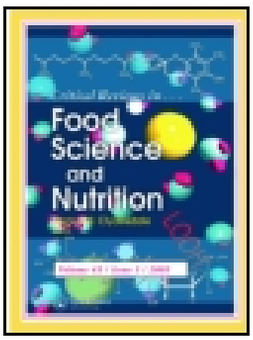

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REVIEW

Beer and its non-alcoholic compounds in health and disease

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ABSTRACT

Moderate alcohol consumption has been associated with beneficial effects on human health. Specifically, consumption of red wine and beer has shown a J-shape relation with many important diseases. While a role of ethanol cannot be excluded, the high content of polyphenols in both beverages has been proposed to contribute to these effects, with beer having the advantage over wine that it is lower in alcohol. In addition to ethanol, beer contains a wide variety of compounds with known medicinal potential such as kaempferol, quercetin, tyrosol and phenolic acids, and it is the main dietary source for the flavones xanthohumol and 8-prenylnaringenin, and bitter acids such as humulones and lupulones. Clinical and pre-clinical evidence for the protective effects of moderate beer consumption against cardiovascular disease and other diseases has been accumulating since the 1990s, and the non-alcoholic compounds of beer likely exert most of the observed beneficial effects. In this review, we summarize and discuss the effects of beer consumption in health and disease as well as the clinical potential of its non-alcoholic compounds which may be promising candidates for new therapies against common chronic diseases.

KEYWORDS

Beer; Beer components; health-span; human diseases; pharmacological interventions

Introduction

Beer is a natural beverage obtained by alcoholic fermentation of an extract of barley. According to the "German Beer Purity Law", it is made of only four traditional ingredients: barley, hop (*Humulus lupulus L.*), yeast and water. The first step of making beer is the malting process, where the barley grains are submerged in water to promote their germination. Then, the grains are roasted, generating the characteristic color and flavor of beer. The cereal is milled and mixed with water at a suitable temperature to extract the sugar from the grain and obtain a sweet must. The must is boiled and then hops are added. Ingredients of the hops form insoluble complexes with proteins, which give the colloidal strength to the beer, decontaminate the wort solution and avoid bacterial growth. Hop is also the ingredient that gives the characteristic scent and bitterness to beer. Fermentation is then initiated by the addition of either of two types of yeast: *Saccharomyces cerevisiae*, a top fermenting yeast that produces ales, porters, and stouts, or *Saccharomyces uvarum*, a bottom fermenting yeast that produces lagers (Vinson et al. 2003).

Based on the earliest known chemical evidence of beer production, it is estimated that beer originated in the fourth millennium BCE (Homan 2004), and it was considered a preponderant component for the ancient Egyptian diet (Samuel 1996). Besides its nutritional value (350 mL beer contain approximately 8 g of carbohydrates, covering 2.4% of the daily intake in a 2000 kcal diet), beer contains minerals such as calcium, iron, magnesium, phosphorus, potassium, sodium, zinc, copper, manganese, selenium, fluoride and silicon (see Table 1). Being a fermented beverage, beer might exert beneficial effects on digestive health, the balance of intestinal microbiota, improve the permeability balance and function of the intestinal barrier, and thereby prevent dysbiosis, as has been shown for other fermented drinks (Bell et al. 2018, Cardona et al. 2013, Marco et al. 2017).

From a chemical perspective, beer is a complex mixture of natural compounds. Several of them have been attributed with antioxidant, antiangiogenic, anti-melanogenic, anti-osteoporotic and anti-inflammatory activity (Figure 1). Several hundreds of interesting compounds have been identified in beer, among them more than fifty polyphenolic compounds. About 75-85% of these compounds derive from malt and 15-25% from hop. These polyphenols are principally flavonoids, phenolic acids, catechins, prenylated chalcones, and proanthocyanidins. Also, hop contains monoacyl phloroglucides, which are transformed to bitter acids (humulones and lupulones) during the brewing process (De Keukeleire et al. 2003). There is growing interest in the effect of beer consumption on human health given consistent evidence suggesting a J-shaped relation between alcohol (as well as beer) and health; in this respect, there are many reports of the protective effect of moderate alcohol consumption compared to complete alcohol abstention and

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heavy drinking (Di Castelnuovo et al. 2006). Likewise, the large variety of non-alcoholic compounds makes beer an important research topic. In the first part of this work we briefly describe the principal beneficial and also harmful impact of moderate beer consumption on the most common diseases; in the second section we explore the principal non-alcoholic compounds of beer and their isolated effects.

Table 1. Daily requirements of minerals, vitamins and macronutrients and content in regular beer and red wine.

Parameter	Daily requirement Female/Male (19-50 years)	Beer (Alcohol 4 %) 350 mL	Red wine 350 mL
Calcium, Ca (mg)	700	28	24.5
Magnesium, Mg (mg)	270/300	24.5	38.5
Iron, Fe (mg)	14.8/8.7	0.35	3.15
Copper, Cu (mg)	1.2	0.035	0.21
Zinc, Zn (mg)	7.0/9.5	0.35	0.35
Manganese, Mn (mg)	2.0 †	0.105	0.35
Selenium, Se (mg)	60/75	Traces	Traces
Phosphorus, P (mg)	550	49	45.5
Potassium, K (mg)	3500	112	385
Sodium, Na (mg)	1600	21	24.5
Thiamin (mg)	0.8/1.0	Traces	Traces
Riboflavin (mg)	1.1/1.3	0.105	0.07
Niacin (mg)	13/17	0.7	0.35
Panthotenic acid (mg)	10 †	0.175	0.14
Vitamin B6 (mg)	1.2/1.4	0.245	0.105
Vitamin B12 (µg)	1.5	Traces	Traces
Biotin (µg)	300 †	3.5	7
Folate, DFE (µg)	200	17.5	3.5
Carbohydrate (g)	300 †	7.7	0.7
Protein (g)	50 †	1.05	0.35
Fat (g)	65 †	Traces	0
Alcohol (g)		10.15	37.45
Energy (Kcal)	2140*/2676*	105	266

Data extracted and modified from McCance and Widdowson's composition of foods integrated dataset on the nutrient content of the UK food supply, 2019 (Free available under the terms of the Open Government Licence v3.0). https://www.gov.uk/government/publications/composition-of-foods-integrated-dataset-cofid

*Mean of 19 to 54 years old.

