, orange, melon, banana, mango, green	Nugget	Buettner and Schieberle (2001a), Buettner and Schieberle (2001b), Carballo et al. (2020), Christensen and Pedersen (2006), Garcia et al. (2012), Gómez et al. (1993), Hayaloglu and Demir (2016), Jeti et al. (2007), Jianrong et al. (2015), Jordán et al. (2001), Klesk et al. (2004), Mehinagic et al. (2006), Pino and Febles (2013), Pu et al. (2020), Rizzolo et al. (2005), Wang and Lin (2014), Wu et al. (2016)
	Hexanol		Alcohols	Appal, strawberry, raspberry, cherry, plum, passion fruit, sweet	Saaz (tetra-hydro isomerized hops extract of Saaz)	Dixon and Hewett (2000), Gonçalves et al. (2014), Jeti et al. (2007), Klesk et al. (2004), Pino and Quijano (2012), Pu et al. (2020), Sun et al. (2010)
2-Nonanol			Alcohols	Pulpy, fruity	Saaz, Lublin, Spalt, Backa, Hallertau	Peacock and McCarty (1992), de Sousa Galvão et al. (2011)

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TABLE 4 (Continued)

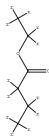
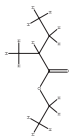
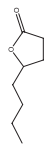
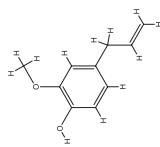
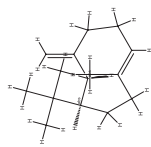
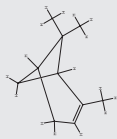
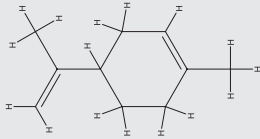
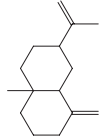
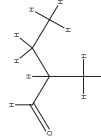
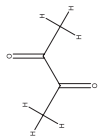
Principal odour	Compound ⁱ	Chemical Structure	Compound type	Odour descriptors	Representative source varieties and others	References
	Ethyl butanoate		Esters	Apple, pear, strawberry, raspberry, blackcurrant, cherry, plum, apricot, kiwi, table grapes, grapefruit, orange, lemon, melon, mango, pineapple, passion fruit	Typical aroma found in beer of dry hopped Hallertauer Mandarina Bavaria, Hallertauer Cascade, or Hallertauer Mittelfrüh, byproducts of the yeast metabolism	Buettner and Schieberle (2001a), Buettner and Schieberle (2001b), Christensen and Pedersen (2006), Garcia et al. (2012), Gómez et al. (1993), Hayaloglu and Demir (2016), Jetti et al. (2007), Jianrong et al. (2015), Jordán et al. (2002), Klesk et al. (2004), Mehinagic et al. (2006), Rizzolo et al. (2005), Tokitomo et al. (2005), Tomiyama et al. (2012), Wang and Lin (2014), Wu et al. (2016)
	Ethyl 2-methyl butanoate		Esters	Apple, raspberry, sweet	Spalter Select	Brendel et al. (2020), Klesk et al. (2004), Mehinagic et al. (2006), Steinhaus and Schieberle (2000)
	2-Undecanone		Ketones	Raspberry, banana, citrus	Hallertau Tradition, Saphir, Spalter Select, Tettnanger	Klesk et al. (2004), Pino and Febles (2013), Van Opstaele et al. (2012), Van Opstaele et al. (2013)
	γ-Octalactone		Lactones	Peach, plum, apricot, melon, mango, pineapple	Sweet aroma can be found in Gueuze and Lambic beers aged in oak	Garcia et al. (2012), Gómez et al. (1993), Jianrong et al. (2015), Pino and Febles (2013), Pino and Mesa (2006), Tokitomo et al. (2005)
	Eugenol		Phenols	Peach, plum, apricot, lemon, melon, banana, mango	Cascade, Hallertauer Hersbrucker, Saaz	Eyres et al. (2007), Garcia et al. (2012), Gómez et al. (1993), Jianrong et al. (2015), Jordán et al. (2001), Pino and Febles (2013), Pino and Mesa (2006), Tomiyama et al. (2012)
	β-Caryophyllene		Terpenoids	mango	Nugget, Perle, Saaz	Pino and Mesa (2006), Vázquez-Araújo et al. (2013)

