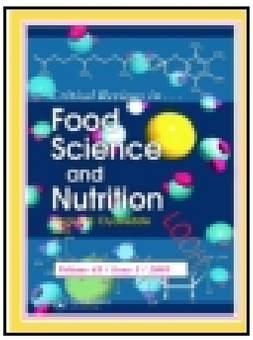

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REVIEW

Hop bioactive compounds in prevention of nutrition-related noncommunicable diseases

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ABSTRACT

Nutrition-related noncommunicable diseases (NR-NCDs) such as cardiovascular disease and type 2 diabetes both negatively impact the quality of life of many individuals and generate a substantial burden on society, demonstrating a need for intervention. Phytochemicals are investigated as a potential approach for combating NR-NCDs, and those found in hops have gained increased attention in recent decades. Hops, the strobile of the plant *Humulus lupulus*, are grown primarily for the brewing industry as they confer taste and increased shelf-life. The bitter acids represent the main compounds of interest for improving beer quality. Additionally, bitter acids as well as the prenylated chalcone xanthohumol, exhibit a wide range of health beneficial properties. This review summarizes those beneficial effects of bitter acids and xanthohumol on NR-NCDs, including inflammatory and immune diseases, obesity and metabolic disorders, as well as cancer prevention.

KEYWORDS

Hops; bitter acids; xanthohumol; obesity; cancer; intestinal health

Introduction

Globally, since the latter part of the twentieth century, the burden generated by nutrition-related noncommunicable disease (NR-NCD), which includes cancer, diabetes, and cardiovascular disease, has increased as a result of demographic and lifestyle changes (Popkin 2002; Popkin and Gordon-Larsen 2004). The rise of sedentary lifestyle, consumption of diets high in fats and sugar, and increased lifespans all contribute to the higher prevalence of NR-NCD (Musaiger and Al-Hazzaa 2012). In 2012, almost 50% of all noninstitutionalized adults in the United States suffered from at least one chronic condition. Among this group of adults, around half of them had two or more chronic conditions (Ward et al. 2014). Thus, it is imperative to reduce the strain resulting from NR-NCDs. Phytochemicals found in commonly cultivated plants display bioactive properties with the potential to help combat NR-NCDs (Zhang et al. 2015).

Hops (*Humulus lupulus)* have interacted with human civilization for centuries and possess unique chemical constituents which have received attention in the last decades. Belonging to the family Cannabaceae, *Humulus* most likely originated in China before spreading elsewhere (Murakami et al. 2006). The genus contains three species, *H. lupulus*, *H. japonicus*, and *H. yunnanensis*, all of which are dioecious, herbaceous vines (Small 1978). Documentation over the cultivation of hops goes as far back as the ninth century AD. Cultivation surged following the Middle Ages, once it became established as the principal flavoring agent of beer (Behre 1999). Outside of brewing, historic usage of hops includes serving as a remedy for different ailments. In various parts of the world, traditional medicine included the intake of hops to treat inflammation, pneumonia, indigestion, insomnia, and dysentery (Zanoli and Zavatti 2008).

The glandular trichomes of the female inflorescences are their most important components when it comes to the production of secondary metabolites of interest. They are also referred to as the lupulin glands and reside on the bracteoles, producing large quantities of bitter acids and prenylated chalcones (De Keukeleire et al. 2003; Naya and Kotake 1971). Bitter acids and xanthohumol, the most abundant prenylated flavonoid in hops (Stevens and Page 2004), are the most widely studied components with regards to health beneficial properties. The present review summarizes the beneficial effects of bitter acids and xanthohumol exert on NR-NCDs.

Structure and absorption

Bitter acids

Structure and chemistry

The bitter acids represent the group of compounds of greatest interest to brewers. Beer relies on bitter acids for flavor, stability, and protection against spoilage microorganisms (De Keukeleire 2000). The bitter acids include two kinds of prenylated phloroglucinols, α- (humulone) and β-acids (lupulone) (Figure 1(A–C)). Humulones contain two prenyl groups, while lupulones differ by containing three prenyl groups. Together humulones and lupulones contribute up to 20% or more of the dry weight of hop cones (De Keukeleire 2000). Within hops, they occur as mixtures with the main forms being humulone/lupulone, cohumulone/colupulone, and adhumulone/adlupulone. Other forms present in lower

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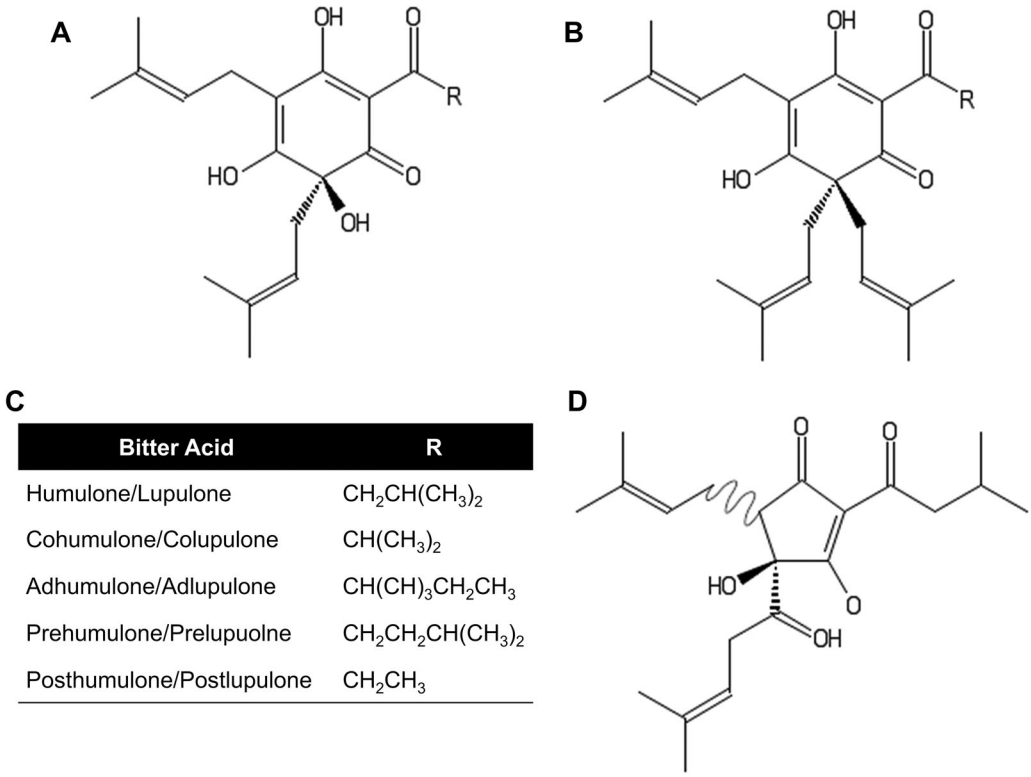