†FDA recommendations.

Effects of beer on body weight

Beer consumption has been associated with increased waist circumference, mostly in men, a phenomenon commonly denominated as "beer belly". The alcohol content in beer is rarely more than 10% (v/v) and most beers are in the range of 3 to 6% (v/v). Alcohol consumption increases the calorie intake, because ethanol *per se* has an energy contribution of 7 Kcal per g (Bamforth 2002, Yeomans 2010a). In addition, beer contains more carbohydrates than wine and spirits. It is also known that alcohol-free beer can increase the food intake and regular beer enhances this response (Yeomans 2010b). Although the effect of alcohol and beer on appetite is not yet well understood, it could be an important factor to the obesity and overweight risk described for beer consumers.

Clinical research about the relation between beer consumption and abdominal obesity has generated inconsistent results, probably due to the difficulty to discriminate the contribution of other important factors such as gender differences from body fat accumulation and habits such as smoking, physical activity, diet and consumption of other alcoholic beverages (Bendsen et al. 2013). Nonetheless, some observational studies excluded confounding factors such as consumption of other alcoholic beverages by either analyzing only subjects who reported to exclusively drink beer

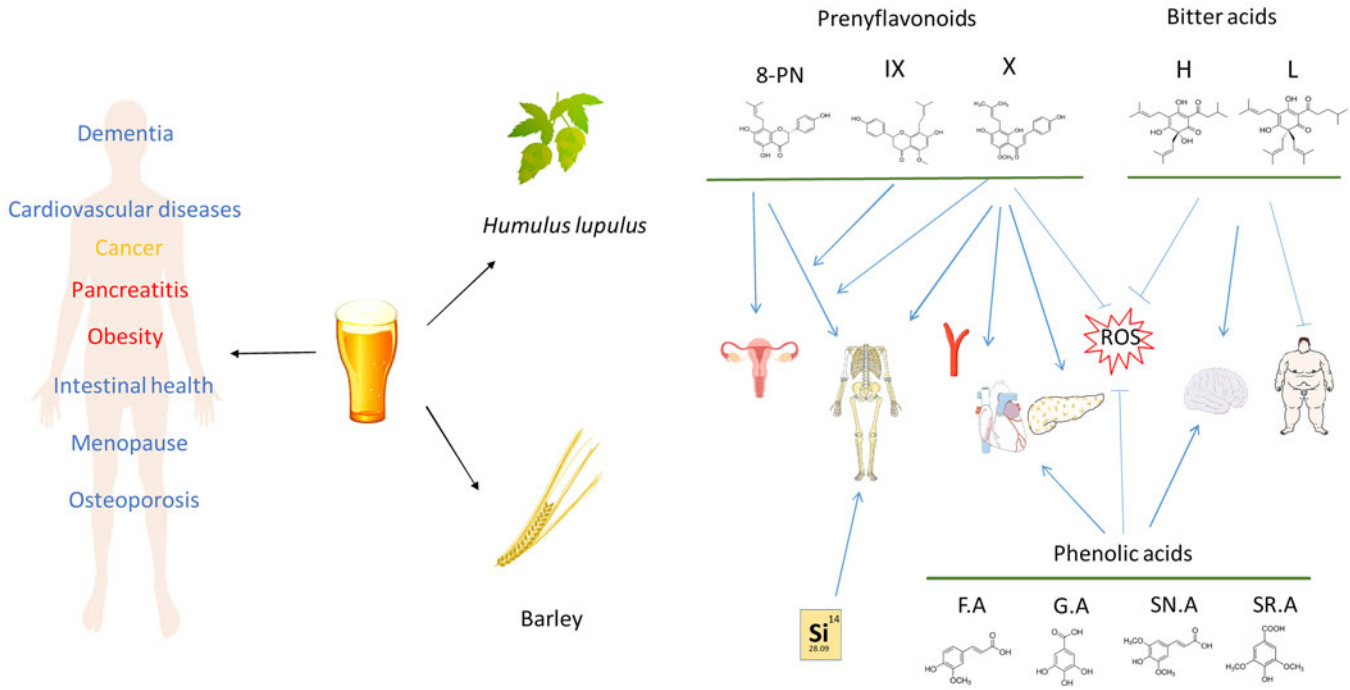

Figure 1. Non-alcoholic compounds in beer and its effects. Beer is a natural beverage; as a fermented brew, it provides many beneficial properties for intestinal health. Also, due to its high content in silicon, mainly coming from malt, it may confer protection from osteoporosis. The effects of xanthohumol, isoxanthohumol, 8-prenylnaringenin, humulones and lupulones have been described as antioxidant, anti-angiogenic, anti-bacterial, anti-inflammatory, anti-carcinogenic, anti-diabetic and estrogenic. Many of the compounds provide protection against cardiovascular diseases, cancer and mitigation of menopause symptoms. However, excessive beer consumption is a risk factor for the same diseases mentioned as well as pancreatitis. In blue, positive effects; in red, harmful effects and in yellow, controversial effects