TABLE 4 (Continued)

Principal odour	Compound ^b	Chemical Structure	Compound type	Odour descriptors	Representative source varieties and others	References
Vegetative ^b	α -pinene		Terpenoids	Herbaceous, pine, resin	Spalter Select, Perle, Hallertauer, Saphir, Hallertauer Tradition, Tettmanger, Cascade	Aberl and Coelhan (2012b), Christensen and Pedersen (2006), Engel and Tressl (1991), Klesk et al. (2004), Pino and Mesa (2006), Rodolfi et al. (2019), Tominaga and Dubourdieu (2000)
	Camphene		Terpenoids	Herbaceous, pine, resin, camphoraceous	Hallertau Mittelfruh	Katsiotis et al. (1989), Lee et al. (2011), Steinhaus and Schieberle (2000), Van Opstaele et al. (2012)
	D,L-limonene		Terpenoids	herbal, lemon, raspberry, blackcurrant, cherry, plum, grape fruit, orange, mango, pineapple, mint	Cascade	Buettner and Schieberle (1999), Cheng et al. (2018), Christensen and Pedersen (2006), Hayaloglu and Demir (2016), Kelebek and Selli (2011), Klesk et al. (2004), PHI et al. (2006), Picard et al. (2018), Pino and Mesa (2006), Pino and Quijano (2012), Rodolfi et al. (2019)
Caramelized ^c	β -Selinene		Terpenoids	Nutty, almonds, floral, globe artichoke, stale, dry grass, hay, herbaceous, woody, celery	Cascade, Agnus, Tomahawk, Nelson Sauvin, Nugget, Cascade, Saaz, Challenger	Gros et al. (2011), Krofta et al. (2018), Lee et al. (2011), Lermusieau and Collin (2001), MacLeod and de Troconis (1982), MacLeod et al. (1982), Moon et al. (2018), Mudge et al. (2019), Pino et al. (2002), Rodolfi et al. (2019)
	2-Methylbutanal		Aldehydes	Cocoa, malty, pineapple, musty, nutty	Spalter Select	Grimm and Steinhaus (2019), Haber et al. (2019), Pino (2013), Steinhaus and Schieberle (2000), Yang et al. (2021)
	2,3-Butanedione		Ketones	Creamy, sour, sweet, strawberry, raspberry, blackcurrant, buttery	Spalter Select	Christensen and Pedersen (2006), Jetti et al. (2007), Klesk et al. (2004), Pu et al. (2020), Steinhaus and Schieberle (2000)

(Continues)

TABLE 4 (Continued)

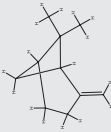
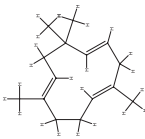
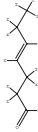
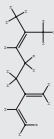
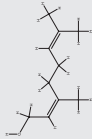
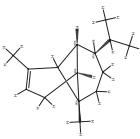
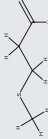
Principal odour	Compound ^d	Chemical Structure	Compound type	Odour descriptors	Representative source (hops varieties and others)	References
Woody ^d	β -pinene		Terpenoids	Woody, resinous, mango, metallic, citrusy	Hallertau mittelfruh, Yeoman	Dharmawan et al. (2009), Katsiotis et al. (1989), Pino and Mesa (2006)
Earthy ^e	α -humulene		Terpenoids	Musty, woody, resin, spicy, clove, herbaceous, mango, citrusy, cool, floral, fragrant, globe artichoke, slightly peppery, balsamic	Cascade	Gros et al. (2011), Lee et al. (2011), Luo et al. (2017), MacLeod and de Troconis (1982), MacLeod et al. (1982), PHI et al. (2006), Pino and Mesa (2006), Rodolfi et al. (2019), Steinhaus and Schieberle (2000), Xiao et al. (2017)
	(E)-4-Heptenal		Aldehydes	Rancid, old cream	Spalter Select	Majcher et al. (2018), Munk et al. (2000), Steinhaus and Schieberle (2000)
Floral ^f	β -Myrcene		Terpenoids	Geraniums, grassy, pungent, metallic, herbal, raspberry, plum, apricot, grape fruit, orange, mango, passion fruit, balsamic, spicy, musty	Cascade	Buettner and Schieberle (1999), Buettner and Schieberle (2001a), Buettner and Schieberle (2001b), Janzantti and Monteiro (2014), Klesk et al. (2004), Luo et al. (2017), Moon et al. (2018), Munafa et al. (2016), PHI et al. (2006), PHI et al. (2006), Pino and Mesa (2006), Pino and Quijano (2012), Jianrong et al. (2015), Rodolfi et al. (2019), Steinhaus and Schieberle (2000), Tamura et al. (1996), Xiao et al. (2017)
	Nonanal		Aldehydes	Floral, rose, candle, orange, fatty, soapy, strawberry, raspberry, cherry, peach, plum, apricot, table grapes, grape fruit, orange, melon, mango,	Spalter Select	Buettner and Schieberle (2001a), Buettner and Schieberle (2001b), Dharmawan et al. (2009), Eduardo et al. (2010), Gómez et al. (1993), Jetti et al. (2007), Klesk et al. (2004), Perry et al. (2009), PHI et al. (2006), Pino and Mesa (2006), Steinhaus and Schieberle (2000), Sun et al. (2010), Wu et al. (2016), Yang et al. (2021), Zhu et al. (2018)