Figure 1. Structure of humulone/lupulone analogues and isohumulone. A: humulone analogues; B: lupulone analogues; C: chemical formula of analogue R-group; D: isohumulone.

concentrations include posthumulone/postlupulone, prehumulone/prelupulone and adprehumulone/adprelupulone (Zhang et al. 2004). When exposed to increased heat, such as those utilized during the worst boiling stage of beer production, α-acids isomerize to either *cis-* or *trans-* iso-α-acids (Figure 1(D)) (Jaskula et al. 2008). The iso-α-acids possess superior bitterness than their precursors, making their contribution to the flavor of beer greater (De Keukeleire 2000).

Absorption and metabolism

The human colon adenocarcinoma line, Caco-2, undergoes spontaneous differentiation, ultimately resembling enterocytes and functioning as a model for intestinal absorption (Balimane et al. 2000). In Caco-2 cell monolayers, humulone displays greater absorption ($P_{app} = 14 \pm 2 \times 10^{-6}$ cm/s) than lupulone ($P_{app} = 0.9 \pm 0.1 \times 10^{-6}$ cm/s). The absorption of lupulone resembles that of atenolol ($P_{app} = 0.45 \pm 0.18 \times 10^{-6}$ cm/s), a marker of lower permeability. Among the analogues of humulone and lupulone, different absorption values occur. Absorption of cohumulone ($P_{app} = 41 \pm 2 \times 10^{-6}$ cm/s) surpasses that of humulone. Colupulone ($P_{app} = 2.1 \pm 0.9 \times 10^{-6}$ cm/s) demonstrates a similar pattern with that of lupulone (Cattoor et al. 2010). The absorption of isohumulone in Caco-2 cells ($P_{app} = 4.62 \pm 1.29 \times 10^{-6}$ cm/s) was greater than that of lupulone (Cattoor et al. 2011).

Following intake, humulones, lupulones, and isohumulones all undergo biotransformation resulting in different metabolites. After being incubated with either human or rabbit liver microsomes for 2 hours, isohumulones displayed the greatest resistance to metabolization (Cattoor et al. 2013). Human liver microsomes metabolized 73 ± 3%, 95 ± 1%, and 48 ± 2% of incubated humulone, lupulone, and isohumulone, respectively, producing humulinones, hulupones, and humulinic acid (Cattoor et al. 2013).

Xanthohumol

Structure and chemistry

Xanthohumol is a prenylated chalcone (Figure 2). Chalcones are open-chain flavonoids with two aromatic rings (Nowakowska 2007). Xanthohumol contributes to 0.1–1% of hop cones' dry weight, making it the major prenylflavonoid constituent (Stevens and Page 2004). Like the bitter acids found in hops, xanthohumol undergoes isomerization to isoxanthohumol (Figure 2) during the brewing process, becoming less biologically active (Stevens et al. 1999). Combined with low solubility, isomerization results in low levels of xanthohumol present in beer (Karabín et al. 2013).

Absorption and metabolism

Xanthohumol is poorly absorbed ($P_{app} = 0.133 \pm 0.003 \times 10^{-6}$ cm/s), similar to sucrose ($P_{app} = 0.196 \pm 0.05 \times 10^{-6}$ cm/s), another marker of low permeability (Pang et al. 2007). Pang et al. (2007) also found that xanthohumol primarily accumulates in the cytosol upon entering enterocytes and binds to cytosolic proteins. Following oral administration, the majority of xanthohumol gets excreted in feces (Avula et al. 2004). The bioavailability of xanthohumol decreases with increased dosage, a trend

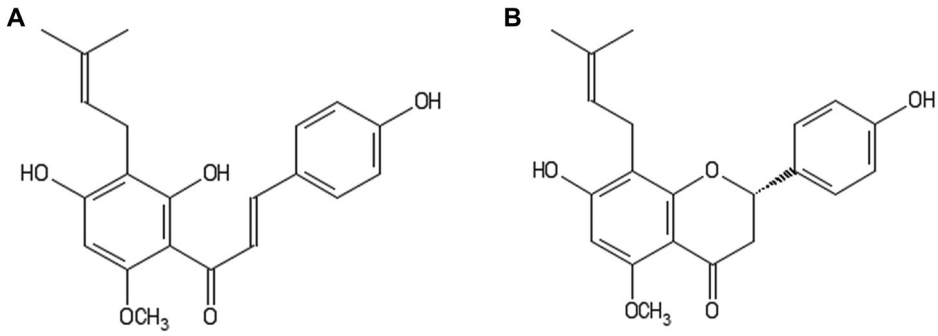

Figure 2. Structure of xanthohumol and isoxanthohumol. A: xanthohumol; B: isoxanthohumol.

exhibited by other flavonoids, with low, medium, and high doses resulting in 33%, 13%, and 11% bioavailability, respectively in rats (Legette et al. 2012). The maximum plasma concentrations of xanthohumol 1 hour following a single oral intake at a dose of 20, 60, or 180 mg were 45 ± 7 μg/L, 67 ± 11 μg/L, and 133 ± 23 μg/L, respectively (Legette et al. 2014).