during a typical week, or by adjustment of statistical models for confounding factors. For example, in 2003, Bobak and coworkers reported that in a cross-sectional study of a Czech population of exclusive beer drinkers, the intake of beer was positively associated with waist-hip ratio (WHR) only in men. This effect disappeared after adjustment for smoking, physical activity and education, suggesting that beer intake per se is not associated with weight gain (Bobak, Skodova, and Marmot 2003). Another cross-sectional study in a French population also found that beer consumption was not related to increased WHR or BMI, while red wine consumption showed a J-shaped relationship with WHR in both sexes, and spirit consumption showed a linear association with BMI, but only in men (Lukasiewicz et al. 2005). Within the European Prospective Investigation into Cancer and Nutrition (EPIC)–Potsdam study, a large prospective study that collected data at baseline and follow-up, cross-sectional relations between beer intake, body weight and waist circumference (WC) were explored (along with other factors such as wine and spirit intake, smoking, and physical activity), and WC changes after a follow up of 8.5 years was correlated with beer intake. At baseline, beer consumption correlated with WC only in men. However, after a 8.5-year follow up, and adjustment for confounding factors such as wine or spirit intake, the odds of WC loss were significantly lower in beer-consuming women compared to abstaining women, and beer-consuming men had increased odds of WC gain, suggesting that beer consumption leads to body weight gain (Schütze et al. 2009).

In summary, while the available evidence about the specific effects of beer on body weight is inconclusive a positive association is likely and may be conferred by calorie intake through ethanol and carbohydrates, and/or stimulation of appetite.

Pancreatic function

The human pancreas is a gland integrated by two different tissues with two major functions. First, the exocrine tissue (around 85% of total mass) stimulates the digestion process through digestive enzyme secretion and second, the endocrine tissue (around 2% of total mass) secretes insulin and glucagon for glycaemic control. It is well known that alcohol abuse damages the exocrine pancreatic tissue, thereby driving pancreatitis which is associated with a high incidence of pancreatic cancer (Dzeletovic et al. 2014). Pancreatitis derives of the accumulation and activation of digestive enzymes in the principal duct of the pancreas and in the acinar cells, mainly by the overflow secretion of these enzymes. Although alcohol abuse has been tightly related with enhanced pancreatic digestive enzyme secretion, the mechanism is not understood. A single ethanol (4% v/v) intragastric application shows no relation with exocrine activity of pancreas, but the administration of 250 mL of beer, which does not increase alcohol content in blood, increases the exocrine activity. Interestingly, ingestion of a major quantity of beer (850 mL) which augments the alcohol content in blood, inhibits pancreatic enzyme secretion (Hajnal, Flores, and Valenzuela 1989), suggesting that alcohol *per se* does not drive pancreatitis. Also, the carbohydrates in beer are an unlikely driver of pancreatitis, because administration of a glucose solution (5.7 to 11% w/v) did not stimulate the exocrine pancreas as beer ingestion did (Chari et al. 1996). It is therefore suggested that non-alcoholic compounds of beer and wine could be the major cause of hyper-stimulation of pancreatic digestion enzyme secretion and that ethanol can counterbalance this effect (Bouchardy et al. 1990, Gupta et al. 2010, Gerloff, Singer, and Feick 2010). However, there are also many reports about beneficial effects of individual non-alcoholic components such as flavonoids; particularly, quercetin showed a protective effect against pancreatic cancer by abated tumor growth, tumor cell apoptosis and prevention of metastatic lesions in vivo (Nothlings et al. 2007, Mouria et al. 2002).

In addition to pancreatitis, chronic alcohol consumption also disturbs the endocrine function, enhancing the risk to develop diabetes type 2. Interestingly, the relationship between alcohol consumption and diabetes type 2 incidence is U-shaped, with a 30% decreased risk of type 2 diabetes for moderate alcohol consumers compared to abstainers (Rachdaoui and Sarkar 2017, Huang, Wang, and Zhang 2017, Koppes et al. 2005). This effect may be due to an improved insulin sensitivity of peripheral tissue (Jugdaohsingh et al. 2006, Avogaro et al. 2004, Metcalf, Scragg, and Jackson 2014). In this respect, Hätönen et al. compared postprandial glucose in individuals who were either given a glucose solution with ethanol (25 g of glucose and 21 g of alcohol), beer, or non-alcoholic beer. They observed an acute impairment of insulin response by a decrease in insulin secretion after moderate alcohol consumption, and this effect was slightly more pronounced after non-alcoholic beer consumption (Hatonen et al. 2012). In this regard, there are reports which demonstrated that non-alcoholic compounds such as xanthohumol ((E)-1-[2,4-dihydroxy-6-methoxy-3-(3-methylbut-2-enyl)phenyl]-3-(4-hydroxyphenyl)prop-2-en-1-one) exhibit hypoglycemic effects (Miranda et al. 2016, Miranda et al. 2018). Therefore, it is likely that, rather than ethanol, the great diversity of non-alcoholic compounds in beer stimulate both the exocrine and endocrine pancreatic tissues producing opposing effects. Due to these heterogeneous bioactivities, the individual effects of non-alcoholic compounds need to be investigated in the future to better characterize their therapeutic potential.

Osteoporosis

Osteoporosis is an age-related disease that is caused by an imbalance of bone resorption, executed by osteoclasts, and bone formation, accomplished by osteoblasts. The consequence is a lower trabecular density and a higher cortical porosity, making the bone more susceptible to fracture. Chronic alcohol consumption diminishes bone mass (BM) as well as bone mineral density (BMD), mainly via decreased bone formation, and it is also well known that heavy alcohol consumption causes osteoporosis (Turner 2000).

Nevertheless, moderate alcohol consumption may be beneficial for the skeletal system, as several reports have shown (Maurel et al. 2012, Tucker et al. 2009, Yin et al. 2011, Jugdaohsingh et al. 2006).