TABLE 4 (Continued)

Principal odour	Compound ⁱ	Chemical Structure	Compound type	Odour descriptors	Representative source (hops varieties and others)	References
	Nerol		Alcohols	Sweet rose, lemon	Marco Polo, SA-1	Liu et al. (2020), Parker (2012)
Spicy ^g	α-Copaene		Terpenoids	Spicy, passion fruit, woody	Premiant, Bullion	Buttery et al. (1967), Janzantti and Monteiro (2014), Luo et al. (2017), Patzak et al. (2001), Pino et al. (2002)
Smoked ^h	3-methylthiopropenal		Sulphur compounds	Toasted and cooked potato, Blackcurrant, Raspberry and grape fruit	Spalter Select	Buettner and Schieberle (1999), Buettner and Schieberle (2001a), Di et al. (2003), Klesk et al. (2004), Lermusieau et al. (2001), Steinhaus and Schieberle (2000), Varming et al. (2004)
	2-sulfanylethyl acetate		Sulphur compounds	Toasted, grilled, burnt	Challenger, Saaz	Chenot et al. (2019), Gros et al. (2012)
	2-sulfanylethan-1-ol		Sulphur compounds	Grilled	Tomahawk, Nelson Sauvin, Cascade, Saaz	Chenot, Briffoz, et al. (2019), Cibaka et al. (2015)

^aFruity aroma including tropical and temperate fruits, such as apple, pear, dark berries, red and black currant, cherry, peach, plum, Kiwi fruits, table wine grapes, grape fruit, orange, melon, lemon, banana, guava, mango, pineapple and passion fruit.

^bVegetative aroma including olive, tea, mint, leaves, thyme, basil, parsley, rosemary, fennel, onion, garlic.

^cCaramelized aroma: honey, chocolate, balsamic, buttery and coffee.

^dWoody aroma: Oak, tobacco, resin and leather.

^eEarthy aroma: musty, mushroom and dusty.

^fFloral aroma: violet, rose, linalool, lily, geranium, carnation, lavender and lilac.

^gSpicy aroma: black pepper, chilli, clove, ginger and cinnamon.

^hSmoked aroma: toasted, grilled and cooked.

ⁱThe odour clarification is derived from the aroma wheel, which was found by Noble et al. (1987).