Out of the prenylated compounds present in hops, 8-prenylnarigenin exerts the greatest estrogenic activity (Milligan et al. 2000). Since it can be produced from isoxanthohumol, there is concern that consumption of dietary xanthohumol and isoxanthohumol results in increased 8-prenylnarigenin exposure (Possemiers et al. 2005). In a human study, test subjects who took xanthohumol had either trace amounts or no circulating 8-prenylnaringenin (Legette et al. 2014). In addition, formation of 8-prenylnaringenin depends on gut microbiota. A study comparing germ-free mice with human microbiota-associated mice found that only the latter contained 8-prenylnaringenin in their excrements (Hanske et al. 2010). Incubation of hop prenylflavonoids with 12 different human intestinal bacteria isolated from feces showed isoxanthohumol converting to 8-prenylnaringenin in one third of the samples (Possemiers et al. 2005). Intestinal microbes involved with the metabolism of xanthohumol and other prenylated chalcones include *Eubacterium limosum* that possess the ability to activate isoxanthohumol to 8-prenylnaringenin through *O*-demethylation and *Eubacterium ramulus* that metabolizes both xanthohumol and 8-prenylnaringenin to desmethylxanthohumol (Paraiso et al. 2019; Possemiers et al. 2005).

Obesity and metabolic syndrome

Metabolic syndrome encompasses a variety of risk factors, and depending on the organization, gets defined differently. Typically, metabolic syndrome's prognosis involves a combination of some or all the following risk factors: hypertension, hyperglycemia, obesity, low levels of high-density lipoprotein, and high triglyceride levels. It is estimated that about one-third of the population of the United States are obese, which is closely associated with metabolic syndrome, and have an increased relative risk of mortality (Saklayen 2018; Wu et al. 2010). This obesity is mainly caused by excessive energy intake, excessive white tissue build-up, and adipocyte hypertrophy, detrimental for human health metabolically (Bartelt and Heeren 2014). The potential of hop-derived bioactive components to mitigate weight gain (Table 1) and other markers of metabolic syndrome (Figure 3) were summarized in this section.

Antiobesity effects

The supplementation of isomerized hop extract to a high fat diet (HFD) attenuated weight and adipose tissue gain in C57BL/6N mice in a dose-dependent manner (Ayabe et al. 2018; Yajima et al. 2005). Similarly, isomerized hop extract supplementation reduced weight gain in KK-A^y mice given a HFD (Yajima et al. 2005). In a randomized, double-blind placebo-controlled human study, matured bitter acid extract reduced both visceral and total body fat in overweight participants (Morimoto-Kobayashi et al. 2015). In addition, dietary xanthohumol supplementation reduced weight gain in HFD-fed male C57BL/6J mice (Miranda et al. 2016). The addition of a xanthohumol-rich extract to HFD fed male Wistar rats also resulted in decreased weight gain compared to the HFD control (Yui et al. 2014).

Brown adipose tissue

Brown adipose tissue (BAT) expresses uncoupling protein 1 (UCP1) which uncouples oxidative phosphorylation to dissipate energy as heat, and functions as a key site for preventing obesity and metabolic dysfunction. BAT can be separated into classic brown adipose tissue that develops during the fetal stage and inducible brown adipocytes (also called beige, brown-in-white adipocytes) which are introduced later in life (Bartelt and Heeren 2014). BAT activity is activated during cold exposure and found to be higher in lean individuals (van Marken Lichtenbelt et al. 2009). BAT recruitment can increase energy expenditure and assist with body fat reduction. It can be initiated by both cold exposure and certain chemicals such as capsinoid analogs (Yoneshiro et al. 2012) and β3-adrenergic receptor agonists (Cypess et al. 2015; Yoneshiro et al. 2013). Dietary polyphenols such as resveratrol (Wang et al. 2015), epigallocatechin-3-gallate (Lee et al. 2017), berberine (Zhang et al. 2014), as well as polyphenol-rich raspberry (Xing et al. 2018) supplementation promote white adipose tissue browning and lipid oxidation.

Consistently, the matured bitter acids stimulate BAT through enhancing BAT sympathetic nerve activity and UCP1 (Morimoto-Kobayashi et al. 2015). A subsequent

Table 1. Anti-obesity effects of bitter acids and xanthohumol.

Compound	Model	Outcomes	References
Matured hop extract	Overweight human participants	Decrease of total fat area Decrease of visceral fat area	(Morimoto-Kobayashi et al. 2015)
Iso-α-acids	Male C57BL/6J mice	Decreased weight and adipose tissue gain resulting from consumption of a high fat diet	(Ayabe et al. 2018)
Isomerized hop extract	Female C57BL/6N mice	Decreased weight gain for both mice receiving standard diets and mice receiving high fat diets	(Yajima et al. 2005)
Isomerized hop extract	Male KK-A^y mice	Decreased weight gain resulting from consumption of a high fat diet.	(Yajima et al. 2005)
Xanthohumol	Male and female Zucker obese fa/fa rats	Decreased weight gain among male rats	(Legette et al. 2013)
Xanthohumol	Male KK-A^y mice	Non-significant decreased weight gain	(Nozawa 2005)

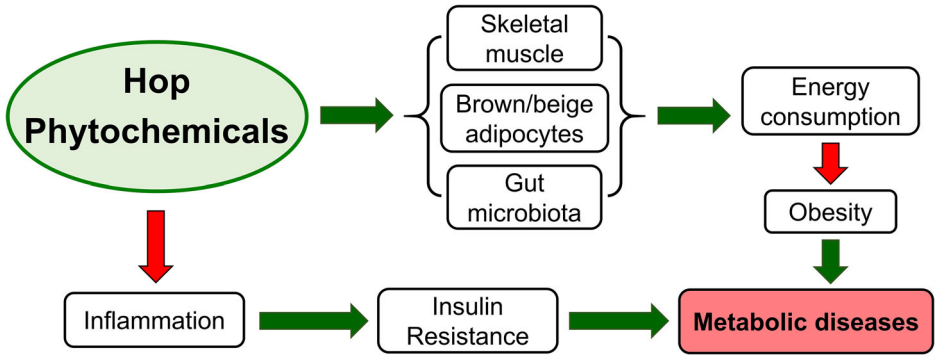

Figure 3. Potential mechanisms of hop phytochemicals in prevention of obesity and metabolic syndromes. Hop phytochemicals regulate energy expenditure through manipulation of skeletal muscle respiration, brown/beige adipose tissue thermogenesis, and bile acid receptor signaling via altering gut microbiome, combating weight gain. Furthermore, hop phytochemicals mitigate inflammation and decrease insulin resistance. Green arrows indicate promotive effects. Red arrows indicate inhibitory effects.

study found that matured bitter acid treatment induces cholecystokinin (CCK) secretion and CCK signaling is required for the upregulation of BAT sympathetic nerve activity, which increases BAT thermogenesis (Yamazaki et al. 2019). Xanthohumol induced AMP-activated protein kinase (AMPK) regulated beiging through promotion of proteins such as UCP1 (Samuels et al. 2018).