The positive effect of moderate alcoholic beverage consumption on bone health has mainly been attributed to inhibition of bone resorption (Jugdaohsingh et al. 2006). Non-alcoholic beer compounds have been implicated in this anti-resorptive effect, such as the prenylflavonoid xanthohumol, which is mainly available in diet through beer consumption (up to 0.96 mg/L) (Jugdaohsingh et al. 2006, Rossi et al. 2014). Along these lines, in 1997, Hiroyasu et al. reported a high potential of hop extract to inhibit bone resorption (i.e., decrease of pit formation on dentine slices by about 50%), through an estrogenic effect. Chemical characterization of the extract revealed humulone and xanthohumol as the active ingredients (Tobe et al. 1997). However, nowadays it is well known that xanthohumol possesses weak or no estrogenic activity and even exerts antiestrogenic effects (Gerhauser et al. 2002, Aichinger, Beisl, and Marko 2018). Still, as we discuss in another section of this review, xanthohumol is metabolized in the gut to one of the most potent phytoestrogens presently described, 8-prenylnaringenin ((2S)-5,7-dihydroxy-2-(4-hydroxyphenyl)-8-(3-methylbut-2-enyl)-2,3-dihydrochromen-4-one), which may be responsible for the anti-resorptive activity in the Hiroyasús hop extract (Milligan et al. 1999). Regardless, to date, there is evidence that xanthohumol exerts a bone anabolic effect because it stimulates osteoblast differentiation via Runt-related transcription factor 2 (RUNX2), an indispensable transcription factor in bone development activation via the p38 MAPK and ERK signal transduction pathways (Li et al. 2015, Suh et al. 2013, Jeong et al. 2011, Schilling et al. 2014).

The dual effect of xanthohumol and its derivate compound, 8-prenylnaringenin as estrogenic/anti-estrogenic agents is actually not uncommon; minimal structure modifications of, for example, phenolic acids (which are also present in beer) such as caffeic acid, ferulic acid, and vanillic acid generate estrogenic/anti-estrogenic activity pairs (Jung et al. 2010, Stromeier, Petereit, and Nahrstedt 2005, Xiao et al. 2014, Nardini et al. 2006). Given the risks of estrogen replacement therapy (Grodstein et al. 1997, Gustafsson and Warner 2000), the dual or modulatory estrogenic effects and bone anabolic capacity of beer would be worth exploring for potential new therapeutic strategies to treat menopause symptoms and prevent osteoporosis.

In addition to phytoestrogens, beer is the main source of silicon in western diet (6.4 to 56.5 mg/L in commercial beers) (Jugdaohsingh et al. 2002, Nielsen 2014, Casey and Bamforth 2010, Sripanyakorn et al. 2004). Although silicon content is also high in bananas, it is present mostly in a polymerized form that is not well absorbed in the intestine, while in beer it is water-soluble, resulting in a better bioavailability (Price, Koval, and Langford 2013). Silicon supplementation in human diet (more than 40 mg/day) inhibits bone resorption and increases BMD. Moreover, silicon stimulates osteoblast differentiation and bone formation, type 1 collagen production, and improves calcium incorporation in bone (Price, Koval, and Langford 2013, Nielsen 2014). It has been proposed that silicon and estrogens interact synergistically to improve bone structure (Macdonald et al. 2012) and this has been suggested as possible mechanism for bone density and mineral improvement in studies of moderate beer consumption (Pedrera-Zamorano et al. 2009, Tucker et al. 2009). Therefore, while alcohol overconsumption can increase osteoporosis risk, moderate beer consumption can be beneficial because it contains phytoestrogens such as 8-prenylnaringenin as well as other bioactive compounds which can stimulate osteoblast cells, that in synergy with silicon can improve bone structure and help to remineralize bone and teeth.

Cardiovascular disease

Since the first report of the protective effect of wine against cardiovascular disease (CVD) in 1979, there is extensive research into health benefits of moderate wine intake (St Leger, Cochrane, and Moore 1979). Nowadays, a bulk of evidence suggests that moderate alcohol consumption is associated with decreased coronary heart disease and stroke mortality, regardless of the type of alcoholic beverage consumed (Ronksley et al. 2011). In a large meta-study, Costanzo and coworkers confirmed the significant protection against vascular risk by moderate wine consumption and, more importantly for this review, they showed for the very first time a J-shaped relationship between beer ingestion and cardiovascular risk. In contrast, no statistically significant relationship with vascular events was detectable for any spirits (Costanzo et al. 2011). It has been observed that moderate intake of any type of alcoholic beverage improves the lipid profile in blood plasma by increasing high-density lipoprotein (HDL) cholesterol and reducing low-density lipoprotein levels (LDL). Also, platelet aggregation is decreased and inflammation is prevented (Renaud and Ruf 1996, Riemens et al. 1997, Rimm et al. 1999, Di Castelnuovo et al. 2009). According to the current literature, it seems that ethanol acts on the lipid profile, while the phenolic constituents of wine and beer seem to have anti-atherogenic and anti-thrombotic effects, and reduce leukocyte adhesion molecules and inflammatory biomarkers (Fragopoulou et al. 2018, Gresele et al. 2011, Piazzon, Forte, and Nardini 2010, Vinson et al. 2003, Chiva-Blanch et al. 2015). Favourable effects of the moderate intake of alcoholic beverages against atherosclerosis have similarly been associated to their non-alcoholic compounds and antioxidant and anti-inflammatory effects, as well as to their actions as vasodilator (Oliveira Neto et al. 2017). A two-arms longitudinal crossover study to explore the effects of alcohol-free beer or regular beer consumption showed that, after four weeks, there were no changes in BMI, vascular endothelial function, lipid levels and other biochemical parameters, but the regular beer consumption showed an augmented antioxidant capacity of HDL (Padro et al. 2018). Likewise, Karatzi and coworkers showed that when comparing postprandial intake of vodka, beer and non-alcoholic beer, the biggest improvement on

endothelial function and pressure wave reflections were caused by beer. These results suggest that consumption of regular beer has a measurable acute beneficial effect on cardiovascular function, and this seems to be mediated by both alcohol and antioxidants (Karatzi et al. 2013). Interestingly, a similar study revealed that red wine (0.8 g/kg body weight) reduced aortic constriction, whereas dealcoholized red wine had no such outcome, suggesting that ethanol had a significant positive effect on arterial constriction (Mahmud and Feely 2002). Additionally, there is ample evidence about the antioxidant capacity of non-alcoholic beer compounds. For example, when assessing LDL and very-low density lipoprotein (VLDL) oxidation *in vitro*, phenols have better antioxidant properties than vitamins (Vinson et al. 2003). To summarize, the beneficial effect of beer on cardiovascular health is likely due to both, the antioxidant and anti-inflammatory properties of its non-alcoholic compounds and ethanol-dependent improvement of the lipid profile in plasma.