TABLE 5 The structures of tetrahydroiso- α -acids, dihydroiso- α -acids, and hexahydroiso- α -acids

Acids	Structure
Iso- α -acids	
dihydroiso- α -acids	
tetrahydroiso- α -acids	
hexahydroiso- α -acid	

TABLE 5 (Continued)

Acids	Structure
R	Iso- α -acids
CH(CH ₃) ₂	Isocohumulone
CH ₂ CH(CH ₃) ₂	Isohumulone
CH(CH ₃)CH ₂ CH ₃	Isoadhumulone
CH ₂ CH ₃	Isoposthumulone
CH ₂ CH ₂ CH(CH ₃) ₂	Isoprehumulone
CH ₂ CH ₂ CH ₂ CH ₂ CH ₃	Isoadprehumulone

The hop essential oils are the mixtures of above-mentioned organic compounds (such as geraniol, linalool, terpineol, terpinene, humulene, myrcene, caryophyllene, esters et al.) and the essential oils are also considered to be among the most identified and important odours in hops. For instance, α -pinene is one of the most broadly encountered terpenoids in nature, belonging to the bicyclic monoterpene (Noma & Asakawa, 2015). It is a broad-spectrum antibiotic (Nissen et al., 2010), in *Sideritis* spp, and is a major component with noticeable activity against Methicillin-resistant *Staphylococcus aureus* (Köse et al., 2010). In humans, an anti-inflammatory function through PGE-1 has been found (Maayah et al., 2020). Perry et al. reported that 1,8-cineole and α -pinene in the essential oil of Sage (*Salvia* spp) showed the activity of cholinesterase inhibition. The activity as an acetylcholinesterase inhibitor, which can aid memories (Perry et al., 2000), can neutralize short-term memory scarcities tempted by tetrahydrocannabinol intoxication (Maayah et al., 2020).

By far the largest group of secondary metabolites is terpenoids, which exist ubiquitously in plants as well as in the hop plant. Derived from five carbon precursor isoprenoids, terpenoids are indispensable components in cosmetics, food and drugs (Lange et al., 2000).

Typically, the esters have sweet and fruity flavour, while citric, spicy, herbaceous and spices categories can be found in terpenoids, ketones have floral notes and aldehydes contribute to the green and herb attributes (Cibaka et al., 2015; Eyres et al., 2007; Steinhaus & Schieberle, 2000; Van Opstaele et al., 2012).

3 | BIOLOGICAL ACTIVITIES

3.1 | Anticarcinogenic activity

Beer α - and β -acids and iso- α -acids, as well as XN, iso-XN are found to have an antiproliferative effect on human colon cancer Caco-2 cells, and its antiproliferative effect depends on the addition of hops during brewing (Cattoor

et al., 2010; Júlio et al., 2017). Keiler et al evaluated the effect on the growth of breast cancer in ovariectomized rats or on the proliferative activity of breast glands in normal rats by using hops extracts containing 0.42% estrogenic flavanone and 8-prenylnaringenin(8-PN) to judge the safety of hops extracts (Keiler, Macejova, et al., 2017). Phytoestrogen 8-PN in hops extracts could regulate the function of E-cadherin/catenin complex in human breast cancer cells and demonstrated a certain preventive effect on the occurrence of breast cancer (Rong et al., 2001). The α -acids and iso- α -acids possess many biological activities relevant for cancer prevention (Gerhauser, 2005a). The antiproliferative activity of α -acids against colon cancer cell lines HT-29 and SW620 and noncancer cell line IEC-6 was demonstrated (Farag & Wessjohann, 2013), and cell proliferation was inhibited even at micromolar concentrations (Hudcová et al., 2014). The α -acid bitter substance of hops induced cysteine protease-dependent apoptosis and inhibited the adhesion of certain cancer cells to bone tissue, thus inhibiting the growth of cancer cells *in vitro* (Tyrrell et al., 2010). Tetrahydroiso- α -acid and hexahydroiso- α -acid, which are iso- α -acid derivatives might inhibit the proliferation of human hepatoma cells and reduce the formation of liver tumours in rats (Starkel et al., 2015). Table 5 shows the structures of tetrahydroiso- α -acids, dihydroiso- α -acids and hexhydroiso- α -acids.