Skeletal muscle respiration

Respiration of skeletal muscle is a potential avenue for combating obesity as skeletal muscle impacts resting metabolic rate, and mice generated to overexpress UCP in their skeletal muscle resisted HFD induced weight gain (Li et al. 2000). Resveratrol is known to exert an effect on mitochondrial function and increases expression of UCP3 in skeletal muscle of mice (Lagouge et al. 2006). Treatment with 16.9 mg/kg BW of xanthohumol decreased weight gain in male Zucker fa/fa rats (Legette et al. 2013). Such effects are likely through mitochondrial uncoupling and stress response induction (Kirkwood et al. 2013).

Bile acid signaling

The farnesoid X receptor (FXR) is a nuclear hormone receptor that interacts with bile acids to help regulate energy expenditure (Ma and Patti 2014). Mice receiving HFD supplemented with a gut-restricted FXR agonist displayed ameliorated weight gain and enhanced browning of white adipose tissue (Fang et al. 2015). Berberine safeguards against HFD induced obesity in wild-type mice but not their FXR knockout counterparts (Sun et al. 2017). Intake of a basal diet containing 1% xanthohumol lowered white adipose tissue weight in HFD KK-A^y mice (Nozawa 2005). The same study identified xanthohumol as a ligand of FXR (Nozawa 2005). In addition, bioactive compounds from hops can alter gut microbiota, which converts primary bile acids to secondary bile acids, which preferably binds to another bile acid receptor, TGR5, to activate intracellular thyroid hormone signaling and prevent obesity and metabolic diseases (Watanabe et al. 2006).

Markers of metabolic syndrome

Antioxidative effects

Adiposity correlates with increased systemic oxidative stress in both humans and animals (Furukawa et al. 2004). Damage from oxidative stress caused by reactive oxygen species (ROS) and reactive nitrogen species (RNS) plays an important role in aging and the progression of different disease states (Lee et al. 2004). Excessive ROS and RNS production generates oxidative stress (Valko et al. 2007), which results in lipid peroxidation, the formation of DNA adducts, and protein damage. Antioxidants prevent the oxidation through various means such as reducing molecular oxygen, removing harmful metal ions, and scavenging radicals that trigger the initiation of oxidation (Pisoschi and Pop 2015).

Table 2. Anti-inflammatory effects of bitter acids and xanthohumol.

Compound	Model	Mechanisms of action	References
Humulone	L929sA fibrosarcoma and COS1L2A fibroblast cells	Inhibited TNF-induced activity of NF-κB, AP-1, and CREB.	(Van Cleemput et al. 2009)
	MC3T3-E1 osteoblast cells	Suppression of TNF-α-induced COX-2 activity	(Yamamoto et al. 2000)
	Mouse skin exposed to TPA	Downregulation of COX-2 expression Suppression of NF-κB, and AP-1 DNA binding Inhibition of IKK and JNK	(Lee et al. 2007)
Lupulone	L929sA fibrosarcoma and COS1L2A fibroblast cells	Inhibited TNFα-induced activity of NF-κB, AP-1, and CREB.	(Van Cleemput et al. 2009)
	RAW 264.7 macrophage cells	Inhibition of LPS-induced NO and PGE_2 activity Down regulation of iNOS and COX-2 Suppression of PI3K/Akt/IKK and ERK1/2	(Tang et al. 2011)
Isohumulone	L929sA fibrosarcoma and COS1L2A fibroblast cells	Inhibition of TNFα-induced activity of NF-κB, AP-1, and CREB.	(Van Cleemput et al. 2009)
	RAW 264.7 macrophage cells	Suppression of PGE2 Inhibition of NF-κB activity	(Konda et al. 2009; Nozawa et al. 2005)
	Male Fischer 344 rats treated with AOM	Suppression of PGE2	(Nozawa et al. 2005)
Xanthohumol	RAW 264.7 macrophage cells	Suppression of NF-κB, STAT-1α, and IRF-1 activity	(Cho et al. 2008)
	Primary human hepatocytes and hepatic stellate cells	Suppression of NF-κB	(Dorn et al. 2010)
	Male C57BL/6 mice treated with DSS	Inhibition of TNF-α and IL-1β induction Inhibition of IκBα phosphorylation Downregulation of COX-2	(Cho et al. 2018)

AP-1: activator protein-1; COX-2: cyclooxygenase-2; CREB: cAMP-response element-binding protein; ERK: extracellular signal-regulated kinase; Iκβ: inhibitor κβ; IKK: Iκβ kinase; IL: interleukin; iNOS: inducible nitric oxide synthase; IRF-1: IFN regulatory factor-1; JNK: c-Jun-N-terminal kinase; LPS: lipopolysaccharide; NF-κB: Nuclear factor-kappa B; PGE2: prostaglandin E2; PI3K: phosphatidylinositol 3-kinase; STAT: signal transducer and activator of transcription; TNF: tumor necrosis factor; TPA: tumor promoter 12-O-tetradecanoylphorbol-13-acetate.

The antioxidant capacity of humulone and lupulone was analyzed utilizing 2,2-diphenyl-1-picrylhydrazyl (DPPH), and it was found that their radical scavenging activities (3.2×10^{-5} and 2.5×10^{-5} M, IC_{50}, respectively) are comparable to those of α-tocopherol and ascorbic acid (Tagashira et al. 1995). Humulone and lupulone inhibited lipid peroxidation with an IC_{50} of 7.9×10^{-6} and 3.9×10^{-5} M, respectively (Tagashira et al. 1995). Using the oxygen radical absorbance capacity (ORAC) assay, xanthohumol was found to be 8.9 times more effective at scavenging hydroxyl radicals and 2.9 times more effective at scavenging peroxyl radicals than Trolox, a vitamin E analogue and reference compound (Gerhauser et al. 2002). Comparing the antioxidant capacity of xanthohumol, humulone, and lupulone, humulone possessed the most effective scavenging activity against nitrite radical and DPPH, while xanthohumol displayed the strongest potential against hydroxyl radical, peroxyl radical, superoxide, and ferric iron (Yamaguchi et al. 2009). In a different analysis of several hop constituents, humulone displayed the greatest hydrogen peroxide scavenging ability (Gorjanović et al. 2013). Xanthohumol pretreatment reduced lipopolysaccharides (LPS) induced reactive oxygen species formation and lessened the depletion of two antioxidant enzymes, superoxide dismutase and glutathione, in the bronchoalveolar lavage fluid and lungs of C57BL/6 mice, respectively (Lv et al. 2017).