Cancer

When alcohol is ingested and processed, it is converted into acetaldehyde, a group 1 carcinogen, which hinders DNA repair and thus increases cancer risk (Brooks and Zakhari 2014). The International Agency for Research on Cancer has therefore classified alcohol as a Group 1 carcinogen (confirmed to cause cancer in humans), the highest risk group. Alcohol consumption has been related to at least seven type of cancers: cancers of the mouth, pharynx, larynx, esophagus, liver, breast and bowel (de Menezes, Bergmann, and Thuler 2013).

Additionally, in the case of beer, which is produced from cereals, the presence of volatile nitrosamines and mycotoxins is considered a risk. Nitrosamines are compounds considered the most potent group of carcinogens. They are generated during the malting process by dehydrating with warm air by straight firing techniques, and are highly carcinogenic. Reports in the 1970s caused the process to be modified to indirect firing techniques, thereby reducing the volatile nitrosamine content in beer to very low levels (Gerhauser 2005). Mycotoxins derive from fungal infections of crops, are highly liposoluble and penetrate the cells quickly, triggering permanent mutagenic alterations in the nucleotide sequence and consequently the development of cancer (Ahmed Adam et al. 2017). Among mycotoxins, ochratoxin A is one of the most mentioned and is not only present in beer, but also wine and other food products, and is a strong teratogen, immune suppressant, nephrotoxic and carcinogenic agent for animals and humans. In order to protect consumers from risks related to this compound, regulatory limits have been established for ochratoxin levels in raw cereal grains and cereal products for human consumption, but there is not yet a restriction for beer because, although this mycotoxin showed detectable levels in beer (usually <0.2 ng/mL), it is far from the concentration reported as toxic (Mateo et al. 2007, Pagkali et al. 2017, Bauer 2016). Likewise, some mycotoxins have been reported to structurally mimic natural hormones able to bind and activate estrogen receptors, which could potentially lead to adverse effects. Among these compounds, zearalenone is the most renowned mycotoxin found in beer. Nevertheless, the xanthohumol present in beer can antagonize the effects of mycotoxins *in vitro* through anti-estrogenic activity, at concentrations (nM) detected in human serum after moderate consumption of beer (Aichinger, Beisl, and Marko 2018).

Studies about beer consumption and the prevalence of cancer are not conclusive yet, because it has been difficult to discriminate the specific effect of beer from other types of alcoholic beverages (spirits or fermented), which are often combined with beer, as well as the use of tobacco. Ethanol consumption, and therefore beer consumption, has been shown to increase cancer risk (Collaborators 2018). However, many in vitro studies have demonstrated an anticancer effect of non-alcoholic beer compounds. For example, Arimoto-Kobayashi and coworkers studied the capacity of beer and many of its dissolved components to inhibit mutagenesis induced by several carcinogens in a *Salmonella* mutation assay and DNA adduct formation in mouse liver. They showed that beer inhibits the mutagenicity of Trp-P-2(NHOH), a proximate form of a mutagenic heterocyclic amine present in cooked food, and DNA adducts in liver were significantly decreased by beer administration. Ethanol alone did not exhibit these effects. Therefore, it was concluded that components of beer, derived from the fermentation processes and/or raw materials, must be the cause of these anti-mutagenic effects, although the nature and identity of such compounds is not established (Arimoto-Kobayashi et al. 1999). It has also been reported that, *in vitro*, different beers protect DNA from oxidative damage in a manner similar to other hydroxyl radical scavengers, such as glutathione (GSH), suggesting that beer contains such scavengers; this effect correlates with the high levels of polyphenols and melanoidin in dark beers (Rivero et al. 2005). Xanthohumol, a flavonoid, is the most studied anticancerogenic agent present in beer (in regular beer up to 0.96 mg/L) (Jiang et al. 2018); nevertheless, there are many reports of the chemoprotective potential of other compounds as well as hop bitter acids, suggesting potential synergic effects (Gerhauser 2005, Machado 2017).

It is important to emphasize that the anticarcinogenic effects of non-alcoholic beer compounds have only been observed *in vitro* and not validated in human studies yet, and that the carcinogenic effects of ethanol most likely outweigh any protective effects of the other compounds (Table 2).

In summary, ethanol and low levels of carcinogens contained in beer increase the risk for cancer. Beer consumption is also related to pancreatic digestive enzyme secretion, and the caloric value and likely appetite-stimulating effect may increase the risk for obesity for beer drinkers. However, a plethora of non-alcoholic compounds of beer, such as phytoestrogens and flavonoids, have shown beneficial effects in vitro and in animal studies and may be responsible for the J-shaped relationship between beer consumption and overall disease risk. Among these compounds, those present in other food sources (e.g., red wine, olive oil and green tea)

Table 2. Principal non alcoholic beer compounds and its potential health benefit.