3.2 | Anti-aging activity

Hops have been used as an antianxiety and hypnotic drug with a certain value (Krause et al., 2014; Zanolli & Zavatti, 2008). The α -acids in hops could prevent the development of the metabolic syndrome (Karabın et al., 2016a; Van Cleemput et al., 2009a, 2009b, 2009c). The daily intake of hops extracts, as a potent phytoestrogen, has good effects on vasomotor symptoms and other menopausal discomforts (Aghamiri et al., 2016; Van Breemen et al., 2014; Heyerick et al., 2006; Keiler et al., 2013; Overk et al., 2008). The iso- α -acid bitter component in beer could

prevent cognitive decline and obesity (Ayabe et al., 2017), and is beneficial to obesity and the attenuation of metabolic syndrome (Ano et al., 2018). Ingestion of iso- α -acids in beer increased the activity of hippocampal dopaminergic neurons and improved spatial and curtain memory. Some reports have reported that dopamine is involved in hippocampal-dependent memory, iso- α -acid can activate the dopaminergic neuronal system, improve memory function. Therefore, the intake of iso- α -acids might promote cognitive decline by activating memory function. The iso- α -acid bitter substance of beer could prevent inflammation and cognitive impairment in Alzheimer's disease (Ano et al., 2017). Transcription levels in the hippocampus of mice were increased by oral administration of iso- α -acids, but there was no effect on the cerebral cortex (Fukuda et al., 2018). Iso- α -acids might inhibit neuroinflammation and improve cognitive function, which may be useful for the prevention of dementia (Ano et al., 2017). Mice with obesity and diabetes were fed tetrahydroiso- α -acids for 8 weeks, resulting in a positive effect on adipocyte metabolism and glucose tolerance in mice (Everard et al., 2012).

3.3 | Cardiovascular impacts

Hops are generally extracted by any organic solvent or supercritical CO₂ into a hop extract and a spent hop. The hop extract mainly consists of extractable hop resins and essential oils and the spent hop consists of remaining polar substances and cellulose. The spent hop extract can be extracted by ethanol/water or water to afford a vast group of polyphenols. The spent hop extract was found to inhibit ADP-induced platelet aggregation, which might have a potential beneficial role in the regulation of platelet and endothelial function (Luzak et al., 2016). In the hop extract, four isomerized α -acid derivatives: iso, dihydro, tetrahydro and hexahydro iso- α -acid with similar structures but different chemical alternations were studied for the long-term stability in whole blood (Rodda et al., 2014).

The 8-prenylnaringenin (8-butenyl naringenin) of flavonoids in hops could be used to treat vascularized forms of cancer and other angiogenesis-related diseases (Pepper et al., 2004). Serum in blood has an antagonistic effect on the bacteriostasis of lupulone (Sacks & Humphreys, 1951), iso- α -acid levels detected in blood and urine correlated with the type of beer consumed (Rodda et al., 2015).

3.4 | Anti-inflammatory

Extraction is the well-established, long-term method of collecting natural substances from solid materials, and

hops extracts is a substitute for pellets in the brewing industry, concentrating the two major ingredients (essential oils and α -acids) is the main purpose of hops extraction, and the final product can result in different composition due to various extraction technologies and conditions (Forster et al., 2014; Sanz et al., 2019). Currently, the most common solvent in brewing industry for the manufacture of hops extracts is supercritical carbon dioxide, which can extract nearly all essential oils, a high ratio of bitter acids and a small amount of other hops components without unpleasant solvents (Cheng et al., 2021; He et al., 2005; Jackowski et al., 2015). Hops extracts (mainly α -, β -acids and essential oils) exerted anti-inflammatory activity on human gastric epithelial cells by inhibiting the secretion of IL-8 (Sangiovanni et al., 2019). The addition of iso- α -acids (isomerized α -acids) enhanced the microglial phagocytosis of A β and inhibited the production of TNF- α through the stimulation of lipopolysaccharide, thus achieving the effect of preventing brain inflammation (Ayabe et al., 2017). Pilna et al tested the in vitro antimicrobial activity of ethanol and supercritical CO₂ hops extracts, which are recognized as safe (GRAS) agents against planktonic cultures of cariogenic, periodontal and candidal bacteria (oral pathogenic microorganisms). The results indicated that the hop extracts (the most active ingredients of α - and β -acids) were promising antiseptic agents of oral care products against *Capsicum annuum*, *Capsicum frutescens*, *Myristica fragrans*, *Punica granatum* and *Zanthoxylum clava-herculis* (Pilna et al., 2015a). It has been known that the constituents of α - and β -acids in hop extract as well as iso- α -acids have excellent inhibitory effects on the growth of Gram-positive bacteria (Chen et al., 2014; Dumas et al., 2009a; Sakamoto & Konings, 2003), and the antimicrobial effect increased with the decrease in pH (Simpson, 1992). In addition, iso- α -acids had moderate antiviral activity against bovine viral diarrhoea virus (BVDV) and cytomegalovirus (CMV) (Buckwold et al., 2004). The β -acids and hexahydro- β -acids have been claimed for inhibition of the growth of *Helicobacter pylori*, which is a common cause of gastric ulcers and chronic active gastritis in humans (Johnson & Haas, 2001). This microorganism induces gastric damage and may be involved in the pathogenesis of gastric cancer. The hop bract extract containing high molecular weight of polyphenol (catechin) had the strongest inhibitory activity against *H. pylori*-vacuolating cytotoxin, VacA. It is suggesting that the hop bract or spent hop extract may be useful for the prevention of gastric ulcer and inflammation caused by VacA (Yahiro et al., 2005). Both α - and iso- α -acids can inhibit tumour necrosis factor-induced inflammation by regulating NF- κ B-, AP-1-, and CREB-dependent gene transcription (Lee et al., 2007; Van