Anti-inflammatory effects

Excessive white adipose tissue accumulation and adipocyte hypertrophy lead to low grade chronic inflammation. Obesity results in increased quantities of macrophages present in adipose tissue contributing to inflammation (Weisberg et al. 2003; Xing et al. 2018; Xu et al. 2003). The macrophages in the white adipose tissue of obese mice also display reduced expression of anti-inflammatory cytokine, IL-10 (Lumeng et al. 2007). Phytochemical and phytochemical-rich dietary supplements suppress inflammatory signaling resulting from obesity. Quercetin suppressed macrophage infiltration into epididymis adipose tissue and inflammation in C57BL/6mice (Dong et al. 2014). Dietary red raspberry supplementation mitigated macrophage infiltration and inflammatory signaling in white adipose tissues of HFD fed mice (Xing et al. 2018). Similarly, bitter acids and xanthohumol are capable of mitigating inflammation by targeting different inflammatory signaling pathways (Table 2).

Nuclear factor-κB (NF-κB), a mediator of inflammatory genes plays a role in the pathogenesis of various inflammatory diseases (Liu et al. 2017). Humulones, lupulones, and isohumulones inhibit NF-κB-dependent gene transcription, with humulone and lupulone being more effective than isohumulone (Van Cleemput et al. 2009). Humulone supplementation suppressed tumor necrosis factor-α (TNF-α) induced transcription of cyclooxygenase-2 (COX-2) in MC3T3-E1 cells (Yamamoto et al. 2000). Humulone downregulated COX-2 in 12-O-tetradecanoylphorbol-13 acetate (TPA)-treated mouse skin, through suppression of NF-κB and activator protein-1 (AP-1), attributed to inhibition of inhibitory kappaB (IκB) kinase (IKK) and c-Jun-N-terminal kinase (JNK) (Lee et al. 2007). Reduced derivatives of lupulone displayed a capacity to downregulate phosphorylation

of extracellular signal–regulated kinase (ERK)1/2 and phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt)/IKK in macrophages treated with LPS, suppressing NF-κB signaling and downregulating the expression of inducible nitric oxide synthase (iNOS) and COX-2 (Tang et al. 2011).

Humulone's isomerized counterparts can also lessen the severity of inflammation through suppression of proinflammatory mediators. In RAW 264.7 macrophage cells, rho iso-α-acids suppressed expression of NF-κB and its downstream targets and reduced glycogen synthase kinase 3α (GSK3α) activity and β-catenin phosphorylation (Konda et al. 2009). Isohumulone supplementation decreased prostaglandin E2 generation in LPS/IFN-γ treated RAW 264.7 cells and azoxymethane (AOM)-treated rats (Nozawa et al. 2005).

Inflammation contributes to the increased risk of cognitive impairment within metabolic syndrome (Yaffe et al. 2004). There is a growing interest in studying the capacity of iso-α-acids in decreasing inflammation in the tissue of the central nervous system. Iso-α-acids reduced the levels of IL-1β, IL-16, IL-12p40, macrophage inflammatory protein-1 alpha (MIP-1α), monocyte chemoattractant protein-1 (MCP-1), and TNF-α in microglial cells treated with LPS (Ano, Yoshikawa, et al. 2019). Dietary iso-α-acids conferred beneficial effects on cerebral inflammation of aged mice. Long-term dietary supplementation of 0.05% (w/w) isohumulones decreased age-related (Ano, Ohya, et al. 2019) and obesity induced (Ayabe et al. 2018) inflammation through decreasing proinflammatory cytokines such as of IL-1β and TNF-α. Furthermore, short-term (3 or 7 days) daily oral administration of 1 mg/kg of isohumulones attenuated inflammatory cytokines such as IL-12p40 and MIP-1α in Alzheimer's disease model mice (Ano, Yoshikawa, et al. 2019). Similarly, xanthohumol lessened LPS-induced inflammation in microglial cells through inhibition of NF-κB activation, and increased the translocation of nuclear factor erythroid 2-related factor 2 (NRF2) into the nucleus (Lee et al. 2011). In senescence-accelerated prone mice (SAMP8), xanthohumol supplementation ameliorated age-related increase of TNF-α and IL-1β in a dose-dependent manner (Rancán et al. 2017).

In RAW 264.7 cells treated with LPS, xanthohumol inhibited NF-κB transcriptional activity in a dose-dependent manner (Cho et al. 2008). The suppression of NF-κB by xanthohumol involved the degradation of IκBα and suppressed p65 translocation in a cysteine-dependent manner (Harikumar et al. 2009). Xanthohumol supplementation decreased levels of MCP-1 and TNF-α in macrophages and in mice fed a nonalcoholic steatohepatitis diet (Dorn et al. 2010; Lupinacci et al. 2009). Similarly, xanthohumol supplementation suppressed NF-κB's signaling pathway and proinflammatory cytokines, TNF-α, IL-1β, and malondialdehyde production in Dextran sulfate sodium (DSS)-induced colitis mice, and further mitigated inflammation-induced damage (Cho et al. 2018).

Insulin resistance and glucose tolerance

A study involving both animal and human test subjects found that isohumulones activate both PPARα and PPARγ impacting insulin resistance (Yajima et al. 2004). A two-week supplementation of isohumulones lowered non-fasting plasma glucose and lower insulin resistance in KK-A^y mice and HFD fed C57BL/6N mice (Yajima et al. 2004). In a randomized double-blind placebo-controlled study with patients diagnosed with prediabetes, 32 mg of isohumulones per day improved hyperglycemia (Obara et al. 2009).