Compound	Biological activity	Potential Health benefit	Model	References
Xanthohumol	Antioxidant	Protects human LDL from oxidation. Prevents cardiovascular diseases such as atherosclerosis. Protection of neuronal cell damage.	In vitro oxidation of human low-density lipoprotein (LDL). HepG2 human hepatoma cells. HL-60 cells and murine macrophages. Neuron-like rat pheochromocytoma cell line PC12.	(Gerhauser et al. 2002, Miranda et al. 2000) (Yao et al. 2015)
	Anti-carcinogenic	Prevents DNA damage by dietary carcinogens.	Ames Salmonella Assay. Human intervention trial. Human hepatoma HepG2 cells.	(Arimoto-Kobayashi et al. 1999) (Miranda et al. 2000) (Pichler et al. 2017) (Plazar et al. 2007)
	Pro-apoptotic	Induces apoptosis of several types of cancer cells.	Human cholangiocarcinoma cell lines CCLP1, SG-231 and CC-SW-1. Laryngeal squamous cell carcinoma SCC4 cells. Gastric cancer in SGC-7901, SNU216, and SNU668 cells. Human chronic lymphocytic leukemia cells. Human hepatocellular carcinoma (HCC) cell lines (HepG2, Hep3B, and SK-Hep-1). Human breast cancer (MCF-7) and human sarcoma (HT1080) cell lines. Human neuroblastoma cell lines NGP, SH-SY-5Y, and SK-N-AS.	(Walden et al. 2017) (Li et al. 2016) (Kunnimalaiyaan et al. 2015) (Cho et al. 2012) (Engelsgjerd et al. 2019)
	Anti-inflammatory	Protective effect against age-related brain damage. Suppresses inflammatory response to warm liver ischemia–reperfusion.	Male senescence-accelerated prone mice (SAMP8) BALB/c mice.	(Dorn et al. 2013, Rancan et al. 2017)
	Anti-microbial	Alternative treatment of nosocomial diarrhea caused by resistant strains.	In vitro assays against B. fragilis, C. perfringens and C. difficile strains.	(Cermak et al. 2017)
	Anti-angiogenic	inhibition of tumor growth	Human umbilical vein endothelial cells. Human pancreatic adenocarcinoma cell lines BxPC-3, MIA PaCa-2 and AsPC-1. Breast cancer xenografts in nude mice.	(Saito et al. 2018) (Gallo et al. 2016) (Monteiro et al. 2008)
	Anti-estrogenic	Prevent carcinogenesis.	Ishikawa human endometrial adenocarcinoma cells. Mammary adenocarcinoma cell line. Rat mammary tumor model.	(Gerhauser et al. 2002) (Aichinger, Beisl, and Marko 2018)
	Hypoglycemic	Improves dysfunctional glucose and lipid metabolism.	Diet-induced obese C57BL/6J mice.	(Miranda et al. 2016)
	Anti-obesity	Induces beiging of white fat activating thermogenic pathways.	Murine 3T3-L1 adipocytes and primary human subcutaneous preadipocytes.	(Samuels, Shashidharamurthy, and Rayalam 2018)
Isoxanthohumol	Antioxidant, anti-angiogenic and antitumoral	Antiproliferative effect in several types of cancer cells.	Human epithelial cancer cell lines from prostatic (PC-3, DU145) Endothelial cells (ECs) and vascular smooth muscle cells (VSMCs). HepG2 cells. MDA-MB-231 cells. Human aortic smooth muscle cells (HASMCs) and human umbilical vein endothelial cells (HUVECs). Colon (HT-29, CaCo-2 HCT115 and SW620) cell lines.	(Delmulle et al. 2006) (Serwe et al. 2012) (Negrao et al. 2013) (Allsopp et al. 2013)
8-prenylnaringenin	Phytoestrogen	Alleviate menopausal and post-menopausal symptoms in women. Osteoporosis prevention.	Prospective, double blind, placebo-controlled study, human trial. Rat calvarial osteoblasts. Osteoclasts from the bone marrow of femora and tibiae of rabbits.	(Heyerick et al. 2006) (Erkkola et al. 2010) (Aghamiri et al. 2016) (Ming et al. 2013)
	Antidiabetic	Prevention of body weight gain, and improved insulin resistance and glucose tolerance.	Type 2 diabetes mellitus mice model.	(Costa et al. 2017)
	Anti-carcinogenic	Important role in therapy of brain tumors, due its	Human glioblastoma U-118 MG cells. U-118 MG cancer cell line.	(Stompor, Uram, and Podgorski 2017) (Busch et al. 2015)

(*continued*)

Table 2. Continued.

Compound	Biological activity	Potential Health benefit	Model	References
		higher toxicity against cancer cells.	PC-3 human prostate cancer cells and UO.31 human renal carcinoma cells.	
Ferulic acid	Antioxidant, anti-inflammatory and neuroprotective	Antidepressant, antinociceptive, anti-allergic, antiepileptic.	Mouse models of despair test. Chronic unpredictable mild stress mice. Chronic constriction injury (CCI)-induced neuropathic pain, male mice. Female BALB/c and C57BL/6 mice.	(Chen et al. 2015) (Lenzi et al. 2015) (Liu et al. 2017) (Xu et al. 2016) (Lee et al. 2015)
Caffeic acid	Antioxidant, anti-inflammatory and neuroprotective	Neuroprotector, antiepileptogenic, antioxidant and genotoxic	Male CF-1 mice Streptozotocin (STZ)-induced experimental dementia of Alzheimer's type in rats.	(Coelho et al. 2015) (Deshmukh et al. 2016)
Vanillic acid	Antioxidant, anti-inflammatory.	Anti-alergic Nephroprotective against cisplatin	Human mast cell line, HMC-1. Wistar rats	(Jeong et al. 2018) (Sindhu, Nishanthi, and Sharmila 2015)
Syringic acid	Antioxidant, anti-inflammatory, neuroprotective and anticarcinogenic.	Protective effect on kidney Ischemia-Reperfusion injury. Protection from ischemia/reperfusion damage. Prevents skin carcinogenesis. Anti-osteoporotic	Male Wistar-Albino rats Ischemia/Reperfusion injury in in a Rat Sciatic Nerve Model. UVB-irradiated SKH-1 hairless mice. Ovariectomized mice	(Sancak et al. 2016) (Tokmak et al. 2017) (Ha et al. 2018) (Tanaka et al. 2017)
Bitter acids: Humulones (α-acids) and Lupulones (β-acids)	Anti-carcinogenic, Anti-inflammatory, pro-apoptotic, anti-obesity	Prevents dyslipidemia and type 2 diabetes. Suppresses brain inflammation and prevents cognitive decline. Cancer chemoprevention.	C57BL/6N Mice Diet-induced obese rodent model. Clinical human triall. Murine model of Alzheimer disease. Male C57BL/6 J mice. Hepatocellular carcinoma (HCC). Mouse fibrosarcoma L929sA cells. Monkey kidney COS1L2A fibroblasts.	(Yajima et al. 2004, Yajima et al. 2005, Miura et al. 2005) (Obara et al. 2009) (Ano et al. 2017) (Ayabe et al. 2018) (Saugspier et al. 2012) (Van Cleemput et al. 2009)