Cleemput et al., 2009a, 2009b, 2009c). Nitric oxide productions could be decreased by both water and ethanol extracts of hops. The water extracts decreased interleukin-6 secretion and tumour necrosis factor- α but presented no effect on interleukin-1 β , while ethanol extracts declined interleukin-1 β and interleukin-6 secretion but increased tumour necrosis factor- α secretion. The ethanol extracts of hops showed higher anti-inflammatory activities than the water extracts, except for tumour necrosis factor- α secretion (Wu et al., 2020).

3.5 | Other activities

For ovariectomized rats, the addition of hops extracts significantly reduced the number of osteoclasts in the metaphysis of the tibia and prevented the decrease in trabecular thickness due to oestradiol depletion (Keiler, Helle, et al., 2017). Hops extracts, however, did not prevent ovariectomy-induced changes in lumbar spine microstructure. Mice treated orally with iso- α -acid-rich hops extracts seemed to exhibit signs of liver protection from acute alcohol-induced steatosis through iNOS activation (Hege et al., 2018; Kanuri et al., 2014; Landmann et al., 2017). Yuan et al studied the possibility of drug-plant interactions caused by hops extracts and hops prenylphenols by inhibiting human cytochrome P450 enzymes. Medicines or botanicals share the same metabolic and transport proteins, including cytochrome P450 (CYP) enzymes, glucuronosyltransferases (UGTs) and P-glycoprotein (Pgp), with over-the-counter and prescription medicines increasing the likelihood of drug-botanical interactions (Yuan et al., 2014). The bitter substance α -acid and other compounds in hops show good antioxidant activity. (Tagashira et al., 1995) The α -acid are bone resorption inhibitor during bone formation and shown a good inhibitory activity (Tobe, Kubota, et al., 1997; Tobe, Muraki, et al., 1997), and its IC₅₀ value was 5.9×10^{-9} M (Tobe, Kubota, et al., 1997; Tobe, Muraki, et al., 1997), and they were also an effective candidate for differentiation therapy of monocytic leukaemia (Honma et al., 1998). The mixture of α - and β -acids (623 mg/g of dry weight) was found to be highly active with 95% alleviated oxidative stress, more than the mixture of α -acids (275 mg/g dry weight) and XN (102 mg/g dry weight) with 65%, in lipid peroxidation and protein carbonylation tests (Kontek et al., 2021).

4 | THE INHIBITION EFFECTS ON *SACCHAROMYCES CEREVISIAE*

Regarding iso- α -acid effects on *S. cerevisiae boulardii* yeast, the results showed that iso- α -acids do not change

the *S. cerevisiae* activity but prevents the culture from being contaminated by *Pediococcus pentosaceus* (Michiu et al., 2019).