Furthermore, dietary xanthohumol supplementation lowered plasma glucose in male Zucker fa/fa rats (Legette et al. 2013). A 20-week dietary supplementation of xanthohumol or 8-prenylnaringenin (10 mg/L in 0.1% ethanol) reduced weight gain, glucose intolerance, and insulin resistance in male C57BL/6 mice fed a HFD which was associated with AMPK activation and downregulated 6-phosphofructo-2-kinase fructose-2,6-biphosphatase 3 (PFKFB3) in liver and skeletal muscle (Costa et al. 2017). *In vitro* study showed that xanthohumol can effectively inhibit α-glucosidase, an enzyme that hydrolyzes carbohydrates and impacts blood glucose levels (Liu et al. 2014).

Cardiovascular disease

Worldwide, the leading cause of mortality is ischemic heart disease (IHD). IHD falls under the category of atherosclerotic cardiovascular disease (ACD), which also includes ischemic stroke, another leading cause of global mortality (Barquera et al. 2015). In atherosclerosis, atheroma and plaque develop. The two ultimately contribute to artery occlusion after rupturing (Hansson and Libby 2006; Herrington et al. 2016). Known risk factors for atherosclerosis related to nutrition include adiposity, blood pressure, and blood cholesterol (Herrington et al. 2016).

The addition of isohumulone to rats fed a diet high in salt helped mitigate the rise in blood pressure induced by high sodium intake (Namikoshi et al. 2007). Feeding isohumulones to mice also increases high-density lipoprotein, and supplementation of 500 mg/kg BW of isomerized hop extract resulted in a decreased atherosclerosis index (Miura et al. 2005). When comparing the ability of different hop constituents to inhibit cholesteryl ester transfer protein (CETP), xanthohumol possessed the greatest activity, which was three times greater than that of humulone and lupulone (Hirata et al. 2012a). An *in vivo* study reported that xanthohumol decreased the accumulation of cholesterol in CETP-Tg mice fed high cholesterol diets (Hirata et al. 2012b).

Gut health

A wide breadth of conditions such as inflammatory bowel disease (IBD), gastritis, and colorectal cancer fall under the umbrella of gastrointestinal diseases, and in 2015, the economic burden generated by gastrointestinal diseases totaled $135.9 billion (Peery et al. 2019). Maintenance of gut health is considered to be largely dependent on both the gastrointestinal microbiome and barrier (Bischoff 2011). Many chronic diseases involving dysregulated inflammatory responses appear to be influenced by host intestinal microbial communities (West et al. 2015). Evidence points toward proper formation of intestinal immune system requiring the

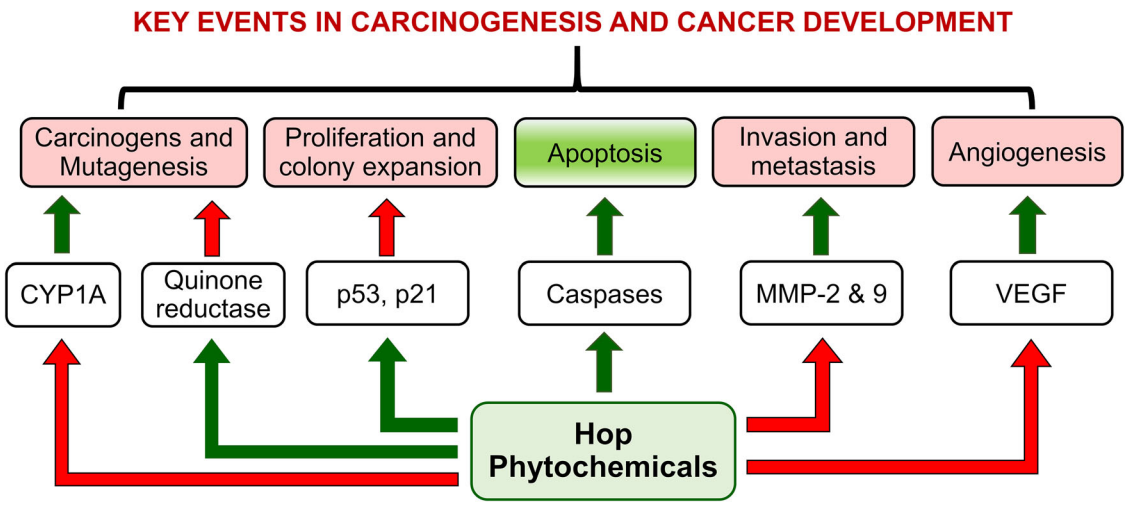

Figure 4. Potential mechanisms of hop phytochemicals on critical events during cancer development and progression. Hop phytochemicals suppress enzymes such as cytochrome P450 1A (CYP1A) that activate procarcinogens, and they enhance detoxifying enzyme quinone reductase; these compounds induce cell cycle arrest by targeting p53 and p21, and apoptosis through activation of the caspase-cascade. Furthermore, hop phytochemicals suppress cancer aggressiveness and metastasis by downregulating matrix metalloproteinases (MMP)-2 and 9, and decrease the development of new blood vessels by inhibiting vascular endothelial growth factor (VEGF). Green arrows indicate promotive effects. Red arrows indicate inhibitory effects.

presence of microorganisms. For example, *Bacteroides fragilis* colonization regulates the immune system by activating development of T-helper cells and correcting cytokine production (Mazmanian et al. 2005). Inflammation also impacts epithelial barrier function, and barrier disruption is a key etiological factor for IBD and a number of associated diseases (Vetrano et al. 2008). Research exploring the potential of hop derived compounds to modulate the gut microbiome and improve intestinal barrier integrity is brief and summarized in this section.