like quercetin, kaempferol, tyrosol and xanthohumol, seem to be the best described for biomedical investigation, with many reports describing their principal properties as antioxidant, anti-carcinogenic, anti-diabetic, anti-inflammatory, antimicrobial, cardio-protective, neuroprotective and other positive bioactive effects (Kawabata, Mukai, and Ishisaka 2015, Calderon-Montano et al. 2011, Karkovic Markovic et al. 2019). In the following chapter, we will describe the principal non-alcoholic compounds described in beer with promising effects on human health.

Principal non-alcoholic compounds of beer

As discussed above, most of the positive effects of beer are conveyed by its non-alcoholic compounds. In this section, we discuss the current evidence for the health benefits of the principal non-alcoholic compounds (Table 2). The non-alcoholic compounds are derived mainly from malt and hops and can vary according to the brewing process (Steenackers, De Cooman, and De Vos 2015). Among the best characterized non-alcoholic ingredients of beer are phenolic compounds such as chalcones, flavonoids, phenolic acids, and bitter acids. Understanding the effects of the individual compounds will improve the understanding of how beer affects health, and also give way to the option to get similar health benefits without having to consume beer.

Phenolic compounds

With almost 8000 naturally occurring varieties described, phenolic compounds comprise a big variety of molecules. Their common structural characteristic is an aromatic ring bearing at least one hydroxyl substituent, the phenolic group. The classification is based in the number of aromatic rings inside the molecule: flavonoids have at least two phenolic rings, tannins contain more than three phenolic rings, and phenolic acids contain a functional carboxylic acid (Robbins 2003). The content and variety of phenolic compounds in beer is vast; high resolution mass spectrometry analysis has identified simple phenolic acids, hydroxycinnamoyl quinics, flavonols, flavones, alkyl methoxy phenols, alpha and iso-alpha-acids, hydroxyphenylacetic acid and prenylflavonoids, to name a few (Quifer-Rada et al. 2015). Phenolic compounds are well known antioxidants (Ghiselli et al. 2000, Polak, Bartoszek, and Stanimirova 2013). Among the more potent compounds are: tyrosol; hydroxycinnamic acids, such as ferulic and caffeic acids; flavonoids, such as catechin, epicatechin and quercetin, and procyanidins. Additionally, beer contains other important flavonoids, such as formononetin, genistein, daidzein, and kaempferol, as well as hydroxybenzoic acid and prenylated chalconoids including xanthohumol and 8-prenylnaringenin (Karatzi et al. 2013). These compounds have shown a great variety of bioactive properties, and beer is the main source of the latter two in human diet (Venturelli et al. 2016).

Xanthohumol, the best known of prenylated flavonoids available in beer, is produced by the female inflorescences of the hop plant (*Humulus lupulus*); during the brewing process, around 20-30% is converted into the prenylated flavonoid isoxanthohumol (Venturelli et al. 2016). This compound displays many bioactive effects such as antioxidant, anti-carcinogenic, anti-inflammatory, anti-microbial, hypoglycemic

and anti-obesity (Samuels, Shashidharamurthy, and Rayalam 2018, Liu et al. 2015). Within its principal activities described, xanthohumol is a potent inhibitor of cholesteryl ester transfer protein (CETP) (activity related with its chalcone structure and its phenyl group) leading to an increase in HDL-cholesterol and a low risk of atherosclerosis (Hirata et al. 2012). Xanthohumol also has shown antimutagenic activity to protect from mutations induced by the food borne mutagen 2-amino-3-methylimidazo[4,5-f]quinoline (IQ), possibly through the inhibition of its metabolic activation by human cytochrome P450 1A2 (CYP1A2) and the binding of IQ metabolites to DNA (Miranda et al. 2000). Finally, the antioxidant capacity of this compound, as free-radicals scavenger or indirectly by activation of the cellular antioxidant system, can be part of the mentioned effects (Liu et al. 2015). With a xanthohumol content of around 200 μg/L, beer is the principal source of this molecule in the human diet (Stevens, Taylor, and Deinzer 1999, Liu et al. 2015).

Isoxanthohumol is the major flavonoid in regular beer, showing a concentration ranging between 0.6 and 3.4 mg/L (Stevens, Taylor, and Deinzer 1999). A bulk of beneficial biological properties, including, antioxidant, antimicrobial and antitumoral activities, have been claimed for isoxanthohumol. *In vivo* and *in vitro* studies have shown that it is a potent inhibitor of CYP2C8, a member of cytochrome P450 family protein that has been related to the development of tumors (Henderson et al. 2000, Yuan et al. 2014, Zolnierczyk et al. 2015). In the intestine, isoxanthohumol is demethylated by the microbiota, and thereby converted to 8-prenylnaringenin (Possemiers et al. 2006).

8-prenylnaringenin is the most powerful phytoestrogen described in nature and is considered a natural selective estrogen receptor regulator (Milligan et al. 1999). Due to this quality it is proposed as a promising treatment for menopausal and postmenopausal symptoms and is thought to help prevent post-menopausal osteoporosis (Stulikova et al. 2018).