Growth inhibition occurred at concentrations of hop iso- α -acids that were an order of magnitude higher than those found with hop-tolerant prokaryotes. Yeast tolerance to hop iso- α -acids involves three major processes, active proton pumping into the vacuole by the vacuolar-type ATPase to enable vacuolar sequestration of iso- α -acids and alteration of cell wall structure and, to a lesser extent, active export of iso- α -acids across the plasma membrane. Furthermore, iso- α -acids were shown to affect cellular metal homeostasis by acting as strong zinc and iron chelators (Hazelwood et al., 2010).

5 | THE INHIBITION EFFECTS ON OTHER MICROORGANISMS

The mixture of α -acids, β -acids, cohumulone or colupulone shows the anti-microorganisms of most Gram-positive bacteria (*Bifidobacterium dentium*, *Bifidobacterium longum*, *Lactobacillus salivarius*, *Streptococcus mutans*, *Streptococcus salivarius* and *Streptococcus sobrinus*) at minimum inhibitory concentration (MIC) = 8–64 μ g/ml, some Gram-negative bacteria (*Aggregatibacter actinomycetemcomitans*, *Eikenella corrodens*, *Fusobacterium nucleatum* and *Porphyromonas gingivalis*) at MIC $\geq$ 32 μ g/ml, and the yeast *Candida albicans* at MIC = 512 μ g/ml (Pilna et al., 2015b).

Ferulic acid, one of simple phenolic acids, exerts weaker activity, but it still has significant activity against several Gram-positive bacteria such as *S. aureus*, *L. monocytogenes* and Gram-negative bacteria, including *Pseudomonas aeruginosa* (Karabın et al., 2016b).

Humulinic acid inhibits *Lactobacillus brevis* at MIC < 10 μ M (Schurr et al., 2015).

Humulone, lupulone as well as XN individually lowered the number of bacterial cells released from the biofilm against a selected group of *Staphylococcus* spp, with the strongest effect seen for lupulone, followed by XN (Bogdanova et al., 2018).

Lupulone was found to against the growth of methicillin-sensitive *Staphylococcus aureus* and methicillin-resistant *Staphylococcus aureus* with MIC values of 0.6–1.2 μ g/ml and 19.5–39 μ g/ml for desmethyloxanthohumol (Bocquet et al., 2019).

Both iso- α and β -acids showed reliable inhibitory effects at pH 6.0–7.0 and pH 4.0–5.0 against *Pediococcus pentosaceus* (Michiu et al., 2019).

The antifungal activity against *Zymoseptoria tritici* has been demonstrated by co-humulone and desmethyloxanthohumol, which has a half-maximal inhibitory

concentration of 0.11 and 0.2 g/L respectively (Bocquet et al., 2018).

Studies showed that XN has a broad spectrum of anti-infective activities against bacteria such as *Streptococcus mutans* (Bhattacharya et al., 2003) and *Staphylococcus aureus* (Yamaguchi et al., 2009). The growth of *Staphylococcus aureus* was inhibited by XN with a MIC range of 15.6–62.5 µg/mL, potent anti-adherent and antibiofilm activity was also found by XN (Rozalski et al., 2013), methicillin-sensitive *Staphylococcus aureus* and methicillin-resistant *Staphylococcus aureus* with MIC values of 9.8–19.5 µg/ml inhibited by XN (Bocquet et al., 2019). Also, XN demonstrates the antifungal activity as evidenced by the inhibition of *Trichophyton mentagrophytes* and *Trichophyton rubrum* (Gerhäuser, 2005). Although it has a broad spectrum of antimicrobial activity, XN does not affect the composition of intestinal microbiota in rats (Hanske et al., 2005), suggesting an unchanged profile for intestinal microbiota when XN is administrated *in vivo*. *In vitro* assays against *Bacteroides fragilis*, *Clostridium perfringens* and *Clostridium difficile* strains, and makes it potentially an alternative treatment of nosocomial diarrhoea caused by resistant strains (Cermak et al., 2017).

The growth of methicillin-sensitive and -resistant *Staphylococcus aureus* and *Staphylococcus epidermidis* was inhibited by α,β -dihydroxanthohumol and 8-prenylnaringenin, which had the lowest MIC₈₀ value of 0.5 µg/ml (Bartmańska et al., 2018).