Effects against pathogenic bacteria and gut microbiota

Dysregulated microflora is associated with many immune-related diseases. Children who suffer from IBD (Maukonen et al. 2015), type 1 diabetes (Murri et al. 2013), and allergies (Candela et al. 2012) show compositional changes in their gut microbial communities compared to their disease-free peers. *Clostridium difficile* infection negatively impacts the levels of commensal intestinal bacteria including butyrate-producers (Antharam et al. 2013); hop bitter acids and xanthohumol exhibit inhibitory effects on pathogenic *C. difficile* isolated from patients with diarrhea, with xanthohumol being the most effective (Cermak et al. 2017). There is limited information regarding the impacts of hops and hop related bioactives on gut microbial composition. In chickens challenged with *Clostridium perfringens*, the addition of lupulone in drinking water decreased the abundance of *C. perfringens* (Tillman et al. 2011). In pigs, spent hops feeding reduced the abundance of *Streptococcus* spp. and *Clostridium* cluster XIVa in the fecal microbiota (Fiesel et al. 2014). However, the intestinal microbial composition of rats did not change following a dosage of 100 mg/kg/body weight of xanthohumol (Hanske et al. 2005). In contrast, a high level of supercritical CO_2 hop extract inhibited probiotic *Bifidobacterium* and butyrate-producing bacteria while increasing both *Enterobacteriaceae* and *Akkermansia* (Blatchford et al. 2019), showing that the effects of hop bioactive compounds on gut microbiota are concentration dependent.

Effects on epithelial barrier function

The epithelium is in a constant state of renewal, requiring a careful balance of proliferation, differentiation, and apoptosis to function properly (Coskun et al. 2011). It not only assists with the transport of nutrients and waste but also serves as a protective barrier against foreign agents present in the luminal environment (Odenwald and Turner 2017). Like dysbiosis, impaired barrier function can be found in conditions such as IBD (König et al. 2016). Biopsies taken from colons of patients diagnosed with Crohn's diseases display impaired barrier function accompanied with decreased expression of tight junction proteins (Zeissig et al. 2007). Barrier function is largely dependent on junction proteins (Marchiando et al. 2011). Tight junction proteins reside on the lateral sides of epithelial cells close to the apical region, binding cells together and functioning as a selectively permeable barrier in the intracellular space (Farquhar and Palade 1963). Plant-derived chemicals and plant extracts such as quercetin (Suzuki and Hara 2009), kaempferol (Suzuki et al. 2011), naringenin (Noda et al. 2013) and polyphenol-rich purple potato extract (Sun et al. 2018) upregulate tight junction expression and enhance barrier function.

Consistently, 8 weeks of reduced iso-humulone supplementation in HFD mice increased intestinal alkaline phosphatase activity, a well-known epithelial differentiation marker, and mRNA expression of tight junction proteins, occludin and zonula occludens-1 (Everard et al. 2012). In Caco-2 cells, 8-prenylnaringenin, but not xanthohumol, pretreatment protected against TNF-α induced tight junction dysfunction (Luescher et al. 2017).

Table 3. Effects of bitter acids and xanthohumol on apoptosis and cell cycle.

Compound	Model	Mechanisms of action	References
Humulone	HL-60 cells	Enhanced expression of Fas and FasL Decreased expression of Bcl-2 and Bcl-X_L Mitochondrial dysfunction	(Chen and Lin 2004)
Lupulone	HL-60 cells	Enhanced expression of Fas and FasL Mitochondrial dysfunction	(Chen and Lin 2004)
	SW620 cells	Enhanced expression of Fas, FasL, TRAIL-R1 and R2 proteins. Mitochondrial dysfunction	(Lamy et al. 2007)
Xanthohumol	40-16 cells	Inhibition of antiapoptotic Bcl-2 Increased activation of caspases-3, −7, and -9	(Pan et al. 2005)
	SKOV3 and OVCAR3 cells	Increased expression of p21 Increased activation of caspase-3	(Drenzek et al. 2011)
	T98G cells	Increased activation of caspase-3 Inhibition of antiapoptotic Bcl-2 Increased intracellular levels of ROS	(Festa et al. 2011)
	Mouse bone marrow dendritic cells	Increased activation of caspases-3 and -8	(Xuan et al. 2010)

Bcl: B-cell lymphoma; Bcl-X_L: Bcl-extra large; Fas: Fas receptor; FasL: Fas ligand; ROS: reactive oxygen species; TRAIL: TNF-related apoptosis-inducing ligand; TRAIL-R1: TRAIL receptor 1/death receptor 4; TRAIL-R2: TRAIL receptor 2/death receptor 5.

Anticarcinogenic effects

Cancer imposes a significant burden on a global scale. It was estimated that in 2018, 18.1 million new cases of cancer and 9.6 million deaths occurred (Bray et al. 2018). The magnitude of cancer cases worldwide and epidemiological data pointing toward lifestyle behaviors such as diet impacting prevalence of certain kinds of cancer have resulted in increased interest in exploring the anticancer potential of various phytochemicals (Kotecha et al. 2016). Dietary anticarcinogenic intervention strives to offer protection of normal cells and disrupt cancer cell progression. The chemopreventative capacity of phytochemicals includes targeting the mechanisms behind mutagenesis, proliferation, angiogenesis, and mutagenesis of cancer cells (Surh 2003) (Figure 4). Carcinogenesis is a multistage process and plant derived chemicals such as polyphenols exert beneficial effects throughout the various stages (Ramos 2008). The capacity of hop derived compounds to exert anticarcinogenic effects was summarized below.

Biotransformation of carcinogens

Certain members of the cytochrome P450 (CYP) family activate various procarcinogens (Shimada et al. 1996). Inhibiting the activity of these enzymes is one strategy of chemoprevention. A study evaluating the potential of various hop prenylated flavonoids to inhibit P450 enzymes identified xanthohumol as a potent inhibitor of CYP1A1 and CYP1B1, both of which are responsible for the activation of carcinogenic polycyclic aromatic hydrocarbons (Henderson et al. 2000). A later study found that in rat hepatoma cells, both xanthohumol and isoxanthohumol inhibit CYP1A ($0.022 \pm 0.002\ \mu$M and $0.30 \pm 0.13\ \mu$M IC_{50}, respectively) (Gerhauser et al. 2002). Unlike xanthohumol's inhibitory effects on P450 enzymes that activate procarcinogens, colupuone induces detoxification P450 enzymes. Mice fed a diet supplemented with colupulone showed increased expression of P4503A and P4502B (Mannering et al. 1992).