Phenolic acids are non-flavonoid phenolic compounds and are widely present in vegetables, fruits and in beverages as green tea, coffee, red wine and beer. There are many reports about their antioxidant capacity, which is conferred by the scavenging activity of a hydroxyl group in their ring (Robbins 2003). In beer, phenolic acids are mainly derived from barley and malt, and are present at a concentration close to 25 μg/mL, bock beer being the one containing the highest concentration (29.1 μg/mL) (Gramshaw 1967, Piazzon, Forte, and Nardini 2010). Among the different phenolic acids, ferulic and gallic acids are the most copious in commercial beer (around 14 and 6 μg/mL, respectively), followed by sinapic, vanillic, caffeic, p-coumaric, syringic, and 4-hydroxyphenylacetic acid (between 0.5 and 4.2 μg/mL) (Haifeng Zhao 2010, Piazzon, Forte, and Nardini 2010). There is also evidence of the presence of chlorogenic, neochlorogenic, *p*-hydroxybenzoic, protocatechuic and gentisic acids (Szwajgier 2009). In agreement with the described antioxidant ability of phenolic acids, their concentration is directly related to the antioxidant activity of the beer in question (Piazzon, Forte, and Nardini 2010). Also, phenolic acids are easily absorbed in the human intestine and diffusion into the bloodstream has been well documented. Phenolic acids are found conjugated or in a free form; around 70% of p-coumaric and 4-hydroxyphenylacetic acid, 10-20% of caffeic, ferulic and sinapic acids, and 50% of vanillic acid are found in a free form in the human blood (Nardini et al. 2006). Therefore, the antioxidant properties of these compounds can be associated with the beneficial effects observed for moderate beer consumers. In addition to the antioxidant activity, neuroprotective effects have been described, among others, antidepressant, antinociceptive, anti-inflammatory, anti-allergic, and antiepileptic activities as well as a partial protection from ischemia reperfusion injury (Szwajgier, Borowiec, and Pustelniak 2017).

Bitter acids (humulones and lupulones)

Bitter acids derive principally from the hop and are present as α-acids (or humulones) and *β*-acids (or lupulones). These molecules are prenylated polyketides synthesized in the hop plant and, as the name suggests, they contribute to the bitter flavour of beer. Humulone concentration in beer is up to 4 mg/L, they improve foam stability, suppress gushing and contribute to the preservation of beer. In contrast, lupulones are present in beer in a much lower concentration than humulones (0.14 to 0.012 mg/L). These compounds are not so bitter and are extremely sensitive to oxidation, giving rise to a number of oxidized compounds, which are hydrophobic and therefore much less soluble in water than humulones (Walker et al. 2012). Hulupones can be present in beer in quantities of a few mg/L (Van Cleemput, Cattoor, et al. 2009). α-acids are isomerized throughout the brewing process to the more water-soluble iso-α-acids (iso-humulones), achieving concentrations from 10 up to 100 mg/L in beer. Bitter acids have been reported to exert a wide range of effects, both *in vitro* and *in vivo*. There is evidence that they participate in the stimulation of gastric acid secretion, an effect attributed to beer drinking as discussed above (Walker et al. 2012). Many other beneficial effects of bitter acids are described in the literature, and most of those effects are conveyed by peroxisome proliferator-activated receptor *γ* (PPAR-*γ*) activation. Moreover, by activation of both intrinsic-mitochondrial and external Fas receptor apoptotic pathways, bitter acids induce apoptosis in leukemia HL-60 cells (Chen and Lin 2004). In a diet-induced obese rodent model, Kondo and coworkers have demonstrated that iso-α-acids prevent dyslipidemia and type 2 diabetes, and in a clinical trial, glucose metabolism was improved, and body fat decreased. Also, intake of iso-α-acids suppresses brain inflammation induced by *β*-amyloid accumulation and prevents cognitive decline in a murine model of Alzheimer's disease (Yajima et al. 2004, Yajima et al. 2005, Miura et al. 2005, Obara et al. 2009, Ano et al. 2017, Ayabe et al. 2018).

Conclusion

Beer is a beverage that is consumed by all social classes worldwide. It was appreciated for its medical qualities and it

has been prescribed for constipation, stomach ailments, coughs, swollen eyes and even used in enemas (Homan 2004, Samuel 1996). In medieval times, hops was introduced to the beer brewing process, which added more beneficial effects, such as amelioration of sleeping disorders, nervousness, gastric function activation, antispasmodic effect and many others (Zanoli and Zavatti 2008). It is therefore not surprising that current scientific literature reports multiple benefits associated with moderate beer consumption. On the other hand, beer consumption has been related to pancreatitis, obesity and certain types of cancer, and a recent meta-analysis concluded that no level of alcohol consumption is safe (Collaborators 2018). Nevertheless, even this study found a J-shaped relationship for alcohol consumption and ischemic heart disease.

It is important to note that clinical studies addressing a moderate beer consumption are difficult to interpret because of habits that come with beer consumption, such as ingestion of other alcoholic drinks and life style factors such as social status, smoking, physical activity and diet. To our knowledge, the only population study exclusively studying beer drinkers was performed in a Czech population (Bobak, Skodova, and Marmot 2003). Furthermore, a few interventional studies compared the effects of beer, non-alcoholic beer and ethanol *per se*, as discussed earlier, but the nature of such studies only allows conclusions about short-term effects. For these reasons, a definitive conclusion about whether the benefits of moderate beer consumption outweigh the risks will likely not be possible; nevertheless, the current evidence warrants a closer investigation of the beneficial effects of the non-alcoholic beer compounds discussed in this review. To unravel mechanisms of action of each of these compounds, or combinations thereof, we believe that studies in simple model organisms such as nematodes or other invertebrate models will be instrumental to shed light on the role of beer non-alcoholic components on health and disease and that such studies could lead to successful preclinical and clinical trials.

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