6 | THE INHIBITION EFFECTS ON MICROORGANISMS BY HOPS-DERIVED COMPOUNDS

The supercritical CO₂ hop extracts as a deodorant, by using clinical underarm odour-reduction test, the function of antibacterial activity against *Corynebacterium xerosis* and *Staphylococcus epidermidis* has been confirmed (Dumas et al., 2009b).

In the microdilution test the hop extract inhibited the growth of *Propionibacterium acnes* and *Staphylococcus aureus* already at a MIC of 3.1 and 9.4 µg/ml respectively. In addition, the antibacterial activity in the agar diffusion test by a gel formulation with 0.3% hop extracts (w/w) against *P. acnes* and *S. aureus* showed an inhibition zone value of 5.5 mm and 3 mm, respectively, which indicated that hops extracts could be a substitute treatment selection for acne-prone skin (Weber et al., 2019).

Kramer et al. studied the antimicrobial effect *in vitro* of several hop extracts against *Listeria monocytogenes*, *Staphylococcus aureus*, *Salmonella enterica* and *Escherichia coli* in a model meat marinade and on

marinated pork tenderloins. The results obtained by authors demonstrated that the Gram-positive bacteria were highly inhibited by hop extracts due to its content in β -acids, but in the case of extracts containing α -acids, the inhibition was lower; in contrast, Gram-negative bacteria exhibited a high resistance against all evaluated hop extracts (Kramer et al., 2015).

The growth of *Aspergillus parasiticus*, *Aspergillus niger*, *Penicillium carneum*, *Penicillium chermesinum*, *Penicillium paneum*, *Penicillium polonicum* and *Penicillium roqueforti* are inhibited by hop extract, and the shelf life, rheological and sensory features of wheat bread adding hop extract have been formulated (Nionelli et al., 2018).

The extracted crude ethyl acetate, acetone and methanol from spent hops displayed antifungal activity against *Fusarium culmorum*, *Fusarium oxysporum*, and *Fusarium semitectum* with the lowest MIC₅₀ of 0.5 mg/ml, whereas the growth of *Botrytis cinerea* was inhibited by methylene chloride extract with the MIC₅₀ of 1 mg/ml (Bartmańska et al., 2018).

Hop seed extracts, which have antioxidant flavan-3-ols, (+)-catechin and (–)-epicatechin identified, showed significant antimicrobial properties, much superior than the positive controls against bacteria named *Bacillus cereus*, *Listeria monocytogenes*, *Enterococcus faecalis*, *Escherichia coli*, and *Salmonella typhimurium* as well as fungi of the genus *Penicillium* (Alonso-Esteban et al., 2019).

7 | CONCLUSIONS AND FUTURE PERSPECTIVES

Hops are traditionally used in brewing, but recent researchers have shown that the rich bioactive molecules in them have a wide range of therapeutic and other properties, and the main studies on hops have focused on the biological activity of single hop components. The main hop compounds and their applied extraction methods as well as healthy effects' descriptions have been reviewed by Hrnčić et al. (2019). The hop extracts and individual compound have not been clinically trialled by randomized, double-blind or placebo-controlled solely, although the sedating property of hops has been proved in laboratory animals. The above listed effects (anti-angiogenetic, antiproliferative and apoptotic) and activities (antioxidant, anti-inflammatory, antilipoperoxidative) are mainly assessed in *in vitro* studies, which reasonably hint at a potential chemopreventive activity. The broad-spectrum anti-infective activity against several microorganisms by hops are also proved. The animal model *in vivo* study of distribution, bioavailability, safety and efficacy of the hop components are in high demand prior to its application in humans. As consumers increasingly demand natural

ingredients with health properties, hop extracts or hop compounds can be used in food, cosmetics, nutraceuticals and pharmaceuticals, thus opening up new alternatives to traditional uses in the formulation of different goods. However, due to the wide variety of biomolecules present in hop extracts, studies on their interactions with other components of the matrix to which they are added and their bioavailability when consumed as part of food are necessary, and the different and even contradictory findings on the activity of the β -acid fraction require detailed reinvestigation. Future research on hops has high academic prospects if it can be focused on safe and effective dosages for humans and their effects on all aspects of health.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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