Along with affecting phase I enzymes, enhancing detoxifying phase II enzymes, such as quinone reductase (QR), serves as an approach for chemoprevention (Cuendet et al. 2006). Xanthohumol enhanced the activity of QR in Hepa 1c1c7 murine hepatoma cells (Dietz et al. 2005; Gerhauser et al. 2002; Miranda et al. 2000). Dietz et al. (2005) showed that the addition of dicumarol, a QR inhibitor, suppressed the ability of xanthohumol to prevent menadione-induced DNA damage. In HepG2 human liver cells, xanthohumol at 0.01 uM protected against the genotoxic effects of benzo(a)-pyrene and 2-amino-3-methylimidazo[4,5-f]quinoline (Plazar et al. 2007). Both humulone and isohumulone enhanced the activity of QR in Hepa1c1c7 cells, but the former also exhibited cytotoxicity (Bohr et al. 2008).

Induction of apoptosis and cell cycle arrest

In different cancer cell lines, hop constituents target an array of pathways to disrupt function and growth, culminating in cell death (Table 3). Utilizing human leukemia cell lines HL-60 and U937, a mixture containing both humulones and lupulones inhibited cell growth, with U937 being more resilient (Chen and Lin 2004). Treatment with bitter acids also altered mitochondrial function and upregulated Fas and FasL (Chen and Lin 2004). Similarly, in SW620 colon carcinoma cells, lupulones displayed the ability to induce apoptosis through activation of Fas as well as the TNFα-related apoptosis-inducing ligand (TRAIL) pathways (Lamy et al. 2007). A subsequent study found that lupulone interacts with death receptor 4 (DR4)/DR5 to activate both the extrinsic and intrinsic pathways, resulting in increased caspase cascade activity (Lamy et al. 2008).

Xanthohumol decreased the viability of various cancer cells such as prostate, breast, colon, and ovarian (Colgate et al. 2007; Miranda et al. 1999). Death-receptor and mitochondrial-mediated pathways of programed cell death both activated as a result of xanthohumol treatment in colon cancer cells (Pan et al. 2005). Xanthohumol also targets the Notch pathway, resulting in cell cycle arrest and apoptosis

in ovarian cancer cells (Drenzek et al. 2011). In dendritic cells and the T98G human malignant glioblastoma cell line, xanthohumol induced caspase activity (Festa et al. 2011; Xuan et al. 2010). In the latter, xanthohumol generated ROS and induced apoptosis through the mitochondrial pathway (Festa et al. 2011).

Inhibition of angiogenesis and metastasis

The ability of cancer cells to develop vascular networks grants them access to nutrients needed for growth and a route by which to invade other parts of the body. Various factors play a role in the progression of angiogenesis. Vascular endothelial growth factor (VEGF) is a mitogen that functions as a main mediator of angiogenesis. Inhibition of VEGF results in suppressed tumor growth (Kim et al. 1993).

The antiangiogenic properties of humulone were discovered a decade ago (Shimamura et al. 2001). Work done *in vitro* found that humulone decreased endothelial cell expression of VEGF and vascular endothelial cell tube formation (Shimamura et al. 2001). Shimamura et al. (2001) also found that humulone inhibited angiogenesis in chick embryo chorioallantoic membranes in a dose-dependent manner. Similarly, lupulone inhibits angiogenesis, supplementation of 0.01% lupulone in drinking water reduced angiogenesis by 50% in mice compared to the control mice without lupulone (Siegel et al. 2008). iNOS has been implicated as a key regulator of VEGF since it generates nitric oxide, which participates in the production of VEGF. Lupulone and xanthohumol both suppressed iNOS in RAW 264.7 cells, with the latter being more effective (Zhao et al. 2003).

Xanthohumol suppressed TNF-α-induced NF-κB activation in leukemia cells (Dell'Eva et al. 2007) and downregulated NF-κB signaling in pancreatic cancer cells, resulting in decreased VEGF expression and production (Saito et al. 2018). In endothelial cells, antiangiogenic effects of xanthohumol involved AMPK activation mediated by calmodulin-dependent kinase kinase β (CAMMKβ) (Gallo et al. 2016). In breast cancer cells, xanthohumol reduced factor VIII, an endothelial marker and inhibited NF-κB signaling (Monteiro et al. 2008). Supplementation of 2 μM or 20 μM xanthohumol in drinking water before injection of Matrigel or Kaposi's sarcoma tumors, respectively, suppressed angiogenesis and tumor growth in mice compared to their respective controls (Albini et al. 2006). In addition, xanthohumol affected the adhesion of breast cancer cells by enhancing the E-cadherin/catenin complex (Vanhoecke et al. 2005).

Among the types of cancer, matrix metalloproteinases (MMP) are almost ubiquitously upregulated, and the various members of the MMP family contribute to the progression of cancer during different stages of development (Egeblad and Werb 2002). MMP-2 and -9 contribute to angiogenesis and invasion, demonstrated by mice with MMP-2 and -9 deficiencies exhibiting impaired tumor invasion and vascularization (Masson et al. 2005). In fibrosarcoma cells, xanthohumol suppressed the activity of MMP-2 and -9 (Kim et al. 2009). In triple negative breast cancer cells xanthohumol suppressed MMP-9 but not MMP-2 (Kim et al. 2013).

Conclusion and perspective

Chronic diseases are both prevalent among the population and generate a significant burden on society. Phytochemicals present in commonly grown agricultural commodities have gained increasing interests in the last several years as potential bioactive compounds capable of ameliorating the complications generated by NR-NCDs. Unlike other sources of health beneficial phytochemicals, hops are not consumed whole. The main source of dietary bitter acids and xanthohumol is beer, and levels tend to be low. An alternative to beer drinking is the development of new hop-derived therapeutics. Hop derived compounds show promise as therapeutics; both *in vitro* and *in vivo* studies support the notion that bitter acids and xanthohumol mitigate symptoms of NR-NCDs. Hop phytochemicals show potential in ameliorating hallmarks of metabolic syndrome by influencing energy expenditure and display anti-cancer properties capable of targeting carcinogenesis at different stages (Figures 3 and 4). While studies have begun elucidating the pathways responsible for the anti-inflammatory, antiobesity, and chemopreventative effects of hop compounds, few have deeply explored their effects on intestinal health and microbiota. Intestinal health impacts overall health, making it an important target for disease prevention, and it remains unclear if manipulation of the gut microbiome is involved in the improvement of biomarkers generated by hops. Moving forward, emphasis should focus on safe, effective dosage for humans and its impacts on facets of intestinal health.

Disclosure statement

Bravo Iniguez and Zhu have no conflicts of interests.

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